ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) AND RELATED LEARNING DISABILITIES

Alfonso MR., Miquel TF., Xavier B. & Blanca AS. (2013). Resting Parietal Electroencephalogram Asymmetries and Self-Reported Attentional Control. *Clin EEG Neurosci.* Mar 31. Research on electroencephalogram (EEG) asymmetries and anxiety proneness has recently spread to emotion regulation capabilities. We studied whether attentional control (AC), a temperamental construct related to emotional regulation, was associated with asymmetrical patterns of resting EEG activity at the frontal and parietal regions, reflected not only in the α frequency band (8-13 Hz) but also in higher bands β1 (13-20 Hz) and β2 (20-30 Hz). Self-reports of AC and trait anxiety, and resting EEG recordings, were obtained from 58 healthy participants. Correlational analysis showed that lower levels of self-reported AC were associated with less α, β1, and β2 powers in the left parietal cortex, while no significant relationships were found between the AC and EEG oscillations in the prefrontal cortex. The role of the left and right parietal lobes in the attentional processes is discussed.

Arnold, L. E., Lofthouse, N., Hersch, S., Pan, X., Hurt, E., Bates, B., Kassouf, K., Moone, S., & Grantier, C. (2013). EEG neurofeedback for ADHD: double-blind sham-controlled randomized pilot feasibility trial. Journal of attention disorders, 17(5), 410–419. https://doi.org/10.1177/1087054712446173. Objective: Preparing for a definitive randomized clinical trial (RCT) of neurofeedback (NF) for ADHD, this pilot trial explored feasibility of a double-blind, sham-controlled design and adherence/palatability/relative effect of two versus three treatments/week. Method: Unmedicated 6- to 12-year-olds with Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) ADHD were randomized to active NF versus sham-NF and to 2X versus 3X/week treatment frequency. Frequency switch was allowed after Treatment 24. Results: In two school years, 39 participants were recruited and 34 (87%) completed all 40 treatments. Child/parent guesses about assigned treatment were no better than chance. At Treatment 24, 38% chose 2X/week and 62% chose 3X/week. Both active NF and sham yielded large pre-post improvement on parent ratings but NF no more than sham. Conclusion: Blinding appears to work, and sham does not prevent recruitment/retention. Treatment frequency of 3X/week seems preferred over 2X/week and was as effective. A large double-blind RCT is feasible and necessary to test specific NF effectiveness.

Arns, M., Feddema, I., & Kenemans, J. L. (2014). Differential effects of theta/beta and SMR neurofeedback in ADHD on sleep onset latency. Frontiers in human neuroscience, 8, 1019. https://doi.org/10.3389/fnhum.2014.01019. Recent studies suggest a role for sleep and sleep problems in the etiology of attention deficit hyperactivity disorder (ADHD) and a recent model about the working mechanism of sensori-motor rhythm (SMR) neurofeedback, proposed that this intervention normalizes sleep and thus improves ADHD symptoms such as inattention and hyperactivity/impulsivity. In this study we compared adult ADHD patients (N = 19) to a control group (N = 28) and investigated if differences existed in sleep parameters such as Sleep Onset Latency (SOL), Sleep Duration (DUR) and overall reported sleep problems (PSQI) and if there is an association between sleep-parameters and ADHD symptoms. Secondly, in 37 ADHD patients we investigated the effects of SMR and Theta/Beta (TBR) neurofeedback on ADHD symptoms and sleep parameters and if these sleep parameters may mediate treatment outcome to SMR and TBR neurofeedback. In this study we found a clear continuous relationship between self-reported sleep problems (PSQI) and inattention in adults with- and without-ADHD. TBR neurofeedback resulted in a small reduction of SOL, this change in SOL did not correlate with the change in ADHD symptoms and the reduction in SOL only happened in the last half of treatment, suggesting this is an effect of symptom improvement not specifically related to TBR neurofeedback. SMR neurofeedback specifically reduced the SOL and PSQI score, and the change in SOL and change in PSQI correlated strongly with the change in inattention, and the reduction in SOL was achieved in the first half of treatment, suggesting the reduction in SOL mediated treatment response to SMR neurofeedback. Clinically, TBR and SMR neurofeedback had similar effects on symptom

reduction in ADHD (inattention and hyperactivity/impulsivity). These results suggest differential effects and different working mechanisms for TBR and SMR neurofeedback in the treatment of ADHD.

Arns, M., van der Heijden, KB., Arnold, LE. & Kenemans, LJ. (2013). Geographic Variation in the Prevalence of Attention-Deficit/Hyperactivity Disorder: The Sunny Perspective. Biological Psychology. Background: Attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood, with average worldwide prevalence of 5.3%, varying by region. Methods: We assessed the relationship between the prevalence of ADHD and solar intensity (SI) (kilowatt hours/square meters/day) on the basis of multinational and cross-state studies. Prevalence data for the U.S. were based on self-report of professional diagnoses; prevalence data for the other countries were based on diagnostic assessment. The SI data were obtained from national institutes. Results: In three datasets (across 49 U.S. states for 2003 and 2007, and across 9 non-U.S. countries) a relationship between SI and the prevalence of ADHD was found, explaining 34%–57% of the variance in ADHD prevalence, with high SI having an apparent preventative effect. Controlling for low birth weight, infant mortality, average income (socioeconomic status), latitude, and other relevant factors did not change these findings. Furthermore, these findings were specific to ADHD, not found for the prevalence of autism spectrum disorders or major depressive disorder. Conclusions: In this study we found a lower prevalence of ADHD in areas with high SI for both U.S. and non-U.S. data. This association has not been reported before in the literature. The preventative effect of high SI might be related to an improvement of circadian clock disturbances, which have recently been associated with ADHD. These findings likely apply to a substantial subgroup of ADHD patients and have major implications in our understanding of the etiology and possibly prevention of ADHD by medical professionals, schools, parents, and manufacturers of mobile devices.

Arns, M., Conners, CK., Kraemer, HC. (2013). A decade of EEG theta/beta ratio research in ADHD: A meta-analysis. *Journal of Attention Disorders*: May DOI:10.1177/108705471246008. Objective: Many EEG studies have reported that ADHD is characterized by elevated Theta/Beta ratio (TBR). In this study we conducted a meta-analysis on the TBR in ADHD. Method: TBR data during Eyes Open from location Cz were analyzed from =children/adolescents 6-18 years of age with and without ADHD. Results: Nine studies were identified with a total of 1253 children/adolescents with and 517 without ADHD. The grand-mean effect size (ES) for the 6-13 year-olds was 0.75 and for the 6-18 year-olds was 0.62. However the test for heterogeneity remained significant; therefore these ESs are misleading and considered an overestimation. Post-hoc analysis found a decreasing difference in TBR across years, explained by an increasing TBR for the non-ADHD groups. Conclusion: Excessive TBR cannot be considered a reliable diagnostic measure of ADHD, however a substantial sub-group of ADHD patients do deviate on this measure and TBR has prognostic value in this sub-group, warranting its use as a prognostic measure rather than a diagnostic measure.

Arns, M., Kenemans, JL. (in press). Neurofeedback in ADHD and insomnia: Vigilance stabilization through sleep spindles and circadian networks. Ne*urosci. Biobehav. Rev*. (2012). In this review article an overview of the history and current status of neurofeedback for the treatment of ADHD and insomnia is provided. Recent insights suggest a central role of circadian phase delay, resulting in sleep onset insomnia (SOI) in a sub-group of ADHD clients. Chronobiological treatments, such as melatonin and early morning bright light, affect the suprachiasmatic nucleus. This nucleus has been shown to project to the noradrenergic locus coeruleus (LC) thereby explaining the vigilance stabilizing effects of such treatments in ADHD. It is hypothesized that both Sensori-Motor Rhythm (SMR) and Slow-Cortical Potential (SCP) neurofeedback impact on the sleep spindle circuitry resulting in increased sleep spindle density, normalization of SOI and thereby affect the noradrenergic LC, resulting in vigilance stabilization. After SOI is normalized, improvements on ADHD symptoms will occur with a delayed onset of effect. Therefore, clinical trials investigating new treatments in ADHD should include assessments at follow-up as their primary endpoint rather than assessments at outtake. Furthermore, an implication requiring further study is that neurofeedback could be stopped when SOI is normalized, which might result in fewer sessions.

Arns M, Drinkenburg W, Leon Kenemans J. (2012). The effects of QEEG-informed neurofeedback in ADHD: an open-label pilot study. *Appl Psychophysiol Biofeedback.* 2012 Sep;37(3):171-80. ADHD several EEG biomarkers have been described before, with relevance to treatment outcome to stimulant medication. This pilot-study aimed at personalizing neurofeedback treatment to these

specific sub-groups to investigate if such an approach leads to improved clinical outcomes. Furthermore, pre- and post-treatment EEG and ERP changes were investigated in a sub-group to study the neurophysiological effects of neurofeedback. Twenty-one patients with ADHD were treated with QEEG-informed neurofeedback and post-treatment effects on inattention (ATT), hyperactivity/impulsivity (HI) and comorbid depressive symptoms were investigated. There was a significant improvement for both ATT, HI and comorbid depressive complaints after QEEG-informed neurofeedback. The effect size for ATT was 1.78 and for HI was 1.22. Furthermore, anterior individual alpha peak frequency (iAPF) demonstrated a strong relation to improvement on comorbid depressive complaints. Pre- and post-treatment effects for the SMR neurofeedback sub-group exhibited increased N200 and P300 amplitudes and decreased SMR EEG power post-treatment. This pilot study is the first study demonstrating that it is possible to select neurofeedback protocols based on individual EEG biomarkers and suggests this results in improved treatment outcome specifically for ATT, however these results should be replicated in further controlled studies. A slow anterior iAPF at baseline predicts poor treatment response on comorbid depressive complaints in line with studies in depression. The effects of SMR neurofeedback resulted in specific ERP and EEG changes.

Arns, M, Conners, C. K., & Kraemer, H (2012). A decade or EEG Theta/Beta Ratio Research in ADHD: A Meta-Analysis. *Journal of Attention Disorders*; (in press). Objective: Many EEG studies have reported that ADHD is characterized by elevated Theta/Beta ratio (TBR). In this study we conducted a meta-analysis on the TBR in ADHD. Method: TBR data during Eyes Open from location Cz were analyzed from children/adolescents 6-18 years of age with and without ADHD. Results: Nine studies were identified with a total of 1253 children/adolescents with and 517 without ADHD. The grand-mean effect size (ES) for the 6-13 year-olds was 0.75 and for the 6-18 year-olds was 0.62. However the test for heterogeneity remained significant; therefore these ESs are misleading and considered an overestimation. Post-hoc analysis found a decreasing difference in TBR across years, explained by an increasing TBR for the non-ADHD groups. Conclusion: Excessive TBR cannot be considered a reliable diagnostic measure of ADHD, however a substantial sub-group of ADHD patients do deviate on this measure and TBR has prognostic value in this sub-group, warranting its use as a prognostic measure rather than a diagnostic measure.

Arns, M., de Ridder, S., Strehl, U., Breteler, M., Coenen, A. (2009). Efficacy of neurofeedback treatment in ADHD: The effects on attention, impulsivity and hyperactivity: A meta-analysis. *Clinical EEG and Neuroscience*; 40(3). 180-189. In order to study the treatment of the children with attention deficit hyperactivity disorder (ADHD), the integrated visual and auditory continuous performance test (IVA-CPT) was clinically applied to evaluate the effectiveness of electroencephalogram (EEG) biofeedback training. Of all the 60 children with ADHD aged more than 6 years, the effective rate of EEG biofeedback training was 91.6% after 40 sessions of EEG biofeedback training. Before and after treatment by EEG biofeedback training, the overall indexes of IVA were significantly improved among predominately inattentive, hyperactive, and combined subtype of children with ADHD ($P<0.001$). It was suggested that EEG biofeedback training was an effective and vital treatment on children with ADHD.

Arns, M., Kleinnijenhuis, M., Fallahpour, K., & Bretler, R. (2007). Golf performance enhancement and real-life neurofeedback training using personalized event-locked EEG profiles. *Journal of Neurotherapy*, 11(4), 11-18. Background. This study reports on a new method for golf performance enhancement employing personalized real-life neurofeedback during golf putting. Method. Participants (n = 6) received an assessment and three real-life neurofeedback training sessions. In the assessment, a personal event-locked electroencephalographic (EEG) profile at FPz was determined for successful versus unsuccessful putts. Target frequency bands and amplitudes marking optimal prefrontal brain state were derived from the profile by two raters. The training sessions consisted of four series of 80 putts in an ABAB design. The feedback in the second and fourth series was administered in the form of a continuous NoGo tone, whereas in the first and third series no feedback was provided. This tone was terminated only when the participants EEG met the assessment-defined criteria. In the feedback series, participants were instructed to perform the putt only after the NoGo tone had ceased. Results. From the personalized event-locked EEG profiles, individual training protocols were established. The interrater reliability was 91%. The overall percentage of successful putts was significantly larger in the second and fourth series (feedback) of training compared to the first and third series (no feedback). Furthermore, most participants improved their performance with feedback on their personalized

EEG profile, with 25% on average. Conclusions. This study demonstrates that the "zone" or the optimal mental state for golf putting shows clear recognizable personalized patterns. The learning effects suggest that this real-life approach to neurofeedback improves learning speed, probably by tapping into learning associated with contextual conditioning rather than operant conditioning, indicating perspectives for clinical applications.

Barabasz, A., & Barabasz, M. (2000). Treating AD/HD with hypnosis and neurotherapy. *Child Study Journal*, 30(1), 25-42. Eighteen children and one young adult ADHD patients were treated with alert hypnosis as an adjunct to neurotherapy. Posttest means for each subscale (Inattentive, Impulsive, and Hyperactive) of the Attention Deficit Disorders Evaluation Scale-Home Version were significantly lower than pretest scores. No comparison group was used, and outcomes were confined to specific therapist.

Bazanova, O. M., Auer, T., & Sapina, E. A. (2018). On the Efficiency of Individualized Theta/Beta Ratio Neurofeedback Combined with Forehead EMG Training in ADHD Children. Frontiers in human neuroscience, 12, 3. https://doi.org/10.3389/fnhum.2018.00003. Background: Neurofeedback training (NFT) to decrease the theta/beta ratio (TBR) has been used for treating hyperactivity and impulsivity in attention deficit hyperactivity disorder (ADHD); however, often with low efficiency. Individual variance in EEG profile can confound NFT, because it may lead to influencing non-relevant activity, if ignored. More importantly, it may lead to influencing ADHD-related activities adversely, which may even result in worsening ADHD symptoms. Electromyogenic (EMG) signal resulted from forehead muscles can also explain the low efficiency of the NFT in ADHD from both practical and psychological point-of-view. The first aim of this study was to determine EEG and EMG biomarkers most related to the main ADHD characteristics, such as impulsivity and hyperactivity. The second aim was to confirm our hypothesis that the efficiency of the TBR NFT can be increased by individual adjustment of the frequency bands and simultaneous training on forehead muscle tension. Methods: We recruited 94 children diagnosed with ADHD (ADHD) and 23 healthy controls (HC). All participants were male and aged between six and nine. Impulsivity and attention were assessed with Go/no-Go task and delayed gratification task, respectively; and 19-channel EEG and forehead EMG were recorded. Then, the ADHD group was randomly subdivided into (1) standard, (2) individualized, (3) individualized+EMG, and (4) sham NFT (control) groups. The groups were compared based on TBR and EEG alpha activity, as well as hyperactivity and impulsivity three times: pre-NFT, post-NFT and 6 months after the NFT (follow-up). Results: ADHD children were characterized with decreased individual alpha peak frequency, alpha bandwidth and alpha amplitude suppression magnitude, as well as with increased alpha1/alpha2 (a1/a2) ratio and scalp muscle tension when c ($\eta 2 \geq 0.212$). All contingent TBR NFT groups exhibited significant NFT-related decrease in TBR not evident in the control group. Moreover, we detected a higher overall alpha activity in the individualized but not in the standard NFT group. Mixed MANOVA considering between-subject factor GROUP and within-subject factor TIME showed that the individualized+EMG group exhibited the highest level of clinical improvement, which was associated with increase in the individual alpha activity at the 6 months follow-up when comparing with the other approaches (post hoc $t = 3.456$, $p = 0.011$). Conclusions: This study identified various (adjusted) alpha activity metrics as biomarkers with close relationship with ADHD symptoms, and demonstrated that TBR NFT individually adjusted for variances in alpha activity is more successful and clinically more efficient than standard, non-individualized NFT. Moreover, these training effects of the individualized TBR NFT lasted longer when combined with EMG.

Bazanova, O.M., Aftanas, L.I. (2010). Individual EEG alpha activity analysis for enhancement neurofeedback efficiency: Two case studies. *Journal of Neurotherapy* 14(3), 244 – 253. The hypothesis was tested of whether neurofeedback training applied in order to increase or decrease power of individual EEG frequency ranges is more efficient than neurofeedback training of standard EEG frequency ranges. The sessions of decreasing the theta/beta ratio and reinforcing alpha neurofeedback training were carried out on two outpatients with attention deficit disorder (a schoolboy) and functional pain contraction (a professional musician). The neurofeedback utilizing standard EEG frequency ranges (theta 4-8, alpha 8-12, beta 13-18) was inefficient and even resulted in aggravation of symptoms in both cases. The individualized neurofeedback that utilized individual frequency ranges resulted in substantial clinical improvement.

Beauregard, M., & Levesque, J. (2006). Functional magnetic resonance imaging investigation of the effects of neurofeedback training on the neural bases of selective attention and response inhibition in children with attention-deficit/hyperactivity disorder. ***Applied Psychophysiology & Biofeedback*****, 31(1), 3-20**. Two functional magnetic resonance imaging (fMRI) experiments were undertaken to measure the effect of neurofeedback training (NFT), in AD/HD children, on the neural substrates of selective attention and response inhibition. Twenty unmedicated AD/HD children participated to these experiments. Fifteen children were randomly assigned to the Experimental (EXP) group whereas the other five children were randomly assigned to the Control (CON) group. Only subjects in the EXP group underwent NFT. EXP subjects were trained to enhance the amplitude of the SMR (12-15 Hz) and beta 1 activity (15-18 Hz), and decrease the amplitude of theta activity (4-7 Hz). Subjects from both groups were scanned one week before the beginning of NFT (Time 1) and 1 week after the end of NFT (Time 2), while they performed a "Counting Stroop" task (Experiment 1) and a Go/No-Go task (Experiment 2). At Time 1, in both groups, the Counting Stroop task was associated with significant activation in the left superior parietal lobule. For the Go/No-Go task, no significant activity was detected in the EXP and CON groups. At Time 2, in both groups, the Counting Stroop task was associated with significant activation of the left superior parietal lobule. This time, however, there were significant loci of activation, in the EXP group, in the right ACC, left caudate nucleus, and left substantia nigra. No such activation loci were seen in CON subjects. For the Go/No-Go task, significant loci of activation were noted, in the EXP group, in the right ventrolateral prefrontal cortex, right ACcd, left thalamus, left caudate nucleus, and left substantia nigra. No significant activation of these brain regions was measured in CON subjects. These results suggest that NFT has the capacity to functionally normalize the brain systems mediating selective attention and response inhibition in AD/HD children.

Becerra J, Fernndez T, Harmony T, Caballero MI, Garcia F, Fernandez-Bouzas A, Santiago-Rodriguez E, Prado-Alcalá RA. (2006) "Follow-up study of learning disabled children treated with neurofeedback or placebo." ***Clinical EEG & Neuroscience*****, 37 (3), 98-203.** This report is a 2-year follow-up to a previous study describing positive behavioral changes and a spurt of EEG maturation with theta/alpha neurofeedback (NFB) training in a group of Learning Disabled (LD) children. In a control paired group, treated with placebo, behavioral changes were not observed and the smaller maturational EEG changes observed were easily explained by increased age. Two years later, the EEG maturational lag in Control Group children increased, reaching abnormally high theta Relative Power values; the absence of positive behavioral changes continued and the neurological diagnosis remained LD. In contrast, after 2 years EEG maturation did continue in children who belonged to the Experimental Group with previous neurofeedback training; this was accompanied by positive behavioral changes, which were reflected in remission of LD symptoms.

Sansevere, A. J., Hahn, C. D., & Abend, N. S. (2019). Conventional and quantitative EEG in status epilepticus. Seizure, 68, 38–45. https://doi.org/10.1016/j.seizure.2018.09.011. Background: Neurofeedback (NF) has gained increasing interest among non-pharmacological treatments for Attention Deficit Hyperactivity Disorder (ADHD). NF training aims to enhance self-regulation of brain activities. The goal of the NEWROFEED study is to assess the efficacy of a new personalized NF training device, using two different protocols according to each child's electroencephalographic pattern, and designed for use at home. This study is a non-inferiority trial comparing NF to methylphenidate. Methods: The study is a prospective, multicentre, randomized, reference drug-controlled trial. One hundred seventy-nine children with ADHD, aged 7 to 13 years will be recruited in 13 clinical centres from 5 European countries. Subjects will be randomized to two groups: NF group (Neurofeedback Training Group) and MPH group (Methylphenidate group). Outcome measures include clinicians, parents and teachers' assessments, attention measures and quantitative EEG (qEEG). Patients undergo eight visits over a three-month period: pre-inclusion visit, inclusion visit, 4 "discovery" (NF group) or titration visits (MPH group), an intermediate and a final visit. Patients will be randomized to either the MPH or NF group. Children in the NF group will undergo either an SMR or a Theta/Beta training protocol according to their baseline Theta/Beta Ratio obtained from the qEEG. Discussion: This is the first non-inferiority study between a personalized NF device and pharmacological treatment. Innovative aspects of Mensia Koala™ include the personalization of the training protocol according to initial qEEG characteristics (SMR or Theta/Beta training protocols) and an improved accessibility of NF due to the opportunity to train at home with monitoring by the clinician through a dedicated web portal.

Boyd, W. D., & Campbell, S. E. (1998). EEG biofeedback in the schools: The use of EEG biofeedback to treat ADHD in a school setting. *Journal of Neurotherapy*, 2(4), 65-71. Six middle school students diagnosed with attention deficit/hyperactivity disorder were selected for sensory motor rhythm (SMR) training with EEG biofeedback. The subjects were evaluated following a 72-hour drug-free period with the WISC-III Digit Span subtest and the Test of Variables of Attention (TOVA). Five of the subjects received 20 sessions of EEG biofeedback and one of the subjects received nine sessions of EEG biofeedback. The subjects were evaluated again following a 72-hour drug-free period. Five of the six subjects improved on their combined Digit Span, TOVA Inattention, and TOVA Impulsivity scores. These results supported previous findings that EEG biofeedback can be effective in the treatment of attention deficit/hyperactivity disorder. More importantly, this study demonstrated that EEG biofeedback could be used in an actual school setting. Recommendations for implementing an EEG biofeedback program in the schools were provided.

Breteler, M. H. M., Arns, M., Peters, S., Giepmans, I., & Verhoeven, L. (2010). Improvements in spelling after QEEG-based neurofeedback in dyslexia: A randomized controlled treatment study. *Applied Psychophysiology & Biofeedback*, 35(1), 5-11. Phonological theories of dyslexia assume a specific deficit in representation, storage and recall of phonemes. Various brain imaging techniques, including qEEG, point to the importance of a range of areas, predominantly the left hemispheric temporal areas. This study attempted to reduce reading and spelling deficits in children who are dyslexic by means of neurofeedback training based on neurophysiological differences between the participants and gender and age matched controls. Nineteen children were randomized into an experimental group receiving qEEG based neurofeedback ($n = 10$) and a control group ($n = 9$). Both groups also received remedial teaching. The experimental group improved considerably in spelling (Cohen's $d = 3$). No improvement was found in reading. An indepth study of the changes in the qEEG power and coherence protocols evidenced no fronto-central changes, which is in line with the absence of reading improvements. A significant increase of alpha coherence was found, which may be an indication that attentional processes account for the improvement in spelling. Consideration of subtypes of dyslexia may refine the results of future studies.

Bluschke, A., Schreiter, M. L., Friedrich, J., Adelhöfer, N., Roessner, V., & Beste, C. (2020). Neurofeedback trains a superordinate system relevant for seemingly opposing behavioral control deficits depending on ADHD subtype. Developmental science, 23(6), e12956. https://doi.org/10.1111/desc.12956. ADHD is one of the most prevalent neuropsychiatric disorders of childhood, but symptoms vary considerably between individuals. Therefore, different ADHD subtypes can be distinguished. Yet, it is widely elusive whether the specific subtype is critical to consider when examining treatment effects. Based on theoretical considerations, this could be the case for EEG theta/beta neurofeedback. We examine the effects of such an intervention on rapid response execution and inhibition processes using a Go/Nogo task in the inattentive (ADD) and the combined (ADHD-C) subtype. We show that a single neurofeedback protocol affects opposing deficits depending on the ADHD subtype - namely the execution (in ADD) and inhibition of action (in ADHD-C). No changes occurred in the healthy controls. These findings are discussed in relation to overarching principles of neural oscillations, particularly in the beta frequency band. The data suggest that theta/beta neurofeedback trains a superordinate system strongly related to the function of neural beta frequency oscillations to tune neural networks important for the sampling of sensory information used for behavioral control.

Budzynski, T. H. (1996). Brain brightening: Can neurofeedback improve cognitive process? *Biofeedback*, 24(2), 14-17. (No abstract available)

Cannon, R., Kerson, C., Hampshire, A. & Coleman, G. L. (2013). Assessing the functional integrity of the default network in adult ADHD with fMRI and sLORETA. *Journal of Neurotherapy*; 16(1). Intrinsic functional connectivity within the default network (DMN) of the brain has gained growing interest in attention deficit/hyperactivity disorder (ADHD). The DMN is proposed to support such core functions as theory of mind, self-related activities such as autobiographical self, stimulus independent thought, self-projection, self-reference and introspective processes as well as central features of self-regulation, task compliance and executive functions. The present study recorded brain activity using both EEG and fMRI during rest and task. The rest data were analyzed using sLORETA and a psychophysiological interaction model respectively. Medial prefrontal and left parietal region connectivity showed the greatest

difference when comparing ADHD to control in theta, alpha1 and alpha 2.

Cannon, R., Kerson, C., Hampshire, A. (2011). sLORETA and fMRI Detection of Medial Prefrontal Default Network Anomalies in Adult ADHD. Journal of Neurotherapy; 15(4). 358-373. Attention deficit hyperactivity disorder (ADHD) is a developmental psychiatric disorder thought to affect approximately 5 to 10% of school-age children, of whom 30%–65% continue to exhibit symptoms into adulthood. The prevalence of ADHD in adults is also an estimated 4%, second only to depression. Across studies there appear to be significant network dysfunctions involved in ADHD. Typically the foci of interest in ADHD included the insular cortices, frontal lobes, basal ganglia and cerebellum. More recently, attention has been directed to the default network of the brain and its functional integrity in ADHD with focus on the precuneus and parietal lobes and interactions with medial prefrontal cortices. Functional Magnetic Resonance Imaging (fMRI) measures neurovascular coupling as measured by the blood oxygenated level dependent signal (BOLD). Electroencephalogram (EEG) measures brain electrical information. Since fMRI is an indirect measure of neuronal activity and EEG is a direct measure combining the results from these two imaging modalities under the same task conditions may provide a more complete story as to the what (EEG) and where (fMRI) activity exists.

Carmody, DP., Radvanski, D. C., Wadhwani, S., Sabo, JJ., & Vergara, L. (2001). EEG biofeedback training and attention-deficit/hyperactivity disorder in an elementary school setting. *Journal of Neurotherapy*, 4(3), 5-27. Method: An experimental group of eight children ages 8-10 completed 35-47 sessions of EEG biofeedback training over a six-month period. Four participants in the experimental group were diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) and four were not diagnosed with ADHD. Eight children in the waitlist control group were matched to the experimental group on age, grade, teacher, and diagnosis. None of the 16 participants were medicated for ADHD. Results: Attention abilities as measured by the Test of Variables of Attention showed the experimental group of children with ADHD reduced errors of commission and anticipation, indicating a reduction in impulsivity. Teacher reports using the McCarney Scale indicated improvements in attention but no changes in impulsivity and hyperactivity. Discussion: Several confounds require exploration before attribution of changes are assigned to neurofeedback. Whether the effects are due to the neurofeedback protocols, attendance at individual sessions away from the classroom, the attention of the technician, or the excitement of a special program cannot be determined with this study. It will be necessary to have a placebo group in order to separate systematically the variables in the training program.

Cohen Kadosh KC, Linden DE, Lau JY. (2013). Plasticity during childhood and adolescence: Innovative approaches to investigating neurocognitive development. *Dev Sci*:16(4). 574-583. doi: 10.1111/desc.12054. Epub 2013 May 28. Adolescence is a period of profound change, which holds substantial developmental milestones, but also unique challenges to the individual. In this opinion paper, we highlight the potential of combining two recently developed behavioural and neural training techniques (cognitive bias modification and functional magnetic neuroimaging-based neurofeedback) into a research approach that could help make the most of increased levels of plasticity during childhood and adolescence. We discuss how this powerful combination could be used to explore changing brain-behaviour relationships throughout development in the context of emotion processing, a cognitive domain that exhibits continuous development throughout the second decade of life. By targeting both behaviour and brain response, we would also be in an excellent position to define sensible time windows for enhancing plasticity, thereby allowing for targeted intervention approaches that can help improve emotion processing in both typically and atypically developing populations.

Deiber, M., Hasler, R., Colin, J., Dayer, A., Aubry, J-M., Baggio, S., Perroud, N., & Ros, T. (2019). Linking alpha oscillations, attention, and inhibitory control in adult ADHD with EEG neurofeedback. Neuroimage Clin. 2020;25:102145. doi: 10.1016/j.nicl.2019.102145. Epub 2019 Dec 24. Abnormal patterns of electrical oscillatory activity have been repeatedly described in adult ADHD. In particular, the alpha rhythm (8-12 Hz), known to be modulated during attention, has previously been considered as candidate biomarker for ADHD. In the present study, we asked adult ADHD patients to self-regulate their own alpha rhythm using neurofeedback (NFB), in order to examine the modulation of alpha oscillations on attentional performance and brain plasticity. Twenty-five adult ADHD patients and 22 healthy controls underwent a 64-channel EEG-recording at resting-state and during a Go/NoGo task,

before and after a 30 min-NFB session designed to reduce (desynchronize) the power of the alpha rhythm. Alpha power was compared across conditions and groups, and the effects of NFB were statistically assessed by comparing behavioral and EEG measures pre-to-post NFB. Firstly, we found that relative alpha power was attenuated in our ADHD cohort compared to control subjects at baseline and across experimental conditions, suggesting a signature of cortical hyper-activation. Both groups demonstrated a significant and targeted reduction of alpha power during NFB. Interestingly, we observed a post-NFB increase in resting-state alpha (i.e. rebound) in the ADHD group, which restored alpha power towards levels of the normal population. Importantly, the degree of post-NFB alpha normalization during the Go/NoGo task correlated with individual improvements in motor inhibition (i.e. reduced commission errors) only in the ADHD group. Overall, our findings offer novel supporting evidence implicating alpha oscillations in inhibitory control, as well as their potential role in the homeostatic regulation of cortical excitatory/inhibitory balance.

Dobrakowski, P., & Łebecka, G. (2020). Individualized Neurofeedback Training May Help Achieve Long-Term Improvement of Working Memory in Children With ADHD. Clinical EEG and neuroscience, 51(2), 94–101. https://doi.org/10.1177/1550059419879020. Background. Children with attention deficit hyperactivity disorder (ADHD) may suffer from working memory deficits, which can adversely affect their academic performance. Neurofeedback training may enhance working memory and provide a solution to this problem. Aim. To investigate the effect of frequency-neurofeedback on working memory in children with ADHD and to check if the effect is long-lasting. Method. Forty-eight children with ADHD (aged 6-12 years) were randomly assigned either to a neurofeedback with training parameters chosen to take into account each child's peak alpha frequency (PAF) or to a waiting list control group. Each trained child underwent 19-channel electroencephalography (EEG). All children had average intelligence and none were receiving treatment, such as medications, for ADHD. Prior to the training, MOXO and n-back tests were performed. Next, neurofeedback training sessions with frequency bands for theta and beta ranges determined using each child's PAF were carried out for 10 weeks. Training parameters were set to increase amplitudes in the low beta range and to decrease amplitudes in the theta and high beta frequency ranges. The n-back test was performed again right after the training and then a year later. Results. During the first n-back test, children from both groups responded correctly to more than 43% of the stimuli. During the second test, children from the waiting list responded correctly to an average of 49% of the stimuli, while children who underwent the neurofeedback training were correct, on average, 69% of the time (significant difference, $P < .001$). During the third n-back test a year later, children from the waiting list responded correctly to 53% of the stimuli, while those who underwent the neurofeedback training responded correctly to nearly 71%. Conclusion. This study found a statistically significant improvement in a measure of working memory in children who did 10 to 12 sessions of neurofeedback training with training frequency ranges for theta and beta defined according to each child's PAF. The beneficial effects were still present a year after training.

Egner, T., & Gruzelier, J. H. (2001). Learned self-regulation of EEG frequency components effects attention and event-related brain potentials in humans. *NeuroReport,* 12, 4155-4159. Learned enhancement of EEG frequency components in the lower beta range by means of biofeedback has been reported to alleviate attention deficit hyperactivity disorder (ADHD) symptoms. In order to elucidate frequency-specific behavioural effects and neurophysiological mediators, this study applied neurofeedback protocols to healthy volunteers, and assessed impact on behavioural and electrocortical attention measures. Operant enhancement of a 12-15Hz component was associated with reduction in commission errors and improved perceptual sensitivity on a continuous performance task (CPT), while the opposite relation was found for 15-18Hz enhancement. Both 12-15Hz and 15-18Hz enhancement were associated with significant increases in P300 event-related brain potential amplitudes in an auditory oddball task. These relations are interpreted as stemming from band-specific effects on perceptual and motor aspects of attention measures.

Egner, T., & Gruzelier, J. H. (2004). EEG biofeedback of low beta band components: Frequency-specific effects on variables of attention and event-related brain potentials. *Clinical Neurophysiology*, 115(1), 131-139. Objective: To test a common assumption underlying the clinical use of electroencephalographic (EEG) biofeedback training (neurofeedback), that the modulation of discreet frequency bands is associated with frequency-specific effects. Specifically, the proposal was assessed that enhancement of the low beta components sensorimotor rhythm (SMR: 12 – 15 Hz) and beta1 (15 – 18 Hz) affect different aspects of attentional processing. Methods:

Subjects (n ¼ 25) were randomly allocated to training with either an SMR or beta1 protocol, or to a non-neurofeedback control group. Subjects were assessed prior and subsequent to the training process on two tests of sustained attention. The neurofeedback participants were also assessed on target P300 event-related potential (ERP) amplitudes in a traditional auditory oddball paradigm. Results: Protocol-specific effects were obtained in that SMR training was associated with increased perceptual sensitivity 'd prime' (d0), and reduced omission errors and reaction time variability. Beta1 training was associated with faster reaction times and increased target P300 amplitudes, whereas no changes were evident in the control group. Conclusions: Neurofeedback training of SMR and beta1 band components led to significant and protocol-specific effects in healthy subjects. The data can be interpreted as indicating a general attention-enhancing effect of SMR training, and an arousal-enhancing effect of beta1 training.

Enriquez-Geppert S, Huster RJ, Scharfenort R, Mokom ZN, Zimmermann J, Herrmann CS. (2013). Modulation of frontal-midline theta by neurofeedback. Biol Psychol. 2013 Mar 15. pii: S0301-0511(13)00070-7. doi: 10.1016/j.biopsycho.2013.02.019. [Epub ahead of print]. Cortical oscillations demonstrate a relationship with cognition. Moreover, they also exhibit associations with task performance and psychiatric mental disorders. This being the case, the modification of oscillations has become one of the key interests of neuroscientific approaches for cognitive enhancement. For such kind of alterations, neurofeedback (NF) of brain activity constitutes a promising tool. Concerning specific higher cognitive functions, frontal-midline theta (fm-theta) has been suggested as an important indicator of relevant brain processes. This paper presents a novel approach for an individualized, eight-session NF training to enhance fm-theta. An individual's dominant fm-theta frequency was determined based on experiments tapping executive functions. Effects of the actual NF training were compared to a pseudo-NF training. Participants of the pseudo-NF training experienced a comparable degree of motivation and commitment as the subjects of the actual NF training, but found the "training" slightly easier. In comparison to the pseudo-NF training, proper NF training significantly enhanced fm-theta amplitude in the actual training sessions, as well as during the whole course of training. However, unspecific changes in the alpha and beta frequency ranges found with both the actual NF and the pseudo-NF training groups emphasize the relevance of active control groups for neurofeedback studies.

Escolano, C., Navarro-Gil, M., Garcia-Campayo, J., Congedo, M. & Minqueez, j. (2014). The effects of individual upper alpha neurofeedback in ADHD: An open-label pilot study. Applied Psychophysiology and Biofeedback: early E-Pub Sept 9 Standardized neurofeedback (NF) protocols have been extensively evaluated in attention-deficit/hyperactivity disorder (ADHD). However, such protocols do not account for the large EEG heterogeneity in ADHD. Thus, individualized approaches have been suggested to improve the clinical outcome. In this direction, an open-label pilot study was designed to evaluate a NF protocol of relative upper alpha power enhancement in fronto-central sites. Upper alpha band was individually determined using the alpha peak frequency as an anchor point. 20 ADHD children underwent 18 training sessions. Clinical and neurophysiological variables were measured pre- and post-training. EEG was recorded pre- and post-training, and pre- and post-training trials within each session, in both eyes closed resting state and eyes open task-related activity. A power EEG analysis assessed long-term and within-session effects, in the trained parameter and in all the sensors in the (1-30) Hz spectral range. Learning curves over sessions were assessed as well. Parents rated a clinical improvement in children regarding inattention and hyperactivity/impulsivity. Neurophysiological tests showed an improvement in working memory, concentration and impulsivity (decreased number of commission errors in a continuous performance test). Relative and absolute upper alpha power showed long-term enhancement in task-related activity, and a positive learning curve over sessions. The analysis of within-session effects showed a power decrease ("rebound" effect) in task-related activity, with no significant effects during training trials. We conclude that the enhancement of the individual upper alpha power is effective in improving several measures of clinical outcome and cognitive performance in ADHD. This is the first NF study evaluating such a protocol in ADHD. A controlled evaluation seems warranted due to the positive results obtained in the current study.

Fehmi, L. G., & Selzer, F. A. (1980). ***Biofeedback and attention training*****. Chapter in S. Boorstein (Ed.),** ***Transpersonal Psychotherapy*****. Palo Alto: Science and Behavior Books.** (no abstract)

Fleischman, M. J., & Othmer, S. (2005). Case study: Improvements in IQ score and maintenance of gains following EEG biofeedback with mildly developmentally delayed twins. ***Journal of Neurotherapy*****, 9(4), 35-46.** This study reports on the improvements in IQ scores and maintenance of the gains following EEG biofeedback with identical twin girls with mild developmental delay and symptoms suggestive of Attention Deficit Hyperactivity Disorder (ADHD). Full Scale IQ scores increased 22 and 23 points after treatment and were maintained at three follow-up retests over a 52-month period. ADHD symptom checklists completed by their mother showed a similar pattern of improvement and maintenance of gains. The extent of improvement is supported by anecdotal reports of behavioral changes. The results are discussed in the context of other studies of EEG biofeedback also showing improved intelligence following EEG biofeedback.

Foks, M. (2005). Neurofeedback training as an educational intervention in a school setting: How the regulation of arousal states can lead to improved attention and behaviour in children with special needs. ***Educational & Child Psychology*****, 22(3), 67-77.** The current choice of treatment for the remediation of attentional and behavioural difficulties among primary school children with special educational needs (SEN) is, increasingly, pharmacological. If-neurofeedback can regulate brain arousal states and thereby improve attention, behaviour and readiness to learn, there may be a case for incorporating it into the special needs provision of mainstream primary schools, thus avoiding the use of potentially damaging stimulant medication as a means of controlling behaviour and promoting inclusion. An experimental design was used, employing the TOVA test as a pre-/post-test measure of attention and the TOVA rating scale as parental pre/post measure of behaviour, plus qualitative feedback as a post-treatment measure of attention/behaviour. Results indicate that neurofeedback may make an important impact on emotions and affect of the SEN individual, leading to improved behaviour and improved attentional capability; quality time spent on a no-failure task of any kind on a one-to-one basis may be beneficial to children with SEN, affecting their personal belief system and behaviour; incorporating neurofeedback as part of the school-based special needs provision is feasible and practicable

Fonseca LC, Tedrus GM, Bianchini MC & Silva TF. (2013). Electroencephalographic alpha reactivity on opening the eyes in children with attention-deficit hyperactivity disorder. ***Clin EEG Neurosci.*** **2013 Jan;44(1):53-7. doi: 10.1177/1550059412445659.** The quantification of differences in alpha electroencephalograph (EEG) activity between the eyes-closed and eyes-open resting conditions could be used as a measure of resting state arousal. The objective of this study was to evaluate the contribution of EEG alpha reactivity on opening the eyes, to the neurophysiology of children with attention-deficit hyperactivity disorder (ADHD). Thirty-eight children with ADHD were assessed using quantitative EEG (qEEG) analysis of absolute band power at rest, with eyes open and closed. Alpha reactivity index was calculated on opening the eyes, defined from the relationship between the absolute powers in the respective bands in the periods with the eyes open and closed. EEG data of 38 sex- and age-matched controls, with no neurological or psychiatric problems, were collected for comparison. There was a significant reduction in absolute alpha power at all electrodes for both ADHD and control groups with eyes open, indicating an increase in the arousal level. However, the alpha reactivity index was greater, corresponding to less reactivity, in the frontal regions of the children with ADHD ($P < .01$). Such a finding suggests alterations in arousal mechanisms in ADHD. This research suggests that alpha reactivity on opening the eyes, allied with other variables from the qEEG, may improve diagnostic accuracy in ADHD.

Fritson, K. K., Wadkins, T. A., Gerdes, P., & Hof, D. (2007). The impact of neurotherapy on college students' cognitive abilities and emotions. ***Journal of Neurotherapy*****, 11(4), 1-9.** Background. In past research, several case studies and five controlled-group studies explored the effect of electroencephalographic (EEG) biofeedback on intelligence, attention, and behavior in children diagnosed with attention deficit hyperactivity disorder, but no studies have explored the effects of EEG biofeedback in nonclinical adults on measures of response control, mood, emotional intelligence, and self-efficacy. Method. Sixteen nonclinical college students were randomly assigned to receive Beta/Sensory Motor Rhythm EEG biofeedback to increase 12 to 15 Hz activity while inhibiting 4 to 7 Hz and 22 to 36 Hz activity. A control group received placebo EEG biofeedback. All participants completed pre- and post measures assessing intelligence scores, attention, impulse control, mood, emotional intelligence, and self-efficacy to assess the effect of EEG biofeedback. Results. Results showed significant improvements in response control but no improvements in attention. Measures of intelligence and

emotional functioning did not change after EEG biofeedback. Conclusions. This study indicates that response control may improve in a few as 20 EEG biofeedback sessions. Implications and shortcomings discussed.

Fuchs, T., Birbaumer, N., Lutzenberger, W., Gruzelier, J. H., & Kaiser, J. (2003). Neurofeedback treatment for attention deficit/hyperactivity disorder in children: A comparison with methylphenidate. ***Applied Psychophysiology and Biofeedback*****, 28, 1-12.** Clinical trials have suggested that neurofeedback may be efficient in treating attention-deficit/hyperactivity disorder (ADHD). We compared the effects of a 3-month electroencephalographic feedback program providing reinforcement contingent on the production of cortical sensorimotor rhythm (12–15 Hz) and beta1 activity (15–18 Hz) with stimulant medication. Participants were N = 34 children aged 8–12 years, 22 of which were assigned to the neurofeedback group and 12 to the methylphenidate group according to their parents' preference. Both neurofeedback and methylphenidate were associated with improvements on all subscales of the Test of Variables of Attention, and on the speed and accuracy measures of the d2 Attention Endurance Test. Furthermore, behaviors related to the disorder were rated as significantly reduced in both groups by both teachers and parents on the IOWA-Conners Behavior Rating Scale. These findings suggest that neurofeedback was efficient in improving some of the behavioral concomitants of ADHD in children whose parents favored a non-pharmacological treatment.

Gani C, Birbaumer N & Strehl U. (2008). Long term effects after feedback of slow cortical potentials and of theta-beta amplitudes in children with attention-deficit/hyperactivity disorder (ADHD). ***International Journal of Bioelectromagnetism*****, 10(4), 209-232.** Though it had already been shown in the 1970s that neurofeedback improves attention, academic performance and social behavior in children with ADHD, it has not been considered as a standard therapy so far. This is mainly due to the small number of controlled studies fulfilling methodological standards - especially long-term data was not available so far. We are the first to present long term data of children undergoing neurofeedback training. 47 patients in the age of 8 – 12 years were randomly assigned to two different training groups. One group was trained to self regulate slow cortical potentials (SCP), the other group tried to influence Theta- and Beta-amplitudes. Follow-up evaluation was carried out 6 months and more than 2 years after the last training session. Eleven children of the SCP group and 12 children of the Theta/Beta group took part in three booster sessions. Parents rated behavioral symptoms as well as frequency and impact of problems. Attention was measured with the Testbatterie zur Aufmerksamkeitsprüfung (TAP). All improvements in behavior and attention that had been observed at previous assessments turned out to be stable. Yet another significant reduction of number of problems and significant improvement in attention was observed. EEG-self regulation skills were preserved. In each group, half of the children no longer met ADHD criteria. Neurofeedback appears to be an alternative or complement to traditional treatments. The stability of changes might be explained by normalizing of brain functions that are responsible for inhibitory control, impulsivity and hyperactivity.

Gevensleben H, Moll GH, Rothenberger A, Heinrich H. (2011). The usage of neurofeedback with children with ADHD: The method and its evaluation. ***Prax Kinderpsychol Kinderpsychiatr*****. 2011;60(8):666-76.** Neurofeedback is a computer-based behavior training, which is gaining increasing interest in the treatment of children with attention-deficit/hyperactivity disorder (ADHD). This article gives an introduction to neurofeedback and summarizes the state of research, discussing inter alia methodical aspects (e. g., requirements to a control training). Evaluation studies conducted so far indicate clinical efficacy. For example, neurofeedback training was superior to a computerized attention training in a randomized controlled trial (medium effect size). Follow-up investigations suggest that treatment effects remain stable (at least six months). At the clinical level, comparable improvements could be obtained for the neurofeedback protocols theta/beta training and training of slow cortical potentials. Neurophysiological findings document different mechanisms of theta/beta training and slow cortical potential training. Future studies should further elucidate the specificity of training effects related to the kind of training and certain disorders and address how to optimize and individualize neurofeedback training.

Gevensleben, H., Holl, B., Albrecht,B., Vogel, C., Schlamp, D., Kratz, O., Studer,P., Rothenberger, A., Moll,G. H. & Heinrich, H. (2009). Is neurofeedback an efficacious treatment for ADHD? A randomized controlled clinical trial. ***The Journal of Child Psychology and Psychiatry*****; 74(2). 149-157.** In a randomized controlled trial, neurofeedback (NF) training was found to be superior to

a computerized attention skills training concerning the reduction of ADHD symptomatology (Gevensleben et al., 2009). The aims of this investigation were to assess the impact of different NF protocols (theta/beta training and training of slow cortical potentials, SCPs) on the resting EEG and the association between distinct EEG measures and behavioral improvements. In 72 (of initially 102) children with ADHD, aged 8-12, EEG changes after either a NF training (n=46) or the control training (n=26) could be studied. The combined NF training consisted of one block of theta/beta training and one block of SCP training, each block comprising 18 units of 50 minutes (balanced order). Spontaneous EEG was recorded in a two-minute resting condition before the start of the training, between the two training blocks and after the end of the training. Activity in the different EEG frequency bands was analyzed. In contrast to the control condition, the combined NF training was accompanied by a reduction of theta activity. Protocol-specific EEG changes (theta/beta training: decrease of posterior-midline theta activity; SCP training: increase of central-midline alpha activity) were associated with improvements in the German ADHD rating scale. Related EEG-based predictors were obtained. Thus, differential EEG patterns for theta/beta and SCP training provide further evidence that distinct neuronal mechanisms may contribute to similar behavioral improvements in children with ADHD.

Ghaziri J, Tucholka A, Larue V, Blanchette-Sylvestre M, Reyburn G, Gilbert G, Lévesque J, Beauregard M. Neurofeedback Training Induces Changes in White and Gray Matter. Clin EEG Neurosci. 2013 Mar 26. The main objective of this structural magnetic resonance imaging (MRI) study was to investigate, using diffusion tensor imaging, whether a neurofeedback training (NFT) protocol designed to improve sustained attention might induce structural changes in white matter (WM) pathways, purportedly implicated in this cognitive ability. Another goal was to examine whether gray matter (GM) volume (GMV) might be altered following NFT in frontal and parietal cortical areas connected by these WM fiber pathways. Healthy university students were randomly assigned to an experimental group (EXP), a sham group, or a control group. Participants in the EXP group were trained to enhance the amplitude of their $\beta 1$ waves at F4 and P4. Measures of attentional performance and MRI data were acquired one week before (Time 1) and one week after (Time 2) NFT. Higher scores on visual and auditory sustained attention were noted in the EXP group at Time 2 (relative to Time 1). As for structural MRI data, increased fractional anisotropy was measured in WM pathways implicated in sustained attention, and GMV increases were detected in cerebral structures involved in this type of attention. After 50 years of research in the field of neurofeedback, our study constitutes the first empirical demonstration that NFT can lead to microstructural changes in white and gray matter.

Hammond, D. C. (2006). What is neurofeedback? *Journal of Neurotherapy*; 10(4). 25-36. EEG biofeedback (neurofeedback) originated in the late 1960s as a method for retraining brainwave patterns through operant conditioning. Since that time a sizable body of research has accumulated on the effectiveness of neurofeedback in the treatment of uncontrolled epilepsy, ADD/ADHD, anxiety, alcoholism, posttraumatic stress disorder, and mild head injuries. Studies also provide encouraging indications that neurofeedback offers a treatment alternative for use with learning disabilities, stroke, depression, fibromyalgia, autism, insomnia, tinnitus, headaches, problems with physical balance, and for the enhancement of peak performance. At a time when an increasing number of people are concerned with negative effects from relying solely on medication treatments, neurofeedback may offer an additional treatment alternative for many conditions. This article assists the reader to understand how neurofeedback works, how assessment allows neurofeedback to be individualized, and briefly reviews evidence for the neurofeedback treatment of many conditions. The public is cautioned that in selecting a practitioner for the treatment of the kinds of medical, psychiatric and psychological conditions cited above, a practitioner should be licensed for independent practice in their state or province and should ideally also be certified by a legitimately recognized body

Hansen, L. M., Trudeau, D., & Grace, L. (1996). Neurotherapy and drug therapy in combination for adult ADHD, personality disorder, and seizure. *Journal of Neurotherapy*, 2(1), 6-14. This is a case report of an adult female patient with ADHD, temporal seizure disorder, and Borderline Personality Disorder treated with 30 weekly sessions of SMR neurofeedback and carbamazepine. Posttreatment measures showed improvements in T.O.V.A., self-report, and QEEG. Both neurofeedback and carbamazepine showed the most effect in early treatment. Progress continued after discontinuance of the drug.

Helps, S., Broyd, SJ., James, CJ., Karl, A., Chen, W. & Sonuga-Barke, EJS. (2010). Altered spontaneous low frequency brain activity in attention deficit/hyperactivity disorder. *Brain Research*: Online February 2010. 134-143. Background: Resting brain activity appears altered in Attention Deficit/Hyperactivity Disorder (ADHD). The default mode interference hypothesis (Sonuga-Barke and Castellanos, 2007) postulates that patterns of spontaneous very low frequency brain activity, typical of the resting brain, cause attention lapses in ADHD when they remain unattenuated following the transition from rest to active task performance. Here we test this hypothesis using DC-EEG. Methods: DC-EEG recordings of very low frequency brain activity (<1.5 Hz) were compared for 16 male children with ADHD and 16 healthy controls during both rest and active task performance (two choice reaction time task). Results: A previously identified very low frequency resting network of electrodes was replicated. At rest ADHD children showed less EEG power in very low frequency bands (i.e., .02–.2 Hz). They also showed less attenuation of power at these frequency bands during rest-to-task transition. Reduced attenuation was associated with a number of measures of performance. Discussion: We confirmed the existence of altered very low frequency brain activity in ADHD. ADHD children may have deficits both in maintaining a resting brain when needed and 'protecting' an active brain from the intrusion of resting state brain activity.

Helps, S., James, C., Debener, S., Karl, A. & Sonuga-Barke, DJS. (2008). Very low frequency EEG oscillations and the resting brain in young adults: a preliminary study of localisation, stability and association with symptoms of inattention. *J Neural Transm*:115. 279-285. Background. Spontaneous very low frequency oscillations (VLFO: <0.2Hz) in functional magnetic-resonance imaging are proposed to identify a default-mode network of resting brain activity. Activity in this network has been related to lapses of attention during goal-directed tasks and may provide a basis for ADHD. This study assessed the relation between scalp-recorded EEG VLFO at rest and ADHD. Methods. 13 young adults with high- and 11 with low self-ratings of ADHD participated. Direct current EEG was recorded during a five minute rest session and was retested after approximately 1 week. Results. A consistent and temporally stable pattern of VLFOs was observed across specific scalp regions in low-ADHD participants. High-ADHD participants had less VLFO power across these locations, especially where inattention self-ratings were high. Inattention was not related to VLFO power in other locations. Discussion. Initial evidence is provided for a pattern of VLFOs at rest which is associated with inattention symptoms.

Heinrich, H., & Rothenberger, A. (2020). Yes, I can - maybe … Effects of placebo-related instructions on neuroregulation in children with ADHD. Journal of neural transmission (Vienna, Austria: 1996), 127(7), 1093–1096. https://doi.org/10.1007/s00702-020-02193-z. Neurofeedback training (NFT) provides strategies for children with ADHD to achieve changes on the neurophysiological and behavioral level to attenuate ADHD symptoms. We assume self-efficacy (an "active attitude"), a core variable in successful NFT. In a randomized, double-blind controlled study, we investigated the impact of a "placebo instruction" on the EEG-regulation performance during two sessions of Theta-Beta-NFT in children with ADHD (age 8-12 years). Children receiving the information "this might be a placebo-training" showed inferior neuroregulation (n = 10) compared to children receiving a standard instruction (n = 12). Results of our pilot study are discussed in view of factors necessary for a valid training (ensuring maximal self-efficacy in the participants) and the fidelity of placebo-controlled trials in NFT-research.

Heinrich, H., Busch, K., Erbe, K., Moll, GH. & Kratz, O. (2014). EEG spectral analysis of attention in ADHD: Implications for neurofeedback training. Frontiers of Human Neuroscience:21(8). 611. OBJECTIVE: In children with attention-deficit/hyperactivity disorder (ADHD), an increased theta/beta ratio in the resting EEG typically serves as a rationale to conduct theta/beta neurofeedback (NF) training. However, this finding is increasingly challenged. As NF may rather target an active than a passive state, we studied the EEG in a condition that requires attention. METHODS: In children with ADHD of the DSM-IV combined type (ADHD-C; N = 15) and of the predominantly inattentive type (ADHD-I; N = 9) and in typically developing children (N = 19), EEG spectral analysis was conducted for segments during the attention network test (ANT) without processing of stimuli and overt behavior. Frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) electrodes were included in the statistical analysis. To investigate if EEG spectral parameters are related to performance measures, correlation coefficients were calculated. RESULTS: Particularly in the ADHD-C group, higher theta and alpha activity was found with the most prominent effect in the upper-theta/lower-alpha (5.5-10.5 Hz) range. In the ADHD-I group, a significantly higher theta/beta ratio was observed at single electrodes (F3, Fz) and a tendency for a higher theta/beta ratio when

considering all electrodes (large effect size). Higher 5.5-10.5 Hz activity was associated with higher reaction time variability with the effect most prominent in the ADHD-C group. A higher theta/beta ratio was associated with higher reaction times, particularly in the ADHD-I group. CONCLUSIONS: (1) In an attention-demanding period, children with ADHD are characterized by an underactivated state in the EEG with subtype-specific differences. (2) The functional relevance of related EEG parameters is indicated by associations with performance (reaction time) measures. (3) Findings provide a rationale for applying NF protocols targeting theta (and alpha) activity and the theta/beta ratio in subgroups of children with ADHD.

Hirshberg, L. M. (2007). Place of electroencephalographic biofeedback for attention deficit/hyperactivity disorder. ***Expert Review of Neurotherapeutics*****, 7(4), 315-319.** Historically, pharmacological treatments for attention-deficit/hyperactivity disorder (ADHD) have been considered to be the only type of interventions effective for reducing the core symptoms of this condition. However, during the past three decades, a series of case-and controlled-group studies examining the effects of EEG biofeedback have reported improved attention and behavioral control, increased cortical activation on quantitative electroencephalographic examination, and gains on tests of intelligence and academic achievement in response to this type of treatment. This review paper critically examines the empirical evidence, applying the efficacy guidelines jointly established by the Association for Applied Psychophysiology and Biofeedback (AAPB) and the International Society for Neuronal Regulation (ISNR). On the basis of these scientific principles, EEG biofeedback was determined to be "probably efficacious" for the treatment of ADHD. Although significant clinical improvement was reported in approximately 75% of the patients in each of the published research studies, additional randomized, controlled group studies are needed in order to provide a better estimate of the percentage of patients with ADHD who will demonstrate such gains in clinical practice.

Heinrich, H., Busch, K., Studer, P., Erbe, K., Moll, G. H., & Kratz, O. (2014). EEG spectral analysis of attention in ADHD: implications for neurofeedback training? Frontiers in human neuroscience, 8, 611. https://doi.org/10.3389/fnhum.2014.00611. Objective: In children with attention-deficit/hyperactivity disorder (ADHD), an increased theta/beta ratio in the resting EEG typically serves as a rationale to conduct theta/beta neurofeedback (NF) training. However, this finding is increasingly challenged. As NF may rather target an active than a passive state, we studied the EEG in a condition that requires attention. Methods: In children with ADHD of the DSM-IV combined type (ADHD-C; N = 15) and of the predominantly inattentive type (ADHD-I; N = 9) and in typically developing children (N = 19), EEG spectral analysis was conducted for segments during the attention network test (ANT) without processing of stimuli and overt behavior. Frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) electrodes were included in the statistical analysis. To investigate if EEG spectral parameters are related to performance measures, correlation coefficients were calculated. Results: Particularly in the ADHD-C group, higher theta and alpha activity was found with the most prominent effect in the upper-theta/lower-alpha (5.5-10.5 Hz) range. In the ADHD-I group, a significantly higher theta/beta ratio was observed at single electrodes (F3, Fz) and a tendency for a higher theta/beta ratio when considering all electrodes (large effect size). Higher 5.5-10.5 Hz activity was associated with higher reaction time variability with the effect most prominent in the ADHD-C group. A higher theta/beta ratio was associated with higher reaction times, particularly in the ADHD-I group. Conclusions: (1) In an attention demanding period, children with ADHD are characterized by an underactivated state in the EEG with subtype-specific differences. (2) The functional relevance of related EEG parameters is indicated by associations with performance (reaction time) measures. (3) Findings provide a rationale for applying NF protocols targeting theta (and alpha) activity and the theta/beta ratio in subgroups of children with ADHD.

Holtman, M., Priewski, B., Wachtlin, D., Wolz, S. Strehl, U. (2014). Neurofeedback in children with attention deficit hyperactivity disorder (ADHD) – A controlled multicenter study of a non-pharmacological treatment approach. BMC Pediatr:14(202). BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood and has often a chronic course persisting into adulthood. However, up to 30% of children treated with stimulants either fail to show an improvement or suffer adverse side effects, including decreased appetite, insomnia and irritability and there is no evidence of long term efficacy of stimulants for ADHD. A series of studies has shown that neurofeedback is an effective additional or alternative treatment for children with ADHD, leading to e.g. significant and stable improvement in behavior, attention and IQ. Significant treatment effects of

neurofeedback have also been verified in meta-analyses. Most of the trials, however, have been criticized for methodological difficulties, particularly lacking appropriate control conditions and number of patients included. This randomized study examines the efficacy of slow cortical potentials (SCP) -neurofeedback, controlling unspecific effects of the setting by comparing two active treatment modalities. METHODS/DESIGN: A total of 144 patients with ADHD, older than six and younger than ten years, in some cases with additional pharmacological treatment, are included in this trial. In five trial centres patients are treated either with SCP-feedback or electromyographic (EMG) -feedback in 25 sessions within 3 months. A comprehensive test battery is conducted before and after treatment and at follow-up 6 month later, to assess core symptoms of ADHD, general psychopathology, attentional performance, comorbid symptoms, intelligence, quality of life and cortical arousal. DISCUSSION: The efficacy of SCP-feedback training for children with ADHD is evaluated in this randomized controlled study. In addition to behavior ratings and psychometric tests neurophysiological parameters serve as dependent variables. Further, the choice of EMG-biofeedback as an active control condition is debated.

Hurt, E., Arnold, AE. & Lofthouse, N. (2014). Quantitative EEG neurofeedback for the treatment of pediatric attention-deficit hyperactivity disorder, autism spectrum disorders, learning disorders and epilepsy. Child and Adolescent Psychiatric Clinics of North America:23(3). 465-86. Neurofeedback (NF) using surface electroencephalographic signals has been used to treat various child psychiatric disorders by providing patients with video/audio information about their brain's electrical activity in real-time. Research data are reviewed and clinical recommendations are made regarding NF treatment of youth with attention deficit/hyperactivity disorder, autism, learning disorders, and epilepsy. Most NF studies are limited by methodological issues, such as failure to use or test the validity of a full-blind or sham NF. The safety of NF treatment has not been thoroughly investigated in youth or adults, although clinical experience suggests reasonable safety.

Jacobs, E. H. (2005). Neurofeedback treatment of two children with learning, attention, mood, social, and developmental deficits. *Journal of Neurotherapy*, 9(4), 55-70. Neurofeedback is biofeedback training of EEG activity through an operant conditioning process by which the individual strained to increase or inhibit the brain's production of electrical activity in specific frequency ranges. Studies have demonstrated efficacy with a variety of disorders, including attention deficit hyperactivity disorder (ADHD), learning problems, and autistic features. This paper describes the application of neurofeedback in a clinical setting with two complex children who manifested multiple diagnoses, including learning disabilities (LD), ADHD, social deficits, mood disorders, and pervasive developmental disorder (PDD). Both boys had adjusted poorly to school, family, and peers. Methods. Subjects were referred to the author's clinical practice. They received individualized protocols based on their symptoms and functional impairments. They were administered semi-weekly 20-minute sessions of one-channel neurofeedback training for approximately six months. In both cases symptoms were identified and tracked with a parent rating scale and one case, with the Symptom Assessment–45 Questionnaire (SA-45) also.

Janssen, T., Geladé, K., Bink, M., van Mourik, R., Twisk, J., Maras, A., & Oosterlaan, J. (2020). Long-term effects of theta/beta neurofeedback on EEG power spectra in children with attention deficit hyperactivity disorder. Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology, 131(6), 1332–1341. https://doi.org/10.1016/j.clinph.2020.02.020. Objective: Neurofeedback has been proposed as an effective alternative for pharmacological treatment in children with attention-deficit/hyperactivity disorder (ADHD), with potentially long-term and delayed benefits. However, the specificity of such long-term behavioral improvements remains inconclusive and therefore additional research into the neurophysiological effects of neurofeedback is needed. We compared long-term effects of theta/beta neurofeedback (NFB) to methylphenidate (MPH) and physical activity (PA, semi-active control intervention) on electroencephalogram (EEG) power spectra. Based on the vigilance stabilization model, we hypothesized further reductions in theta and alpha power in the NFB compared to the control groups. Method: EEG power spectra (theta, alpha and beta) during resting and task conditions were recorded at pre-, post-intervention and 6-months follow-up in 67 children, aged 7-13 (NFB: n = 24, MPH: n = 23, or PA: n = 20). Results: Analyses revealed no power spectra differences at follow-up between MPH and NFB (range p = .165-.905) and PA and NFB (range p = .172-.822). Conclusions: No evidence was found for the specificity of theta/beta NFB at follow-up. Significance: This was the first study into long-

term neurophysiological effects of theta/beta NFB. Future studies are encouraged to explore both specific and non-specific mechanisms of NFB.

Janssen, TW., Bink, M., Gelade, K., van Mourik, R., Maras, A. & Oosterlaan, J. (2016). A randomized controlled trial into the effects of neurofeedback, methylphenidate, and physical activity on EEG power spectra in children with ADHD. J. Child Psychology and Psychiatry: doi10.1111/jcpp.12517. Background: The clinical and neurophysiological effects of neurofeedback (NF) as treatment for children with ADHD are still unclear. This randomized controlled trial (RCT) examined electroencephalogram (EEG) power spectra before and after NF compared to methylphenidate (MPH) treatment and physical activity (PA) – as semi-active control group – during resting and active (effortful) task conditions to determine whether NF can induce sustained alterations in brain function. Methods: Using a multicentre three-way parallel group RCT design, 112 children with a DSM-IV diagnosis of ADHD, aged between 7 and 13 years, were initially included. NF training consisted of 30 sessions of theta/beta training at Cz over a 10-week period. PA training was a semi-active control group, matched in frequency and duration. Methylphenidate was titrated using a double-blind placebo controlled procedure in 6 weeks, followed by a stable dose for 4 weeks. EEG power spectra measures during eyes open (EO), eyes closed (EC) and task (effortful) conditions were available for 81 children at pre- and post intervention (n = 29 NF, n = 25 MPH, n = 27 PA). Clinical trials registration: Train Your Brain? Exercise and Neurofeedback Intervention for ADHD, https://clinicaltrials.gov/show/NCT01363544, Ref. No. NCT01363544. Results: Both NF and MPH resulted in comparable reductions in theta power from pre- to postintervention during the EO condition compared to PA (gp2 = .08 and .12). For NF, greater reductions in theta were related to greater reductions in ADHD symptoms. During the task condition, only MPH showed reductions in theta and alpha power compared to PA (gp2 = .10 and .12). Conclusions: This study provides evidence for specific neurophysiological effects after theta/beta NF and MPH treatment in children with ADHD. However, for NF these effects did not generalize to an active task condition, potentially explaining reduced behavioural effects of NF in the classroom. Keywords: ADHD; neurofeedback; methylphenidate; physical activity; EEG; RCT.

Kaiser, A., Aggensteiner, P. M., Holtmann, M., Fallgatter, A., Romanos, M., Abenova, K., Alm, B., Becker, K., Döpfner, M., Ethofer, T., Freitag, C. M., Geissler, J., Hebebrand, J., Huss, M., Jans, T., Jendreizik, L. T., Ketter, J., Legenbauer, T., Philipsen, A., Poustka, L., … On Behalf Of The ESCAlife-Consortium (2021). EEG Data Quality: Determinants and Impact in a Multicenter Study of Children, Adolescents, and Adults with Attention-Deficit/Hyperactivity Disorder (ADHD). Brain sciences, 11(2), 214. https://doi.org/10.3390/brainsci11020214. Electroencephalography (EEG) represents a widely established method for assessing altered and typically developing brain function. However, systematic studies on EEG data quality, its correlates, and consequences are scarce. To address this research gap, the current study focused on the percentage of artifact-free segments after standard EEG pre-processing as a data quality index. We analyzed participant-related and methodological influences, and validity by replicating landmark EEG effects. Further, effects of data quality on spectral power analyses beyond participant-related characteristics were explored. EEG data from a multicenter ADHD-cohort (age range 6 to 45 years), and a non-ADHD school-age control group were analyzed (ntotal = 305). Resting-state data during eyes open, and eyes closed conditions, and task-related data during a cued Continuous Performance Task (CPT) were collected. After pre-processing, general linear models, and stepwise regression models were fitted to the data. We found that EEG data quality was strongly related to demographic characteristics, but not to methodological factors. We were able to replicate maturational, task, and ADHD effects reported in the EEG literature, establishing a link with EEG-landmark effects. Furthermore, we showed that poor data quality significantly increases spectral power beyond effects of maturation and symptom severity. Taken together, the current results indicate that with a careful design and systematic quality control, informative large-scale multicenter trials characterizing neurophysiological mechanisms in neurodevelopmental disorders across the lifespan are feasible. Nevertheless, results are restricted to the limitations reported. Future work will clarify predictive value.

Kaiser, D. A., & Othmer, S. (2000). Effect of Neurofeedback on variables of attention in a large multi-center trial. *Journal of Neurotherapy*, 4(1), 5-15. Since the first reports of Neurofeedback treatment in ADHD in 1976 many studies have been carried out investigating the effects of Neurofeedback on different symptoms of ADHD such as inattention, impulsivity and hyperactivity. This technique is also used by many practitioners, but the question as to the evidence-based level of this treatment is still unclear. In this study

selected research on Neurofeedback treatment for ADHD was collected and a meta-analysis was performed. Both prospective controlled studies and studies employing a pre- and post-design found large effect sizes (ES) for Neurofeedback on impulsivity and inattention and a medium ES for hyperactivity. Randomized studies demonstrated a lower ES for hyperactivity suggesting that hyperactivity is probably most sensitive to non-specific treatment factors. Due to the inclusion of some very recent and sound methodological studies in this meta-analysis potential confounding factors such as small studies, lack of randomization in previous studies and a lack of adequate control groups have been addressed and the clinical effects of Neurofeedback in the treatment of ADHD can be regarded as clinically meaningful. Four randomized controlled trials have shown Neurofeedback to be superior to a (semi- active) control group, whereby the requirements for Level 4: Efficacious are fulfilled (Criteria for evaluating the level of evidence for efficacy established by the AAPB and ISNR). Three studies have employed a semi-active control group, which can be regarded as a credible sham control providing an equal level of cognitive training and client-therapist interaction. Therefore, in line with the AAPB and ISNR guidelines for rating clinical efficacy, we conclude that Neurofeedback treatment for ADHD can be considered 'Efficacious and Specific' (Level 5) with a large ES for inattention and impulsivity and a medium ES for hyperactivity.

Karch, S., Loy, F., Krause, D., Schwartz, S., Kiesewetter, J., Segmiller, F., Chrobok, A., Keeser, D. & Pogarell, O. (2016). Increased event-related potentials and alpha-, beta-, and gamma-activity associated with intentional actions. Frontiers in Psychology: January doi: 10.3389/fpsyg.2016.00007. Objective: Internally-guided actions are defined as being purposeful, self-generated and offering choices between alternatives. Intentional actions are essential to reach individual goals. In previous empirical studies, internally guided actions were predominantly related to functional responses in frontal and parietal areas. The aim of the present study was to distinguish event-related potentials and oscillatory responses of intentional actions and externally guided actions. In addition, we compared neurobiological findings of the decision which action to perform with those referring to the decision whether or not to perform an action. Methods: Twenty-eight subjects participated in adapted go/nogo paradigms, including a voluntary selection condition allowing participants to (1) freely decide whether to press the response button or (2) to decide whether they wanted to press the response button with the right index finger or the left index finger. Results: The reaction times were increased when participants freely decided whether and how they wanted to respond compared to the go condition. Intentional processes were associated with a fronto-centrally located N2 and P3 potential. N2 and P3 amplitudes were increased during intentional actions compared to instructed responses (*go*). In addition, increased activity in the alpha-, beta- and gamma-frequency range was shown during voluntary behavior rather than during externally guided responses. Conclusion: These results may indicate that an additional cognitive process is needed for intentional actions compared to instructed behavior. However, the neural responses were comparatively independent of the kind of decision that was made (1) decision which action to perform; (2) decision whether or not to perform an action). Significance: The study demonstrates the importance of fronto-central alpha-, beta-, and gamma oscillations for voluntary behavior.

Keng Ang, Choon Guan Lim, & Tih Shih Lee (2017). Personalized features for attention detection in children with Attention Deficit Hyperactivity Disorder. Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference, 2017, 414–417. https://doi.org/10.1109/EMBC.2017.8036850. Measuring attention from electroencephalogram (EEG) has found applications in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). It is of great interest to understand what features in EEG are most representative of attention. Intensive research has been done in the past and it has been proven that frequency band powers and their ratios are effective features in detecting attention. However, there are still unanswered questions, like, what features in EEG are most discriminative between attentive and non-attentive states? Are these features common among all subjects or are they subject-specific and must be optimized for each subject? Using Mutual Information (MI) to perform subject-specific feature selection on a large data set including 120 ADHD children, we found that besides theta beta ratio (TBR) which is commonly used in attention detection and neurofeedback, the relative beta power and theta/(alpha+beta) (TBAR) are also equally significant and informative for attention detection. Interestingly, we found that the relative theta power (which is also commonly used) may not have sufficient discriminative information itself (it is informative only for 3.26% of ADHD children). We have also demonstrated that although these features (relative beta power, TBR and TBAR) are the most important measures to detect attention on average, different subjects have different set of most discriminative features.

Kerson C; Collaborative Neurofeedback Group. (2013). A Proposed Multisite Double-Blind Randomized Clinical Trial of Neurofeedback for ADHD: Need, Rationale, and Strategy. J Atten Disord. 2013 Jul;17(5):420-36. doi: 10.1177/1087054713482580. Epub:Apr 16. Objective: Additional treatments with persisting benefit are needed for ADHD. Because ADHD often shows excessive theta electroencephalogram (EEG) power, low beta, and excessive theta-beta ratio (TBR), a promising treatment is neurofeedback (NF) downtraining TBR. Although several nonblind randomized clinical trials (RCTs) show a medium-large benefit for NF, a well-blinded, sham-controlled RCT is needed to differentiate specific from nonspecific effects. Method: Experts in NF, ADHD, clinical trials, and statistics collaborated to design a double-blind multisite RCT. Results/Conclusion: At four sites, 180 children aged 7 to 10 years with rigorously diagnosed ADHD and TBR ≥ 5 will be randomized to active TBR-NF versus sham NF of equal duration, intensity, and appearance. Sham, utilizing prerecorded EEGs with participant artifacts superimposed, will keep participants and staff blind. Treatment fidelity will be trained/monitored by acknowledged NF leaders. Multidomain assessments before, during, and after treatment (follow-up to 2 years) will also include tests of blinding and sham inertness.

Kerson, C., deBeus, R., Lightstone, H., Arnold, L. E., Barterian, J., Pan, X., & Monastra, V. J. (2020). EEG Theta/Beta Ratio Calculations Differ Between Various EEG Neurofeedback and Assessment Software Packages: Clinical Interpretation. Clinical EEG and neuroscience, 51(2), 114–120. The quantitative electroencephalographic (QEEG) theta/beta power ratio (TBR) has been shown to have an association with attention-deficit hyperactivity disorder (ADHD), with a previous tacit assumption of equivalence across hardware and software systems. Therefore, the International Collaborative ADHD Neurofeedback (ICAN) randomized clinical trial used a fixed TBR ≥ 4.5 cutoff as measured by the Thought Technology Monastra-Lubar Assessment Suite as an inclusion criterion, 1.5 SD above norms collected with that system. However, a difference was noted between the TBR calculated by that assessment suite and the TBR computed by EEGer, the neurofeedback software used for treatment, leading us to investigate the discrepancy. The difference may arise from different calculation methods. This article explains and compares various computational methods used to calculate and display EEG values, including TBR, elucidating why the values are not equivalent across equipment and software programs. Two major sources of variance are (1) how "spectral leakage" at the ends of bands is handled and (2) whether voltages of bins within a band are first averaged and then squared to get bandwidth power or are first squared to get power (turning negative voltages into positive power) and then averaged to get the bandwidth power; the latter method results in higher band power. This article compares methods of computing the TBR. Biofeedback practitioners and investigators should be aware of the algorithms their systems use when interpreting TBRs and require normative comparison data collected with the same system.

Kirk, L. (2007). ***Neurofeedback protocols for subtypes of attention deficit/hyperactivity disorder*****. Chapter in J. R. Evans (Ed.), Handbook of Neurofeedback. Binghampton, NY: Haworth Medical Press, pp. 267-299.**

Kropotov, J. D., Grin-Yatsenko, V. A., Ponomarev, V. A., Chutko, L. S., Yakovenko, E. A., & Nikishena, I. S. (2007). Changes in EEG spectograms, event-related potentials and event-related desynchronization induced by relative beta training in ADHD children. ***Journal of Neurotherapy*****, 11(2), 3-11.** Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder that, by current definition, has onset prior to age 7 years. MRI studies have provided some insight into brain differences associated with ADHD, but thus far have almost exclusively focused on children ages 7 years and older. To better understand the neurobiological development of ADHD, cortical and subcortical brain development should be systematically examined in younger children presenting with symptoms of the disorder. High-resolution anatomical (MPRAGE) images, acquired on a 3.0T scanner, were analyzed in a total of 26 preschoolers, ages 4–5 years (13 with ADHD, 13 controls, matched on age and sex). The ADHD sample was diagnosed using DSM-IV criteria, and screened for language disorders. Cortical regions were delineated and measured using automated methods in Freesurfer; basal ganglia structures were manually delineated. Children with ADHD showed significantly reduced caudate volumes bilaterally; in contrast there were no significant group differences in cortical volume or thickness in this age range. After controlling for age and total cerebral volume, left caudate volume was a significant predictor of hyperactive/impulsive, but not inattentive symptom severity. Anomalous basal ganglia, particularly caudate, development appears to play an important role among children presenting with early onset symptoms of ADHD.

Kropotov, J. D., Grin-Yatsenko, V. A., Ponomarev, V. A., Chutko, L. S., Yakovenko, E. A., Nildshena, I. S. (2005). ERP correlates of EEG relative beta training in ADHD children. ***International Journal of Psychophysiology*****, 55(1), 23-34.** Eighty-six children (ages 9-14) with attention deficit hyperactivity disorder (ADHD) participated in this study. Event-related potentials (ERPs) were recorded in auditory GO/NOGO task before and after15–22 sessions of EEG biofeedback. Each session consisted of 20 min of enhancing the ratio of the EEG power in15–18 Hz band to the EEG power in the rest of spectrum, and 7–10 min of enhancing of the ratio of the EEG power in12–15 Hz to the EEG power in the rest of spectrum with C3-Fz electrodes' placements for the first protocol and C4-Pz for the second protocol. On the basis of quality of performance during training sessions, the patients were divided into two groups: good performers and bad performers. ERPs of good performers to GO and NOGO cues gained positive components evoked within 180–420ms latency. At the same time, no statistically significant differences between pre- and post-training ERPs were observed for bad performers. The ERP differences between post- and pre treatment conditions for good performers were distributed over frontal–central areas and appear to reflect an activation of frontal cortical areas associated with beta training.

Kraus, D., Folkerts, M., Karch, S., Keeser, D., Chrobok, A., Zaudig, M., Hergerl, U., Juckel, G. & Pogarel, O. (2016). Prediction of treatment outcome in patients with obsessive-compulsive disorder with low-resolution brain electromagnetic tomography: A prospective study. Frontiers in Psychology: January doi: 10.3389/fpsyg.2015.01993. The issue of predicting treatment response and identifying, in advance, which patient will profit from treating obsessive-compulsive disorder (OCD) seems to be an elusive goal. This prospective study investigated brain electric activity [using Low-Resolution Brain Electromagnetic Tomography (LORETA)] for the purpose of predicting response to treatment. Forty-one unmedicated patients with a DSM-IV diagnosis of OCD were included. A resting 32-channel EEG was obtained from each participant before and after 10 weeks of standardized treatment with sertraline and behavioral therapy. LORETA was used to localize the sources of brain electrical activity. At week 10, patients were divided into responders and non-responders (according to a reduction of symptom severity >50% on the Y-BOCS). LORETA analysis revealed that at baseline responders showed compared to non-responders a significantly lower brain electric activity within the beta 1 ($t = 2.86$, $p < 0.05$), 2 ($t = 2.81$, $p < 0.05$), and 3 ($t = 2.76$, $p < 0.05$) frequency bands and ROI analysis confirmed a reduced activity in alpha 2 ($t = 2.06$, $p < 0.05$) in the anterior cingulate cortex (ACC). When baseline LORETA data were compared to follow-up data, the analysis showed in the responder group a significantly lower brain electrical resting activity in the beta 1 ($t = 3.17$. $p < 0.05$) and beta 3 ($t = 3.11$. $p < 0.05$) frequency bands and equally for the ROI analysis of the orbitofrontal cortex (OFC) in the alpha 2 ($t = 2.15$. $p < 0.05$) frequency band. In the group of non-responders the opposite results were found. In addition, a positive correlation between frequency alpha 2 (rho = 0.40, $p = 0.010$), beta 3 (rho = 0.42, $p = 0.006$), delta (rho = 0.33, $p = 0.038$), theta (rho = 0.34, $p = 0.031$), alpha 1 (rho = 0.38, $p = 0.015$), and beta1 (rho = 0.34, $p = 0.028$) of the OFC and the bands delta (rho = 0.33, $p = 0.035$), alpha 1 (rho = 0.36, $p = 0.019$), alpha 2 (rho = 0.34, $p = 0.031$), and beta 3 (rho = 0.38, $p = 0.015$) of the ACC with a reduction of the Y-BOCS scores was identified. Our results suggest that measuring brain activity with LORETA could be an efficient and applicable technique to prospectively identify treatment responders in OCD.

Kubik, A., Kubik, P., Stanios, M., & Kraj, B. (2016). Wyniki kliniczne i neurofizjologiczne terapii neurofeedback u dzieci z zespołem ADHD [Clinical and neurophysiological data of neurofeedback therapy in children with ADHD]. Przeglad lekarski, 73(3), 148–151. Introduction: ADHD occurs in 3% of school-age children (and in 70% of them in adulthood) and represents an important medical and social problem. It is characterized by attention deficits, hyperactivity and impulsiveness. Neurofeedback therapy (EEG biofeedback, NF) is carried out based on the analysis of EEG. Objective: To investigate the effect of NF therapy on clinical status and parameters of the EEG in ADHD. Materials and methods: In the years 2007-2014, 287 children (191 boys), aged 6-17 years were included into the study. Some children with ADHD had other coexisting disorders like: tics, dyslexia, emotional or behavior disorders. Visual analysis of EEG was made and 7 selected parameters of bioelectrical activity were assessed. EEG tracing before and after NF therapy were compared. NF therapy lasted from 9 months to 3 years (mean 1.5 years). 60-240 NF training sessions were performed with the use of NF device, video-games and 16-channel Elmiko devices. Statistical analysis of the results was made. Results: Children with ADHD additionally presented low self-esteem, anxiety and sleep disorders. The baseline theta/beta ratio in children with ADHD and ADHD with cooccurring dyslexia was >4.0 and in children with ADHD and coexisting tics 3.0-3.8, with coexisting behavioral disorders 3.7-4.0 and emotional disorders 3.3-3.7. After therapy, this ratio decreased significantly in all groups, but most significantly in ADHD

and ADHD with dyslexia group. In the group with dyslexia theta and alpha activity in the left fronto-temporo-parietal region (the speech centers) has been increased. In children with ADHD and behavior disorders right-sided paroxysmal changes in the form of slow and sharp waves in the temporo-centro-parietal regions were found. In emotionally disturbed children increased fast beta activity in the right hemisphere (anxiety, fear) was observed. Initially NF therapy reduced hyperactivity and impulsivity of children, subsequently improvement of attention was observed and eventually reduction of emotional and behavior disturbances was noticed. Noticeable improvement in the self-esteem was observed as well. The therapy had a positive impact on the spatial organization of EEG in each group. It proved to be particularly useful in children with ADHD and dyslexia. Conclusions: Neurofeedback therapy is a valuable tool with beneficial impact on children with ADHD and accompanying disorders. Characteristics of brain bioelectric activity provides a reliable basis to establish individual EEG bio-feedback protocols of therapy in children and monitor the effectiveness of treatment. In the last 4 years the number of children with ADHD and cooccurring tics who applied for neurofeedback therapy has increased significantly.

Kwon, H., Cho, J., Lee, E. (2009). EEG asymmetry analysis of the left and right brain activities during simple versus complex arithmetic learning. ***Journal of Neurotherapy*** **13(2), 109 – 116.** Repeated practice of simple arithmetic such as addition, subtraction, and multiplication has been widely used for effective math education. Brain activity patterns during simple and complex arithmetic calculation have been explored by several research groups using magnetic resonance images (MRI) and functional MRI (fMRI), and some have reported that the balanced whole brain (both left andright brain) activities during simple arithmetic in contrast to the predominant left brain activities during complex arithmetic. Methods. In this work, we have identified the characteristic brainwaves and asymmetric activation patterns of the left and right brain during the process of simple and complex arithmetic by measuring theta, alpha, Sensory Motor Response (SMR), and beta brainwaves of 24 participants from the location FP1 (left brain) and FP2 (right brain) using EEG. Results. Simple statistics analysis showed the significantly different beta activities from the left brain during complex arithmetic compared to simple arithmetic process, and through the asymmetry analysis of the left and right brain activities, less symmetrical brain activation during complex calculation, that is, specifically higher SMR, and beta brainwaves in the left hemisphere more than right hemisphere was identified, which is consistent with recent fMRI findings. Conclusion. The results imply that simple arithmetic process may improve the whole brain activities in a balanced way while complex arithmetic induce unbalanced activities of the left and right brain.

Liechti, M. D., Maurizio, S., Heinrich, H., Jäncke, L., Meier, L., Steinhausen, H. C., Walitza, S., Drechsler, R., & Brandeis, D. (2012). First clinical trial of tomographic neurofeedback in attention-deficit/hyperactivity disorder: evaluation of voluntary cortical control. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 123(10), 1989–2005. https://doi.org/10.1016/j.clinph.2012.03.016. Objective: Tomographic neurofeedback (tNF) training was evaluated as a treatment for attention-deficit/hyperactivity disorder (ADHD). To investigate the specificity of the treatment, outcomes were related to learning during tNF. Methods: Thirteen children with ADHD trained over 36 lessons to regulate their brain activity in the anterior cingulate cortex (ACC) using both theta-beta frequency and slow cortical potential (SCP) protocols. Thirty-channel electroencephalogram (EEG) was used to calculate low-resolution electromagnetic tNF and to assess the course of the training. Pre- and post-assessments included questionnaires, tests of attention, EEG recordings, and cognitive event-related potentials. Results: Despite behavioural improvement and EEG artefact reduction, only partial learning was found for ACC parameters. Successful regulation was observed only for a simple feedback variant of SCP training, but with ACC-specific effects. Over training, resting EEG analysis indicated individual frequency normalisation rather than unidirectional changes across subjects. Conclusions: These results indicate that clinical improvement after ACC-tNF training can parallel artefact reduction without substantial learning of improved cortical control. However, individual normalisation of resting EEG activity and partial SCP control proved possible in this specific brain region affected in ADHD using tNF. Further studies are needed to clarify which critical aspects mediate region-specific learning in neurofeedback.

Leins, U., Goth, G., Hinterberger, T., Klinger, C., Rumpf, M., & Strehl, U. (2007). Neurofeedback for children with ADHD: A comparison of SCP and theta/beta protocols. ***Applied Psychophysiology & Biofeedback*****, 32.** Behavioral and cognitive improvements

in children with ADHD have been consistently reported after neurofeedback treatment. However, neurofeedback has not been commonly accepted as a treatment for ADHD. This study addresses previous methodological shortcomings while comparing a neurofeedback training of Theta-Beta frequencies and training of slow cortical potentials (SCPs). The study aimed at answering (a) whether patients were able to demonstrate learning of cortical self-regulation, (b) if treatment leads to an improvement in cognition and behavior and (c) if the two experimental groups differ in cognitive and behavioral outcome variables. SCP participants were trained to produce positive and negative SCP-shifts while the Theta/Beta participants were trained to suppress Theta (4–8 Hz) while increasing Beta (12–20 Hz). Participants were blind to group assignment. Assessment included potentially confounding variables. Each group was comprised of 19 children with ADHD (aged 8–13 years). The treatment procedure consisted of three phases of 10 sessions each. Both groups were able to intentionally regulate cortical activity and improved in attention and IQ. Parents and teachers reported significant behavioral and cognitive improvements. Clinical effects for both groups remained stable six months after treatment. Groups did not differ in behavioural or cognitive outcome.

Leins, U., Goth, G., Hinterberger, T., Klinger, C., Rumpf, N., & Strehl, U. (2007). Neurofeedback for children with ADHD: A comparison of SCP and theta/beta protocols. ***Applied Psychophysiology & Biofeedback*****, 32(2), 73-88.** Behavioral and cognitive improvements in children with ADHD have been consistently reported after neurofeedback-treatment. However, neurofeedback has not been commonly accepted as a treatment for ADHD. This study addresses previous methodological shortcomings while comparing a neurofeedback-training of Theta-Beta frequencies and training of slow cortical potentials (SCPs). The study aimed at answering (a) whether patients were able to demonstrate learning of cortical self-regulation, (b) if treatment leads to an improvement in cognition and behavior and (c) if the two experimental groups differ in cognitive and behavioral outcome variables. SCP participants were trained to produce positive and negative SCP-shifts while the Theta/Beta participants were trained to suppress Theta (4-8 Hz) while increasing Beta (12-20 Hz). Participants were blind to group assignment. Assessment included potentially confounding variables. Each group was comprised of 19 children with ADHD (aged 8-13 years). The treatment procedure consisted of three phases of 10 sessions each. Both groups were able to intentionally regulate cortical activity and improved in attention and IQ. Parents and teachers reported significant behavioral and cognitive improvements. Clinical effects for both groups remained stable six months after treatment. Groups did not differ in behavioural or cognitive outcome.

Lenartowitz, A., Delorme, A., Walshaw, PD., Cho, AL., Bilder, RM., McGough, JJ., McCracken, JT., Makeaig, S & Loo, S. (2014). Electroencephalography Correlates of Spatial Working Memory Deficits in Attention-Deficit/Hyperactivity Disorder: Vigilance, Encoding, and Maintenance. ***Journal of Neuroscience:*****34(4). 1171-1182.** In the current study we sought to dissociate the component processes of working memory (WM) (vigilance, encoding and maintenance) that may be differentially impaired in attention-deficit/ hyperactivity disorder (ADHD). We collected electroencephalographic (EEG) data from 52 children with ADHD and 47 typically developing (TD) children, ages 7–14 years, while they performed a spatial Sternberg working memory task. We used independent component analysis and time-frequency analysis to identify mid occipital alpha (8 –12 Hz) to evaluate encoding processes and frontal midline theta (4 –7 Hz) to evaluate maintenance processes. We tested for effects of task difficulty and cue processing to evaluate vigilance. Children with ADHD showed attenuated alpha band event-related desynchronization (ERD) during encoding. This effect was more pronounced when task difficulty was low (consistent with impaired vigilance) and was predictive of memory task performance and symptom severity. Correlated with alpha ERD during encoding were alpha power increases during the maintenance period (relative to baseline), suggesting a compensatory effort. Consistent with this interpretation, midfrontal theta power increases during maintenance were stronger in ADH D and in high-load memory conditions. Furthermore, children with ADHD exhibited a maturational lag in development of posterior alpha power whereas age-related changes in frontal theta power deviated from the TD pattern. Last, subjects with ADHD showed age-independent attenuation of evoked responses to warning cues, suggesting low vigilance. Combined, these three EEG measures predicted diagnosis with 70% accuracy. We conclude that the interplay of impaired vigilance and encoding in ADHD may compromise maintenance and lead to impaired WM performance in this group.

Leuchter, A. F., McGough, J. J., Korb, A. S., Hunter, A. M., Glaser, P. E., Deldar, A., Durell, T. M., & Cook, I. A. (2014). Neurophysiologic predictors of response to atomoxetine in young adults with attention deficit hyperactivity disorder: a pilot project. Journal of psychiatric research, 54, 11–18. https://doi.org/10.1016/j.jpsychires.2014.03.009. Atomoxetine is a non-stimulant medication with sustained benefit throughout the day, and is a useful pharmacologic treatment option for young adults with Attention-Deficit/Hyperactivity Disorder (ADHD). It is difficult to determine, however, those patients for whom atomoxetine will be both effective and advantageous. Patients may need to take the medication for several weeks before therapeutic benefit is apparent, so a biomarker that could predict atomoxetine effectiveness early in the course of treatment could be clinically useful. There has been increased interest in the study of thalamocortical oscillatory activity using quantitative electroencephalography (qEEG) as a biomarker in ADHD. In this study, we investigated qEEG absolute power, relative power, and cordance, which have been shown to predict response to reuptake inhibitor antidepressants in Major Depressive Disorder (MDD), as potential predictors of response to atomoxetine. Forty-four young adults with ADHD (ages 18-30) enrolled in a multi-site, double-blind placebo-controlled study of the effectiveness of atomoxetine and underwent serial qEEG recordings at pretreatment baseline and one week after the start of medication. qEEG measures were calculated from a subset of the sample (N = 29) that provided useable qEEG recordings. Left temporoparietal cordance in the theta frequency band after one week of treatment was associated with ADHD symptom improvement and quality of life measured at 12 weeks in atomoxetine-treated subjects, but not in those treated with placebo. Neither absolute nor relative power measures selectively predicted improvement in medication-treated subjects. Measuring theta cordance after one week of treatment could be useful in predicting atomoxetine treatment response in adult ADHD.

Levesque, J., Beauregard, M., & Mensour, B. (2006). Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. *Neuroscience Letters*, 394(3), 216-221. Attention Deficit Hyperactivity Disorder (AD/HD) is a neurodevelopmental disorder mainly characterized by impairments in cognitive functions. Functional neuroimaging studies carried out in individuals with AD/HD have shown abnormal functioning of the anterior cingulate cortex (ACC) during tasks involving selective attention. In other respects, there is mounting evidence that neurofeedback training (NFT) can significantly improve cognitive functioning in AD/HD children. In this context, the present functional magnetic resonance imaging (fMRI) study was conducted to measure the effect of NFT on the neural substrates of selective attention in children with AD/HD. Twenty AD/HD children—not taking any psychostimulant and without co-morbidity-participated to the study. Fifteen children were randomly assigned to the Experimental (EXP) group (NFT), whereas the other five children were assigned to the Control (CON) group (no NFT). Subjects from both groups were scanned 1 week before the beginning of the NFT (Time 1) and 1 week after the end of this training (Time 2), while they performed a Counting Stroop task. At Time 1, for both groups, the Counting Stroop task was associated with significant loci of activation in the left superior parietal lobule. No activation was noted in the ACC. At Time 2, for both groups, the Counting Stroop task was still associated with significant activation of the left superior parietal lobule. This time, however, for the EXP group only there was a significant activation of the right ACC. These results suggest that in AD/HD children, NFT has the capacity to normalize the functioning of the ACC, the key neural substrate of selective attention.

Liao, Y. C., Guo, N. W., Su, B. Y., Chen, S. J., Tsai, H. F., & Lee, K. Y. (2021). Frontal Beta Activity in the Meta-Intention of Children With Attention Deficit Hyperactivity Disorder. Clinical EEG and neuroscience, 52(2), 136–143. https://doi.org/10.1177/1550059420933142. Children with attention deficit hyperactivity disorder (ADHD) have high theta and low beta activity in the frontal lobe. The higher the theta/beta ratio, the lower the level of central nervous system (CNS) cortical arousal. However, there is seldom evidence between electroencephalograms (EEGs) and the patient's intentionality to regulate the cortical activity of executive attention tasks. We investigated whether children with ADHD intended to improve their performance in executive attention tasks and whether that increased their brain activity. Fifty-one children with ADHD (ADHD) and 51 typical developing (TD) children were investigated using focused attention (FA) and search attention (SA) tasks and a simultaneous EEG. The children were then regrouped as faster (ADHD-F, TD-F) and slower (ADHD-S, TD-S) depending on reaction time (RT). Quantitative EEGs of frontal lobe theta and beta activity at frontal F3, F4, and Fz were used. Twenty-eight (54.9%) ADHD children were regrouped as ADHD-S and 14

(27.5%) as TD-S. The ADHD-S group, however, had poorer FA and SA performance than the other 3 groups did: fewer correct answers, more frequent impulsive and missing errors, and higher RT variations. There were no significant differences in theta activity, but the TD-S group had higher beta activity than the ADHD-S group did. We conclude that the ADHD-F and ADHD-S groups had different attention processes. beta activity did not increase in the ADHD-S group, and their executive attention performance in the FA and SA tests was poor. It seems ADHD-S had poor meta-intention function. The frontal beta activity might be a feasible training target of neurofeedback in ADHD-S patients.

Linden, M., Habib, T., & Radojevic, V. (1996). A controlled study of the effects of EEG biofeedback on cognition and behavior of children with attention deficit disorder and learning disabilities. *Biofeedback & Self-Regulation*, 21(1), 35-49. Eighteen children with ADD/ADHD, some of whom were also LD, ranging in ages from 5 through 15 were randomly assigned to one of two conditions. The experimental condition consisted of 40 45-minute sessions of training in enhancing beta activity and suppressing theta activity, spaced over 6 months. The control condition, waiting list group, received no EEG biofeedback. No other psychological treatment or medication was administered to any subjects. All subjects were measured at pretreatment and at posttreatment on an IQ test and parent behavior rating scales for inattention, hyperactivity, and aggressive/defiant (oppositional) behaviors. At posttreatment the experimental group demonstrated a significant increase (mean of 9 points) on the K-Bit IQ Composite as compared to the control group ($p < .05$). The experimental group also significantly reduced inattentive behaviors as rated by parents ($p < .05$). The significant improvements in intellectual functioning and attentive behaviors might be explained as a result of the attentional enhancement affected by EEG biofeedback training. Further research utilizing improved data collection and analysis, more stringent control groups, and larger sample sizes are needed to support and replicate these findings.

Lofthouse N, Arnold LE, Hersch S, Hurt E, DeBeus R. (2011). A review of neurofeedback for pediatric ADHD. *Journal of Attention Disorders*; 16(5). 351-372. The aim of this paper was to review all randomized published trials and unpublished conference presentations on the neurofeedback (NF) treatment of pediatric ADHD, and their relevance, strengths, and limitations. METHOD: Via PsychInfo and Medline searches and contacts with NF researchers 14 studies were identified and reviewed. RESULTS: The majority were conducted from 1994 to 2010, with 5- to 15-year-olds, usually male and White with the combined type of ADHD. Most studies used theta/beta NF with a unipolar-electrode placement at Cz and demonstrated, where reported, an overall ADHD mean effect size of $d = 0.69$, a medium effect. Main study strengths, within some studies, include use of randomization, treatment control conditions, Diagnostic and Statistical Manual of Mental Disorders criteria, evidence-based assessment of ADHD, standard treatment outcome measures, multi-domain assessment, and, for some studies, moderate sample size, some type of blind and the identification of medication as a concomitant treatment. Main study limitations (and directions for future research) include the lack of adequate blinding of participants, raters and NF trainers, a sham-NF/blinded control treatment condition, post treatment follow-up, generalizability, specific details about delivery of NF, identification and control of comorbidity, and the identification, measurement, and control of concomitant treatments and potential side effects. CONCLUSION: Based on the results and methodologies of published studies, this review concludes that NF for pediatric ADHD can be currently considered as "probably efficacious."

Loo, S., & Barkley, R. (2005). Clinical utility of EEG in attention deficit hyperactivity disorder. *Applied Neuropsychology*, 12(2), 64-76. Electrophysiological measures were among the first to be used to study brain processes in children with attention deficit hyperactivity disorder (ADHD; Diagnostic and Statistical Manual of Mental Disorders [4th ed.], American Psychiatric Association, 1994) and have been used as such for over 30 years (see Hastings & Barkley, 1978, for an early review). More recently, electroencephalography (EEG) has been used both in research to describe and quantify the underlying neurophysiology of ADHD, but also clinically in the assessment, diagnosis, and treatment of ADHD. This review will first provide a brief overview of EEG and then present some of the research findings of EEG correlates in ADHD. Then, the utility of EEG in making an ADHD diagnosis and predicting stimulant response will be examined. Finally, and more controversially, we will review the results of the most recent studies on EEG biofeedback (neurofeedback) as a treatment for ADHD and the issues that remain to be addressed in the research examining the efficacy this therapeutic approach.

Lubar, J. F. (2003). ***Neurofeedback for the management of attention-deficit / hyperactivity disorders*****. Chapter in M. S. Schwartz & F. Andrasik (Eds.), Biofeedback: A Practitioner's Guide (Third Edition. New York, Guilford, 409-437.**

Lubar, J. O., & Lubar, J. F. (1984). Electroencephalographic biofeedback of SMR and beta for treatment of attention deficit disorders in a clinical setting. ***Biofeedback & Self-Regulation*****, 9, 1-23.** Six children were provided with long-term biofeedback and academic treatment for attention deficit disorders. Their symptoms were primarily learning disabilities, and, in some cases, there were varying degrees of hyperkinesis. The training consisted of two sessions per week for ten to 27 months, with a gradual phase-out. Feedback was provided for either increasing 12-15 Hz SMR or 16-20 beta activity. Inhibit circuits were employed for SMR or beta when either gross movement excessive EMG, or theta (4-8 HZ) activity was present. Treatment also consisted of combining the biofeedback with academic training, including reading, arithmetic and spatial tasks to improve their attention. All children increased SMR or beta and decreased slow EEG and EMG activity. Changes could be seen in their power spectra after training in terms of increased beta and decreased slow activity. All six children demonstrated considerable improvement in their schoolwork in terms of grades or achievement test scores. None of the children are currently on any medications for hyperkinetic behavior. The results indicate that EEG biofeedback training, if applied comprehensively, can be highly effective in helping to remediate children who are experiencing attention deficit disorders.

Lubar, J. F., & Shouse, M. N. (1976). EEG and behavioral changes in a hyperactive child concurrent with training of the sensorimotor rhythm (SMR): A preliminary report. ***Biofeedback & Self-Regulation*****, 1(3), 293-306.** Reduced seizure incidence coupled with voluntary motor inhibition accompanied conditioned increases in the sensorimotor rhythm (SMR), a 12-14 Hz rhythm appearing over rolandic cortex. Although SMR biofeedback training has been successfully applied to various forms of epilepsy in humans, its potential use in decreasing hyperactivity has been limited to a few cases in which a seizure history was also a significant feature. The present study represents a first attempt to explore the technique's applicability to the problem of hyperkinesis independent of the epilepsy issue. The results of several months of EEG biofeedback training in a hyperkinetic child tend to corroborate and extend previous findings. Feedback presentations for SMR were contingent on the production of 12-14-Hz activity in the absence of 4- 7-Hz slow-wave activity. A substantial increase in SMR occurred with progressive SMR training and was associated with enhanced motor inhibition, as gauged by laboratory measures of muscular tone (chin EMG) and by a global behavioral assessment in the classroom. Opposite trends in motor inhibition occurred when the training procedure was reversed and feedback presentations were contingent on the production of 4-7 Hz in the absence of 12-14-Hz activity. Although the preliminary nature of these results is stressed, the subject population has recently been increased to establish the validity and generality of the findings and will include the use of SMR biofeedback training after medication has been withdrawn.

Lubar, J. F., Swartwood, M. O., Swartwood, J. N., & O'Donnell, P. H. (1995). Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in T.O.V.A., scores, behavioral ratings, and WISC-R performance. ***Biofeedback & Self-Regulation*****, 20(1), 83-99.** A study with three component parts was performed to assess the effectiveness of neurofeedback treatment for Attention Deficit/Hyperactivity Disorder (ADHD). The subject pool consisted of 23 children and adolescents ranging in age from 8 to 19 years with a mean of 11.4 years who participated in a 2-to 3-month summer program of intensive neurofeedback training. Feedback was contingent on the production of 16-20 hertz (beta) activity in the absence of 4-8 hertz (theta) activity. Posttraining changes in EEG activity, T.O.V.A. performance, (ADDES) behavior ratings, and WISC-R performance were assessed. Part I indicated that subjects who successfully decreased theta activity showed significant improvement in T.O.V.A. performance; Part II revealed significant improvement in parent ratings following neurofeedback training; and Part III indicated significant increases in WISC-R scores following neurofeedback training. This study is significant in that it examines the effects of neurofeedback training on both objective and subjective measures under relatively controlled conditions. Our findings corroborate and extend previous research, indicating that neurofeedback training can be an appropriate and efficacious treatment for children with ADHD.

Lutzenberger W, Elbert T, Rockstroh B, Birbaumer N. (1982) Biofeedback produced slow brain potentials and task performance. *Biological Psychology*, 14, 99-111. Twenty subjects learned to control slow potential (SP) shifts of the brain by means of a biofeedback procedure. Depending upon the pitch of a signal tone, negative SP shifts had to be increased or reduced during intervals of 6 sec each. Visual feedback of the actual SP shift was given. Blocks of training trials alternated with blocks of test trials without any feedback of the SPs. At the end of every test trial a simple arithmetic problem had to be solved by the subjects. Subjects performed the computation in a shorter time interval if an increased negativity preceded task onset as compared to slower response times during suppression of negativity. Results suggest that cortical negativity reflects unspecific preparation for cerebral performance.

Maurizio, S., Liechti, MD., Heinrich, H., Jancke, L., Steinhausen, HC., Walitza, S., Brandeis, D. & Drechsler, R. (2014). Comparing tomographic EEG neurofeedback and EMG biofeedback in children with attention-deficit hyperactivity disorder. Biological Psychology:Jan:95 31-44. Two types of biofeedback (BF), tomographic electroencephalogram (EEG) neurofeedback (NF) and electromyographic biofeedback (EMG-BF), both with phasic and tonic protocols, were compared for treatment effects and specificity in attention-deficit/hyperactivity disorder (ADHD). Thirteen children with ADHD trained their brain activity in the anterior cingulate cortex (ACC), and twelve trained activity of arm muscles involved in fine motor skills. In each training session, resting state 24-channel EEG and training performances were recorded. Both groups showed similar behavioral improvements and artifact reduction in selected conditions, with no significant advantages despite medium effect sizes on primary outcomes for NF. Only the EMG-BF group, however, showed clear improvement in training regulation performance, and specific motor coordination effects. The NF group tended to present individual normalization of trained frequency bands in the ACC during rest across training. The results provide evidence for some specific effects in our small sample, albeit only to a small extent.

Mayer, K., Blume, F., Wyckoff, SN., Brokmeier, LL. & Strehl, U. (2015). Neurofeedback of slow cortical potentials as a treatment for adults with Attention Deficit-/Hyperactivity Disorder. Objective: Attention Deficit-/Hyperactivity Disorder (ADHD) has been treated successfully in children with neurofeedback (NF). In this study, for the first time NF is investigated in adults with ADHD. To answer the question of specificity the relationship between treatment outcome and self-regulation ability is assessed. Methods: Twenty-four participants underwent 30 sessions of slow cortical potential NF. Measurements of ADHD and comorbid symptoms, as well as neurophysiological data (reaction time (RT) and RT variability (RTV) and contingent negative variation (CNV)) were performed before and after treatment, and again six months after sessions were completed. Participants were categorized into self-regulation learners and non-learners. Results: Significant improvements on all symptom scales were observed with medium to large effect sizes after treatment and six months post treatment. RT and RTV decreased significantly and there was a trend for an increased CNV. Half of the participants successfully learned to regulate their brain activity. In the long-term, symptoms in the group of learners improved more than in non-learners with large effect sizes. Conclusion: NF is effective in treating adult ADHD long-term. The impact of self-regulation ability and possible unspecific effects still require further investigation. Significance: This study is the first to investigate the effects of NF in adults with ADHD, relating clinical outcome to self-regulation performance.

Mayer K, Wyckoff SN, Strehl U.(2013).One size fits all? Slow cortical potentials neurofeedback: a review. J Atten Disord. 2013 Jul;17(5):393-409. doi: 10.1177/1087054712468053. Epub 2012 Dec 20. *Objective:* The intent of this manuscript was to review all published studies on slow cortical potentials (SCP) neurofeedback for the treatment of ADHD, with emphasis on neurophysiological rationale, study design, protocol, outcomes, and limitations. *Method*: For review, PubMed, MEDLINE, ERIC, and Google Scholar searches identified six studies and six subsequent publications. In addition to five studies focusing on children with Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV)-diagnosed ADHD, one study reports on adults. *Results*: SCP protocols utilize unipolar-electrode placement at Cz, randomized bidirectional signal regulation, feedback/transfer trials, and discrete feedback/rewards. Results demonstrated learning of SCP self-regulation, moderate to large within group effect sizes for core ADHD symptom reduction, and enhancement of event-related potentials/electroencephalogram components. Neurophysiological and session variables were predictive of treatment outcome, but open questions of specific and nonspecific effects remain. Study limitations and future directions are discussed. *Conclusion*: SCP is an efficacious and standardized neurofeedback protocol that addresses behavioral and neurophysiological deficits in ADHD.

Miskovic, V., Ma, X., Chou, C., Fan, M., Owens, M., Sayama, H. & Gibb, BE. (2015). Development changes in spontaneous electrical activity and network organization from early to late childhood. NeuroImage: 118. 237-247. We investigated the development of spontaneous (resting state) cerebral electric fields and their network organization from early to late childhood in a large community sample of children. Critically, we examined electrocortical maturation across one-year windows rather than creating aggregate averages that can miss subtle maturational trends. We implemented several novel methodological approaches including a more fine grained examination of spectral features across multiple electrodes, the use of phase-lagged functional connectivity to control for the confounding effects of volume conduction and applying topological network analyses to weighted cortical adjacency matrices. Overall, there were major decreases in absolute EEG spectral density (particularly in the slow wave range) across cortical lobes as a function of age. Moreover, the peak of the alpha frequency increased with chronological age and there was a redistribution of relative spectral density toward the higher frequency ranges, consistent with much of the previous literature. There were age differences in long range functional brain connectivity, particularly in the alpha frequency band, culminating in the most dense and spatially variable networks in the oldest children. We discovered age-related reductions in characteristic path lengths, modularity and homogeneity of alpha-band cortical networks from early to late childhood. In summary, there is evidence of large scale reorganization in endogenous brain electric fields from early to late childhood, suggesting reduced signal amplitudes in the presence of more functionally integrated and band limited coordination of neuronal activity across the cerebral cortex.

Micoulaud-Franchi, J. A., Geoffroy, P. A., Fond, G., Lopez, R., Bioulac, S., & Philip, P. (2014). EEG neurofeedback treatments in children with ADHD: an updated meta-analysis of randomized controlled trials. Frontiers in human neuroscience, 8, 906. https://doi.org/10.3389/fnhum.2014.00906. Objective: We undertook a meta-analysis of published Randomized Controlled Trials (RCT) with semi-active control and sham-NF groups to determine whether Electroencephalogram-neurofeedback (EEG-NF) significantly improves the overall symptoms, inattention, and hyperactivity/impulsivity dimensions for probably unblinded assessment (parent assessment) and probably blinded assessment (teacher assessment) in children with Attention Deficit Hyperactivity Disorder (ADHD). Data sources: A systematic review identified independent studies that were eligible for inclusion in a random effects meta-analysis. Data extraction: Effect sizes for ADHD symptoms were expressed as standardized mean differences (SMD) with 95% confidence intervals. Results: Five identified studies met eligibility criteria, 263 patients with ADHD were included, 146 patients were trained with EEG-NF. On parent assessment (probably unblinded assessment), the overall ADHD score (SMD = -0.49 [-0.74, -0.24]), the inattention score (SMD = -0.46 [-0.76, -0.15]) and the hyperactivity/impulsivity score (SMD = -0.34 [-0.59, -0.09]) were significantly improved in patients receiving EEG-NF compared to controls. On teacher assessment (probably blinded assessment), only the inattention score was significantly improved in patients receiving EEG-NF compared to controls (SMD = -0.30 [-0.58, -0.03]). Conclusions: This meta-analysis of EEG-NF in children with ADHD highlights improvement in the inattention dimension of ADHD symptoms. Future investigations should pay greater attention to adequately blinded studies and EEG-NF protocols that carefully control the implementation and embedding of training.

Monastra, V. J., (2005). Electroencephalographic biofeedback (neurotherapy) as a treatment for attention deficit hyperactivity disorder: Rationale and empirical foundation. *Child & Adolescent Psychiatric Clinics of North America*, 14(1), 55-82. During the past three decades, electroencephalographic (EEG) biofeedback has emerged as a nonpharmacologic treatment for attention-deficit/hyperactivity disorder (ADHD). This intervention was derived from operant conditioning studies that demonstrated capacity for neurophysiologic training in humans and other mammals and targets atypical patterns of cortical activation that have been identified consistently in neuroimaging and quantitative EEG studies of patients diagnosed with ADHD. This article presents the rationale for EEG biofeedback and examines the empirical support for this treatment using efficacy guidelines established by the Association for Applied Psychophysiology and Biofeedback and the International Society for Neuronal Regulation. Based on these guidelines, EEG biofeedback is considered to be "probably efficacious" for the treatment of ADHD and merits consideration as a treatment for patients who are stimulant "nonresponders." Although research findings published to date indicate positive clinical response in approximately 75% of patients treated in controlled group studies, additional randomized, controlled trials are needed to provide a better estimate of the robustness of this treatment.

Monastra, V. J., Lynn, S., Linden, M., Lubar, J. F., Gruzelier, J., & LaVaque, T. J. (2005). Electroencephalographic biofeedback in the treatment of attention-deficit/hyperactivity disorder. ***Applied Psychophysiology & Biofeedback*****, 30(2), 95-114.** Historically, pharmacological treatments for attention-deficit/hyperactivity disorder (ADHD) have been considered to be the only type of interventions effective for reducing the core symptoms of this condition. However, during the past three decades, a series of case and controlled group studies examining the effects of EEG biofeedback have reported improved attention and behavioral control, increased cortical activation on quantitative electroencephalographic examination, and gains on tests of intelligence and academic achievement in response to this type of treatment. This review paper critically examines the empirical evidence, applying the efficacy guidelines jointly established by the Association for Applied Psychophysiology and Biofeedback (AAPB) and the International Society for Neuronal Regulation (ISNR). On the basis of these scientific principles, EEG biofeedback was determined to be "probably efficacious" for the treatment of ADHD. Although significant clinical improvement was reported in approximately 75% of the patients in each of the published research studies, additional randomized, controlled group studies are needed in order to provide a better estimate of the percentage of patients with ADHD who will demonstrate such gains in clinical practice.

Monastra, V. J., Monastra, D. M., & George, S. (2002). The effects of stimulant therapy, EEG biofeedback, and parenting style on the primary symptoms of attention-deficit/hyperactivity disorder. ***Applied Psychophysiology & Biofeedback*****, 27(4), 231-249.**One hundred children, ages 6–19, who were diagnosed with attention-deficit/hyperactivity disorder (ADHD), either inattentive or combined types, participated in a study examining the effects of Ritalin, EEG biofeedback, and parenting style on the primary symptoms of ADHD. All of the patients participated in a 1-year, multimodal, outpatient program that included Ritalin, parent counseling, and academic support at school (either a 504 Plan or an IEP). Fifty-one of the participants also received EEG biofeedback therapy. Post treatment assessments were conducted both with and without stimulant therapy. Significant improvement was noted on the Test of Variables of Attention (TOVA; L. M. Greenberg, 1996) and the Attention Deficit Disorders Evaluation Scale (ADDES; S. B. McCarney, 1995) when participants were tested while using Ritalin. However, only those who had received EEG biofeedback sustained these gains when tested without Ritalin. The results of a Quantitative Electroencephalographic Scanning Process (QEEG-Scan; V. J. Monastra et al., 1999) revealed significant reduction in cortical slowing only in patients who had received EEG biofeedback. Behavioral measures indicated that parenting style exerted a significant moderating effect on the expression of behavioral symptoms at home but not at school.

Mulholland, T. Goodman, D., & Boudrot, R. (1983). Attention and regulation of EEG alpha-attenuation responses. ***Biofeedback & Self-Regulation,*** **8(4), 585-600.** Two experiments with 16 normal adults of both sexes tested the hypothesis that inattention to a biofeedback display is associated with increased variability of those physiological processes that had been regulated by the biofeedback. Each experiment was a repeated-measures-on-independent-subjects-design. Dependent variables were the time durations and the mean rms power of two mutually exclusive segments of the parietal-occipital EEG: alpha and not-alpha segments. Independent variables were combination of counting tasks and instructions to look at, listen to, and count visual and auditory flashes and clicks. The durations of alpha and not-alpha segments were controlled or regulated by means of an alpha-contingent visual feedback stimulus; attention to the feedback stimulus was challenged by instructions to count other, noncontingent stimuli. Control of alpha and not-alpha segments was least for conditions of (1) "sham" feedback, and (2) feedback with instructions to count noncontingent auditory clicks, which were presented 3/sec while the feedback visual stimuli were occurring. A new EEG test of attention and distraction was suggested.

Nash, J. K. (2000). Treatment of attention-deficit hyperactivity disorder with neurotherapy. ***Clinical Electroencephalography*****, 31(1), 30-37.** Significant public health concerns exist regarding our current level of success in treating ADHD. Medication management is very helpful in 60-70% of patients. Side effects, lack of compliance and the fact that stimulant medications cannot be given late in the day limit the benefits largely to school hours. While stimulants improve behavior and attention, less of an effect has been noted on academic and social performance. Continuing concerns exist about long-term safety, and studies on long-term cardiovascular and neurophysiological effects have not been carried out. Neurotherapy for ADHD offers an effective alternate for patients whose treatment is limited by side effects, poor medication response and in cases in which the patients and/or their parents refuse to consider medications.

Studies indicate clinical improvement is largely related to measurable improvements in the EEG signature, evidenced by declining theta/beta ratios over frontal/central cortex and/or reduced theta/alpha band amplitudes.

Norouzi, E., Hossieni, F., & Solymani, M. (2018). Effects of Neurofeedback Training on Performing Bimanual Coordination In-phase and Anti-phase Patterns in Children with ADHD. Applied psychophysiology and biofeedback, 43(4), 283–292. https://doi.org/10.1007/s10484-018-9408-2. It is generally accepted that children with attention-deficit/hyperactivity disorder (ADHD) have poor motor control, especially in bimanual coordination tasks. Such children characteristically have impaired fine motor ability, problems with force control, and poor motor coordination. They are at particular risk of loss of motor control and reduced bimanual coordination. We tested whether, compared to a control condition, neurofeedback training (NFT) could improve bimanual coordination among children with ADHD. 20 Children with ADHD (mean age 7.9 years; SD 2.11) were randomly assigned either to NFT or to a control condition. All participants completed a bimanual coordination test at the following time points: baseline, assessment 1, assessment 2, assessment 3, and again 12 session later at posttest. NFT consisted of Sensory Motor Rhythm (SMR) training to achieve increased SMR in C3 and C4, while participants in the control condition were under mock NFT conditions. Bimanual coordination accuracy and consistency improved from baseline to completion of the intervention (significant Time effect), but in the NFT condition (significant time × group interaction). Compared to the control condition, the NFT group had fewer errors in both patterns of bimanual coordination (significant Group effect). Among children with ADHD, SMR neurofeedback training (NFT) led to significant improvements in a bimanual coordination task. The SMR NFT thus appears to have the potential to improve and enhance the motor control of ADHD patients.

Ogrim, G., & Kropotov, J. D. (2020). Event Related Potentials (ERPs) and other EEG Based Methods for Extracting Biomarkers of Brain Dysfunction: Examples from Pediatric Attention Deficit/Hyperactivity Disorder (ADHD). Journal of visualized experiments : JoVE, (157), 10.3791/60710. Neuropsychiatric diagnoses like ADHD are based on subjective methods like interviews, rating scales and observations. There is a need for more brain-based supplements. Stimulant medication is the most common treatment for ADHD. Clinically useful predictors of response have so far not been reported. The aim of this paper is to describe the EEG based methods we apply to extract potential biomarkers for brain dysfunction. Examples relate to biomarkers for pediatric ADHD, and prediction of medication response. The main emphasis is on Event Related Potentials (ERPs). A nineteen channel EEG is recorded during a 3 min eyes-opened task, a 3 min eyes-closed task, and a 20 min cued visual GO/NOGO task (VCPT). ERPs are recorded during this task. The goal of the ERP protocol is to extract biomarkers of assumed brain dysfunctions that significantly differentiate between a patient group and healthy controls. The protocol includes recording during standard conditions and artifact correction. ERP waves can be used or transformed into latent components. The components of the patient group are compared with controls, empathizing components that, when compared, show relatively high effect sizes. Sub-groups of the patients are selected on the basis of the cluster analysis in the space of the components. Treatment procedure (such as medication, tDCS or neurofeedback protocol) can be applied and the changes in components related to treatment in the subgroups are observed, forming the basis for clinical recommendations. The methods described were applied in a study of 87 pediatric ADHD patients. The index of medication response discriminated significantly between responders and non-responders with a large, and clinically meaningful effect size (d = 1.84). In an ongoing study comparing ADHD children with matched controls, several variables discriminate significantly between patients and controls. The global index will exceed d = .8. The EEG based methods described here could be clinically meaningful.

Ojeda, D., Bioulac, S., Blasco-Fontecilla, H., Brandeis, D., Purper Ouakil, D., Ros, T., & Mayaud, L. (2019). Is there a cluster of high theta-beta ratio patients in attention deficit hyperactivity disorder?. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 130(8), 1387–1396. https://doi.org/10.1016/j.clinph.2019.02.02. Objective: It has been suggested that there exists a subgroup of ADHD patients that have a high theta-beta ratio (TBR). The aim of this study was to analyze the distribution of TBR values in ADHD patients and validate the presence of a high-TBR cluster using objective metrics. Methods: The TBR was extracted from eyes-open resting state EEG recordings of 363 ADHD patients, aged 5-21 years. The TBR distribution was estimated with three Bayesian Gaussian Mixture Models (BGMMs) with one, two, and three components, respectively.

The pairwise comparison of BGMMs was carried out with deviance tests to identify the number of components that best represented the data. Results: The two-component BGMM modeled the TBR values significantly better than the one-component BGMM (p-value = 0.005). No significant difference was observed between the two-component and three-component BGMM (p-value = 0.850). Conclusion: These results suggest that there exist indeed two TBR clusters within the ADHD population. Significance: This work offers a global framework to understanding values found in the literature and suggest guidelines on how to compute theta-beta ratio values. Moreover, using objective data-driven method we confirm the existence of a high theta-beta ratio cluster.

Omizo, M. M., & Michael, W. B. (1982). Biofeedback-induced relaxation training and impulsivity, attention to task, and locus of control among hyperactive boys. *Journal of Learning Disabilities*:15(2). 414–416. This study examines the effects of biofeedback-induced relaxation training on impulsivity, attention to task, and locus of control among 32 hyperactive boys. Subjects, who were identified through teacher ratings on the abbreviated form of the Conners' Behavior Rating Scale, were randomly assigned to experimental (n= 16) and control (n= 16) groups. The experimental treatment consisted of four sessions of biofeedback-induced relaxation training spaced approximately two weeks apart. Multivariate analysis of variance results indicated a significant difference between groups, F (3, 28) = 19.62, p<.01. Univariate F tests and discriminant analysis procedures revealed that impulsivity and attention to task measures were significant discriminators, both p<.01. The locus of control variable did not prove to be a valid discriminator. It was concluded that biofeedback-induced relaxation training increased attention to task and reduced impulsivity but did not affect the measure of locus of control on the population studied.

Othmer, S., Othmer, SF., Kaiser, DA. & Putman, D. (2014). Endogenous neuromodulation at infra-slow frequencies. Semin Pediatr Neurol:20(4). Neuromodulation in the bioelectrical domain is an attractive option for the remediation of functionally-based deficits. Most of the interest to date has focused on exogenous methods such as repetitive transcranial magnetic stimulation (rTMS), transient DC Stimulation (tDCS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS). Much less attention has been given to endogenous methods of exploiting latent brain plasticity. These have reached a level of sophistication and maturity that invites attention. Over the last seven years the domain of infra-low frequencies has been exploited productively for the enhancement of neuroregulation. The principal mechanism is putatively the re-normalization of functional connectivity of our resting state networks. The endogeneous techniques are particularly attractive for the pediatric population, where they can be utilized before dysfunctional patterns of brain behavior become consolidated and further elaborated into clinical syndromes.

Pakdaman, F., Irani, F., Tajikzadeh, F., & Jabalkandi, S. A. (2018). The efficacy of Ritalin in ADHD children under neurofeedback training. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 39(12), 2071–2078. https://doi.org/10.1007/s10072-018-3539-3. Current research has shown that neurofeedback (NF) is a viable treatment for attention deficit hyperactivity disorder (ADHD), however having pharmacological approach alongside such stimulants is still inevitable. Therefore, the purpose of this study is the comparison of neurofeedback with Ritalin and without Ritalin in treating children with ADHD. This study was causal-comparative in design. Participants were children aged 5-10 years with ADHD; seven participants were in neurofeedback group with Ritalin and seven in neurofeedback without Ritalin group according to random split and parent's conformation. Clinical Q, Conner's continuous performance test (CPT), and WISC-R were used before and after treatment. For analyzing data, we used descriptive statistical and Mann Whitney U tests. Results showed that even if the two groups were modified in all components, modifications of commission and reaction time of the CPT and F4 theta/alpha of the clinical Q were more accurate in NF with Ritalin treatment rather than the other group. These findings suggest that neurofeedback is efficient in improving some of the behavioral concomitants of ADHD in children whose parents favored non-pharmacological treatment, but Ritalin and neurofeedback combination is more efficient. So, multimodal approach is strongly recommended for ADHD treatment.

Pérez-Elviral, R., Oltra-Cucarella, J., & Antonio Carrobles, J. (2021). Effects of quantitative electroencephalogram normalization using 4-channel live z-score training neurofeedback for children with learning disabilities: preliminary data. Behavioral Psychology/Psicología Conductual, Vol. 29, Nº 1, 2021, pp. 191-206 https://doi.org/10.51668/bp.8321110n. Children

with learning disabilities (LD) can have difficulties in reading at word level, text comprehension, writing or arithmetic. Several studies have shown the efficacy of neurofeedback (NF) in improving learning skills through brainwave operant conditioning in children with LD. The aim of this work was to show the efficacy of live z-score NF training (LZT) for quantitative electroencephalogram (QEEG) normalization in school children with LD. Twenty-eight children aged 10-15 years with LD participated. Ten 30-min sessions of QEEG-guided LZT using patient's highly preferred feedback were applied. After 10 sessions of QEEG-guided LZT, participants showed statistically significant improvements in QEEG normalization and a statistically significant small to medium improvement in the Cognitive and Emotional Checklist. The results suggest that LZT-NF produces a tendency towards normalization of brain waves in children with LD, and might be advised as a therapeutic alternative or coadjuvant along with cognitive interventions.

Pérez-Elvira, R., Oltra-Cucarella, J., & Carrobles, J. A. (2020). Comparing live Z-score training and Theta/Beta protocol to reduce Theta-to-Beta ratio: A pilot study. NeuroRegulation, 7(2), 58–63. https://doi.org/10.15540/nr.7.2.58. Objective/Background: Theta-to-Beta ratio is one of the most studied electroencephalography findings in ADHD in the neurotherapy field, alongside the neurofeedback (NF) protocols whose objective is reducing it. The NF field has developed to a great level in the last decade. One of the approaches that became of particular interest to the clinicians has been Z-score training (ZT). In general, there are still a few studies about the efficacy of ZT and even fewer that compare this technique with the classic protocols. This study aimed to check the efficacy of ZT in reducing Theta-to-Beta ratio. Participants: 15 patients diagnosed with combined type ADHD aged 7 to 18, recruited in retrospect. Methods: The participants were divided in two groups. One of the groups was provided with the ZT intervention and the other one, the Theta/Beta (T/B) protocol. Both groups went through ten 30-min NF sessions using videos selected by themselves as a reinforcement. The main outcomes of this study were the patients' Theta-to-Beta ratio metrics. Results: Both groups showed a decrease in Theta-to-Beta ratio; the ZT group showed a decrease of 1.02 points average and the T/B group showed a decrease of 0.15 points average, only being statistically significant for the ZT group.

Perreau-Linck, E., Lessard, N., Lévesque, J., Beauregard, M. (2010). Effects of neurofeedback training on inhibitory capacities in ADHD children: A single-blind, randomized, placebo-controlled study. *Journal of Neurotherapy* 14(3), 229 – 242. Introduction: Studies performed during the last decades suggest that neurofeedback (NF) training can effectively reduce symptomatology in children with Attention-Deficit/Hyperactivity Disorder (ADHD). Yet, questions remain concerning specific effects of NF training in ADHD children since these studies did not use a randomized, placebo-controlled approach. To address this issue, such an approach was used in the present study to measure the impact of NF training on inhibitory capacities. Methods: Nine ADHD children (with no comorbidity), aged 8 to 13 years, were randomly assigned to either an experimental group (n = 5) or a placebo group (n = 4). For both groups, training protocols comprised 40 one-hour sessions (20 meetings of two sessions each). SMR/Theta training was used in the experimental group. Pre-recorded sessions of the first author's EEG activity were used in the placebo group. Pre- and post-training assessments consisted of the Conner's Parent Rating Scales (CPRS-R) and neuropsychological tests. A multiple case study strategy was applied for data analysis using a Reliable Change Index (RCI) when applicable. Results: One experimental subject was a drop-out and one placebo subject had to be discontinued due to adverse effects. The latter subject accepted to undergo post-training evaluations; hence an Intention-To-Treat analysis was performed on this subject's data. Remaining subjects showed significant improvements on the CPRS-R. Improvements were measured on the Variability measure of the CPT-II consistently across the placebo group and on the Inhibition Condition of the Stroop Task for all but one placebo subject. The same trend was found for the Inhibition/Switching Condition (Stroop Task) across the experimental group (n=4).

Pigott, H. E., Cannon, R., & Trullinger, M. (2021). The Fallacy of Sham-Controlled Neurofeedback Trials: A Reply to Thibault and Colleagues (2018). Journal of attention disorders, 25(3), 448–457. https://doi.org/10.1177/1087054718790802. Background: Sham-controlled neurofeedback (NFB) trials consistently find no separation on ADHD outcome measures leading many to conclude that NFB's beneficial effects are due to placebo. Method: We deconstruct the NFB training methodology and findings of six sham-controlled trials that assessed for evidence of learning. Results: All six studies found no evidence NFB subjects learned to self-modulate the targeted electroencephalogram (EEG). Careful analyses revealed these studies' training methodologies were antithetical to the established science

of operant conditioning thereby preventing subjects from learning to self-modulate. These findings are in marked contrast to NFB studies whose methodology mirror the best practices of operant conditioning. Conclusion: The premise that NFB's beneficial effects are due to placebo phenomenon is unproven as these studies compared two forms of false-feedback, not operant conditioning of the EEG. Because these studies are highly cited and considered the gold standard in scientific rigor, a reappraisal of the evidence is urgently needed.

Ponomev, VA., Mueller, A., Candrian, G., Grin-Yatensko, VA, & Kropotov, J. (2013). Group Independent Component Analysis (gICA) and Current Source Density (CSD) in the study of EEG in ADHD adults. Clinical Neurophysiology: http://dx.doi.org/10.1016/j.clinph.2013.06.015. Objective: To investigate the performance of the spectral analysis of resting EEG, Current Source Density (CSD) and group independent components (gIC) in diagnosing ADHD adults. Methods: Power spectra of resting EEG, CSD and gIC (19 channels, linked ears reference, eyes open/closed) from 96 ADHD and 376 healthy adults were compared between eyes open and eyes closed conditions, and between groups of subjects. Results: Pattern of differences in gIC and CSD spectral power between conditions was approximately similar, whereas it was more widely spatially distributed for EEG. Size effect (Cohen's d) of differences in gIC and CSD spectral power between groups of subjects was considerably greater than in the case of EEG. Significant reduction of gIC and CSD spectral power depending on conditions was found in ADHD patients. Reducing power in a wide frequency range in the fronto-central areas is a common phenomenon regardless of whether the eyes were open or closed. Conclusions: Spectral power of local EEG activity isolated by gICA or CSD in the fronto-central areas may be a suitable marker for discrimination of ADHD and healthy adults. Significance: Spectral analysis of gIC and CSD provides better sensitivity to discriminate ADHD and healthy adults.

Pulvermuller, F., Mohr, B., Schleichert, H., & Veit, R. (2000). Operant conditioning of left-hemispheric slow cortical potentials and its effect on word processing. *Biological Psychology,* 53, 177-215. This study investigated whether language-related cognitive processes can be modified by learned modulation of cortical activity. Study participants received feedback of slow cortical potentials (SCPs) recorded above left-hemispheric language cortices and were reinforced for producing negative and positive shifts upon two different discriminative stimuli. In all subjects who achieved reliable control of left-hemispheric brain responses, substantial modification of word processing was observed. Behavioral modification could be documented in two experiments in which word probes were presented following discriminative stimuli. When negative shifts of the EEG were required, lexical decisions on words were substantially speeded, while they were slowed during positivity conditions. There was no indication for any performance difference between conditions in control subjects who failed to achieve control over SCPs after feedback training. This result was replicated in an experiment using lateralized-tachistoscopic stimulus presentation. Comparisons of word and pseudoword responses in both experiments indicated that behavioral modification was most pronounced for word responses. It was also not seen in a simple reaction time task not involving language materials. This argues against a global effect related to perception, visuo-spatial attention, or motor processes. We conclude that linguistic processes can be influenced by modification of cortical activity due to operant conditioning. In closing, tentative explanations of the present results based on theories of language and attention processes are being discussed.

Rajabi, S., Pakize, A., & Moradi, N. (2020). Effect of combined neurofeedback and game-based cognitive training on the treatment of ADHD: A randomized controlled study. Applied neuropsychology. Child, 9(3), 193–205. https://doi.org/10.1080/21622965.2018.1556101. Neurofeedback (NF) is referred to as a "possibly efficacious" treatment in the current evidence-based reviews; therefore, more research is needed to determine its effects especially in combination with other treatments. The present study examines the effect of NF and game-based cognitive training on children with attention deficit hyperactivity disorder (ADHD). Thirty-two male students with ADHD were assigned to NF (N = 16; Mage=10.20; SD = 1.03) and waiting list control (N = 16; Mage = 10.05; SD = 0.83) in a randomized double-blind trial. The children in the NF group based on quantitative electroencephalography (QEEG) attended 30 three times-weekly sessions. The children were examined in pretest and post-test with EEG, Integrated Visual and Auditory Continuous Performance (IVA), and Conners Parent, and Teacher Rating Scales-Revised. The treatment was found significant all the symptom variables except for attention deficit (AD) and auditory response control (ARC). Normalization of the atypical EEG features with reduced [Formula: see text] wave and increased sensory motor (SMR) activity in central zero (Cz) was recorded in the NF condition participants. However, except for SMR activity there were no significant changes in the waves of

frontocentral zero (FCz). It is concluded that technology developments provide an interesting vehicle for interposing interventions and that combined NF and game-based cognitive training can produce positive therapeutic effects on brainwaves and ADHD symptomatology.

Rasey, H. W., Lubar, J. E., McIntyre, A., Zoffuto, A. C., & Abbott, P. L. (1996). EEG biofeedback for the enhancement of attentional processing in normal college students. ***Journal of Neurotherapy*****, 1(3), 15-21.** College students diagnosed as free of any neurological or attention deficit disorder received EEG biofeedback to enhance beta (16-22 HZ) activity while simultaneously inhibiting high theta and low alpha (6-10 Hz) activity in order to evaluate improvements in attentional measurers. Following short-term treatment (mean number of sessions = 20), subjects were evaluated as either learners or non-learners based upon standard pre- and post-treatment neurofeedback measurers. Attention quotients taken from pre- and post-treatment measurements using the Integrated Visual and Auditory Continuous Performance Test (IVA) identified significant improvements in attentional measures in learners, while non-learners showed no significant improvements. Results suggest that some "normal" young adults can learn to increase EEG activity associated with improved attention. Twenty sessions, however, even for this population may represent the lower limit for achieving significant improvement.

Razoki B. (2018). Neurofeedback versus psychostimulants in the treatment of children and adolescents with attention-deficit/hyperactivity disorder: a systematic review. Neuropsychiatric disease and treatment, 14, 2905–2913. https://doi.org/10.2147/NDT.S178839. This systematic review aimed to evaluate the efficacy of neurofeedback (NF) compared to stimulant medication in treating children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Included in this review are eight randomized controlled trials that compared an NF condition, either alone or combined with medication, to a medication condition, which was mainly methylphenidate. Outcome measures included behavioral assessments by parents and teachers, self-reports, neurocognitive measures, electroencephalogram power spectra and event-related potentials. When only trials are considered that include probably blinded ratings or those that are sham-NF or semi-active controlled or those that employed optimally titration procedures, the findings do not support theta/beta NF as a standalone treatment for children or adolescents with ADHD. Nevertheless, an additive treatment effect of NF was observed on top of stimulants and theta/beta NF was able to decrease medication dosages, and both results were maintained at 6-month follow-up. This review concludes that the present role of NF in treating children diagnosed with ADHD should be considered as complementary in a multimodal treatment approach, individualized to the needs of the child, and may be considered a viable alternative to stimulants for a specific group of patients. Particularly patients with the following characteristics may benefit from NF treatment: low responders to medication, intolerable side effects due to medication, higher baseline theta power spectra and possibly having no comorbid psychiatric disorders. Future research should prioritize the identification of markers that differentiate responders from nonresponders to NF treatment, the potential of NF to decrease stimulant dosage, the standardization of NF treatment protocols and the identification of the most favorable neurophysiological treatment targets.

Rockstroh, B., Elbert, T., Lutzenberger, W., & Birbaumer, N. (1990). Biofeedback: Evaluation and therapy in children with attentional dysfunction. Chapter in A. Rothenberger (Ed.), ***Brain and Behaviour in Child Psychiatry*****. Berlin: Springer Verlag, pp. 345-357.** Background: Learned self-control of slow cortical potentials (SCPs) may lead to behavioral improvement in attention-deficit/hyperactivity disorder (ADHD). Hence, training effects should also be reflected at the neurophysiological level. Methods: Thirteen children with ADHD, aged 7–13 years, performed 25 SCP training sessions within 3 weeks. Before and after training, the German ADHD rating scale was completed by parents, and event-related potentials were recorded in a cued continuous performance test (CPT). For a waiting-list group of nine children with ADHD, the same testing was applied. Results: ADHD symptomatology was reduced by approximately 25% after SCP training. Moreover, a decrease of impulsivity errors and an increase of the contingent negative variation were observed in the CPT task. Conclusions: This study provides first evidence for both positive behavioral and specific neurophysiological effects of SCP training in children with ADHD.

Rodrak, S., & Wongsawat, Y. (2013). EEG brain mapping and brain connectivity index for subtypes classification of attention deficit hyperactivity disorder children during the eye-opened period. Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual International Conference, 2013, 7400–7403. https://doi.org/10.1109/EMBC.2013.6611268. Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent neurological disorders. It is classified by the DSM-IV into three subtypes, i.e. 1) predominately inattentive type, 2) predominately hyperactive-impulsive type, and (3) combined type. In order to make the treatment via the neurofeedback or the occupational therapy, quantitative evaluations as well as ADHD subtype classification are the important problems to be solved to enhance an alternative way to treat ADHD. Hence, in this paper, we systematically classify all of these three subtypes by the 19-channel EEG data. Three brain mapping (QEEG) techniques, i.e. absolute power of frequency bands, coherence, and phase lag, are employed to visualize each type of the ADHD. ADHD children with combined type have deficit in delta theta and alpha activity. For the inattentive type, there are excessive delta and theta absolute power in the frontal area as well as the excessive coherence in beta and high beta frequency bands. For the hyperactivity and impulsive type, the behavior is dominated by the slow wave. This information will give benefits to the psychiatrist, psychologist, neurofeedback therapist as well as the occupational therapist for quantitatively planning and analyzing the treatment.

Rommel, A. S., James, S. N., McLoughlin, G., Brandeis, D., Banaschewski, T., Asherson, P., & Kuntsi, J. (2017). Altered EEG spectral power during rest and cognitive performance: a comparison of preterm-born adolescents to adolescents with ADHD. European child & adolescent psychiatry, 26(12), 1511–1522. https://doi.org/10.1007/s00787-017-1010-2. Preterm birth has been associated with an increased risk for ADHD-like behavioural symptoms and cognitive impairments. However, direct comparisons across ADHD and preterm-born samples on neurophysiological measures are limited. The aim of this analysis was to test whether quantitative EEG (QEEG) measures identify differences or similarities in preterm-born adolescents, compared to term-born adolescents with and without ADHD, during resting-state and cognitive task conditions. We directly compared QEEG activity between 186 preterm-born adolescents, 69 term-born adolescents with ADHD and 135 term-born control adolescents during an eyes-open resting-state condition (EO), which previously discriminated between the adolescents with ADHD and controls, and during a cued continuous performance task (CPT-OX). Absolute delta power was the only frequency range to demonstrate a significant group-by-condition interaction. The preterm group, like the ADHD group, displayed significantly higher delta power during EO, compared to the control group. In line with these findings, parent-rated ADHD symptoms in the preterm group were significantly correlated with delta power during rest. While the preterm and control groups did not differ with regard to absolute delta power during CPT-OX, the ADHD group showed significantly higher absolute delta power compared to both groups. Our results provide evidence for overlapping excess in the absolute delta range in preterm-born adolescents and term-born adolescents with ADHD during rest. During CPT-OX, preterm-born adolescents resembled controls. Increased delta power during rest may be a potential general marker of brain trauma, pathology or neurotransmitter disturbances.

Rossiter, T. (2002). Neurofeedback for AD/HD: A ratio feedback case study. *Journal of Neurotherapy*, 6(3), 9-35. Introduction. The case study of a 13-year-old AD/HD male treated with neurofeedback is the subject matter for a tutorial on Ratio feedback. Method. Neurofeedback was conducted at C3 (increase 15 to 18 Hz, decrease 2 to 10 Hz) and C4 (increase 12 to 15 Hz, decrease 2 to 7 Hz). Protocols provided visual and auditory feedback based on the ratio of slow wave activity to be suppressed divided by fast wave activity to be enhanced (Ratio feedback). Results. The patient demonstrated marked improvement in processing speed and variability on the Test of Variables of Attention-Auditory, a 19-point increase in IQ on the Kaufman Brief Intelligence Test, significant behavioral improvement based on parental (Behavior Assessment System for Children) and patient (Brown ADD Scale) reports, and a 7.5 grade equivalent increase in reading scores (Kaufman Test of Educational Achievement-Brief Form). At the 17-month follow-up parent questionnaires indicated that the patient's behavioral gains had been maintained or were slightly improved. EEG data showed significant declines in the C4/SMR Ratio (10*2 to 7 Hz/12 to 15 Hz) and 2 to 7 Hz amplitude, a tendency toward an increase in 12 to 15 Hz amplitude, a significant increase in 8 to 11 Hz amplitude, and a decline in 22 to 30 Hz amplitude. Beta activity (15 to 18 Hz) was unchanged. An unexpected finding was that C3/Beta (10*2 to 10 Hz/15 to 18 Hz) and C4/SMR protocols had similar effects on the EEG even though they targeted different bands to enhance and suppress. It appears that suppression of slow wave activity (2 to 7 Hz) may be the active component in

both Ratio protocols and that fast wave enhancement either plays a minor (12 to 15 Hz) or no role (15 to 18 Hz). Discussion. The findings cast doubt on the assumption that the C3/Beta and C4/SMR protocols have unique effects on EEG activity. Nevertheless, they may have differential effects on brain functions related to the training sites employed. It would be useful to analyze EEG changes in successfully treated individual AD/HD patients as a first step toward understanding the effects of various treatment protocols. What the protocols are intended to do, and the actual effects on the EEG may be different. If there are active components common to the various AD/HD treatment protocols reported in the literature, this is one way of beginning to recognize them. Brain maps collected before, during, and at the conclusion of treatment would enhance our understanding of treatment effects of various neurofeedback protocols, lead to more focused and productive research, and ultimately facilitate the development of more efficient treatment paradigms.

Rossiter, T. R., & La Vaque, T. J. (1995). A comparison of EEG biofeedback and psychostimulants in treating attention deficit/hyperactivity disorders. *Journal of Neurotherapy*, 1, 48-59. The study compared the effects of EEG biofeedback and stimulant medication in reducing AD/HD symptoms. Stimulants are the most widely used treatment for AD/HD but have drawbacks. The most serious is that symptom reduction is only temporary unless medication is taken indefinitely. In addition, stimulants may have side effects and long-term compliance with taking the medication is poor, especially among adolescents. The study compared treatment programs with 20 sessions of EEG biofeedback (n = 23) or stimulants (n = 23) as their primary components. An EEG group (EEG) was matched with a stimulant group (MED) by age, IQ, gender, and diagnosis. The Test of Variables of Attention (TOVA) was administered pre and post-treatment. Both the EEG and MED groups improved ($p < .05$) on TOVA measures of inattention, impulsivity, information processing, and variability but did not differ from each other ($p > 0.3$) on TOVA change scores. The results indicate that the EEG biofeedback program is an effective alternative to stimulants and may be the treatment of choice when medication is ineffective, has side effects, or compliance is a problem. Previous studies suggest that EEG biofeedback leads to lasting symptom reduction. This needs to be confirmed with larger samples using standardized assessment procedures.

Ryoo, M., & Son, C. (2015). Effects of Neurofeekback Training on EEG, Continuous Performance Task (CPT), and ADHD Symptoms in ADHD-prone College Students. Journal of Korean Academy of Nursing, 45(6), 928–938. https://doi.org/10.4040/jkan.2015.45.6.928. Purpose: This study explored the effects of neurofeedback training on Electroencephalogram (EEG), Continuous Performance Task (CPT) and ADHD symptoms in ADHD prone college students. Methods: Two hundred forty seven college students completed Korean Version of Conners' Adult ADHD Rating Scales (CAARS-K) and Korean Version of Beck Depression Inventory (K-BDI). The 16 participants who ranked in the top 25% of CAARS-K score and had 16 less of K-BDI score participated in this study. Among them, 8 participants who are fit for the research schedule were assigned to neurofeedback training group and 8 not fit for the research schedule to the control group. All participants completed Adult Attention Deficiency Questionnaire, CPT and EEG measurement at pretest. The neurofeedback group received 15 neurofeedback training sessions (5 weeks, 3 sessions per week). The control group did not receive any treatment. Four weeks after completion of the program, all participants completed CAARS-K, Adult Attention Deficiency Questionnaire, CPT and EEG measurement for post-test. Results: The neurofeedback group showed more significant improvement in EEG, CPT performance and ADHD symptoms than the control group. The improvements were maintained at follow up. Conclusion: Neurofeedback training adjusted abnormal EEG and was effective in improving objective and subjective ADHD symptoms in ADHD prone college students.

Schönenberg M, Weingärtner AL, Weimer K, Scheeff J. Believing is achieving - On the role of treatment expectation in neurofeedback applications. Prog Neuropsychopharmacol Biol Psychiatry. 2021 Mar 8;105:110129. doi: 10.1016/j.pnpbp.2020.110129. Epub 2020 Oct 5. PMID: 33031860. In neurofeedback applications, neural activity is recorded, processed in real-time and fed back to the user in order to facilitate self-regulation of the putative neural mechanisms that underlie cognition and behavior. Numerous studies suggest that neurofeedback interventions are an efficacious treatment particularly for patients with attention-deficit/hyperactivity disorder (ADHD). In recent years, however, findings of several well-controlled studies raised doubts concerning the proposed mechanism of action behind the behavioral effect of neurofeedback. This study investigated the impact of expectation on the efficacy of a sensorimotor rhythm (SMR) training. In a within-subjects design 30 blinded volunteers with ADHD

symptoms received a standard SMR training session after inducing no (no-expectancy condition), positive (placebo condition), and negative (nocebo condition) expectations regarding the effectiveness of neurofeedback (by telling them that they would train a specific frequency band that was previously shown to be either unrelated to attention, should improve attention, or interfere with attentional processes). After each training, participants were presented with a cognitive test and subsequently requested to rate their performance on it. We could show that participants were able to successfully modify their EEG signal during training. Further, we found an effect over trainings on objective attentional performance. Most importantly, we found that the expectancy of positive or negative treatment effects considerably changed participants' perception of neurofeedback's efficacy even in the absence of any objective evidence. This study presents strong first evidence for a substantial effect of self-confirming response expectancies as one factor underlying the efficacy of neurofeedback. Future research has to carefully consider the impact of such psychosocial mechanisms when evaluating the (specific) efficacy of neuromodulatory treatments.

Sherlin, L., Arns, M., Lubar, J., & Sokhadze, E. (2010). A position paper on neurofeedback for the treatment of ADHD. *Journal of Neurotherapy*, 14, 66-78. This position paper provides the current evidence supporting the use of neurofeedback in the treatment of ADHD and recommendations on the implementation of neurofeedback in clinical practice. The paper also provides basic information regarding the diagnosis and psychophysiological etiology of ADHD. The paper does not focus on a specific age range of a clinical population. Unless otherwise noted, we are referring to all subtypes of ADHD (inattentive, hyperactive only, and combined). Conclusions and recommendation are based on the most recent research; however, we also refer to relevant historical studies that support our position on neurofeedback. The readers are strongly advised to research behavioral diagnostic criteria and testing methods elsewhere. This paper is not intended as a comprehensive educational tool for diagnosis or treatment of ADHD. Our purpose is to demonstrate the rationale and to reference the necessary support for neurofeedback in order to be recognized as a legitimate, scientific, and evidence-based intervention for the treatment of ADHD.

Simkin, DR., Thatcher, RW. & Lubar, J. (2014). Quantitative EEGB and Neurofeedback in Children and adolescents: Anxiety disorders, depressive disorders, comorbid addiction and attention-deficit/hyperactivity disorder and brain injury. *Child and Adolescent Psychiatric Clinics of North America*:23(3). 427-464. This article explores the science surrounding neurofeedback. Both surface neurofeedback (using 2-4 electrodes) and newer interventions, such as real-time z-score neurofeedback (electroencephalogram [EEG] biofeedback) and low-resolution electromagnetic tomography neurofeedback, are reviewed. The limited literature on neurofeedback research in children and adolescents is discussed regarding treatment of anxiety, mood, addiction (with comorbid attention-deficit/hyperactivity disorder), and traumatic brain injury. Future potential applications, the use of quantitative EEG for determining which patients will be responsive to medications, the role of randomized controlled studies in neurofeedback research, and sensible clinical guidelines are considered.

Shin, D. I., Lee, J. H., Lee, S. M., Kim, I. Y., & Kim, S. I. (2004). Neurofeedback training with virtual reality for inattention and impulsiveness. *Cyberpsychology & Behavior*, 7(5), 519-526. In this research, the effectiveness of neurofeedback, along with virtual reality (VR), in reducing the level of inattention and impulsiveness was investigated. Twenty-eight male participants, aged 14-18, with social problems, took part in this study. They were separated into three groups: a control group, a VR group, and a non-VR group. The VR and non-VR groups underwent eight sessions of neurofeedback training over 2 weeks, while the control group just waited during the same period. The VR group used a head-mounted display (HMD) and a head tracker, which let them look around the virtual world. Conversely, the non-VR group used only a computer monitor with a fixed viewpoint. All participants performed a continuous performance task (CPT) before and after the complete training session. The results showed that both the VR and non-VR groups achieved better scores in the CPT after the training session, while the control group showed no significant difference. Compared with the other groups, the VR group presented a tendency to get better results, suggesting that immersive VR is applicable to neurofeedback for the rehabilitation of inattention and impulsiveness.

Shouse, M. N., & Lubar, J. F. (1979). Operant conditioning of EEG rhythms and Ritalin in the treatment of hyperkinesis. ***Biofeedback & Self-Regulation*****, 4(4), 299-311.** Enhanced voluntary motor inhibition regularly accompanies conditioned increases in the sensorimotor rhythm (SMR), a 12--14-Hz Rolandic EEG rhythm in cats. A similar rhythm, presumably SMR, has also been identified in the human EEG. The clinical effectiveness of SMR operant conditioning has been claimed for epilepsy, insomnia, and hyperkinesis concurrent with seizure disorders. The present report attempts to follow up and replicate preliminary findings that suggested the technique's successful application to hyperkinesis uncomplicated by a history of epilepsy. SMR was defined as 12--14-Hz EEG activity in the absence of high-voltage slow-wave activity between 4 and 7 Hz. Anticipated treatment effects were indexed by systematic behavioral assessments of undirected motor activity and short attention span in the classroom. EEG and behavioral indices were monitored in four hyperkinetic children under the following six conditions: (1) No Drug, (2) Drug Only, (3) Drug and SMR Training I, (4) Drug and SMR Reversal Training, (5) Drug and SMR Training II, (6) No Drug and SMR Training. All hyperkinetic subjects were maintained on a constant drug regimen throughout the phases employing chemotherapy. Contingent increases and decreases in SMR occurred in three of four training subjects and were associated with similar changes in classroom assessments of motor inactivity. Combining medication and SMR training resulted in substantial improvements that exceeded the effects of drugs alone and were sustained with SMR training after medication was withdrawn. In contrast, these physiological and behavioral changes were absent in one highly distractible subject who failed to acquire the SMR task. Finally, pretraining levels of SMR accurately reflected both the seveity of original motor deficits and the susceptibility of hyperkinetic subjects to both treatments. Although the procedure clearly reduced hyperkinetic behavior, a salient, specific therapeutic factor could not be identified due to the dual EEG contingency imposed combined with associated changes in EMG. Despite these and other qualifying factors, the findings suggested the prognostic and diagnostic value of the SMR in the disorder when overactivity rather than distractibility is the predominant behavioral deficit.

Steiner, NJ., Frenette, EC., Rene, KM., Brennan, RT & Perrin, EC. (2014). In-school neurofeedback training for ADHD: Sustained improvements from a randomized control trial. Pediatrics:133. 483. OBJECTIVE: To evaluate sustained improvements 6 months after a 40-session, in-school computer attention training intervention using neurofeedback or cognitive training (CT) administered to 7- to 11-year-olds with attention-deficit/hyperactivity disorder (ADHD). METHODS: One hundred four children were randomly assigned to receive neurofeedback, CT, or a control condition and were evaluated 6 months postintervention. A 3-point growth model assessed change over time across the conditions on the Conners 3–Parent Assessment Report (Conners 3-P), the Behavior Rating Inventory of Executive Function Parent Form (BRIEF), and a systematic double-blinded classroom observation (Behavioral Observation of Students in Schools). Analysis of variance assessed community-initiated changes in stimulant medication. RESULTS: Parent response rates were 90% at the 6-month follow-up. Six months postintervention, neurofeedback participants maintained significant gains on Conners 3-P (Inattention effect size [ES] = 0.34, Executive Functioning ES = 0.25, Hyperactivity/Impulsivity ES = 0.23) and BRIEF subscales including the Global Executive Composite (ES = 0.31), which remained significantly greater than gains found among children in CT and control conditions. Children in the CT condition showed delayed improvement over immediate postintervention ratings only on Conners 3- P Executive Functioning (ES = 0.18) and 2 BRIEF subscales. At the 6- month follow-up, neurofeedback participants maintained the same stimulant medication dosage, whereas participants in both CT and control conditions showed statistically and clinically significant increases (9 mg [P = .002] and 13 mg [P , .001], respectively). CONCLUSIONS: Neurofeedback participants made more prompt and greater improvements in ADHD symptoms, which were sustained at the 6-month follow-up, than did CT participants or those in the control group. This finding suggests that neurofeedback is a promising attention training treatment for children with ADHD. Pediatrics 2014;133:483– 492.

Steiner, NJ., Frenette, EC., Rene, KM., Brennan, RT & Perrin, EC. (2014). Neurofeedback and cognitive attention training for children with attention-deficit hyperactivity disorder in schools. J Dev Bahav Peadiatr:35(1). 18-27. OBJECTIVE: To evaluate the efficacy of 2 computer attention training systems administered in school for children with attention-deficit hyperactivity disorder (ADHD). METHOD: Children in second and fourth grade with a diagnosis of ADHD (n = 104) were randomly assigned to neurofeedback (NF) (n = 34), cognitive training (CT) (n = 34), or control (n = 36) conditions. A 2-point growth model assessed change from pre-post intervention on parent reports (Conners 3-Parent [Conners 3-P]; Behavior Rating Inventory of Executive Function [BRIEF] rating scale),

teacher reports (Swanson, Kotkin, Agler, M-Flynn and Pelham scale [SKAMP]; Conners 3-Teacher [Conners 3-T]), and systematic classroom observations (Behavioral Observation of Students in Schools [BOSS]). Paired t tests and an analysis of covariance assessed change in medication. RESULTS: Children who received NF showed significant improvement compared with those in the control condition on the Conners 3-P Attention, Executive Functioning and Global Index, on all BRIEF summary indices, and on BOSS motor/verbal off-task behavior. Children who received CT showed no improvement compared to the control condition. Children in the NF condition showed significant improvements compared to those in the CT condition on Conners 3-P Executive Functioning, all BRIEF summary indices, SKAMP Attention, and Conners 3-T Inattention subscales. Stimulant medication dosage in methylphenidate equivalencies significantly increased for children in the CT (8.54 mg) and control (7.05 mg) conditions but not for those in the NF condition (0.29 mg). CONCLUSION: Neurofeedback made greater improvements in ADHD symptoms compared to both the control and CT conditions. Thus, NF is a promising attention training treatment intervention for children with ADHD.

Strehl, U., Leins, U., Goth, G., Klinger, C., Hinterberger, T., and Birbaumer, N. (2006). Self-regulation of slow cortical potentials: A new treatment for children with attention deficit/hyperactivity disorder. ***Pediatrics*****, 118, 1530-1540.** We investigated the effects of self-regulation of slow cortical potentials for children with attention-deficit/hyperactivity disorder. Slow cortical potentials are slow event-related direct-current shifts of the electroencephalogram. Slow cortical potential shifts in the electrical negative direction reflect the depolarization of large cortical cell assemblies, reducing their excitation threshold. This training aims at regulation of cortical excitation thresholds considered to be impaired in children with attention-deficit/hyperactivity disorder. Electroencephalographic data from the training and the 6-month follow-up are reported, as are changes in behavior and cognition. Twenty-three children with attention-deficit/hyperactivity disorder aged between 8 and 13 years received 30 sessions of self-regulation training of slow cortical potentials in 3 phases of 10 sessions each. Increasing and decreasing slow cortical potentials at central brain regions was fed back visually and auditorily. Transfer trials without feedback were intermixed with feedback trials to allow generalization to everyday-life situations. In addition to the neurofeedback sessions, children exercised during the third training phase to apply the self-regulation strategy while doing their homework. For the first time, electroencephalographic data during the course of slow cortical potential neurofeedback are reported. Measurement before and after the trials showed that children with attention-deficit/hyperactivity disorder learn to regulate negative slow cortical potentials. After training, significant improvement in behavior, attention, and IQ score was observed. The behavior ratings included Diagnostic and Statistical Manual of Mental Disorders criteria, number of problems, and social behavior at school and were conducted by parents and teachers. The cognitive variables were assessed with the Wechsler Intelligence Scale for Children and with a computerized test battery that measures several components of attention. All changes proved to be stable at 6 months' follow-up after the end of training. Clinical outcome was predicted by the ability to produce negative potential shifts in transfer sessions without feedback.

Studer, P., Kratz, O., Gevensleben, H., Rothenberger, A., Moll, GH., Hautzinger, M & Heinrich, H. (2014). Frontiers in Human Neuroscience:24(8) 555. Neurofeedback (NF) is being successfully applied, among others, in children with attention deficit/hyperactivity disorder (ADHD) and as a peak performance training in healthy subjects. However, the neuronal mechanisms mediating a successful NF training have not yet been sufficiently uncovered for both theta/beta (T/B), and slow cortical potential (SCP) training, two protocols established in NF in ADHD. In the present, randomized, controlled investigation in adults without a clinical diagnosis (n = 59), the specificity of the effects of these two NF protocols on attentional processes and motor system excitability were to be examined, focusing on the underlying neuronal mechanisms. Neurofeedback training consisted of 10 double sessions, and self-regulation skills were analyzed. Pre- and post-training assessments encompassed performance and event-related potential measures during an attention task, and motor system excitability assessed by transcranial magnetic stimulation. Some NF protocol-specific effects have been obtained. However, due to the limited sample size medium effects did not reach the level of significance. Self-regulation abilities during negativity trials of the SCP training were associated with increased contingent negative variation amplitudes, indicating improved resource allocation during cognitive preparation. Theta/beta training was associated with increased response speed and decreased target-P3 amplitudes after successful theta/beta regulation suggested reduced attentional resources necessary for stimulus evaluation. Motor system excitability effects after theta/beta training paralleled the effects of methylphenidate. Overall, our results are limited by the non-sufficiently acquired self-regulation skills, but some specific effects between good and poor learners could be

described. Future studies with larger sample sizes and sufficient acquisition of self-regulation skills are needed to further evaluate the protocol-specific effects on attention and motor system excitability reported.

Swingle, P. G. (2001). Parameters associated with rapid neurotherapeutic treatment of common ADD (CADD). ***Journal of Neurotherapy*****, 5(4), 73-84.** Paralysis after stroke or neurotrauma is among the leading causes of long-term disability in adults. The development of brain-computer-interface (BCI) systems that allow online classification of electric or metabolic brain activity and their translation into control signals of external devices or computers have led to two major approaches in tackling the problem of paralysis. While assistive BCI systems strive for continuous high-dimensional control of robotic devices or functional electric stimulation (FES) of paralyzed muscles to substitute for lost motor functions in a daily life environment (e.g. Velliste et al. 2008 [1], Hochberg et al. 2006 [2], Pfurtscheller et al. 2000 [3]), restorative BCI systems aim at normalization of neurophysiologic activity that might facilitate motor recovery (e.g. Birbaumer et al. 2007, 2009 [4,5]; Daly et al. 2008 [6]). In order to make assistive BCI systems work in daily life, high BCI communication speed is necessary, an issue that by now can only be achieved by invasive recordings of brain activity (e.g. via multi-unit arrays, MUA, or electrocorticogramm, ECoG). Restorative BCI systems, in contrast, were developed as training tools based on non-invasive methods such as electro- or magnetoencephalography (EEG / MEG). More recently developed approaches use real-time functional magnetic resonance imaging (rtfMRI) or near-infrared spectroscopy (NIRS). Here, we provide an overview of the current state in the development and application of assistive and restorative BCI and introduce novel approaches to improve BCI control with brain stimulation such as transcranial direct current stimulation (tDCS). The outlook of using BCI in rehabilitation of stroke and neurotrauma is discussed.

Tansey, M. A. (1984). EEG sensorimotor rhythm biofeedback training: Some effects on the neurological precursors of learning disabilities. ***International Journal of Psychophysiology*****, 3, 85-99.** This study presents a clinical treatment regime for pathological interhemispheric dysfunction with respect to a population of learning disabled boys. The results obtained replicate and extend earlier findings with respect to operantly conditioned increases in amplitude of sensorimotor transactions and its positive effect on learning disability. Specifically, the biofeedback, and subsequent conditioning, of increased 14 Hz neural discharge patterns (sensorimotor rhythm-SMR) over the central Rolandic cortex, appeared to increase bilateral sensorimotor transactions resulting in substantive reduction/remediation in the learning disabilities of the recipients of such EEG biofeedback training.

Tansey, M. A. (1985). Brainwave signatures--An index reflective of the brain's functional neuroanatomy: Further findings on the effect of EEG sensorimotor rhythm biofeedback training on the neurologic precursors of learning disabilities. ***International Journal of Psychophysiology*****, 3, 85-89.** Eight boys, ages 7 years 11 months to 15 years 3 months, were provided with long-term--symptom duration--sensorimotor rhythm biofeedback training for the remediation of their learning disabilities. Concurrently, the simultaneous recording of five frequency bands of brainwave activity (5 Hz, 7 Hz, 10 Hz, 12 Hz and 14 Hz), from one active electrode equidistant from reference and ground, was intended to provide a glimpse of the 'brainwave signature' reflective of the dynamic and synergistic processes involved in such cerebro-neural activation and the brain's global response to such an alteration in the sensorimotor subnetwork. Overall, the main effect of this procedure, for the biofeedback and subsequent conditioning of increased 14 Hz neural discharge patterns over the central Rolandic cortex in a clinical office setting, seems to be to increase bilateral sensorimotor transactions resulting in substantive remediation of the learning disabilities of the recipients of such training--by way of internally exercising of, and/or recruitment of additional neural activation within, the sensorimotor subnetwork/matrix. Observation of the changing brainwave signatures showed a tendency for decreased slow wave activity concomitant with increases in fast wave activity, for cases with a Full Scale I.Q. within the range of 76 and 85; with those cases with a Full Scale I.Q. within the range of 102 and 116 exhibiting increased amplitudes over most of the monitored bands, but with the increases being much less at the slower frequencies. It is noteworthy that those four subjects with either a significant Verbal greater than Performance, or Performance greater than Verbal, I.Q. Score discrepancy exhibited no less than a 40% greater increase in the lower of the two I.Q. scores; indicating that this SMR training procedure also resulted in an increased symmetry in the interhemispheric interactions reflective of the higher cortical functions for these no longer learning disabled boys.

Tansey, M. A. (1993). Ten-year stability of EEG biofeedback results for a hyperactive boy who failed fourth grade perceptually impaired class. *Biofeedback & Self-Regulation*, 18, 33-44. Ten years ago, the first successful application of a clinical, private-practice based, EEG 14-Hz biofeedback training regimen for the treatment of learning disorders was performed by the author. After the 10-year-old boy, with presenting symptomatology including a developmental reading disorder, hyperactivity, and an educational classification of perceptually impaired, continued symptom free for a period of two years, his case was submitted for publication. Ten years after his termination from successful treatment, his ongoingly normal social and academic functioning is noted and his EEG brainwave signature examined and compared with a population of 24 "used-to-be" learning disabled, one-half of which had a pretreatment state including the educational classification of perceptually impaired. This 10-year follow-up confirms the long-term stability of the results of this EEG 14-Hz biofeedback regimen. Current findings on recent medical research identifying a major cerebral locus of dysfunction for hyperkinesis and how it supports the electrode placements of this clinical office setting regimen is also discussed.

Tansey, M. A., & Bruner, R. L. (1983). EMG and EEG biofeedback training in the treatment of 10-year old hyperactive boy with a developmental reading disorder. *Biofeedback & Self-Regulation*, 8(1), 25-37. The serial application of electromyographic (EMG) and sensorimotor (SMR) biofeedback training was attempted with a 10-year-old boy presenting a triad of symptoms: an attention deficit disorder with hyperactivity, developmental reading disorder, and ocular instability. Symptom elimination was achieved, for all three aspects of the triad, following the procedure of first conditioning a decrease in EMG-monitored muscle tension and then conditioning increases in the amplitude of sensorimotor rhythm over the Rolandic cortex. The learned reduction of monitored EMG levels was accompanied by a reduction in the child's motoric activity level to below that which had been achieved by past administration of Ritalin. In addition, the attention deficit disorder with hyperactivity was no longer diagnosable following the EMG biofeedback training. The learned increase in the amplitude of monitored SMR was accompanied by remediation of the developmental reading disorder and the ocular instability. These results remained unchanged, as ascertained by follow-ups conducted over a 24-month period subsequent to the termination of biofeedback training.

Thibault, R. T., Konrad, K., & Sorger, B. (2020). The Potential of Functional Near-Infrared Spectroscopy-Based Neurofeedback-A Systematic Review and Recommendations for Best Practice. Frontiers in neuroscience, 14, 594. https://doi.org/10.3389/fnins.2020.00594. Background: The effects of electroencephalography (EEG) and functional magnetic resonance imaging (fMRI)-neurofeedback on brain activation and behaviors have been studied extensively in the past. More recently, researchers have begun to investigate the effects of functional near-infrared spectroscopy-based neurofeedback (fNIRS-neurofeedback). FNIRS is a functional neuroimaging technique based on brain hemodynamics, which is easy to use, portable, inexpensive, and has reduced sensitivity to movement artifacts. Method: We provide the first systematic review and database of fNIRS-neurofeedback studies, synthesizing findings from 22 peer-reviewed studies (including a total of N = 441 participants; 337 healthy, 104 patients). We (1) give a comprehensive overview of how fNIRS-neurofeedback training protocols were implemented, (2) review the online signal-processing methods used, (3) evaluate the quality of studies using pre-set methodological and reporting quality criteria and also present statistical sensitivity/power analyses, (4) investigate the effectiveness of fNIRS-neurofeedback in modulating brain activation, and (5) review its effectiveness in changing behavior in healthy and pathological populations. Results and discussion: (1-2) Published studies are heterogeneous (e.g., neurofeedback targets, investigated populations, applied training protocols, and methods). (3) Large randomized controlled trials are still lacking. In view of the novelty of the field, the quality of the published studies is moderate. We identified room for improvement in reporting important information and statistical power to detect realistic effects. (4) Several studies show that people can regulate hemodynamic signals from cortical brain regions with fNIRS-neurofeedback and (5) these studies indicate the feasibility of modulating motor control and prefrontal brain functioning in healthy participants and ameliorating symptoms in clinical populations (stroke, ADHD, autism, and social anxiety). However, valid conclusions about specificity or potential clinical utility are premature. Conclusion: Due to the advantages of practicability and relatively low cost, fNIRS-neurofeedback might provide a suitable and powerful alternative to EEG and fMRI neurofeedback and has great potential for clinical translation of neurofeedback. Together with more rigorous research and reporting practices, further methodological improvements may lead to a more solid understanding of fNIRS-neurofeedback. Future research will benefit from exploiting the advantages of fNIRS, which offers unique opportunities for neurofeedback research.

Thompson, L., & Thompson, M. (1998). Neurofeedback combined with training in metacognitive strategies: Effectiveness in students with ADD. ***Applied Psychophysiology & Biofeedback*****, 23(4), 243-263.** Seven autistic children diagnosed with autism spectrum disorders (ASD) received a neurofeedback treatment that aimed to improve their level of executive control. Neurofeedback successfully reduced children's heightened theta/beta ration by inhibiting theta activation and enhancing beta activation over sessions. Following treatment children's executive capacities were found to have improved greatly relative to pre-treatment assessment on a range of executive function tasks. Additional improvements were found in children's social, communicative and typical behavior, relative to a waiting list control group. These findings suggest a basic executive function impairment in ASD that can be alleviated through specific neurofeedback treatment. Possible neural mechanisms that may underlie neurofeedback mediated improvement in executive functioning in autistic children are discussed.

Williams, J. (2010). Does neurofeedback help reduce attention-deficit hyperactivity disorder? ***Journal of Neurotherapy*****; 14(4), 261-279.** Introduction: Neurofeedback is an alternative treatment for Attention Deficit Hyperactivity Disorder (ADHD), but its efficacy is unknown. This narrative review examines rigorous studies conducted utilizing neurofeedback as a treatment for ADHD. Methods: Studies were located by searching the Web of Science and PsycINFO databases with the keywords ADHD or attention deficit hyperactivity disorder AND neurofeedback or EEG biofeedback or electroencephalogram biofeedback. Located studies were chosen for initial review if they met the following criteria: (a) randomized controlled trial or quasi-experiment, (b) ADHD diagnosis based on DSM criteria, (c) published at any time prior to March 2010, (d) English language, and (e) published in a peer-reviewed journal. Participants included children, adolescents, and adults diagnosed with ADHD. Results: Twelve articles reporting 9 different studies met the eligibility criteria and were included in the review. All 9 studies produced results that indicated significant improvements on either tests scores or behavioral conduct for individuals who were treated with neurofeedback for ADHD. Alternative treatments also demonstrated effectiveness. Conclusion: Neurofeedback may be an effective treatment for ADHD. Future research is needed with larger sample sizes, comparing the efficacy of neurofeedback with the efficacy of other ADHD treatments and comparing different neurofeedback protocols.

Vachon-Presseau, E., Achim, A., Benoit-Lajoie, A. (2009). Direction of SMR and beta change with attention in adults. ***Journal of Neurotherapy*** **13(1), 22 – 29.** Introduction. The aim of this study was to clarify the interpretation of sensory-motor rhythm (SMR; 13–15 Hz) and beta (16–20 Hz) changes with respect to attention states. Method. For this purpose, EEG was recorded from 11 participants during (a) a multiple object tracking task (MOT), which required externally directed attention; (b) the retention phase of a visuo-spatial memory task (VSM), which required internally directed attention and avoidance of sensory distraction; and (c) the waiting intervals between trials, which constituted a no-task-imposed control condition. The 2 active tasks were consecutively presented at 2 difficulty levels (i.e., easy and hard). Two analyses of variance were conducted on EEG log spectral amplitudes in the alpha (8–12 Hz), SMR, and beta bands from F3, F4, C3, C4 and P3, P4. Results. The first 15 analysis compared the MOT to the VSM by difficulty levels and revealed a significant task effect ($p < .0005$) but no effect of difficulty. The results showed that externally directed attention (MOT) resulted in lower values than internally directed attention (VSM) in all three bands. The second analysis averaged the difficulty levels together and added the no-task-imposed reference condition. The results again showed a significant task effect that did not interact with site, hemisphere, or, more important, band. Post hoc tests revealed that both MOT and VSM produced significantly smaller means than the no-task-imposed condition. This pattern of log-amplitude means and the lack of task interaction with any other factor indicate that task-induced attention reduces EEG power in the same proportion across the 3 bands and the 6 channels studied. Conclusions. These results contradict a frequent interpretation concerning the relationship between the brain's aptitude to increase low beta in neurofeedback programs and improved sustain attention capacities.

Valdez, M. (1985). Effects of biofeedback-assisted attention training in a college population. ***Biofeedback & Self-Regulation*****, 10(4), 315-324.** A program of stress management employing open-focus attention-training workshops was developed at Baruch College to bring the benefits of stress reduction to students. The purpose of the research reported here was to evaluate the results of the open-focus attention-training technique. Open-focus technique without biofeedback training was used for two semesters. Biofeedback training was incorporated in the third semester. In the first study, changes in grade point average (GPA), stress-related symptoms, and physiological

measures were examined. The experimental subjects' stress data for this study was reported previously (Valdés, 1985). In the second study, changes in the same variables for experimental and control subjects were evaluated. Students in the control group showed decreased GPA, while those who participated in open-focus training showed a trend toward improved GPA. Stress-related symptoms associated with anxiety and management of emotional problems showed significant posttraining improvement, as did physiological measures in all of the biofeedback modalities in which the experimental subjects were specifically trained. The results support the hypothesis that the workshops were successful in reducing stress levels, and suggest that further controlled research be conducted to verify these findings, and to identify the most effective components of the training procedure.

Van Doren, J., Arns, M., Heinrich, H., Vollebregt, M. A., Strehl, U., & K Loo, S. (2019). Sustained effects of neurofeedback in ADHD: a systematic review and meta-analysis. European child & adolescent psychiatry, 28(3), 293–305. https://doi.org/10.1007/s00787-018-1121-4. Neurofeedback (NF) has gained increasing interest in the treatment of attention-deficit/hyperactivity disorder (ADHD). Given learning principles underlie NF, lasting clinical treatment effects may be expected. This systematic review and meta-analysis addresses the sustainability of neurofeedback and control treatment effects by considering randomized controlled studies that conducted follow-up (FU; 2-12 months) assessments among children with ADHD. PubMed and Scopus databases were searched through November 2017. Within-group and between-group standardized mean differences (SMD) of parent behavior ratings were calculated and analyzed. Ten studies met inclusion criteria (NF: ten studies, N = 256; control: nine studies, N = 250). Within-group NF effects on inattention were of medium effect size (ES) (SMD = 0.64) at post-treatment and increased to a large ES (SMD = 0.80) at FU. Regarding hyperactivity/impulsivity, NF ES were medium at post-treatment (SMD = 0.50) and FU (SMD = 0.61). Non-active control conditions yielded a small significant ES on inattention at post-treatment (SMD = 0.28) but no significant ES at FU. Active treatments (mainly methylphenidate), had large ES for inattention (post: SMD = 1.08; FU: SMD = 1.06) and medium ES for hyperactivity/impulsivity (post: SMD = 0.74; FU: SMD = 0.67). Between-group analyses also revealed an advantage of NF over non-active controls [inattention (post: SMD = 0.38; FU: SMD = 0.57); hyperactivity-impulsivity (post: SMD = 0.25; FU: SMD = 0.39)], and favored active controls for inattention only at pre-post (SMD = - 0.44). Compared to non-active control treatments, NF appears to have more durable treatment effects, for at least 6 months following treatment. More studies are needed for a properly powered comparison of follow-up effects between NF and active treatments and to further control for non-specific effects.

Vernon, D., Egner, T., Cooper, N., Compton, T., Neilands, C., Sheri, A., & Gruzelier, J. (2003). The effect of training distinct neurofeedback protocols on aspects of cognitive performance. ***International Journal of Psychophysiology*****, 47, 75-85.** The use of neurofeedback as an operant conditioning paradigm has disclosed that participants are able to gain some control over particular aspects of their electroencephalogram (EEG). Based on the association between theta activity (4-7 Hz) and working memory performance, and sensorimotor rhythm (SMR) activity (12-15 Hz) and attentional processing, we investigated the possibility that training healthy individuals to enhance either of these frequencies would specifically influence a particular aspect of cognitive performance, relative to a non-neurofeedback control-group. The results revealed that after eight sessions of neurofeedback the SMR-group were able to selectively enhance their SMR activity, as indexed by increased SMR/theta and SMR/beta ratios. In contrast, those trained to selectively enhance theta activity failed to exhibit any changes in their EEG. Furthermore, the SMR-group exhibited a significant and clear improvement in cued recall performance, using a semantic working memory task, and to a lesser extent showed improved accuracy of focused attentional processing using a 2-sequence continuous performance task. This suggests that normal healthy individuals can learn to increase a specific component of their EEG activity, and that such enhanced activity may facilitate semantic processing in a working memory task and to a lesser extent focused attention. We discuss possible mechanisms that could mediate such effects and indicate a number of directions for future research.

Vollenbregt, MA., van Dongen-Boomsma, M., Slaats-Willemse, D. & Buitelaar, JK. (2014). What future research should bring to help resolving the debate about the efficacy of EEG-neurofeedback in children with ADHD. Frontiers in Human Neuroscience:15(8). 321. In recent years a rising amount of randomized controlled trials, reviews, and meta-analyses relating to the efficacy of electroencephalographic-neurofeedback (EEG-NF) in children with attention-deficit/hyperactivity disorder (ADHD) have

been published. Although clinical reports and open treatment studies suggest EEG-NF to be effective, double blind placebo-controlled studies as well as a rigorous meta-analysis failed to find support for the efficacy of EEG-NF. Since absence of evidence does not equate with evidence of absence, we will outline how future research might overcome the present methodological limitations. To provide conclusive evidence for the presence or absence of the efficacy of EEG-NF in the treatment of ADHD, there is a need to set up a well-designed study that ensures optimal implementation and embedding of the training, and possibly incorporates different forms of neurofeedback.

Wadhwani, S., Radvanski, D. C., & Carmody, D. P. (1998). Neurofeedback training in a case of attention deficit hyperactivity disorder. *Journal of Neurotherapy*, 3(1), 42-49. Electroencephalographic biofeedback, also known as neurofeedback, has been used to improve attention in children with Attention Deficit Hyperactivity Disorder (ADHD). In the present case study, a ten-year-old boy completed 37 sessions of neurofeedback training over a six-month period on-site in a school setting. Beta brainwave training was applied for sessions 1 – 22 and replaced by sensorimotor rhythm training for sessions 23 – 37. A review of his national achievement test scores for four years revealed he improved performance the year he received neurofeedback and the gain was lost the year after treatment was completed. The participant had been receiving methylphenidate for the previous two years and remained on the medication throughout neurofeedback and for the year after neurofeedback treatment. Findings are suggestive of the advantages of incorporating neurofeedback training as part of a multimodal treatment program in a school setting for children with ADHD.

Walker, J. E., & Norman, C. A. (2006). The neurophysiology of dyslexia: A selective review with implications for neurofeedback remediation and results of treatment in twelve consecutive patients. *Journal of Neurotherapy*, 10(1), 45-55. Dyslexia is a common and important problem in all industrial societies, with a prevalence rate of five to ten percent, for which no consistently effective treatment is available. Recent advances in imaging (morphometric MRI, functional MRI, PET, regional cerebral blood flow), as well as in neurophysiology (evoked potentials, QEEG, event-related desynchronization, coherence studies, magnetic source imaging, reading difference topography) have clarified our understanding of the normal circuitry involved in reading and differences seen in individuals who have trouble learning to read. These studies have important implications for the use of neurofeedback to help dyslexic individuals learn to read more easily. First, we obtain a QEEG and a reading difference topograph. We then train down any abnormalities that are significantly increased and train up any abnormalities that are significantly decreased. Increasing 16–18 Hz activity at T3 (left mid-temporal area) has also proved quite helpful in improving reading speed and comprehension. These combined approaches have been helpful in all cases of dyslexia we have treated, dramatically so in some cases. Each of the 12 individuals treated improved by at least two grade levels after 30 to 35 sessions.

Wang, S., Zhang, D., Fang, B., Liu, X., Yan, G., Sui, G., Huang, Q., Sun, L., & Wang, S. (2021). A Study on Resting EEG Effective Connectivity Difference before and after Neurofeedback for Children with ADHD. Neuroscience, 457, 103–113. https://doi.org/10.1016/j.neuroscience.2020.12.038. Altered functional networks in attention deficit/hyperactivity disorder (ADHD) have been frequently reported, but effective connectivity has hardly been studied. Especially the differences of effective connectivity in children with ADHD after receiving neurofeedback (NF) training have been merely reported. Therefore, this study aimed to explore the effective networks of ADHD and the positive influence of NF on the effective networks. Electroencephalogram (EEG) data were recorded from 22 children with ADHD (including data from children pretraining and posttraining) and 15 age-matched healthy controls during an eyes-closed resting state. Phase transfer entropy (PTE) was used to construct the effective connectivity. The topological properties of networks and flow gain were measured separately in four bands (delta, theta, alpha, and beta). Results revealed the following: pretraining children with ADHD manifested a higher clustering coefficient and lower characteristic path length in the delta band than healthy controls; weakened anterior-to-posterior flow gain in the delta band, strengthened posterior-to-anterior flow gain in the alpha band and strengthened anterior-to-posterior flow gain in the beta band were observed in pretraining children with ADHD; The topological properties and flow gain in posttraining children with ADHD were close to those of healthy controls. Moreover, parent's SWAN presented significant improvements of ADHD symptoms after NF. Our findings revealed that the effective connectivity of ADHD

was altered and that NF could improve the brain function of ADHD. The present study provided the first evidence that children with ADHD differed from healthy children in phase-based effective connectivity and that NF could reduce the differences.

Xiong, Z., Shi, S., & Xu, H. (2005). A controlled study of the effectiveness of EEG biofeedback training on children with attention deficit hyperactivity disorder. ***Journal of Huazhong University of Science & Technology*****, 25(3), 368-370.** In order to study the treatment of the children with attention deficit hyperactivity disorder (ADHD), the integrated visual and auditory continuous performance test (IVA-CPT) was clinically applied to evaluate the effectiveness of electroencephalogram (EEG) biofeedback training. Of all the 60 children with ADHD aged more than 6 years, the effective rate of EEG biofeedback training was 91.6% after 40 sessions of EEG biofeedback training. Before and after treatment by EEG biofeedback training, the overall indexes of IVA were significantly improved among predominately inattentive, hyperactive, and combined subtype of children with ADHD ($P<0.001$). It was suggested that EEG biofeedback training was an effective and vital treatment on children with ADHD.

Zuberer, A., Minder, F., Brandeis, D., & Drechsler, R. (2018). Mixed-Effects Modeling of Neurofeedback Self-Regulation Performance: Moderators for Learning in Children with ADHD. Neural plasticity, 2018, 2464310. https://doi.org/10.1155/2018/2464310. Introduction: Neurofeedback (NF) has gained increasing popularity as a training method for children and adults with attention deficit hyperactivity disorder (ADHD). However, it is unclear to what extent children learn to regulate their brain activity and in what way NF learning may be affected by subject- and treatment-related factors. Methods: In total, 48 subjects with ADHD (age 8.5-16.5 years; 16 subjects on methylphenidate (MPH)) underwent 15 double training sessions of NF in either a clinical or a school setting. Four mixed-effects models were employed to analyze learning: training within-sessions, across-sessions, with continuous feedback, and with transfer in which performance feedback is delayed. Results: Age and MPH affected the NF performance in all models. Cross-session learning in the feedback condition was mainly moderated by age and MPH, whereas NF learning in the transfer condition was mainly boosted by MPH. Apart from IQ and task types, other subject-related or treatment-related effects were unrelated to NF learning. Conclusion: This first study analyzing moderators of NF learning in ADHD with a mixed-effects modeling approach shows that NF performance is moderated differentially by effects of age and MPH depending on the training task and time window. Future studies may benefit from using this approach to analyze NF learning and NF specificity. The trial name Neurofeedback and Computerized Cognitive Training in Different Settings for Children and Adolescents With ADHD is registered with NCT02358941.

ANXIETY, PTSD, OCD, AND PANIC DISORDERS

Al-Ezzi, A., Kamel, N., Faye, I., & Gunaseli, E. (2020). Review of EEG, ERP, and Brain Connectivity Estimators as Predictive Biomarkers of Social Anxiety Disorder. Frontiers in psychology, 11, 730. Social anxiety disorder (SAD) is characterized by a fear of negative evaluation, negative self-belief and extreme avoidance of social situations. These recurrent symptoms are thought to maintain the severity and substantial impairment in social and cognitive thoughts. SAD is associated with a disruption in neuronal networks implicated in emotional regulation, perceptual stimulus functions, and emotion processing, suggesting a network system to delineate the electrocortical endophenotypes of SAD. This paper seeks to provide a comprehensive review of the most frequently studied electroencephalographic (EEG) spectral coupling, event-related potential (ERP), visual-event potential (VEP), and other connectivity estimators in social anxiety during rest, anticipation, stimulus processing, and recovery states. A search on Web of Science provided 97 studies that document electrocortical biomarkers and relevant constructs pertaining to individuals with SAD. This study aims to identify SAD neuronal biomarkers and provide insight into the differences in these biomarkers based on EEG, ERPs, VEP, and brain connectivity networks in SAD patients and healthy controls (HC). Furthermore, we proposed recommendations to improve methods of delineating the electrocortical endophenotypes of SAD, e.g., a fusion of EEG with other modalities such as functional magnetic resonance imaging (fMRI) and magnetoencephalograms (MEG), to realize better effectiveness than EEG alone, in order to ultimately evolve the treatment selection process, and to review the possibility of using electrocortical measures in the early diagnosis and endophenotype examination of SAD.

Askovic M, Watters AJ, Coello M, Aroche J, Harris AWF, Kropotov J. Evaluation of Neurofeedback for Posttraumatic Stress Disorder Related to Refugee Experiences Using Self-Report and Cognitive ERP Measures. Clin EEG Neurosci. 2020 Mar;51(2):79-86. Background. Neurofeedback holds promise as an intervention for the psychophysiological dysfunction found in posttraumatic stress disorder (PTSD). Few empirical studies have assessed the efficacy of neurofeedback for PTSD, and none in individuals with refugee trauma. A proposed mechanism for neurofeedback efficacy in PTSD is through remediating deficits in cognitive control. We assessed pre- and postchanges in symptoms and neurocognitive functioning of refugee clients participating in a neurofeedback intervention for PTSD. Methods: Clinical data for 13 adult refugees with chronic PTSD who participated in neurofeedback combined with trauma counseling (NFT) was compared with 13 adult refugees placed on a waitlist to receive neurofeedback. Waitlist clients continued to receive trauma counseling alone (TC). NFT was additionally assessed pre- and posttherapy for changes in event-related potentials (ERPs) and behavioral indices of cognitive control using a visual continuous performance task (VCPT). Comparison VCPT data from healthy controls (HC) was available from the Human Brain Index database. Results. Posttherapy, NFT had significantly lower symptoms of trauma, anxiety, and depression compared with TC. NFT demonstrated an increased P3 amplitude and improved behavioral performance suggesting a normalization of cognitive control. Conclusions. These preliminary observations are consistent with a possible benefit of neurofeedback for remediating PTSD. This may be achieved at least partially by an improvement in cognitive control. Further confirmation of the effectiveness of the treatment now requires a randomized controlled trial that considers issues such as placebo response, nonspecific therapist effects, and duration of treatment.

Banerjee S, Argáez C. Neurofeedback and Biofeedback for Mood and Anxiety Disorders: A Review of Clinical Effectiveness and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Nov 13. PMID: 30299634. Excerpt: Two previous CADTH Rapid Response reviews reported on neurofeedback and biofeedback for mood and anxiety disorders. The review published in 2012 reported that evidence from mostly preliminary analyses suggested that neurofeedback and biofeedback may have potential for the treatment of post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), or depression. The review published in 2014, assessed evidence identified since the publication of the review of 2012 and reported that limited evidence suggested that biofeedback may decrease the symptoms of PTSD or depression. Both the reviews reported that no relevant evidence based guidelines on neurofeedback or biofeedback were identified. The purpose of this review is to evaluate the more recent evidence

regarding the clinical effectiveness of neurofeedback or biofeedback compared with other modalities for the treatment of mood and anxiety disorders (PTSD, GAD, or depression) in adults. Additionally, this review aims to review recent evidence-based guidelines regarding the use of neurofeedback or biofeedback for the treatment of mood and anxiety disorders (PTSD, GAD, or depression) in adults.

Bazanova, OM., Balioz, NV., Muravleva, KB. & Skoraia, MV. (2013). Voluntary alpha-power increasing training impact on the heart rate variability. Fiziol Cheloveka: Jan-Feb; 39(1). 103-116. In order to study the effect of the alpha EEG power increasing training at heart rate variability (HRV) as the index of the autonomic regulation of cognitive functions there were follow tasks: (1) to figure out the impact of biofeedback in the voluntary increasing the power in the individual high-frequency alpha-band effect on heart rate variability and related characteristics of cognitive and emotional spheres, (2) to determine the nature of the relationship between alpha activity indices and heart rate variability, depending on the alpha-frequency EEG pattern at rest (3) to examine how the individual alpha frequency EEG pattern is reflected in changes HRV as a result of biofeedback training. Psychometric indicators of cognitive performance, the characteristics of the alpha-EEG activity and heart rate variability (HRV) as LF/HF and pNN50 were recorded in 27 healthy men aged 18-34 years, before, during, and after 10 sessions of training of voluntary increase in alpha power in the individual high-frequency alpha band with eyes closed. To determine the biofeedback effect on the alpha power increasing training, data subjects are compared in 2 groups: experimental (14) with the real and the control group (13 people)--with mock biofeedback. The follow up effect of trainings was studied through month over the 10 training sessions. Results showed that alpha biofeedback training enhanced the fluency and accuracy in cognitive performance, decreased anxiety and frontal EMG, increased resting frequency, width and power in individual upper alpha range only in participants with low baseline alpha frequency. While mock biofeedback increased resting alpha power only in participants with high baseline resting alpha frequency and did change neither cognitive performance, nor HRV indices. Biofeedback training eliminated the alpha power decrease in response to arithmetic task in both with high and low alpha frequency participants and this effect was followed up over the month. Mock biofeedback training has no such effect. The positive correlation between the alpha-peak frequency and pNN50 in patients with initially low, but negative--those with high baseline alpha frequency explains the multidirectional biofeedback effects on HRV in low and high alpha frequency subjects. The individual alpha-frequency EEG pattern determines the effectiveness of the alpha EEG biofeedback training in changing heart rate variability, which provides a basis for predicting the results and develop individual approaches to the biofeedback technology implementation that can be used in clinical practice for treatment and rehabilitation of psychosomatic syndromes and in educational training.

Bisson, J. I., van Gelderen, M., Roberts, N. P., & Lewis, C. (2020). Non-pharmacological and non-psychological approaches to the treatment of PTSD: results of a systematic review and meta-analyses. European journal of psychotraumatology, 11(1), 1795361. Background: Non-pharmacological and non-psychological approaches to the treatment of post-traumatic stress disorder (PTSD) have often been excluded from systematic reviews and meta-analyses. Consequently, we know little regarding their efficacy. Objective: To determine the effect sizes of non-pharmacological and non-psychological treatment approaches for PTSD. Method: We undertook a systematic review and meta-analyses following Cochrane Collaboration guidelines. A pre-determined definition of clinical importance was applied to the results and the quality of evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. Results: 30 randomised controlled trials (RCTs) of a range of heterogeneous non-psychological and non-pharmacological interventions (28 in adults, two in children and adolescents) were included. There was emerging evidence for six different approaches (acupuncture, neurofeedback, saikokeishikankyoto (a herbal preparation), somatic experiencing, transcranial magnetic stimulation, and yoga). Conclusions: Given the level of evidence available, it would be premature to offer non-pharmacological and non-psychological interventions routinely, but those with evidence of efficacy provide alternatives for people who do not respond to, do not tolerate or do not want more conventional evidence-based interventions. This review should stimulate further research in this area.

Brody, S., Rau, H., Kohler, F., Schupp, H., Lutzenberger, W., & Birbaumer, N. (1994). Slow cortical potential biofeedback and the startle reflex. *Biofeedback & Self-Regulation*, 19(1), 1-12. The negativity of slow cortical potentials (SCP) of the surface EEG is a measure of brain excitability, correlating with motor and cognitive preparation. Self-control of SCP positivity has been shown to reduce

seizure activity. Following SCP biofeedback from a central EEG electrode position, subjects gained bidirectional control over their SCP. The current study used a modified feedback methodology, and found a positive relationship between negativity and magnitude of EMG startle response (a measure of cortical and subcortical arousal, particularly aversive response disposition). Greater success in SCP differentiation was associated with self-report of less relaxation during negativity training.

Chen, C., Yu, X., Belkacem, A. N., Lu, L., Li, P., Zhang, Z., Wang, X., Tan, W., Gao, Q., Shin, D., Wang, C., Sha, S., Zhao, X., & Ming, D. (2021). EEG-Based Anxious States Classification Using Affective BCI-Based Closed Neurofeedback System. Journal of medical and biological engineering, 1–10. Advance online publication. Purpose: Anxiety disorder is one of the psychiatric disorders that involves extreme fear or worry, which can change the balance of chemicals in the brain. To the best of our knowledge, the evaluation of anxiety state is still based on some subjective questionnaires and there is no objective standard assessment yet. Unlike other methods, our approach focuses on study the neural changes to identify and classify the anxiety state using electroencephalography (EEG) signals. Methods: We designed a closed neurofeedback experiment that contains three experimental stages to adjust subjects' mental state. The EEG resting state signal was recorded from thirty-four subjects in the first and third stages while EEG-based mindfulness recording was recorded in the second stage. At the end of each stage, the subjects were asked to fill a Visual Analogue Scale (VAS). According to their VAS score, the subjects were classified into three groups: non-anxiety, moderate or severe anxiety groups. Results: After processing the EEG data of each group, support vector machine (SVM) classifiers were able to classify and identify two mental states (non-anxiety and anxiety) using the Power Spectral Density (PSD) as patterns. The highest classification accuracies using Gaussian kernel function and polynomial kernel function are 92.48 ± 1.20% and 88.60 ± 1.32%, respectively. The highest average of the classification accuracies for healthy subjects is 95.31 ± 1.97% and for anxiety subjects is 87.18 ± 3.51%. Conclusions: The results suggest that our proposed EEG neurofeedback-based classification approach is efficient for developing affective BCI system for detection and evaluation of anxiety disorder states.

Chen, T. C., & Lin, I. M. (2020). The learning effects and curves during high beta down-training neurofeedback for patients with major depressive disorder. Journal of affective disorders, 266, 235–242. Background: Electroencephalography (EEG) has revealed increased beta activity in patients with comorbid major depressive disorder (MDD) and anxiety symptoms. Negative emotions and high beta activity could be decreased by a high beta down-training neurofeedback (NFB) protocol. The present study utilized three objective parameters - trainability, independence, and interpretability - to validate the effects of high beta down-training sessions. Methods: EEG data were collected from 23 patients with comorbid MDD and anxiety symptoms during high beta down-training sessions. Participants received five weeks of training, two sessions per week, to down-train high beta amplitude (20-32 Hz) at EEG sites P3 and P4. Three efficacy parameters were examined by comparing pre-training and post-training EEG. Results: The trainability index revealed the learning curves of reduced high beta activity at P3 and P4, confirming training effects across and within sessions. The independence index revealed only beta band activity decreased. The interpretability index revealed the decreased high beta activity was positively correlated with decreased severity of depression, especially for cognitive depression. Limitations: With only ten sessions in this study, it is unknown whether the NFB training caused extended and stable learning effects. Additionally, combining high beta down-training protocol with enhancing another target band could better ensure the desired changes in brain activity. Finally, the effect of medication on EEG cannot be excluded in present study. Conclusions: The trainability, independence and interpretability of the high beta down-training NFB protocol were confirmed, supporting the protocol's use in future research and clinical applications.

Chiba, T., Ide, K., Taylor, J. E., Boku, S., Toda, H., Kanazawa, T., Kato, S., Horiuchi, Y., Hishimoto, A., Maruyama, T., Yamamoto, T., Shirakawa, M., Sora, I., Kawato, M., & Koizumi, A. (2020). A reciprocal inhibition model of alternations between under-/overemotional modulatory states in patients with PTSD. Molecular psychiatry, 10.1038/s41380-020-0827-0. Advance online publication. Patients with posttraumatic stress disorder (PTSD) appear to manifest two opposing tendencies in their attentional biases and symptoms. However, whether common neural mechanisms account for their opposing attentional biases and symptoms remains unknown. We here propose a model in which reciprocal inhibition between the amygdala and ventromedial prefrontal cortex (vmPFC) predicts synchronized alternations between emotional under- and overmodulatory states at the neural, behavioral, and symptom levels within the same patients. This reciprocal inhibition model predicts that when the amygdala is dominant, patients enter an emotional

undermodulatory state where they show attentional bias toward threat and manifest re-experiencing symptoms. In contrast, when the vmPFC is dominant, patients are predicted to enter an emotional overmodulatory state where they show attentional bias away from threat and avoidance symptoms. To test the model, we performed a behavioral meta-analysis (total N = 491), analyses of own behavioral study (N = 20), and a neuroimaging meta-analysis (total N = 316). Supporting the model, we found the distributions of behavioral attentional measurements to be bimodal, suggesting alternations between the states within patients. Moreover, attentional bias toward threat was related to re-experiencing symptoms, whereas attentional bias away from threat was related with avoidance symptoms. We also found that the increase and decrease of activity in the left amygdala activity was related with re-experiencing and avoidance symptoms, respectively. Our model may help elucidate the neural mechanisms differentiating nondissociative and dissociative subtypes of PTSD, which usually show differential emotional modulatory levels. It may thus provide a new venue for therapies targeting each subtype.

Chiba T, Kanazawa T, Koizumi A, Ide K, Taschereau-Dumouchel V, Boku S, Hishimoto A, Shirakawa M, Sora I, Lau H, Yoneda H, Kawato M. Current Status of Neurofeedback for Post-traumatic Stress Disorder: A Systematic Review and the Possibility of Decoded Neurofeedback. Front Hum Neurosci. 2019 Jul 17;13:233. Background: Post-traumatic stress disorder (PTSD) is a neuropsychiatric affective disorder that can develop after traumatic life-events. Exposure-based therapy is currently one of the most effective treatments for PTSD. However, exposure to traumatic stimuli is so aversive that a significant number of patients drop-out of therapy during the course of treatment. Among various attempts to develop novel therapies that bypass such aversiveness, neurofeedback appears promising. With neurofeedback, patients can unconsciously self-regulate brain activity via real-time monitoring and feedback of the EEG or fMRI signals. With conventional neurofeedback methods, however, it is difficult to induce neural representation related to specific trauma because the feedback is based on the neural signals averaged within specific brain areas. To overcome this difficulty, novel neurofeedback approaches such as Decoded Neurofeedback (DecNef) might prove helpful. Instead of the average BOLD signals, DecNef allows patients to implicitly regulate multivariate voxel patterns of the BOLD signals related with feared stimuli. As such, DecNef effects are postulated to derive either from exposure or counter-conditioning, or some combination of both. Although the exact mechanism is not yet fully understood. DecNef has been successfully applied to reduce fear responses induced either by fear-conditioned or phobic stimuli among non-clinical participants. Methods: Follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic review was conducted to compare DecNef effect with those of conventional EEG/fMRI-based neurofeedback on PTSD amelioration. To elucidate the possible mechanisms of DecNef on fear reduction, we mathematically modeled the effects of exposure-based and counter conditioning separately and applied it to the data obtained from past DecNef studies. Finally, we conducted DecNef on four PTSD patients. Here, we review recent advances in application of neurofeedback to PTSD treatments, including the DecNef. This review is intended to be informative for neuroscientists in general as well as practitioners planning to use neurofeedback as a therapeutic strategy for PTSD. Results: Our mathematical model suggested that exposure is the key component for DecNef effects in the past studies. Following DecNef a significant reduction of PTSD severity was observed. This effect was comparable to those reported for conventional neurofeedback approach. Conclusions: Although a much larger number of participants will be needed in future, DecNef could be a promising therapy that bypasses the unpleasantness of conscious exposure associated with conventional therapies for fear related disorders, including PTSD.

Chisholm, R. C., DeGood, D. E., & Hartz, M. A. (1977). Effects of alpha feedback training on occipital EEG, heart rate, and experiential reactivity to a laboratory stressor. *Psychophysiology*, 14(2), 157-163. The intent of this study was to examine whether brief alpha biofeedback training would alter the degree of physiological and experiential stress evidenced in an aversive laboratory situation. While occipital alpha and heart rate were monitored, 36 subjects underwent 8 presentations of a warning tone preceding fingertip electric shock by 30 sec. Subjects were then placed into one of three treatments taking place in dim light with eyes open. Group 1 received 24 min of contingent feedback. Group 2 received an equivalent amount of non-contingent feedback and Group 3, a no-feedback control condition, listened to music. Following the treatment period, 12 additional tone-shock pairings were presented, equally divided between eyes-open and eyes-closed trials, also with and without continuation of the treatment period "signal" (i.e. contingent, non-contingent feedback, or music). The results revealed that, in general, enhanced alpha density was maintained by the contingent feedback group during the post-treatment aversive situation. However, the reduction in alpha suppression was not systematically accompanied by corresponding heart rate and self-report reductions in situational reactivity. It was concluded that alpha feedback training

was not sufficient to produce a generalized relaxation to the aversive situation. Alternative accounts of the results, focusing primarily on independence of response systems, are discussed.

Clemans, Z., El-Baz, A., Hollifield, M., & Sokhadze, E. (2012). Single trial time-frequency analysis of error processing in PTSD. ***Neuroscience Letters*****. E-publication.** Error processing studies in psychology and psychiatry are relatively common. Event-related potentials (ERPs) are often used as measures of error processing, two such response-locked ERPs being the error-related negativity (ERN) and the error-related positivity (Pe). The ERN and Pe occur following committed error in reaction time tasks as low frequency (4-8 Hz) electroencephalographic (EEG) oscillations registered at the midline fronto-central sites. We created an alternative method for analyzing error processing using time-frequency analysis in the form of a wavelet transform. A study was conducted in which subjects with PTSD and healthy control completed a forced-choice task. Single trial EEG data from errors in the task were processed using a continuous wavelet transform. Coefficients from the transform that corresponded to the theta range were averaged to isolate a theta waveform in the time-frequency domain. Measures called the time-frequency ERN and Pe were obtained from these waveforms for five different channels and then averaged to obtain a single time-frequency ERN and Pe for each error trial. A comparison of the amplitude and latency for the time-frequency ERN and Pe between the PTSD and control group was performed. A significant group effect was found on the amplitude of both measures. These results indicate that the developed single trial time-frequency error analysis method is suitable for examining error processing in PTSD and possibly other psychiatric disorders.

Cohen DJ, Begley A, Alman JJ, Cashmere DJ, Pietrone RN, Seres RJ, Germain A. (2013). Quantitative electroencephalography during rapid eye movement (REM) and non-REM sleep in combat-exposed veterans with and without post-traumatic stress disorder. J Sleep Res. 2013 Feb;22(1):76-82. doi: 10.1111/j.1365-2869.2012.01040.x. Epub 2012 Jul 30. Sleep disturbances are a hallmark feature of post-traumatic stress disorder (PTSD), and associated with poor clinical outcomes. Few studies have examined sleep quantitative electroencephalography (qEEG), a technique able to detect subtle differences that polysomnography does not capture. We hypothesized that greater high-frequency qEEG would reflect 'hyperarousal' in combat veterans with PTSD (n = 16) compared to veterans without PTSD (n = 13). EEG power in traditional EEG frequency bands was computed for artifact-free sleep epochs across an entire night. Correlations were performed between qEEG and ratings of PTSD symptoms and combat exposure. The groups did not differ significantly in whole-night qEEG measures for either rapid eye movement (REM) or non-REM (NREM) sleep. Non-significant medium effect sizes suggest less REM beta (opposite to our hypothesis), less REM and NREM sigma and more NREM gamma in combat veterans with PTSD. Positive correlations were found between combat exposure and NREM beta (PTSD group only), and REM and NREM sigma (non-PTSD group only). Results did not support global hyperarousal in PTSD as indexed by increased beta qEEG activity. The correlation of sigma activity with combat exposure in those without PTSD and the non-significant trend towards less sigma activity during both REM and NREM sleep in combat veterans with PTSD suggests that differential information processing during sleep may characterize combat-exposed military veterans with and without PTSD.

Egner, T., Strawson, E., & Gruzelier, J. H. (2002). EEG signature and phenomenology of alpha/theta neurofeedback training versus mock feedback. ***Applied Psychophysiology & Biofeedback*****, 27(4), 261-270.** Alpha/theta (a/t) neurofeedback training has in the past successfully been used as a complementary therapeutic relaxation technique in the treatment of alcoholism. In spite of positive clinical outcomes, doubts have been cast on the protocol's specificity when compared to alternative relaxation regimes. This study investigated the basic tenet underlying the a/t training rationale, that accurate a/t feedback representation facilitates the generation of these frequency components. Two groups of healthy volunteers were randomly assigned to either (a) real contingent a/t feedback training or (b) a noncontingent mock feedback control condition. The groups were compared on measures of theta/alpha (t/a) ratios within and across training sessions, as well as activational self-report scales after each session. The contingent a/t feedback group displayed significant within-session t/a ratio increments not evident in the mock control group, as well as higher overall t/a ratios in some but not all of the training sessions. No differences were found between the groups in terms of subjective activational phenomenology, in that both groups reported significantly lower levels of activation after training sessions. The data demonstrate that irrespective of considerations of clinical relevance, accurate a/t neurofeedback effectively facilitates production of higher within-session t/a ratios than do noncontingent feedback relaxation.

Garrett, B. L., & Silver, M. P. (1976). The use of EMG and alpha biofeedback to relieve test anxiety in college students. Chapter in I. Wickramasekera (Ed.), Biofeedback, Behavior Therapy, and Hypnosis. Chicago: Nelson-Hall. (No abstract available.)

Gadea, M., Aliño, M., Hidalgo, V., Espert, R., & Salvador, A. (2020). Effects of a single session of SMR neurofeedback training on anxiety and cortisol levels. Neurophysiologie clinique = Clinical neurophysiology, 50(3), 167–173. Objectives: According to some studies, a putatively calming effect of EEG neurofeedback training could be useful as a therapeutic tool in psychiatric practice. With the aim of elucidating this possibility, we tested the efficacy of a single session of ↑sensorimotor (SMR)/↓theta neurofeedback training for mood improvement in 32 healthy men, taking into account trainability, independence and interpretability of the results. Methods: A pre-post design, with the following dependent variables, was applied: (i) psychometric measures of mood with regards to anxiety, depression, and anger (Profile of Mood State, POMS, and State Trait Anxiety Inventory, STAI); (ii) biological measures (salivary levels of cortisol); (iii) neurophysiological measures (EEG frequency band power analysis). In accordance with general recommendations for research in neurofeedback, a control group receiving sham neurofeedback was included. Results: Anxiety levels decreased after the real neurofeedback and increased after the sham neurofeedback ($P<0.01$, size effect 0.9 for comparison between groups). Cortisol decreased after the experiment in both groups, though with significantly more pronounced effects in the desired direction after the real neurofeedback ($P<0.04$; size effect 0.7). The group receiving real neurofeedback significantly enhanced their SMR band ($P<0.004$; size effect 0.88), without changes in the theta band. The group receiving sham neurofeedback did not show any EEG changes. Conclusions: The improvement observed in anxiety was greater in the experimental group than in the sham group, confirmed by both subjective (psychometric) measures and objective (biological) measures. This was demonstrated to be associated with the real neurofeedback, though a nonspecific (placebo) effect likely also contributed.

Gapen, M., van der Kolk, B. A., Hamlin, E., Hirshberg, L., Suvak, M., & Spinazzola, J. (2016). A Pilot Study of Neurofeedback for Chronic PTSD. Applied psychophysiology and biofeedback, 41(3), 251–261. EEG Biofeedback (also known as neurofeedback) has been in use as a clinical intervention for well over 30 years; however, it has made very little impact on clinical care. One reason for this has been the difficulty in designing research to measure clinical change in the real world. While substantial evidence exists for its efficacy in treating attention deficit/hyperactivity disorder, relatively little evidence exists for its utility in other disorders including posttraumatic stress disorder (PTSD). The current study represents a "proof-of-concept" pilot for the use of neurofeedback with multiply-traumatized individuals with treatment-resistant PTSD. Participants completed 40 sessions of neurofeedback training two times per week with sensors randomly assigned (by the study coordinator, who was not blind to condition) to sensor placements of either T4-P4 or T3-T4. We found that neurofeedback significantly reduced PTSD symptoms (Davidson Trauma Scale scores averaged 69.14 at baseline to 49.26 at termination), and preceded gains in affect regulation (Inventory of Altered Self-Capacities-Affect Dysregulation scores averaged 23.63 at baseline to 17.20 at termination). We discuss a roadmap for future research.

Gruzelier, JH., Thompson, T., Redding, E., Brandt, R. & Steffert, T. (2014). Application of alpha/theta neurofeedback and heart rate variability training to young contemporary dancers: State anxiety and creativity. Int J Psychophysiol Jul:93(1). 105-111. As one in a series on the impact of EEG-neurofeedback in the performing arts, we set out to replicate a previous dance study in which alpha/theta (A/T) neurofeedback and heart rate variability (HRV) biofeedback enhanced performance in competitive ballroom dancers compared with controls. First year contemporary dance conservatoire students were randomised to the same two psychophysiological interventions or a choreology instruction comparison group or a no-training control group. While there was demonstrable neurofeedback learning, there was no impact of the three interventions on dance performance as assessed by four experts. However, HRV training reduced anxiety and the reduction correlated with improved technique and artistry in performance; the anxiety scale items focussed on autonomic functions, especially cardiovascular activity. In line with the putative impact of hypnogogic training on creativity A/T training increased cognitive creativity with the test of unusual uses, but not insight problems. Methodological and theoretical implications are considered.

Hammond, D. C. (2005). Neurofeedback with anxiety and affective disorders. ***Child & Adolescent Psychiatric Clinics of North America*****, 14(1), 105-123.** A robust body of neurophysiologic research is reviewed on functional brain abnormalities associated with depression, anxiety, and obsessive-compulsive disorder. A review of more recent research finds that pharmacologic treatment may not be as effective as previously believed. A more recent neuroscience technology, electroencephalographic (EEG) biofeedback (neurofeedback), seems to hold promise as a methodology for retraining abnormal brain wave patterns. It has been associated with minimal side effects and is less invasive than other methods for addressing biologic brain disorders. Literature is reviewed on the use of neurofeedback with anxiety disorders, including posttraumatic stress disorder and obsessive-compulsive disorder, and with depression. Case examples are provided.

Hammond, D. C. (2003). QEEG-guided neurofeedback in the treatment of obsessive compulsive disorder. ***Journal of Neurotherapy*****, 7(2), 25-52.** Introduction. Blinded, placebo-controlled research (e.g., Sterman, 2000) has documented the ability of brainwave biofeedback to recondition brain wave patterns. Neurofeedback has been used successfully with uncontrolled epilepsy, ADD/ADHD, learning disabilities, anxiety, and head injuries. However, nothing has been published on the treatment of obsessive-compulsive disorder (OCD) with neurofeedback.
Method. Quantitative EEGs were gathered on two consecutive OCD patients who sought treatment. This assessment guided protocol selection for subsequent neurofeedback training. Results. Scores on the Yale-Brown Obsessive-Compulsive Scale and the Padua Inventory normalized following treatment. An MMPI was administered pre-post to one patient, and she showed dramatic improvements not only in OCD symptoms, but also in depression, anxiety, somatic symptoms, and in becoming extroverted rather than introverted and withdrawn. Discussion. In follow-ups of the two cases at 15 and 13 months after completion of treatment, both patients were maintaining improvements in OCD symptoms as measured by the Padua Inventory and as externally validated through contacts with family members. Since research has found that pharmacologic treatment of OCD produces only very modest improvements and behavior therapy utilizing exposure with response prevention is experienced as quite unpleasant and results in treatment dropouts, neurofeedback appears to have potential as a new treatment modality.

Hardt, J. V., & Kamiya, J. (1978). Anxiety change through electroencephalographic alpha feedback seen only in high anxiety subjects. ***Science*****, 201, 79-81. S**ubjects who were either high or low in trait anxiety used alpha feedback to increase and to decrease their electroencephalographic alpha activity. The alpha changes were tightly linked to anxiety changes, but only in high anxiety subjects (for whom anxiety was reduced in proportion to alpha increases, and was increased in proportion to alpha suppression). Low trait-anxiety subjects were superior at both enhancement and suppression training, but their alpha changes were not related to anxiety changes. In both groups, anxiety changes were generally unrelated to either resting levels or changes in frontalis electromyograms and respiration rate. These results suggest that long-term alpha feedback training (at least 5 hours) may be useful in anxiety therapy.

Harlé KM, Simmons AN, Norman SB, Spadoni AD. Neural affective mechanisms associated with treatment responsiveness in veterans with PTSD and comorbid alcohol use disorder. Psychiatry Res Neuroimaging. 2020 Aug 20;305:111172. Post-traumatic stress disorder (PTSD) is associated with neuro-physiological abnormalities reflecting increased anticipatory anxiety and reactivity to traumatic cues. It remains unclear whether neural mechanisms associated with PTSD treatment responsiveness, i.e. hyperactivation of the affective salience network in the brain, extend to a comorbid PTSD and substance use disorder population. Thirty-one Veterans with PTSD and co-occurring alcohol use disorder (AUD) were randomly assigned to either prolonged exposure or a non-exposure based treatment. They completed an affective anticipation task while undergoing fMRI, immediately prior and after completing treatment. After controlling for type and length of treatment, larger reduction of PTSD symptoms was associated with decreased anticipatory activation to negative trauma-related cues in the right pre-Supplementary Motor Area (pre-SMA), a region associated with emotion regulation. Smaller reduction in PTSD severity was associated with enhanced anticipatory activation to those cues within the right para-hippocampal region, an affective processing region. Our findings suggest that post-treatment reductions in anticipatory reactivity to trauma-related cues in the pre-SMA and para-hippocampal area are associated with larger PTSD symptom reduction in individuals with co-occurring PTSD and AUD. These results may offer neurofeedback training targets as an alternative to or enhancement of other PTSD treatment modalities in this population.

Holmes, D. S., Burish, T. G., & Frost, R. O. (1980). Effects of instructions and biofeedback in EEG-alpha production and the effects of EEG-alpha biofeedback training for controlled arousal in a subsequent stressful situation. *Journal of Research in Personality*, 14(2), 212-223. (No abstract available.)

Hou, Y., Zhang, S., Li, N., Huang, Z., Wang, L., & Wang, Y. (2021). Neurofeedback training improves anxiety trait and depressive symptom in GAD. Brain and behavior, 11(3), e02024. Objective: To investigate the effectiveness of alpha activity neurofeedback training over the parietal lobe in GAD patients. Methods: Twenty-six female patients who had been diagnosed as GAD according to the Diagnostic and Statistical Manual of Mental Disorders (5th edition, DSM-V) criteria were included in this study. Patients were randomized into two groups: the left parietal lobe training group (LPL group, n = 13) and the right parietal lobe training group (RPL group, n = 13), and then received ten 40-minute alpha training sessions in the relevant area. Evaluations included severity of anxiety (by State-Trait Anxiety Inventory, STAI) and depression (by Beck Depression Inventory, BDI-II) after the fifth training session and the last training session. Results: The scores of STAI-S decreased significantly two weeks after the fifth training session in both groups (LPL group: from 47.15 ± 10.65 to 38.69 ± 8.78, $p<.05$; RPL group: from 44.92 ± 12.37 to 37.31 ± 6.41, $p < .05$) and decreased further at the four weeks' time point after the last training session (LPL group: 35.15 ± 9.24; RPL group: 29.85 ± 6.18). Compared with baseline, the scores of STAI-T, BDI-II and ISI decrease at two weeks, no significant difference found between LPL group and RPL group. The scores of STAI-T, BDI-II and ISI decreased at four weeks when compared with two weeks, and no significant difference found between LPL group and RPL group.

Huang,-Storms, L., Bodenhamer-Davis, E., Davis, R., & Dunn, J. (2006). QEEG-guided neurofeedback for children with histories of abuse and neglect: Neurodevelopmental rationale and pilot study. *Journal of Neurotherapy*, 10(4), 3-16. Background. Poor self-regulation of arousal is central to the behavioral difficulties experienced by children with traumatic caretaker attachment histories. EEG biofeedback teaches children to self-regulate brain rhythmicity, which may in turn affect global improvements in the areas of attention, aggression, impulse control, and trust formation. Research literature reports successful use of neurofeedback for children with ADHD, autism, asthma, stroke, and migraine. This study extends current research by investigating the effectiveness of neurofeedback in reducing behavioral problems commonly observed in abused/neglected children. Methods. Treatment records of twenty adopted children with histories of removal from their biological home by Child Protective Services were obtained from a private neurofeedback practice. All of the children were assessed prior to treatment using the Child Behavior Checklist (CBCL) and the Test of Variables of Attention (TOVA) and again after 30 sessions of individualized, qEEG-guided neurofeedback. Results. T-test analysis of pre- and post-scores on the CBCL showed significant changes in the areas of externalizing problems, internalizing problems, social problems, aggressive behavior, thought problems, delinquent behavior, anxiety/depression, and attention problems ($p < .05$). TOVA omission error, commission error, and variability scores also improved significantly following neurofeedback training ($p < .05$). Some pre-treatment qEEG patterns common to this group of children were identified. Conclusions. The CBCL and TOVA score improvements observed in this study indicate that neurofeedback is effective in reducing behavioral, emotional, social, and cognitive problems in children with histories of neglect and/or abuse.

Kerson, C., Sherman, R.A., Kozlowski, G.P. (2009). Alpha suppression and symmetry training for generalized anxiety disorders. Journal of Neurotherapy,13(3) 146-158. Alpha suppression and symmetry training for generalized anxiety symptoms. Journal of Neurotherapy 13(3), 146 – 155. Introduction. Twenty-eight anxious adults were assessed for frontal lobe alpha asymmetry, a brain state associated with depression and anxiety. Fifteen of the 28 exhibited significant asymmetry and 12 agreed to participate in a biofeedback program addressed at reducing frontal alpha asymmetry. Method. The program consisted of earlobe temperature biofeedback (ETB) and two forms of neurofeedback, alpha suppression and alpha symmetry training. Individuals were instructed to warm their right earlobe for six sessions, and half succeeded, though success was not required to advance to the next stage of training. For subsequent EEG training, two anterior sites were selected on the basis of poor alpha coherence. Individuals were trained to reduce alpha magnitude at these sites by 10% for 30 min or more, which took from 6 to 16 sessions to achieve. Once successful with alpha suppression, individuals were trained to improve alpha symmetry between the sites by 15% for 30 min or more. Results. This feat took 8 to 32 sessions to achieve, and

eventually all eight individuals were able to reduce alpha asymmetry. The State–Trait Anxiety Inventory (STAI) was used to measured anxiety levels after each training type and both state and trait scores significantly improved by a 6-month follow-up. Conclusion. Participants also completed a daily shortened version of the STAI, which indicated that anxiety improved after neurofeedback but not after ETB.

Kleutsch, RC., Ros, T., Theberge, J., Frewen, PA., Calhoun, VD., Schmal, C., Jetly, R. & Lanius, RA. (2014). Plastic modulation of PTSD resting state networks and subjective wellbeing by EEG neurofeedback. Acta Psychiatr Scand Aug:130(2). 123-36. OBJECTIVE: Electroencephalographic (EEG) neurofeedback training has been shown to produce plastic modulations in salience network and default mode network functional connectivity in healthy individuals. In this study, we investigated whether a single session of neurofeedback training aimed at the voluntary reduction of alpha rhythm (8-12 Hz) amplitude would be related to differences in EEG network oscillations, functional MRI (fMRI) connectivity, and subjective measures of state anxiety and arousal in a group of individuals with post-traumatic stress disorder (PTSD). METHOD: Twenty-one individuals with PTSD related to childhood abuse underwent 30 min of EEG neurofeedback training preceded and followed by a resting-state fMRI scan. RESULTS: Alpha desynchronizing neurofeedback was associated with decreased alpha amplitude during training, followed by a significant increase ('rebound') in resting-state alpha synchronization. This rebound was linked to increased calmness, greater salience network connectivity with the right insula, and enhanced default mode network connectivity with bilateral posterior cingulate, right middle frontal gyrus, and left medial prefrontal cortex.
CONCLUSION: Our study represents a first step in elucidating the potential neurobehavioural mechanisms mediating the effects of neurofeedback treatment on regulatory systems in PTSD. Moreover, it documents for the first time a spontaneous EEG 'rebound' after neurofeedback, pointing to homeostatic/compensatory mechanisms operating in the brain.

KopŤivová J, Congedo M, Raszka M, Praško J, Brunovský M, HoráČek J. (2013). Prediction of treatment response and the effect of independent component neurofeedback in obsessive-compulsive disorder: a randomized, sham-controlled, double-blind study. Neuropsychobiology. 2013;67(4):210-23. doi: 10.1159/000347087. Epub 2013 Apr 27. Aims: The goal of this study was to assess the effect of independent component neurofeedback (NFB) on EEG and clinical symptoms in patients with obsessive-compulsive disorder (OCD). Subsequently, we explored predictors of treatment response and EEG correlates of clinical symptoms. Methods: In a randomized, double-blind, parallel design, 20 inpatients with OCD underwent 25 sessions of NFB or sham feedback (SFB). NFB aimed at reducing EEG activity in an independent component previously reported abnormal in this diagnosis. Resting-state EEG recorded before and after the treatment was analyzed to assess its posttreatment changes, relationships with clinical symptoms and treatment response. Results: Overall, clinical improvement in OCD patients was not accompanied by EEG change as assessed by standardized low-resolution electromagnetic tomography and normative independent component analysis. Pre- to posttreatment comparison of the trained component and frequency did not yield significant results; however, in the NFB group, the nominal values at the downtrained frequency were lower after treatment. The NFB group showed significantly higher percentage reduction of compulsions compared to the SFB group ($p = 0.015$). Pretreatment higher amount of delta (1-6 Hz) and low alpha oscillations as well as a lower amount of high beta activity predicted a worse treatment outcome. Source localization of these delta and high beta oscillations corresponded with previous EEG resting-state findings in OCD patients compared to healthy controls. Conclusion: Independent component NFB in OCD proved useful in percentage improvement of compulsions. Based on our correlation analyses, we hypothesize that we targeted a network related to treatment resistance.

Kreifelts, B., Weigel, L., Ethofer, T., Brück, C., Erb, M., & Wildgruber, D. (2019). Cerebral resting state markers of biased perception in social anxiety. Brain structure & function, 224(2), 759–777. Social anxiety (SA) comprises a multitude of persistent fears around the central element of dreaded negative evaluation and exclusion. This very common anxiety is spectrally distributed among the general population and associated with social perception biases deemed causal in its maintenance. Here, we investigated cerebral resting state markers linking SA and biased social perception. To this end, resting state functional connectivity (RSFC) was assessed as the neurobiological marker in a study population with greatly varying SA using fMRI in the first step of the experiment. One month later the impact of unattended laughter-exemplifying social threat-on a face rating task was evaluated as a measure of biased social perception.

Applying a dimensional approach, SA-related cognitive biases tied to the valence, dominance and arousal of the threat signal and their underlying RSFC patterns among central nodes of the cerebral emotion, voice and face processing networks were identified. In particular, the connectivity patterns between the amygdalae and the right temporal voice area met all criteria for a cerebral mediation of the association between SA and the laughter valence-related interpretation bias. Thus, beyond this identification of non-state-dependent cerebral markers of biased perception in SA, this study highlights both a starting point and targets for future research on the causal relationships between cerebral connectivity patterns, SA and biased perception, potentially via neurofeedback methods.

Kummar, A. S., Correia, H., & Fujiyama, H. (2019). A Brief Review of the EEG Literature on Mindfulness and Fear Extinction and its Potential Implications for Posttraumatic Stress Symptoms (PTSS). Brain sciences, 9(10), 258. Neuroimaging studies in the area of mindfulness research have provided preliminary support for the idea of fear extinction as a plausible underlying mechanism through which mindfulness exerts its positive benefits. Whilst brain regions identified in the fear extinction network are typically found at a subcortical level, studies have also demonstrated the feasibility of cortical measures of the brain, such as electroencephalogram (EEG), in implying subcortical activations of the fear extinction network. Such EEG studies have also found evidence of a relationship between brain reactivity to unpleasant stimuli (i.e., fear extinction) and severity of posttraumatic stress symptoms (PTSS). Therefore, the present paper seeks to briefly review the parallel findings between the neurophysiological literature of mindfulness and fear extinction (particularly that yielded by EEG measures), and discusses the implications of this for fear-based psychopathologies, such as trauma, and finally presents suggestions for future studies. This paper also discusses the clinical value in integrating EEG in psychological treatment for trauma, as it holds the unique potential to detect neuromarkers, which may enable earlier diagnoses, and can also provide neurofeedback over the course of treatment.

Leem, J., Cheong, M. J., Yoon, S. H., Kim, H., Jo, H. G., Lee, H., Kim, J., Kim, H. Y., Kim, G. W., & Kang, H. W. (2020). Neurofeedback self-regulating training in patients with Post traumatic stress disorder: A randomized controlled trial study protocol. Integrative medicine research, 9(4), 100464. Background: Post-traumatic stress disorder (PTSD) has become an important public health problem. However, the conventional therapeutic strategy, including pharmacotherapy and cognitive behavioral therapy, has limitations. Neurofeedback is a technique that utilizes electroencephalography (EEG) signaling to monitor human physiological functions and is widely used to treat patients with PTSD. The purpose of our study is to assess the efficacy and safety level of neurofeedback treatment in patients with PTSD using quantitative EEG. Methods: This is a randomized, waitlist-controlled, assessor-blinded, clinical trial. Forty-six patients with PTSD will be randomly assigned at a 1:1 ratio into two groups. The participants in the treatment group will receive neurofeedback treatment for 50 min, twice a week, for 8 weeks (16 sessions). Quantitative EEG will be utilized to monitor the physiological functions and brain waves of the participants. A four-week follow-up period is planned. The participants in the control group will wait for 12 weeks. The primary outcome is the Korean version of PTSD Checklist-5 (PCL-5-K) score. The PCL-5-K scores on week 8 will be compared between the two groups. Anxiety, depression, insomnia, emotions, EEG, quality-of-life, and safety level will be assessed as secondary outcomes. Discussion: This trial will describe a clinical research methodology for neurofeedback in patients with PTSD. The numerous subjective and objective secondary outcomes add to the value of this trial's results. It will also suggest a therapeutic strategy for utilizing quantitative EEG in patients with PTSD. Our trial will provide basic evidence for the management of PTSD via an integrative treatment.

Lin IM, Chen TC, Lin HY, Wang SY, Sung JL, Yen CW. Electroencephalogram patterns in patients comorbid with major depressive disorder and anxiety symptoms: Proposing a hypothesis based on hypercortical arousal and not frontal or parietal alpha asymmetry. J Affect Disord. 2021. Background: Major depressive disorder (MDD) is often comorbid with anxiety disorders or symptoms. Brain hyperactivity, frontal alpha asymmetry (FAA), and parietal alpha asymmetry (PAA) have been considered as trait markers in patients with MDD. This study investigated the electroencephalogram (EEG) patterns among patients with MDD comorbid with anxiety symptoms. Methods: One hundred and thirty-five patients with MDD comorbid with anxiety (MDD group) and 135 healthy controls (HC group) were analyzed. The Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI) were completed, and 19 EEG channels were measured during the resting state, depressive recall and recovery tasks, and happiness recall and recovery tasks. FAA and PAA were computed by log (F4 alpha)-log (F3 alpha) and log (P4 alpha)-log (P3 alpha). Results: The FAA and PAA indices

between the two groups showed no significant differences; however, compared with the HC group, the MDD group had lower total delta and theta values, and higher total beta, low beta, and high beta values in the resting state. The total beta value positively correlated with the BDI-II and BAI scores in the MDD group. Limitations: Most patients had anxious MDD and taking prescriptions, antidepressants or benzodiazepine may affect EEG patterns. Conclusion: Compared with HCs, patients with MDD comorbid with anxiety had a higher beta activity in the entire brain region, supporting the role of brain hyperactivity, instead of FAA or PAA, as a trait marker in these patients. A neurofeedback protocol could be developed in future based on the brain hyperactivity findings.

Linhartová, P., Látalová, A., Kóša, B., Kašpárek, T., Schmahl, C., & Paret, C. (2019). fMRI neurofeedback in emotion regulation: A literature review. NeuroImage, 193, 75–92. Objectives: Emotion regulation is one of the most prevalent objectives for real-time fMRI neurofeedback (rt-fMRI-NF) studies. The existing studies differ in a number of methodological parameters. This study provides a literature review of the main parameters and results of studies using rt-fMRI-NF for emotion regulation enhancement. Method: A search of the Web of Science database up through November 8, 2018, identified 144 articles written in English, 89 of which were excluded as irrelevant for this study. The remaining 51 original studies and four secondary analyses of previously published original studies were included in the literature review. The selection of target brain areas, target populations, emotion regulation protocols, NF presentation, control group types, and emotion regulation instructions were examined in relation to achieved brain regulation and changes in cognitive or clinical outcomes. Study results were evaluated in terms of their statistical robustness. Results: The results show that healthy people are able to regulate their brain activity in the presence of rt-fMRI-NF from various brain regions related to emotion regulation, including the amygdala, anterior insula, and anterior cingulate cortex. The regulation of brain activity using rt-fMRI-NF from prefrontal-limbic connectivity or from individually navigated brain areas is feasible as well. Most studies that used a control group show that rt-fMRI-NF actually induces some effects on brain regulation, cognitive variables, and clinical variables. Generally, the success of ROI regulation during NF training is related to the combination of target brain region, the type of emotion regulation task, and the population undergoing the training. In terms of patient groups, the strongest support for the beneficial effects of rt-fMRI-NF has been shown in increased positive emotion experiencing in patients with depression and in decreased anxiety in patients with anxiety disorders. Symptom reduction following NF training has been also reported in patients with PTSD, BPD, and schizophrenia, but direct comparisons with control groups in these studies makes it impossible to evaluate the added value of NF. Studies often do not report all the relevant analyses for evaluating NF success and many studies lack statistical robustness. Conclusions: Overall, rt-fMRI-NF seems a promising tool for emotion regulation enhancement with the potential to induce long-term symptom reduction in patients with various mental disorders. Preplanning of statistical analyses, careful interpretations of the results, and evaluations of the NF effect on symptom reduction in patient groups is recommended.

Lipp, A., & Cohen Kadosh, K. (2020). Training the anxious brain: using fMRI-based neurofeedback to change brain activity in adolescence. Developmental medicine and child neurology, 62(11), 1239–1244. Anxiety disorders are a leading cause of morbidity and entail a lot of costs. Adolescence is characterized by social fears and poor emotion regulation abilities which together increase the likelihood of the emergence of anxiety disorders. This emotion dysregulation is potentially caused by the emotion regulating brain areas, such as the prefrontal cortex and temporal cortex, that are still undergoing developmental changes throughout late adolescence. Recently, new approaches have used functional magnetic resonance imaging-based neurofeedback to help participants gain control over emotion regulation brain networks by receiving real-time feedback on their brain activity and to use effective emotion regulation abilities. In this review, we provide an overview of the developmental changes in the brain and the corresponding behavioural changes, and explore how these can be influenced during adolescence using neurofeedback. We conclude that recent studies show promising results that children and adolescents can self-regulate emotion regulation brain networks thereby supporting the development of effective emotion regulation abilities. WHAT THIS PAPER ADDS: Functional magnetic resonance imaging-based neurofeedback can be used for brain self-regulation in development. The emotion regulation networks play a key role in treating social anxiety with neurofeedback.

Lisk, S., Kadosh, K. C., Zich, C., Haller, S. P., & Lau, J. Y. (2020). Training negative connectivity patterns between the dorsolateral prefrontal cortex and amygdala through fMRI-based neurofeedback to target adolescent socially-avoidant behaviour. Behaviour research and therapy, 135, 103760. Social anxiety is prevalent in adolescence. Given its role in maintaining

fears, reducing social avoidance through cognitive reappraisal may help attenuate social anxiety. We used fMRI-based neurofeedback (NF) to increase 'adaptive' patterns of negative connectivity between the dorsolateral prefrontal cortex (DLPFC) and the amygdala to change reappraisal ability, and alter social avoidance and approach behaviours in adolescents. Twenty-seven female participants aged 13-17 years with varying social anxiety levels completed a fMRI-based NF training task where they practiced cognitive reappraisal strategies, whilst receiving real-time feedback of DLPFC-amygdala connectivity. All participants completed measures of cognitive reappraisal and social approach-avoidance behaviour before and after NF training. Avoidance of happy faces was associated with greater social anxiety pre-training. Participants who were unable to acquire a more negative pattern of connectivity through NF training displayed significantly greater avoidance of happy faces at post-training compared to pre-training. These 'maladaptive' participants also reported significant decreases in re-appraisal ability from pre to post-training. In contrast, those who were able to acquire a more 'adaptive' connectivity pattern did not show these changes in social avoidance and re-appraisal. Future research could consider using strategies to improve the capacity of NF training to boost youth social-approach behaviour.

Lorenzetti, V., Melo, B., Basílio, R., Suo, C., Yücel, M., Tierra-Criollo, C. J., & Moll, J. (2018). Emotion Regulation Using Virtual Environments and Real-Time fMRI Neurofeedback. Frontiers in neurology, 9, 390. Neurofeedback (NFB) enables the voluntary regulation of brain activity, with promising applications to enhance and recover emotion and cognitive processes, and their underlying neurobiology. It remains unclear whether NFB can be used to aid and sustain complex emotions, with ecological validity implications. We provide a technical proof of concept of a novel real-time functional magnetic resonance imaging (rtfMRI) NFB procedure. Using rtfMRI-NFB, we enabled participants to voluntarily enhance their own neural activity while they experienced complex emotions. The rtfMRI-NFB software (FRIEND Engine) was adapted to provide a virtual environment as brain computer interface (BCI) and musical excerpts to induce two emotions (tenderness and anguish), aided by participants' preferred personalized strategies to maximize the intensity of these emotions. Eight participants from two experimental sites performed rtfMRI-NFB on two consecutive days in a counterbalanced design. On one day, rtfMRI-NFB was delivered to participants using a region of interest (ROI) method, while on the other day using a support vector machine (SVM) classifier. Our multimodal VR/NFB approach was technically feasible and robust as a method for real-time measurement of the neural correlates of complex emotional states and their voluntary modulation. Guided by the color changes of the virtual environment BCI during rtfMRI-NFB, participants successfully increased in real time, the activity of the septo-hypothalamic area and the amygdala during the ROI based rtfMRI-NFB, and successfully evoked distributed patterns of brain activity classified as tenderness and anguish during SVM-based rtfMRI-NFB. Offline fMRI analyses confirmed that during tenderness rtfMRI-NFB conditions, participants recruited the septo-hypothalamic area and other regions ascribed to social affiliative emotions (medial frontal / temporal pole and precuneus). During anguish rtfMRI-NFB conditions, participants recruited the amygdala and other dorsolateral prefrontal and additional regions associated with negative affect. These findings were robust and were demonstrable at the individual subject level, and were reflected in self-reported emotion intensity during rtfMRI-NFB, being observed with both ROI and SVM methods and across the two sites. Our multimodal VR/rtfMRI-NFB protocol provides an engaging tool for brain-based interventions to enhance emotional states in healthy subjects and may find applications in clinical conditions associated with anxiety, stress and impaired empathy among others.

Mennella, R., Patron, E., & Palomba, D. (2017). Frontal alpha asymmetry neurofeedback for the reduction of negative affect and anxiety. Behaviour research and therapy, 92, 32–40. Frontal alpha asymmetry has been proposed to underlie the balance between approach and withdrawal motivation associated to each individual's affective style. Neurofeedback of EEG frontal alpha asymmetry represents a promising tool to reduce negative affect, although its specific effects on left/right frontal activity and approach/withdrawal motivation are still unclear. The present study employed a neurofeedback training to increase frontal alpha asymmetry (right - left), in order to evaluate discrete changes in alpha power at left and right sites, as well as in positive and negative affect, anxiety and depression. Thirty-two right-handed females were randomly assigned to receive either the neurofeedback on frontal alpha asymmetry, or an active control training (N = 16 in each group). The asymmetry group showed an increase in alpha asymmetry driven by higher alpha at the right site ($p < 0.001$), as well as a coherent reduction in both negative affect and anxiety symptoms ($ps < 0.05$), from pre-to post-training. No training-specific modulation emerged for positive affect and depressive symptoms. These findings provide a strong rationale for the use of frontal alpha asymmetry neurofeedback for the reduction of negative affect and anxiety in clinical settings.

Mills, G. K., & Solyom, L. (1974). Biofeedback of EEG alpha in the treatment of obsessive ruminations: An exploration. *Journal of Behaviour Therapy & Experimental Psychiatry*, 5, 37-41. The enhancement of EEG alpha through various meditative techniques and biofeedback has been shown to correlate with alterations in mental as well as muscular activity towards a state of relaxation. We thought that such mental relaxation might be reciprocally inhibitory to ruminative activity characteristic of the obsessive neurotic. Five ruminating obsessives were given 7–20 biofeedback training sessions to learn control of EEG alpha. Results indicate that (1) some obsessives can learn EEG control; (2) special augmented instructions seem no better than standard, minimal instructions in aiding *S*s to produce alpha; (3) subjective states during alpha are reported as relaxed, daydreaming and not thinking; and (4) although difficult to generalize beyond the feedback situation, virtually no ruminations occur during alpha regardless of the amount of alpha produced. Further study is indicated before a treatment program can be considered.

Misaki M, Phillips R, Zotev V, Wong CK, Wurfel BE, Krueger F, Feldner M, Bodurka J. Brain activity mediators of PTSD symptom reduction during real-time fMRI amygdala neurofeedback emotional training. Neuroimage Clin. 2019;24:102047. Self-regulation of brain activation with real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf) is emerging as a promising treatment for psychiatric disorders. The association between the regulation and symptom reduction, however, has not been consistent, and the mechanisms underlying the symptom reduction remain poorly understood. The present study investigated brain activity mediators of the amygdala rtfMRI-nf training effect on combat veterans' PTSD symptom reduction. The training was designed to increase a neurofeedback signal either from the left amygdala (experimental group; EG) or from a control region not implicated in emotion regulation (control group; CG) during positive autobiographical memory recall. We employed a structural equation model mapping analysis to identify brain regions that mediated the effects of the rtfMRI-nf training on PTSD symptoms. Symptom reduction was mediated by low activation in the dorsomedial prefrontal cortex (DMPFC) and the middle cingulate cortex. There was a trend toward less activation in these regions for the EG compared to the CG. Low activation in the precuneus, the right superior parietal, the right insula, and the right cerebellum also mediated symptom reduction while their effects were moderated by the neurofeedback signal; a higher signal was linked to less effect on symptom reduction. This moderation was not specific to the EG. MDD comorbidity was associated with high DMPFC activation, which resulted in less effective regulation of the feedback signal. These results indicated that symptom reduction due to the neurofeedback training was not specifically mediated by the neurofeedback target activity, but broad regions were involved in the process.

Misaki, M., Phillips, R., Zotev, V., Wong, C. K., Wurfel, B. E., Krueger, F., Feldner, M., & Bodurka, J. (2018). Real-time fMRI amygdala neurofeedback positive emotional training normalized resting-state functional connectivity in combat veterans with and without PTSD: a connectome-wide investigation. NeuroImage. Clinical, 20, 543–555.

Self-regulation of brain activation using real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf) is an emerging approach for treating mood and anxiety disorders. The effect of neurofeedback training on resting-state functional connectivity warrants investigation as changes in spontaneous brain activation could reflect the association between sustained symptom relief and brain alteration. We investigated the effect of amygdala-focused rtfMRI-nf training on resting-state functional connectivity in combat veterans with and without posttraumatic stress disorder (PTSD) who were trained to increase a feedback signal reflecting left amygdala activity while recalling positive autobiographical memories (Zotev et al., 2018). The analysis was performed in three stages: i) first, we investigated the connectivity in the left amygdala region; ii) next, we focused on the abnormal resting-state functional connectivity identified in our previous analysis of this data (Misaki et al., 2018); and iii) finally, we performed a novel data-driven longitudinal connectome-wide analysis. We introduced a longitudinal multivariate distance matrix regression (MDMR) analysis to comprehensively examine neurofeedback training effects beyond those associated with abnormal baseline connectivity. These comprehensive exploratory analyses suggested that abnormal resting-state connectivity for combat veterans with PTSD was partly normalized after the training. This included hypoconnectivities between the left amygdala and the left ventrolateral prefrontal cortex (vlPFC) and between the supplementary motor area (SMA) and the dorsal anterior cingulate cortex (dACC). The increase of SMA-dACC connectivity was associated with PTSD symptom reduction. Longitudinal MDMR analysis found a connectivity change between the precuneus and the left superior frontal cortex. The connectivity increase was associated with a decrease in hyperarousal symptoms. The abnormal connectivity for combat veterans without PTSD - such as hypoconnectivity in the precuneus with a superior frontal region and

hyperconnectivity in the posterior insula with several regions - could also be normalized after the training. These results suggested that the rtfMRI-nf training effect was not limited to a feedback target region and symptom relief could be mediated by brain modulation in several regions other than in a feedback target area. While further confirmatory research is needed, the results may provide valuable insight into treatment effects on the whole brain resting-state connectivity.

Moore, N. C. (2000). A review of EEG biofeedback treatment of anxiety disorders. ***Clinical Electroencephalography*****, 31(1), 1-6.** Alpha, theta and alpha-theta enhancements are effective treatments of the anxiety disorders (Table 1). Alpha suppression is also effective, but less so (Table 2). Perceived success in carrying out the task plays an important role in clinical improvement. Research is needed to find out how much more effective they are than placebo, and which variables are important for efficacy. Variables needing study are: duration of treatment, type and severity of anxiety, number and type of EEG waveforms used, pretreatment with other kinds of feedback, position and number of electrodes, and presence of concomitant medication.

Morgenroth, E., Saviola, F., Gilleen, J., Allen, B., Lührs, M., W Eysenck, M., & Allen, P. (2020). Using connectivity-based real-time fMRI neurofeedback to modulate attentional and resting state networks in people with high trait anxiety. NeuroImage. Clinical, 25, 102191. High levels of trait anxiety are associated with impaired attentional control, changes in brain activity during attentional control tasks and altered network resting state functional connectivity (RSFC). Specifically, dorsolateral prefrontal cortex to anterior cingulate cortex (DLPFC - ACC) functional connectivity, thought to be crucial for effective and efficient attentional control, is reduced in high trait anxious individuals. The current study examined the potential of connectivity-based real-time functional magnetic imaging neurofeedback (rt-fMRI-nf) for enhancing DLPFC - ACC functional connectivity in trait anxious individuals. We specifically tested if changes in DLPFC - ACC connectivity were associated with reduced anxiety levels and improved attentional control. Thirty-two high trait anxious participants were assigned to either an experimental group (EG), undergoing veridical rt-fMRI-nf, or a control group (CG) that received sham (yoked) feedback. RSFC (using resting state fMRI), anxiety levels and Stroop task performance were assessed pre- and post-rt-fMRI-nf training. Post-rt-fMRI-nf training, relative to the CG, the EG showed reduced anxiety levels and increased DLPFC-ACC functional connectivity as well as increased RSFC in the posterior default mode network. Moreover, in the EG, changes in DLPFC - ACC functional connectivity during rt-fMRI-nf training were associated with reduced anxiety levels. However, there were no group differences in Stroop task performance. We conclude that rt-fMRI-nf targeting DLPFC - ACC functional connectivity can alter network connectivity and interactions and is a feasible method for reducing trait anxiety.

Nicholson AA, Ros T, Densmore M, Frewen PA, Neufeld RWJ, Théberge J, Jetly R, Lanius RA. A randomized, controlled trial of alpha-rhythm EEG neurofeedback in posttraumatic stress disorder: A preliminary investigation showing evidence of decreased PTSD symptoms and restored default mode and salience network connectivity using fMRI. Neuroimage Clin. 2020;28:102490. Objective: The default-mode network (DMN) and salience network (SN) have been shown to display altered connectivity in posttraumatic stress disorder (PTSD). Restoring aberrant connectivity within these networks with electroencephalogram neurofeedback (EEG-NFB) has been shown previously to be associated with acute decreases in symptoms. Here, we conducted a double-blind, sham-controlled randomized trial of alpha-rhythm EEG-NFB in participants with PTSD (n = 36) over 20-weeks. Our aim was to provide mechanistic evidence underlying clinical improvements by examining changes in network connectivity via fMRI. Methods: We randomly assigned participants with a primary diagnosis of PTSD to either the experimental group (n = 18) or sham-control group (n = 18). We collected resting-state fMRI scans pre- and post-NFB intervention, for both the experimental and sham-control PTSD groups. We further compared baseline brain connectivity measures pre-NFB to age-matched healthy controls (n = 36). Results: With regard to the primary outcome measure of PTSD severity, we found a significant main effect of time in the absence of a group × time interaction. Nevertheless, we found significantly decreased PTSD severity scores in the experimental NFB group only, when comparing post-NFB ($dz = 0.71$) and 3-month follow-up scores ($dz = 0.77$) to baseline measures. Interestingly, we found evidence to suggest a shift towards normalization of DMN and SN connectivity post-NFB in the experimental group only. Both decreases in PTSD severity and NFB performance were correlated to DMN and SN connectivity post-NFB in the experimental group. Critically, remission rates of PTSD were significant higher in the experimental group (61.1%) as compared to the sham-control group (33.3%). Conclusion: The current study shows mechanistic evidence for therapeutic changes in DMN and SN connectivity that are known to be associated with PTSD

psychopathology with no patient dropouts. This preliminary investigation merits further research to demonstrate fully the clinical efficacy of EEG-NFB as an adjunctive therapy for PTSD.

Nicholson AA, Rabellino D, Densmore M, Frewen PA, Paret C, Kluetsch R, Schmahl C, Théberge J, Ros T, Neufeld RWJ, McKinnon MC, Reiss JP, Jetly R, Lanius RA. Intrinsic connectivity network dynamics in PTSD during amygdala downregulation using real-time fMRI neurofeedback: A preliminary analysis. Hum Brain Mapp. 2018 Nov;39(11):4258-4275. Posttraumatic stress disorder (PTSD) has been associated with a disturbance in neural intrinsic connectivity networks (ICN), including the central executive network (CEN), default mode network (DMN), and salience network (SN). Here, we conducted a preliminary investigation examining potential changes in ICN recruitment as a function of real-time fMRI neurofeedback (rt-fMRI-NFB) during symptom provocation where we targeted the downregulation of neural response within the amygdala-a key region-of-interest in PTSD neuropathophysiology. Patients with PTSD (n = 14) completed three sessions of rt-fMRI-NFB with the following conditions: (a) regulate: decrease activation in the amygdala while processing personalized trauma words; (b) view: process trauma words while not attempting to regulate the amygdala; and (c) neutral: process neutral words. We found that recruitment of the left CEN increased over neurofeedback runs during the regulate condition, a finding supported by increased dlPFC activation during the regulate as compared to the view condition. In contrast, DMN task-negative recruitment was stable during neurofeedback runs, albeit was the highest during view conditions and increased (normalized) during rest periods. Critically, SN recruitment was high for both the regulate and the view conditions, a finding potentially indicative of CEN modality switching, adaptive learning, and increasing threat/defense processing in PTSD. In conclusion, this study provides provocative, preliminary evidence that downregulation of the amygdala using rt-fMRI-NFB in PTSD is associated with dynamic changes in ICN, an effect similar to those observed using EEG modalities of neurofeedback.

Nicholson, A. A., Ros, T., Frewen, P. A., Densmore, M., Théberge, J., Kluetsch, R. C., Jetly, R., & Lanius, R. A. (2016). Alpha oscillation neurofeedback modulates amygdala complex connectivity and arousal in posttraumatic stress disorder. NeuroImage. Clinical, 12, 506–516. Objective: Electroencephalogram (EEG) neurofeedback aimed at reducing the amplitude of the alpha-rhythm has been shown to alter neural networks associated with posttraumatic stress disorder (PTSD), leading to symptom alleviation. Critically, the amygdala is thought to be one of the central brain regions mediating PTSD symptoms. In the current study, we compare directly patterns of amygdala complex connectivity using fMRI, before and after EEG neurofeedback, in order to observe subcortical mechanisms associated with behavioural and alpha oscillatory changes among patients. Method: We examined basolateral (BLA), centromedial (CMA), and superficial (SFA) amygdala complex resting-state functional connectivity using a seed-based approach via SPM Anatomy Toolbox. Amygdala complex connectivity was measured in twenty-one individuals with PTSD, before and after a 30-minute session of EEG neurofeedback targeting alpha desynchronization. Results: EEG neurofeedback was associated with a shift in amygdala complex connectivity from areas implicated in defensive, emotional, and fear processing/memory retrieval (left BLA and left SFA to the periaqueductal gray, and left SFA to the left hippocampus) to prefrontal areas implicated in emotion regulation/modulation (right CMA to the medial prefrontal cortex). This shift in amygdala complex connectivity was associated with reduced arousal, greater resting alpha synchronization, and was negatively correlated to PTSD symptom severity. Conclusion: These findings have significant implications for developing targeted non-invasive treatment interventions for PTSD patients that utilize alpha oscillatory neurofeedback, showing evidence of neuronal reconfiguration between areas highly implicated in the disorder, in addition to acute symptom alleviation.

Nicholson, A. A., Rabellino, D., Densmore, M., Frewen, P. A., Paret, C., Kluetsch, R., Schmahl, C., Théberge, J., Neufeld, R. W., McKinnon, M. C., Reiss, J., Jetly, R., & Lanius, R. A. (2017). The neurobiology of emotion regulation in posttraumatic stress disorder: Amygdala downregulation via real-time fMRI neurofeedback. Amygdala dysregulation has been shown to be central to the pathophysiology of posttraumatic stress disorder (PTSD) representing a critical treatment target. Here, amygdala downregulation was targeted using real-time fMRI neurofeedback (rt-fMRI-nf) in patients with PTSD, allowing us to examine further the regulation of emotional states during symptom provocation. Patients (n = 10) completed three sessions of rt-fMRI-nf with the instruction to downregulate activation in the amygdala, while viewing personalized trauma words. Amygdala downregulation was assessed by contrasting (a) regulate trials, with (b) viewing trauma words and not attempting to regulate. Training was followed by one transfer run not involving neurofeedback. Generalized psychophysiological interaction (gPPI) and dynamic causal modeling (DCM) analyses were

also computed to explore task-based functional connectivity and causal structure, respectively. It was found that PTSD patients were able to successfully downregulate both right and left amygdala activation, showing sustained effects within the transfer run. Increased activation in the dorsolateral and ventrolateral prefrontal cortex (PFC), regions related to emotion regulation, was observed during regulate as compared with view conditions. Importantly, activation in the PFC, rostral anterior cingulate cortex, and the insula, were negatively correlated to PTSD dissociative symptoms in the transfer run. Increased functional connectivity between the amygdala- and both the dorsolateral and dorsomedial PFC was found during regulate, as compared with view conditions during neurofeedback training. Finally, our DCM analysis exploring directional structure suggested that amygdala downregulation involves both top-down and bottom-up information flow with regard to observed PFC-amygdala connectivity. This is the first demonstration of successful downregulation of the amygdala using rt-fMRI-nf in PTSD, which was critically sustained in a subsequent transfer run without neurofeedback, and corresponded to increased connectivity with prefrontal regions involved in emotion regulation during the intervention. Hum Brain Mapp 38:541-560, 2017.

Norris, S. L., Lee, C-T., Burshteyn, D., & Cea-Aravena, J. (2001). The effects of performance enhancement training on hypertension, human attention, stress, and brain wave patterns: A case study. *Journal of Neurotherapy*, 4(3), 29-44. Background: The purpose of this study was to evaluate the effects of alpha-increase neurofeedback training (Performance Enhancement Training) on blood pressure, stress reduction, attention, and observe changes in brainwave patterns. A forty-nine-year-old male college student diagnosed with essential hypertension controlled by medication had undergone twenty-six sessions of alpha-increase biofeedback (8-13 Hz) at PZ electrode site for a period of 15 weeks. Method: Pre- and post-blood pressure measurements were taken for every session. At the beginning of week number eight, the participant discontinued his medication as advised by his physician. Pre- and post-visual TOVA CPT test was administered to assess the changes in accuracy, reaction time (RT), and RT variability. Osterkamp and Press Self-Assessment Stress Inventory was administered before and after training to assess the level of stress. QEEG evaluation was conducted prior, as well as upon completion of the study. Results: Mean Arterial Blood Pressure (MAP) yielded statistically significant results between pre- and post-sessions within participant blood pressure measurements. The participant's systolic and diastolic blood pressures during the first thirteen sessions were not significantly different from those of the last thirteen sessions when his medication was discontinued, suggesting his ability to control his blood pressure within normal limits without the use of medication. The results of the TOVA test clearly indicate an improvement in individuals' reaction time and the reaction time variability. The results of the Osterkamp and Press Self-Assessment Stress Inventory indicated an improvement in two of the scales: Work and Social Life. Statistical analysis showed that before and after QEEG evaluations were within normal limits. Discussion: The mechanism through which Performance Enhancement Training simultaneously affects blood pressure, reaction time (RT), and variability needs further investigation. However, the positive changes in the measured variables appear to be a function of enhanced self-awareness that leads to the improved self-regulation.

Peeters, F., Ronner, J., Bodar, L., van Os, J. & Louisberg, R. (2013). Validation of a neurofeedback paradigm: Manipulating frontal EEG alpha-activity and its impact on mood. Int J Psychophysiol. doi: 10.1016/j.ijpsycho.2013.06.010. It is claimed that neurofeedback (NF) is an effective treatment for a variety of psychiatric disorders. NF, within an operant conditioning framework, helps individuals to regulate cortical electroencephalographic (EEG) activity while receiving feedback from a visual or acoustic signal. For example, changing asymmetry between left and right frontal brain alpha activity by NF, is claimed to be an efficacious treatment for major depressive disorder. However, the specificity of this intervention in occasioning electrophysiological changes at target locations and target wave-frequencies, and its relation to changes in mood, has not been established. During a single session of NF, it was tested if the balance between left and right frontal alpha-activity could be changed, regardless of direction, in 40 healthy females. Furthermore, we investigated whether this intervention was electrophysiologically specific and if it was associated with changes in mood. Participants were able to decrease or increase frontal alpha-asymmetry during the intervention. However, no changes in mood were observed. (*Note from bibliographer: one session would rarely provide changes in behavior*). Changes in EEG activity were specific in terms of location and wave-frequency.

Peniston, E. G., & Kulkosky, P. J. (1991). Alpha-theta brainwave neuro-feedback therapy for Vietnam veterans with combat-related post-traumatic stress disorder. *Medical Psychotherapy*, 4, 47-60. The Minnesota Personality Inventory (MMPI) was used to

assess personality changes in Vietnam combat veterans with PTSD after either traditional medical treatment (TC) or alpha-theta brainwave neuro-feedback therapy (BWT). Application of brainwave training for thirty 30-minute sessions resulted in decreases in MMPI T-scores on clinical scales labeled hypochondriasis, depression, hysteria, psychopathis deviate masculinity-femininity, paranoia, psychasthenia, schizophrenia, hypomania and social introversion-extroversion. The traditional medical control group showed decreases in T-scores only on the scale labeled schizophrenia. All 14 BWT patients initially receiving psychotropic medication reduced their dosages after treatment, but only one of thirteen TC patients reduced dosage. A thirty-month follow up study showed that all fourteen TC patients had relapsed, in contract to only three of fifteen BWT patients. These findings indicate that application of alpha-theta brainwave training I a more efficacious treatment modality in the treatment of PTSD and preventative of relapse.

Peniston, E. G., Marrinan, D. A., Deming, W. A., & Kulkosky, P. J. (1993). EEG alpha-theta brainwave synchronization in Vietnam theater veterans with combat-related post-traumatic stress disorder and alcohol abuse. ***Advances in Medical Psychotherapy*****, 6, 37-50**. (No abstract available.)

Putnam, J. (2000). The effects of brief, eyes-open alpha brain wave training with audio and video relaxation induction on the EEG of 77 Army reservists. ***Journal of Neurotherapy,*** **4(1), 17-28.** Background: Recently, psychologist Barry Sterman of the UCLA School of Medicine became involved in measuring the brain wave activity of pilots engaged in a variety of tasks for the purpose of identifying the brain wave correlates of peak performance under different load conditions. Sterman found that during a manageable periodic challenge the brain waves exhibited, in parietal areas, a consistent cycling between resting state alpha (when in the attentive readiness state) and an alpha desynchronized, elevated low beta state when engaged in the response mode. As the tasks came closer together, hence allowing for no alpha respite, there was a deterioration in performance accompanied by an increase in theta activity. In this paper, the effects of brief, eyes-open alpha brain wave enhancement training will be examined for the general purpose of suggesting possible methods for increasing functional integrity and cortical flexibility through increased alpha brain wave production. Methods: The subjects were 77 U.S. Army reservists. The EEG biofeedback system used was the BioIntegrator manufactured by the Bio-Research Institute. Alpha enhancement training was employed with electrode placement at Pz. Results: It was found that eyes-open alpha enhancement training resulted in substantial increases in activity in the feedback band (alpha) with smaller increases in low beta and decreases in theta. This is quite a different result than one would expect from general "relaxation" training that is usually accomplished with eyes closed and yields substantial increases in both alpha and theta. Conclusion: When engaged in this training, even for brief periods, the EEG moves in a direction quite different to that of Sterman's burnout profile. It would be of interest to demonstrate rigorously that the training could, if administered preventatively, diminish poor performance in persons performing tasks that demand prolonged periods of external focus under high load conditions.

Raymond, J., Varney, C., Parkinson, L. A., & Gruzelier, J.H. (2005). The effects of alpha/theta neurofeedback on personality and mood. ***Brain Research & Cognitive Brain Research*****, 23(2-3), 287-292.** Alpha/theta neurofeedback has been shown to be successful both in treating addictions and in enhancing artistry in music students. How its effects are mediated are not yet clear. The present study aimed to test the hypothesis that alpha/theta neurofeedback works inter alia by normalising extreme personality and raising feelings of wellbeing. 12 participants with high scores for Withdrawal (as measured by the PSQ) were given either alpha/theta neurofeedback or mock feedback and their personality and mood were assessed. Withdrawal scores on the PSQ-80 were not found to change in either group but significant effects were found for the Profile Of Mood States (POMS), with real feedback producing higher overall scores than mock feedback ($P = 0.056$). Real feedback caused participants to feel significantly more energetic ($P < 0.01$) than did mock feedback. Sessions of real feedback made participants feel more composed ($P < 0.01$), agreeable ($P < 0.01$), elevated ($P < 0.01$) and confident ($P < 0.05$), whilst sessions of mock feedback made participants feel more tired ($P < 0.05$), yet composed ($P < 0.01$). These findings suggest that, whilst 9 sessions of alpha/theta neurofeedback was insufficient to change personality, improvements in mood may provide a partial explanation for the efficacy of alpha/theta neurofeedback.

Ribas, V. R., Ribas, R. G., Nóbrega, J. A., da Nóbrega, M. V., Espécie, J., Calafange, M. T., Calafange, C., & Martins, H. (2018). Pattern of anxiety, insecurity, fear, panic and/or phobia observed by quantitative electroencephalography (QEEG). Dementia &

neuropsychologia, 12(3), 264–271. Stress is a response in which an individual wants to have more control over a situation. A constant state of stress is called anxiety. Some patients deny symptoms. An instrument can help arrive at a diagnosis. Objective: Using TQ-7 QEEG, this study aimed to evaluate the association of symptoms of anxiety, insecurity, fear, panic and phobia with hot temporals defined as Beta (15-23 Hz) >17% and High-Beta waves (23-38 Hz) >10% at T3 and T4. Methods: Five hundred and forty-three patients of both genders with ages ranging from 16-59 years were evaluated, divided into two groups: Control (without hot temporals: n=274) and Case Group (with hot temporals: n=269). The Chi-square test was used (p-values ≤0.05). Results: There was a significant association (p-value <0.001) between the symptoms related to amygdala activation, expressed in the temporals (Beta >17% and High-Beta >10%). (Anxiety, T3=89.6% - T4=88.8%; T3=92.6% - T4=93.3%), (Fear, T3=80.7% - T4=84.4%; T3=82.9% - T4=95.9%), (Insecurity, T3=82.2% - T4=81.4%; T3=69.5% - T4=97.8%), (Panic, T3=52.4 - T4=72.5%; T3=90.3% - T4=74.0%), (Phobia, T3=17.5% - T4=22.7%; T3=19.7% - T4=27.1%), when compared to the respective controls (Beta control, T3=8.4%, 10.2%, 21.2%, 1.1%, 0.4% and T4=11.3%, 4.4%, 23.0%, 2.6%, 1.1%) (High-Beta control, T3=4.0%, 6.9%, 6.2%, 0.4%, 0.0% and T4=17.5%, 6.2%, 3.3%, 4.0%, 0.7%). Conclusion: Anxiety, insecurity, fear, panic and phobia are observed by QEEG when the levels of total Beta >17% and High-Beta waves >10% at T3 and T4.

Rice, K. M., Blanchard, E. B., & Purcell, M. (1993). Biofeedback treatments of generalized anxiety disorder: Preliminary results. ***Biofeedback & Self-Regulation*****, 18, 93-105.** Forty-five individuals with generalized anxiety (38 with GAD as defined by DSM-III) were randomized to 4 treatment conditions or a waiting list control. Patients received 8 sessions of either frontal EMG biofeedback, biofeedback to increase EEG alpha, biofeedback to decrease EEG alpha, or a pseudomeditation control condition. All treated subjects showed significant reductions in STAI-Trait Anxiety and psychophysiologic symptoms on the Psychosomatic Symptom Checklist. Only alpha-increase biofeedback subjects showed significant reductions in heart rate reactivity to stressors at a separate psychophysiological testing session. Decreased self-report of anxiety was maintained at 6 weeks post treatment.

Rogel A, Loomis AM, Hamlin E, Hodgdon H, Spinazzola J, van der Kolk B. The impact of neurofeedback training on children with developmental trauma: A randomized controlled study. Psychol Trauma. 2020 Nov;12(8):918-929. Objective: Developmental trauma or chronic early childhood exposure to abuse and neglect by caregivers has been shown to have a long-lasting pervasive impact on mental and neural development, including problems with attention, impulse control, self-regulation, and executive functioning. Its long-term effects are arguably the costliest public health challenge in the United States. Children with developmental trauma rarely have a satisfactory response to currently available evidence-based psychotherapeutic and pharmacological treatments. Neurofeedback training (NFT) is a clinical application of brain computer interface technology, aiming to alter electrical brain activity associated with various mental dysfunctions. NFT has shown promise to improve posttraumatic stress disorder (PTSD) symptoms. Method: This randomized controlled study examined the effects of NFT on 37 children, aged 6-13 years with developmental trauma. Participants were randomly divided into active NFT (n = 20) or treatment-as-usual control (n = 17). Both groups underwent 4 assessments during equivalent timelines. The active group received 24 NFT sessions twice a week. Results: This pilot study demonstrated that 24 sessions of NFT significantly decreased PTSD symptoms, internalizing, externalizing, other behavioral and emotional symptoms, and significantly improved the executive functioning of children aged 6-13 years with severe histories of abuse and neglect who had not significantly benefited from any previous therapy. Conclusions: NFT offers the possibility to improve learning, enhance self-efficacy, and develop better social relationships in this hitherto largely treatment-resistant population.

Scheinost D, Stoica T, Saksa J, Papademetris X, Constable RT, Pittenger C & Hampson M. (2013). Orbitofrontal cortex neurofeedback produces lasting changes in contamination anxiety and resting-state connectivity. Transl Psychiatry. 2013 Apr 30;3:e250. doi: 10.1038/tp.2013.24. Anxiety is a core human emotion but can become pathologically dysregulated. We used functional magnetic resonance imaging (fMRI) neurofeedback (NF) to noninvasively alter patterns of brain connectivity, as measured by resting-state fMRI, and to reduce contamination anxiety. Activity of a region of the orbitofrontal cortex associated with contamination anxiety was measured in real time and provided to subjects with significant but subclinical anxiety as a NF signal, permitting them to learn to modulate the target brain region. NF altered network connectivity of brain regions involved in anxiety regulation: subjects exhibited reduced resting-state connectivity in limbic circuitry and increased connectivity in the dorsolateral

prefrontal cortex. NF has been shown to alter brain connectivity in other contexts, but it has been unclear whether these changes persist; critically, we observed changes in connectivity several days after the completion of NF training, demonstrating that such training can lead to lasting modifications of brain functional architecture. Training also increased subjects' control over contamination anxiety several days after the completion of NF training. Changes in resting-state connectivity in the target orbitofrontal region correlated with these improvements in anxiety. Matched subjects undergoing a sham feedback control task showed neither a reorganization of resting-state functional connectivity nor an improvement in anxiety. These data suggest that NF can enable enhanced control over anxiety by persistently reorganizing relevant brain networks and thus support the potential of NF as a clinically useful therapy.

Simkin, DR., Thatcher, RW. & Lubar, J. (2014). Quantitative EEGB and Neurofeedback in Children and adolescents: Anxiety disorders, depressive disorders, comorbid addiction and attention-deficit/hyperactivity disorder and brain injury. ***Child and Adolescent Psychiatric Clinics of North America*****:23(3). 427-464.** This article explores the science surrounding neurofeedback. Both surface neurofeedback (using 2-4 electrodes) and newer interventions, such as real-time z-score neurofeedback (electroencephalogram [EEG] biofeedback) and low-resolution electromagnetic tomography neurofeedback, are reviewed. The limited literature on neurofeedback research in children and adolescents is discussed regarding treatment of anxiety, mood, addiction (with comorbid attention-deficit/hyperactivity disorder), and traumatic brain injury. Future potential applications, the use of quantitative EEG for determining which patients will be responsive to medications, the role of randomized controlled studies in neurofeedback research, and sensible clinical guidelines are considered.

Sittenfeld, P., Budzynski, T. H., & Stoyva, J. M. (1976). ***Differential shaping of EEG theta rhythms*****. Biofeedback & Self-Regulation, 1, 31-46.** Heart rate, EEG, frontal EMG, and forearm EMG were recorded in 20 subjects for 3 baseline, 8 feedback, and 2 postbaseline sessions in order to compare two biofeedback methods of teaching subjects to increase theta EEG activity. Subjects were divided into high- and low-EMG groups. Five high-EMG subjects, and 5 low-EMG subjects then received 8 sessions of strictly theta feedback. The remaining 10 subjects, 5 from the high-EMG group, and 5 from the low-EMG group, received a "graduated" training, which involved shaping the target response. This procedure consisted of 4 initial sessions of EMG feedback, followed by a second phase consisting of 4 sessions of theta feedback. Results showed a clear relationship between subjects' baseline frontal EMG levels and the effect of the training methods. Although subjects with high-EMG baseline increased their theta output only with the two-phase training, subjects with low-EMG baseline levels performed better when given theta feedback only. This result shows not only that amounts of theta can be reliably increased, but that training techniques should be adapted to the physiological characteristics of the individual--in this case, baseline levels of frontal EMG levels.

Sokhadze, E., Singh, S., Stewart, C., Hollifield, M., El-Baz, A., Tasman, A. (2008). Attentional bias to drug- and stress-related pictorial cues in cocaine addiction comorbid with Posttraumatic Stress Disorder. ***Journal of Neurotherapy*****;12(4), 205 – 225**. Introduction. Cocaine addiction places a specific burden on mental health services through its comorbidity with other psychiatric disorders. Treatment of patients with cocaine abuse is more complicated when addiction is co-occurring with posttraumatic stress disorder (PTSD). This study used dense-array event-related potential (ERP) technique to investigate whether the patients with this form of dual diagnosis display excessive reactivity to both trauma and drug cues as compared to neutral cues. Cue reactivity refers to a phenomenon in which individuals with a history of drug dependence exhibit verbal, physiological, and behavioral responses to cues associated with their preferred substance of abuse. This study explores ERP differences associated with cue-related responses to both drug and trauma cues in a three-category oddball task using neutral, drug-related, and trauma-related pictorial stimuli. Methods. The study was conducted on 14 cocaine dependent participants, 11 participants with cocaine-dependence comorbid with PTSD, and 9 age- and gender-matched control subjects. A 128-channel Electrical Geodesics EEG system was used to record ERP during the visual three-category oddball task with three categories (neutral, drug, stress) of affective pictures. Results. Patients with cocaine dependence and PTSD, as compared to patients with only cocaine addiction and control participants, showed excessive cue reactivity to both drug- and trauma-related visual stimuli. Most profound differences were found in the amplitude and latency of frontal P3a, and centro-parietal P3b ERP components. Group differences were found as well between patients with cocaine abuse (both addiction-only and dual diagnosis

groups) versus controls on most ERP measures for drug-related cues. Conclusion. We propose that the employed ERP cue reactivity variables could be used as valuable functional outcome measures in dually diagnosed drug addicts undergoing behavioral treatment.

Steingrimsson S, Bilonic G, Ekelund AC, Larson T, Stadig I, Svensson M, Vukovic IS, Wartenberg C, Wrede O, Bernhardsson S. Electroencephalography-based neurofeedback as treatment for post-traumatic stress disorder: A systematic review and meta-analysis. Eur Psychiatry. 2020 Jan 31;63(1):e7. Background: Post-traumatic stress disorder (PTSD) is debilitating for patients and society. There are a number of treatment methods albeit not all patients respond to these and an interesting method using electroencephalography-based neurofeedback (EEG-NF) has become more prominent in recent years. This systematic review aimed to assess whether EEG-NF, compared with sham NF, other treatment, or no treatment, is effective for PTSD. Primary outcomes were self-harm, PTSD symptoms, level of functioning and health-related quality of life. Methods: Systematic literature searches for randomized controlled trials (RCTs) were conducted in six databases. Random effects meta-analysis was performed. Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation. Results: Four RCTs were included (123 participants). Suicidal thoughts were significantly reduced after EEG-NF compared with a waiting list in a small study. PTSD symptoms were assessed in all studies with different instruments. Results were consistently in favor of EEG-NF with large effect sizes (standardized mean difference -2.30 (95% confidence interval: -4.37 to -0.24). One study reported significantly improved level of executive functioning and one study a reduction in use of psychotropic medication. Complications were scarcely reported. Certainty of evidence was assessed as very low for the four assessed outcomes. Conclusions: Based on four RCTs, with several study limitations and imprecision, it is uncertain whether EEG-NF reduces suicidal thoughts, PTSD symptoms, medication use, or improves function. Although all studies showed promising results, further studies are needed to increase the certainty of evidence.

Thomas, J. E., & Sattlberger, B. A. (1997). Treatment of chronic anxiety disorder with neurotherapy: A case study. *Journal of Neurotherapy,* 2(2), 14-19. The objective of the present case study is to report the effects of alpha-decrease biofeedback training on a patient diagnosed with Anxiety Disorder. Three Minnesota Multiphasic Personality Inventories (MMPI and MMPI-2) were used as objective measures of treatment efficacy. Following 15 sessions of slow wave inhibit/fast wave increase EEG feedback training, the patient reported a significant reduction in anxiety-related symptoms. At three-year follow-up, results of an MMPI-2 showed all clinical scales within normal range. In addition, self-reports confirmed that the patient was symptom free. After treating the patient with several other clinical modalities, only the alpha-decrease feedback training produced effective, long-term improvement of symptoms.

Tolin, D. F., Davies, C. D., Moskow, D. M., & Hofmann, S. G. (2020). Biofeedback and Neurofeedback for Anxiety Disorders: A Quantitative and Qualitative Systematic Review. Advances in experimental medicine and biology, 1191, 265–289. Biofeedback refers to the operant training of physiological responding. Variants include electromyography (EMG), electrodermal activity (EDA), skin temperature, heart rate (HR) and heart rate variability (HRV), respiratory biofeedback of end-tidal CO2 (ETCO2), electroencephalography (EEG) signal, and blood oxygen-level dependent signal using functional magnetic resonance imaging (fMRI). This chapter presents a qualitative and quantitative systematic review of randomized controlled trials of biofeedback for anxiety disorders as defined by the 3rd through 5th editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Meta-analytic results indicated that biofeedback (broadly defined) is superior to wait list, but has not been shown to be superior to active treatment conditions or to conditions in which patients are trained to change their physiological responding in a countertherapeutic direction. Thus, although biofeedback appears generally efficacious for anxiety disorders, the specific effects of biofeedback cannot be distinguished from nonspecific effects of treatment. Further, significant limitations were identified in the existing literature, with the majority receiving a "weak" rating according to Effective Public Health Practice Project (EPHPP) rating system guidelines. Future directions for research are discussed.

van der Kolk, B. A., Hodgdon, H., Gapen, M., Musicaro, R., Suvak, M. K., Hamlin, E., & Spinazzola, J. (2016). A Randomized Controlled Study of Neurofeedback for Chronic PTSD. PloS one, 11(12), e0166752. Introduction: Brain/Computer Interaction (BCI) devices are designed to alter neural signals and, thereby, mental activity. This study was a randomized, waitlist (TAU) controlled trial of a BCI, EEG neurofeedback training (NF), in patients with chronic PTSD to explore the capacity of NF to reduce PTSD symptoms and

increase affect regulation capacities. Study design: 52 individuals with chronic PTSD were randomized to either NF (n = 28) or waitlist (WL) (n = 24). They completed four evaluations, at baseline (T1), after week 6 (T2), at post-treatment (T3), and at one month follow up (T4). Assessment measures were:1. Traumatic Events Screening Inventory (T1); 2. the Clinician Administered PTSD Scale (CAPS; T1, T3, T4); 3. the Davidson Trauma Scale (DTS; T1-T4) and 4. the Inventory of Altered Self-Capacities (IASC; T1-T4). NF training occurred two times per week for 12 weeks and involved a sequential placement with T4 as the active site, P4 as the reference site. Results: Participants had experienced an average of 9.29 (SD = 2.90) different traumatic events. Post-treatment a significantly smaller proportion of NF (6/22, 27.3%) met criteria for PTSD than the WL condition (15/22, 68.2%), $\chi 2$ (n = 44, df = 1) = 7.38, p = .007. There was a significant treatment condition x time interaction (b = -10.45, t = -5.10, p< .001). Measures of tension reduction activities, affect dysregulation, and affect instability exhibited a significant Time x Condition interaction. The effect sizes of NF (d = -2.33 within, d = -1.71 between groups) are comparable to those reported for the most effective evidence based treatments for PTSD. Discussion: Compared with the control group NF produced significant PTSD symptom improvement in individuals with chronic PTSD, as well as in affect regulation capacities. NF deserves further investigation for its potential to ameliorate PTSD and to improve affect regulation, and to clarify its mechanisms of action.

Vanathy, S., Sharma, P. S. V. N., & Kumar, K. B. (1998). The efficacy of alpha and theta neurofeedback training in treatment of generalized anxiety disorder. ***Indian Journal of Clinical Psychology,*** **25(2), 136-143. (**No abstract available.)

Vasa, RA., Carroll, LM., Nozzolillio, AA., Mahajan, R., Mazurek, MO., Bennett, AE., Wink, LK. & Bernal, MP. (2014). A systematic review of treatments for anxiety in youth with autism spectrum disorders. J Autism Dev Disord. July 2014 Early e-pub. This study systematically examined the efficacy and safety of psychopharmacological and non-psychopharmacological treatments for anxiety in youth with autism spectrum disorders (ASD). Four psychopharmacological, nine cognitive behavioral therapy (CBT), and two alternative treatment studies met inclusion criteria. Psychopharmacological studies were descriptive or open label, sometimes did not specify the anxiety phenotype, and reported behavioral activation. Citalopram and buspirone yielded some improvement, whereas fluvoxamine did not. Non-psychopharmacological studies were mainly randomized controlled trials (RCTs) with CBT demonstrating moderate efficacy for anxiety disorders in youth with high functioning ASD. Deep pressure and neurofeedback provided some benefit. All studies were short-term and included small sample sizes. Large scale and long term RCTs examining psychopharmacological and non-psychopharmacological treatments are sorely needed.

Wang, S. Y., Lin, I. M., Fan, S. Y., Tsai, Y. C., Yen, C. F., Yeh, Y. C., Huang, M. F., Lee, Y., Chiu, N. M., Hung, C. F., Wang, P. W., Liu, T. L., & Lin, H. C. (2019). The effects of alpha asymmetry and high-beta down-training neurofeedback for patients with the major depressive disorder and anxiety symptoms. Journal of affective disorders, 257, 287–296. Background: Alpha-asymmetry neurofeedback (ALAY) was applied to patients with major depressive disorder (MDD) based on the theory of frontal alpha asymmetry. Neurophysiological studies have found a higher high-beta activity of electroencephalography (EEG) at the posterior cortex among patients with comorbid MDD and anxiety symptoms. The present study examined the effects of ALAY and high-beta down-training (Beta) neurofeedback in symptoms of depression and anxiety and EEG parameters. Method: Eighty-seven patients with comorbid MDD and anxiety symptoms were allocated to the ALAY, Beta, or control groups. Both neurofeedback groups received ten-session neurofeedback. All participants completed the Beck Depression Inventory II (BDI-II), Beck Anxiety Inventory (BAI), and five minutes resting EEG recording at pre-test and post-test. EEG raw signals were transformed into an A1 score [log (F4 alpha) - log (F3 alpha)], P3 and P4 high-beta power. Results: BDI-II and BAI scores decreased at post-test in both ALAY and Beta groups, but no significant difference between the two groups. No significant interaction effect in A1 score at pre-test and post-test between the ALAY, Beta, and control groups. The P3 high-beta was significantly decreased in the Beta group, an increase in the control group, and no change in the ALAY group at post-test compared to the pre-test. Conclusions: Both neurofeedback groups decreased symptoms of depression and anxiety. The Beta group was more effective in decreasing high-beta power at the parietal cortex compared to other groups. This non-invasive psychological intervention can be used in the future for patients with comorbid MDD and anxiety symptoms.

Watson, C. G., Herder, J., & Passini, F. T. (1978). Alpha biofeedback therapy in alcoholics: An 18-month follow-up. *Journal of Clinical Psychology*, 34(2), 765-769. In an earlier study on patients with alcohol problems, an experimental group given 10 hour-long alpha biofeedback training sessions showed greater improvement on State and Trait Anxiety scores than did a control sample. In the present study an 18-month follow-up was done on those Ss. The differences between the experimentals and controls in State and Trait Anxiety after 18 months were essentially identical to the differences between them immediately after treatment, which indicates that alpha training had long-range therapeutic effects. A difference between the groups on the Alcohol Rehabilitation Followup Questionnaire also suggested that alpha training may have been associated with some reduction in alcohol consumption as well.

Weaver, S. S., Birn, R. M., & Cisler, J. M. (2020). A Pilot Adaptive Neurofeedback Investigation of the Neural Mechanisms of Implicit Emotion Regulation Among Women With PTSD. Frontiers in systems neuroscience, 14, 40. Posttraumatic stress disorder (PTSD) is widely associated with deficits in implicit emotion regulation. Recently, adaptive fMRI neurofeedback (A-NF) has been developed as a methodology that offers a unique probe of brain networks that mediate implicit emotion regulation and their impairment in PTSD. We designed an A-NF paradigm in which difficulty of an emotional conflict task (i.e., embedding trauma distractors onto a neutral target stimulus) was controlled by a whole-brain classifier trained to differentiate attention to the trauma distractor vs. target. We exploited this methodology to test whether PTSD was associated with: (1) an altered brain state that differentiates attention towards vs. away from trauma cues; and (2) an altered ability to use concurrent feedback about brain states during an implicit emotion regulation task. Adult women with a current diagnosis of PTSD (n = 10) and healthy control (n = 9) women participated in this task during 3T fMRI. During two initial non-feedback runs used to train a whole-brain classifier, we observed: (1) poorer attention performance in PTSD; and (2) a linear relationship between brain state discrimination and attention performance, which was significantly attenuated among the PTSD group when the task contained trauma cues. During the A-NF phase, the PTSD group demonstrated poorer ability to regulate brain states as per attention instructions, and this poorer ability was related to PTSD symptom severity. Further, PTSD was associated with the heightened encoding of feedback in the insula and hippocampus. These results suggest a novel understanding of whole-brain states and their regulation that underlie emotion regulation deficits in PTSD.

Weerdmeester, J., van Rooij, M. M., Engels, R. C., & Granic, I. (2020). An Integrative Model for the Effectiveness of Biofeedback Interventions for Anxiety Regulation: Viewpoint. Journal of medical Internet research, 22(7), e14958. Stress is a response in which an individual wants to have more control over a situation. A constant state of stress is called anxiety. Some patients deny symptoms. An instrument can help arrive at a diagnosis. Objective: Using TQ-7 QEEG, this study aimed to evaluate the association of symptoms of anxiety, insecurity, fear, panic and phobia with hot temporals defined as Beta (15-23 Hz) >17% and High-Beta waves (23-38 Hz) >10% at T3 and T4. Methods: Five hundred and forty-three patients of both genders with ages ranging from 16-59 years were evaluated, divided into two groups: Control (without hot temporals: n=274) and Case Group (with hot temporals: n=269). The Chi-square test was used (p-values $\leq$0.05). Results: There was a significant association (p-value <0.001) between the symptoms related to amygdala activation, expressed in the temporals (Beta >17% and High-Beta >10%). (Anxiety, T3=89.6% - T4=88.8%; T3=92.6% - T4=93.3%), (Fear, T3=80.7% - T4=84.4%; T3=82.9% - T4=95.9%), (Insecurity, T3=82.2% - T4=81.4%; T3=69.5% - T4=97.8%), (Panic, T3=52.4 - T4=72.5%; T3=90.3% - T4=74.0%), (Phobia, T3=17.5% - T4=22.7%; T3=19.7% - T4=27.1%), when compared to the respective controls (Beta control, T3=8.4%, 10.2%, 21.2%, 1.1%, 0.4% and T4=11.3%, 4.4%, 23.0%, 2.6%, 1.1%) (High-Beta control, T3=4.0%, 6.9%, 6.2%, 0.4%, 0.0% and T4=17.5%, 6.2%, 3.3%, 4.0%, 0.7%). Conclusion: Anxiety, insecurity, fear, panic and phobia are observed by QEEG when the levels of total Beta >17% and High-Beta waves >10% at T3 and T4.

Zhao, Z., Yao, S., Li, K., Sindermann, C., Zhou, F., Zhao, W., Li, J., Lührs, M., Goebel, R., Kendrick, K. M., & Becker, B. (2019). Real-Time Functional Connectivity-Informed Neurofeedback of Amygdala-Frontal Pathways Reduces Anxiety. Psychotherapy and psychosomatics, 88(1), 5–15. Background: Deficient emotion regulation and exaggerated anxiety represent a major transdiagnostic psychopathological marker. On the neural level these deficits have been closely linked to impaired, yet treatment-sensitive, prefrontal regulatory control over the amygdala. Gaining direct control over these pathways could therefore provide an innovative and promising intervention to regulate exaggerated anxiety. To this end the current proof-of-concept study evaluated the feasibility, functional relevance and maintenance of a novel connectivity-informed real-time fMRI neurofeedback training. Methods: In a randomized crossover sham-

controlled design, 26 healthy subjects with high anxiety underwent real-time fMRI-guided neurofeedback training to enhance connectivity between the ventrolateral prefrontal cortex (vlPFC) and the amygdala (target pathway) during threat exposure. Maintenance of regulatory control was assessed after 3 days and in the absence of feedback. Training-induced changes in functional connectivity of the target pathway and anxiety ratings served as primary outcomes. Results: Training of the target, yet not the sham control, pathway significantly increased amygdala-vlPFC connectivity and decreased levels of anxiety. Stronger connectivity increases were significantly associated with higher anxiety reduction on the group level. At the follow-up, volitional control over the target pathway was maintained in the absence of feedback. Conclusions: The present results demonstrate for the first time that successful self-regulation of amygdala-prefrontal top-down regulatory circuits may represent a novel intervention to control anxiety. As such, the present findings underscore both the critical contribution of amygdala-prefrontal circuits to emotion regulation and the therapeutic potential of connectivity-informed real-time neurofeedback.

Zhukov K. (2019). Current Approaches for Management of Music Performance Anxiety: An Introductory Overview. Medical problems of performing artists, 34(1), 53–60. Music performance anxiety (MPA) is a complex area with many individual factors contributing to the level of anxiety experienced by musicians during live performances. This paper provides an overview of research literature on performance anxiety, intended for music teachers, students, and professional musicians, to highlight strategies that have been suggested to manage the accompanying physical and cognitive symptoms. Treatment of MPA includes mindfulness-based approaches, physiological/physically-based therapies, cognitive/behavioural therapies, prescribed medication, music therapy, and psychotherapy. The most popular approaches for managing the physical symptoms are relaxation techniques, in particular, deep breathing exercises, yoga, and meditation. Other strategies include Alexander technique, bio- and neuro-feedback, healthy lifestyle, and prescription drugs. Self-handicapping and perfectionism are some of the examples of negative behaviours in musicians. Management of cognitive symptoms of MPA includes cognitive restructuring, realistic goal-setting, systematic desensitisation, music therapy, and/or psychotherapy. Combining behavioural techniques with cognitive therapy strategies appears to be the most promising approach among interventions aimed at reducing MPA and improving the quality of music performance. Cautious interpretation of the efficacy of interventions is needed due to methodological weaknesses of some research, and this overview of current approaches is intended to facilitate understanding for those less familiar with this topic.

Zich, C., Johnstone, N., Lührs, M., Lisk, S., Haller, S. P., Lipp, A., Lau, J. Y., & Kadosh, K. C. (2020). Modulatory effects of dynamic fMRI-based neurofeedback on emotion regulation networks in adolescent females. NeuroImage, 220, 117053. Research has shown that difficulties with emotion regulation abilities in childhood and adolescence increase the risk for developing symptoms of mental disorders, e.g anxiety. We investigated whether functional magnetic resonance imaging (fMRI)-based neurofeedback (NF) can modulate brain networks supporting emotion regulation abilities in adolescent females. We performed three experiments (Experiment 1: N = 18; Experiment 2: N = 30; Experiment 3: N = 20). We first compared different NF implementations regarding their effectiveness of modulating prefrontal cortex (PFC)-amygdala functional connectivity (fc). Further we assessed the effects of fc-NF on neural measures, emotional/metacognitive measures and their associations. Finally, we probed the mechanism underlying fc-NF by examining concentrations of inhibitory and excitatory neurotransmitters. Results showed that NF implementations differentially modulate PFC-amygdala fc. Using the most effective NF implementation we observed important relationships between neural and emotional/metacognitive measures, such as practice-related change in fc was related with change in thought control ability. Further, we found that the relationship between state anxiety prior to the MRI session and the effect of fc-NF was moderated by GABA concentrations in the PFC and anterior cingulate cortex. To conclude, we were able to show that fc-NF can be used in adolescent females to shape neural and emotional/metacognitive measures underlying emotion regulation. We further show that neurotransmitter concentrations moderate fc-NF-effects.

Zotev, V., Phillips, R., Misaki, M., Wong, C. K., Wurfel, B. E., Krueger, F., Feldner, M., & Bodurka, J. (2018). Real-time fMRI neurofeedback training of the amygdala activity with simultaneous EEG in veterans with combat-related PTSD. NeuroImage. Clinical, 19, 106–121. Posttraumatic stress disorder (PTSD) is a chronic and disabling neuropsychiatric disorder characterized by insufficient top-down modulation of the amygdala activity by the prefrontal cortex. Real-time fMRI neurofeedback (rtfMRI-nf) is an

emerging method with potential for modifying the amygdala-prefrontal interactions. We report the first controlled emotion self-regulation study in veterans with combat-related PTSD utilizing rtfMRI-nf of the amygdala activity. PTSD patients in the experimental group (EG, n = 20) learned to upregulate blood-oxygenation-level-dependent (BOLD) activity of the left amygdala (LA) using the rtfMRI-nf during a happy emotion induction task. PTSD patients in the control group (CG, n = 11) were provided with a sham rtfMRI-nf. The study included three rtfMRI-nf training sessions, and EEG recordings were performed simultaneously with fMRI. PTSD severity was assessed before and after the training using the Clinician-Administered PTSD Scale (CAPS). The EG participants who completed the study showed a significant reduction in total CAPS ratings, including significant reductions in avoidance and hyperarousal symptoms. They also exhibited a significant reduction in comorbid depression severity. Overall, 80% of the EG participants demonstrated clinically meaningful reductions in CAPS ratings, compared to 38% in the CG. No significant difference in the CAPS rating changes was observed between the groups. During the first rtfMRI-nf session, functional connectivity of the LA with the orbitofrontal cortex (OFC) and the dorsolateral prefrontal cortex (DLPFC) was progressively enhanced, and this enhancement significantly and positively correlated with the initial CAPS ratings. Left-lateralized enhancement in upper alpha EEG coherence also exhibited a significant positive correlation with the initial CAPS. Reduction in PTSD severity between the first and last rtfMRI-nf sessions significantly correlated with enhancement in functional connectivity between the LA and the left DLPFC. Our results demonstrate that the rtfMRI-nf of the amygdala activity has the potential to correct the amygdala-prefrontal functional connectivity deficiencies specific to PTSD.

Zweerings, J., Sarkheil, P., Keller, M., Dyck, M., Klasen, M., Becker, B., Gaebler, A. J., Ibrahim, C. N., Turetsky, B. I., Zvyagintsev, M., Flatten, G., & Mathiak, K. (2020). Rt-fMRI neurofeedback-guided cognitive reappraisal training modulates amygdala responsivity in posttraumatic stress disorder. NeuroImage. Clinical, 28, 102483. Background: Traumatic experiences are associated with neurofunctional dysregulations in key regions of the emotion regulation circuits. In particular, amygdala responsivity to negative stimuli is exaggerated while engagement of prefrontal regulatory control regions is attenuated. Successful application of emotion regulation (ER) strategies may counteract this disbalance, however, application of learned strategies in daily life is hampered in individuals afflicted by posttraumatic stress disorder (PTSD). We hypothesized that a single session of real-time fMRI (rtfMRI) guided upregulation of prefrontal regions during an emotion regulation task enhances self-control during exposure to negative stimuli and facilitates transfer of the learned ER skills to daily life. Methods: In a cross-over design, individuals with a PTSD diagnosis after a single traumatic event (n = 20) according to DSM-IV-TR criteria and individuals without a formal psychiatric diagnosis (n = 21) underwent a cognitive reappraisal training. In randomized order, all participants completed two rtfMRI neurofeedback (NF) runs targeting the left lateral prefrontal cortex (lPFC) and two control runs without NF (NoNF) while using cognitive reappraisal to reduce their emotional response to negative scenes. During the NoNF runs, two %%-signs were displayed instead of the two-digit feedback (FB) to achieve a comparable visual stimulation. The project aimed at defining the clinical potential of the training according to three success markers: (1) NF induced changes in left lateral prefrontal cortex and bilateral amygdala activity during the regulation of aversive scenes compared to cognitive reappraisal alone (primary registered outcome), (2) associated changes on the symptomatic and behavioral level such as indicated by PTSD symptom severity and affect ratings, (3) clinical utility such as indicated by perceived efficacy, acceptance, and transfer to daily life measured four weeks after the training. Results: In comparison to the reappraisal without feedback, a neurofeedback-specific decrease in the left lateral PFC (d = 0.54) alongside an attenuation of amygdala responses (d = 0.33) emerged. Reduced amygdala responses during NF were associated with symptom improvement (r = -0.42) and less negative affect (r = -0.63) at follow-up. The difference in symptom scores exceeds requirements for a minimal clinically important difference and corresponds to a medium effect size (d = 0.64). Importantly, 75% of individuals with PTSD used the strategies in daily life during a one-month follow-up period and perceived the training as efficient. Conclusion: Our findings suggest beneficial effects of the NF training indicated by reduced amygdala responses that were associated with improved symptom severity and affective state four weeks after the NF training as well as patient-centered perceived control during the training, helpfulness and application of strategies in daily life. However, reduced prefrontal involvement was unexpected. The study suggests good tolerability of the training protocol and potential for clinical use in the treatment of PTSD.

Zweerings, J., Pflieger, E. M., Mathiak, K. A., Zvyagintsev, M., Kacela, A., Flatten, G., & Mathiak, K. (2018). Impaired Voluntary Control in PTSD: Probing Self-Regulation of the ACC With Real-Time fMRI. Frontiers in psychiatry, 9, 219.

Background: Post-traumatic stress disorder (PTSD) is characterized by deficits in the self-regulation of cognitions and emotions. Neural networks of emotion regulation may exhibit reduced control mediated by the anterior cingulate cortex (ACC), contributing to aberrant limbic responses in PTSD. Methods: Real-time fMRI neurofeedback (rt-fMRI NF) assessed self-regulation of the ACC in nine patients with PTSD after single trauma exposure and nine matched healthy controls. All participants were instructed to train ACC upregulation on three training days. Results: Both groups achieved regulation, which was associated with wide-spread brain activation encompassing the ACC. Compared to the controls, regulation amplitude and learning rate was lower in patients, correlating with symptom severity. In addition, a frontopolar activation cluster was associated with self-regulation efforts in patients. Conclusions: For the first time, we tested self-regulation of the ACC in patients with PTSD. The observed impairment supports models of ACC-mediated regulation deficits that may contribute to the psychopathology of PTSD. Controlled trials in a larger sample are needed to confirm our findings and to directly investigate whether training of central regulation mechanisms improves emotion regulation in PTSD.

AUTISM SPECTRUM DISORDERS

Baruth, J., Casanova, M., Sears, L. & Sokhadze, E., (2010). Early-stage visual processing abnormalities in high-functioning autism spectrum disorder (ASD). *Translational Neuroscience*, 1(2), 177-187. It has been reported that individuals with autism spectrum disorder (ASD) have abnormal responses to the sensory environment. For these individuals sensory overload can impair functioning, raise physiological stress, and adversely affect social interaction. Early-stage (i.e. within 200 ms of stimulus onset) auditory processing abnormalities have been widely examined in ASD using event-related potentials (ERP), while ERP studies investigating early-stage visual processing in ASD are less frequent. We wanted to test the hypothesis of early-stage visual processing abnormalities in ASD by investigating ERPs elicited in a visual oddball task using illusory figures. Our results indicate that individuals with ASD have abnormally large cortical responses to task irrelevant stimuli over both parieto-occipital and frontal regions-of-interest (ROI) during early stages of visual processing compared to the control group. Furthermore, ASD patients showed signs of an overall disruption in stimulus discrimination, and had a significantly higher rate of motor response errors.

Baruth, J., Williams, E., Sokhadze, E., El-Baz, A., Sears, L., & Casanova, M.F. (2011). Repetitive transcranial stimulation (rTMS) improves electroencephalographic and behavioral outcome measures in autism spectrum disorders (ASD). *Autism Science Digest*, 1(1), 52-57. No abstract.

Baruth, J., Casanova, M., El-Baz, A., Horrell, T., Mathai, G., Sears, L., & Sokhadze, E. (2010). Low-frequency repetitive transcranial magnetic stimulation modulates evoked-gamma frequency oscillations in autism spectrum disorders. *Journal of Neurotherapy*, 14 (3), 179-194. In our previous study on individuals with autism spectrum disorder (ASD) (Sokhadze et al., Appl Psychophysiol Biofeedback 34:37-51, 2009a) we reported abnormalities in the attention-orienting frontal event-related potentials (ERP) and the sustained-attention centro-parietal ERPs in a visual oddball experiment. These results suggest that individuals with autism over-process information needed for the successful differentiation of target and novel stimuli. In the present study we examine the effects of low-frequency, repetitive Transcranial Magnetic Stimulation (rTMS) on novelty processing as well as behavior and social functioning in 13 individuals with ASD. Our hypothesis was that low-frequency rTMS application to dorsolateral prefrontal cortex (DLFPC) would result in an alteration of the cortical excitatory/inhibitory balance through the activation of inhibitory GABAergic double bouquet interneurons. We expected to find post-TMS differences in amplitude and latency of early and late ERP components. The results of our current study validate the use of low-frequency rTMS as a modulatory tool that altered the disrupted ratio of cortical excitation to inhibition in autism. After rTMS the parieto-occipital P50 amplitude decreased to novel distracters but not to targets; also the amplitude and latency to targets increased for the frontal P50 while decreasing to non-target stimuli. Low-frequency rTMS minimized early cortical responses to irrelevant stimuli and increased responses to relevant stimuli. Improved selectivity in early cortical responses lead to better stimulus differentiation at later-stage responses as was made evident by our P3b and P3a component findings. These results indicate a significant change in early, middle-latency and late ERP components at the frontal, centro-parietal, and parieto-occipital regions of interest in response to target and distracter stimuli as a result of rTMS treatment. Overall, our preliminary results show that rTMS may prove to be an important research tool or treatment modality in addressing the stimulus hypersensitivity characteristic of autism spectrum disorders.

Carrick, F. R., Pagnacco, G., Hankir, A., Abdulrahman, M., Zaman, R., Kalambaheti, E. R., Barton, D. A., Link, P. E., & Oggero, E. (2018). The Treatment of Autism Spectrum Disorder With Auditory Neurofeedback: A Randomized Placebo Controlled Trial Using the Mente Autism Device. Frontiers in neurology, 9, 537. Introduction: Children affected by autism spectrum disorder (ASD) often have impairment of social interaction and demonstrate difficulty with emotional communication, display of posture and facial expression, with recognized relationships between postural control mechanisms and cognitive functions. Beside standard biomedical interventions and psychopharmacological treatments, there is increasing interest in the use of alternative non-invasive treatments such

as neurofeedback (NFB) that could potentially modulate brain activity resulting in behavioral modification. Methods: Eighty-three ASD subjects were randomized to an Active group receiving NFB using the Mente device and a Control group using a Sham device. Both groups used the device each morning for 45 minutes over a 12 week home based trial without any other clinical interventions. Pre and Post standard ASD questionnaires, qEEG and posturography were used to measure the effectiveness of the treatment. Results: Thirty-four subjects (17 Active and 17 Control) completed the study. Statistically and substantively significant changes were found in several outcome measures for subjects that received the treatment. Similar changes were not detected in the Control group. Conclusions: Our results show that a short 12 week course of NFB using the Mente Autism device can lead to significant changes in brain activity (qEEG), sensorimotor behavior (posturography), and behavior (standardized questionnaires) in ASD children.

Casanova, M., Baryth, J., El-Baz, A., Tasman, A., Sears, L., & Sokhadze, E. (2012). Repetitive transcranial magnetic stimulation (rTMS) modulates event-related potential (ERP) indices of attention in autism. ***Translational Neuroscience*****: 3(2) 170-180.** In our previous study on individuals with autism spectrum disorder (ASD) (Sokhadze et al., Appl Psychophysiol Biofeedback 34:37-51, 2009a) we reported abnormalities in the attention-orienting frontal event-related potentials (ERP) and the sustained-attention centro-parietal ERPs in a visual oddball experiment. These results suggest that individuals with autism over-process information needed for the successful differentiation of target and novel stimuli. In the present study we examine the effects of low-frequency, repetitive Transcranial Magnetic Stimulation (rTMS) on novelty processing as well as behavior and social functioning in 13 individuals with ASD. Our hypothesis was that low-frequency rTMS application to dorsolateral prefrontal cortex (DLFPC) would result in an alteration of the cortical excitatory/inhibitory balance through the activation of inhibitory GABAergic double bouquet interneurons. We expected to find post-TMS differences in amplitude and latency of early and late ERP components. The results of our current study validate the use of low-frequency rTMS as a modulatory tool that altered the disrupted ratio of cortical excitation to inhibition in autism. After rTMS the parieto-occipital P50 amplitude decreased to novel distracters but not to targets; also the amplitude and latency to targets increased for the frontal P50 while decreasing to non-target stimuli. Low-frequency rTMS minimized early cortical responses to irrelevant stimuli and increased responses to relevant stimuli. Improved selectivity in early cortical responses lead to better stimulus differentiation at later-stage responses as was made evident by our P3b and P3a component findings. These results indicate a significant change in early, middle-latency and late ERP components at the frontal, centro-parietal, and parieto-occipital regions of interest in response to target and distracter stimuli as a result of rTMS treatment. Overall, our preliminary results show that rTMS may prove to be an important research tool or treatment modality in addressing the stimulus hypersensitivity characteristic of autism spectrum disorders.

Casanova, M., Mott, M., & Sokhadze, E. (2012) Neuropathology of autism: Review of current literature. ***Siberian Journal of Special Education*** **(in press)(in Russian).**

Coben R, Linden M, Myers TE. (2012). Neurofeedback for autistic spectrum disorder: a review of the literature. ***Appl Psychophysiol Biofeedback*****. 2010 Mar;35(1):83-105.** There is a need for effective interventions to address the core symptoms and problems associated with autistic spectrum disorder (ASD). Behavior therapy improves communication and behavioral functioning. Additional treatment options include psychopharmacological and biomedical interventions. Although these approaches help children with autistic problems, they may be associated with side effects, risks or require ongoing or long-term treatment. Neurofeedback is a noninvasive approach shown to enhance neuroregulation and metabolic function in ASD. We present a review of the literature on the application of Neurofeedback to the multiple problems associated with ASD. Directions for future research are discussed.

Coben, R., & Myers, T. E. (2010). The relative efficacy of connectivity guided and symptom based EEG biofeedback for autistic disorders. ***Applied Psychophysiology & Biofeedback*****, 35(1), 13-23.** Autism is a neurodevelopmental disorder characterized by deficits in communication, social interaction, and a limited range of interests with repetitive stereotypical behavior. Various abnormalities have been documented in the brains of individuals with autism, both anatomically and functionally. The connectivity theory of autism is a recently developed theory of the neurobiological cause of Autistic symptoms. Different patterns of hyper- and hypo-connectivity have been identified with the use of quantitative electroencephalography (QEEG), which may be amenable to neurofeedback. In this study,

we compared the results of two published controlled studies examining the efficacy of neurofeedback in the treatment of autism. Specifically, we examined whether a symptom based approach or an assessment/connectivity guided based approach was more effective. Although both methods demonstrated significant improvement in symptoms of autism, connectivity guided neurofeedback demonstrated greater reduction on various subscales of the Autism Treatment Evaluation Checklist (ATEC). Furthermore, when individuals were matched for severity of symptoms, the amount of change per session was significantly higher in the Coben and Padolsky (J Neurotherother 11:5-23, 2007) study for all five measures of the ATEC. Our findings suggest that an approach guided by QEEG based connectivity assessment may be more efficacious in the treatment of autism. This permits the targeting and amelioration of abnormal connectivity patterns in the brains of people who are autistic.

Coben, R., & Pudolsky, I. (2007). Assessment-guided neurofeedback for autistic spectrum disorder. ***Journal of Neurotherapy,*****11(1), 5-23.** Background. Research reviewing the epidemiology of Autism (Medical Research Council, 2001) indicated that approximately 60 per 10,000 children (1/166) are diagnosed with Autistic Spectrum Disorder (ASD). Jarusiewicz (2002) published the only controlled study documenting the effectiveness of neurofeedback for Autism based on one outcome measure. The present study extended these findings with a larger sample size, broader range of assessments, and physiological measures of brain functioning. Methods. Assessment-guided neurofeedback was conducted in 20 sessions for 37 patients with ASD. The experimental and control groups were matched for age, gender, race, handedness, other treatments, and severity of ASD. Results. Improved ratings of ASD symptoms reflected an 89% success rate. Statistical analyses revealed significant improvement in Autistics who received Neurofeedback compared to a wait list control group. Other major findings included a 40% reduction in core ASD symptomatology (indicated by ATEC Total Scores), and 76% of the experimental group had decreased hyper-connectivity. Reduced cerebral hyperconnectivity was associated with positive clinical outcomes in this population. In all cases of reported improvement in ASD symptomatology, positive treatment outcomes were confirmed by neuropsychological and neurophysiological assessment. Conclusions. Evidence from multiple measures has demonstrated that neurofeedback can be an effective treatment for ASD. In this population, a crucial factor in explaining improved clinical outcomes in the experimental group may be the use of assessment-guided neurofeedback to reduce cerebral hyperconnectivity. Implications of these findings are discussed.

Datko, M., Pineda, J. A., & Müller, R. A. (2018). Positive effects of neurofeedback on autism symptoms correlate with brain activation during imitation and observation. The European journal of neuroscience, 47(6), 579–591. Autism has been characterized by atypical task-related brain activation and functional connections, coinciding with deficits in sociocommunicative abilities. However, evidence of the brain's experience-dependent plasticity suggests that abnormal activity patterns may be reversed with treatment. In particular, neurofeedback training (NFT), an intervention based on operant conditioning resulting in self-regulation of brain electrical oscillations, has shown increasing promise in addressing abnormalities in brain function and behavior. We examined the effects of ≥ 20 h of sensorimotor mu-rhythm-based NFT in children with high-functioning autism spectrum disorders (ASD) and a matched control group of typically developing children (ages 8-17). During a functional magnetic resonance imaging imitation and observation task, the ASD group showed increased activation in regions of the human mirror neuron system following the NFT, as part of a significant interaction between group (ASD vs. controls) and training (pre- vs. post-training). These changes were positively correlated with behavioral improvements in the ASD participants, indicating that mu-rhythm NFT may be beneficial to individuals with ASD.

Eldeeb, S., Susam, B. T., Akcakaya, M., Conner, C. M., White, S. W., & Mazefsky, C. A. (2021). Trial by trial EEG based BCI for distress versus non distress classification in individuals with ASD. Scientific reports, 11(1), 6000. Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is often accompanied by impaired emotion regulation (ER). There has been increasing emphasis on developing evidence-based approaches to improve ER in ASD. Electroencephalography (EEG) has shown success in reducing ASD symptoms when used in neurofeedback-based interventions. Also, certain EEG components are associated with ER. Our overarching goal is to develop a technology that will use EEG to monitor real-time changes in ER and perform intervention based on these changes. As a first step, an EEG-based brain computer interface that is based on an Affective Posner task was developed to identify patterns associated with ER on a single trial basis, and EEG data collected from 21 individuals with ASD. Accordingly, our aim in this

study is to investigate EEG features that could differentiate between distress and non-distress conditions. Specifically, we investigate if the EEG time-locked to the visual feedback presentation could be used to classify between WIN (non-distress) and LOSE (distress) conditions in a game with deception. Results showed that the extracted EEG features could differentiate between WIN and LOSE conditions (average accuracy of 81%), LOSE and rest-EEG conditions (average accuracy 94.8%), and WIN and rest-EEG conditions (average accuracy 94.9%).

Freidrich, EV., Suttie, N., Sivanathan, A., Lim, T., Louchart, S. & Pineda, J. (2014). Brain-computer interface game applications for combined neurofeedback and biofeedback treatment for children on the autism spectrum. Frontiers in Neuroengineering: Jul 3(7). 21. Individuals with autism spectrum disorder (ASD) show deficits in social and communicative skills, including imitation, empathy, and shared attention, as well as restricted interests and repetitive patterns of behaviors. Evidence for and against the idea that dysfunctions in the mirror neuron system are involved in imitation and could be one underlying cause for ASD is discussed in this review. Neurofeedback interventions have reduced symptoms in children with ASD by self-regulation of brain rhythms. However, cortical deficiencies are not the only cause of these symptoms. Peripheral physiological activity, such as the heart rate and its variability, is closely linked to neurophysiological signals and associated with social engagement. Therefore, a combined approach targeting the interplay between brain, body, and behavior could be more effective. Brain-computer interface applications for combined neurofeedback and biofeedback treatment for children with ASD are currently nonexistent. To facilitate their use, we have designed an innovative game that includes social interactions and provides neural- and body-based feedback that corresponds directly to the underlying significance of the trained signals as well as to the behavior that is reinforced.

Gotts, S. J., Ramot, M., Jasmin, K., & Martin, A. (2019). Altered resting-state dynamics in autism spectrum disorder: Causal to the social impairment?. Progress in neuro-psychopharmacology & biological psychiatry, 90, 28–36. Autism spectrum disorder (ASD) is characterized by profound impairments in social abilities and by restricted interests and repetitive behaviors. Much work in the past decade has been dedicated to understanding the brain-bases of ASD, and in the context of resting-state functional connectivity fMRI in high-functioning adolescents and adults, the field has established a set of reliable findings: decreased cortico-cortical interactions among brain regions thought to be engaged in social processing, along with a simultaneous increase in thalamo-cortical and striato-cortical interactions. However, few studies have attempted to manipulate these altered patterns, leading to the question of whether such patterns are actually causally involved in producing the corresponding behavioral impairments. We discuss a few such recent attempts in the domains of fMRI neurofeedback and overt social interaction during scanning, and we conclude that the evidence of causal involvement is somewhat mixed. We highlight the potential role of the thalamus and striatum in ASD and emphasize the need for studies that directly compare scanning during multiple cognitive states in addition to the resting-state.

Hurt, E., Arnold, AE. & Lofthouse, N. (2014). Quantitative EEG neurofeedback for the treatment of pediatric attention-deficit hyperactivity disorder, autism spectrum disorders, learning disorders and epilepsy. Child and Adolescent Psychiatric Clinics of North America:23(3). 465-86. Neurofeedback (NF) using surface electroencephalographic signals has been used to treat various child psychiatric disorders by providing patients with video/audio information about their brain's electrical activity in real-time. Research data are reviewed and clinical recommendations are made regarding NF treatment of youth with attention deficit/hyperactivity disorder, autism, learning disorders, and epilepsy. Most NF studies are limited by methodological issues, such as failure to use or test the validity of a full-blind or sham NF. The safety of NF treatment has not been thoroughly investigated in youth or adults, although clinical experience suggests reasonable safety.autism

Jarusiewicz, G. (2007). ***Use of neurofeedback with autistic spectrum disorders*****. Chapter in J. R. Evans (Ed.), Handbook of Neurofeedback. Binghampton, NY: Haworth Medical Press, pp. 321-339.**

Jarusiewicz, B. (2002). Efficacy of neurofeedback for children in the autistic spectrum: A pilot study. ***Journal of Neurotherapy*****, 6(4), 39-49.** Background. The efficacy of neurofeedback training was evaluated in 12 children in the autistic spectrum with matched controls, based on established training protocols for other conditions with similar symptoms. Method. Twenty-four autistic children were

divided into two groups, matched by sex, age, and disorder severity. One group received neurofeedback training and the second acted as a control group. Responses to the Autism Treatment Evaluation Checklists (ATEC) and parental assessments of problem behaviors were analyzed to evaluate the effectiveness of neurofeedback training for this condition. Results. Neurofeedback training resulted in a 26% average reduction in total ATEC rated autism symptoms, compared to 3% for the control group. Parental assessments reported improvement in all behavioral categories: socialization, vocalization, anxiety, schoolwork, tantrums, and sleep, compared with minimal changes in the control group. Discussion. Autistic spectrum children who underwent neurofeedback training showed significant improvements in autism symptoms and behaviors. The magnitude of improvement was independent of initial severity or age.

Kouijzer, M. E. UJ., de Moor, J. M. H., Gerrits, B. J. L., Buitelaar, J. K., & van Schie, H. T. (2009). Long-term effects of neurofeedback treatment in autism. ***Research in Autism Spectrum Disorders*****, 3, 496-501.** Previously we demonstrated significant improvement of executive functions and social behavior in children with autism spectrum disorders (ASD) treated with 40 sessions of EEG neurofeedback in a nonrandomized waiting list control group design. In this paper we extend these findings by reporting the long-term results of neurofeedback treatment in the same group of children with ASD after 12 months. The present study indicates maintenance of improvement of executive functions and social behavior after 12 months in comparison with the immediate outcomes. Neurofeedback mediated suppression of theta power is supposed to promote more flexible functioning of the brain by enhancing activation in the medial prefrontal cortex and improving flexibility of activation in the default mode network supporting the improvement of executive functions and theory of mind in ASD.

LaMarca, K., Gevirtz, R., Lincoln, A. J., & Pineda, J. A. (2018). Facilitating Neurofeedback in Children with Autism and Intellectual Impairments Using TAGteach. Journal of autism and developmental disorders, 48(6), 2090–2100. Individuals with autism and intellectual impairments tend to be excluded from research due to their difficulties with methodological compliance. This study focuses on using Teaching with Acoustic Guidance-TAGteach-to behaviorally prepare children with autism and a IQ ≤ 80 to participate in a study on neurofeedback training (NFT). Seven children (ages 6-8) learned the prerequisite skills identified in a task analysis in an average of 5 h of TAGteach training, indicating that this is a feasible method of preparing intellectually-impaired children with autism to participate in NFT and task-dependent electroencephalography measures. TAGteach may thus have the potential to augment this population's ability to participate in less accessible treatments and behavioral neuroscientific studies.

Mekkawy L. (2021). Efficacy of neurofeedback as a treatment modality for children in the autistic spectrum. Bulletin of the National Research Centre, 45(1), 45. Background: Neurofeedback (NFB) has been conceded as a convenient measure for both identifying and remodeling neural pliability of brain cells; it is a mean through which participants can have voluntary control on their brain waves being expressed on the EEG. Forty-two autistic children received a NFB therapy aiming at improving their cognitive abilities.

Results: NFB succeeded to decrease children's high theta/beta ratio by inhibiting theta activity and intensifying beta activity over different sessions. Following therapy, the children's cognitive functions were found to show comparative improvement compared to pre-treatment assessment on a range of different tasks. Auxiliary improvements were found in their social, thought and attention domains.

Conclusion: These findings propose a basic cognitive function impairment in autism spectrum disorder that can be reduced through specific NFB treatment.

Pereira JA, Sepulveda P, Rana M, Montalba C, Tejos C, Torres R, Sitaram R, Ruiz S. Self-Regulation of the Fusiform Face Area in Autism Spectrum: A Feasibility Study With Real-Time fMRI Neurofeedback. Front Hum Neurosci. 2019 Dec 20;13:446. One

of the most important and early impairments in autism spectrum disorder (ASD) is the abnormal visual processing of human faces. This deficit has been associated with hypoactivation of the fusiform face area (FFA), one of the main hubs of the face-processing network. Neurofeedback based on real-time fMRI (rtfMRI-NF) is a technique that allows the self-regulation of circumscribed brain regions, leading to specific neural modulation and behavioral changes. The aim of the present study was to train participants with ASD to achieve up-regulation of the FFA using rtfMRI-NF, to investigate the neural effects of FFA up-regulation in ASD. For this purpose, three groups of volunteers with normal I.Q. and fluent language were recruited to participate in a rtfMRI-NF protocol of eight training runs in 2 days. Five subjects with ASD participated as part of the experimental group and received contingent feedback to up-regulate bilateral FFA. Two control groups, each one with three participants with typical development (TD), underwent the same protocol: one group with contingent feedback and the other with sham feedback. Whole-brain and functional connectivity analysis using each fusiform gyrus as independent seeds were carried out. The results show that individuals with TD and ASD can achieve FFA up-regulation with contingent feedback. RtfMRI-NF in ASD produced more numerous and stronger short-range connections among brain areas of the ventral visual stream and an absence of the long-range connections to insula and inferior frontal gyrus, as observed in TD subjects. Recruitment of inferior frontal gyrus was observed in both groups during FAA up-regulation. However, insula and caudate nucleus were only recruited in subjects with TD. These results could be explained from a neurodevelopment perspective as a lack of the normal specialization of visual processing areas, and a compensatory mechanism to process visual information of faces. RtfMRI-NF emerges as a potential tool to study visual processing network in ASD, and to explore its clinical potential.

Pineda, JA., Carrasco, K., Datko, M., Pillen, S. & Schalles, M. (2014). Neurofeedback training produces normalization in behavioral and electrophysical measures of high functioning autism. Philos Trans R Soc Lond B Biol Sci: Apr 28;369. Autism spectrum disorder (ASD) is a neurodevelopmental condition exhibiting impairments in behaviour, social and communication skills. These deficits may arise from aberrant functional connections that impact synchronization and effective neural communication. Neurofeedback training (NFT), based on operant conditioning of the electroencephalogram (EEG), has shown promise in addressing abnormalities in functional and structural connectivity. We tested the efficacy of NFT in reducing symptoms in children with ASD by targeting training to the mirror neuron system (MNS) via modulation of EEG mu rhythms. The human MNS has provided a neurobiological substrate for understanding concepts in social cognition relevant to behavioural and cognitive deficits observed in ASD. Furthermore, mu rhythms resemble MNS phenomenology supporting the argument that they are linked to perception and action. Thirty hours of NFT on ASD and typically developing (TD) children were assessed. Both groups completed an eyes-open/-closed EEG session as well as a mu suppression index assessment before and after training. Parents filled out pre- and post-behavioural questionnaires. The results showed improvements in ASD subjects but not in TDs. This suggests that induction of neuroplastic changes via NFT can normalize dysfunctional mirroring networks in children with autism, but the benefits are different for TD brains.

Pineda, JA., Friedrich, EV. LaMarca, K. (2014). Neurorehabilitation of social dysfunctions: A model-based neurofeedback approach for low and high-functioning autism. Frontiers in Neuroengineering.: Aug 7(7) 29. Autism Spectrum Disorder (ASD) is an increasingly prevalent condition with core deficits in the social domain. Understanding its neuroetiology is critical to providing insights into the relationship between neuroanatomy, physiology and social behaviors, including imitation learning, language, empathy, theory of mind, and even self-awareness. Equally important is the need to find ways to arrest its increasing prevalence and to ameliorate its symptoms. In this review, we highlight neurofeedback studies as viable treatment options for high-functioning as well as low-functioning children with ASD. Lower-functioning groups have the greatest need for diagnosis and treatment, the greatest barrier to communication, and may experience the greatest benefit if a treatment can improve function or prevent progression of the disorder at an early stage. Therefore, we focus on neurofeedback interventions combined with other kinds of behavioral conditioning to induce neuroplastic changes that can address the full spectrum of the autism phenotype.

Pineda JA, Juavinett A, Datko M. (2012). Self-regulation of brain oscillations as a treatment for aberrant brain connections in children with autism. *Med Hypotheses.* 2012 Dec;79(6):790-8. doi: 10.1016/j. Autism is a highly varied developmental disorder typically characterized by deficits in reciprocal social interaction, difficulties with verbal and nonverbal

communication, and restricted interests and repetitive behaviors. Although a wide range of behavioral, pharmacological, and alternative medicine strategies have been reported to ameliorate specific symptoms for some individuals, there is at present no cure for the condition. Nonetheless, among the many incompatible observations about aspects of the development, anatomy, and functionality of the autistic brain, it is widely agreed that it is characterized by widespread aberrant connectivity. Such disordered connectivity, be it increased, decreased, or otherwise compromised, may complicate healthy synchronization and communication among and within different neural circuits, thereby producing abnormal processing of sensory inputs necessary for normal social life. It is widely accepted that the innate properties of brain electrical activity produce pacemaker elements and linked networks that oscillate synchronously or asynchronously, likely reflecting a type of functional connectivity. Using phase coherence in multiple frequency EEG bands as a measure of functional connectivity, studies have shown evidence for both global hypoconnectivity and local hyperconnectivity in individuals with ASD. However, the nature of the brain's experience-dependent structural plasticity suggests that these abnormal patterns may be reversed with the proper type of treatment. Indeed, neurofeedback (NF) training, an intervention based on operant conditioning that results in self-regulation of brain electrical oscillations, has shown promise in addressing marked abnormalities in functional and structural connectivity. It is hypothesized that neurofeedback produces positive behavioral changes in ASD children by normalizing the aberrant connections within and between neural circuits. NF exploits the brain's plasticity to normalize aberrant connectivity patterns apparent in the autistic brain. By grounding this training in known anatomical (e.g., mirror neuron system) and functional markers (e.g., mu rhythms) of autism, NF training holds promise to support current treatments for this complex disorder. The proposed hypothesis specifically states that neurofeedback-induced alpha mu (8-12Hz) rhythm suppression or desynchronization, a marker of cortical activation, should induce neuroplastic changes and lead to normalization in relevant mirroring networks that have been associated with higher-order social cognition.

Pineda, J. A., Brang, D., Futagaki, C., Hecht, E., Grichanik, M., Wood, L., Bacon, M., & Carey, S. (2007). *Effects of neurofeedback training on action comprehension and imitation learning*. Chapter in Puckhaber, H. L. (Ed.), New research in biofeedback. Hauppauge, NY: Nova Science Publishers, pp. 133-152.

Pineda JA, Brang D, Hecht E, Edwards L, Carey S, Bacon M, Futagaki C, Suk D, Tom J, Birnbaum C, Rork A. (2008). Positive behavioral and electrophysiological changes following neurofeedback training in children with autism. *Research in Autism Spectrum Disorders* 2. 557-581. Two electrophysiological studies tested the hypothesis that operant conditioning of mu rhythms via neurofeedback training can renormalize mu suppression, an index of mirror neuron activity, and improve behavior in children diagnosed with autism spectrum disorders (ASD). In Study 1, eight high-functioning ASD participants were assigned to placebo or experimental groups before 10 weeks of training of the mu frequency band (8–13 Hz). Following training, experimental participants showed decreased mu power and coherence, increased sustained attention ability, and improved scores on subscales of the ATEC compared to the placebo group. Both groups showed improvement in imitation ability. In Study 2, 19 high-functioning ASD children underwent a similar procedure with verified diagnoses, a modified double-blind protocol, and training of the high mu band (10–13 Hz). The results showed decreases in amplitude but increases in phase coherence in mu rhythms and normalization of mu rhythm suppression in experimental participants compared to placebo. Furthermore, like Study 1, participants showed improvements in sustained attention and in ATEC scores but no improvements in imitation following training. This suggests that training of the mu rhythm can be effective in producing changes in EEG and behavior in high-functioning ASD children, but does not affect imitation behavior *per se*.

Plener, P. L., & Poustka, L. (2021). Volitional modification of brain activity in adolescents with Autism Spectrum Disorder: A Bayesian analysis of Slow Cortical Potential neurofeedback. NeuroImage. Clinical, 29, 102557. Autism spectrum disorder is (ASD) characterized by a persisting triad of impairments of social interaction, language as well as inflexible, stereotyped and ritualistic behaviors. Increasingly, scientific evidence suggests a neurobiological basis of these emotional, social and cognitive deficits in individuals with ASD. The aim of this randomized controlled brain self-regulation intervention study was to investigate whether the core symptomatology of ASD could be reduced via an electroencephalography (EEG) based brain self-regulation training of Slow Cortical Potentials (SCP). 41 male adolescents with ASD were recruited and allocated to a) an experimental group undergoing 24 sessions of EEG-based brain training (n1 = 21), or to b) an active control group undergoing conventional treatment (n2 = 20), that is, clinical

counseling during a 3-months intervention period. We employed real-time neurofeedback training recorded from a fronto-central electrode intended to enable participants to volitionally regulate their brain activity. Core autistic symptomatology was measured at six time points during the intervention and analyzed with Bayesian multilevel approach to characterize changes in core symptomatology. Additional Bayesian models were formulated to describe the neural dynamics of the training process as indexed by SCP (time-domain) and power density (PSD, frequency-domain) measures. The analysis revealed a substantial improvement in the core symptomatology of ASD in the experimental group (reduction of 21.38 points on the Social Responsiveness Scale, SD = 5.29), which was slightly superior to that observed in the control group (evidence Ratio = 5.79). Changes in SCP manifested themselves as different trajectories depending on the different feedback conditions and tasks. Further, the model of PSD revealed a continuous decrease in delta power, parallel to an increase in alpha power. Most notably, a non-linear (quadratic) model turned out to be better at predicting the data than a linear model across all analyses. Taken together, our analyses suggest that behavioral and neural processes of change related to neurofeedback training are complex and non-linear. Moreover, they have implications for the design of future trials and training protocols.

Pop-Jordanova, N & Plasevska-Karanfilska, D. (2014). Autism – Genetics, electrophysiology and clinical syndromes. Prilozi;35(1). 133-46. (Full text is available at http://www.manu.edu.mk/prilozi). Autism is a severe and the most heritable developmental disorder, whose pathogenesis is still largely unknown. The rising incidence of autism in the last decade has increased the scientific interest and research. More than a thousand papers concerned with information about the etiology of this "static disorder of the immature brain" can be found on Pub Med. The aim of this paper is to give a review of published genetic chromosomal anomalies associated with autistic spectrum disorders, as well as to discuss common syndromes associated with autistic traits. In addition, some of our own findings in genetics, as well as in quantitative electroencephalography and neurofeedback training in autistic children, will be presented and discussed. Generally, the subsequent analyses indicate that the causes of autism include fewer common single-gene mutations and chromosomal abnormalities, as well as multiple interacting genes of weak effect. Genome-wide linkage analysis has identified several susceptibility loci and positional and functional candidate genes which appear to represent possible risks of the autistic spectrum. Electrophysiological findings showed high delta/theta activity in frontal-central regions, while in 25% high beta activity was detected as a result of anxiety. Neurofeedback is a promising therapy for symptom mitigation.

Scolnick, B. (2005). Effects of electroencephalogram biofeedback with Asperger's syndrome. ***International Journal of Rehabilitation Research*****, 28(2), 159-163.** This article reports the pilot study of electroencephalogram (EEG) biofeedback to improve focusing and decrease anxiety in 10 adolescent boys diagnosed with Asperger's syndrome attending a therapeutic day school. Five of the boys dropped out of the study before 12 sessions were completed. The analysis of pre- and post-intervention quantitative EEGs for the five students who completed the study showed a trend to "normalization", but did not reach statistical significance. All five boys who completed 24 sessions showed improved behavior as rated by parents and teachers, but other factors, such as maturation could not be ruled out as causes of the improvement. The challenges facing this research and proposals for further exploration are outlined.

Ramot, M., Kimmich, S., Gonzalez-Castillo, J., Roopchansingh, V., Popal, H., White, E., Gotts, S. J., & Martin, A. (2017). Direct modulation of aberrant brain network connectivity through real-time NeuroFeedback. eLife, 6, e28974. The existence of abnormal connectivity patterns between resting state networks in neuropsychiatric disorders, including Autism Spectrum Disorder (ASD), has been well established. Traditional treatment methods in ASD are limited, and do not address the aberrant network structure. Using real-time fMRI neurofeedback, we directly trained three brain nodes in participants with ASD, in which the aberrant connectivity has been shown to correlate with symptom severity. Desired network connectivity patterns were reinforced in real-time, without participants' awareness of the training taking place. This training regimen produced large, significant long-term changes in correlations at the network level, and whole brain analysis revealed that the greatest changes were focused on the areas being trained. These changes were not found in the control group. Moreover, changes in ASD resting state connectivity following the training were correlated to changes in behavior, suggesting that neurofeedback can be used to directly alter complex, clinically relevant network connectivity patterns.

Sichel, A. G., Fehmi, L. G., & Goldstein, D. M. (1995). Positive outcome with neurofeedback treatment of a case of mild autism. ***Journal of Neurotherapy*****, 1(1), 60-64.** This article looks at the experience of Frankie, an autistic 8 ½ year old boy. He was diagnosed as mildly autistic by several specialists. Our specialists claimed he was brain damaged and "autistic-like" and that there was no hope for improvement. At Frankie's mother's request, neurotherapy diagnosis and treatment was begun. Affter 31 sessions, Frankie showed positive changes in all the diagnostic dimensions defining autism in DSM-III-R. This has profound implications for treatment in a field with few low-risk alternatives.

Sokhadze, E., Singh, S., El-Baz, A., Baruth, J., Mathai, G., Sears, L., &Casanova M. (2009). Effect of a low-frequency repetitive transcranial magnetic stimulation (rTMS) on induced gamma frequency oscillations and event-related potentials during processing of illusory figures in autism spectrum disorders. ***Journal of Autism and Developmental Disorders*****, 39, 619-634.** Previous studies by our group suggest that the neuropathology of autism is characterized by a disturbance of cortical modularity. In this model a decrease in the peripheral neuropil space of affected minicolumns provides for an inhibitory deficit and a readjustment in their signal to noise bias during information processing. In this study we proposed using low frequency transcranial magnetic stimulation (rTMS) as a way increasing the surround inhibition of minicolumns in autism. Thirteen patients (ADOS and ADI-R diagnosed) and equal number of controls participated in the study. Repetitive TMS was delivered at 0.5 Hz, 2 times per week for 3 weeks. Outcome measures based on event-related potentials (ERP), induced gamma activity, and behavioral measures showed significant post-TMS improvement. The results suggest that rTMS offers a potential therapeutic intervention for autism.

Sokhadze, E., Baruth, J., Tasman, A., Sears, L., Mathai, G., El-Baz, A., & Casanova, M. (2009). Event-related potential study of novelty processing abnormalities in autism. ***Applied Psychophysiology & Biofeedback*****, 34, 37-51.** To better understand visual processing abnormalities in autism we studied the attention orienting related frontal event potentials (ERP) and the sustained attention related centro-parietal ERPs in a three stimulus oddball experiment. The three stimulus oddball paradigm was aimed to test the hypothesis that individuals with autism abnormally orient their attention to novel distracters as compared to controls. A dense-array 128 channel EGI electroencephalographic (EEG) system was used on 11 high-functioning children and young adults with autism spectrum disorder (ASD) and 11 age-matched, typically developing control subjects. Patients with ASD showed slower reaction times but did not differ in response accuracy. At the anterior (frontal) topography the ASD group showed significantly higher amplitudes and longer latencies of early ERP components (e.g., P100, N100) to novel distracter stimuli in both hemispheres. The ASD group also showed prolonged latencies of late ERP components (e.g., P2a, N200, P3a) to novel distracter stimuli in both hemispheres. However, differences were more profound in the right hemisphere for both early and late ERP components. Our results indicate augmented and prolonged early frontal potentials and a delayed P3a component to novel stimuli, which suggest low selectivity in pre-processing and later-stage under-activation of integrative regions in the prefrontal cortices. Also, at the posterior (centro-parietal) topography the ASD group showed significantly prolonged N100 latencies and reduced amplitudes of the N2b component to target stimuli. In addition, the latency of the P3b component was prolonged to novel distracters in the ASD group. In general, the autistic group showed prolonged latencies to novel stimuli especially in the right hemisphere. These results suggest that individuals with autism over-process information needed for the successful differentiation of target and novel stimuli. We propose the potential application of ERP evaluations in a novelty task as outcome measurements in the biobehavioral treatment (e.g., EEG biofeedback, TMS) of autism.

Sokhadze, E., Sokhadze, G., & Casanova, M. (2012). Neuromodulation using transcranial DC Stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS) as a translational neuroscience approach to treat autism. ***NeuroConnections*****, 30, 16-18.** Transcranial Direct Current Stimulation (tDCS) is a non-invasive neuromodulation procedure used to increase (anodal tDCS) or decrease (cathodal tDCS) cortical excitability. Recently, tDCS has been increasingly used to investigate cognitive functions in both healthy subjects and psychiatric patients. Our team was first to report positive effects of repetitive Transcranial Magnetic Stimulation (rTMS) in autism and provided rationale to consider it to be theory-driven neurotherapy. Although tDCS produces cortical effects over a longer period of time, it has several practical advantages over rTMS. First, tDCS is less prone to artifacts and is more suitable for controlled study designs. Second, tDCS is not as expensive as rTMS and can be performed with compact equipment. Third, tDCS can

be administered while recording electroencephalogram (EEG) and autonomic nervous system activity, thus allowing for concurrent investigation of physiological effects of neuromodulation. Fourth, tDCS may have great potential for cognitive and behavioral enhancement targeting to treat some of the core autism symptoms.

Sokhadze, E., Baruth, J., & Casanova, M. (2009). Neuropathological theories and EEG gamma oscillation abnormalities in autism. ***NeuroConnections*****, Fall, 34-37.** To better understand visual processing abnormalities in autism we studied the attention orienting related frontal event potentials (ERP) and the sustained attention related centro-parietal ERPs in a three stimulus oddball experiment. The three stimulus oddball paradigm was aimed to test the hypothesis that individuals with autism abnormally orient their attention to novel distracters as compared to controls. A dense-array 128 channel EGI electroencephalographic (EEG) system was used on 11 high-functioning children and young adults with autism spectrum disorder (ASD) and 11 age-matched, typically developing control subjects. Patients with ASD showed slower reaction times but did not differ in response accuracy. At the anterior (frontal) topography the ASD group showed significantly higher amplitudes and longer latencies of early ERP components (e.g., P100, N100) to novel distracter stimuli in both hemispheres. The ASD group also showed prolonged latencies of late ERP components (e.g., P2a, N200, P3a) to novel distracter stimuli in both hemispheres. However, differences were more profound in the right hemisphere for both early and late ERP components. Our results indicate augmented and prolonged early frontal potentials and a delayed P3a component to novel stimuli, which suggest low selectivity in pre-processing and later-stage under-activation of integrative regions in the prefrontal cortices. Also, at the posterior (centro-parietal) topography the ASD group showed significantly prolonged N100 latencies and reduced amplitudes of the N2b component to target stimuli. In addition, the latency of the P3b component was prolonged to novel distracters in the ASD group. In general, the autistic group showed prolonged latencies to novel stimuli especially in the right hemisphere. These results suggest that individuals with autism over-process information needed for the successful differentiation of target and novel stimuli. We propose the potential application of ERP evaluations in a novelty task as outcome measurements in the biobehavioral treatment (e.g., EEG biofeedback, TMS) of autism.

Sokhadze, E., Baruth, J., Tasman, A., Mansoor, M., Ramaswamy, R., Sears, L., Mathai, G., El -Baz, A., & Casanova, M. F. (2010). Low-frequency repetitive transcranial magnetic stimulation (rTMS) affects event-related potential measures of novelty processing in autism. ***Applied Psychophysiology & Biofeedback*** **35(2), 147-161.** In our previous study on individuals with autism spectrum disorder (ASD) (Sokhadze et al., Appl Psychophysiol Biofeedback 34:37-51, 2009a) we reported abnormalities in the attention-orienting frontal event-related potentials (ERP) and the sustained-attention centro-parietal ERPs in a visual oddball experiment. These results suggest that individuals with autism over-process information needed for the successful differentiation of target and novel stimuli. In the present study we examine the effects of low-frequency, repetitive Transcranial Magnetic Stimulation (rTMS) on novelty processing as well as behavior and social functioning in 13 individuals with ASD. Our hypothesis was that low-frequency rTMS application to dorsolateral prefrontal cortex (DLFPC) would result in an alteration of the cortical excitatory/inhibitory balance through the activation of inhibitory GABAergic double bouquet interneurons. We expected to find post-TMS differences in amplitude and latency of early and late ERP components. The results of our current study validate the use of low-frequency rTMS as a modulatory tool that altered the disrupted ratio of cortical excitation to inhibition in autism. After rTMS the parieto-occipital P50 amplitude decreased to novel distracters but not to targets; also the amplitude and latency to targets increased for the frontal P50 while decreasing to non-target stimuli. Low-frequency rTMS minimized early cortical responses to irrelevant stimuli and increased responses to relevant stimuli. Improved selectivity in early cortical responses lead to better stimulus differentiation at later-stage responses as was made evident by our P3b and P3a component findings. These results indicate a significant change in early, middle-latency and late ERP components at the frontal, centro-parietal, and parieto-occipital regions of interest in response to target and distracter stimuli as a result of rTMS treatment. Overall, our preliminary results show that rTMS may prove to be an important research tool or treatment modality in addressing the stimulus hypersensitivity characteristic of autism spectrum disorders.

Sokhadze, E., Baruth, J., El-Baz, A., Horrell, T., Sokhadze, G., Carroll, T., Tasman, A., Sears, L. & Casanova, M. (2010). Impaired error monitoring and correction function in autism. ***Journal of Neurotherapy*****,14, 79-95.** One important executive function

known to be compromised in autism spectrum disorder (ASD) is related to response error monitoring and post-error response correction. Several reports indicate that children with ASD show reduced error processing and deficient behavioral correction after an error is committed. Error sensitivity can be readily examined by measuring event-related potentials (ERP) associated with responses to errors, the fronto-central error-related negativity (ERN), and the error-related positivity (Pe). The goal of our study was to investigate whether reaction time (RT), error rate, post-error RT change, ERN, and Pe will show positive changes following 12-week long slow frequency repetitive TMS (rTMS) over dorsolateral prefrontal cortex (DLPFC) in high functioning children with ASD. We hypothesized that 12 sessions of 1 Hz rTMS bilaterally applied over the DLPFC will result in improvements reflected in both behavioral and ERP measures. Participants were randomly assigned to either active rTMS treatment or wait-list (WTL) groups. Baseline and post-TMS/or WTL EEG was collected using 128 channel EEG system. The task involved the recognition of a specific illusory shape, in this case a square or triangle, created by three or four inducer disks. ERN in TMS treatment group became significantly more negative. The number of omission errors decreased post-TMS. The RT did not change, but post-error RT became slower. There were no changes in RT, error rate, post-error RT slowing, nor in ERN/Pe measures in the wait-list group. Our results show significant post-TMS differences in the response-locked ERP such as ERN, as well as behavioral response monitoring measures indicative of improved error monitoring and correction function. The ERN and Pe, along with behavioral performance measures, can be used as functional outcome measures to assess the effectiveness of neuromodulation (e.g., rTMS) in children with autism and thus may have important practical implications.

Sokhadze, E., Baruth, J. M., Sears, L., Sokhadze, GE., El-Baz, A. S., & Casanova, MF. (2012). Prefrontal neuromodulation using rTMS improves error monitoring and correction functions in autism. ***Applied Psychophysiology & Biofeedback*****, 37(2), 91-102.** One important executive function known to be compromised in autism spectrum disorder (ASD) is related to response error monitoring and post-error response correction. Several reports indicate that children with ASD show reduced error processing and deficient behavioral correction after an error is committed. Error sensitivity can be readily examined by measuring event-related potentials (ERP) associated with responses to errors, the fronto-central error-related negativity (ERN), and the error-related positivity (Pe). The goal of our study was to investigate whether reaction time (RT), error rate, post-error RT change, ERN, and Pe will show positive changes following 12-week long slow frequency repetitive TMS (rTMS) over dorsolateral prefrontal cortex (DLPFC) in high functioning children with ASD. We hypothesized that 12 sessions of 1 Hz rTMS bilaterally applied over the DLPFC will result in improvements reflected in both behavioral and ERP measures. Participants were randomly assigned to either active rTMS treatment or wait-list (WTL) groups. Baseline and post-TMS/or WTL EEG was collected using 128 channel EEG system. The task involved the recognition of a specific illusory shape, in this case a square or triangle, created by three or four inducer disks. ERN in TMS treatment group became significantly more negative. The number of omission errors decreased post-TMS. The RT did not change, but post-error RT became slower. There were no changes in RT, error rate, post-error RT slowing, nor in ERN/Pe measures in the wait-list group. Our results show significant post-TMS differences in the response-locked ERP such as ERN, as well as behavioral response monitoring measures indicative of improved error monitoring and correction function. The ERN and Pe, along with behavioral performance measures, can be used as functional outcome measures to assess the effectiveness of neuromodulation (e.g., rTMS) in children with autism and thus may have important practical implications.

Sokhadze, E., Baruth, J., Sears, L., Sokhadze, GE., El-Baz, A., Williams, E., Klapheke, R., & Casanova, MF. (2012). Event related potentials study of attention regulation during illusory figure categorization task in ADHD, autism spectrum disorders, and typical children. ***Journal of Neurotherapy*****,16, 12-31.** Autism spectrum disorders (ASD) and attention deficit/hyperactivity disorder (ADHD) are very common developmental disorder that share some similar symptoms of social, emotional, and attentional deficits. This study is aimed to help understand the differences and similarities of these deficits using analysis of dense-array event-related potentials (ERP) during an illusory figure recognition task. Although ADHD and ASD seem very distinct, they have been shown to share some similarities in their symptoms. Our hypothesis was that children with ASD will show less pronounced differences in ERP responses to target and nontarget stimuli as compared to typical children and, to a lesser extent, ADHD. Participants were children with ASD (N=16), ADHD (N=16), and controls (N=16). EEG was collected using a 128-channel EEG system. The task involved the recognition of a specific illusory shape, in this case a square or triangle, created by three or four inducer disks. There were no between-group differences

in reaction time (RT) to target stimuli, but both ASD and ADHD committed more errors; specifically, the ASD group had statistically higher commission error rate than controls. Posterior RT in ASD group was exhibited in a posterror speeding rather than corrective RT slowing typical for the controls. The ASD group also demonstrated an attenuated error-related negativity as compared to ADHD and controls. The fronto-central P200, N200, and P300 were enhanced and less differentiated in response to target and nontarget figures in the ASD group. The same ERP components were marked by more prolonged latencies in the ADHD group as compared to both ASD and typical controls. The findings are interpreted according to the "minicolumnar" hypothesis proposing existence of neuropathological differences in ASD and ADHD, specifically minicolumnar number/width morphometry spectrum differences. In autism, a model of local hyperconnectivity and long-range hypoconnectivity explains many of the behavioral and cognitive deficits present in the condition, whereas the inverse arrangement of local hypoconnectivity and long-range hyperconnectivity in ADHD explains some deficits typical for this disorder. The current ERP study supports the proposed suggestion that some between-group differences could be manifested in the frontal ERP indices of executive functions during performance on an illusory figure categorization task.

Sokhadze, E., Sokhadze, G., & Casanova, M. (2012). Neuromodulation using transcranial DC Stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS) as a translational neuroscience approach to treat autism. NeuroConnections, 30, 16-18.

Steiner, NJ., Frenette, E., Hynes, C., Pisarik, E., Tomasetti, K., Perrin, EC. & Rene, K. (2014). A pilot feasibility study of neurofeedback for children with autism. Applied Psychophysiology and Biobeedback:39(2). 99-107. Neurofeedback (NFB) is an emerging treatment for children with autism spectrum disorder (ASD). This pilot study examined the feasibility of NFB for children with ASD. Ten children ages 7-12 with high functioning ASD and attention difficulties received a NFB attention training intervention. A standardized checklist captured feasibility, including focus during exercises and academic tasks, as well as off-task behaviors. Active behaviors and vocalizations were the most frequent off-task behaviors. Positive reinforcement and breaks including calm breathing exercises were the most common supports. Low motivation was associated with higher feasibility challenges, yet parental involvement and accommodations were helpful. This pilot study shows that it is feasible to conduct NFB sessions with children with high functioning autism and attention difficulties.

Thompson L, Thompson M, Reid A. (2010). Functional neuroanatomy and the rationale for using EEG biofeedback for clients with Asperger's syndrome. *Appl Psychophysiol Biofeedback*. 2010 Mar;35(1):39-6. This paper reviews the symptoms of Asperger's Syndrome (AS), a disorder along the autism continuum, and highlights research findings with an emphasis on brain differences. Existing theories concerning AS are described, including theory of mind (Hill and Frith in Phil Trans Royal Soc Lond, Bull 358:281-289, 2003), mirror neuron system (Ramachandran and Oberman in Sci Am 295(5):62-69, 2006), and Porges' (Ann N Y Acad Sci 1008:31-47, 2003, The neurobiology of autism, Johns Hopkins University Press, Baltimore, 2004) polyvagal theory. (A second paper, Outcomes using EEG Biofeedback Training in Clients with Asperger's Syndrome, summarizes clinical outcomes obtained with more than 150 clients.) Patterns seen with QEEG assessment are then presented. Single channel assessment at the vertex (CZ) reveals patterns similar to those found in Attention-Deficit/Hyperactivity Disorder. Using 19-channel data, significant differences (z-scores > 2) were found in the amplitude of both slow waves (excess theta and/or alpha) and fast waves (beta) at various locations. Differences from the norm were most often found in mirror neuron areas (frontal, temporal and temporal-parietal). There were also differences in coherence patterns, as compared to a normative database (Neuroguide). Low Resolution Electromagnetic Tomography Analysis (Pascual-Marqui et al. in Methods Find Exp Clin Pharmacol 24C:91-95, 2002) suggested the source of the abnormal activity was most often the anterior cingulate. Other areas involved included the amygdala, uncus, insula, hippocampal gyrus, parahippocampal gyrus, fusiform gyrus, and the orbito-frontal and/or ventromedial areas of the prefrontal cortex. Correspondence between symptoms and the functions of the areas found to have abnormalities is evident and those observations are used to develop a rationale for using EEG biofeedback, called neurofeedback (NFB), intervention. NFB training is targeted to improve symptoms that include difficulty reading and mirroring emotions, poor attention to the outside world, poor self-regulation skills, and anxiety. Porges' polyvagal theory is used to emphasize the need to integrate NFB with biofeedback (BFB), particularly heart rate variability training. We term this emerging understanding the Systems Theory of Neural

Synergy. The name underscores the fact that NFB and BFB influence dynamic circuits and emphasizes that, no matter where we enter the nervous system with an intervention, it will seek its own new balance and equilibrium.

Thompson, L., Thompson, M., Reid, A. (2010). Neurofeedback outcomes with clients with Asperger's syndrome. ***Applied Psychophysiology and Biofeedback*****, 35(1) 63-81.** This paper summarizes data from a review of neurofeedback (NFB) training with 150 clients with Asperger's Syndrome (AS) and 9 clients with Autistic Spectrum Disorder (ASD) seen over a 15 year period (1993–2008) in a clinical setting. The main objective was to investigate whether electroncephalographic (EEG) biofeedback, also called neuro feedback (NFB), made a significant difference in clients diagnosed with AS. An earlier paper (Thompson et al. 2009) reviews the symptoms of AS, highlights research findings and theories concerning this disorder, discusses QEEG patterns in AS (both single and 19-channel), and details a hypothesis, based on functional neuroanatomy, concerning how NFB, often paired with biofeedback (BFB), might produce a change in symptoms. A further aim of the current report is to provide practitioners with a detailed description of the method used to address some of the key symptoms of AS in order to encourage further research and clinical work to refine the use of NFB plus BFB in the treatment of AS. All charts were included for review where there was a diagnosis of AS or ASD and pre- and post-training testing results were available for one or more of the standardized tests used. Clients received 40–60 sessions of NFB, which was combined with training in metacognitive strategies and, for most older adolescent and adult clients, with BFB of respiration, electrodermal response, and, more recently, heart rate variability. For the majority of clients, feedback was contingent on decreasing slow wave activity (usually 3–7 Hz), decreasing beta spindling if it was present (usually between 23 and 35 Hz), and increasing fast wave activity termed sensorimotor rhythm (SMR) (12–15 or 13–15 Hz depending on assessment findings). The most common initial montage was referential placement at the vertex (CZ) for children and at FCz (midway between FZ and CZ) for adults, referenced to the right ear. Metacognitive strategies relevant to social understanding, spatial reasoning, reading comprehension, and math were taught when the feedback indicated that the client was relaxed, calm, and focused. Significant improvements were found on measures of attention (T.O.V.A. and IVA), core symptoms (Australian Scale for Asperger's Syndrome, Conners' Global Index, SNAP version of the DSM-IV criteria for ADHD, and the ADD-Q), achievement (Wide Range Achievement Test), and intelligence (Wechsler Intelligence Scales). The average gain for the Full Scale IQ score was 9 points. A decrease in relevant EEG ratios was also observed. The ratios measured were $(4–8\ Hz)^2/(13–21\ Hz)^2$, (4–8 Hz)/(16–20 Hz), and (3–7 Hz)/(12–15 Hz). The positive outcomes of decreased symptoms of Asperger's and ADHD (including a decrease in difficulties with attention, anxiety, aprosodias, and social functioning) plus improved academic and intellectual functioning, provide preliminary support for the use of neurofeedback as a helpful component of effective intervention in people with AS.

Vasa, RA., Carroll, LM., Nozzolillio, AA., Mahajan, R., Mazurek, MO., Bennett, AE., Wink, LK. & Bernal, MP. (2014). A systematic review of treatments for anxiety in youth with autism spectrum disorders. J Autism Dev Disord. July 2014 Early e-pub. This study systematically examined the efficacy and safety of psychopharmacological and non-psychopharmacological treatments for anxiety in youth with autism spectrum disorders (ASD). Four psychopharmacological, nine cognitive behavioral therapy (CBT), and two alternative treatment studies met inclusion criteria. Psychopharmacological studies were descriptive or open label, sometimes did not specify the anxiety phenotype, and reported behavioral activation. Citalopram and buspirone yielded some improvement, whereas fluvoxamine did not. Non-psychopharmacological studies were mainly randomized controlled trials (RCTs) with CBT demonstrating moderate efficacy for anxiety disorders in youth with high functioning ASD. Deep pressure and neurofeedback provided some benefit. All studies were short-term and included small sample sizes. Large scale and long term RCTs examining psychopharmacological and non-psychopharmacological treatments are sorely needed.

COGNITIVE, SPORT, & CORPORATE OPTIMAL/PEAK PERFORMANCE

Angelakis, E., Stathopoulou, S., Frymiare, J. L., Green, D. L., Lubar, J. F., & Kounios, J. (2007). EEG neurofeedback: A brief overview and an example of peak alpha frequency training for cognitive enhancement in the elderly. *Clinical Neuropsychology*, 21(1), 110-129. OBJECTIVE: Electroencephalographic (EEG) peak alpha frequency (PAF) (measured in Hz) has been correlated to cognitive performance between healthy and clinical individuals, and among healthy individuals. PAF also varies within individuals across developmental stages, among different cognitive tasks, and among physiological states induced by administration of various substances. The present study suggests that, among other things, PAF reflects a trait or state of cognitive preparedness. METHODS: Experiment 1 involved 19-channel EEG recordings from 10 individuals with traumatic brain injury (TBI) and 12 healthy matched controls, before, during, and after tasks of visual and auditory attention. Experiment 2 involved EEG recordings from 19 healthy young adults before and after a working memory task (WAIS-R Digit Span), repeated on 2 different days to measure within-individual differences. RESU LTS: Experiment 1 showed significantly lower PAF in individuals with TBI, mostly during post-task rest. Experiment 2 showed PAF during pre-task baseline to be significantly correlated with Digit Span performance of the same day but not with Digit Span performance of another day. Moreover, PAF was significantly increased after Digit Span for those participants whose PAF was lower than the sample median before the task, but not for those who had it higher. Finally, both PAF and Digit Span performance were increased during the second day. CONCLUSIONS: PAF was shown to detect both trait and state differences in cognitive preparedness, as well as to be affected by cognitive tasks. Traits are better reflected during post-task rest, whereas states are better reflected during initial resting baseline recordings.

Behzadfar, N., Firoozabadi, S. M., & Badie, K. (2016). Low-Complexity Discriminative Feature Selection From EEG Before and After Short-Term Memory Task. Clinical EEG and neuroscience, 47(4), 291–297. https://doi.org/10.1177/1550059416633951. A reliable and unobtrusive quantification of changes in cortical activity during short-term memory task can be used to evaluate the efficacy of interfaces and to provide real-time user-state information. In this article, we investigate changes in electroencephalogram signals in short-term memory with respect to the baseline activity. The electroencephalogram signals have been analyzed using 9 linear and nonlinear/dynamic measures. We applied statistical Wilcoxon examination and Davis-Bouldian criterion to select optimal discriminative features. The results show that among the features, the permutation entropy significantly increased in frontal lobe and the occipital second lower alpha band activity decreased during memory task. These 2 features reflect the same mental task; however, their correlation with memory task varies in different intervals. In conclusion, it is suggested that the combination of the 2 features would improve the performance of memory based neurofeedback systems.

Bertollo, M., Bortoli, L., Gramaccione, G., Hanin, Y., Comani, S. & Robazza, C. (2013). Behavioral and psychophiologica l correlates of athletic performance: A test of the multi-action plan model. Applkied Psychophysiology and Biofeedback: 38(2). 91-99. The main purposes of the present study were to substantiate the existence of the four types of performance categories (i.e., optimal-automatic, optimal-controlled, suboptimal- controlled, and suboptimal-automatic) as hypothesised in the multi-action plan (MAP) model, and to investigate whether some specific affective, behavioural, psychophysiological, and postural trends may typify each type of performance. A 20- year-old athlete of the Italian shooting team, and a 46-year-old athlete of the Italian dart-throwing team participated in the study. Athletes were asked to identify the core components of the action and then to execute a large number of shots/flights. A 2 × 2 (optimal/suboptimal × automated/controlled) within subjects multivariate analysis of variance was performed to test the differences among the four types of performance. Findings provided preliminary evidence of psychophysiological and postural differences among four performance categories as conceptualized within the MAP model. Monitoring the entire spectrum of psychophysiological and behavioural features related to the different types of performance is important to develop and

implement biofeedback and neurofeedback techniques aimed at helping athletes to identify individual zones of optimal functioning and to enhance their performance.

Boynton, T. (2001). Applied research using alpha/theta training for enhancing creativity and well-being. ***Journal of Neurotherapy,*** **5(1-2), 5-18.** Introduction. Previous research has supported anecdotal reports of a possible correlation between the state of hypnagogia and the enhancement of creative ability (Green, 1972; Green, Green, & Walters, 1970, 1974; Parks, 1996; Stembridge, 1972; Whisenant & Murphy, 1977). Some psychologists (e.g., Maslow, 1963; Rogers, 1978) have suggested that there is also a correlation between creative ability and enhanced well-being. Methods. This study utilized an 8-week repeated-measures experimental design to investigate the effects of electroencephalogram (EEG) biofeedback on the willful use of hypnagogia for increasing creativity and well-being. The sample size of 62 (30 experimental subjects and 32 controls) was comprised of both sexes with a mean age of 45. The EEG parameters of hypnagogia were broadly defined as the presence and pre-dominance of alpha and theta brain wave activity. Creativity was defined by the three most readily agreed upon divergent thinking abilities: (a) fluency (the ability to generate numerous ideas), (b) flexibility (the ability to see a given problem from multiple perspectives), and (c) originality (the ability to come up with new and unique ideas). Results. Hypnagogia was analyzed through multiple univariate analyses of variance. The EEG data showed that both experimental and control participants were able to achieve light to deep hypnagogic states in every training session. T-tests results on fluency and originality scores from the Torrance Test of Creative Thinking and the Christensen-Guilford Associational Fluency Test showed no significant changes in pre- and post-tests for either group. However, flexibility in thinking, as measured by the Alternate Uses Test was significantly increased ($p < .001$) for all participants. Well-being, as measured by the Friedman Well-Being Scale, also significantly increased for all participants ($p = .002$). Discussion. The data suggest that willful use of hynagogia may indeed increase creativity and well-being. Participants reported increased personal creativity, stress reduction, heightened self- awareness, emotional equanimity, and improved work performance.

Budzynski, T., Budzynski, H. K., &l Tang, H-Y. (2007). ***Brain brightening: restoring the aging mind*****. Chapter in J. R. Evans (Ed.), Handbook of Neurofeedback. Binghamton, NY: Haworth Medical Press, pp. 231-265**. (No abstract available)

Budzynski, T. H. (1996). Brain brightening: Can neurofeedback improve cognitive process? ***Biofeedback*****, 24(2), 14-17.** (No abstract available)

Cannon R, Lubar J, Congedo M, Thornton K, Towler K, Hutchens T. (2007). The effects of neurofeedback training in the cognitive division of the anterior cingulate gyrus. ***Int J Neurosci*****;117(3):337-57.** This study examines the efficacy of neurofeedback training in the cognitive division of the anterior cingulate gyrus and describes its relationship with cortical regions known to be involved in executive functions. This study was conducted with eight non-clinical students, four male and four female, with a mean age of twenty-two. Learning occurred in the ACcd at significant levels over sessions and in the anterior regions that receive projections from the AC. There appears to be a multidimensional executive circuit that increases in the same frequency in apparent synchrony with the AC and it may be possible to train this sub-cortical region using LNFB.

Dekker, MK., Van den Berg, BR., Denissen, AJ., Sitskoom, MM. & Van Boxtel, GJ. (2014). Feasibility of eyes open alpha power training for mental enhancement in elite gymnasts. J Sports Sci: Aug32(16). 1550-1560. Abstract This study focuses on a novel, easy to use and instruction-less method for mental training in athletes. Previous findings suggest that particular mental capacities are needed for achieving peak performance; including attentional control, focus, relaxation and positive affect. Electroencephalography (EEG) alpha brain activity has been associated with neural inhibition during processes of selective attention, for improving efficiency in information processing. Here we hypothesised

that eyes open alpha power training by music teaches athletes to (1) learn to self-regulate their brain activity, and (2) learn to increase their baseline alpha power, herewith improving mental capacities such as focusing the allocation of attention. The study was double-blind and placebo-controlled. Twelve elite gymnasts were either given eyes open alpha power training or random beta power training (controls). Results indicate small improvements in sleep quality, mental and physical shape. In our first attempt at getting a grip on mental capacities in athletes, we think this novel training method can be promising. Because gymnastics is one of the most mentally demanding sports, we value even small benefits for the athlete and consider them indicative for future research.

Egner, T., & Gruzelier, J. H. (2004). EEG biofeedback of low beta band components: Frequency-specific effects on variables of attention and event-related brain potentials. ***Clinical Neurophysiology*****, 115, 131-139.** Objective: To test a common assumption underlying the clinical use of electroencephalographic (EEG) biofeedback training (neurofeedback), that the modulation of discreet frequency bands is associated with frequency-specific effects. Specific ally, the proposal was assessed that enhancement of the low beta components sensorimotor rhythm (SMR: 1215 Hz) and beta1 (1518 Hz) affect different aspects of attentional processing. Methods: Subjects (n=25) were randomly allocated to training with either an SMR or beta1 protocol, or to a non- neurofeedback control group. Subjects were assessed prior and subsequent to the training process on two tests of sustained attention. The neurofeedback participants were also assessed on target P300 event-related potential (ERP) amplitudes in a traditional auditory oddball paradigm. Results: Protoc ol-specific effects were obtained in that SMR training was associated with increased perceptual sensitivity d prime (d), and reduced omission errors and reaction time variability. Beta1 training was associated with faster reaction times and increased target P300 amplitudes, whereas no changes were evident in the control group. Conclusions: Neurofeedback training of SMR and beta1 band components led to significant and protocol-specific effects in healthy subjects. The data can be interpreted as indicating a general attention-enhancing effect of SMR training, and an arousal-enhancing effect of beta1 training.

Egner, T., & Gruzelier, J. H. (2004). The temporal dynamics of electroencephalographic responses to alpha/theta neurofeedback training in healthy subjects. ***Journal of Neurotherapy,*** **8(1), 43-57.** Background. It has been shown recently that accurate feedback of alpha and theta electroencephalographic (EEG) activity, as employed in the commonly used "alpha/theta protocol," induced linear increments in within-session theta-over-alpha ratios in comparison to non-contingent feedback in a healthy sample. These data verify that alpha/theta feedback can facilitate within-session operant control over the EEG signature targeted by the training protocol. However, it is neither known whether any between-session theta/alpha ratio changes do reliably occur, nor what kind of temporal dynamics between the alpha and theta band amplitudes characterize within-session and/or between-session theta/alpha ratio changes. Method. In order to address these issues, analyses of an extensive data set (n = 48) of alpha/theta training in healthy volunteers were carried out. Specific ally, alpha, theta, and theta/alpha ratio EEG dynamics were contrasted between groups of subjects that engaged in 10 sessions of training at PZ (n = 28), five sessions of training at PZ (n = 10), and 10 sessions at FZ (n = 10). Results. For alpha/theta training at PZ, significant within-session increments in theta/alpha ratios were mediated by slightly less pronounced decrements in theta than in alpha activity during the sessions. The traditional alpha/theta protocol at PZ was nevertheless associated with significant theta activity increments across the training process. For training at FZ, no significant within- or between-session changes in theta, alpha, or theta/alpha ratio values were found, but a progressively higher rate of within-session theta/alpha ratio modulation was evident across sessions. Furthermore, in contrast to the PZ groups, any changes in theta/alpha ratio at FZ were mediated by increases in theta relative to alpha amplitudes. Conclusions. These data elucidate the dynamics underlying the within-session theta/alpha ratio increments associated with posterior alpha/theta training, and document an increase in theta activity across 10 sessions of training, offering further evidence for a neurophysiological impact of this training protocol. In addition, the contrasting EEG characteristics associated with frontal versus posterior alpha/theta training underline the heterogeneous nature of these frequency components across varying scalp sites.

Egner, T. & Gruzelier, JH. (2003). Ecological validity of neurofeedback: modulation of slow wave EEG enhances musical performance. ***NeuroReport*****, 14(9) 1221-1224.** Biofeedback-assisted modulation of electrocortical activity has been established to have intrinsic clinical benefits and has been shown to improve cognitive performance in healthy humans. In order to further investigate the pedagogic relevance of electroencephalograph (EEG) biofeedback (neurofeedback) for enhancing normal function, a series of investigations assessed the training's impact on an ecologically valid real-life behavioural performance measure: music performance under stressful conditions in conservatoire students. In a pilot study, single-blind expert ratings documented improvements in musical performance in a student group that received training on attention and relaxation related neurofeedback protocols, and improvements were highly correlated with learning to progressively raise theta (5-8 Hz) over alpha (8-11 Hz) band amplitudes. These findings were replicated in a second experiment where an alpha/theta training group displayed significant performance enhancement not found with other neurofeedback training protocols or in alternative interventions, including the widely applied Alexander technique.

Gruzelier, JH. (2014). EEG-neurofeedback for optimizing performance. III: A review of methodological and theoretical considerations. Neurosci Biobehav Rev: Jul:44. 159-182. In continuing this three-part review on validation of EEG-neurofeedback for optimal performance evidence is first provided for feedback influences on the CNS, the integration of EEG with fMRI methodology as well as anatomical correlates. Then whereas Parts I and II reviewed the considerable behavioural outcome gains and evidence for their feedback causation, part III lays bare the not inconsiderable methodological and theoretical conundrums. Cardinal assumptions amongst practitioners about specificity of topography, behavioural outcome and frequency bands are critically examined. The hitherto mostly neglected nature of feedback learning is reviewed including evidence of within- and between-session and successive baseline learning; the enduring impact on the tonic EEG; implications for experimental design, individual differences and the trainer-participant interface; distinguishing between the learning and mastery of self-regulation; connectivity, ratio, unidirectional and multimodal feedback protocols. A thorough grounding in human neuroscience plus interpersonal skills are considered prerequisites for scientific advancement and ethically sound practice.

Gruzelier, JH. (2014). EEG-neurofeedback for optimizing performance. II: Creativity, the performing arts and ecological validity. Neurosci Biobehav Rev: Jul:44. 142-158. As a continuation of a review of evidence of the validity of cognitive/affective gains following neurofeedback in healthy participants, including correlations in support of the gains being mediated by feedback learning (Gruzelier, 2014a), the focus here is on the impact on creativity, especially in the performing arts including music, dance and acting. The majority of research involves alpha/theta (A/T), sensory-motor rhythm (SMR) and heart rate variability (HRV) protocols. There is evidence of reliable benefits from A/T training with advanced musicians especially for creative performance, and reliable benefits from both A/T and SMR training for novice music performance in adults and in a school study with children with impact on creativity, communication/presentation and technique. Making the SMR ratio training context ecologically relevant for actors enhanced creativity in stage performance, with added benefits from the more immersive training context. A/T and HRV training have benefitted dancers. The neurofeedback evidence adds to the rapidly accumulating validation of neurofeedback, while performing arts studies offer an opportunity for ecological validity in creativity research for both creative process and product.

Gruzelier, JH. (2014). EEG-neurofeedback for optimizing performance. I: A review of cognitive and affective outcome in healthy participants. Neurosci Biobehav Rev: Jul:44. 124-141. A re-emergence of research on EEG-neurofeedback followed controlled evidence of clinical benefits and validation of cognitive/affective gains in healthy participants including correlations in support of feedback learning mediating outcome. Controlled studies with healthy and elderly participants, which have increased exponentially, are reviewed including protocols from the clinic: sensory-motor rhythm, beta1 and alpha/theta ratios, down-training theta maxima, and from neuroscience: upper-alpha, theta, gamma, alpha desynchronisation. Outcome gains include sustained attention, orienting and executive attention, the P300b, memory, spatial rotation, RT, complex psychomotor skills, implicit procedural memory, recognition memory, perceptual binding, intelligence, mood and

well-being. Twenty-three of the controlled studies report neurofeedback learning indices along with beneficial outcomes, of which eight report correlations in support of a meditation link, results which will be supplemented by further creativity and the performing arts evidence in Part II. Validity evidence from optimal performance studies represents an advance for the neurofeedback field demonstrating that cross fertilisation between clinical and optimal performance domains will be fruitful. Theoretical and methodological issues are outlined further in Part III.

Gruzelier, JH, Foks, M, Steffert, T, Chen, MJ. & Ros, T. (2013). Beneficial outcome from EEG-neurofeedback on creative music performance, attention and well-being in school children. *Biol Psychol.* 2013 Apr 25. pii: S0301-0511(13)00099-9. doi:10.1016/j.biopsycho.2013.04.005. [Epub ahead of print]. We earlier reported benefits for creativity in rehearsed music performance from alpha/theta (A/T) neurofeedback in conservatoire studies (Egner & Gruzelier, 2003) which were not found with SMR, Beta1, mental skills, aerobics or Alexander training, or in standby controls. Here the focus was the impact on novice music performance. A/T and SMR training were compared in 11- year old school children along with non-intervention controls with outcome measures not only of rehearsed music performance but also of creative improvisation, as well as sustained attention and phenomenology. Evidence of effective learning in the school setting was obtained for A/T and SMR/beta2 ratios. Preferential benefits from A/T for rehearsed music performance were replicated in children for technique and communication ratings. Benefits extended to creativity and communication ratings for creative improvisation which were shared with SMR training, disclosing an influence of SMR on unrehearsed music performance at a novice level with its greater cognitive demands. In a first application of A/T for improving sustained attention (TOVA), it was found to be more successful than SMR training, with a notable reduction in commission errors in the children, 15/33 of whom had attention indices in the ADHD range. Phenomenological reports were in favour of neurofeedback and well-being benefits. Implementing neurofeedback in the daily school setting proved feasible and holds pedagogic promise.

Gruzelier JH., Thompson T., Redding E., Brandt R & Steffert T. (2013). Application of alpha/theta neurofeedback and heart rate variability training to young contemporary dancers: State anxiety and creativity. Int J Psychophysiol. 2013 May 15. doi:10.1016/j.ijpsycho.2013.05.004. As one in a series on the impact of EEG-neurofeedback in the performing arts, we set out to replicate a previous dance study in which alpha/theta (A/T) neurofeedback and heart rate variability (HRV) biofeedback enhanced performance in competitive ballroom dancers compared with controls. First year contemporary dance conservatoire students were randomized to the same two psychophysiological interventions or a choreology instruction comparison group or a no- training control group. While there was demonstrable neurofeedback learning, there was no impact of the three interventions on dance performance as assessed by four experts. However, HRV training reduced anxiety and the reduction correlated with improved technique and artistry in performance; the anxiety scale items focused on autonomic functions, especially cardiovascular activity. In line with the putative impact of hypnogogic training on creativity A/T training increased cognitive creativity with the test of unusual uses, but not insight problems. Methodological and theoretical implications are considered.

Gruzelier, J . (2009). A theory of alpha/theta neurofeedback, creative performance enhancement, long distance functional connectivity and psychological integration. *Cognitive Processing*, 10 (Suppl 1), S101-109. Professionally significant enhancement of music and dance performance and mood has followed training with an EEG- neurofeedback protocol which increases the ratio of theta to alpha waves using auditory feedback with eyes closed. While originally the protocol was designed to induce hypnogogia, a state historically associated with creativity, the outcome was psychological integration, while subsequent applications focusing on raising the theta -alpha ratio, reduced depression and anxiety in alcoholism and resolved post traumatic stress syndrome (PTSD). In optimal performance studies we confirmed associations with creativity in musical performance, but effects also included technique and communication. We extended efficacy to dance and social anxiety. Diversity of outcome has a counterpart in wide ranging associations between theta oscillations and behaviour in cognitive and affective neuroscience: in animals with sensory-motor activity in exploration, effort,

working memory, learning, retention and REM sleep; in man with meditative concentration, reduced anxiety and sympathetic autonomic activation, as well as task demands in virtual spatial navigation, focussed and sustained attention, working and recognition memory, and having implications for synaptic plasticity and long term potentiation. Neuroanatomical circuitry involves the ascending mescencephalic-cortical arousal system, and limbic circuits subserving cognitive as well as affective/motivational functions. Working memory and meditative bliss, representing cognitive and affective domains, respectively, involve coupling between frontal and posterior cortices, exemplify a role for theta and alpha waves in mediating the interaction between distal and widely distributed connections. It is posited that this mediation in part underpins the integrational attributes of alpha-theta training in optimal performance and psychotherapy, creative associations in hypnogogia, and enhancement of technical, communication and artistic domains of performance in the arts.

Hannah ST, Balthazard PA, Waldman DA, Jennings PL & Thatcher RW. (2103). The psychological and neurological bases of leader self-complexity and effects on adaptive decision-making. J Appl Psychol. 2013 May;98(3):393-411. doi:10.1037/a0032257. Epub 2013 Apr 1. Complex contexts and environments require leaders to be highly adaptive and to adjust their behavioral responses to meet diverse role demands. Such adaptability may be contingent upon leaders having requisite complexity to facilitate effectiveness across a range of roles. However, there exists little empirical understanding of the etiology or basis of leader complexity. To this end, we conceptualized a model of leader self-complexity that is inclusive of both the mind (the complexity of leaders' self-concepts) and the brain (the neuroscientific basis for complex leadership). We derived psychometric and neurologically based measures, the latter based on quantitative electroencephalogram (qEEG) profiles of leader self-complexity, and tested their separate effects on the adaptive decision-making of 103 military leaders. Results demonstrated that both measures accounted for unique variance in external ratings of adaptive decision-making. We discuss how these findings provide a deeper understanding of the latent and dynamic mechanisms that und erpin leaders' self- complexity and their adaptability. (PsycINFO Database Record (c) 2013 APA, all rights reserved).

Hanslmayer, S., Sauseng, P., Doppelmayr, M., Schabus, M., & Klimesch, W. (2005). Increasing individual upper alpha by neurofeedback improves cognitive performance in human subjects. *Applied Psychophysiology & Biofeedback*, 30(1), 1-10. The hypothesis was tested of whether neurofeedback training (NFT)—applied in order to increase upper alpha but decrease theta power—is capable of increasing cognitive performance. A mental rotation task was performed before and after upper alpha and theta NFT. Only those subjects who were able to increase their upper alpha power (responders) performed better on mental rotations after NFT. Training success (extent of NFT-induced increase in upper alpha power) was positively correlated with the improvement in cognitive performance. Furthermore, the EEG of NFT responders showed a significant increase in reference upper alpha power (i.e. in a time interval preceding mental rotation). This is in line with studies showing that increased upper alpha power in a prestimulus (reference) interval is related to good cognitive performance.

Hatfield, B, Haufler, A. (2009). Brain processes and neurofeedback for performance enhancement of precision motor behavior. *NeuroImage,* 5638 810-817. Based on a number of empirical investigations of cerebral cortical dynamics during precision aiming tasks (i.e. marksmanship) employing electroencephalography (EEG) refinement of cortical activity and attenuation of nonessential cortico-cortical communication with the motor planning regions of the brain results in superior performance. Employment of EEG neurofeedback during the aiming period of target shooting designed to reduce cortical activation resulted in improved performance in skilled marksmen. Such an effect implies that refinement of cortical activity is causally related to performance. Recently, we examined cerebral cortical dynamics during the stress of competitive target shooting and observed increased activation and cortico-cortical communication between non-motor and motor regions relative to a practice-alone condition. As predicted, this finding was associated with degradation of shooting performance. These findings imply that neurofeedback targeted to brain regions related to emotional responding may preserve the cortical dynamics associated with superior performance resulting in improved accuracy of precision aiming performance.

Hsueh, J. J., Chen, T. S., Chen, J. J., & Shaw, F. Z. (2016). Neurofeedback training of EEG alpha rhythm enhances episodic and working memory. Human brain mapping, 37(7), 2662–2675. https://doi.org/10.1002/hbm.23201. Neurofeedback training (NFT) of the alpha rhythm has been used for several decades but is still controversial in regards to its trainability and effects on working memory. Alpha rhythm of the frontoparietal region are associated with either the intelligence or memory of healthy subjects and are also related to pathological states. In this study, alpha NFT effects on memory performances were explored. Fifty healthy participants were recruited and randomly assigned into a group receiving a 8-12-Hz amplitude (Alpha) or a group receiving a random 4-Hz amplitude from the range of 7 to 20 Hz (Ctrl). Three NFT sessions per week were conducted for 4 weeks. Working memory was assessed by both a backward digit span task and an operation span task, and episodic memory was assessed using a word pair task. Four questionnaires were used to assess anxiety, depression, insomnia, and cognitive function. The Ctrl group had no change in alpha amplitude and duration. In contrast, the Alpha group showed a progressive significant increase in the alpha amplitude and total alpha duration of the frontoparietal region. Accuracies of both working and episodic memories were significantly improved in a large proportion of participants of the Alpha group, particularly for those with remarkable alpha-amplitude increases. Scores of four questionnaires fell in a normal range before and after NFT. The current study provided supporting evidence for alpha trainability within a small session number compared with that of therapy. The findings suggested the enhancement of working and episodic memory through alpha NFT.

Jirayucharoensak, S., Israsena, P., Pan-Ngum, S., Hemrungrojn, S., & Maes, M. (2019). A game-based neurofeedback training system to enhance cognitive performance in healthy elderly subjects and in patients with amnestic mild cognitive impairment. Clinical interventions in aging, 14, 347–360. https://doi.org/10.2147/CIA.S189047. Introduction: This study examines the clinical efficacy of a game-based neurofeedback training (NFT) system to enhance cognitive performance in patients with amnestic mild cognitive impairment (aMCI) and healthy elderly subjects. The NFT system includes five games designed to improve attention span and cognitive performance. The system estimates attention levels by investigating the power spectrum of Beta and Alpha bands. Methods: We recruited 65 women with aMCI and 54 healthy elderly women. All participants were treated with care as usual (CAU); 58 were treated with CAU + NFT (20 sessions of 30 minutes each, 2-3 sessions per week), 36 with CAU + exergame-based training, while 25 patients had only CAU. Cognitive functions were assessed using the Cambridge Neuropsychological Test Automated Battery both before and after treatment. Results: NFT significantly improved rapid visual processing and spatial working memory (SWM), including strategy, when compared with exergame training and no active treatment. aMCI was characterized by impairments in SWM (including strategy), pattern recognition memory, and delayed matching to samples. Conclusion: In conclusion, treatment with NFT improves sustained attention and SWM. Nevertheless, NFT had no significant effect on pattern recognition memory and short-term visual memory, which are the other hallmarks of aMCI. The NFT system used here may selectively improve sustained attention, strategy, and executive functions, but not other cognitive impairments, which characterize aMCI in women.

Kober, SE., Witte, M., Stangl, M., Vaijarnae, A., Neuper, C. & Wood, G. (2014). Shutting down sensory motor interference unblocks the networks for stimulus processing: An SMR neurofeedback training study. Clinical Neurophysiology:April 13. OBJECTIVE: In the present study, we investigated how the electrical activity in the sensorimotor cortex contributes to improved cognitive processing capabilities and how SMR (sensorimotor rhythm, 12-15Hz) neurofeedback training modulates it. Previous evidence indicates that higher levels of SMR activity reduce sensorimotor interference and thereby promote cognitive processing. METHODS: Participants were randomly assigned to two groups, one experimental (N=10) group receiving SMR neurofeedback training, in which they learned to voluntarily increase SMR, and one control group (N=10) receiving sham feedback. Multiple cognitive functions and electrophysiological correlates of cognitive processing were assessed before and after 10 neurofeedback training sessions. RESULTS: The experimental group but not the control group showed linear increases in SMR power over training runs, which was associated with behavioural improvements in memory and attentional performance. Additionally, increasing SMR led to a more salient stimulus processing as indicated by increased N1 and P3 event-related potential amplitudes after the

training as compared to the pre-test. Finally, functional brain connectivity between motor areas and visual processing areas was reduced after SMR training indicating reduced sensorimotor interference. CONCLUSIONS: These results indicate that SMR neurofeedback improves stimulus processing capabilities and consequently leads to improvements in cognitive performance. SIGNIFICANCE: The present findings contribute to a better understanding of the mechanisms underlying SMR neurofeedback training and cognitive processing and implicate that SMR neurofeedback might be an effective cognitive training tool.

Kober, SE., Witte, M., Ninaus, M., Neuper, C. & Wood, G. (2013). Learning to modulate one's own brain activity: The effect of spontaneous mental strategies. Frontiers in Human Neuroscience: Oct 18(7). 695. Using neurofeedback (NF), individuals can learn to modulate their own brain activity, in most cases electroencephalographic (EEG) rhythms. Although a large body of literature reports positive effects of NF training on behavior and cognitive functions, there are hardly any reports on how participants can successfully learn to gain control over their own brain activity. About one third of people fail to gain significant control over their brain signals even after repeated training sessions. The reasons for this failure are still largely unknown. In this context, we investigated the effects of spontaneous mental strategies on NF performance. Twenty healthy participants performed either a SMR (sensorimotor rhythm, 12-15 Hz) based or a Gamma (40-43 Hz) based NF training over ten sessions. After the first and the last training session, they were asked to write down which mental strategy they have used for self-regulating their EEG. After the first session, all participants reported the use of various types of mental strategies such as visual strategies, concentration, or relaxation. After the last NF training session, four participants of the SMR group reported to employ no specific strategy. These four participants showed linear improvements in NF performance over the ten training sessions. In contrast, participants still reporting the use of specific mental strategies in the last NF session showed no changes in SMR based NF performance over the ten sessions. This effect could not be observed in the Gamma group. The Gamma group showed no prominent changes in Gamma power over the NF training sessions, regardless of the mental strategies used. These results indicate that successful SMR based NF performance is associated with implicit learning mechanisms. Participants stating vivid reports on strategies to control their SMR probably overload cognitive resources, which might be counterproductive in terms of increasing SMR power.

Leach, J., Bulpin, K., Khan, S., Rass, A., ChammoropPremuzic, T., Nelson, C., Gruzelier, J. (2006). Controlled study of neurofeedback with novice singers. ***Society of Applied Neuroscience Conference presentation*****. Swansea.** This is a pilot for a larger study with the aim of extending with novice musicians the findings of Egner and Gruzelier (2003) with elite musicians. They demonstrated professionally significant gains in artistry in music performance following alpha/theta training, but not with SMR or beta 1training, nor with aerobic exercise or mental skills/rehearsal training or the Alexander technique. Here are presented the results of 12 novice singers from London music colleges who were randomly assigned in equal numbers to ten sessions over two months of alpha/theta (A/T) training or SMR training. The study and analysis are ongoing. Results are presented for pre and post training assessment of music performance, attention, memory, mood and processes associated with creativity. There was evidence of significant within and between session learning in increasing the theta/alpha ratio ($p<0.001$ & $p<0.047$), but not in elevating the SMR/theta ratio. Despite the latter limitation semantic cued memory increased in the SMR group in support of Vernon et al (2003) ($p<0.049$, one tailed). Otherwise there were several suggestive differential effects advantaging the A/T group over the SMR group in music performance, creativity and attention, the latter in the direction of the results of Egner and Gruzelier (2004) though not reaching significance in their study. The Test of Variables of Attention (TOVA) showed an increase in sensitivity (d') with A/T ($p<0.04$) and the reverse with SMR (Group x Time $p<0.04$), largely due to a reduction in omission errors with A/T and the opposite mean change in the SMR group (G x T, $p<0.066$). There was also a reduction in RT variability ($p<0.012$). Support for associations with creativity followed improvement in flexibility on the Guildford Alternative Uses Test ($p<0.055$), and the rule breaking subscale of the Adaptor/Innovator Test ($p<0.022$). The Baddeley Sentence Checking Test which involves working memory and reasoning was also advantaged ($p<0.047$) by A/T training. Finally blind lay

evaluations from video clips of expressiveness, confidence and stage presence disclosed improvement following A/T (all $p<0.001$) in contrast to SMR training (G x T, all $p<0.002$).

Markovska-Simoska S, Pop-Jordanova N, Georgiev D. (2008). Simultaneous EEG and EMG biofeedback for peak performance in musicians. ***Prilozi*****, 29(1): 239-252.** The aim of this study was to determine the effects of alpha neurofeedback and EMG biofeedback protocols for improvement of musical performance in violinists. The sample consisted of 12 music students (10 violinists and 2 viola players) from the Faculty of Music, Skopje (3 males, mean age of 20 +/- 0 and 9 females, mean age = 20.89 +/- 2.98). Six of them had a low alpha peak frequency (APF) (< 10 Hz), and six a high APF (> 10 Hz). The sample was randomized in two groups. The students from the experimental group participated in 20 sessions of biofeedback (alpha/EMG), combined with music practice, while the students from the control group did only music practice. Average absolute power, interhemispheric coherence in the alpha band, alpha peak frequency (APF), individual alpha band width (IABW), amount of alpha suppression (AAS) and surface forehead integrated EMG power (IEMG), as well as a score on musical performance and inventories measuring anxiety, were assessed. Alpha-EEG/EMG-biofeedback was associated with a significant increase in average alpha power, APF and IABW in all the participants and with decreases in IEMG only in high-APF musicians. The biofeedback training success was positively correlated with the alpha power, IcoH, APF, IABW and baseline level of APF and IABW. Alpha-EEG/EMG biofeedback is capable of increasing voluntary self-regulation and the quality of musical performance. The efficiency of biofeedback training depends on the baseline EEG alpha activity status, in particular the APF.

Raymond, J., Sajid, I., Parkinson, L. A., & Gruzelier, J. H. (2005). Biofeedback and dance performance: A preliminary investigation. ***Applied Psychophysiology & Biofeedback*****, 30(1), 65-74.** Alpha-theta neurofeedback has been shown to produce professionally significant performance improvements in music students. The present study aimed to extend this work to a different performing art and compare alpha-theta neurofeedback with another form of biofeedback: heart rate variability (HRV) biofeedback. Twenty-four ballroom and Latin dancers were randomly allocated to three groups, one receiving neurofeedback, one HRV biofeedback and one no intervention. Dance was assessed before and after training. Performance improvements were found in the biofeedback groups but not in the control group. Neurofeedback and HRV biofeedback benefited performance in different ways. A replication with larger sample sizes is required.

Sherlin, LH., Larson, SC. & Sherlin, RM. (2013). Developing a performance training approach for baseball: A process analysis with descriptive data. Applied Psychophysiology and Biofeedback:38(1). 29-44. Neurofeedback may be useful for improving sports performance but few studies have examined this potential. Here we present data of five development players from a major league baseball team. The aims were to evaluate the feasibility of conducting sessions within a professional organization, assess changes in quantitative electroencephalograph (QEEG), NeuroPerformance Profile™, and report qualitative self-report data before and after brain training. The EEG was recorded with 19 electrodes for 20 min of baseline conditions and approximately 21 min of a continuous performance test. The fast Fourier transform analysis provided average cross-spectral matrices for bands delta (1-3.5 Hz), theta (4-7.5 Hz), alpha (8-12 Hz), low beta (13-16 Hz), beta 1 (13-21 Hz), beta 2 (22-32 Hz), and gamma (32-45 Hz) from the pre and post intervention evaluations in the baseline condition of eyes open. The continuous performance test metrics included the errors of omission, errors of commission, response time and response time variability. The 9 scales of the NeuroPerformance Profile™ were examined. The QEEG data, CPT data and NeuroPerformance Profile™ data were all compared between the pre and post 15 sessions of brain training using a within subject paired t test design corrected for multiple comparisons using false discovery rate method. Following brain training, comparative QEEG, CPT and NeuroPerformance Profile™ analyses illustrated significant differences. The QEEG findings of all participants illustrated significant changes within the training parameters but also across other frequency bands and electrode sites. Overall, the positive findings in both objective and subjective measures suggest further inquiry into the utility of brain training for performance enhancement with the specific application of sport

is warranted. Particularly QEEG and CPT gains were noted in the areas that correspond to client self-report data demonstrating improvement in attention, decreased intrusive thought patterns and improvements in sleep patterns.

Sokhadze, E. (2012). Peak performance training using prefrontal EEG biofeedback. *Biofeedback*, 39, 7-15. The use of biofeedback training to self-regulate EEG patterns with the aim of recovering or optimizing function and behavioral performance is becoming increasingly established. The most reasonable approach is to learn to generate and maintain optimal brain wave patterns and produce associated peak performance states on demand. We report two studies where 12 sessions of prefrontal EEG feedback were used to improve performance in both clinical and nonclinical populations. Neurofeedback using Focus, Alertness, and 40 Hz (Neureka!) measures resulted in improved selective attention and other cognitive functions. We discuss other potential applications of neurofeedback in the areas of "under-pressure" activity, where peak performance state is an essential part of the job, such as in sports or the performing arts, as well as for human operators, such as air traffic dispatchers and military personnel on duty.

Thompson, T., Steffert, T., Ros, T., Leach, J., & Gruzelier, J. (2008). EEG applications for sport and performance. *Methods*, 45, 279-288. One approach to understanding processes that underlie skilled performing has been to study electrical brain activity using electroencephalography (EEG). A notorious problem with EEG is that genuine cerebral data is often contaminated by artifacts of non-cerebral origin. Unfortunately, such artifacts tend to be exacerbated when the subject is in motion, meaning that obtaining reliable data during exercise is inherently problematic. These problems may explain the limited number of studies using EEG as a methodological tool in the sports sciences. This paper discusses how empirical studies have generally tackled the problem of movement artifact by adopting alternative paradigms, which avoid recording during actual physical exertion. Moreover, the specific challenges that motion presents to obtaining reliable EEG data are discussed along with practical and computational techniques to confront these challenges. Finally, as EEG recording in sports is often underpinned by a desire to optimize performance, a brief review of EEG-biofeedback and peak performance studies is also presented. A knowledge of practical aspects of EEG recording along with the advent of new technology and increasingly sophisticated processing models offer a promising approach to minimizing, if perhaps not entirely circumventing, the problem of obtaining reliable EEG data during motion.

Witte, M., Kober, SE., Ninaus, M., Neuper, C. & Wood, G. (2013). Control beliefs can predict the ability to up-regulate sensorimotor rhythm during neurofeedback training. Frontiers in Human Neuroscience:15(7). 478. Technological progress in computer science and neuroimaging has resulted in many approaches that aim to detect brain states and translate them to an external output. Studies from the field of brain-computer interfaces (BCI) and neurofeedback (NF) have validated the coupling between brain signals and computer devices; however a cognitive model of the processes involved remains elusive. Psychological parameters usually play a moderate role in predicting the performance of BCI and NF users. The concept of a locus of control, i.e., whether one's own action is determined by internal or external causes, may help to unravel inter- individual performance capacities. Here, we present data from 20 healthy participants who performed a feedback task based on EEG recordings of the sensorimotor rhythm (SMR). One group of 10 participants underwent 10 training sessions where the amplitude of the SMR was coupled to a vertical feedback bar. The other group of ten participants participated in the same task but relied on sham feedback. Our analysis revealed that a locus of control score focusing on control beliefs with regard to technology negatively correlated with the power of SMR. These preliminary results suggest that participants whose confidence in control over technical devices is high might consume additional cognitive resources. This higher effort in turn may interfere with brain states of relaxation as reflected in the SMR. As a consequence, one way to improve control over brain signals in NF paradigms may be to explicitly instruct users not to force mastery but instead to aim at a state of effortless relaxation.

DEPRESSION AND BIPOLAR DISORDER

Allen, J. B.., & Cavendar, J. H. (1996). Biofeedback alters EEG asymmetry. *Psychophysiology*, 33(suppl), S17, Individual differences in resting asymmetrical frontal brain activity have been found to predict subsequent emotional responses. The question of whether frontal brain asymmetry can cause emotional responses has yet to be addressed. Biofeedback training designed to alter the asymmetry of frontal brain activity was therefore examined. Eighteen right-handed female participants were randomly assigned to receive biofeedback training designed to increase right frontal alpha relative to left frontal alpha (n = 9) or to receive training in the opposite direction (n = 9). Five consecutive days of biofeedback training provided signals of reward or nonreward depending on whether the difference between right (F4) and left (F3) frontal alpha exceeded a criterion value in the specified direction. Systematic alterations of frontal EEG asymmetry were observed as a function of biofeedback training. Moreover, subsequent self-reported affect and facial muscle activity in response to emotionally evocative film clips were influenced by the direction of biofeedback training.

Baehr, E., Miller, E., Rosenfeld, J. P., & Baehr, R. (2004). Changes in frontal brain asymmetry associated with premenstrual dysphoric disorder: A single case study. *Journal of Neurotherapy*, 8(1), 29-42. *Background*. In a pilot study, Baehr (2001) reports changes in frontal cortical alpha asymmetry during the luteal phase of the menstrual cycle were documented in five depressed women who also experienced Premenstrual Dysphoric Disorder (PMDD). In this paper detailed data is presented for one of these subjects and two comparison subjects who were part of the first study. The goal was two-fold: (a) to study how patterns of mood changes during the luteal phase of the menstrual cycle correlated with changes in frontal alpha brainwave asymmetry, and (b) to determine whether treatment strategies, tailored to ameliorate symptoms, would be reflected in brainwave changes. *Method*. Neurofeedback, medical interventions, and prospective charting were collected over a period of six months for one patient. These data were compared with data collected for two monthly cycles from two non-PMDD comparison subjects. *Results*. The patient responded well to the neurofeedback protocol for depression and was normalizing her scores by the second week in treatment except for setbacks which occurred during the luteal phase of her menstrual cycle. Extreme mood changes correlated with changes in brainwave asymmetry during this period. A combination of neurofeedback and medication worked to stabilize her mood swings and asymmetry scores. *Conclusion*. This case study demonstrated how brainwave changes in frontal alpha asymmetry occurred during the luteal phase of the menstrual cycle in a woman who suffered from PMDD. Two comparison subjects, who were undergoing similar treatment for depression but did not suffer from PMDD, had stable alpha asymmetry scores during the entire menstrual cycle. Anomalies in serotonergic and/or gabergic function in the luteal phases of PMDD are pinpointed as possible underlying factors in this disorder.

Baehr, E., Rosenfeld, J. P., & Baehr, R. (1997). The clinical use of an alpha asymmetry protocol in the neurofeedback treatment of depression: Two case studies. *Journal of Neurotherapy*, 2(3), 10-23. In this study we are presenting case studies of two depressed women who were trained with more than 34 sessions each of EEG biofeedback (neurofeedback) using an Alpha Asymmetry protocol, the purpose of this training was to determine if depression could be alleviated when the subjects learned to increase the activation of the left hemisphere and/ or decrease the activation of the right hemisphere. The MMPI-2 was administered before and after training to measure changes in personality factors, including depression. The results suggest that Alpha Asymmetry neurofeedback training may be an effective adjunct to psychotherapy in the treatment of certain types of mood disorders.

Baehr, E., Rosenfeld, J. P., & Baehr, R. (2001). Clinical use of an alpha asymmetry neurofeedback protocol in the treatment of mood disorders: Follow-up study one to five years post therapy. *Journal of Neurotherapy*, 4(4), 11-18.
Background: This study reports on three of six patients who have completed an average of 27 neurofeedback sessions using a patented alpha asymmetry protocol for the treatment of depression. *Method:* The follow-up data, from one to five years post therapy, were derived from a single session re-test using the same alpha asymmetry protocol and the Beck Depression Inventory. *Results:* The three patients originally diagnosed as having unipolar depression reached the training criteria for the non-depressed range by the end of their initial

training, and they have maintained their normal scores for right hemisphere alpha asymmetry training over time. The follow-up Beck Depression Inventory scores were also within the normal range. *Discussion:* This finding is contrary to the previously held demonstrations by Davidson and Henriques regarding the stability of decreased left anterior cortical activation in remitted depression. While some patients have reported mood changes with life's vicissitudes, none have experienced clinical depression since they have terminated therapy.

Berg, K., Siever, D. (2009). A controlled comparison of audio-visual entrainment for treating Seasonal Affective Disorder. Journal of Neurotherapy 13(3), 166 – 175. *Introduction*. Seasonal Affective Disorder (SAD) affects up to 6% of the population, primarily in the winter months and at higher latitudes. *Methods*. Light-box therapy has been the traditional intervention for SAD, where the individual is exposed to a bright light for substantial periods in an effort to replace the lack of sunshine. Audio-visual entrainment (AVE) is a technique using flashing lights through a pair of specially designed glasses and pulses of tones through headphones. The expectation of AVE is to affect brain wave activity through auditory and visual stimulation at specific frequencies. The objective of this study was to determine if AVE is a viable treatment for SAD. The study involved 74 participants in a comparison design with a control group (no flashing lights or pulsed tones) and an AVE group that received a placebo treatment (AVE at 1 Hz flashing lights and pulsed tones) for 2 weeks, followed by an active treatment phase (20 Hz flashing lights and pulsed tones) for another 2 weeks. *Results*. The results indicated that the placebo phase produced mild reductions in depression and no improvements in anxiety sensitivity, whereas 20 Hz AVE reduced both depression and anxiety symptoms. *Conclusion*. The 20 Hz AVE treatment condition also produced significant improvements in social life with the family and at work, and increased happiness and energy. The 20-Hz treatment also produced a significant decrease in eating, appetite, and carbohydrate intake.

Brenninkmeijer J. (2010). Taking care of one's brain: how manipulating the brain changes people's selves. *Hist Human Sci.* 2010;23(1):107-26. The increasing attention to the brain in science and the media, and people's continuing quest for a better life, have resulted in a successful self-help industry for brain enhancement. Apart from brain books, foods and games, there are several devices on the market that people can use to stimulate their brains and become happier, healthier or more successful. People can, for example, switch their brain state into relaxation or concentration with a light-and-sound machine, they can train their brain waves to cure their Attention Deficit Hyperactivity Disorder (ADHD) or solve their sleeping problems with a neurofeedback device, or they can influence the firing of their neurons with electric or magnetic stimulation to overcome their depression and anxieties. Working on your self with a brain device can be seen as a contemporary form of Michel Foucault's "technologies of the self." Foucault described how since antiquity people had used techniques such as reading manuscripts, listening to teachers, or saying prayers to "act on their selves" and control their own thoughts and behaviours. Different techniques, Foucault stated, are based on different precepts and constitute different selves. I follow Foucault by stating that using a brain device for self-improvement indeed constitutes a new self. Drawing on interviews with users of brain devices and observations of the practices in brain clinics, I analyse how a new self takes shape in the use of brain devices; not a monistic (neuroscientific) self, but a "layered" self of all kinds of entities that exchange and control each other continuously.

Cantor, D.S., Stevens, E. (2009). QEEG correlates of auditory-visual entrainment treatment efficacy of refractory depression. *Journal of Neurotherapy* 13(2), 100 – 108. *Introduction.* It is well established that the number of people diagnosed and suffering from depression is on the increase. Many of these patients are not responsive to first-line pharmacological intervention or simply cannot use medications for other reasons. As such, there has been a growing need for nonmedication approaches to treatment. The purpose of this study was to examine the use of auditory-visual EEG entrainment (AVE) at a 14 Hz (beta) frequency to decrease symptoms of depression with corresponding changes in neurophysiology. *Method.* Sixteen participants ranged in age from 20 to 67 years and were screened utilizing the Beck Depression Inventory–II (BDI–II) and broken into two groups of 8 (simulated, AVE treatment groups), with a cross-over design. Both groups were given the BDI–II and QEEG testing at baseline, 4 weeks following either AVE or simulated treatment, and then again after an additional 4 weeks and a switch in treatment in the cross-over design. *Results.* Results revealed significant reduction of depression only after the 4 weeks on AVE therapy of the BDI–II scores ($p > .01$). QEEG scores adjusted for normal age deviations demonstrate significant EEG change scores over time in cortical regions associated with mood regulation. *Conclusion.* The findings indicate that AVE therapy may be a viable nonmedication therapeutic intervention.

Choi SW, Chi SE, Chung SY, Kim JW, Ahn CY, Kim HT. (2011). Is alpha wave neurofeedback effective with randomized clinical trials in depression? A pilot study. *Neuropsychobiology.* 2011;63(1):43-51. Frontal asymmetric activation has been proposed to be the underlying mechanism for depression. Some case studies have reported that the enhancement of a relative right frontal alpha activity by an asymmetry neurofeedback training leads to improvement in depressive symptoms. In the present study, we examined whether a neurofeedback training designed to increase the relative activity of the right frontal alpha band would have an impact on symptoms of depressive subjects suffering from emotional, behavioral, and cognitive problems. Our results indicated that the asymmetry neurofeedback training increased the relative right frontal alpha power, and it remained effective even after the end of the total training sessions. In contrast to the training group, the placebo control group did not show a difference. The neurofeedback training had profound effects on emotion and cognition. First, we replicated earlier findings that enhancing the left frontal activity led to alleviation of depressive symptoms. Moreover, cognitive tests revealed that the asymmetry training improved performance of executive function tests, whereas the placebo treatment did not show improvement. We preliminarily concluded that the asymmetry training is important for controlling and regulating emotion, and it may facilitate the left frontal lobe function.

Choobforoushzadeh, A., Neshat-Doost, H. T., Molavi, H., & Abedi, M. R. (2015). Effect of neurofeedback training on depression and fatigue in patients with multiple sclerosis. Applied psychophysiology and biofeedback, 40(1), 1–8. https://doi.org/10.1007/s10484-014-9267-4. Depression and fatigue are common symptoms of multiple sclerosis (MS) and are the primary determinants of impaired quality of life in this demyelinating neurological disease. Untreated depression is associated with suicidal ideation, impaired cognitive function and poor adherence to immunomodulatory treatment. For these reasons, systematic screening and management of depressive symptoms and fatigue is recommended for all patients with MS. The objective of this study was to evaluate the effectiveness of neurofeedback in treating depression and fatigue in persons with MS. We conducted a randomized trial with 24 MS patients with primary fatigue and depression. Participants were randomized into two groups: neurofeedback training group (16 sessions of NFB) or treatment as usual. Participants were evaluated at 3 time points (baseline, end of the treatment, and 2-month follow-up) using the Fatigue Severity Scale and Depression subscale of the Hospital Anxiety and Depression Scale as outcome measures. A repeated measures analysis of variance was used to examine differences between the groups. NFB significantly reduced symptoms of depression and fatigue in patients with MS patients, compared to treatment as usual ($p < .05$), and these effects were maintained the 2-month follow-up ($p < .05$).

Escalano, C., Navarro-Gil, M., Garcia-Campayo, J & Minguez, J. (2013). EEG-based upper-alpha neurofeedback for cognitive enhancement in major depressive disorder: a preliminary, uncontrolled study. Conference Proceedings: IEEE 2103:6293-6. Conditioning of the upper-alpha rhythm to improve cognitive performance in healthy users by means of neurofeedback (NF) has been evaluated by several studies, however its effectiveness in people with severe cognitive deficits, such as depressive subjects, remains underexplored. This paper reports on a preliminary uncontrolled study to assess the effects of an upper-alpha NF intervention on patients with major depressive disorder (MDD). The NF effects on the EEG and cognitive performance were assessed. The EEG results showed that patients were able to modulate the upper-alpha rhythm in task-related EEG and during training, in both cases across the executions of the NF sessions, and pre and post within each session. The behavioral results showed the effectiveness of this intervention in a variety of cognitive functions such as working memory, attention, and executive functions.

Hammond, D. C. (2001). Neurofeedback treatment of depression with the Roshi. *Journal of Neurotherapy*, 4(2), 45-56. *Introduction*. A patient with severe, medication resistant depression was found to have the frontal alpha asymmetry described in Davidson's (1998a) research as demonstrating a predisposition to depression. *Treatment*. Initial sessions of EEG neurofeedback using Rosenfeld's (1997) protocol for correcting the alpha asymmetry were discouraging, actually producing slight negative change. Therefore, treatment shifted to using the Roshi, a two channel unit combining neurofeedback and photic stimulation, doing primarily left hemisphere beta training. *Results*. The very first Roshi session produced positive changes, and within five sessions the patient reported feeling less depressed and more energetic. At the conclusion of thirty training sessions, objective testing documented dramatic reductions in depression, somatic symptoms, overemotionality, anxiety, rumination, and fatigue. *Discussion*. In support of Henriques and Davidson's

(1991) belief that hypoactivation of the left hemisphere results in an "approach deficit" and more withdrawal behavior, post-testing and interview data also documented that the patient had become less withdrawn, more active, sociable, and less distrustful. Eight and one-half month follow-up documented maintenance of changes. Continued exploration of left hemisphere beta protocols in treating depression, and of the combined use of neurofeedback with photic stimulation are encouraged.

Hardman, E., Gruzelier, J., Chessman, K., Jones, C., Liddiard, D., Schleichert, H., & Birbaumer, N. (1997). Frontal interhemispheric asymmetry: Self-regulation and individual differences in humans. ***Neuroscience Letters,*** **221, 117-120.** Sixteen subjects naive to biofeedback learned lateralised interhemispheric control of slow cortical potentials (SCPs) across electrode sites F3-F4 during three sessions of visual electroencephalograph (EEG) biofeedback. Subjects were required to generate slow negativity shifts either towards the left or the right hemisphere in sixty pseudorandomly ordered trials per session. Group 1 (n = 8) were told to use emotional strategies in the task (positive emotions for left hemisphere activation, negative emotion for right hemisphere activation), group 2 received no guidance. Both groups received feedback in the form of an on-screen rocket-ship, initially centrally placed, which rose to indicate an increase in left hemisphere negativity (relative to the right hemisphere) and fell to indicate an increase in right hemisphere negativity (relative to the left hemisphere). A 2 x 3 x 3 x 2 ANOVA (group x session x block x trial) showed no performance differences between the strategy and no strategy groups. Both groups learned to produce correct direction shifts in the final third of each session during both trial types ($P < 0.001$). The no strategy group showed a particularly strong within session learning effect ($P < 0.0037$) with poor performance in the early part of the sessions, and strong shifts at the end. Subjects high on withdrawal showed stronger rightward shifts in keeping with right hemisphere involvement in behavioural withdrawal. This is the first demonstration of self regulation of interhemispheric frontal asymmetry.

Jenkins, P., & Moore, W. H. (1985). The effects of visual feedback on hemispheric alpha asymmetries and reported processing strategies: A single-subject experimental design. ***Brain & Cognition*****, 4(1), 47-58.** A double reversal single-subject experimental design was used to study the effects of visual feedback on the hemispheric alpha asymmetries of a male subject during a linguistic task. Results indicated that the subject demonstrated flexibility in hemispheric alpha and corresponding processing strategies employed when an alpha biofeedback procedure was used. These results provide further support for the notion that right and left hemispheric activation is associated with different, yet compatible, cognitive strategies and that both can be manipulated under conditions of feedback.

Kotchoubey, B., Schleichert, H., Lutzenberger, W., Anokhin, A. P., & Birbaumer, N. (1996). Self-regulation of interhemispheric asymmetry in humans. ***Neuroscience Letters*****, 215, 91-94.** Five healthy right-handed subjects learned to control hemispheric asymmetry with biofeedback of the amplitude difference of slow cortical potentials between the left and the right precentral areas. Six training sessions were conducted with subject I, 12 sessions with subjects II and III, and 14 sessions, with subjects IV and V. Performance of four out of five subjects improved continuously as a function of sessions. Towards the end of training, these subjects demonstrated highly significant differentiation between conditions where right versus left precentral negativity was required. In subject V, no improvement was observed after 14 training sessions. The data indicate that most subjects can learn to self-generate fast electroencephalograph (EEG) differences between the left and the right sensorimotor cortical regions.

Kumano, H., Horie, H., Shidara, T., Kuboki, T. et al. (1996). Treatment of a depressive disorder patient with EEG-driven photic stimulation. ***Biofeedback & Self-Regulation,*** **21(4), 323-334.** This study examined the effects of electroencephalographic- (EEG-) driven photic stimulation on a case of depressive disorder, as measured by a psychometric test of mood states, EEG parameters, and several autonomic indices. The EEG-driven photic stimulation enhances the alpha rhythm of brain waves using photic signals, the brightness of which is modulated by a subject's own alpha rhythm. The patient was a 37-year-old businessman, who was treated for depression with medication during the 13 months prior to his first visit to our hospital. He underwent two sets of inpatient treatment sessions, comprising first 16 and then 18 treatment sessions. The treatments brought about the following changes: an improvement in general mood state, alpha rhythm increase, cardiac parasympathetic suppression, and increased skin conductance level. In addition, significant correlations between alpha rhythm increase and cardiac parasympathetic suppression or cardiac sympathetic predominance

were observed with each inpatient treatment. Significant correlations between alpha rhythm increase, cardiac parasympathetic suppression, or cardiac sympathetic predominance and the improvement of general mood state were also observed. Thus, from these observations, it was concluded that the alpha enhancement induced by EEG-driven photic stimulation produced an improvement in the patient's depressive symptomatology connected with cardiac parasympathetic suppression and sympathetic predominance.

Linden DE, Habes I, Johnston SJ, Linden S, Tatineni R, Subramanian L, Sorger B, Healy D, Goebel R. (2012). Real-time self-regulation of emotion networks in patients with depression. *PLoS One.* 2012;7(6):e38115. doi: 10.1371/journal.pone.0038115. Epub 2012 Jun 4. Many patients show no or incomplete responses to current pharmacological or psychological therapies for depression. Here we explored the feasibility of a new brain self-regulation technique that integrates psychological and neurobiological approaches through neurofeedback with functional magnetic resonance imaging (fMRI). In a proof-of-concept study, eight patients with depression learned to upregulate brain areas involved in the generation of positive emotions (such as the ventrolateral prefrontal cortex (VLPFC) and insula) during four neurofeedback sessions. Their clinical symptoms, as assessed with the 17-item Hamilton Rating Scale for Depression (HDRS), improved significantly. A control group that underwent a training procedure with the same cognitive strategies but without neurofeedback did not improve clinically. Randomised blinded clinical trials are now needed to exclude possible placebo effects and to determine whether fMRI-based neurofeedback might become a useful adjunct to current therapies for depression.

Mennella, R., Patron, E., & Palomba, D. (2017). Frontal alpha asymmetry neurofeedback for the reduction of negative affect and anxiety. Behaviour research and therapy, 92, 32–40. https://doi.org/10.1016/j.brat.2017.02.002. Frontal alpha asymmetry has been proposed to underlie the balance between approach and withdrawal motivation associated to each individual's affective style. Neurofeedback of EEG frontal alpha asymmetry represents a promising tool to reduce negative affect, although its specific effects on left/right frontal activity and approach/withdrawal motivation are still unclear. The present study employed a neurofeedback training to increase frontal alpha asymmetry (right - left), in order to evaluate discrete changes in alpha power at left and right sites, as well as in positive and negative affect, anxiety and depression. Thirty-two right-handed females were randomly assigned to receive either the neurofeedback on frontal alpha asymmetry, or an active control training (N = 16 in each group). The asymmetry group showed an increase in alpha asymmetry driven by higher alpha at the right site ($p < 0.001$), as well as a coherent reduction in both negative affect and anxiety symptoms ($ps < 0.05$), from pre-to post-training. No training-specific modulation emerged for positive affect and depressive symptoms. These findings provide a strong rationale for the use of frontal alpha asymmetry neurofeedback for the reduction of negative affect and anxiety in clinical settings.

Peeters, F., Oehlen, M., Ronner, J., van Os, J & Lousberg, R. (2014). Neurofeedback as a treatment for major depressive disorder – A pilot study. PLoS One Mar 18;9(3). Biofeedback potentially provides non-invasive, effective psychophysiological interventions for psychiatric disorders. The encompassing purpose of this review was to establish how biofeedback interventions have been used to treat select psychiatric disorders [anxiety, autistic spectrum disorders, depression, dissociation, eating disorders, schizophrenia and psychoses] to date and provide a useful reference for consultation by clinicians and researchers planning to administer a biofeedback treatment. A systematic search of EMBASE, MEDLINE, PsycINFO, and WOK databases and hand searches in Applied Psychophysiology and Biofeedback, and Journal of Neurotherapy, identified 227 articles; 63 of which are included within this review. Electroencephalographic neurofeedback constituted the most investigated modality (31.7%). Anxiety disorders were the most commonly treated (68.3%). Multi-modal biofeedback appeared most effective in significantly ameliorating symptoms, suggesting that targeting more than one physiological modality for bio-regulation increases therapeutic efficacy. Overall, 80.9% of articles reported some level of clinical amelioration related to biofeedback exposure, 65.0% to a statistically significant ($p < .05$) level of symptom reduction based on reported standardized clinical parameters. Although the heterogeneity of the included studies warrants caution before explicit efficacy statements can be made. Further development of standardized controlled methodological protocols tailored for specific disorders and guidelines to generate comprehensive reports may contribute towards establishing the value of biofeedback interventions within mainstream psychiatry.

Peeters, F., Ronner, J., Bodar, L., van Os, J., Louisberg, R. (2013). Validation of a neurofeedback paradigm: Manipulating frontal EEG alpha-activity and its impact on mood. Int J Psychophysiol. doi: 10.1016/j.ijpsycho.2013.06.010. It is claimed that neurofeedback (NF) is an effective treatment for a variety of psychiatric disorders. NF, within an operant conditioning framework, helps individuals to regulate cortical electroencephalographic (EEG) activity while receiving feedback from a visual or acoustic signal. For example, changing asymmetry between left and right frontal brain alpha activity by NF, is claimed to be an efficacious treatment for major depressive disorder. However, the specificity of this intervention in occasioning electrophysiological changes at target locations and target wave-frequencies, and its relation to changes in mood, has not been established. During a single session of NF, it was tested if the balance between left and right frontal alpha-activity could be changed, regardless of direction, in 40 healthy females. Furthermore, we investigated whether this intervention was electrophysiologically specific and if it was associated with changes in mood. Participants were able to decrease or increase frontal alpha-asymmetry during the intervention. However, no changes in mood were observed. (*Note from bibliographer: one session would rarely provide changes in behavior*). Changes in EEG activity were specific in terms of location and wave-frequency.

Putnam, J. A., (2001). EEG biofeedback on a female stroke patient with depression: A case study. *Journal of Neurotherapy*, 5(3), 27-38. *Background*. This single case concerns the treatment of a 71-year-old female stroke patient. The patient's MRI revealed that the location of the stroke was in the right side basal ganglia with damage extending into the anterior limb of the internal capsule. She presented with a virtual paralysis of the left side of her body (hemiplegia with immobilized left arm, contracted fist, minimal motor control over left leg, absence of muscle tonus in left side of face and slurred, monotonic speech). *Method*. The client was provided with EEG biofeedback training on a one to two half-hour sessions per week schedule. Bipolar montages were used along with single site protocols. This was based largely on the idea of reciprocal communication loops between widely separated cortical generators. It was thought that encouraging communication between cortical sites would have a beneficial impact on impairments related to both functional and structural damage. EEG training protocols included SMR (12-15 Hz) enhancement at C4, C4-Pz and T3-T4 with theta suppression; beta (15-18 Hz) enhancement with theta suppression at C3, C3-Fpz and at C3-Fp1. *Results*. Patient showed significant improvement in gross motor control and range of movement of left arm and leg. The most dramatic improvement was observed in speech (articulation, strength and tone). While substantial improvements were observed in motor ability, restoration of mood stability proved somewhat more elusive. Since she was receiving additional treatment (physical therapy and medication management), it is impossible to attribute the improvement in functioning solely to the EEG training. However, the consensus among the attending medical personnel was that the improvements noted above took place with unusual expeditiousness. *Discussion*. When performing EEG biofeedback it may be most practical to adopt an "exercise model" approach in which the regulatory mechanisms in the brain are challenged through the sequential use of multiple protocol configurations. In this case several different training protocols proved useful in her ongoing recovery. While improvements in functioning were a result of a concerted effort involving multiple therapeutic interventions, it is likely that neurofeedback played a vital synergistic role.

Raymond, J., Varney, C., Parkinson, L. A., & Gruzelier, J. H. (2005). The effects of alpha/theta neurofeedback on personality and mood. *Cognitive Brain Research,* 23, 287-292. Alpha/theta neurofeedback has been shown to be successful both in treating addictions and in enhancing artistry in music students. How its effects are mediated are not yet clear. The present study aimed to test the hypothesis that alpha/theta neurofeedback works inter alia by normalising extreme personality and raising feelings of well-being. 12 participants with high scores for Withdrawal (as measured by the PSQ) were given either alpha/theta neurofeedback or mock feedback and their personality and mood were assessed. Withdrawal scores on the PSQ-80 were not found to change in either group but significant effects were found for the Profile Of Mood States (POMS), with real feedback producing higher overall scores than mock feedback ($P = 0.056$). Real feedback caused participants to feel significantly more energetic ($P < 0.01$) than did mock feedback. Sessions of real feedback made participants feel more composed ($P < 0.01$), agreeable ($P < 0.01$), elevated ($P < 0.01$) and confident ($P < 0.05$), whilst sessions of mock feedback made participants feel more tired ($P < 0.05$), yet composed ($P < 0.01$). These findings suggest that, whilst 9 sessions of alpha/theta neurofeedback was insufficient to change personality, improvements in mood may provide a partial explanation for the efficacy of alpha/theta neurofeedback.

Robbins, J. (2000). On the track with neurofeedback. A new treatment may help with problems from ADD to depression, sleep disorders and epilepsy. *Newsweek*. 2000 Jun 19;135(25):76. (No abstract available)

Rockstroh, B., Elbert, T., Birbaumer, N. J., & Lutzenberger, W. (1990). Biofeedback-produced hemispheric asymmetry of slow cortical potentials and its behavioural effects. *International Journal of Psychophysiology*, 9, 151-165. Two studies served to examine behavioural effects of slow cortical potentials (SPs). SPs were manipulated by means of a biofeedback procedure. The ability of human subjects to alter SPs differentially between the two hemispheres--specifically over the lateral aspects of the central sulcus--was tested by providing feedback of the SP difference between C3 and C4. In Expt. I, 21 of the 45 subjects produced hemispheric asymmetries of more than 2 microV between C3 and C4 on an average after 80 trials of analogue, continuous and immediate feedback. In Expt. II, SP changes were fed back digitally at the end of each trial. Within 120 trials, 20 of the 48 subjects reached the criterion of a minimum 2-microV difference in SPs between C3 and C4 on the average. Average differentiation remained significantly below the SP differentiations achieved for continuous feedback. Trials with feedback were followed by 'task' trials without feedback, during which subjects were still requested to produce SP changes but also had to complete a task: Either sensorimotor tasks (Expt. I) or forced choice handedness tasks (Expt. II) were presented to evaluate behavioural consequences of hemispheric SP differences. In subjects achieving the required SP differentiation it affected the behavioural output in agreement with the known functions of the respective cortical area.

Rosenfeld, J. P., Baehr, E., Baehr, R., Gotlib, I. H., & Ranganath, C. (1996). Preliminary evidence that daily changes in frontal alpha asymmetry correlate with changes in affect in therapy sessions. *International Journal of Psychophysiology,* 23, 137-141. Frontal EEG alpha asymmetry was recorded from five depressed outpatients during early EEG biofeedback sessions. Mood was assessed prior to and after each session, and affect change scores were also derived by subtracting pre-session from post-session scores. Alpha magnitude was obtained via Fast Fourier Transforms. All scores (EEG alpha asymmetry and affect) were converted to deviation scores by subtracting each patient's daily score from that patient's mean across all available sessions for that patient. Pearson correlations were then computed between asymmetry and affect scores using the deviation scores combined over patients. There was little evidence of correlation between day-to-day asymmetry score and any single affect score. Strong correlations were obtained, however, between asymmetry score and affect change score and, in particular, between asymmetry score and change in positive affect.

Rosenfeld, J. P., Cha, G., Blair, T., & Gotlib, I. (1995). Operant biofeedback control of left-right frontal alpha power differences. *Biofeedback & Self-Regulation*, 20, 241-258. Two experiments were done with subjects from a paid pool of undergraduates. In each study, there were five 1-hour sessions on each of 5 days: (1) Baseline: Rewards given for randomly selected 20% of the 700-ms sequential epochs; mean and SD of baseline power differences determined. 2) Exploration: Subjects were rewarded when right minus left alpha differences in an epoch were greater than the baseline mean plus about .85 SD ($p = .20$); subjects told to discover how to generate rewards. (3)-(5). Training: Subjects were paid (over and above the $8/h flat rate) in proportion to their hit rates. In the first study (in which active filters passed 8-12 Hz activity, and the rectified, integrated amplitude was utilized), 6 of 8 subjects met learning criteria (a significant difference between baseline and training scores). In the second study (in which on-line FFTs were used to extract alpha power), 3 of 5 subjects met learning criteria.

Saxby, E., & Peniston, E. G. (1995). Alpha-theta brainwave neurofeedback training: an effective treatment for male and female alcoholics with depressive symptoms. *Journal of Clinical Psychology,* 51, 685-693. This was an experimental study of 14 alcoholic outpatients using the Peniston and Kulkosky (1989, 1991) brainwave treatment protocol for alcohol abuse. After temperature biofeedback pretraining, experimental subjects completed 20 40-minute sessions of alpha-theta brainwave neurofeedback training (BWNT). Experimentally treated alcoholics with depressive syndrome showed sharp reductions in self-assessed depression (Beck's Depression Inventory). On the Millon Clinical Multiaxial Inventory-I, the experimental subjects showed significant decreases on the BR scores: schizoid, avoidant, dependent, histrionic, passive-aggression, schizotypal, borderline, anxiety, somatoform, hypomanic, dysthmic, alcohol abuse, drug abuse, psychotic thinking, and psychotic depression. Twenty-one-month follow-up data indicated sustained prevention of relapse in alcoholics who completed BWNT.

Simkin, DR., Thatcher, RW. & Lubar, J. (2014). Quantitative EEGB and Neurofeedback in Children and adolescents: Anxiety disorders, depressive disorders, comorbid addiction and attention-deficit/hyperactivity disorder and brain injury. *Child and Adolescent Psychiatric Clinics of North America*:23(3). 427-464. This article explores the science surrounding neurofeedback. Both surface neurofeedback (using 2-4 electrodes) and newer interventions, such as real-time z-score neurofeedback (electroencephalogram [EEG] biofeedback) and low-resolution electromagnetic tomography neurofeedback, are reviewed. The limited literature on neurofeedback research in children and adolescents is discussed regarding treatment of anxiety, mood, addiction (with comorbid attention-deficit/hyperactivity disorder), and traumatic brain injury. Future potential applications, the use of quantitative EEG for determining which patients will be responsive to medications, the role of randomized controlled studies in neurofeedback research, and sensible clinical guidelines are considered.

Sokhadze, E., Tasman, A., Tamas, R., & El-Mallakh, R. (2011). Event-related potential study of the effects of emotional facial expressions on task performance in euthymic bipolar patients. *Applied Psychophysiology & Biofeedback*, 36(1), 1-13. There appears to be a significant disconnect between symptomatic and functional recovery in bipolar disorder (BD). Some evidence points to interepisode cognitive dysfunction. We tested the hypothesis that some of this dysfunction was related to emotional reactivity in euthymic bipolar subjects may effect cognitive processing. A modification of emotional gender categorization oddball task was used. The target was gender (probability 25%) of faces with negative, positive, and neutral emotional expression. The experiment had 720 trials (3 blocks × 240 trials each). Each stimulus was presented for 150 ms, and the EEG/ERP responses were recorded for 1,000 ms. The inter-trial interval was varied in 1,100-1,500 ms range to avoid expectancy effects. Task took about 35 min to complete. There were 9 BD and 9 control subjects matched for age and gender. Reaction time (RT) was globally slower in BD subjects. The centro-parietal amplitudes at N170 and N200, and P200 and P300 were generally smaller in the BD group compared to controls. Latency was shorter to neutral and negative targets in BD. Frontal P200 amplitude was higher to emotional negative facial non-targets in BD subjects. The frontal N200 in response to positive facial emotion was less negative in BD subjects. The frontal P300 of BD subjects was lower to emotionally neutral targets. ERP responses to facial emotion in BD subjects varied significantly from normal controls. These variations are consistent with the common depressive symptomology seen in long term studies of bipolar subjects.

Takamura, M., Okamoto, Y., Shibasaki, C., Yoshino, A., Okada, G., Ichikawa, N., & Yamawaki, S. (2020). Antidepressive effect of left dorsolateral prefrontal cortex neurofeedback in patients with major depressive disorder: A preliminary report. Journal of affective disorders, 271, 224–227. https://doi.org/10.1016/j.jad.2020.03.080. Background: Real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf) have recently attracted attention as a novel, individualized treatment method for major depressive disorder (MDD). In this study, the antidepressant effect of neurofeedback training for left dorsolateral prefrontal cortex (DLPFC) activity was examined. Methods: Six patients with MDD completed 5 days of neurofeedback training sessions. In each session, the patients observed a BOLD signal within their left DLPFC as a line graph and attempted to up-regulate the signal using the graphical cue. Primary outcome measures were clinical scales of severity of depression and rumination. Results: After neurofeedback training, the clinical measures were improved significantly. In addition, patient proficiency for neurofeedback training was related significantly to the improvement of the rumination symptom. Limitations Study limitations include the lack of a control group or condition, the lack of transfer run, and the small number of participants. Conclusions: This small sample study suggests the possible efficacy of DLPFC activity regulation training for the treatment of MDD. As a next step, a sham-controlled randomized clinical trial is needed to confirm the antidepressive effect of left DLPFC neurofeedback.

Uhlmann, C., & Froscher, W. (2001). Biofeedback treatment in patients with refractory epilepsy: Changes in depression and control orientation. Seizure, 10, 34-38. Depression is a common and serious interictal problem in patients with epilepsy. The genesis of depressive disorders is multifactorial. One aetiological aspect focuses on psychosocial factors. It was hypothesized that uncontrollable, unpredictable chronic aversive events (i.e. epileptic seizures) result in cognitive deficits of external control orientation. If this is true, biofeedback training could represent a possible treatment strategy to lower depression, because biofeedback is known to mediate success experiences and control. Measures of depression and locus of control were administered to 20 patients with refractory partial epilepsy before and after biofeedback treatment. The biofeedback consisted of slow cortical potentials or breathing parameters in 10 patients each.

A clear relationship occurred between depression and locus of control in the subjects. After biofeedback training control orientation moved towards a more internal locus of control. Also, depression scores were significantly reduced six months after training. Results show that in patients with refractory epilepsy depression is highly correlated with locus of control, in a way that external control orientation relates to high depression scores. Biofeedback is able to improve internal control orientation through personal success mediation.

Unterrainer, HF., Chen, MJ. & Gruzelier, JH. (2014). EEG-neurofeedback and psychodynamic psychotherapy in a case of adolescent anhedonia with substance misuse: mood:theta relations. International Journal of Psychophysiology:Jul;93(1). 84-95. There is substantial evidence confirming the efficacy of neurofeedback with applications in clinical, educational and optimal performance domains. However, a psychodynamically informed NF-approach needs exploration. A male (19 y), college student whose first year was being seriously compromised after severe, 18-month, polydrug misuse, was treated with 11 sessions including a 2-month follow-up of neurofeedback combined with short-term psychodynamic psychotherapy. Pre/post-treatment and follow-up assessment with the Brief Psychiatric Rating Scale (BPRS) and the Montgomery-Asberg Depression Rating Scale confirmed that levels of psychopathology dropped almost to zero. Correlational evidence disclosed that SMR/theta training was positively associated with reduction in psychopathological ratings, largely due to theta amplitude reduction; the strongest relation being with reduced BPRS activation. Alpha/theta training was not correlated with clinical improvement. The combined treatment was found to be highly effective with the student who learned to deal with feelings of anhedonia and alienation. There was no relapse during the follow-up phase. Further research is recommended.

Walker, J. E., Lawson, R., & Kozlowski, G. (2007). Current status of QEEG and neurofeedback in the treatment of depression. Chapter in J. R. Evans (Ed.), *Handbook of Neurofeedback*. Binghampton, NY: Haworth Medical Press, pp. 341-351. (No abstract available)

Young, K. D., Siegle, G. J., Zotev, V., Phillips, R., Misaki, M., Yuan, H., Drevets, W. C., & Bodurka, J. (2017). Randomized Clinical Trial of Real-Time fMRI Amygdala Neurofeedback for Major Depressive Disorder: Effects on Symptoms and Autobiographical Memory Recall. The American journal of psychiatry, 174(8), 748–755. https://doi.org/10.1176/appi.ajp.2017.16060637. Objective: Patients with depression show blunted amygdala hemodynamic activity to positive stimuli, including autobiographical memories. The authors examined the therapeutic efficacy of real-time functional MRI neurofeedback (rtfMRI-nf) training aimed at increasing the amygdala's hemodynamic response to positive memories in patients with depression. Method: In a double-blind, placebo-controlled, randomized clinical trial, unmedicated adults with depression (N=36) were randomly assigned to receive two sessions of rtfMRI-nf either from the amygdala (N=19) or from a parietal control region not involved in emotional processing (N=17). Clinical scores and autobiographical memory performance were assessed at baseline and 1 week after the final rtfMRI-nf session. The primary outcome measure was change in score on the Montgomery-Åsberg Depression Rating Scale (MADRS), and the main analytic approach consisted of a linear mixed-model analysis. Results: In participants in the experimental group, the hemodynamic response in the amygdala increased relative to their own baseline and to the control group. Twelve participants in the amygdala rtfMRI-nf group, compared with only two in the control group, had a >50% decrease in MADRS score. Six participants in the experimental group, compared with one in the control group, met conventional criteria for remission at study end, resulting in a number needed to treat of 4. In participants receiving amygdala rtfMRI-nf, the percent of positive specific memories recalled increased relative to baseline and to the control group. Conclusions: rtfMRI-nf training to increase the amygdala hemodynamic response to positive memories significantly decreased depressive symptoms and increased the percent of specific memories recalled on an autobiographical memory test. These data support a role of the amygdala in recovery from depression.

EPILEPSY AND SEIZURE DISORDERS

Andrews, D. J., & Schonfeld, W. H. (1992). Predictive factors for controlling seizures using a behavioural approach. *Seizure*, 1(2), 111-116. A behavioural approach using EEG biofeedback for controlling complex-partial seizures has been successful at the Andrews/Reiter Epilepsy Research Program. Records for a random sample of 83 patients with uncontrolled seizures, one third of those receiving care between 1980 and 1985, document that 69 (83%) achieved control by completion of the programme. Additional data about initial age of seizure onset, number of years seizures had been uncontrolled and seizure frequency when treatment started were collected to determine whether these factors predicted seizure control. Only frequency was significantly related to whether seizures were controlled when treatment ended. Further study using discriminant analysis showed that earlier onset age and higher seizure frequency were associated with a significantly greater number of treatment sessions required. Thus, these two factors predicted difficulty in controlling seizures, as measured by number of sessions, although onset age did not predict whether control was eventually achieved. Since even the subgroup achieving the lowest rate of control (i.e., patients having daily seizures when treatment started) had 67% success, these results suggest that a behavioural approach can be useful for many people with currently uncontrolled complex-partial seizures regardless of their characteristics on factors examined in this study.

Cott, A., Pavloski, R. P., & Black, A. H. (1979). Reducing epileptic seizures through operant conditioning of central nervous system activity: Procedural variables. *Science*, 203, 73-75. Operant conditioning of the sensorimotor rhythm of the human electroencephalogram with time-outs contingent on epileptiform activity reduces epileptic seizure rates in patients whose seizures are not well controlled by medication. A comparison of this procedure with time-out training alone demonstrates that operant conditioning of the sensorimotor rhythm is neither necessary nor sufficient for seizure reduction.

Daum, I., Rockstroh, B., Birbaumer, N., Elbert, T., Canavan, A., Lutzenberger, W. (1993). Behavioral treatment of slow cortical potentials in intractable epilepsy: Neuropsychological predictors of outcome. *Journal of Neurosurgery & Psychiatry*, 56 94-97. The study aimed to explore the predictive value of neuropsychological tests within the context of acquisition of slow cortical potential (SCP) self-control, a technique which has beneficial effects on seizure frequency in epilepsy. Patients with epilepsy who successfully achieved SCP control had longer digit or block-tapping spans than less successful patients. Patients who showed a better learning rate across training also displayed better verbal memory and learning abilities. Seizure reduction was related to block-tapping spans only. The results indicate that measures of attention, as indicated by digit spans or block-tapping spans, offer some predictive value for acquisition of SCP control and treatment outcome, whilst measures of visuospatial or frontal lobe function are unrelated to SCP acquisition and seizure reduction.

Egner T., Sterman MB. (2006). Neurofeedback treatment of epilepsy: from basic rationale to practical application. *Expert Rev Neurother*.;6(2):247-57. The treatment of epilepsy through operant conditioning of the sensorimotor rhythm electroencephalogram has a 35-year history. Neurophysiological studies have shown that this phasic oscillation reflects an inhibitory state of the sensorimotor system. Operant learning of sensory motor rhythm production results in an upregulation of excitation thresholds within the thalamocortical sensory and motor circuitry, which in turn is associated with reduced susceptibility to seizures. The clinical benefits derived from this neurofeedback training protocol, particularly in patients that are nonresponsive to pharmacotherapy, have been documented in many independent laboratories. Recent advances in computer technology have resulted in the availability of relatively inexpensive high-quality equipment for the application of neurofeedback therapy, thus presenting a viable and promising treatment alternative to the interested clinician.

Engel, J., Troupin, A. S., Crandall, P. H., Sterman, M. B., & Wasterlain, C. G. (1982). Recent developments in the diagnosis and therapy of epilepsy. *Annals of Internal Medicine*, 97, 584-598. Recent advances in the diagnosis of epilepsy include the development of a clinically useful classification of epileptic seizures and the recognition of specific epileptic disorders. These advances have been

aided by the advent of x-ray computed tomography, long-term electroencephalographic telemetry, and video monitoring. Techniques for functional imaging of the human brain promise even greater diagnostic capabilities. New antiepileptic drugs have improved medical management, and technical and theoretical advances in pharmacokinetics have permitted physicians to design balanced dosing for individual patients. Although currently underused, surgical treatment of partial complex epilepsy can be safe and effective when used appropriately. Operant conditioning of electroencephalography may become another practical alternative therapy. Contributions of basic research to understanding the complications of status epilepticus have influenced treatment protocols and greatly improved the prognosis of this potentially lethal condition.

Finley, W. W. (1976). Effects of sham-feedback following successful SMR training in an epileptic: A follow-up study. *Biofeedback & Self-Regulation*, 1, 227-235. After 1 year of SMR biofeedback training of a severe epileptic teenage male, incidence of atonic seizures decreased from 8/hr to less than 1/3 hr. SMR increased from 10% to 70%. Epileptiform discharges decreased from 45% to 15%. Unknown to the patient, his family, or certain members of our research staff, noncontingent feedback was introduced on 7/22/74, ending 9/11/74. A significant decrease occurred for SMR (down 8%), and a significant increase for epileptiform discharges (up 4%). Rate of seizures increased, but was not statistically significant over preceding months of contingent feedback. Incidence of seizures associated with urine loss increased from approximately 6/month to 23/month during noncontingent feedback, a significant increase. Urine-loss results suggest that although seizures did not become more frequent, those the patient did experience were "harder," i.e., more severe. Contingent feedback was reinstituted following the 7-wk sham, and recovery of all variables to their former levels (prior to sham) occurred.

Finley, W. W. (1977). Operant conditioning of the EEG in two patients with epilepsy: Methodologic and clinical considerations. *Pavlovian Journal of Biological Science*, 12(2), 93-111. Methodologic and clinical considerations are discussed in sensorimotor rhythm (SMR) biofeedback research on two dissimilar but severe epileptic males. The first case, an akinetic epileptic who prior to feedback training experienced 80-100 clinical seizures every 10 hours, showed considerable seizure reduction after 6 months of SMR and epileptiform training. A number of methodologic and instrumentation advances were pioneered with the akinetic patient: (1) development of and ultra-sharp band-pass filter; (2) use of epileptiform inhibit and feedback circuitry; (3) use of monetary rewards as additional incentive; (4) use of correlational analysis for evaluation of acquisition in the major dependent variables and; (5) use of noncontingent feedback and reinforcement as control techniques. The second case, a psychomotor epileptic, also showed therapeutic benefit from SMR training. Clinical information regarding the effect of anticonvulsant medications on the course and therapeutic outcome of SMR training are described. In conjunction with operant conditioning of 12 Hz activity, corresponding changes for other EEG parameters are examined.

Finley, W. W., Smith, H. A., & Etherton, M. D. (1975). Reduction of seizures and normalization of the EEG in a severe epileptic following sensorimotor biofeedback training: Preliminary study. *Biological Psychiatry*, 2, 189-203. Sensorimotor rhythm (SMR) biofeedback training was attempted in a 13-year-old male with frequent epileptic seizures. Prior to training the subject was averaging almost eight clinical seizures an hour. The SMR filter was tuned sharply to 12 plus or minus 1 Hz. Feedback was conducted over approximately six months and continues to the present. In that time the subject's percentage of SMR increased from about 10%, prior to training, to 65% after the 34th training session. Correspondingly, his rate of clinical seizures decreased by a factor of 10 and a significant reduction in percentage of epileptiform discharges was noted. Beginning with trial 35, the subject was provided feedback of epileptiform activity in combination with 12 Hz activity. The combined effect of these two treatment variables was to reduce the trial-to-trial variance in the dependent variables of interest.

Frey LC and Koberda JL (2015) LORETA Z-score Neurofeedback in Patients with Medically Refractory Epilepsy. J Neurol Neurobiol, Volume1.1: http://dx.doi.org/10.16966/2379-7150.102. Rationale: Published studies suggest that augmentation of the sensorimotor rhythm (SMR), a commonly-used neurofeedback protocol for patients with epilepsy, can be an effective means of reducing seizure frequency, even in patients with medically-refractory seizures. However, SMR protocols are limited to training a few frequency bands over sensorimotor cortex. Newer neurofeedback technology allows for the selection of multiple frequency bands in multiple head regions for training purposes and thus allows for training of neural networks.Functional MRI studies have shown abnormal connectivity

within the default mode network (DMN) in patients with both focal-onset and primary generalized epilepsy syndromes. The DMN has also been shown to have altered activity concurrent with interictalepileptiform discharges. The effectiveness of newer neurofeedback techniques in reducing seizure frequency for patients with medically-refractory seizures has not yet been established. This case series explores the potential effectiveness of using LORETA z-score training within the DMN in reducing seizure frequency in patients with medically-refractory seizures. Methods: The records for all consecutive patients seen in the Neurofeedback Clinic at a single academic medical center over a one year period (n=6) were retrospectively reviewed. All patients had medically-refractory epilepsy and were either not candidates for epilepsy surgery (based on consensus decision of the center's faculty) or had refused to consider surgery for personal reasons. Data on patient demographics, duration of epilepsy prior to training, seizure types and frequencies, antiepileptic drugs (AEDs), psychiatric and medical comorbidities, imaging results, neurophysiological results, and the duration of neurofeedback training were abstracted and analyzed. Patient-reported seizure frequency was also analyzed. Results: 125 total training sessions were reviewed. Mean patient age was 33 +/- 6.1 years with mean duration of epilepsy prior to training of 17.2 +/- 3.2 years. Five out of six patients had focal onset epilepsy. None of the patients had a structural lesion on MRI that correlated with their seizure focus. Five out of 6 patients had a history of comorbid mood disorder. No patient had ever been seizure free for more than 1 year. Patients had been trained using LORETA z-score training within the DMN for an average of 20.8 +/- 5.2weeks (1-2 sessions per weekfor 20-30 minutes per session) at the time of analysis. Five out of 6 patients trained had a subjective reduction in reported weekly seizure frequency after LORETA z-score neurofeedback training began. Conclusions: In this small case series, DMN training using LORETA z-score neurofeedback techniques resulted in subjective improvement in seizure frequency from reported baseline for five out of the six patients in this series.Larger studies are needed to more definitively assess the effectiveness of these techniques for reducing seizure frequency in patients with medically-refractory seizures who are not, for either medical or personal reasons, candidates for surgical intervention.

Hanson, L. M., Trudeau, D. L., & Grace, D. L. (1996). Neurotherapy and drug therapy in combination for adult ADHD, personality disorder, and seizure disorder: A case report. *Journal of Neurotherapy*, 2(1) 6-14. This is a case report of an adult female patient with ADHD, temporal seizure disorder, and Borderline Personality Disorder treated with 30 weekly sessions of SMR neurofeedback and carbamazepine. Post-treatment measures showed improvements in T.O.V.A., self report, and QEEG. Both neurofeedback and carbamazepine showed the most effect in early treatment. Progress continued after discontinuance of the drug.

Haut SR, Gursky JM, Privitera M. (2019). Behavioral interventions in epilepsy. Curr Opin Neurol. 2019 Apr;32(2):227-236. doi: 10.1097/WCO.0000000000000661. PMID: 30694921. Purpose of review: Behavioral intervention describes multiple modalities of treatments which are of increasing interest in epilepsy. This review addresses recent behavioral clinical trials in epilepsy including cognitive behavioral therapy (CBT), mindfulness, progressive muscle relaxation (PMR), and self-management. Results and conclusions from updated Cochrane reviews and the recent International League Against Epilepsy Psychology task force are presented. Recent findings: Two recent large randomized controlled trials (mindfulness and progressive muscle relaxation) reported improved seizure frequency with behavioral treatments. In both studies, participants in both the active and the attentional control arms showed significant seizure reduction, whereas quality of life and stress reduction were better noted in the active arms. Additional behavioral modalities have reported improved seizure control including yoga, bio/neurofeedback, and music therapy. Significant improvements in multiple quality of life, cognitive domains, and medication adherence have been reported from randomized and open label trials of cognitive behavioral therapy, and self-management programs. Multiple promising self-management programs have been recently reported, often utilizing the power of web-based apps, and digitally delivered group therapy. In 2018, the International League Against Epilepsy Psychology task force recommended that 'psychological interventions should be incorporated into comprehensive epilepsy care. Summary: Behavioral treatments are successful and likely underutilized in the treatment of epilepsy. Given the challenge of conducting randomized clinical trials of behavioral therapy, much remains to be studied. However, for motivated and interested patients, appropriately chosen behavioral therapies appear to be important adjuncts to standard therapy. The timing is currently optimal to take best advantage of smartphone apps and web-based delivery systems, both for research and therapeutic purposes.

Hurt, E., Arnold, AE. & Lofthouse, N. (2014). Quantitative EEG neurofeedback for the treatment of pediatric attention-deficit hyperactivity disorder, autism spectrum disorders, learning disorders and epilepsy. Child and Adolescent Psychiatric Clinics of North America:23(3). 465-86. Neurofeedback (NF) using surface electroencephalographic signals has been used to treat various child psychiatric disorders by providing patients with video/audio information about their brain's electrical activity in real-time. Research data are reviewed and clinical recommendations are made regarding NF treatment of youth with attention deficit/hyperactivity disorder, autism, learning disorders, and epilepsy. Most NF studies are limited by methodological issues, such as failure to use or test the validity of a full-blind or sham NF. The safety of NF treatment has not been thoroughly investigated in youth or adults, although clinical experience suggests reasonable safety.

Kaplan, B. J. (1975). Biofeedback in epileptics: Equivocal relationship of reinforced EEG frequency to seizure reduction. *Epilepsia*, 16, 477-485. It has been reported that biofeedback training of 12- to 14-Hz activity recorded over Rolandic cortex was accompanied by a reduction in seizure incidence in four human epileptics (Sterman et al., 1974). Biofeedback training of 12- to 14-Hz activity was provided for two epileptics and had no effect on clinical EEGs, seizure incidence, or proportion of EEG spectral power in the frequency range being trained. Subsequently, biofeedback training of 6- to 12-Hz Rolandic activity was provided for three epileptics. Two patients experienced reductions in seizure not accompanied by medication changes. Since no learning of 6- to 12-Hz activity was detected, the changes in seizure incidence are not attributed to EEG biofeedback. It is suggested that the experience in the feedback setting provided these two patients with new techniques of relaxation. In view of the lack of statistical evidence of EEG changes following EEG biofeedback and the small number of patients trained to date, it appears wise to maintain a cautious attitude until the issue of causality is clear.

Kotchoubey, B., Busch, S., Strehl, U., & Birbaumer, N. (1999). Changes in EEG power spectra during biofeedback of slow cortical potentials in epilepsy. *Applied Psychophysiology & Biofeedback*, 24(4), 213-233. The goal of the study was to explore parallel changes in EEG spectral frequencies during biofeedback of slow cortical potentials (SCPs) in epilepsy patients. Thirty-four patients with intractable focal epilepsy participated in 35 sessions of SCP self-regulation training. The spectral analysis was carried out for the EEG recorded at the same electrode site (Cz) that was used for SCP feedback. The most prominent effect was the increase in the theta 2 power (6.0-7.9 Hz) and the relative power decrement in all other frequency bands (particularly delta 1, alpha 2 and beta 2) in transfer trials (i.e., where patients controlled their SCPs without continuous feedback) compared with feedback trials. In the second half of the training course (i.e., sessions 21-35) larger power values in the delta, theta, and alpha bands were found when patients were required to produce positive versus negative SCP shifts. Both across-subject and across-session (within-subject) correlations between spectral EEG parameters, on the one hand, and SCP data, on the other hand, were low and inconsistent, contrary to high and stable correlations between different spectral variables. This fact, as well as the lack of considerable task-dependent effects during the first part of training, indicates that learned SCP shifts did not directly lead to the specific dynamics of the EEG power spectra. Rather, these dynamics were related to nonspecific changes in patients' brain state.

Kotchoubey, B., Strehl, U., Uhlmann, C., Holzapfel, S., Konig, M., Froscher, W., Blankenhorn, V., & Birbaumer, N. (2001). Modification of slow cortical potentials in patients with refractory epilepsy: A controlled outcome study. *Epilepsia*, 42(3), 406-416. The goal of the study was to explore parallel changes in EEG spectral frequencies during biofeedback of slow cortical potentials (SCPs) in epilepsy patients. Thirty-four patients with intractable focal epilepsy participated in 35 sessions of SCP self-regulation training. The spectral analysis was carried out for the EEG recorded at the same electrode site (Cz) that was used for SCP feedback. The most prominent effect was the increase in the theta 2 power (6.0-7.9 Hz) and the relative power decrement in all other frequency bands (particularly delta 1, alpha 2 and beta 2) in transfer trials (i.e., where patients controlled their SCPs without continuous feedback) compared with feedback trials. In the second half of the training course (i.e., sessions 21-35) larger power values in the delta, theta, and alpha bands were found when patients were required to produce positive versus negative SCP shifts. Both across-subject and across-session (within-subject) correlations between spectral EEG parameters, on the one hand, and SCP data, on the other hand, were low and inconsistent, contrary to high and stable correlations between different spectral variables. This fact, as well as the lack of considerable

task-dependent effects during the first part of training, indicates that learned SCP shifts did not directly lead to the specific dynamics of the EEG power spectra. Rather, these dynamics were related to nonspecific changes in patients' brain state.

Kuhlman, W. N. (1978). EEG feedback training of epileptic patients: Clinical and electroencephalographic analysis. *Electroencephalography & Clinical Neurophysiology*, 45(6), 699-710. To evaluate the clinical efficacy and mechanisms underlying EEG feedback training of epileptic patients, 5 adult patients with poorly controlled seizures were studied for 4--10 months during which quantitative analysis of seizures, the EEG, and serum anticonvulsant levels was conducted. Sustained seizure reduction did not occur during the first 4--5 weeks in which feedback signals were presented randomly in relation to the EEG. When feedback was then made contingent upon central 9--14 c/sec activity, seizures declined by 60% in 3 patients. Power spectral analysis showed upward shifts in EEG frequency, decreases in abnormal slow activity, and enhancement of alpha rhythm activity as a function of contingent training, but no specific EEG change was associated with seizure reduction in all patients. No evidence was obtained for the hypothesized involvement of a 'sensorimotor rhythm' or motor inhibition in the training effects. The lack of effect in two patients could not be attributed to insufficient training, lack of motivation, or to differences in seizure classification. A second phase of research showed that continued laboratory training was both sufficient and necessary for maintaining clinical and EEG effects. Results indicate that: (1) significant seizure reductions can occur with EEG feedback training which are not related to placebo effects, non-specific factors or to changes in medication; (2) EEG changes associated with such training can best be described as 'normalization'; (3) continued clinical investigation of EEG feedback training as a non-pharmacological adjunct to conventional therapy appears justified.

Kuhlman, W. N., & Allison, T. (1977). EEG feedback training in the treatment of epilepsy: Some questions and some answers. *Pavlovian Journal of Biological Science*, 12(2), 112-122. A basic question in EEG feedback training of epileptic patients is whether the decrease in seizures is specifically due to the training or to other factors. Questions may also be raised as to what EEG changes are involved. Preliminary results in five patients suggest that seizure reductions can occur with training which are not due to placebo or nonspecific effects or to changes in medication compliance. These changes occurred rapidly during EEG-contingent feedback training but not when feedback was random in relation to the EEG. Reliable changes in the EEG were also observed, but the question of which mechanism accounts for these results has yet to be answered.

Lantz, D., & Sterman, M. B. (1988). Neuropsychological assessment of subjects with uncontrolled epilepsy: Effects of EEG biofeedback training. *Epilepsia*, 29(2), 163-171. A battery of neuropsychological tests was administered at baseline, post-control period, and post-training period to 24 drug-refractory subjects with epilepsy participating in a study of sensorimotor electroencephalographic (EEG) normalization feedback training. Results revealed the following. First, subjects exhibited significant baseline deficits in psychosocial, cognitive and motor functioning. Second, certain tests discriminated subjects before training who were subsequently above and below the median in seizure reduction following EEG training. Subjects who showed the greatest seizure reduction performed better on a test of general problem-solving ability but not on other cognitive tests and worse on tests involving strong motor components and were more intact psychosocially. These subjects also took significantly fewer medications in combination than did less successful subjects. Third, improvement on several measures occurred following participation in the study. Cognitive and motor functioning improved only in subjects with the greatest seizure reduction and only after actual training as opposed to control conditions. Psychological functioning, as measured by the Minnesota Multiphasic Personality Inventory (MMPI) improved in both outcome groups. MMPI improvement, unlike cognitive improvement, was as likely to occur after control conditions, when seizure reduction had not yet occurred, as after EEG training. Thus, MMPI changes apparently reflected the nonspecific benefits of participation in this study.

Legarda SB, McMahon D, Othmer S, Othmer S. (2011). Clinical neurofeedback: Case studies, proposed mechanism, and implications for pediatric neurology practice. *J Child Neurol.* 2011 Aug;26(8):1045-51. Trends in alternative medicine use by American health care consumers are rising substantially. Extensive literature exists reporting on the effectiveness of neurofeedback in the treatment of autism, closed head injury, insomnia, migraine, depression, attention deficit hyperactivity disorder, epilepsy, and

posttraumatic stress disorder. We speculated that neurofeedback might serve as a therapeutic modality for patients with medically refractory neurological disorders and have begun referring patients to train with clinical neurofeedback practitioners. The modality is not always covered by insurance. Confident their child's medical and neurological needs would continue to be met, the parents of 3 children with epilepsy spectrum disorder decided to have their child train in the modality. The children's individual progress following neurofeedback are each presented here. A proposed mechanism and practice implications are discussed.

Lubar, J. F., & Bahler, W. W. (1976). Behavioral management of epileptic seizures following EEG biofeedback training of the sensorimotor rhythm. ***Biofeedback & Self-Regulation,*** **7, 77-104.** Eight severely epileptic patients, four males and four females, ranging in age from 10 to 29 years, were trained to increase 12-14 Hzeta EEG activity from the regions overlying the Rolandic area. This activity, the sensorimotor rhythm (SMR), has been hypothesized to be related to motor inhibitory processes (Sterman, 1974). The patients represented a cross-section of several different types of epilepsy, including grand mal, myoclonic, akinetic, focal, and psychomotor types. Three of them had varying degrees of mental retardation. SMR was detected by a combination of an analog filtering system and digital processing. Feedback, both auditory and/or visual, was provided whenever one-half second of 12-14-Hz activity was detected in the EEG. Patients were provided with additional feedback keyed by the output of a 4-7-Hz filter which indicated the presence of epileptiform spike activity, slow waves, or movement. Feedback for SMR was inhibited whenever slow-wave activity spikes or movement was also present. During the treatment period most of the patients showed varying degrees of improvement. Two of the patients who had been severely epileptic, having multiple seizures per week, have been seizure free for periods of up to 1 month. Other patients have developed the ability to block many of their seizures. Seizure intensity and duration have also decreased. Furthermore, the successful patients demonstrated an increase in the amount of SMR and an increase in amplitude of SMR during the training period. Spectral analyses for the EEGs were performed periodically. The effectiveness of SMR conditioning for the control of epileptic seizures is evaluated in terms of patient characteristics and type of seizures.

Lubar, J. F., Shabsin, H. S., Natelson, S. E. et al. (1981). EEG operant conditioning in intractable epileptics. ***Archives of Neurology*****, 38, 700-704.** Eight epileptic patients with mixed seizures refractory to medical control participated in a double-blind crossover study to determine the effectiveness of operant conditioning of the EEG as an anticonvulsant procedure. Baseline levels of seizures were recorded for four months prior to the beginning of treatment. Participants then received false (noncontingent) feedback for two months followed by an ABA-patterned training program lasting a total of ten months. Subjects were assigned to three treatment groups based on different schedules of EEG feedback. They were first trained (A1 phase) either to suppress slow activity (3 to 8 Hz), to enhance 12- to 15-Hz activity, or to simultaneously suppress 3- to 8-Hz and enhance 11- to 19-Hz activity. This was followed by a B phase, in which patients were trained to enhance slow activity (3 to 8 Hz). In the final phase (A2), the initial training contingencies were reinstated. Neuropsychological tests were performed before and after training, and changes in EEG activity as determined by Fast Fourier spectral analyses were analyzed. Five of eight patients experienced a decrease in their mean monthly seizure rate at the completion of feedback training as compared with their initial baseline level.

Micoulaud-Franchi JA, Lanteaume L, Pallanca O, Vion-Dury J, Bartolomei F. (2014). Biofeedback et épilepsie pharmacorésistante : le retour d'une thérapeutique ancienne? [Biofeedback and drug-resistant epilepsy: back to an earlier treatment?]. Rev Neurol (Paris). 2014 Mar;170(3):187-96. French. doi: 10.1016/j.neurol.2013.10.011. Epub 2014 Feb 24. PMID: 24576530. Biofeedback is a complementary non-pharmacological and non-surgical therapeutic developed over the last thirty years in the management of drug-resistant epilepsy. Biofeedback allows learning cognitive and behavioral strategies via a psychophysiological feedback loop. Firstly, this paper describes the different types of biofeedback protocols used for the treatment of drug-refractory epilepsy and their physiological justifications. Secondly, this paper analyzes the evidence of effectiveness, from a medical point of view, on reducing the numbers of seizures, and from a neurophysiological point of view, on the changing brain activity. Electroencephalography (EEG) biofeedback (neurofeedback) protocol on sensorimotor rhythms (SMR) has been investigated in many studies, the main limitation being small sample sizes and lack of control groups. The newer neurofeedback protocol on slow cortical potential (SCP) and galvanic skin response (GSR) biofeedback protocols have been used in a smaller number of studies. But, these studies are more rigorous with

larger sized samples, matched control groups, and attempts to control the placebo effect. These protocols also open the way for innovative neurophysiological researches and may predict a renewal of biofeedback techniques. Biofeedback would have legitimacy in the field of clinical drug-resistant epilepsy at the interface between therapeutic and clinical neurophysiology.

Monderer, R. S., Harrison, D. M., & Haut, S. R. (2002). Review: Neurofeedback and epilepsy. ***Epilepsy & Behavior*****, 3, 214-218.** Over the past three decades, researchers have examined various behavioral approaches to the treatment of epilepsy. One prominent line of inquiry concerns the effectiveness of neurofeedback, which entails the entrainment of specific electroencephalographic frequencies for the purpose of decreasing seizure frequencies in patients with epilepsy. This article reviews the current literature on the efficacy of neurofeedback in reducing seizure frequency. While it is clear that neurofeedback had a positive effect in most of the studies reviewed, these findings are limited due to multiple confounding factors. In the absence of any rigorously controlled studies, the relationship between neurofeedback and seizure frequency cannot be firmly established. Despite these limitations, the promising role of neurofeedback as a treatment for epilepsy is illustrated.

Nagai, Y. (2014). Biofeedback treatment for epilepsy. Nihon Rinsho: May:7(5). 887-893. Pharmacological treatment is the mainstay for the treatment of epilepsy. However concerns regarding long-term side effects of drugs are increasingly voiced. Behavioral treatments including biofeedback, represents an alternative management option for the control of epilepsy. Biofeedback is a non-invasive bio-behavioral procedure through which patients can learn to gain psychophysiological control over seizures. This article will first overview seizure precipitation from a psychological perspective, and then introduce three major biofeedback treatments. Sensory motor rhythm (SMR) and slow cortical potential(SCP) biofeedback uses electroencephalographic parameters and are categorized as neurofeedback. Electrodermal activity (EDA) biofeedback focuses on modulation of peripheral sympathetic tone. The neural mechanisms underlying biofeedback treatment will be discussed in relation to thalamo-cortical regulation (of neural excitability across brain networks).

Nagai Y, Matsuura M. (2011). Biofeedback for Epilepsy. ***Brain Nerve*****. 2011 Apr;63(4):385-92.** Anti-epileptic drugs are the mainstay in the management of epilepsy. However, approximately 30% of patients continue to have seizures despite optimal drug therapy. Behavioural interventions that include biofeedback have become increasingly popular over the last 3 decades, and the results have mostly been encouraging. Biofeedback is a non-invasive behavioural treatment that enables a patient to gain volitional control over a physiological process. In epilepsy, targeted parameters for biofeedback include electroencephalographic (EEG) measures of cortical activity, such as different EEG frequencies or cortical potentials (i.e., neurofeedback), and peripheral autonomic activity, such as Galvanic Skin Response (GSR). In this review, biofeedback using Sensory Motor Rhythm (SMR), Slow Cortical Potentials (SCP), and GSR are discussed. SMR biofeedback was established in the 1970s and is the most prominent methodology for biofeedback treatment of epilepsy in published literature. The technique is now regaining its popularity. SCP biofeedback was introduced in the 1990s. In contrast to SMR biofeedback, which modulates the frequency components of EEG, SCP biofeedback focuses on the regulation of potential changes (amplitude of DC shift). The clinical trials conducted using SCP biofeedback were larger than those conducted using SMR biofeedback, and their overall outcomes were promising. GSR biofeedback is a relatively new methodology in its application to epilepsy and focuses on the modulation of electrodermal measures of sympathetic activity. Compared to the neurofeedback approach, GSR biofeedback is much easier to implement, and evidence suggests that its clinical benefits can be achieved more rapidly. Although the biofeedback treatment may never achieve the status of an alternative to pharmacotherapy for epilepsy, current research findings strongly suggest that biofeedback has the potential to become a potent adjunctive non-pharmacological approach to reduce seizure frequency in patient with drug-resistant epilepsy. Further research, especially a well-controlled large clinical trial, is necessary and anticipated.

Nigro SE. (2019). The Efficacy of Neurofeedback for Pediatric Epilepsy. Appl Psychophysiol Biofeedback. 2019 Dec;44(4):285-290. doi: 10.1007/s10484-019-09446-y. PMID: 31407122. Approximately 470,000 children (birth to 18 years old) are affected by Epilepsy (CDC in Epilepsy. https://www.cdc.gov/epilepsy/index.html, 2018). Since the initial findings in the 1970s, Sensorimotor Rhythm (SMR) has been continuously utilized for the treatment of seizures. Studies have consistently demonstrated that SMR reduces

the frequency and severity of seizure activity. Although a mix of pediatric cases, adolescents and adults have been sampled in previous studies, no age effects have been reported. There continues to be a lack of research in the area of neurofeedback for the treatment of epilepsy in the pediatric population. To date, no randomized control trial specific to pediatric epilepsy has been published. The existing research regarding the use of neurofeedback in the treatment of epilepsy provides strong evidence that neurofeedback training might be an effective treatment for pediatric epilepsy. However, existing studies are not specific to the pediatric population. Moreover, there is a lack of rigor in the studies in which the effects of neurofeedback in children and adolescents with epilepsy are documented. Therefore, based on the current literature, there is not enough evidence to state that neurofeedback is efficacious for the treatment of pediatric epilepsy. However, the APBB criteria for evidence-based practices indicate that neurofeedback for pediatric epilepsy is Possibly Efficacious (Level 2). Future research in which a randomized controlled trial approach is utilized will greatly help to increase support for the use of neurofeedback as an efficacious treatment for epilepsy.

Osterhagen L, Breteler M, van Luijtelaar G. (2010). Does arousal interfere with operant conditioning of spike-wave discharges in genetic epileptic rats? *Epilepsy Res*. 2010 Jun;90(1-2):75-82. One of the ways in which brain computer interfaces can be used is neurofeedback (NF). Subjects use their brain activation to control an external device, and with this technique it is also possible to learn to control aspects of the brain activity by operant conditioning. Beneficial effects of NF training on seizure occurrence have been described in epileptic patients. Little research has been done about differentiating NF effectiveness by type of epilepsy, particularly, whether idiopathic generalized seizures are susceptible to NF. In this experiment, seizures that manifest themselves as spike-wave discharges (SWDs) in the EEG were reinforced during 10 sessions in 6 rats of the WAG/Rij strain, an animal model for absence epilepsy. EEG's were recorded before and after the training sessions. Reinforcing SWDs let to decreased SWD occurrences during training; however, the changes during training were not persistent in the post-training sessions. Because behavioural states are known to have an influence on the occurrence of SWDs, it is proposed that the reinforcement situation increased arousal which resulted in fewer SWDs. Additional tests supported this hypothesis. The outcomes have implications for the possibility to train SWDs with operant learning techniques.

Quy, R. J., Hutt, S. J., & Forrest, S. (1979). Sensorimotor rhythm feedback training and epilepsy: Some methodological and conceptual issues. *Biological Psychology*, 9, 129-149. This study examined the hypothesis that the enhancement of a 12-16 Hz sensorimotor rhythm in the EEG is inhibitory to epileptic seizure activity. The effects of training to enhance 12-16 Hz central EEG, to enhance 8-10 Hz central EEG, to suppress high voltage EEG activity, and of random feedback were compared over a period of 12 months in three adult patients suffering from chronic, drug-refractory epilepsy. All three patients experienced a significant reduction in seizure rate by the end of the study, but this was not related to any one particular training condition. It is suggested that the therapeutic mechanism might involve placebo effects, relaxation training, or a facilitation of EEG desynchronization, the effect being idiosyncratic to the individual patient.

Rockstroh, B., Elbert, T., Birbaumer, N., Wolf, P., Duchting-Roth, A., Reker, M., Daum, I., Lutzenberger, W., & Dichgans, J. (1993). Cortical self-regulation in patients with epilepsies. *Epilepsy Research*, 14. 63-72. The present study aimed at investigating to what extent the regulation of excitability in cortical networks, as indicated by surface-negative slow cortical potentials (SCPs), is impaired in epileptic patients and to what extent training of SCP self-regulation by means of biofeedback and instrumental learning procedures might affect seizure frequency. Twenty-five patients suffering from drug-refractory epilepsies (complex focal, grand mal, and absence type of seizures) participated in 28 1-h sessions of feedback and instrumental conditioning of their SCPs. Subjects' EEGs were obtained from the vertex. Depending on discriminative stimuli DC shifts towards increased or suppressed negativity relative to the pre-trial baseline were demonstrated by on-line visual feedback during intervals of 8 s each; each session comprised 110 trials. While performance on the SCP self-regulation task was initially below normal (as compared to healthy subjects), significant increases in SCP control were achieved by the patients across the 28 training sessions. In 18 patients at least 1-year follow-up data are available. Changes in seizure frequency were related to transfer of SCP control with six of the patients becoming seizure-free. Age affected the ability to acquire SCP control and its impact on seizure frequency.

Seifert, A. R.,& Lubar, J. F. (1975). Reduction of epileptic seizures through EEG biofeedback training. *Biological Psychology*, 3, 157-184. Biofeedback training of the sensorimotor rhythm (SMR) was carried out in three male and three female adolescent epileptics and in two normal controls. The patients represented a cross-section of epilepsies including grand mal, myoclonic, afocal and psychomotor types. Three of the cases were mentally retarded. 12-14 Hz (SMR) activity was detected by a combination of sharp analog filtering and digital processing. The patients were provided with feedback whenever they produced 0.5 sec of 12-14 Hz activity of a specified amplitude. Additional feedback was provided for epileptiform activity slow waves or movement. Furthermore, feedback for SMR production was inhibited by digital logic circuitry when movement, slow waves or spikes were present. Seizure reduction was obtained in five of the six epileptics. Several patients showed increased percentage of SMR when feedback was provided and varying degrees of normalization in their EEG as demonstrated by fast Fourier, crossed power spectral density and coherence analyses.

Sterman, M. B. (2000). Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. *Clinical Electroencephalography*, 31(1), 45-55. Two issues concerning sensorimotor EEG operant conditioning, or biofeedback, as a therapeutic modality for the treatment of seizure disorders are the focus of this review. The first relates to the question of whether relevant physiological changes are associated with this procedure. This question is addressed through review of an extensive neurophysiological literature that is likely unfamiliar to many clinicians but that documents both immediate and sustained functional changes that are consistent with elevation of seizure thresholds. The second focuses on the clinical efficacy of this method and whether it should carry the designation of "experimental". This designation is challenged through an assessment of over 25 years of peer-reviewed research demonstrating impressive EEG and clinical results achieved with the most difficult subset of seizure patients.

Sterman, M. B. (1977). *Effects of sensorimotor EEG feedback on sleep and clinical manifestations of epilepsy*. Chapter in J. Beatty & H. Legewie (Eds.), Biofeedback and Behavior. New York: Plenum, pp. 167-200. (No abstract available.)

Sterman, M. B. (1977). Sensorimotor EEG operant conditioning: Experimental and clinical effects. *Pavlovian Journal of Biological Sciences*, 12(2), 63-92. (No abstract available.)

Sterman, M. B. (1973). Neurophysiological and clinical studies of sensorimotor EEG biofeedback training: Some effects on epilepsy. *Seminars in Psychiatry*, 5(4), 507-525. (No abstract available.)

Sterman MB, Egner T. (2006). Foundation and practice of neurofeedback for the treatment of epilepsy. *Appl Psychophysiology & Biofeedback.* 2006 Mar;31(1):21-35.This review provides an updated overview of the neurophysiological rationale, basic and clinical research literature, and current methods of practice pertaining to clinical neurofeedback. It is based on documented findings, rational theory, and the research and clinical experience of the authors. While considering general issues of physiology, learning principles, and methodology, it focuses on the treatment of epilepsy with sensorimotor rhythm (SMR) training, arguably the best established clinical application of EEG operant conditioning. The basic research literature provides ample data to support a very detailed model of the neural generation of SMR, as well as the most likely candidate mechanism underlying its efficacy in clinical treatment. Further, while more controlled clinical trials would be desirable, a respectable literature supports the clinical utility of this alternative treatment for epilepsy. However, the skilled practice of clinical neurofeedback requires a solid understanding of the neurophysiology underlying EEG oscillation, operant learning principles and mechanisms, as well as an in-depth appreciation of the ins and outs of the various hardware/software equipment options open to the practitioner. It is suggested that the best clinical practice includes the systematic mapping of quantitative multi-electrode EEG measures against a normative database before and after treatment to guide the choice of treatment strategy and document progress towards EEG normalization. We conclude that the research literature reviewed in this article justifies the assertion that neurofeedback treatment of epilepsy/seizure disorders constitutes a well-founded and viable alternative to anticonvulsant pharmacotherapy.

Sterman, M. B., Macdonald, L. R., & Stone, R. K. (1974). Biofeedback training of the sensorimotor electroencephalogram rhythm in man: Effects on epilepsy. *Epilepsia*, 15(3), 395-416. (No abstract available.).

Sterman, M. B., & Macdonald, L. R. (1978). Effects of central cortical EEG feedback training on incidence of poorly controlled seizures. *Epilepsia*, 19(3), 207-222. This study examined the clinical effects of central cortical EEG feedback training in 8 patients with poorly controlled seizures. After base-line recordings, patients were trained in the laboratory and then initiated on a double or triple crossover design using portable equipment at home, with bimonthly laboratory test sessions. Performance at home was monitored by a strip chart recorder with the portable unit. Training was based on the simultaneous detection of two central cortical (C3--T3) EEG frequency bands (6--9 Hz and either 12--15 or 18--23 Hz), with reward provided for the occurrence of one in the absence of the other. The design consisted of successive 3 month periods of training, with reward contingencies reversed after each period without the subject's knowledge. Seizure incidence records were compared statistically before, during, and after the design. Six of the 8 patients reported significant and sustained seizure reductions, which averaged 74%, following reward for either 12--15 or 18--23 Hz in the absence of 6--9 Hz. Response to positive reward for 12--15 Hz was specific, with seizure rates returning to base line when reinforcement contingencies were reversed. Reduced seizure rates following positive reward for 18--23 Hz were not altered with contingency reversals. A nonspecific interpretation of these effects is rejected in favor of an EEG normalizing hypothesis.

Sterman, M. B., & Shouse, M. N. (1980). Quantitative analysis of training, sleep EEG and clinical response to EEG operant conditioning in epileptics. *Electroencephalography & Clinical Neurophysiology*, 49, 558-576. This report is a follow-up to a previous paper which described seizure rate changes with central cortical EEG feedback training in 8 poorly controlled epileptic subjects. Data examined here include associated training compliance and performance, sleep EEG spectra, clinical EEG and anticonvulsant blood levels. The study employed a double-cross-over, single blind ABA design applied to two subgroups of epileptic patients. Both groups had in common two training periods (A1, A2) in which either 12--15 c/sec (subgroup I, n = 4) or 18--23 c/sec (subgroup II, n = 4) was reinforced in the absence of 6--9 c/sec, movement or epileptiform discharge, and one training period (B) in which 6--9 c/sec was reinforced in the absence of 12--15 or 18--23 c/sec as well as movement and epileptiform discharge. Training periods occurred primarily in the home and lasted 3 months. Compliance with training instructions and response acquisition were demonstrated. Overall anticonvulsant blood levels were low and unrelated to EEG or seizure changes. Clinical EEG findings corresponded to sleep EEG and seizure rate outcomes. Power spectral analysis of sampled non-REM sleep from all-night EEG recordings obtained after each training phase indicated contingency specific changes which were limited to sensorimotor recordings in subgroup I and corresponded to the pattern of seizure rate changes in this group. EEG changes were also limited to sensorimotor cortex in subgroup II, but were linear and paralleled a progressive decrease in seizure rate. Both groups, however, showed the same pattern of EEG changes with seizure reductions; low and high frequencies were reduced and intermediate, rhythmic frequencies increased. Correlational analysis confirmed this relationship. The pattern, duration and topographic specificity of these changes suggested a normalization of sensorimotor EEG substrates related to the EEG feedback training.

Strehl, U., Birkle, SM., Worz, S. & Kotchoubey, B. (2014). Sustained reduction of seizures in patients with intractable epilepsy after self-regulation training of slow cortical potentials - 10 years after. Front Hum Neurosci. 2014 Aug 8;8:604. The aim of this study was to determine whether the reduction of seizures in patients with intractable epilepsy after self-regulation of slow cortical potentials (SCPs) was maintained almost 10 years after the end of treatment. Originally, 41 patients received training with SCP-neurofeedback. A control group of 12 patients received respiratory feedback while another group of 11 patients had their anticonvulsant medications reviewed. Nineteen patients in the experimental group participated at least in parts of the long-term follow-up, but only two patients from each control group agreed to do so. The follow-up participants completed the same seizure diaries as in the original study. Patients of the experimental group also took part in three SCP-training sessions at the follow-up evaluation. Due to the small sample size, the results of participants in the control groups were not considered in the analysis. A significant decrease in seizure frequency was found about 10 years after the end of SCP treatment. The clinical significance of this result is considered medium to high. All patients were still able to self-regulate their SCPs during the feedback condition. This success was achieved without booster sessions. This is the longest follow-up evaluation of the outcome of a psychophysiological treatment in patients with epilepsy ever reported. Reduced seizure frequency may be the result of patients continued ability to self-regulate their SCPs. Given such a long follow-up period, the possible impact of confounding variables should be taken into account. The small number of patients participating in this follow-up evaluation

diminishes the ability to make causal inferences. However, the consistency and duration of improvement for patients who received SCP-feedback training suggests that such treatment may be considered as a treatment for patients with intractable epilepsy and as an adjunct to conventional therapies.

Strehl, U., Trevorrow, T., Veit, R., Hinterberger, T., Kotchoubey, B., Erb, M., & Birbaumer, N. (2006). Deactivation of brain areas during self-regulation of slow cortical potentials in seizure patients. Applied Psychophysiology & Biofeedback, 31(1), 85-94. This study investigates the neurophysiological basis of EEG feedback for patients with epilepsy. Brain areas are identified that become hemodynamically deactivated when epilepsy patients, trained in EEG self-regulation, generate positive slow cortical potentials (SCPs). Five patients were trained in producing positive SCPs, using a training protocol previously established to reduce seizure frequency in patients with drug refractory epilepsy. Patients attempted to produce positive SCP shifts in a functional magnetic resonance imaging (fMRI) scanner. Two patients were able to reliably produce positive SCP shifts. When these successful regulators were prompted to produce positive SCPs, blood oxygen level-dependent (BOLD) response indicated deactivation, in comparison to a control state, around the recording electrode, frontal lobe, and thalamus. Unsuccessful regulators' BOLD response indicated no deactivation in cortical areas proximal to the active electrode. No thalamic deactivation was found in poor regulators. Decreased seizure frequency from SCP training may be the result of positively reinforced inhibition in cortical areas proximal to active electrode placement, the frontal cortex, and the thalamus.

Swingle, P. G. (1998). Neurofeedback treatment of pseudo seizure disorder. *Biological Psychiatry*, 44(11), 1-4. BACKGROUND: Previous research has shown that the suppression of theta wave activity and the enhancement of sensorimotor rhythm (SMR) through electroencephalographic (EEG) biofeedback is an effective treatment for epilepsy. The current research reports the results of EEG biofeedback treatment for patients presenting with seizure behaviors in the absence of eliptiform EEG activity. METHODS: In addition to psychotherapy, 3 patients, 2 women and 1 man, were trained, using EEG feedback once per week, to reduce the ratio of theta band to SMR band EEG amplitudes. RESULTS: The results showed that reductions in seizure activity were related to reductions in the theta-SMR ratio. CONCLUSIONS: These findings support the view that theta-SMR feedback training, in conjunction with psychotherapy, is an effective adjunctive treatment for pseudoseizure disorder.

Tan, G., Thornby, J., Hammond, D. C., Strehl, U., Canady, B., Arnemann, K., & Kaiser, D. K. (2009). Meta-analysis of EEG biofeedback in treating epilepsy. *Clinical EEG & Neuroscience*, 40(3), 173-179. About one third of patients with epilepsy do not benefit from medical treatment. For these patients electroencephalographic (EEG) biofeedback is a viable alternative. EEG biofeedback, or neurofeedback, normalizes or enhances EEG activity by means of operant conditioning. While dozens of scientific reports have been published on neurofeedback for seizure disorder, most have been case series with too few subjects to establish efficacy. The purpose of this paper is to meta-analyze existing research on neurofeedback and epilepsy. We analyzed every EEG biofeedback study indexed in MedLine, PsychInfo, and PsychLit databases between 1970 and 2005 on epilepsy that provided seizure frequency change in response to feedback. Sixty-three studies have been published, 10 of which provided enough outcome information to be included in a meta-analysis. All studies consisted of patients whose seizures were not controlled by medical therapies, which is a very important factor to keep in mind when interpreting the results. Nine of 10 studies reinforced sensorimotor rhythms (SMR) while 1 study trained slow cortical potentials (SCP). All studies reported an overall mean decreased seizure incidence following treatment and 64 out of 87 patients (74%) reported fewer weekly seizures in response to EEG biofeedback. Treatment effect was mean log (post/pre) where pre and post represent number of seizures per week prior to treatment and at final evaluation, respectively. Due to prevalence of small groups, Hedges's g was computed for effect size. As sample heterogeneity was possible (Q test, $p=.18$), random effects were assumed and the effect of intervention was -0.233, SE = 0.057, $z = -4.11$, $p<.001$. Based on this meta-analysis, EEG operant conditioning was found to produce a significant reduction on seizure frequency. This finding is especially noteworthy given the patient group, individuals who had been unable to control their seizures with medical treatment.

Tansey, M. A. (1985). The response of a case of petit mal epilepsy to EEG sensorimotor rhythm biofeedback training. ***International Journal of Psychophysiology*****, 3, 81-84.** A 14-year-old girl, with a long history of absence seizures, sudden rages, spatial disorientation, and academic difficulties received long-term (33 sessions) EEG sensorimotor rhythm biofeedback training. Operantly conditioned increases in the average amplitude of the 14 Hz neural discharge rhythm, over the central Rolandic cortex and cerebrolongitudinal fissure, resulted in a total cessation of her absence seizures; which had, prior to the EEG sensorimotor rhythm biofeedback training, occurred at the rate of 4-5 absences per hour. Concurrently, her sudden rages, spatial disorientation, and academic functioning all evidenced significant remediation.

Tozzo, C.A., Elfner, L. F., & May Jr., J. G. (1988). Biofeedback and relaxation training in the control of epileptic seizures. ***International Journal of Psychophysiology*****, 6, 185-194.** Research utilizing sensorimotor rhythm (SMR) biofeedback with epileptics suggests that it is useful in decreasing seizures. Subjects were 6 young adults with a diagnosis of epilepsy of at least two years who had been unable to control their seizures with different regimens of anticonvulsant medications. Subjects ranged from severely mentally handicapped to above average functioning. Seizure type, frequency, and duration were recorded by subjects and caretakers. Measures of operant learning were percent time in SMR. The experiment utilized a single subject multiple baseline design which consisted of 6 phases: baseline one, relaxation training; baseline two, biofeedback training one; baseline three, biofeedback treatment two and follow-up. The results of this study are in agreement with other studies using SMR biofeedback. All subjects were able to significantly increase percent time in SMR. Five out of the 6 subjects demonstrated decreases in seizure frequency during the treatment phase. Two of the 6 subjects benefited from relaxation training. Four subjects demonstrated significant negative correlations between percent SMR and seizure rats. Consistent with other studies utilizing multiple baseline designs, a majority of the subjects did not follow the design of the study.

Uhlmann, C., & Froscher, W. (2001). Biofeedback treatment in patients with refractory epilepsy: Changes in depression and control orientation. ***Seizure*****, 10(1), 34-38.** Depression is a common and serious interictal problem in patients with epilepsy. The genesis of depressive disorders is multifactorial. One aetiological aspect focuses on psychosocial factors. It was hypothesized that uncontrollable, unpredictable chronic aversive events (i.e. epileptic seizures) result in cognitive deficits of external control orientation. If this is true, biofeedback training could represent a possible treatment strategy to lower depression, because biofeedback is known to mediate success experiences and control. Measures of depression and locus of control were administered to 20 patients with refractory partial epilepsy before and after biofeedback treatment. The biofeedback consisted of slow cortical potentials or breathing parameters in 10 patients each. A clear relationship occurred between depression and locus of control in the subjects. After biofeedback training control orientation moved towards a more internal locus of control. Also, depression scores were significantly reduced six months after training. Results show that in patients with refractory epilepsy depression is highly correlated with locus of control, in a way that external control orientation relates to high depression scores. Biofeedback is able to improve internal control orientation through personal success mediation.

Upton, A. R., & Longmere, D. (1975). The effects of feedback on focal epileptic discharges in man: A preliminary report. ***Canadian Journal of Neurological Sciences,*** **2, 153-167.** The history of the control of epileptic disturbances by conditioning techniques is reviewed. The preliminary results of a three year trial of feedback techniques in 13 epileptic patients are presented. Thirteen epileptic patients (age 2.5 leads to 39 mean, 15.1 years) with lateralized focal discharges in the EEG were given repeated trials of feedback, the focal discharges being used to trigger auditory and somatosensory stimuli. Dosages and serum levels of medication were unchanged throughout the experimental period. The number of epileptic spikes per 15 seconds was assessed by automatic trend analysis during 20 to 30 minute control, biofeedback and post-feedback epochs. On-going EEG activity was quantified by 8 channel frequency analysis over 10 second epochs. The patients made efforts to increase and decrease the number of spike discharges with and without feedback and the results of both triggered and random auditory, somatosensory, photic and combined stimulation were compared at various intervals over a period of up to three years. A marked reduction in the number of focal discharges was noted in eight (61.5%) patients during and immediately following the sessions. Intermittent biofeedback sessions were not associated with a serial reduction in the

number of focal EEG discharges. There was a reduction in the number of clinical epileptic disturbances in six patients (46%) and possible reasons for this improvement are discussed. One patient suffered an increase in focal temporal lobe discharges during triggered and random auditory stimulation whereas there was a marked reduction in the number of discharges during minimal electrical stimulation of the contralateral arm. The need for careful assessment of each patient to determine appropriate feedback stimulation is stressed. One aim of this research has been to assess the feasibility of using miniature units for continuous feedback of focal discharges in epileptic patients.

Walker, J. E. (2008). Power spectral frequency and coherence abnormalities in patients with intractable epilepsy and their usefulness in long-term remediation of seizures using neurofeedback. ***Clinical EEG & Neuroscience*****, 39(4), 203-204.** Medically intractable seizures appear to be highly correlated with focal slow activity (delta or theta). They also correlate highly with decreases in the coherence of theta. Normalization of focal slowing and of decreased theta coherence will probably be the neurofeedback approaches most likely to decrease or eliminate seizures in future cases. Neurofeedback has been used for over 35 years to reduce the incidence and severity of seizures. With power training to decrease theta and increase the sensorimotor rhythm (12-15 Hz), an average of 82% of patients experienced a significant reduction in seizure frequency, and occasional remissions were seen. Recent improvements using QEEG to guide neurofeedback training have made it possible to eliminate seizures in most patients, even those with intractable seizures. Following our previous study in 2005, we report an additional 25 patients so treated. We also report an analysis of the frequency of QEEG abnormalities in this patient group. All of the intractable epileptic patients had one or more slow foci (excessive theta or delta compared with the normal database). One third had a relative deficiency of beta power. One fourth had a deficiency of absolute delta. Eighteen percent had excessive absolute alpha power, 18% had deficient absolute alpha power, 18% percent had excessive absolute beta power, and 18% percent had deficient absolute beta power. Hypocoherence of theta was found in 75%, and decreases in alpha coherence were noted in 42%. Hypocoherence of beta was found in 50%, and hypocoherence of delta was found in 25%. Increases in alpha coherence were noted in 33%. Seventeen percent had no coherence abnormalities. When most of the power and coherence abnormalities were normalized with neurofeedback training, all the patients became seizure-free; 76% no longer required an anticonvulsant for seizure control.

Walker, J. E., & Kozlowski, G. P. (2005). Neurofeedback treatment of epilepsy. ***Child & Adolescent Psychiatric Clinics of North America*****, 14(1), 163-176.** With electroencephalographic (EEG) biofeedback (or neurofeedback), it is possible to train the brain to de-emphasize rhythms that lead to generation and propagation of seizure and emphasize rhythms that make seizures less likely to occur. With recent improvements in quantitative EEG measurement and improved neurofeedback protocols, it has become possible in clinical practice to eliminate seizures or reduce the amount of medication required to control them. In this article, the history of neurofeedback for epilepsy is presented followed by discussions of the relevant neurophysiology of epilepsy. A model of how neurofeedback might raise the seizure threshold is then presented. Clinical experience using a quantitative EEG-guided approach is described, including a representative case study.

Whitsett, S. F., Lubar, J. F., Holder, G. S., et al. (1982). A double-blind investigation of the relationship between seizure activity and the sleep EEG following EEG biofeedback training. ***Biofeedback & Self-Regulation,*** **7, 193-209.** The sleep EEGs of eight medically refractory epileptic patients were examined as part of a double-blind, ABA crossover study designed to determine the effectiveness of EEG biofeedback for the control of seizures. The patients were initially reinforced for one of three EEG criteria recorded from electrodes placed over sensorimotor cortex: (a) suppression of 3- to 7-Hz activity, (b) enhancement of 12- to 15-Hz activity, or (c) simultaneous suppression of 3- to 7-Hz and enhancement of 11- to 19-Hz activity. Reinforcement contingencies were reversed during the second or B phase, and then reinstated in their original form during the final A' phase. All-night polysomnographic recordings were obtained at the end of each conditioning phase and were subjected to both visual and computer-based power spectral analyses. Four of the patients showed changes in their nocturnal paroxysmal activity that were either partially or totally consistent with the ABA' contingencies of the study. The spectral data proved difficult to interpret, though two trends emerged from the analyses. Decreases in nocturnal 4- to 7-Hz activity were correlated with decreases in seizure activity, and increases in 8- to 11-Hz activity were correlated with

decreases in seizure activity. These findings were shown to strengthen the hypothesis that EEG biofeedback may produce changes in the sleep EEG that are related to seizure incidence.

Wyler, A. R., Robbins, C. A., & Dodrill, C. B. (1979). EEG operant conditioning for control of epilepsy. *Epilepsia*, 20, 279-286. We report the results of 23 severely epileptic patients who were given EEG feedback training. The paradigm reinforced the patients' 18 Hz activity over the scalp approximation of their focus while suppressing temporalis EMG and low frequency EEG activity. In contrast to other studies using EEG feedback, only 43% of patients showed significant changes in seizure occurrence and a lesser number were felt to have benefited clinically. None of our neuropsychological test parameters were helpful in identifying (prospectively or retrospectively) patients most likely to respond to this treatment. Although a few patients were significantly helped by this training, the mechanism for this effect is unclear.

Zhao, L., Liang, Z., Hu, G., & Wu, W. (2005). Nonlinear analysis in treatment of intractable epilepsy with EEG biofeedback. *Conference Proceedings IEEE Engineering, Medical, & Biological Science*, 5, 4568-4571. About 25% epilepsy patients are suffering from medically intractable epileptic seizure. Many studies have shown that electroencephalogram (EEG) biofeedback therapy has the exciting potential for seizure control. In this paper, five patients with intractable epilepsy were trained to increase the production of sensorimotor (12~15Hz) activity and decrease the production of slow theta (4~7Hz) activity. Nonlinear analyses are proposed to evaluate the effect of biofeedback training. In all the five patients, the complexity and approximate entropy of EEG increased significantly ($P<0.05$) after (about 1-month) the biofeedback treatment.

FMRI NEUROFEEDBACK

Alegria, A. A., Wulff, M., Brinson, H., Barker, G. J., Norman, L. J., Brandeis, D., Stahl, D., David, A. S., Taylor, E., Giampietro, V., & Rubia, K. (2017). Real-time fMRI neurofeedback in adolescents with attention deficit hyperactivity disorder. Human brain mapping, 38(6), 3190–3209. https://doi.org/10.1002/hbm.23584. Attention Deficit Hyperactivity Disorder (ADHD) is associated with poor self-control, underpinned by inferior fronto-striatal deficits. Real-time functional magnetic resonance neurofeedback (rtfMRI-NF) allows participants to gain self-control over dysregulated brain regions. Despite evidence for beneficial effects of electrophysiological-NF on ADHD symptoms, no study has applied the spatially superior rtfMRI-NF neurotherapy to ADHD. A randomized controlled trial tested the efficacy of rtfMRI-NF of right inferior prefrontal cortex (rIFG), a key region that is compromised in ADHD and upregulated with psychostimulants, on improvement of ADHD symptoms, cognition, and inhibitory fMRI activation. To control for region-specificity, an active control group received rtfMRI-NF of the left parahippocampal gyrus (lPHG). Thirty-one ADHD boys were randomly allocated and had to learn to upregulate their target brain region in an average of 11 rtfMRI-NF runs over 2 weeks. Feedback was provided through a video-clip of a rocket that had to be moved up into space. A transfer session without feedback tested learning retention as a proximal measure of transfer to everyday life. Both NF groups showed significant linear activation increases with increasing number of runs in their respective target regions and significant reduction in ADHD symptoms after neurotherapy and at 11-month follow-up. Only the group targeting rIFG, however, showed a transfer effect, which correlated with ADHD symptom reductions, improved at trend level in sustained attention, and showed increased IFG activation during an inhibitory fMRI task. This proof-of-concept study demonstrates for the first time feasibility, safety, and shorter- and longer-term efficacy of rtfMRI-NF of rIFG in adolescents with ADHD.

Baumeister, S., Wolf, I., Hohmann, S., Holz, N., Boecker-Schlier, R., Banaschewski, T., & Brandeis, D. (2019). The impact of successful learning of self-regulation on reward processing in children with ADHD using fMRI. Attention deficit and hyperactivity disorders, 11(1), 31–45. https://doi.org/10.1007/s12402-018-0269-6. Neurofeedback (NF) is a non-pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD) that is targeting self-regulation, is efficacious when standard protocols are used and induces partly specific neurophysiological changes in the inhibitory network. However, its effects on reward processing, which is also considered an important aspect of ADHD and has been linked to neurophysiological deficits, remain unknown. Children with ADHD (N = 15, mean age 11.8, SD 1.52) were randomly assigned to either slow cortical potential NF (n = 8) or EMG biofeedback control training (n = 7) and received 20 sessions of training under comparable conditions. Learning was defined as the slope of successful training runs across all transfer sessions. Whole brain analysis, region-of-interest analysis of anticipatory ventral striatal (VS) activation, and analysis of behavioral data were performed. Clinically, the NF group improved more than the EMG group. Whole brain analysis indicated increased activation in the left superior frontal gyrus in the control group only, and in medial prefrontal cortex and dorsolateral prefrontal gyrus (DLPFC) after treatment across all groups. Only successful learners of self-regulation (n = 8) showed increased left inferior frontal gyrus and DLPFC activation after treatment. Left VS activation was increased after treatment and showed a significant time*medication-status interaction. Specific treatment effects were found in left frontal regions for the control treatment and successful learners. Also, unmedicated participants, irrespective of treatment type or successful learning, showed treatment-induced improvement in reward processing. The results suggest no prominent specific effect of NF on reward processing. However, cautious interpretation is warranted due to the small sample.

Cortese, A., Amano, K., Koizumi, A., Lau, H., & Kawato, M. (2017). Decoded fMRI neurofeedback can induce bidirectional confidence changes within single participants. NeuroImage, 149, 323–337. https://doi.org/10.1016/j.neuroimage.2017.01.069. Neurofeedback studies using real-time functional magnetic resonance imaging (rt-fMRI) have recently incorporated the multi-voxel

pattern decoding approach, allowing for fMRI to serve as a tool to manipulate fine-grained neural activity embedded in voxel patterns. Because of its tremendous potential for clinical applications, certain questions regarding decoded neurofeedback (DecNef) must be addressed. Specifically, can the same participants learn to induce neural patterns in opposite directions in different sessions? If so, how does previous learning affect subsequent induction effectiveness? These questions are critical because neurofeedback effects can last for months, but the short- to mid-term dynamics of such effects are unknown. Here we employed a within-subjects design, where participants underwent two DecNef training sessions to induce behavioural changes of opposing directionality (up or down regulation of perceptual confidence in a visual discrimination task), with the order of training counterbalanced across participants. Behavioral results indicated that the manipulation was strongly influenced by the order and the directionality of neurofeedback training. We applied nonlinear mathematical modeling to parametrize four main consequences of DecNef: main effect of change in confidence, strength of down-regulation of confidence relative to up-regulation, maintenance of learning effects, and anterograde learning interference. Modeling results revealed that DecNef successfully induced bidirectional confidence changes in different sessions within single participants. Furthermore, the effect of up- compared to down-regulation was more prominent, and confidence changes (regardless of the direction) were largely preserved even after a week-long interval. Lastly, the effect of the second session was markedly diminished as compared to the effect of the first session, indicating strong anterograde learning interference. These results are interpreted in the framework of reinforcement learning and provide important implications for its application to basic neuroscience, to occupational and sports training, and to therapy.

Emmert, K., Kopel, R., Koush, Y., Maire, R., Senn, P., Van De Ville, D., & Haller, S. (2017). Continuous vs. intermittent neurofeedback to regulate auditory cortex activity of tinnitus patients using real-time fMRI - A pilot study. NeuroImage. Clinical, 14, 97–104. https://doi.org/10.1016/j.nicl.2016.12.023. The emerging technique of real-time fMRI neurofeedback trains individuals to regulate their own brain activity via feedback from an fMRI measure of neural activity. Optimum feedback presentation has yet to be determined, particularly when working with clinical populations. To this end, we compared continuous against intermittent feedback in subjects with tinnitus. Fourteen participants with tinnitus completed the whole experiment consisting of nine runs (3 runs × 3 days). Prior to the neurofeedback, the target region was localized within the auditory cortex using auditory stimulation (1 kHz tone pulsating at 6 Hz) in an ON-OFF block design. During neurofeedback runs, participants received either continuous (n = 7, age 46.84 ± 12.01, Tinnitus Functional Index (TFI) 49.43 ± 15.70) or intermittent feedback (only after the regulation block) (n = 7, age 47.42 ± 12.39, TFI 49.82 ± 20.28). Participants were asked to decrease auditory cortex activity that was presented to them by a moving bar. In the first and the last session, participants also underwent arterial spin labeling (ASL) and resting-state fMRI imaging. We assessed tinnitus severity using the TFI questionnaire before all sessions, directly after all sessions and six weeks after all sessions. We then compared neuroimaging results from neurofeedback using a general linear model (GLM) and region-of-interest analysis as well as behavior measures employing a repeated-measures ANOVA. In addition, we looked at the seed-based connectivity of the auditory cortex using resting-state data and the cerebral blood flow using ASL data. GLM group analysis revealed that a considerable part of the target region within the auditory cortex was significantly deactivated during neurofeedback. When comparing continuous and intermittent feedback groups, the continuous group showed a stronger deactivation of parts of the target region, specifically the secondary auditory cortex. This result was confirmed in the region-of-interest analysis that showed a significant down-regulation effect for the continuous but not the intermittent group. Additionally, continuous feedback led to a slightly stronger effect over time while intermittent feedback showed best results in the first session. Behaviorally, there was no significant effect on the total TFI score, though on a descriptive level TFI scores tended to decrease after all sessions and in the six weeks follow up in the continuous group. Seed-based connectivity with a fixed-effects analysis revealed that functional connectivity increased over sessions in the posterior cingulate cortex, premotor area and part of the insula when looking at all patients while cerebral blood flow did not change significantly over time. Overall, these results show that continuous feedback is suitable for long-term neurofeedback experiments while intermittent feedback presentation promises good results for single session experiments when using the auditory cortex as a target region. In particular, the down-regulation effect is more pronounced in the secondary auditory cortex, which might be more susceptible to voluntary modulation in comparison to a primary sensory region.

Emmert, K., Kopel, R., Sulzer, J., Brühl, A. B., Berman, B. D., Linden, D., Horovitz, S. G., Breimhorst, M., Caria, A., Frank, S., Johnston, S., Long, Z., Paret, C., Robineau, F., Veit, R., Bartsch, A., Beckmann, C. F., Van De Ville, D., & Haller, S. (2016).

Meta-analysis of real-time fMRI neurofeedback studies using individual participant data: How is brain regulation mediated?. NeuroImage, 124(Pt A), 806–812. https://doi.org/10.1016/j.neuroimage.2015.09.042. An increasing number of studies using real-time fMRI neurofeedback have demonstrated that successful regulation of neural activity is possible in various brain regions. Since these studies focused on the regulated region(s), little is known about the target-independent mechanisms associated with neurofeedback-guided control of brain activation, i.e. the regulating network. While the specificity of the activation during self-regulation is an important factor, no study has effectively determined the network involved in self-regulation in general. In an effort to detect regions that are responsible for the act of brain regulation, we performed a post-hoc analysis of data involving different target regions based on studies from different research groups. We included twelve suitable studies that examined nine different target regions amounting to a total of 175 subjects and 899 neurofeedback runs. Data analysis included a standard first- (single subject, extracting main paradigm) and second-level (single subject, all runs) general linear model (GLM) analysis of all participants taking into account the individual timing. Subsequently, at the third level, a random effects model GLM included all subjects of all studies, resulting in an overall mixed effects model. Since four of the twelve studies had a reduced field of view (FoV), we repeated the same analysis in a subsample of eight studies that had a well-overlapping FoV to obtain a more global picture of self-regulation. The GLM analysis revealed that the anterior insula as well as the basal ganglia, notably the striatum, were consistently active during the regulation of brain activation across the studies. The anterior insula has been implicated in interoceptive awareness of the body and cognitive control. Basal ganglia are involved in procedural learning, visuomotor integration and other higher cognitive processes including motivation. The larger FoV analysis yielded additional activations in the anterior cingulate cortex, the dorsolateral and ventrolateral prefrontal cortex, the temporo-parietal area and the visual association areas including the temporo-occipital junction. In conclusion, we demonstrate that several key regions, such as the anterior insula and the basal ganglia, are consistently activated during self-regulation in real-time fMRI neurofeedback independent of the targeted region-of-interest. Our results imply that if the real-time fMRI neurofeedback studies target regions of this regulation network, such as the anterior insula, care should be given whether activation changes are related to successful regulation, or related to the regulation process per se. Furthermore, future research is needed to determine how activation within this regulation network is related to neurofeedback success.

Florin, E. & Baillet, S. (2015). The brain's resting state activity is shaped by synchronized cross-frequency coupling of neural oscillations NeuroImage: 111 26-35. Functional imaging of the resting brain consistently reveals broad motifs of correlated blood oxygen level dependent (BOLD) activity that engages cerebral regions from distinct functional systems. Yet, the neurophysiological processes underlying these organized, large-scale fluctuations remain to be uncovered. Using magnetoencephalography (MEG) imaging during rest in 12 healthy subjects we analyze the resting state networks and their underlying neurophysiology. We first demonstrate non-invasively that cortical occurrences of high-frequency oscillatory activity are conditioned to the phase of slower spontaneous fluctuations in neural ensembles. We further show that resting-state networks emerge from synchronized phase–amplitude coupling across the brain. Overall, these findings suggest a unified principle of local-to-global neural signaling for long-range brain communication.

Herwig, U., Lutz, J., Scherpiet, S., Scheerer, H., Kohlberg, J., Opialla, S., Preuss, A., Steiger, V. R., Sulzer, J., Weidt, S., Stämpfli, P., Rufer, M., Seifritz, E., Jäncke, L., & Brühl, A. B. (2019). Training emotion regulation through real-time fMRI neurofeedback of amygdala activity. NeuroImage, 184, 687–696. https://doi.org/10.1016/j.neuroimage.2018.09.068. Being in control of one's emotions is not only desirable in many everyday situations but is also a great challenge in a variety of mental disorders. Successful intentional emotion regulation is related to down-regulation of amygdala activity. Training mental interventions supported by neurofeedback of one's own amygdala activity using real-time (rt-)fMRI might be beneficial for mental health and well-being. Rt-fMRI guided amygdala-downregulation using cognitive interventions such as a "reality check", however, have not been well-investigated. Fifteen healthy subjects underwent four rt-fMRI sessions with neurofeedback of their own amygdala activity while applying a reality check as an emotion regulation strategy in order to down-regulate their amygdala signal during a stimulation with emotional pictures. The Control group comprised of eleven subjects also trained emotion regulation but without obtaining feedback. We hypothesized more prominent down-regulation of amygdala activity at the end of the training in the Feedback group. We investigated effects over time and between groups and further task specific connectivity of the amygdala by using psychophysiological interaction analyses. Four weekly amygdala-based feedback sessions resulted in significantly decreased amygdala activity ($p = 0.003$, $d = 0.93$), also compared to the

Control group (p = 0.014, d = 1.12). Task specific connectivity of the amygdala with the anterior cingulate cortex, hippocampus and distinct prefrontal areas was increased in the Feedback group. Training of emotion regulation supported by rt-fMRI neurofeedback resulted in a prominent amygdala down-regulation compared to training without feedback. The finding implicates successful emotion regulation, compliant with emotion control models, through an easily applicable reality check strategy. Rt-fMRI neurofeedback may support emotion regulation learning and bears clinical potential for psychotherapy.

Keynan, J. N., Cohen, A., Jackont, G., Green, N., Goldway, N., Davidov, A., Meir-Hasson, Y., Raz, G., Intrator, N., Fruchter, E., Ginat, K., Laska, E., Cavazza, M., & Hendler, T. (2019). Electrical fingerprint of the amygdala guides neurofeedback training for stress resilience. Nature human behaviour, 3(1), 63–73. https://doi.org/10.1038/s41562-018-0484-3. Real-time functional magnetic resonance imaging (rt-fMRI) has revived the translational perspective of neurofeedback (NF)1. Particularly for stress management, targeting deeply located limbic areas involved in stress processing2 has paved new paths for brain-guided interventions. However, the high cost and immobility of fMRI constitute a challenging drawback for the scalability (accessibility and cost-effectiveness) of the approach, particularly for clinical purposes3. The current study aimed to overcome the limited applicability of rt-fMRI by using an electroencephalography (EEG) model endowed with improved spatial resolution, derived from simultaneous EEG-fMRI, to target amygdala activity (termed amygdala electrical fingerprint (Amyg-EFP))4-6. Healthy individuals (n = 180) undergoing a stressful military training programme were randomly assigned to six Amyg-EFP-NF sessions or one of two controls (control-EEG-NF or NoNF), taking place at the military training base. The results demonstrated specificity of NF learning to the targeted Amyg-EFP signal, which led to reduced alexithymia and faster emotional Stroop, indicating better stress coping following Amyg-EFP-NF relative to controls. Neural target engagement was demonstrated in a follow-up fMRI-NF, showing greater amygdala blood-oxygen-level-dependent downregulation and amygdala-ventromedial prefrontal cortex functional connectivity following Amyg-EFP-NF relative to NoNF. Together, these results demonstrate limbic specificity and efficacy of Amyg-EFP-NF during a stressful period, pointing to a scalable non-pharmacological yet neuroscience-based training to prevent stress-induced psychopathology.

Kim, H. C., Tegethoff, M., Meinlschmidt, G., Stalujanis, E., Belardi, A., Jo, S., Lee, J., Kim, D. Y., Yoo, S. S., & Lee, J. H. (2019). Mediation analysis of triple networks revealed functional feature of mindfulness from real-time fMRI neurofeedback. NeuroImage, 195, 409–432. https://doi.org/10.1016/j.neuroimage.2019.03.066. The triple networks, namely the default-mode network (DMN), the central executive network (CEN), and the salience network (SN), play crucial roles in disorders of the brain, as well as in basic neuroscientific processes such as mindfulness. However, currently, there is no consensus on the underlying functional features of the triple networks associated with mindfulness. In this study, we tested the hypothesis that (a) the partial regression coefficient (i.e., slope): from the SN to the DMN, mediated by the CEN, would be one of the potential mindfulness features in the real-time functional magnetic resonance imaging (rtfMRI) neurofeedback (NF) setting, and (b) this slope level may be enhanced by rtfMRI-NF training. Sixty healthy mindfulness-naïve males participated in an MRI session consisting of two non-rtfMRI-runs, followed by two rtfMRI-NF runs and one transfer run. Once the regions-of-interest of each of the triple networks were defined using the non-rtfMRI-runs, the slope level was calculated by mediation analysis and used as neurofeedback information, in the form of a thermometer bar, to assist with participant mindfulness during the rtfMRI-NF runs. The participants were asked to increase the level of the thermometer bar while deploying a mindfulness strategy, which consisted of focusing attention on the physical sensations of breathing. rtfMRI-NF training was conducted as part of a randomized controlled trial design, in which participants were randomly assigned to either an experimental group or a control group. The participants in the experimental group received contingent neurofeedback information, which was obtained from their own brain signals, whereas the participants in the control group received non-contingent neurofeedback information that originated from matched participants in the experimental group. Our results indicated that the slope level from the SN to the DMN, mediated by the CEN, was associated with mindfulness score (rtfMRI-NF runs: r = 0.53, p = 0.007; p-value was corrected from 10,000 random permutations) and with task-performance feedback score (rtfMRI-NF run: r = 0.61, p = 0.001) in the experimental group only. In addition, during the rtfMRI-NF runs the level of the partial regression coefficient feature was substantially increased in the experimental group compared to the control group ($p < 0.05$ from the paired t-test; the p-value was corrected from 10,000 random permutations). To the best of our knowledge, this is the first study to demonstrate a partial regression coefficient feature of mindfulness in the rtfMRI-NF setting

obtained by triple network mediation analysis, as well as the possibility of enhancement of the partial regression coefficient feature by rtfMRI-NF training.

Kohl, S. H., Veit, R., Spetter, M. S., Günther, A., Rina, A., Lührs, M., Birbaumer, N., Preissl, H., & Hallschmid, M. (2019). Real-time fMRI neurofeedback training to improve eating behavior by self-regulation of the dorsolateral prefrontal cortex: A randomized controlled trial in overweight and obese subjects. NeuroImage, 191, 596–609. https://doi.org/10.1016/j.neuroimage.2019.02.033. Obesity is associated with altered responses to food stimuli in prefrontal brain networks that mediate inhibitory control of ingestive behavior. In particular, activity of the dorsolateral prefrontal cortex (dlPFC) is reduced in obese compared to normal-weight subjects and has been linked to the success of weight-loss dietary interventions. In a randomized controlled trial in overweight/obese subjects, we investigated the effect on eating behavior of volitional up-regulation of dlPFC activity via real-time functional magnetic resonance imaging (fMRI) neurofeedback training. Thirty-eight overweight or obese subjects (BMI 25-40 kg/m2) took part in fMRI neurofeedback training with the aim of increasing activity of the left dlPFC (dlPFC group; n = 17) or of the visual cortex (VC/control group; n = 21). Participants were blinded to group assignment. The training session took place on a single day and included three training runs of six trials of up-regulation and passive viewing. Food appraisal and snack intake were assessed at screening, after training, and in a follow-up session four weeks later. Participants of both groups succeeded in up-regulating activity of the targeted brain area. However, participants of the control group also showed increased left dlPFC activity during up-regulation. Functional connectivity between dlPFC and ventromedial PFC, an area that processes food value, was generally increased during up-regulation compared to passive viewing. At follow-up compared to baseline, both groups rated pictures of high-, but not low-calorie foods as less palatable and chose them less frequently. Actual snack intake remained unchanged but palatability and choice ratings for chocolate cookies decreased after training. We demonstrate that one session of fMRI neurofeedback training enables individuals with increased body weight to up-regulate activity of the left dlPFC. Behavioral effects were observed in both groups, which might have been due to dlPFC co-activation in the control group and, in addition, unspecific training effects. Improved dlPFC-vmPFC functional connectivity furthermore suggested enhanced food intake-related control mechanisms. Neurofeedback training might support therapeutic strategies aiming at improved self-control in obesity, although the respective contributions of area-specific mechanisms and general regulation effects are in need of further investigation.

Li, Z., Tong, L., Guan, M., He, W., Wang, L., Bu, H., Shi, D., & Yan, B. (2016). Altered Resting-State Amygdala Functional Connectivity after Real-Time fMRI Emotion Self-Regulation Training. BioMed research international, 2016, 2719895. https://doi.org/10.1155/2016/2719895. Real-time fMRI neurofeedback (rtfMRI-nf) is a promising tool for enhancing emotion regulation capability of subjects and for the potential alleviation of neuropsychiatric disorders. The amygdala is composed of structurally and functionally distinct nuclei, such as the basolateral amygdala (BLA) and centromedial amygdala (CMA), both of which are involved in emotion processing, generation, and regulation. However, the effect of rtfMRI-nf on the resting-state functional connectivity (rsFC) of BLA and CMA remains to be elucidated. In our study, participants were provided with ongoing information on their emotion states by using real-time multivariate voxel pattern analysis. Results showed that participants presented significantly increased rsFC of BLA and CMA with prefrontal cortex, rostral anterior cingulate cortex, and some others related to emotion after rtfMRI-nf training. The findings provide important evidence for the emotion regulation effectiveness of rtfMRI-nf training and indicate its usefulness as a tool for the self-regulation of emotion.

Linhartová, P., Látalová, A., Kóša, B., Kašpárek, T., Schmahl, C., & Paret, C. (2019). fMRI neurofeedback in emotion regulation: A literature review. NeuroImage, 193, 75–92. https://doi.org/10.1016/j.neuroimage.2019.03.011. Objectives: Emotion regulation is one of the most prevalent objectives for real-time fMRI neurofeedback (rt-fMRI-NF) studies. The existing studies differ in a number of methodological parameters. This study provides a literature review of the main parameters and results of studies using rt-fMRI-NF for emotion regulation enhancement. **Method:** A search of the Web of Science database up through November 8, 2018, identified 144 articles written in English, 89 of which were excluded as irrelevant for this study. The remaining 51 original studies and four secondary analyses of previously published original studies were included in the literature review. The selection of target brain areas, target populations, emotion regulation protocols, NF presentation, control group types, and emotion regulation instructions were examined in

relation to achieved brain regulation and changes in cognitive or clinical outcomes. Study results were evaluated in terms of their statistical robustness. Results: The results show that healthy people are able to regulate their brain activity in the presence of rt-fMRI-NF from various brain regions related to emotion regulation, including the amygdala, anterior insula, and anterior cingulate cortex. The regulation of brain activity using rt-fMRI-NF from prefrontal-limbic connectivity or from individually navigated brain areas is feasible as well. Most studies that used a control group show that rt-fMRI-NF actually induces some effects on brain regulation, cognitive variables, and clinical variables. Generally, the success of ROI regulation during NF training is related to the combination of target brain region, the type of emotion regulation task, and the population undergoing the training. In terms of patient groups, the strongest support for the beneficial effects of rt-fMRI-NF has been shown in increased positive emotion experiencing in patients with depression and in decreased anxiety in patients with anxiety disorders. Symptom reduction following NF training has been also reported in patients with PTSD, BPD, and schizophrenia, but direct comparisons with control groups in these studies makes it impossible to evaluate the added value of NF. Studies often do not report all the relevant analyses for evaluating NF success and many studies lack statistical robustness. Conclusions: Overall, rt-fMRI-NF seems a promising tool for emotion regulation enhancement with the potential to induce long-term symptom reduction in patients with various mental disorders. Preplanning of statistical analyses, careful interpretations of the results, and evaluations of the NF effect on symptom reduction in patient groups is recommended.

Paul, RH., Gunstad, J., Cooper, N. & Williams, LM., Clark, CR., Cohen, RA., Lawrence, JJ & Gordon, E. (2007). Cross-cultural assessment of neurophysiological performance and electrical brain function measures: Additional validation of an international brain database. International Journal of Neuroscience:117: 549-568. Previous studies have revealed significant differences in performance on non-language
dependent cognitive tests across international settings among younger individuals, with less pronounced differences evident among older individuals (>54 years of age). The present study examined a broad range of cognitive performance as well as electrophysiological indices of brain function in a multisite and international context. A total of 200 individuals in the United States, 233 individuals in Europe, and 829 individuals in Australia were administered a standardized computerized neuropsychological battery, and complementary electroencephalogram (EEG) recordings were completed. Results revealed no significant differences in cognitive function or electrophysiology across the three continents. Similarly, although there was a main effect for age, the interaction between age and continent was not significant in any of the omnibus analyses. These findings indicate a high degree of similarity in neurocognitive and electrophysiological function among individuals
residing in developed Western cultures, consistent with a trait-like status and the high heritability of the EEG.

Pasqual-Marqui, RD., Lehmann, D., Faber, P., Milz, P., Kochi, K., Yoshimura, M., Nishida, K., Isotani, T. & Kinoshita, T. (2006). The resting microstate (RMN): Cortical distributions, dynamics, and frequency specific information flow. A brain microstate is characterized by a unique, fixed spatial distribution of electrically active neurons with time varying amplitude. It is hypothesized that a microstate implements a functional/physiological state of the brain during which specific neural computations are performed. Based on this hypothesis, brain electrical activity is modeled as a time sequence of non-overlapping microstates with variable, finite durations (Lehmann and Skrandies 1980, 1984; Lehmann et al 1987). In this study, EEG recordings from 109 participants during eyes closed resting condition are modeled with four microstates. In a first part, a new confirmatory statistics method is introduced for the determination of the cortical distributions of electric neuronal activity that generate each microstate. All microstates have common posterior cingulate generators, while three microstates additionally include activity in the left occipital/parietal, right occipital/parietal, and anterior cingulate cortices. This appears to be a fragmented version of the metabolically (PET/fMRI) computed default mode network (DMN), supporting the notion that these four regions activate sequentially at high time resolution, and that slow metabolic imaging corresponds to a low-pass filtered version. In the second part of this study, the microstate amplitude time series are used as the basis for estimating the strength, directionality, and spectral characteristics (i.e., which oscillations are preferentially transmitted) of the connections that are mediated by the microstate transitions. The results show that the posterior cingulate is an important hub, sending alpha and beta oscillatory information to all other microstate generator regions. Interestingly, beyond alpha, beta oscillations are essential in the maintenance of the brain during resting state.

Patel, K., Sutherland, H., Henshaw, J., Taylor, J. R., Brown, C. A., Casson, A. J., Trujillo-Barreton, N. J., Jones, A., & Sivan, M. (2020). Effects of neurofeedback in the management of chronic pain: A systematic review and meta-analysis of clinical trials. European journal of pain (London, England), 24(8), 1440–1457. https://doi.org/10.1002/ejp.1612. Background and objective: Neurofeedback (NFB) provides real-time feedback about neurophysiological signals to patients, thereby encouraging modulation of pain-associated brain activity. This review aims to evaluate the effectiveness and safety of NFB in alleviating pain and pain-associated symptoms in chronic pain patients. Methods: MEDLINE, PUBMED, Web of Science and PsycINFO databases were searched using the strategy: ("Neurofeedback" OR "EEG Biofeedback" OR "fMRI Biofeedback") AND ("Pain" or "Chronic Pain"). Clinical trials reporting changes in pain following electroencephalogram (EEG) or functional magnetic resonance imaging (fMRI) NFB in chronic pain patients were included. Only Randomized-controlled trials (RCT), non-randomized controlled trials (NRCT) and case series were included. Effect size was pooled for all RCTs in a meta-analysis. Results: Twenty-one studies were included. Reduction in pain following NFB was reported by one high-quality RCT, five of six low-quality RCT or NRCT and 13 of 14 case-series. Pain reduction reported by studies ranged from 6% to 82%, with 10 studies reporting a clinically significant reduction in pain of >30%. The overall effect size was medium (cohen's d -0.76, 95% confidence interval -1.31 to -0.20). Studies were highly heterogeneous (Q [df = 5] = 18.46, p = .002, I2 = 73%). Improvements in depression, anxiety, fatigue and sleep were also seen in some studies. Common side-effects included headache, nausea and drowsiness. These generally did not lead to withdrawal of therapy except in one study. Conclusions: Neurofeedback is a safe and effective therapy with promising but largely low-quality evidence supporting its use in chronic pain. Further high-quality trials comparing different protocols is warranted to determine the most efficacious way to deliver NFB. Significance: Neurofeedback is a novel neuromodulatory approach which can be used to reduce the severity of pain and pain-associated symptoms such as sleep disturbances, mood disturbances, fatigue and anxiety in a number of chronic pain conditions. It has a potential to provide integrative non-pharmacological management for chronic pain patients with pain refractory to pharmacological agents with high side-effect profiles. Further high-quality double-blinded randomized sham-controlled trials are needed in order to fully explore the potential of this therapy.

Rubia, K., Criaud, M., Wulff, M., Alegria, A., Brinson, H., Barker, G., Stahl, D., & Giampietro, V. (2019). Functional connectivity changes associated with fMRI neurofeedback of right inferior frontal cortex in adolescents with ADHD. NeuroImage, 188, 43–58. https://doi.org/10.1016/j.neuroimage.2018.11.055. Attention Deficit Hyperactivity Disorder (ADHD) is associated with poor self-control, underpinned by inferior fronto-striatal deficits. We showed previously that 18 ADHD adolescents over 11 runs of 8.5 min of real-time functional magnetic resonance neurofeedback of the right inferior frontal cortex (rIFC) progressively increased activation in 2 regions of the rIFC which was associated with clinical symptom improvement. In this study, we used functional connectivity analyses to investigate whether fMRI-Neurofeedback of rIFC resulted in dynamic functional connectivity changes in underlying neural networks. Whole-brain seed-based functional connectivity analyses were conducted using the two clusters showing progressively increased activation in rIFC as seed regions to test for changes in functional connectivity before and after 11 fMRI-Neurofeedback runs. Furthermore, we tested whether the resulting functional connectivity changes were associated with clinical symptom improvements and whether they were specific to fMRI-Neurofeedback of rIFC when compared to a control group who had to self-regulate another region. rIFC showed increased positive functional connectivity after relative to before fMRI-Neurofeedback with dorsal caudate and anterior cingulate and increased negative functional connectivity with regions of the default mode network (DMN) such as posterior cingulate and precuneus. Furthermore, the functional connectivity changes were correlated with clinical improvements and the functional connectivity and correlation findings were specific to the rIFC-Neurofeedback group. The findings show for the first time that fMRI-Neurofeedback of a typically dysfunctional frontal region in ADHD adolescents leads to strengthening within fronto-cingulo-striatal networks and to weakening of functional connectivity with posterior DMN regions and that this may be underlying clinical improvement.

Sherwood, M. S., Parker, J. G., Diller, E. E., Ganapathy, S., Bennett, K. B., Esquivel, C. R., & Nelson, J. T. (2019). Self-directed down-regulation of auditory cortex activity mediated by real-time fMRI neurofeedback augments attentional processes, resting cerebral perfusion, and auditory activation. NeuroImage, 195, 475–489. https://doi.org/10.1016/j.neuroimage.2019.03.078. In this work, we investigated the use of real-time functional magnetic resonance

imaging (fMRI) with neurofeedback training (NFT) to teach volitional down-regulation of the auditory cortex (AC) using directed attention strategies as there is a growing interest in the application of fMRI-NFT to treat neurologic disorders. Healthy participants were separated into two groups: the experimental group received real feedback regarding activity in the AC; the control group was supplied sham feedback yoked from a random participant in the experimental group and matched for fMRI-NFT experience. Each participant underwent five fMRI-NFT sessions. Each session contained 2 neurofeedback runs where participants completed alternating blocks of "rest" and "lower" conditions while viewing a continuously-updated bar representing AC activation and listening to continuous noise. Average AC deactivation was extracted from each closed-loop neuromodulation run and used to quantify the control over AC (AC control), which was found to significantly increase across training in the experimental group. Additionally, behavioral testing was completed outside of the MRI on sessions 1 and 5 consisting of a subjective questionnaire to assess attentional control and two quantitative tests of attention. No significant changes in behavior were observed; however, there was a significant correlation between changes in AC control and attentional control. Also, in a neural assessment before and after fMRI-NFT, AC activity in response to continuous noise stimulation was found to significantly decrease across training while changes in AC resting perfusion were found to be significantly greater in the experimental group. These results may be useful in formulating effective therapies outside of the MRI, specifically for chronic tinnitus which is often characterized by hyperactivity of the primary auditory cortex and altered attentional processes. Furthermore, the modulation of attention may be useful in developing therapies for other disorders such as chronic pain.

Young, K. D., Misaki, M., Harmer, C. J., Victor, T., Zotev, V., Phillips, R., Siegle, G. J., Drevets, W. C., & Bodurka, J. (2017). Real-Time Functional Magnetic Resonance Imaging Amygdala Neurofeedback Changes Positive Information Processing in Major Depressive Disorder. Biological psychiatry, 82(8), 578–586. https://doi.org/10.1016/j.biopsych.2017.03.013. Background: In participants with major depressive disorder who are trained to upregulate their amygdalar hemodynamic responses during positive autobiographical memory recall with real-time functional magnetic resonance imaging neurofeedback (rtfMRI-nf) training, depressive symptoms diminish. This study tested whether amygdalar rtfMRI-nf also changes emotional processing of positive and negative stimuli in a variety of behavioral and imaging tasks. Methods: Patients with major depressive disorder completed two rtfMRI-nf sessions (18 received amygdalar rtfMRI-nf, 16 received control parietal rtfMRI-nf). One week before and following rtfMRI-nf training, participants performed tasks measuring responses to emotionally valenced stimuli including a backward-masking task, which measures the amygdalar hemodynamic response to emotional faces presented for traditionally subliminal duration and followed by a mask, and the Emotional Test Battery in which reaction times and performance accuracy are measured during tasks involving emotional faces and words. Results: During the backward-masking task, amygdalar responses increased while viewing masked happy faces but decreased to masked sad faces in the experimental versus control group following rtfMRI-nf. During the Emotional Test Battery, reaction times decreased to identification of positive faces and during self-identification with positive words and vigilance scores increased to positive faces and decreased to negative faces during the faces dot-probe task in the experimental versus control group following rtfMRI-nf. Conclusions: rtfMRI-nf training to increase the amygdalar hemodynamic response to positive memories was associated with changes in amygdalar responses to happy and sad faces and improved processing of positive stimuli during performance of the Emotional Test Battery. These results may suggest that amygdalar rtfMRI-nf training alters responses to emotional stimuli in a manner similar to antidepressant pharmacotherapy.

Young, K. D., Siegle, G. J., Zotev, V., Phillips, R., Misaki, M., Yuan, H., Drevets, W. C., & Bodurka, J. (2017). Randomized Clinical Trial of Real-Time fMRI Amygdala Neurofeedback for Major Depressive Disorder: Effects on Symptoms and Autobiographical Memory Recall. The American journal of psychiatry, 174(8), 748–755. https://doi.org/10.1176/appi.ajp.2017.16060637. Objective: Patients with depression show blunted amygdala hemodynamic activity to positive stimuli, including autobiographical memories. The authors examined the therapeutic efficacy of real-time functional MRI neurofeedback (rtfMRI-nf) training aimed at increasing the amygdala's hemodynamic response to positive memories in patients with depression. Method: In a double-blind, placebo-controlled, randomized clinical trial, unmedicated adults with depression (N=36) were randomly assigned to receive two sessions of rtfMRI-nf either from the amygdala (N=19) or from a parietal control region not involved in emotional processing (N=17). Clinical scores and autobiographical memory performance were assessed at baseline and 1

week after the final rtfMRI-nf session. The primary outcome measure was change in score on the Montgomery-Åsberg Depression Rating Scale (MADRS), and the main analytic approach consisted of a linear mixed-model analysis. Results: In participants in the experimental group, the hemodynamic response in the amygdala increased relative to their own baseline and to the control group. Twelve participants in the amygdala rtfMRI-nf group, compared with only two in the control group, had a >50% decrease in MADRS score. Six participants in the experimental group, compared with one in the control group, met conventional criteria for remission at study end, resulting in a number needed to treat of 4. In participants receiving amygdala rtfMRI-nf, the percent of positive specific memories recalled increased relative to baseline and to the control group. Conclusions: rtfMRI-nf training to increase the amygdala hemodynamic response to positive memories significantly decreased depressive symptoms and increased the percent of specific memories recalled on an autobiographical memory test. These data support a role of the amygdala in recovery from depression.

Zahn, R., Weingartner, J. H., Basilio, R., Bado, P., Mattos, P., Sato, J. R., de Oliveira-Souza, R., Fontenelle, L. F., Young, A. H., & Moll, J. (2019). Blame-rebalance fMRI neurofeedback in major depressive disorder: A randomised proof-of-concept trial. NeuroImage. Clinical, 24, 101992. https://doi.org/10.1016/j.nicl.2019.101992. Previously, using fMRI, we demonstrated lower connectivity between right anterior superior temporal (ATL) and anterior subgenual cingulate (SCC) regions while patients with major depressive disorder (MDD) experience guilt. This neural signature was detected despite symptomatic remission which suggested a putative role in vulnerability. This randomised controlled double-blind parallel group clinical trial investigated whether patients with MDD are able to voluntarily modulate this neural signature. To this end, we developed a fMRI neurofeedback software (FRIEND), which measures ATL-SCC coupling and displays its levels in real time. Twenty-eight patients with remitted MDD were randomised to two groups, each receiving one session of fMRI neurofeedback whilst retrieving guilt and indignation/anger-related autobiographical memories. They were instructed to feel the emotion whilst trying to increase the level of a thermometer-like display on a screen. Active intervention group: The thermometer levels increased with increasing levels of ATL-SCC correlations in the guilt condition. Control intervention group: The thermometer levels decreased when correlation levels deviated from the previous baseline level in the guilt condition, thus reinforcing stable correlations. Both groups also received feedback during the indignation condition reinforcing stable correlations. We confirmed our predictions that patients in the active intervention group were indeed able to increase levels of ATL-SCC correlations for guilt vs. indignation and their self-esteem after training compared to before training and that this differed significantly from the control intervention group. These data provide proof-of-concept for a novel treatment target for MDD patients and are in keeping with the hypothesis that ATL-SCC connectivity plays a key role in self-worth. https://clinicaltrials.gov/ct2/show/results/NCT01920490.

Zhao, Z., Yao, S., Li, K., Sindermann, C., Zhou, F., Zhao, W., Li, J., Lührs, M., Goebel, R., Kendrick, K. M., & Becker, B. (2019). Real-Time Functional Connectivity-Informed Neurofeedback of Amygdala-Frontal Pathways Reduces Anxiety. Psychotherapy and psychosomatics, 88(1), 5–15. https://doi.org/10.1159/000496057. Background: Deficient emotion regulation and exaggerated anxiety represent a major transdiagnostic psychopathological marker. On the neural level these deficits have been closely linked to impaired, yet treatment-sensitive, prefrontal regulatory control over the amygdala. Gaining direct control over these pathways could therefore provide an innovative and promising intervention to regulate exaggerated anxiety. To this end the current proof-of-concept study evaluated the feasibility, functional relevance and maintenance of a novel connectivity-informed real-time fMRI neurofeedback training. Methods: In a randomized crossover sham-controlled design, 26 healthy subjects with high anxiety underwent real-time fMRI-guided neurofeedback training to enhance connectivity between the ventrolateral prefrontal cortex (vlPFC) and the amygdala (target pathway) during threat exposure. Maintenance of regulatory control was assessed after 3 days and in the absence of feedback. Training-induced changes in functional connectivity of the target pathway and anxiety ratings served as primary outcomes. Results: Training of the target, yet not the sham control, pathway significantly increased amygdala-vlPFC connectivity and decreased levels of anxiety. Stronger connectivity increases were significantly associated with higher anxiety reduction on the group level. At the follow-up, volitional control over the target pathway was maintained in the absence of feedback. Conclusions: The present results demonstrate for the first time that successful self-regulation of amygdala-prefrontal top-down regulatory circuits may represent a novel intervention to control anxiety. As such, the present findings underscore both the critical contribution of amygdala-prefrontal circuits to emotion regulation and the therapeutic potential of connectivity-informed real-time neurofeedback.

Zilverstand, A., Sorger, B., Slaats-Willemse, D., Kan, C. C., Goebel, R., & Buitelaar, J. K. (2017). fMRI Neurofeedback Training for Increasing Anterior Cingulate Cortex Activation in Adult Attention Deficit Hyperactivity Disorder. An Exploratory Randomized, Single-Blinded Study. PloS one, 12(1), e0170795. https://doi.org/10.1371/journal.pone.0170795.
Attention Deficit Hyperactivity Disorder (ADHD) is characterized by poor cognitive control/attention and hypofunctioning of the dorsal anterior cingulate cortex (dACC). In the current study, we investigated for the first time whether real-time fMRI neurofeedback (rt-fMRI) training targeted at increasing activation levels within dACC in adults with ADHD leads to a reduction of clinical symptoms and improved cognitive functioning. An exploratory randomized controlled treatment study with blinding of the participants was conducted. Participants with ADHD (n = 7 in the neurofeedback group, and n = 6 in the control group) attended four weekly MRI training sessions (60-min training time/session), during which they performed a mental calculation task at varying levels of difficulty, in order to learn how to up-regulate dACC activation. Only neurofeedback participants received continuous feedback information on actual brain activation levels within dACC. Before and after the training, ADHD symptoms and relevant cognitive functioning was assessed. Results showed that both groups achieved a significant increase in dACC activation levels over sessions. While there was no significant difference between the neurofeedback and control group in clinical outcome, neurofeedback participants showed stronger improvement on cognitive functioning. The current study demonstrates the general feasibility of the suggested rt-fMRI neurofeedback training approach as a potential novel treatment option for ADHD patients. Due to the study's small sample size, potential clinical benefits need to be further investigated in future studies.

OTHER

GENERAL APPLICATIONS:

Krigbaum, G., Wigton, N.L. A Methodology of Analysis for Monitoring Treatment Progression with 19-Channel Z-Score Neurofeedback (19ZNF) in a Single-Subject Design. Appl Psychophysiol Biofeedback 40, 139–149 (2015). https://doi.org/10.1007/s10484-015-9274-0. 19-Channel Z-Score Neurofeedback (19ZNF) is a modality using 19-electrodes with real-time normative database z-scores, suggesting effective clinical outcomes in fewer sessions than traditional neurofeedback. Thus, monitoring treatment progression and clinical outcome is necessary. The area of focus in this study was a methodology of quantitative analysis for monitoring treatment progression and clinical outcome with 19ZNF. This methodology is noted as the Sites-of-Interest, which included repeated measures analyses of variance (rANOVA) and t-tests for z-scores; it was conducted on 10 cases in a single subject design. To avoid selection bias, the 10 sample cases were randomly selected from a pool of 17 cases that met the inclusion criteria. Available client outcome measures (including self-report) are briefly discussed. The results showed 90 % of the pre-post comparisons moved in the targeted direction (z = 0) and of those, 96 % (80 % Bonferroni corrected) of the t-tests and 96 % (91 % Bonferroni corrected) of the rANOVAs were statistically significant; thus indicating a progression towards the mean in 15 or fewer 19ZNF sessions. All cases showed and reported improvement in all outcome measures (including quantitative electroencephalography assessment) at case termination.

Larsen, S. & Sherlin, L. (2013). Neurofeedback: an emerging technology for treating central nervous system dysregulation. Psychiatr Clin North Am. 2013 Mar;36(1):163-8. doi: 10.1016/j.psc.2013.01.005. Neurofeedback is a machine-mediated noninvasive treatment modality based on the analysis and "feeding back" of electroencephalogram brainwaves, which has shown efficacy with a variety of central nervous system-based problems. It has special application where patients have adverse reaction to psychopharmacologic treatments and psychotherapy, cognitive behavioral therapy, and dialectical behavior therapy have proved ineffective. Treatment modalities include active forms based on operant conditioning, involving a subject's response to stimuli. Neurofeedback is strong in clinical confirmations of efficacy (case studies) and has thus far limited controlled studies in the peer-reviewed journals.

Pérez-Elvira, R., Oltra-Cucarella, J., Carrobles, J. A., Moltó, J., Flórez, M., Parra, S., Agudo, M., Saez, C., Guarino, S., Costea, R. M., & Neamtu, B. (2021). Enhancing the Effects of Neurofeedback Training: The Motivational Value of the Reinforcers. Brain sciences, 11(4), 457. https://doi.org/10.3390/brainsci11040457. The brain activity that is measured by electroencephalography (EEG) can be modified through operant conditioning, specifically using neurofeedback (NF). NF has been applied to several disorders claiming that a change in the erratic brain activity would be accompanied by a reduction of the symptoms. However, the expected results are not always achieved. Some authors have suggested that the lack of an adequate response may be due to an incorrect application of the operant conditioning principles. A key factor in operant conditioning is the use of reinforcers and their value in modifying behavior, something that is not always sufficiently taken into account. This work aims to clarify the relevance of the motivational value versus the purely informational value of the reinforcer. In this study, 113 subjects were randomly assigned two different reinforcer conditions: a selected

reinforcer-the subjects subjectively selected the reinforcers-or an imposed reinforcer-the reinforcers were assigned by the experimenter-and both groups undertook NF sessions to enhance the sensorimotor rhythm (SMR). In addition, the selected reinforcer group was divided into two subgroups: one receiving real NF and the other one sham NF. There were no significant differences between the groups at baseline in terms of SMR amplitude. After the intervention, only those subjects belonging to the selected reinforcer group and receiving real NF increased their SMR. Our results provide evidence for the importance of the motivational value of the reinforcer in Neurofeedback success.

Rance, M., Walsh, C., Sukhodolsky, D. G., Pittman, B., Qiu, M., Kichuk, S. A., Wasylink, S., Koller, W. N., Bloch, M., Gruner, P., Scheinost, D., Pittenger, C., & Hampson, M. (2018). Time course of clinical change following neurofeedback. NeuroImage, 181, 807–813. https://doi.org/10.1016/j.neuroimage.2018.05.001. Neurofeedback - learning to modulate brain function through real-time monitoring of current brain state - is both a powerful method to perturb and probe brain function and an exciting potential clinical tool. For neurofeedback effects to be useful clinically, they must persist. Here we examine the time course of symptom change following neurofeedback in two clinical populations, combining data from two ongoing neurofeedback studies. This analysis reveals a shared pattern of symptom change, in which symptoms continue to improve for weeks after neurofeedback. This time course has several implications for future neurofeedback studies. Most neurofeedback studies are not designed to test an intervention with this temporal pattern of response. We recommend that new studies incorporate regular follow-up of subjects for weeks or months after the intervention to ensure that the time point of greatest effect is sampled. Furthermore, this time course of continuing clinical change has implications for crossover designs, which may attribute long-term, ongoing effects of real neurofeedback to the control intervention that follows. Finally, interleaving neurofeedback sessions with assessments and examining when clinical improvement peaks may not be an appropriate approach to determine the optimal number of sessions for an application.

Simkin, D. R., Thatcher, R. W., & Lubar, J. (2014). Quantitative EEG and neurofeedback in children and adolescents: anxiety disorders, depressive disorders, comorbid addiction and attention-deficit/hyperactivity disorder, and brain injury. Child and adolescent psychiatric clinics of North America, 23(3), 427–464. https://doi.org/10.1016/j.chc.2014.03.001. This article explores the science surrounding neurofeedback. Both surface neurofeedback (using 2-4 electrodes) and newer interventions, such as real-time z-score neurofeedback (electroencephalogram [EEG] biofeedback) and low-resolution electromagnetic tomography neurofeedback, are reviewed. The limited literature on neurofeedback research in children and adolescents is discussed regarding treatment of anxiety, mood, addiction (with comorbid attention-deficit/hyperactivity disorder), and traumatic brain injury. Future potential applications, the use of quantitative EEG for determining which patients will be responsive to medications, the role of randomized controlled studies in neurofeedback research, and sensible clinical guidelines are considered.

Wigton, N. L., & Krigbaum, G. (2019). Attention, Executive Function, Behavior, and Electrocortical Function, Significantly Improved With 19-Channel Z-Score Neurofeedback in a Clinical Setting: A Pilot Study. Journal of attention disorders, 23(4), 398–408. https://doi.org/10.1177/1087054715577135. Objective: Neurofeedback (NF) is gaining recognition as an evidence-based intervention grounded in learning theory, and 19-channel z-score NF (19ZNF) is a new NF model. This pilot study sought to evaluate the efficacy of 19ZNF in a clinical setting. Method: Outcome measures framed groups such that 19ZNF was evaluated, as it relates to the neuropsychological constructs of attention (n = 10), executive function (n = 12), behavior (n = 14), and electrocortical functioning (n = 21). One-tailed t tests compared pre-post difference scores. Results: For all pre-post comparisons, the direction of change was in the predicted direction, and differences were statistically significant (p = .000 to p = .008, effect sizes 1.29 to 3.42). Conclusion: Results suggest 19ZNF improved attention, executive function, behavior, and electrocortical function. This study provides beginning evidence of 19ZNF's efficacy, adds to what is known about 19ZNF, and offers an innovative approach for using quantitative electroencephalographic (QEEG) metrics as outcome measures.

REVIEWS & HISTORICAL CONTEXT OF NFB AND BFB:

Schoenberg, PL. & David, AS. (2014). Biofeedback for psychiatric disorders: A systematic review. Applied Psychophysiology and Biofeedback:39(2). 109-135. Biofeedback potentially provides non-invasive, effective psychophysiological interventions for

psychiatric disorders. The encompassing purpose of this review was to establish how biofeedback interventions have been used to treat select psychiatric disorders [anxiety, autistic spectrum disorders, depression, dissociation, eating disorders, schizophrenia and psychoses] to date and provide a useful reference for consultation by clinicians and researchers planning to administer a biofeedback treatment. A systematic search of EMBASE, MEDLINE, PsycINFO, and WOK databases and hand searches in Applied Psychophysiology and Biofeedback, and Journal of Neurotherapy, identified 227 articles; 63 of which are included within this review. Electroencephalographic neurofeedback constituted the most investigated modality (31.7%). Anxiety disorders were the most commonly treated (68.3%). Multi-modal biofeedback appeared most effective in significantly ameliorating symptoms, suggesting that targeting more than one physiological modality for bio-regulation increases therapeutic efficacy. Overall, 80.9% of articles reported some level of clinical amelioration related to biofeedback exposure, 65.0% to a statistically significant ($p < .05$) level of symptom reduction based on reported standardized clinical parameters. Although the heterogeneity of the included studies warrants caution before explicit efficacy statements can be made. Further development of standardized controlled methodological protocols tailored for specific disorders and guidelines to generate comprehensive reports may contribute towards establishing the value of biofeedback interventions within mainstream psychiatry.

Thatcher, R. W., Lubar, J. F., & Koberda, J. L. (2019). Z-Score EEG Biofeedback: Past, Present, and Future. Biofeedback, 47(4), 89-103. Human electroencephalogram (EEG) biofeedback (neurofeedback) started in the 1940s using one EEG recording channel, then four channels in the 1990s, and in 2004, expanded to 19 channels using Low Resolution Electromagnetic Tomography (LORETA) of the microampere three-dimensional current sources of the EEG. In 2004–2006 the concept of a real-time comparison of the EEG to a healthy reference database was developed and tested using surface EEG z score neurofeedback based on a statistical bell curve called real-time z scores. The real-time or live normative reference database comparison was developed to help reduce the uncertainty of what threshold to select to activate a feedback signal and to unify all EEG measures to a single value (i.e., the distance from the mean of an age-matched reference sample). In 2009 LORETA z score neurofeedback further increased specificity by targeting brain network hubs referred to as Brodmann areas. A symptom checklist program to help link symptoms to dysregulation of brain networks based on fMRI and positron emission tomography (PET) and neurology was created in 2009. The symptom checklist and National Institutes of Health–based networks linking symptoms to brain networks grew out of the human brain mapping program started in 1990 that continues today. A goal is to increase specificity of EEG biofeedback by targeting brain network hubs and connections between hubs likely linked to the patient's symptoms. Developments first introduced in 2017 provide increased resolution of three-dimensional source localization with 12,700 voxels using swLORETA with the capacity to conduct cerebellar neurofeedback and neurofeedback of subcortical brain hubs such as the thalamus, amygdala, and habenula. Future applications of swLORETA z score neurofeedback represent another example of the transfer of knowledge gained by the human brain mapping initiatives to further aid in helping people with cognition problems as well as balance problems and parkinsonism. A brief review of the past, present, and future predictions of z score neurofeedback are discussed with special emphasis on new developments that point toward a bright and enlightened future in the field of EEG biofeedback.

CANCER:

Alvarez J, Meyer FL, Granoff DL & Lundy A. (2013). The Effect of EEG Biofeedback on Reducing Postcancer Cognitive Impairment. Integr Cancer Ther. 2013 Apr 12. [Epub ahead of print]. BACKGROUND AND HYPOTHESES. Postcancer cognitive impairment (PCCI) is observed in a substantial number of breast cancer survivors, persisting for as long as 20 years in some subgroups. Although compensatory strategies are frequently suggested, no restorative interventions have yet been identified. This study examined the feasibility of EEG biofeedback ("neurofeedback") and its potential effectiveness in reducing PCCI as well as the fatigue, sleep disturbance, and psychological symptoms that frequently accompany PCCI. STUDY DESIGN: This was a 6-month prospective study with a waitlist control period followed by an active intervention. Participants were female breast cancer survivors (n = 23), 6 to 60 months postchemotherapy, with self-reported cognitive impairment. METHODS: Four self-report outcome measures (Functional Assessment of Cancer Therapy-Cognitive Function [FACT-Cog], Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue], Pittsburgh Sleep Quality Index [PSQI], and Brief Symptom Inventory [BSI]-18) were administered 3 times during a 10-week waitlist control period, 3 times during a 10-week (20-session) neurofeedback training regimen, and once at 4 weeks post neurofeedback. RESULTS: All 23 participants completed the study, demonstrating the feasibility of EEG biofeedback in this population. Initially, the

sample demonstrated significant dysfunction on all measures compared with general population norms. Repeated-measures ANOVAs revealed strongly significant improvements (P < .001) on all 4 cognitive measures (perceived cognitive impairment, comments from others, perceived cognitive abilities, and impact on quality of life [QOL]), the fatigue scale, and the 4 psychological scales (somatization, depression, anxiety and global severity index) as well as on 3 of 8 sleep scales (quality, daytime dysfunction, and global). Two of the other sleep scales (latency and disturbance) were significant at P < .01, and 1 (use of medication) at P < .05; 2 were not significant. Improvements were generally linear across the course of training, and were maintained at the follow-up testing. At the follow-up testing, the sample no longer differed significantly from normative populations on 3 of the 4 FACT-Cog measures (impairment, impact on QOL, and comments), FACIT-Fatigue, PSQI sleep quality and habitual efficiency, or any of the BSI-18 measures of psychological disturbance. CONCLUSIONS: Data from this limited study suggest that EEG biofeedback has potential for reducing the negative cognitive and emotional sequelae of cancer treatment as well as improving fatigue and sleep patterns.

Prinsloo, S., Rosenthal, D. I., Lyle, R., Garcia, S. M., Gabel-Zepeda, S., Cannon, R., Bruera, E., & Cohen, L. (2019). Exploratory Study of Low Resolution Electromagnetic Tomography (LORETA) Real-Time Z-Score Feedback in the Treatment of Pain in Patients with Head and Neck Cancer. Brain topography, 32(2), 283–285. https://doi.org/10.1007/s10548-018-0686-z. Acute pain from mucositis in patients with head and neck cancer (HNC) undergoing radiation therapy (RT) is common, and may not respond well to narcotics. We used low resolution electromagnetic tomography z-score neurofeedback (LFBz) to investigate whether patients could modify brain wave activity associated with acute pain and whether this would reduce the experience of pain. HNC patients scheduled for RT had baseline pre-pain onset measures (EEG and numeric rating scale) collected before RT and then at pain onset before using analgesics, after each LFBz session and at the end of RT. Up to six sessions of LFBz training were offered over the remaining RT. Up to six 20-min sessions of LFBz were offered over the remaining RT. Data were collected before and after each LFBz session and at the end of RT. Seventeen patients recruited; fourteen were treated and reported decreased pain perception. LFBz allowed patients to modify their brain activity in predesignated areas of the pain matrix toward the direction of their baseline, pre-pain condition (including Brodmann areas (BAs) 3, 4, 5, 13, 24, and 33). LFBz can modify brain regions relevant for pain and these changes were associated with self-reported decreases in pain perception.

COGNITIVE DECLINE:

Becker, J. T., Mintun, M. A., Aleva, K., Wiseman, M. B., Nichols, T., & DeKosky, S. T. (1996). Compensatory reallocation of brain resources supporting verbal episodic memory in Alzheimer's disease. Neurology, 46(3), 692–700. https://doi.org/10.1212/wnl.46.3.692. Conscious recall of past events that have specific temporal and spatial contexts, termed episodic memory, is mediated by a system of interrelated brain regions. In Alzheimer's disease (AD) this system breaks down, resulting in an inability to recall events from the immediate past. Using subtraction techniques with PET-acquired images of regional cerebral blood flow, we demonstrate that AD patients show a greater activation of regions of cerebral cortex normally involved in auditory-verbal memory, as well as activation of cortical areas not activated by normal elderly subjects. These results provide clear evidence of functional plasticity in the AD patient's brain even if those changes do not result in normal memory function, and provide insights into the mechanism by which the AD brain attempts to compensate for neurodegeneration.

Fonseca LC, Tedrus GM, Carvas PN, Machado EC. (2103). Comparison of quantitative EEG between patients with Alzheimer's disease and those with Parkinson's disease dementia. Clin Neurophysiol. 2013 Jun 5. pii: S1388-2457(13)00636-6. doi: 10.1016/j.clinph.2013.05.001. [Epub ahead of print]. OBJECTIVE: Dementia frequently occurs in Parkinson's disease (PD) but its pathophysiological basis is little known. Comparative EEG studies of Alzheimer's disease (AD) and Parkinson's disease dementia (PDD) are still rare, but could provide knowledge on the different pathophysiological mechanisms involved. The objective of the present study was to comparatively evaluate the absolute power and coherence on the EEG for patients with AD and PDD. METHODS: This study assessed 38 adults with AD, 12 with PDD, 31 with Parkinson's disease without dementia, and 37 controls (CG) by a neurological evaluation, CERAD neuropsychological battery, executive functions tests and qEEG, calculating global absolute powers for the delta, theta, alpha and beta bands and inter- and intra-hemispheric coherences. RESULTS: The delta and theta powers were highest in PDD and lowest in CG ($p<0.05$). The beta frontal-occipital inter-hemispheric coherence was highest in PDD ($p<0.05$). Whereas, alpha and

beta frontal inter-hemispheric coherence was highest in PDD and lowest in AD ($p<0.05$). CONCLUSION: These results suggest that qEEG power and coherence measures are different in AD and PDD. SIGNIFICANCE: These qEEG differences must be related to the distinct mechanisms of cortical neural connections in AD and PDD.

Jang, J. H., Kim, J., Park, G., Kim, H., Jung, E. S., Cha, J. Y., Kim, C. Y., Kim, S., Lee, J. H., & Yoo, H. (2019). Beta wave enhancement neurofeedback improves cognitive functions in patients with mild cognitive impairment: A preliminary pilot study. Medicine, 98(50), e18357. https://doi.org/10.1097/MD.0000000000018357. Background: Mild cognitive impairment (MCI) is a symptom characterizing cognitive decline and a transitional state between normal aging and dementia; however, there is no definitive diagnosis and treatment for MCI. Neurofeedback (NF), which is a training mechanism that employs operant conditioning to regulate brain activity, has been increasingly investigated concerning its beneficial effects for dementia and MCI. Methods: This study investigated cognitive improvement and hemodynamic changes in the prefrontal cortex (PFC) following NF training in patients with MCI. Five patients with MCI received NF training for enhanced beta band activity in the dorsolateral PFC-16 sessions for 8 weeks-with each session divided into 9 5-minute trials. The primary outcome measure was a cognitive assessment tool: the Korean version of the Montreal Cognitive Assessment. The secondary outcome measures were the Central Nervous System Vital Signs for neurocognitive testing, hemodynamic changes using functional near-infrared spectroscopy in the PFC during a working-memory task, and Beck Depression Inventory scores. Results: After completing the training, patients' cognitive function significantly improved in domains such as composite memory, cognitive flexibility, complex attention, reaction time, and executive function. Increased electroencephalogram beta power was observed over NF training sessions (Spearman rank correlation test: $r = 0.746$, $P = .001$). The threshold value for gaining positive feedback from pre-NF baseline on beta power significantly increased (Spearman rank correlation test: $r = 0.805$, $P = .001$). Hemodynamic response in PFC changed after NF training, and individual differences were identified. Specifically, hypoactivation of the hemodynamic response by emotional distraction recovered following NF training. Conclusion: We suggest that patients' cognitive processing efficiency was improved by the NF training. These beneficial results suggest that NF training may have potential therapeutic applications to prevent the progression from MCI to dementia.

FMRI AND STRUCTURAL BRAIN CHANGES AFTER NFB:

Ruiz S, Buyukturkoglu K, Rana M, Birbaumer N, Sitaram R. (2013) Real-time fMRI brain computer interfaces: Self-regulation of single brain regions to networks. Biol Psychol. 2013 May 1. doi: 10.1016/j.biopsycho.2013.04.010. With the advent of brain computer interfaces based on real-time fMRI (rtfMRI-BCI), the possibility of performing neurofeedback based on brain hemodynamics has become a reality. In the early stage of the development of this field, studies have focused on the volitional control of activity in circumscribed brain regions. However, based on the understanding that the brain functions by coordinated activity of spatially distributed regions, there have recently been further developments to incorporate real-time feedback of functional connectivity and spatio-temporal patterns of brain activity. The present article reviews the principles of rtfMRI neurofeedback, its applications, benefits and limitations. A special emphasis is given to the discussion of novel developments that have enabled the use of this methodology to achieve self-regulation of the functional connectivity between different brain areas and of distributed brain networks, anticipating new and exciting applications for cognitive neuroscience and for the potential alleviation of neuropsychiatric disorders.

Ghaziri J, Tucholka A, Larue V, Blanchette-Sylvestre M, Reyburn G, Gilbert G, Lévesque J, Beauregard M. Neurofeedback Training Induces Changes in White and Gray Matter. Clin EEG Neurosci. 2013 Mar 26. The main objective of this structural magnetic resonance imaging (MRI) study was to investigate, using diffusion tensor imaging, whether a neurofeedback training (NFT) protocol designed to improve sustained attention might induce structural changes in white matter (WM) pathways, purportedly implicated in this cognitive ability. Another goal was to examine whether gray matter (GM) volume (GMV) might be altered following NFT in frontal and parietal cortical areas connected by these WM fiber pathways. Healthy university students were randomly assigned to an experimental group (EXP), a sham group, or a control group. Participants in the EXP group were trained to enhance the amplitude of their $\beta 1$ waves at F4 and P4. Measures of attentional performance and MRI data were acquired one week before (Time 1) and one week after (Time 2) NFT. Higher scores on visual and auditory sustained attention were noted in the EXP group at Time 2 (relative to Time 1). As for structural MRI data, increased fractional anisotropy was measured in WM pathways implicated in sustained attention, and

GMV increases were detected in cerebral structures involved in this type of attention. After 50 years of research in the field of neurofeedback, our study constitutes the first empirical demonstration that NFT can lead to microstructural changes in white and gray matter.

Zotev V., Phillips R., Yuan H., Misaki M. & Bodurka J. (2013) **Self-regulation of human brain activity using simultaneous real-time fMRI and EEG neurofeedback. Neuroimage. doi: 10.1016/j.neuroimage.2013.04.126.** Neurofeedback is a promising approach for non-invasive modulation of human brain activity with applications for treatment of mental disorders and enhancement of brain performance. Neurofeedback techniques are commonly based on either electroencephalography (EEG) or real-time functional magnetic resonance imaging (rtfMRI). Advances in simultaneous EEG-fMRI have made it possible to combine the two approaches. Here we report the first implementation of simultaneous multimodal rtfMRI and EEG neurofeedback (rtfMRI-EEG-nf). It is based on a novel system for real-time integration of simultaneous rtfMRI and EEG data streams. We applied the rtfMRI-EEG-nf to training of emotional self-regulation in healthy subjects performing a positive emotion induction task based on retrieval of happy autobiographical memories. The participants were able to simultaneously regulate their BOLD fMRI activation in the left amygdala and frontal EEG power asymmetry in the high-beta band using the rtfMRI-EEG-nf. Our proof-of-concept results demonstrate the feasibility of simultaneous self-regulation of both hemodynamic (rtfMRI) and electrophysiological (EEG) activities of the human brain. They suggest potential applications of rtfMRI-EEG-nf in the development of novel cognitive neuroscience research paradigms and enhanced cognitive therapeutic approaches for major neuropsychiatric disorders, particularly depression.

MEDITATION:

Fingelkurts, A. A., Fingelkurts, A. A., & Kallio-Tamminen, T. (2015). EEG-guided meditation: A personalized approach. Journal of physiology, Paris, 109(4-6), 180–190. https://doi.org/10.1016/j.jphysparis.2015.03.001. The therapeutic potential of meditation for physical and mental well-being is well documented, however the possibility of adverse effects warrants further discussion of the suitability of any particular meditation practice for every given participant. This concern highlights the need for a personalized approach in the meditation practice adjusted for a concrete individual. This can be done by using an objective screening procedure that detects the weak and strong cognitive skills in brain function, thus helping design a tailored meditation training protocol. Quantitative electroencephalogram (qEEG) is a suitable tool that allows identification of individual neurophysiological types. Using qEEG screening can aid developing a meditation training program that maximizes results and minimizes risk of potential negative effects. This brief theoretical-conceptual review provides a discussion of the problem and presents some illustrative results on the usage of qEEG screening for the guidance of mediation personalization.

MOTOR LEARNING:

Ros T., Munneke MA., Parkinson LA. & Gruzelier JH. (2013). Neurofeedback facilitation of implicit motor learning. Biol Psychol. doi: 10.1016/j.biopsycho.2013.04.013. BACKGROUND*:* Mu rhythm desynchronization via EEG-neurofeedback (NFB) has been previously shown to induce durable motor-cortical disinhibition for at least 20min. It was hypothesized that the presentation of a novel procedural learning task immediately after this NFB protocol would boost motor performance. METHOD: The protocol consisted of firstly activating the right primary motor cortex with a single session of Mu (8-12Hz) suppression via NFB for a total of 30min. Shortly after, and with their non-dominant (left) hand, subjects (n=10) performed the serial reaction time task (SRTT), which is used to assess reaction time improvement over multiple trials. During another occasion (1 week before/after), the same subjects were tested on a different sequence without prior NFB, as part of a counterbalanced control condition. RESULTS: Compared to a "cross-over" condition without NFB, subjects who received NFB immediately prior to SRTT performance exhibited a significantly faster rate of learning, reflected in a greater reduction of reaction times across blocks ($p=0.02$). This occurred in the absence of explicit awareness of a repeating sequence. Moreover, no significant differences were observed between conditions in error rate or reaction time variability. CONCLUSION: Our results suggest that a single NFB session may be directly used to facilitate the early acquisition of a procedural motor task, and are the first to demonstrate that neurofeedback effects could be exploited immediately after individual training sessions so as to boost behavioural performance and learning.

Sterman, M. B., Howe, R. D., & Macdonald, L. R. (1970). Facilitation of spindle-burst sleep by conditioning of electroencephalographic activity while awake. *Science*, 167, 1146-1148. A slow-wave electroencephalographic rhythm recorded from the sensorimotor cortex of the waking cat has been correlated behaviorally with the suppression of movement. Facilitation of this rhythm through conditioning selectively enhances a similar pattern recorded during sleep, the familiar spindle burst. The training also produced longer epochs of undisturbed sleep. The specific neural mechanism manipulated during wakefulness appears to function also in sleep and to be involved with the regulation of phasic motor behavior.

PAIN:

Jensen, M. P., A. Gianas, L. H. Sherlin and J. D. Howe (2015). "Pain Catastrophizing and EEG-alpha Asymmetry." Clin J Pain 31(10): 852-858. ISBN/1536-5409 (Electronic) 0749-8047 (Linking) DOI: 10.1097/AJP.0000000000000182. OBJECTIVES: Pain catastrophizing is thought to play a causal role in the development and maintenance of chronic pain and its negative impact on functioning. However, few studies have examined the factors that might contribute to the development and maintenance of catastrophizing. The Anterior Asymmetry and Emotion (AAE) model hypothesizes that more activity in left anterior brain regions is associated with a tendency to engage in approach responses (often, but not always, associated with positive valance), and that more right anterior activity is associated with a tendency to engage in more withdrawal responses (often associated with negative valance). Given the consistent associations found between catastrophizing and both (1) approach versus avoidance pain coping style; and (2) affective responses to pain, the AAE model would predict that more left (vs. right) anterior brain activity would prospectively predict future catastrophizing. METHODS: Anterior asymmetry measures computed using electroencephalogram data from 30 individuals with spinal cord injury were correlated with catastrophizing scores obtained 2 years after the electroencephalograph recording. RESULTS: Consistent with the AAE model, anterior asymmetry scores reflecting greater left than right anterior activity were negatively associated with subsequent catastrophizing. CONCLUSIONS: The study findings identify a biological factor that may be associated with greater vulnerability to pain-related catastrophizing. If replicated in future research, the findings suggest new possibilities for treating catastrophizing, which may then contribute to improved pain treatment outcomes.

Jensen, M. P., S. Hakimian, L. H. Sherlin and F. Fregni (2008). "New insights into neuromodulatory approaches for the treatment of pain." J Pain 9(3): 193-199. ISBN/1526-5900 (Print) 1526-5900 (Linking) DOI: 10.1016/j.jpain.2007.11.003. OBJECTIVE: Two lines of evidence about the association between the experience of pain and brain state (measured via electroencephalogram or EEG) have recently come to light. First, research from a number of sources suggests a link between brain EEG activity and the experience of pain. Specifically, this research suggests that the subjective experience of pain is associated with relatively lower amplitudes of slower wave (delta, theta, and alpha) activity and relatively higher amplitudes of faster wave (beta) activity. Second, there has been a recent increase in interest in interventions that impact the cortical neuromodulation of pain, including behavioral treatments (such as self-hypnosis training and neurofeedback) and both invasive and noninvasive brain stimulation. Although a direct causal link between experience of pain and brain activity as measured by EEG has not been established, the targeting of pain treatment at a cortical level by trying to affect EEG rhythms directly is an intriguing possibility. PERSPECTIVE: Preliminary evidence suggests the possibility, which has not yet adequately tested or proven, that the experience of chronic pain is linked to cortical activity as assessed via an electroencephalogram. Support for this hypothesis would have important implications for understanding the mechanisms that underlie a number of pain treatments, and for developing new innovative treatments for chronic pain management.

Jensen, M. P., L. H. Sherlin, R. L. Askew, F. Fregni, G. Witkop, A. Gianas, J. D. Howe and S. Hakimian (2013). "Effects of non-pharmacological pain treatments on brain states." Clin Neurophysiol 124(10): 2016-2024. ISBN/1872-8952 (Electronic) 1388-2457 (Linking) DOI: 10.1016/j.clinph.2013.04.009. OBJECTIVE: To (1) evaluate the effects of a single session of four non-pharmacological pain interventions, relative to a sham tDCS procedure, on pain and electroencephalogram- (EEG-) assessed brain oscillations, and (2) determine the extent to which procedure-related changes in pain intensity are associated with changes in brain oscillations. METHODS: 30 individuals with spinal cord injury and chronic pain were given an EEG and administered measures of pain before and after five procedures (hypnosis, meditation, transcranial direct current stimulation [tDCS], neurofeedback, and a control sham tDCS procedure). RESULTS: Each procedure was associated with a different pattern of changes in brain activity, and all active

procedures were significantly different from the control procedure in at least three bandwidths. Very weak and mostly non-significant associations were found between changes in EEG-assessed brain activity and pain. CONCLUSIONS: Different non-pharmacological pain treatments have distinctive effects on brain oscillation patterns. However, changes in EEG-assessed brain oscillations are not significantly associated with changes in pain, and therefore such changes do not appear useful for explaining the benefits of these treatments. SIGNIFICANCE: The results provide new findings regarding the unique effects of four non-pharmacological treatments on pain and brain activity.

Jensen, M. P., L. H. Sherlin, K. J. Gertz, A. L. Braden, A. E. Kupper, A. Gianas, J. D. Howe and S. Hakimian (2013). "Brain EEG activity correlates of chronic pain in persons with spinal cord injury: clinical implications." Spinal Cord 51(1): 55-58. ISBN/1476-5624 (Electronic) 1362-4393 (Linking) DOI: 10.1038/sc.2012.84. STUDY DESIGN: Group comparison and cross-sectional study. OBJECTIVES: To replicate previous findings regarding electroencephalographic (EEG) pattern differences in a larger sample of patients with spinal cord injury (SCI) and chronic pain than previously studied, and examine associations between pain severity and EEG activity in a sample of patients with SCI and chronic pain. SETTING: USA. METHODS: EEG data were collected in an eyes-closed condition from 38 individuals with SCI and chronic pain, 16 individuals with SCI who did not have chronic pain and 28 healthy controls. Pain intensity experienced during the EEG assessment was assessed in the chronic pain group. Absolute and relative power in four frequency bands (delta, theta, alpha, and beta) were compared between the groups, and correlation coefficients between bandwidth activity and pain intensity in the pain group were computed. RESULTS: Previously identified activity pattern differences (that is, more theta and less alpha) in those with SCI and chronic pain versus individuals with SCI and no pain and healthy controls were largely replicated. However, few significant associations between pain severity and EEG activity measures activity were found, and those that were found (more alpha activity associated with more pain as measured from frontal electrode sites) was in a direction opposite than predicted. CONCLUSION: The findings indicate that certain EEG activity patterns may be associated with more pain or a vulnerability to experience chronic pain in persons with SCI. Research examining the extent to which changes in this EEG activity may result in pain relief is warranted.

Jensen MP, Gertz KJ, Kupper AE, Braden AL, Howe JD, Hakimian S, Sherlin LH. (2013). Steps toward developing an EEG biofeedback treatment for chronic pain. Appl Psychophysiol Biofeedback. 2013 Jun;38(2):101-8. doi: 10.1007/s10484-013-9214-9. Chronic pain, usually refractory to analgesics, is a significant problem for many individuals with spinal cord injury (SCI). Preliminary studies suggest that electroencephalography (EEG) biofeedback (also known as neurofeedback, NF) has the potential to help patients with otherwise refractory chronic pain. However, there remain many unanswered questions about the effects and mechanisms of this treatment. We studied 13 individuals with SCI and chronic pain with NF. Ten of the 13 individuals completed 4 sessions each of three different neurofeedback protocols assigned in random order for a total of 12 NF sessions. All three protocols had similar immediate effects on pain intensity. In addition, the participants reported modest pre- to post-treatment decreases in worst pain and pain unpleasantness following completion of the 12 NF sessions. These improvements were maintained at 3-month follow-up. The majority of the participants felt they benefited from and were satisfied with the treatment. No significant effects on measures of other outcome domains (sleep quality, pain interference and fatigue) were observed, although there was a non-significant trend for an increase in fatigue. Finally, pre- to post-treatment changes in EEG bandwidth activity, consistent with the training protocols, were observed in θ and α but not β frequencies. The findings provide preliminary support for the potential efficacy of NF for the treatment of SCI-related pain, and suggest that further clinical studies are warranted.

MILD TRAUMATIC BRAIN INJURY:

Koberda JL (2015) LORETA Z-score Neurofeedback-Effectiveness in Rehabilitation of Patients Suffering from Traumatic Brain Injury. J Neurol Neurobiol 1(4): doi http://dx.doi.org/10.16966/2379- 7150.113. This is a multi-case study involving sixty-seven patients diagnosed with Traumatic Brain Injury (TBI) that were subjected to Z-score neurofeedback (NFB) therapy. Most of the patients were diagnosed with mild TBI and treated within the first year after brain injury. A few patients were diagnosed with more severe TBI and treated after one year or later following their head injury incident. Most of the patients complained of headaches and cognitive problems while some of them also suffered from dizziness and overlapping depression. Those who complained of cognitive problems

were subjected to analysis with computerized cognitive testing (NeuroTrax, Inc.) before and after ten sessions of NFB. During the NFB therapy the subjective response from patients was collected in order to discern whether or not there was an improvement of their symptoms. In addition, QEEG maps were completed before each NFB session initiation in order to see an objective improvement of QEEG abnormalities. Subsequent analysis revealed that 59 out of 67 patients (88%) noticed subjective improvement of their symptoms within 10 sessions of NFB therapy, out of which most of them reported an improvement after only 1-3 NFB sessions. 54 patients also had an objective improvement of QEEG maps (80%) manifesting as reduction of excessive beta activity and/or normalization of delta or theta power.

STROKE:

Finnigan S, van Putten MJ. (2013). EEG in ischaemic stroke: quantitative EEG can uniquely inform (sub-)acute prognoses and clinical management. *Clin Neurophysiol*. Jan;124(1):10-9. doi: 10.1016/j.clinph.2012.07.003. Epub 2012 Aug 2. Investigations of (sub-)acute ischaemic stroke (IS) employing quantitative electroencephalographic (QEEG) methods, in concert with other assessments, are reviewed. Numerous outcomes from hundreds of patients collectively indicate that (sub-)acute QEEG indices from standard systems can uniquely inform clinical management, particularly prognostication of outcomes from IS. Two classes of QEEG indices have proven particularly informative. The first quantifies the power of abnormal, slow activity relative to that of faster activity and the second, interhemispheric voltage asymmetry (broadband). Both have been identified as statistically significant predictors of outcomes assessed (via routine clinical scales) in the weeks and months following IS. Furthermore both have demonstrated higher predictive value than concomitant neurological assessments and scales, and to improve upon outcome prediction afforded by neuroimaging alone. These indices also may continuously provide unique, real-time insights into the efficacy of thrombolytic therapy, prior to clinical changes. Two key applications of QEEG which should prove valuable for future clinical management of IS are: (1) continuous, acute monitoring to inform about the efficacy of thrombolysis and decisions about potential additional interventions, and; (2) brief, subacute recording to inform outcome prognostication and clinical decisions about, for example, rehabilitation strategies. Ongoing research and technological developments will continue to facilitate clinical translation of QEEG investigations reviewed herein.

Alwhaibi, R., Mahmoud, N. F., Basheer, M. A., M Zakaria, H., Elzanaty, M. Y., Ragab, W. M., Al Awaji, N. N., & R Elserougy, H. (2021). Impact of Somatosensory Training on Neural and Functional Recovery of Lower Extremity in Patients with Chronic Stroke: A Single Blind Controlled Randomized Trial. International journal of environmental research and public health, 18(2), 583. https://doi.org/10.3390/ijerph18020583. Recovery of lower extremity (LE) function in chronic stroke patients is considered a barrier to community reintegration. An adequate training program is required to improve neural and functional performance of the affected LE in chronic stroke patients. The current study aimed to evaluate the effect of somatosensory rehabilitation on neural and functional recovery of LE in stroke patients. Thirty male and female patients were recruited and randomized to equal groups: control group (GI) and intervention group (GII). All patients were matched for age, duration of stroke, and degree of motor impairment of the affected LE. Both groups received standard program of physical therapy in addition to somatosensory rehabilitation for GII. The duration of treatment for both groups was eight consecutive weeks. Outcome measures used were Functional Independent Measure (FIM) and Quantitative Electroencephalography (QEEG), obtained pre- and post-treatment. A significant improvement was found in the FIM scores of the intervention group (GII), as compared to the control group (GI) ($p < 0.001$). Additionally, QEEG scores improved within the intervention group post-treatment. QEEG scores did not improve within the control group post-treatment, except for "Cz-AR", compared to pretreatment, with no significant difference between groups. Adding somatosensory training to standard physical therapy program results in better improvement of neuromuscular control of LE function in chronic stroke patients.

TINNITUS:

Dohrmann K., Weisz N., Schlee W., Hartmann T. & Elbert T. (2007). Neurofeedback for treating tinnitus. Prog Brain Res. 2007;166:473-85. Many individuals with tinnitus have abnormal oscillatory brain activity. Led by this finding, we have developed a way to normalize such pathological activity by neurofeedback techniques (Weisz et al. (2005). PLoS Med., 2: e153). This is achieved mainly through enhancement of tau activity, i.e., oscillatory activity produced in perisylvian regions within the alpha frequency range (8-12 Hz) and concomitant reduction in delta power range (0.5-4 Hz). This activity is recorded from electrodes placed on the frontal

scalp. We have found that modification of the tau-to-delta ratio significantly reduces tinnitus intensity. Participants who successfully modified their oscillatory pattern profited from the treatment to the extent that the tinnitus sensation became completely abolished. Overall, this neurofeedback training was significantly superior in reducing tinnitus-related distress than frequency discrimination training.

Hartmann T, Lorenz I., Müller N., Langguth B. & Weisz N. (2013). The Effects of Neurofeedback on Oscillatory Processes Related to Tinnitus. Brain Topogr. Although widely used, no proof exists for the feasibility of neurofeedback for reinstating the disordered excitatory-inhibitory balance, marked by a decrease in auditory alpha power, in tinnitus patients. The current study scrutinizes the ability of neurofeedback to focally increase alpha power in auditory areas in comparison to the more common rTMS. Resting-state MEG was measured before and after neurofeedback (n = 8) and rTMS (n = 9) intervention respectively. Source level power and functional connectivity were analyzed with a focus on the alpha band. Only neurofeedback produced a significant decrease in tinnitus symptoms and-more important for the context of the study-a spatially circumscribed increase in alpha power in right auditory regions. Connectivity analysis revealed higher outgoing connectivity in a region ultimately neighboring the area in which power increases were observed. Neurofeedback decreases tinnitus symptoms and increases alpha power in a spatially circumscribed manner. In addition, compared to a more established brain stimulation-based intervention, neurofeedback is a promising approach to renormalize the excitatory-inhibitory imbalance putatively underlying tinnitus. This study is the first to demonstrate the feasibility of focally enhancing alpha activity in tinnitus patients by means of neurofeedback.

Moazami-Goudarzi, M., Michels, L., Weitz, N., Jeanmonod, D. (2010). Temporo-insular enhancement of EEG low and high frequencies in patients with chronic tinnitus. QEEG study of chronic tinnitus patients. BMC Neuroscience. 11:40. http://www.biomedcentral.com/1471-2202/11/40. Background: The physiopathological mechanism underlying the tinnitus phenomenon is still the subject of an ongoing debate. Since oscillatory EEG activity is increasingly recognized as a fundamental hallmark of cortical integrative functions, this study investigates deviations from the norm of different resting EEG parameters in patients suffering from chronic tinnitus. Results: Spectral parameters of resting EEG of male tinnitus patients (n = 8, mean age 54 years) were compared to those of age-matched healthy males (n = 15, mean age 58.8 years). On average, the patient group exhibited higher spectral power over the frequency range of 2-100 Hz. Using LORETA source analysis, the generators of delta, theta, alpha and beta power increases were localized dominantly to left auditory (Brodmann Areas (BA) 41,42, 22), temporo-parietal, insular posterior, cingulate anterior and parahippocampal cortical areas. Conclusions: Tinnitus patients show a deviation from the norm of different resting EEG parameters, characterized by an overproduction of resting state delta, theta and beta brain activities, providing further support for the microphysiological and magnetoencephalographic evidence pointing to a thalamocortical dysrhythmic process at the source of tinnitus. These results also provide further confirmation that reciprocal involvements of both auditory and associative/paralimbic areas are essential in the generation of tinnitus.

Sedley, W., Gander, PE., Kumar, S., Oya, H. . . . . Griffiths, TD. (2015). Intracranial mapping of a cortical tinnitus system using residual inhibition. Current Biology Report (open access) http://dx.doi.org/10.1016/j.cub.2015.02.075. Tinnitus can occur when damage to the peripheral auditory system leads to spontaneous brain activity that is interpreted as sound. Many abnormalities of brain activity are associated with tinnitus, but it is unclear how these relate to the phantom sound itself, as opposed to predisposing factors or secondary consequences. Demonstrating ‘‘core’’ tinnitus correlates (processes that are both necessary and sufficient for tinnitus perception) requires high-precision recordings of neural activity combined with a behavioral paradigm in which the perception of tinnitus is manipulated and accurately reported by the subject. This has been previously impossible in animal and human research. Here we present extensive intracranial recordings from an awake, behaving tinnitus patient during short-term modifications in perceived tinnitus loudness after acoustic stimulation (residual inhibition), permitting robust characterization of core tinnitus processes. As anticipated, we observed tinnitus-linked low-frequency (delta) oscillations, thought to be triggered by low-frequency bursting in the thalamus. Contrary to expectation, these delta changes extended far beyond circumscribed auditory cortical regions to encompass almost all of auditory cortex, plus large parts of temporal, parietal, sensorimotor, and limbic cortex. In discrete auditory, parahippocampal, and inferior parietal ‘‘hub’’ regions, these delta oscillations interacted with middle frequency (alpha) and high-

frequency (beta and gamma) activity, resulting in a coherent system of tightly coupled oscillations associated with high level functions including memory and perception.

TOURETTE'S SYNDROME:

Tansey, MA. (1989). A simple and a complex tic (Tourette's Syndrome): Their response to EEG sensorimotor rhythm biofeedback training. International Journal of Psychophysiology:4. 91-97. This study presents a clinical treatment regime for the treatment of tic manifestation, both simple and complex. The response of a case of simple tic and a case of complex tic (Giles de la Tourette's syndrome) to EEG sensorimotor rhythm biofeedback training are presented. Specifically, the simple and the complex tic, both of long duration, were eliminated via this EEG biofeedback training procedure. It is hypothesized that this exercising of the sensorimotor cortex resulted in increased activation of this cerebrocortical subsystem and was reflected in increased voluntary muscle control and a heightened threshold for random motor discharge, resulting in the elimination of both tics as in the response of cases of epilepsy with motor involvement to EEG sensorimotor rhythm biofeedback training. The additional psychophysiologic sequelae of the complex tic-attention deficit disorder-remediated in the manner of the response of learning-disabled to EEG sensorimotor rhythm biofeedback training.

QEEG

Azabou, E., Fischer, C., Guerit, J. M., Annane, D., Mauguiere, F., Lofaso, F., & Sharshar, T. (2017). Neurophysiological assessment of brain dysfunction in critically ill patients: an update. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 38(5), 715–726. https://doi.org/10.1007/s10072-017-2824-x. The aim of this review was to provide up-to-date information about the usefulness of clinical neurophysiology testing in the management of critically ill patients. Evoked potentials (EPs) and electroencephalogram (EEG) are non-invasive clinical neurophysiology tools that allow an objective assessment of the central nervous system's function at the bedside in intensive care unit (ICU). These tests are quite useful in diagnosing cerebral complications, and establishing the vital and functional prognosis in ICU. EEG keeps a particularly privileged importance in detecting seizures phenomena such as subclinical seizures and non-convulsive status epilepticus. Quantitative EEG (QEEG) analysis techniques commonly called EEG Brain mapping can provide obvious topographic displays of digital EEG signals characteristics, showing the potential distribution over the entire scalp including filtering, frequency, and amplitude analysis and color mapping. Evidences of usefulness of QEEG for seizures detection in ICU are provided by several recent studies. Furthermore, beyond detection of epileptic phenomena, changes of some QEEG panels are early warning indicators of sedation level as well as brain damage or dysfunction in ICU. EPs offer the opportunity for assessing brainstem's functional integrity, as well as subcortical and cortical brain areas. A multimodal use, combining EEG and various modalities of EPs is recommended since this allows a more accurate functional exploration of the brain and helps caregivers to tailor therapeutic measures according to neurological worsening trends and to anticipate the prognosis in ICU.

Arns, M., Bruder, G., Hegerl, U., Spooner, C., Palmer, D. M., Etkin, A., Fallahpour, K., Gatt, J. M., Hirshberg, L., & Gordon, E. (2016). EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 127(1), 509–519. https://doi.org/10.1016/j.clinph.2015.05.032. Objective: To determine whether EEG occipital alpha and frontal alpha asymmetry (FAA) distinguishes outpatients with major depression (MDD) from controls, predicts antidepressant treatment outcome, and to explore the role of gender. **Methods:** In the international Study to Predict Optimized Treatment in Depression (iSPOT-D), a multi-center, randomized, prospective open-label trial, 1008 MDD participants were randomized to escitalopram, sertraline or venlafaxine-extended release. The study also recruited 336 healthy controls. Treatment response was established after eight weeks and resting EEG was measured at baseline (two minutes eyes open and eyes closed). Results: No differences in EEG alpha for occipital and frontal cortex, or for FAA, were found in MDD participants compared to controls. Alpha in the occipital and frontal cortex was not associated with treatment outcome. However, a gender and drug-class interaction effect was found for FAA. Relatively greater right frontal alpha (less cortical activity) in women only was associated with a favorable response to the Selective Serotonin Reuptake Inhibitors escitalopram and sertraline. No such effect was found for venlafaxine-extended release. Conclusions: FAA does not differentiate between MDD and controls, but is associated with antidepressant treatment response and remission in a gender and drug-class specific manner. Significance: Future studies investigating EEG alpha measures in depression should a-priori stratify by gender.

Arns, M. & Gordon, E. (2014). Quantitative EEG (QEEG) in psychiatry: Diagnostic or prognostic use? Clinical Neurophysiology: 125(8). 1504-1506. In July 2013 the FDA approved marketing of the 'first brain wave test to help assess children and teens for ADHD'1 which is commercialized by NEBA.2 This brain wave test employs the often-published Theta/Beta ratio obtained from the EEG and this milestone has generated significant debate about its veracity, clinical utility and scalability. Most of the media referred to it as a first brain test to diagnose children with ADHD. So should we be positive or cautious about this unprecedented endorsement of EEG into the psychiatric diagnostic

process? Or perhaps a bit of both? On one hand it finally heralds an FDA sanctioned objective biological brain marker into Psychiatry and Pediatrics, which will hopefully be exemplar of more to come. On the other hand it may inadvertently be over-used simplistically as a diagnostic tool.

Arns, M., Vollebregt, M. A., Palmer, D., Spooner, C., Gordon, E., Kohn, M., Clarke, S., Elliott, G. R., & Buitelaar, J. K. (2018). Electroencephalographic biomarkers as predictors of methylphenidate response in attention-deficit/hyperactivity disorder. European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology, 28(8), 881–891. https://doi.org/10.1016/j.euroneuro.2018.06.002. EEG biomarkers have shown promise in predicting non-response to stimulant medication in ADHD and could serve as translational biomarkers. This study aimed to replicate and extend previous EEG biomarkers. The international Study to Predict Optimized Treatment for ADHD (iSPOT-A), a multi-center, international, prospective open-label trial, enrolled 336 children and adolescents with ADHD (11.9 yrs; 245 males; prescribed methylphenidate) and 158 healthy children. Treatment response was established after six weeks using the clinician rated ADHD-Rating Scale-IV. Theta/Beta ratio (TBR) and alpha peak frequency (APF) were assessed at baseline as predictors for treatment outcome. No differences between ADHD and controls were found for TBR and APF. 62% of the ADHD group was classified as a responder. Responders did not differ from non-responders in age, medication dosage, and baseline severity of ADHD symptoms. Male-adolescent non-responders exhibited a low frontal APF (Fz: R = 9.2 Hz vs. NR = 8.1 Hz; ES = 0.83), whereas no effects were found for TBR. A low APF in male adolescents was associated with non-response to methylphenidate, replicating earlier work. Our data suggest that the typical maturational EEG changes observed in ADHD responders and controls are absent in non-responders to methylphenidate and these typical changes start emerging in adolescence.

Babiloni C, Barry RJ, BaŞar E, Blinowska KJ, Cichocki A, Drinkenburg WHIM, Klimesch W, Knight RT, Lopes da Silva F, Nunez P, Oostenveld R, Jeong J, Pascual-Marqui R, Valdes-Sosa P, Hallett M. (2019). International Federation of Clinical Neurophysiology (IFCN) - EEG research workgroup: Recommendations on frequency and topographic analysis of resting state EEG rhythms. Part 1: Applications in clinical research studies. Clin Neurophysiol. 2020 Jan;131(1):285-307. doi: 10.1016/j.clinph.2019.06.234. Epub 2019 Sep 19. PMID: 31501011. In 1999, the International Federation of Clinical Neurophysiology (IFCN) published "IFCN Guidelines for topographic and frequency analysis of EEGs and EPs" (Nuwer et al., 1999). Here a Workgroup of IFCN experts presents unanimous recommendations on the following procedures relevant for the topographic and frequency analysis of resting state EEGs (rsEEGs) in clinical research defined as neurophysiological experimental studies carried out in neurological and psychiatric patients: (1) recording of rsEEGs (environmental conditions and instructions to participants; montage of the EEG electrodes; recording settings); (2) digital storage of rsEEG and control data; (3) computerized visualization of rsEEGs and control data (identification of artifacts and neuropathological rsEEG waveforms); (4) extraction of "synchronization" features based on frequency analysis (band-pass filtering and computation of rsEEG amplitude/power density spectrum); (5) extraction of "connectivity" features based on frequency analysis (linear and nonlinear measures); (6) extraction of "topographic" features (topographic mapping; cortical source mapping; estimation of scalp current density and dura surface potential; cortical connectivity mapping), and (7) statistical analysis and neurophysiological interpretation of those rsEEG features. As core outcomes, the IFCN Workgroup endorsed the use of the most promising "synchronization" and "connectivity" features for clinical research, carefully considering the limitations discussed in this paper. The Workgroup also encourages more experimental (i.e. simulation studies) and clinical research within international initiatives (i.e., shared software platforms and databases) facing the open controversies about electrode montages and linear vs. nonlinear and electrode vs. source levels of those analyses.

Barbanoj, M. J., Riba, J., Morte, A., Antonijoan, R. M., & Jané, F. (2002). Basics of PK-PD using QEEG: acute/repetitive administration, interactions. Focus on anxiolytics with different neurochemical mechanisms as examples. Methods and findings in experimental and clinical pharmacology, 24 Suppl C, 67–83. Utilizing computer-assisted quantitative analysis of the electroencephalogram (EEG) in combination with certain statistical procedures and under specific design conditions, it is possible to objectively evaluate the functional bioavailability of psychotropic substances in the target organ: the human brain. Specifically, one may determine whether a drug is active in the central nervous system (CNS) compared with placebo in humans, the dose effect (including nonmonotonic drug effects along the continuum range of concentrations) and the time effect (including time-dependent

pharmacodynamic phenomena as tolerance and sensitization), as well as its activity in relation to the formulation and route of application. Methodological aspects are introduced, discussing the usefulness of evaluating different treatments, doses, time points, states, target variables, electrodes and even different groups. Several issues are raised in relation to acute vs. repetitive administration, particularly those dealing with statistical comparisons when making conclusions about acute, repetitive or superimposed effects, and in relation to human psychotropic interactions, such as mechanistic drug-drug interaction descriptions, drug metabolites and enantiomers, as well as the importance of acquiring drug plasma concentrations, elapse of time and topographic distributions to accurately identify its occurrence. PK-PD modeling is introduced as a tool to enlarge the scope of inferences that can be derived when using pharmaco-EEG. The examples presented in order to develop the arguments are mainly focused on anxiolytic compounds belonging to the different neurochemical groups, benzodiazepines and azaspirones. Questions that have yet to been resolved are also addressed.

Brust-Carmona H, Valadez G, Flores-Avalos B, Martínez JA, Sánchez A, Rodríguez MA, Peñaloza Y & Yáñez O. (2103). Absolute power of cortical oscillations and their topographical distribution in a sample of young adults during resting wakefulness and unspecific attention]. [Article in Spanish] Rev Invest Clin. 2013 Jan-Feb;65(1):52-64. INTRODUCTION: The EEG records neuronal membrane potential oscillations that depend on the morpho-functional characteristics of the membrane and of modifications by postsynaptic excitatory (PSEP) and inhibitory (PSIP) potentials. The quantitative EEG (qEEG) measures the absolute power (AP) of oscillations separated in frequencies, resulting from the interaction among subcortical-cortical-subcortical ensembles. The hypothesis is that neuronal networks function at a given frequency and that their APs are codes that, by becoming synchronized in diverse ensembles, generate behavior. OBJECTIVE: To establish the spectral power of cortical oscillations under diverse study paradigms and in different populations. In particular, to identify the AP and topographical distribution of four cerebral frequency bands under resting wakefulness and activation, and to integrate results into a database to establish comparison standards. MATERIAL AND METHODS: Undergraduate students, average age of 20.6 +/- 2.6 years, who participated voluntarily in the study. Recordings were made with a Nicolet EEG. We chose, in the first stage, closed eyes (CE) three samples of 12 s each. In the second stage, we chose pairs of 6 s samples, first with CE and then with OE. For their analysis, we applied the Welch periodogram and we plotted the average AP (AAP) and standard deviation (SD) of delta, theta, alpha, and beta per lead. Differences were compared through non-parametric tests (Wilcoxon and Dunnett T3); setting statistical significance at a = 0.05. RESULTS: Average APs of each frequency band differ significantly in intensity and topographic distribution generating a profile of each rhythm. When opening the eyes, rhythms desynchronized significantly at different intensities in the diverse leads, except for beta in the left fronto-frontal lead. DISCUSSION: Results indicate the existence of cortical ensembles that synchronize at a determined frequency and are modified by visual stimulation, indicating the effects of the subcortico-cortical circuits. The integrated database provides comparison standards to support diagnoses and treatments.

Caudill, M. M., Hunter, A. M., Cook, I. A., & Leuchter, A. F. (2015). The Antidepressant Treatment Response Index as a Predictor of Reboxetine Treatment Outcome in Major Depressive Disorder. Clinical EEG and neuroscience, 46(4), 277–284. https://doi.org/10.1177/1550059414532443. Biomarkers to predict clinical outcomes early during the treatment of major depressive disorder (MDD) could reduce suffering and improve outcomes. A quantitative electroencephalogram (qEEG) biomarker, the Antidepressant Treatment Response (ATR) index, has been associated with outcomes of treatment with selective serotonin reuptake inhibitor antidepressants in patients with MDD. Here, we report the results of a post hoc analysis initiated to evaluate whether the ATR index may also be associated with reboxetine treatment outcome, given that its putative mechanism of action is via norepinephrine reuptake inhibition (NRI). Twenty-five adults with MDD underwent qEEG studies during open-label treatment with reboxetine at doses of 8 to 10 mg daily for 8 weeks. The ATR index calculated after 1 week of reboxetine treatment was significantly associated with overall Hamilton Depression Rating Scale (HAM-D) improvement at week 8 ($r=0.605$, $P=.001$), even after controlling for baseline depression severity ($P=.002$). The ATR index predicted response ($\geq$50% reduction in HAM-D) with 70.6% sensitivity and 87.5% specificity, and remission (final HAM-D$\leq$7) with 87.5% sensitivity and 64.7% specificity. These results suggest that the ATR index may be a useful biomarker of clinical response during NRI treatment of adults with MDD. Future studies are warranted to investigate further the potential utility of the ATR index as a predictor of noradrenergic antidepressant treatment response.

Chatzikonstantinou S, McKenna J, Karantali E, Petridis F, Kazis D, Mavroudis I. Electroencephalogram in dementia with Lewy bodies: a systematic review. Aging Clin Exp Res. 2021 May;33(5):1197-1208. doi: 10.1007/s40520-020-01576-2. Epub 2020 May 7. PMID: 32383032. Dementia with Lewy bodies (DLB) belongs to the spectrum of Lewy body dementia (LBD) that also encompasses Parkinson's disease dementia (PDD). It is a common neurodegenerative disorder characterized by memory decline, cognitive fluctuations, visual hallucinations, autonomic nervous system disturbance, REM sleep behavior disorder, and parkinsonism. Definite diagnosis can be established only through neuropathological confirmation of Lewy bodies' presence in brain tissue. Probable or possible diagnosis relies upon clinical features, imaging, polysomnography, and electroencephalogram (EEG) findings. Potential neurophysiological biomarkers for the diagnosis, management, and evaluation of treatment-response in DLB should be affordable and widely available outside academic centers. Increasing evidence supports the use of quantitative EEG (qEEG) as a potential DLB biomarker, with promising results in discriminating DLB from other dementias and in identifying subjects who are on the trajectory to develop DLB. Several studies evaluated the diagnostic value of EEG in DLB. Visual analysis and qEEG techniques have been implemented, showing a superiority of the last in terms of sensitivity and objectivity. In this systematic review, we attempt to provide a general synthesis of the current knowledge on EEG application in DLB. We review the findings from original studies and address the issues remaining to be further clarified.

Chiarenza G. A. (2021). Quantitative EEG in Childhood Attention Deficit Hyperactivity Disorder and Learning Disabilities. Clinical EEG and neuroscience, 52(2), 144–155. https://doi.org/10.1177/1550059420962343. The clinical use of the quantitative EEG (QEEG) from the pioneering work of John has received a new impetus thanks to new neuroimaging techniques and the possibility of using a number of normative databases both of normal subjects and of subjects with definite pathologies. In this direction, the term personalized medicine is becoming more and more common, a medical procedure that separates patients into different groups based on their predicted response to the quantitative EEG. This has allowed the study of single subjects and to customize health care, with decisions and treatments tailored to each individual patient, as well as improvement of knowledge of the pathophysiological mechanisms of specific diseases. This review article will present the most recent evidence in the field of developmental neuropsychiatric disorders obtained from the application of quantitative EEG both in clinical group studies (attention deficit hyperactivity disorder, developmental dyslexia, oppositional defiant disorder) and in individual case studies not yet published.

Chinoy, E. D., Frey, D. J., Kaslovsky, D. N., Meyer, F. G., & Wright, K. P., Jr (2014). Age-related changes in slow wave activity rise time and NREM sleep EEG with and without zolpidem in healthy young and older adults. Sleep medicine, 15(9), 1037–1045. https://doi.org/10.1016/j.sleep.2014.05.007. Objective: Whether there are age-related changes in slow wave activity (SWA) rise time, a marker of homeostatic sleep drive, is unknown. Additionally, although sleep medication use is highest among older adults, the quantitative electroencephalographic (EEG) profile of the most commonly prescribed sleep medication, zolpidem, in older adults is also unknown. We therefore quantified age-related and regional brain differences in sleep EEG with and without zolpidem. Methods: Thirteen healthy young adults aged 21.9 ± 2.2 years and 12 healthy older adults aged 67.4 ± 4.2 years participated in a randomized, double-blind, within-subject study that compared placebo to 5 mg zolpidem. Results: Older adults showed a smaller rise in SWA and zolpidem increased age-related differences in SWA rise time such that age differences were observed earlier after latency to persistent sleep. Age-related differences in EEG power differed by brain region. Older, but not young, adults showed zolpidem-dependent reductions in theta and alpha frequencies. Zolpidem decreased stage 1 in older adults and did not alter other age-related sleep architecture parameters. Conclusions: SWA findings provide additional support for reduced homeostatic sleep drive or reduced ability to respond to sleep drive with age. Consequences of reduced power in theta and alpha frequencies in older adults remain to be elucidated.

Colom-Cadena M, Spires-Jones T, Zetterberg H, Blennow K, Caggiano A, DeKosky ST, Fillit H, Harrison JE, Schneider LS, Scheltens P, de Haan W, Grundman M, van Dyck CH, Izzo NJ, Catalano SM. (2020). Synaptic Health Endpoints Working Group. The clinical promise of biomarkers of synapse damage or loss in Alzheimer's disease. Alzheimers Res Ther. 2020 Mar 2;12(1):21. doi: 10.1186/s13195-020-00588-4. PMID: 32122400; PMCID: PMC7053087. Background: Synapse damage and loss are fundamental to the pathophysiology of Alzheimer's disease (AD) and lead to reduced cognitive function. The goal of this review is to address the challenges of forging new clinical development approaches for AD therapeutics that can demonstrate reduction of synapse

damage or loss. The key points of this review include the following: Synapse loss is a downstream effect of amyloidosis, tauopathy, inflammation, and other mechanisms occurring in AD.Synapse loss correlates most strongly with cognitive decline in AD because synaptic function underlies cognitive performance. Compounds that halt or reduce synapse damage or loss have a strong rationale as treatments of AD. Biomarkers that measure synapse degeneration or loss in patients will facilitate clinical development of such drugs. The ability of methods to sensitively measure synapse density in the brain of a living patient through synaptic vesicle glycoprotein 2A (SV2A) positron emission tomography (PET) imaging, concentrations of synaptic proteins (e.g., neurogranin or synaptotagmin) in the cerebrospinal fluid (CSF), or functional imaging techniques such as quantitative electroencephalography (qEEG) provides a compelling case to use these types of measurements as biomarkers that quantify synapse damage or loss in clinical trials in AD. Conclusion: A number of emerging biomarkers are able to measure synapse injury and loss in the brain and may correlate with cognitive function in AD. These biomarkers hold promise both for use in diagnostics and in the measurement of therapeutic successes.

Cozac, V. V., Gschwandtner, U., Hatz, F., Hardmeier, M., Rüegg, S., & Fuhr, P. (2016). Quantitative EEG and Cognitive Decline in Parkinson's Disease. Parkinson's disease, 2016, 9060649. https://doi.org/10.1155/2016/9060649. Cognitive decline is common with the progression of Parkinson's disease (PD). Different candidate biomarkers are currently studied for the risk of dementia in PD. Several studies have shown that quantitative EEG (QEEG) is a promising predictor of PD-related cognitive decline. In this paper we briefly outline the basics of QEEG analysis and analyze the recent publications addressing the predictive value of QEEG in the context of cognitive decline in PD. The MEDLINE database was searched for relevant publications from January 01, 2005, to March 02, 2015. Twenty-four studies reported QEEG findings in various cognitive states in PD. Spectral and connectivity markers of QEEG could help to discriminate between PD patients with different level of cognitive decline. QEEG variables correlate with tools for cognitive assessment over time and are associated with significant hazard ratios to predict PD-related dementia. QEEG analysis shows high test-retest reliability and avoids learning effects associated with some neuropsychological testing; it is noninvasive and relatively easy to repeat.

D'Rozario, A. L., Cross, N. E., Vakulin, A., Bartlett, D. J., Wong, K., Wang, D., & Grunstein, R. R. (2017). Quantitative electroencephalogram measures in adult obstructive sleep apnea - Potential biomarkers of neurobehavioural functioning. Sleep medicine reviews, 36, 29–42. https://doi.org/10.1016/j.smrv.2016.10.003. Obstructive sleep apnea (OSA) results in significantly impaired cognitive functioning and increased daytime sleepiness in some patients leading to increased risk of motor vehicle and workplace accidents and reduced productivity. Clinicians often face difficulty in identifying which patients are at risk of neurobehavioural dysfunction due to wide inter-individual variability, and disparity between symptoms and conventional metrics of disease severity such as the apnea hypopnea index. Quantitative electroencephalogram (EEG) measures are determinants of awake neurobehavioural function in healthy subjects. However, the potential value of quantitative EEG (qEEG) measurements as biomarkers of neurobehavioural function in patients with OSA has not been examined. This review summarises the existing literature examining qEEG in OSA patients including changes in brain activity during wake and sleep states, in relation to daytime sleepiness, cognitive impairment and OSA treatment. It will speculate on the mechanisms which may underlie changes in EEG activity and discuss the potential utility of qEEG as a clinically useful predictor of neurobehavioural function in OSA.

Daly I., Nicolaou N., Nasuto SJ. & Warwick K. (2013) Automated Artifact Removal From the Electroencephalogram: A Comparative Study. Clin EEG Neurosci. PMID: 23666954. Contamination of the electroencephalogram (EEG) by artifacts greatly reduces the quality of the recorded signals. There is a need for automated artifact removal methods. However, such methods are rarely evaluated against one another via rigorous criteria, with results often presented based upon visual inspection alone. This work presents a comparative study of automatic methods for removing blink, electrocardiographic, and electromyographic artifacts from the EEG. Three methods are considered; wavelet, blind source separation (BSS), and multivariate singular spectrum analysis (MSSA)-based correction. These are applied to data sets containing mixtures of artifacts. Metrics are devised to measure the performance of each method. The BSS method is seen to be the best approach for artifacts of high signal to noise ratio (SNR). By contrast, MSSA performs well at low SNRs but at the expense of a large number of false positive corrections.

Duff J. (2004). The usefulness of quantitative EEG (QEEG) and neurotherapy in the assessment and treatment of post-concussion syndrome. Clinical EEG and neuroscience, 35(4), 198–209. https://doi.org/10.1177/155005940403500410 Mild traumatic brain injury (TBI) is associated with damage to frontal, temporal and parietal lobes. Post-concussion syndrome has been used to describe a range of residual symptoms that persist 12 months or more after the injury, often despite a lack of evidence of brain abnormalities on MRI and CT scans. The core deficits of post-concussion syndrome are similar to those of ADHD and mood disorders, and sufferers often report memory, socialization problems and frequent headaches. While cognitive rehabilitation and psychological support are widely used, neither has been shown to be effective in redressing the core deficits of post-concussion syndrome. On the other hand, quantitative EEG has been shown to be highly sensitive (96%) in identifying post-concussion syndrome, and neurotherapy has been shown in a number of studies to be effective in significantly improving or redressing the symptoms of post-concussion syndrome, as well as improving similar symptoms in non-TBI patients.

Haneef Z, Levin HS, Frost JD Jr, Mizrahi EM. (2013). Electroencephalography and quantitative electroencephalography in mild traumatic brain injury. *J Neurotrauma.* 2013 Apr 15;30(8):653-6. doi: 10.1089/neu.2012.2585. Mild traumatic brain injury (mTBI) causes brain injury resulting in electrophysiologic abnormalities visible in electroencephalography (EEG) recordings. Quantitative EEG (qEEG) makes use of quantitative techniques to analyze EEG characteristics such as frequency, amplitude, coherence, power, phase, and symmetry over time independently or in combination. QEEG has been evaluated for its use in making a diagnosis of mTBI and assessing prognosis, including the likelihood of progressing to the post concussive syndrome (PCS) phase. We review the EEG and qEEG changes of mTBI described in the literature. An attempt is made to separate the findings seen during the acute, subacute, and chronic phases after mTBI. Brief mention is also made of the neurobiological correlates of qEEG using neuroimaging techniques or in histopathology. Although the literature indicates the promise of qEEG in making a diagnosis and indicating prognosis of mTBI, further study is needed to corroborate and refine these methods.

Hanley, D., Prichep, L. S., Badjatia, N., Bazarian, J., Chiacchierini, R., Curley, K. C., Garrett, J., Jones, E., Naunheim, R., O'Neil, B., O'Neill, J., Wright, D. W., & Huff, J. S. (2018). A Brain Electrical Activity Electroencephalographic-Based Biomarker of Functional Impairment in Traumatic Brain Injury: A Multi-Site Validation Trial. Journal of neurotrauma, 35(1), 41–47. https://doi.org/10.1089/neu.2017.5004. The potential clinical utility of a novel quantitative electroencephalographic (EEG)-based Brain Function Index (BFI) as a measure of the presence and severity of functional brain injury was studied as part of an independent prospective validation trial. The BFI was derived using quantitative EEG (QEEG) features associated with functional brain impairment reflecting current consensus on the physiology of concussive injury. Seven hundred and twenty adult patients (18-85 years of age) evaluated within 72 h of sustaining a closed head injury were enrolled at 11 U.S. emergency departments (EDs). Glasgow Coma Scale (GCS) score was 15 in 97%. Standard clinical evaluations were conducted and 5 to 10 min of EEG acquired from frontal locations. Clinical utility of the BFI was assessed for raw scores and percentile values. A multinomial logistic regression analysis demonstrated that the odds ratios (computed against controls) of the mild and moderate functionally impaired groups were significantly different from the odds ratio of the computed tomography (CT) postive (CT+, structural injury visible on CT) group ($p = 0.0009$ and $p = 0.0026$, respectively). However, no significant differences were observed between the odds ratios of the mild and moderately functionally impaired groups. Analysis of variance (ANOVA) demonstrated significant differences in BFI among normal (16.8%), mild TBI (mTBI)/concussed with mild or moderate functional impairment, (61.3%), and CT+ (21.9%) patients ($p < 0.0001$). Regression slopes of the odds ratios for likelihood of group membership suggest a relationship between the BFI and severity of impairment. Findings support the BFI as a quantitative marker of brain function impairment, which scaled with severity of functional impairment in mTBI patients. When integrated into the clinical assessment, the BFI has the potential to aid in early diagnosis and thereby potential to impact the sequelae of TBI by providing an objective marker that is available at the point of care, hand-held, non-invasive, and rapid to obtain.

Hansen, G. L., Foli-Andersen, P., Fredheim, S., Juhl, C., Remvig, L. S., Rose, M. H., Rosenzweig, I., Beniczky, S., Olsen, B., Pilgaard, K., & Johannesen, J. (2016). Hypoglycemia-Associated EEG Changes in Prepubertal Children With Type 1 Diabetes. Journal of diabetes science and technology, 10(6), 1222–1229. https://doi.org/10.1177/1932296816634357. Background: The purpose of this study was to explore the possible difference in the electroencephalogram (EEG) pattern between euglycemia and

hypoglycemia in children with type 1 diabetes (T1D) during daytime and during sleep. The aim is to develop a hypoglycemia alarm based on continuous EEG measurement and real-time signal processing. Method: Eight T1D patients aged 6-12 years were included. A hyperinsulinemic hypoglycemic clamp was performed to induce hypoglycemia both during daytime and during sleep. Continuous EEG monitoring was performed. For each patient, quantitative EEG (qEEG) measures were calculated. A within-patient analysis was conducted comparing hypoglycemia versus euglycemia changes in the qEEG. The nonparametric Wilcoxon signed rank test was performed. A real-time analyzing algorithm developed for adults was applied. Results: The qEEG showed significant differences in specific bands comparing hypoglycemia to euglycemia both during daytime and during sleep. In daytime the EEG-based algorithm identified hypoglycemia in all children on average at a blood glucose (BG) level of 2.5 ± 0.5 mmol/l and 18.4 (ranging from 0 to 55) minutes prior to blood glucose nadir. During sleep the nighttime algorithm did not perform. Conclusions: We found significant differences in the qEEG in euglycemia and hypoglycemia both during daytime and during sleep. The algorithm developed for adults detected hypoglycemia in all children during daytime. The algorithm had too many false alarms during the night because it was more sensitive to deep sleep EEG patterns than hypoglycemia-related EEG changes. An algorithm for nighttime EEG is needed for accurate detection of nocturnal hypoglycemic episodes in children. This study indicates that a hypoglycemia alarm may be developed using real-time continuous EEG monitoring.

Ianof, J. N., & Anghinah, R. (2017). Traumatic brain injury: An EEG point of view. Dementia & neuropsychologia, 11(1), 3–5. https://doi.org/10.1590/1980-57642016dn11-010002. Traumatic brain injury (TBI) is a silent epidemic. Mild traumatic brain injury (mTBI) causes brain injury that results in electrophysiologic abnormalities visible on electroencephalography (EEG) recordings. The purpose of this brief review was to discuss the importance of EEG findings in traumatic brain injury. Relevant articles published during the 1996-2016 period were retrieved from Medline (PubMed). The keywords were in English and included "traumatic brain injury", "EEG" and "quantitative EEG". We found 460 articles, analyzed 52 and selected 13 articles. EEG after TBI shows slowing of the posterior dominant rhythm and increased diffuse theta slowing, which may revert to normal within hours or may clear more slowly over many weeks. There are no clear EEG or quantitative EEG (qEEG) features unique to mild traumatic brain injury. Although the literature indicates the promise of qEEG in reaching a diagnosis and indicating prognosis of mTBI, further study is needed to corroborate and refine these methods.

Kamei S. (2012). Brain and nerve = Shinkei kenkyu no shinpo, 64(4), 433–443. This article reviews recent quantitative electroencephalogram (qEEG) and event-related potential (ERP) analyses in Parkinson disease (PD). We reported the first qEEG evaluation in PD not only employing multiple logistic regression analysis but also estimating the distribution of qEEG changes (Serizawa K, et al: 2008). We calculated the spectral ratio, i.e., the sum of the power values in the alpha and beta waves divided by the sum of the values in the slow waves. The significant predictive variables in PD were the spectral ratios at all electrode locations except for the frontal pole. The PD patients presented diffuse slowing in the qEEG as compared with age-adjusted normal controls. We also assessed the relationship between the progression of PD and qEEG (Morita A, et al: 2009). At all electrode locations, the spectral ratio significantly decreased with the progression of PD. Moreover, we studied qEEG alterations in PD patients with executive dysfunction (ExD) (Kamei S et al: 2010) and cognitive impairment (Morita A, et al: 2011). An increase in slow waves was observed in the frontal and frontal-pole locations in patients with ExD and presented in all locations in those with dementia. A recent report showed that qEEG findings have the potential for use as a predictive biomarker for the incidence of dementia in PD (Klassen BT, 2011). QEEG analysis is thus not only useful as a tool for studying pathophysiological findings but also as a predictive biomarker for dementia. ERP is a also useful tool for the evaluation of neuropsychological impairments in PD. P3 is elicited by target in the classic oddball task. P3b findings in PD have shown inconsistent results, with certain studies showing no changes and others showing prolonged P3b latency, and decreases and increases in P3b amplitude. However, prolonged P3b latency in PD patients with dementia have been consistently observed. Visual cognitive dysfunction and facial expression recognition in PD have been recently assessed with ERP techniques. ERP has a high potential for use in the detailed evaluation of cognitive dysfunction in PD.

Kesebir S, Yosmaoğlu A. (2018). QEEG in affective disorder: about to be a biomarker, endophenotype and predictor of treatment response. Heliyon. 2018 Aug 22;4(8):e00741. doi: 10.1016/j.heliyon.2018.e00741. PMID: 30148219; PMCID:

PMC6106696. QEEG is a relatively easy to apply, cost effective method among many electrophysiologic and functional brain imaging techniques used to assess individuals for diagnosis and determination of the most suitable treatment. Its temporal resolution provides an important advantage. Many specific EEG indicators play a role in the differential diagnosis of neuropsychiatric disorders. QEEG has advantages over EEG in the dimensional approach to symptomatology of psychiatric disorders. The prognostic value of EEG has a long history. Slow wave EEG rhythm has been reported as a predictor and measure of clinical improvement under ECT. The induction level in delta band activity predicts the long-term effect of ECT. Current studies focus on the predictive power of EEG on response to pharmacotherapy and somatic treatments other than ECT. This paper discusses either QEEG can be a biomarker and/or an endophenotype in affective disorders, if it has diagnostic and prognostic value and if it can contribute to personalized treatment design, through a review of relevant literature.

Kopańska, M., Banaś-Ząbczyk, A., Łagowska, A., Kuduk, B., & Szczygielski, J. (2021). Changes in EEG Recordings in COVID-19 Patients as a Basis for More Accurate QEEG Diagnostics and EEG Neurofeedback Therapy: A Systematic Review. Journal of clinical medicine, 10(6), 1300. https://doi.org/10.3390/jcm10061300. Introduction and purpose: The SARS-CoV-2 virus is able to cause abnormalities in the functioning of the nervous system and induce neurological symptoms with the features of encephalopathy, disturbances of consciousness and concentration and a reduced ability to sense taste and smell as well as headaches. One of the methods of detecting these types of changes in COVID-19 patients is an electroencephalogram (EEG) test, which allows information to be obtained about the functioning of the brain as well as diagnosing diseases and predicting their consequences. The aim of the study was to review the latest research on changes in EEG in patients with COVID-19 as a basis for further quantitative electroencephalogram (QEEG) diagnostics and EEG neurofeedback training. Description of the state of knowledge: Based on the available scientific literature using the PubMed database from 2020 and early 2021 regarding changes in the EEG records in patients with COVID-19, 17 publications were included in the analysis. In patients who underwent an EEG test, changes in the frontal area were observed. A few patients were not found to be responsive to external stimuli. Additionally, a previously non-emerging, uncommon pattern in the form of continuous, slightly asymmetric, monomorphic, biphasic and slow delta waves occurred. Conclusion: The results of this analysis clearly indicate that the SARS-CoV-2 virus causes changes in the nervous system that can be manifested and detected in the EEG record. The small number of available articles, the small number of research groups and the lack of control groups suggest the need for further research regarding the short and long term neurological effects of the SARS-CoV-2 virus and the need for unquestionable confirmation that observed changes were caused by the virus per se and did not occur before. The presented studies described non-specific patterns appearing in encephalograms in patients with COVID-19. These observations are the basis for more accurate QEEG diagnostics and EEG neurofeedback training.

Khoury S, Chouchou F, Amzica F, Giguère JF, Denis R, Rouleau GA, Lavigne GJ. (2013). Rapid EEG activity during sleep dominates in mild traumatic brain injury patients with acute pain. *J Neurotrauma*. 2013 Apr 15;30(8):633-41. doi: 10.1089/neu.2012.2519. Epub 2013 Apr 18. Chronic pain is a highly prevalent post-concussion symptom occurring in a majority of patients with mild traumatic brain injury (mTBI). About half of patients with mTBI report sleep-wake disturbances. It is known that pain can alter sleep quality in this population, but the interaction between pain and sleep is not fully understood. This study aimed to identify how pain affects subjective sleep (Pittsburgh Sleep Quality Index [PSQI]), sleep architecture, and quantitative electroencephalographic (qEEG) brain activity after mTBI. Twenty-four mTBI patients complaining of sleep-wake disturbances, with and without pain (8 and 16, respectively), were recruited 45 (±22.7) days post-trauma on average. Data were compared with those of 18 healthy controls (no sleep or pain complaints). The PSQI, sleep architecture, and qEEG activity were analyzed. Pain was assessed using questionnaires and a 100-mm visual analogue scale. Patients with mTBI reported three times poorer sleep quality than controls on the PSQI. Sleep architecture significantly differed between patients with mTBI and controls but was within normal range. Global qEEG showed lower delta (deep sleep) and higher beta and gamma power (arousal) at certain EEG derivations in patients with mTBI compared with controls ($p<0.04$). Patients with mTBI with pain, however, showed greater increase in rapid EEG frequency bands, mostly during REM sleep, and beta bands in non-REM sleep compared with patients with mTBI without pain and controls ($p<0.001$). Pain in patients with mTBI was associated with more rapid qEEG activity, mostly during REM sleep, suggesting that pain is associated with poor sleep and is a critical factor in managing post-concussion symptoms.

Koberda JL., Moses A., Koberda P. & Koberda L. (2013). Clinical Advantages of Quantitative Electroencephalogram (QEEG)-Electrical Neuroimaging Application in General Neurology Practice. Clin EEG Neurosci. EPub: Mar 26. QEEG-electrical neuroimaging has been underutilized in general neurology practice for uncertain reasons. Recent advances in computer technology have made this electrophysiological testing relatively inexpensive. Therefore, this study was conducted to evaluate the clinical usefulness of QEEG/electrical neuroimaging in neurological practice. Over the period of approximately 6 months, 100 consecutive QEEG recordings were analyzed for potential clinical benefits. The patients who completed QEEG were divided into 5 groups based on their initial clinical presentation. The main groups included patients with seizures, headaches, post-concussion syndrome, cognitive problems, and behavioral dysfunctions. Subsequently, cases were reviewed and a decision was made as to whether QEEG analysis contributed to the diagnosis and/or furthered patient's treatment. Selected and representative cases from each group are presented in more detail, including electrical neuroimaging with additional low-resolution electromagnetic tomography analysis or using computerized cognitive testing. Statistical analysis showed that QEEG analysis contributed to 95% of neurological cases, which indicates great potential for wider application of this modality in general neurology. Many patients also began neurotherapy, depending on the patient's desire to be involved in this treatment modality.

Leuchter, M. K., Donzis, E. J., Cepeda, C., Hunter, A. M., Estrada-Sánchez, A. M., Cook, I. A., Levine, M. S., & Leuchter, A. F. (2017). Quantitative Electroencephalographic Biomarkers in Preclinical and Human Studies of Huntington's Disease: Are They Fit-for-Purpose for Treatment Development?. Frontiers in neurology, 8, 91. https://doi.org/10.3389/fneur.2017.00091. A major focus in development of novel therapies for Huntington's disease (HD) is identification of treatments that reduce the burden of mutant huntingtin (mHTT) protein in the brain. In order to identify and test the efficacy of such therapies, it is essential to have biomarkers that are sensitive to the effects of mHTT on brain function to determine whether the intervention has been effective at preventing toxicity in target brain systems before onset of clinical symptoms. Ideally, such biomarkers should have a plausible physiologic basis for detecting the effects of mHTT, be measureable both in preclinical models and human studies, be practical to measure serially in clinical trials, and be reliably measurable in HD gene expansion carriers (HDGECs), among other features. Quantitative electroencephalography (qEEG) fulfills many of these basic criteria of a "fit-for-purpose" biomarker. qEEG measures brain oscillatory activity that is regulated by the brain structures that are affected by mHTT in premanifest and early symptom individuals. The technology is practical to implement in the laboratory and is well tolerated by humans in clinical trials. The biomarkers are measureable across animal models and humans, with findings that appear to be detectable in HDGECs and translate across species. We review here the literature on recent developments in both preclinical and human studies of the use of qEEG biomarkers in HD, and the evidence for their usefulness as biomarkers to help guide development of novel mHTT lowering treatments.

Leuchter, A. F., Hunter, A. M., Jain, F. A., Tartter, M., Crump, C., & Cook, I. A. (2017). Escitalopram but not placebo modulates brain rhythmic oscillatory activity in the first week of treatment of Major Depressive Disorder. Journal of psychiatric research, 84, 174–183. https://doi.org/10.1016/j.jpsychires.2016.10.002. Serotonin modulates brain oscillatory activity, and serotonergic projections to the thalamus and cortex modulate the frequency of prefrontal rhythmic oscillations. Changes in serotonergic tone have been reported to shift oscillations between the combined delta-theta (2.5-8 Hz) and the alpha (8-12 Hz) frequency ranges. Such frequency shifts may constitute a useful biomarker for the effects of selective serotonin reuptake inhibitor (SSRI) medications in Major Depressive Disorder (MDD). We utilized quantitative electroencephalography (qEEG) to measure shifts in prefrontal rhythmic oscillations early in treatment with either the SSRI escitalopram or placebo, and examined the relationship between these changes and remission of depressive symptoms. Prefrontal delta-theta and alpha power were calculated for 194 subjects with moderate MDD prior to and one week after start of treatment. Changes at one week in delta-theta and alpha power, as well as the delta-theta/alpha ratio, were examined in three cohorts: initial (N = 70) and replication (N = 76) cohorts treated with escitalopram, and a cohort treated with placebo (N = 48). Mean delta-theta power significantly increased and alpha power decreased after one week of escitalopram treatment, but did not significantly change with placebo treatment. The delta-theta/alpha ratio change was a specific predictor of the likelihood of remission after seven weeks of medication treatment: a large increase in this ratio was associated with non-remission in escitalopram-treated subjects, but not placebo-

treated subjects. Escitalopram and placebo treatment have differential effects on delta-theta and alpha frequency oscillations. Early increase in delta-theta/alpha may constitute a replicable biomarker for non-remission during SSRI treatment of MDD.

Leuchter, A. F., Hunter, A. M., Krantz, D. E., & Cook, I. A. (2014). Intermediate phenotypes and biomarkers of treatment outcome in major depressive disorder. Dialogues in clinical neuroscience, 16(4), 525–537. https://doi.org/10.31887/DCNS.2014.16.4/aleuchter. Major depressive disorder (MDD) is a pleomorphic illness originating from gene x environment interactions. Patients with differing symptom phenotypes receive the same diagnosis and similar treatment recommendations without regard to genomics, brain structure or function, or other physiologic or psychosocial factors. Using this present approach, only one third of patients enter remission with the first medication prescribed, and patients may take longer than 1 year to enter remission with repeated trials. Research to improve treatment effectiveness recently has focused on identification of intermediate phenotypes (IPs) that could parse the heterogeneous population of patients with MDD into subgroups with more homogeneous responses to treatment. Such IPs could be used to develop biomarkers that could be applied clinically to match patients with the treatment that would be most likely to lead to remission. Putative biomarkers include genetic polymorphisms, RNA and protein expression (transcriptome and proteome), neurotransmitter levels (metabolome), additional measures of signaling cascades, oscillatory synchrony, neuronal circuits and neural pathways (connectome), along with other possible physiologic measures. All of these measures represent components of a continuum that extends from proximity to the genome to proximity to the clinical phenotype of depression, and there are many levels along this continuum at which useful IPs may be defined. Because of the highly integrative nature of brain systems and the complex neurobiology of depression, the most useful biomarkers are likely to be those with intermediate proximity both to the genome and the clinical phenotype of MDD. Translation of findings across the spectrum from genotype to phenotype promises to better characterize the complex disruptions in signaling and neuroplasticity that accompany MDD, and ultimately to lead to greater understanding of the causes of depressive illness.

Liechti, MD., Valko, L., Muller, UC., Mirko Dohnert, M., Drechsler, R., Steinhausen, H. & Brandeis, D. (2012). Diagnostic value of resting electroencephalogram in attention-deficit/hyperactivity disorder across the lifespan. Brain Topography: Online Oct 2012. The resting electroencephalogram (EEG) reflects development and arousal, but whether it can support clinical diagnosis of attention-deficit/hyperactivity disorder (ADHD) remains controversial. Here we examined whether theta power and theta/beta ratio are consistently elevated in ADHD and younger age as proposed. Topographic 48-channel EEG from 32 children (8–16 years) and 22 adults (32–55 years) with ADHD and matched healthy controls (n = 30 children/21 adults) was compared. Following advanced artefact correction, resting EEG was tested for increased theta and theta/beta activity due to ADHD and due to normal immaturity. Discriminant analyses tested classification performance by ADHD and age using these EEG markers as well as EEG artefacts and deviant attentional event-related potentials (ERPs). No consistent theta or theta/beta increases were found with ADHD. Even multivariate analyses indicated only marginal EEG power increases in children with ADHD. Instead, consistent developmental theta decreases were observed, indicating that maturational lags of fewer than 3 years would have been detected in children. Discriminant analysis based on proposed simple spectral resting EEG markers was successful for age but not for ADHD (81 vs. 53 % accuracy). Including ERP markers and EEG artefacts improved discrimination, although not to diagnostically useful levels. The lack of consistent spectral resting EEG abnormalities in ADHD despite consistent developmental effects casts doubt upon conventional neurometric approaches towards EEG-based ADHD diagnosis, but is consistent with evidence that ADHD is a heterogeneous disorder, where the resting state is not consistently characterised by maturational lag.

Livint Popa L, Dragos H, Pantelemon C, Verisezan Rosu O, Strilciuc S. (2020). The Role of Quantitative EEG in the Diagnosis of Neuropsychiatric Disorders. J Med Life. 2020 Jan-Mar;13(1):8-15. doi: 10.25122/jml-2019-0085. PMID: 32341694; PMCID: PMC7175442.

Quantitative electroencephalography (QEEG) is a modern type of electroencephalography (EEG) analysis that involves recording digital EEG signals which are processed, transformed, and analyzed using complex mathematical algorithms. QEEG has brought new techniques of EEG signals feature extraction: analysis of specific frequency band and signal complexity, analysis of connectivity, and network analysis. The clinical application of QEEG is extensive, including neuropsychiatric disorders, epilepsy, stroke, dementia, traumatic brain

injury, mental health disorders, and many others. In this review, we talk through existing evidence on the practical applications of this clinical tool. We conclude that to date, the role of QEEG is not necessarily to pinpoint an immediate diagnosis but to provide additional insight in conjunction with other diagnostic evaluations in order to objective information necessary for obtaining a precise diagnosis, correct disease severity assessment, and specific treatment response evaluation.

Mane, R., Chew, E., Phua, K. S., Ang, K. K., Robinson, N., Vinod, A. P., & Guan, C. (2019). Prognostic and Monitory EEG-Biomarkers for BCI Upper-Limb Stroke Rehabilitation. IEEE transactions on neural systems and rehabilitation engineering: a publication of the IEEE Engineering in Medicine and Biology Society, 27(8), 1654–1664. https://doi.org/10.1109/TNSRE.2019.2924742. With the availability of multiple rehabilitative interventions, identifying the one that elicits the best motor outcome based on the unique neuro-clinical profile of the stroke survivor is a challenging task. Predicting the potential of recovery using biomarkers specific to an intervention hence becomes important. To address this, we investigate intervention-specific prognostic and monitory biomarkers of motor function improvements using quantitative electroencephalography (QEEG) features in 19 chronic stroke patients following two different upper extremity rehabilitative interventions viz. Brain-computer interface (BCI) and transcranial direct current stimulation coupled BCI (tDCS-BCI). Brain symmetry index was found to be the best prognostic QEEG for clinical gains following BCI intervention (r = -0.80 , p = 0.02), whereas power ratio index (PRI) was observed to be the best predictor for tDCS-BCI (r = -0.96 , p = 0.004) intervention. Importantly, statistically significant between-intervention differences observed in the predictive capabilities of these features suggest that intervention-specific biomarkers can be identified. This approach can be further pursued to distinctly predict the expected response of a patient to available interventions. The intervention with the highest predicted gains may then be recommended to the patient, thereby enabling a personalized rehabilitation regime.

Morales-Quezada, L., Saavedra, L. C., Rozisky, J., Hadlington, L., & Fregni, F. (2014). Intensity-dependent effects of transcranial pulsed current stimulation on interhemispheric connectivity: a high-resolution qEEG, sham-controlled study. Neuroreport, 25(13), 1054–1058. https://doi.org/10.1097/WNR.0000000000000228. Defining optimal parameters for stimulation is a critical step in the development of noninvasive neuromodulation techniques. Transcranial pulsed current stimulation (tPCS) is emerging as another option in the field of neuromodulation; however, little is known about its mechanistic effects on electrical brain activity and how it can modulate its oscillatory patterns. The aim of this study was to identify the current intensity needed to exert an effect on quantitative electroencephalogram (qEEG) measurements. Forty healthy volunteers were randomized to receive a single session of sham or active stimulation at 0.2, 1, or 2 mA current intensity with a random frequency with an oscillatory pulsed range between 1 and 5 Hz. We conducted an exploratory frequency domain analysis to detect changes in absolute power for theta, alpha, and beta frequency bands and also interhemispheric coherence for alpha, theta, and four different sub-bands. Cognitive and nonspecific adverse effects were also recorded. Our results showed that both 1 and 2 mA can modulate interhemispheric coherence at the fronto-temporal areas for the theta band as compared with sham, while 2 mA also increased the low-beta and high-beta interhemispheric coherence at the same anatomical location. There were no group differences for adverse effects and participants could not guess correctly whether they received active versus sham stimulation. On the basis of our results, we conclude that tPCS is associated with an intensity-dependent facilitatory effect on interhemispheric connectivity. These results can guide future tPCS applications and will define its role as a neuromodulatory technique in the field.

Nagy, I., & Fabó, D., (2018). Klinikai neurofiziológiai módszerek a cerebrovascularis betegségek diagnózisában és kezelésében [Clinical neurophysiological methods in diagnosis and treatment of cerebrovascular diseases]. Ideggyogyaszati szemle, 71(1-02), 7–14. https://doi.org/10.18071/isz.71.0007. Neurophysiological methods are gaining ground in the diagnosis and therapy of cerebrovascular disease. While the role of the EEG (electroencephalography) in the diagnosis of post-stroke epilepsy is constant, quantitative EEG para-meters, as new indicators of early efficiency after thrombolysis or in prognosis of patient's condition have proved their effectiveness in several clinical studies. In intensive care units, continuous EEG monitoring of critically ill patients became part of neurointenzive care protocols. SSEP (somatosesnsory evoked potencial) and EEG performed during carotid endarterectomy, are early indicative intraoperativ neuromonitoring methods of poor outcome. Neurorehabilitation is a newly discovered area of neurophysiology.

Clinical studies have demonstrated the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in the rehabilitation of stroke patients. Brain computer interface mark the onset of modern rehabi-litation, where the function deficit is replaced by robotic tehnology.

Öksüz, Ö., Günver, G., Oba, M. Ç., & Arıkan, K. (2020). Psychiatry to dermatology; panic disorder. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia, 81, 316–320. https://doi.org/10.1016/j.jocn.2020.09.071. Objective: Anxiety is commonly observed together with skin diseases and can aggravate them, while skin diseases can increase anxiety. The relationship of skin diseases observed in panic disorder with quantitative electroencephalography (QEEG) findings has not been investigated yet. The aim of this study is to compare the absolute alpha and delta power of panic disorder patients with and without skin disease. Methods: 246 panic disorder patients, 19 of whom had skin disease and 227 of whom did not have skin disease, were included in the study. Panic disorder severity scale (PDSS) scores of patients were recorded, and QEEG recording was performed. Absolute alpha and delta power and PDSS scores were compared between the two groups. Results: It was found that the absolute delta power in the left hemisphere was lower and PDSS scores were higher in the patients with skin diseases compared to the control group. In the patients with skin disease, decreased delta power in the left hemisphere may cause impairment in the processing of positive emotions and may cause trait anxiety. Conclusion: Trait anxiety may increase susceptibility to skin diseases by disrupting cutaneous homeostasis resulting from the prolonged sympathetic nervous system activation.

Olbrich, S., & Arns, M. (2013). EEG biomarkers in major depressive disorder: discriminative power and prediction of treatment response. International review of psychiatry (Abingdon, England), 25(5), 604–618. https://doi.org/10.3109/09540261.2013.816269. Major depressive disorder (MDD) has high population prevalence and is associated with substantial impact on quality of life, not least due to an unsatisfactory time span of sometimes several weeks from initiation of treatment to clinical response. Therefore extensive research focused on the identification of cost-effective and widely available electroencephalogram (EEG)-based biomarkers that not only allow distinguishing between patients and healthy controls but also have predictive value for treatment response for a variety of treatments. In this comprehensive overview on EEG research on MDD, biomarkers that are either assessed at baseline or during the early course of treatment and are helpful in discriminating patients from healthy controls and assist in predicting treatment outcome are reviewed, covering recent decades up to now. Reviewed markers include quantitative EEG (QEEG) measures, connectivity measures, EEG vigilance-based measures, sleep-EEG-related measures and event-related potentials (ERPs). Further, the value and limitations of these different markers are discussed. Finally, the need for integrated models of brain function and the necessity for standardized procedures in EEG biomarker research are highlighted to enhance future research in this field.

Pinheiro, E. S., de Queirós, F. C., Montoya, P., Santos, C. L., do Nascimento, M. A., Ito, C. H., Silva, M., Nunes Santos, D. B., Benevides, S., Miranda, J. G., Sá, K. N., & Baptista, A. F. (2016). Electroencephalographic Patterns in Chronic Pain: A Systematic Review of the Literature. PloS one, 11(2), e0149085. https://doi.org/10.1371/journal.pone.0149085. The main objective of this study is to review and summarize recent findings on electroencephalographic patterns in individuals with chronic pain. We also discuss recent advances in the use of quantitative Electroencephalography (qEEG) for the assessment of pathophysiology and biopsychosocial factors involved in its maintenance over time. Data collection took place from February 2014 to July 2015 in PubMed, SciELO and PEDro databases. Data from cross-sectional studies and longitudinal studies, as well as clinical trials involving chronic pain participants were incorporated into the final analysis. Our primary findings related to chronic pain were an increase of theta and alpha EEG power at rest, and a decrease in the amplitude of evoked potentials after sensory stimulation and cognitive tasks. This review suggests that qEEG could be considered as a simple and objective tool for the study of brain mechanisms involved in chronic pain, as well as for identifying the specific characteristics of chronic pain condition. In addition, results show that qEEG probably is a relevant outcome measure for assessing changes in therapeutic studies.

Prichep L. S. (2005). Use of normative databases and statistical methods in demonstrating clinical utility of QEEG: importance and cautions. Clinical EEG and neuroscience, 36(2), 82–87. https://doi.org/10.1177/155005940503600207 The clinical utility of the EEG, especially in psychiatric, learning and cognitive disorders, has been greatly enhanced by the use of quantitative analysis (QEEG) and comparisons to a normative database. Of primary importance in the use of such a reference database are the following considerations

and cautions: adequate sampling across a broad age range; consideration of inclusion/exclusion criteria; adequate sample of artifact-free data to demonstrate reliability and replicability of norms; demonstration of specificity and sensitivity. A normative database meeting these criteria allows the multivariate description of patterns of QEEG abnormalities in patients as compared to age-appropriate normative values, and the exploration of neurophysiological heterogeneity within populations. Demonstrations of the clinical significance of this approach exist in the scientific literature and demonstrate that QEEG provides high sensitivity and specificity to abnormalities in brain function seen in psychiatric populations.

Puskás, S., Kozák, N., Sulina, D., Csiba, L., & Magyar, M. T. (2017). Quantitative EEG in obstructive sleep apnea syndrome: a review of the literature. Reviews in the neurosciences, 28(3), 265–270. https://doi.org/10.1515/revneuro-2016-0064. Obstructive sleep apnea syndrome (OSAS) is characterized by the recurrent cessation (apnea) or reduction (hypopnea) of airflow due to the partial or complete upper airway collapse during sleep. Respiratory disturbances causing sleep fragmentation and repetitive nocturnal hypoxia are responsible for a variety of nocturnal and daytime complaints of sleep apnea patients, such as snoring, daytime sleepiness, fatigue, or impaired cognitive functions. Different techniques, such as magnetic resonance imaging, magnetic resonance spectroscopy, and positron emission tomography, are used to evaluate the structural and functional changes in OSAS patients. With quantitative electroencephalographic (qEEG) analysis, the possible existence of alterations in the brain electrical activity of OSAS patients can be investigated. We review the articles on qEEG results of sleep apnea patients and summarize the possible explanations of these qEEG measures. Finally, we review the impact of continuous positive airway pressure (CPAP) treatment on these alterations to assess whether CPAP use can eliminate alterations in the brain activity of OSAS patients.

Rapp, P. E., Keyser, D. O., Albano, A., Hernandez, R., Gibson, D. B., Zambon, R. A., Hairston, W. D., Hughes, J. D., Krystal, A., & Nichols, A. S. (2015). Traumatic brain injury detection using electrophysiological methods. Frontiers in human neuroscience, 9, 11. https://doi.org/10.3389/fnhum.2015.00011. Measuring neuronal activity with electrophysiological methods may be useful in detecting neurological dysfunctions, such as mild traumatic brain injury (mTBI). This approach may be particularly valuable for rapid detection in at-risk populations including military service members and athletes. Electrophysiological methods, such as quantitative electroencephalography (qEEG) and recording event-related potentials (ERPs) may be promising; however, the field is nascent and significant controversy exists on the efficacy and accuracy of the approaches as diagnostic tools. For example, the specific measures derived from an electroencephalogram (EEG) that are most suitable as markers of dysfunction have not been clearly established. A study was conducted to summarize and evaluate the statistical rigor of evidence on the overall utility of qEEG as an mTBI detection tool. The analysis evaluated qEEG measures/parameters that may be most suitable as fieldable diagnostic tools, identified other types of EEG measures and analysis methods of promise, recommended specific measures and analysis methods for further development as mTBI detection tools, identified research gaps in the field, and recommended future research and development thrust areas. The qEEG study group formed the following conclusions: (1) Individual qEEG measures provide limited diagnostic utility for mTBI. However, many measures can be important features of qEEG discriminant functions, which do show significant promise as mTBI detection tools. (2) ERPs offer utility in mTBI detection. In fact, evidence indicates that ERPs can identify abnormalities in cases where EEGs alone are non-disclosing. (3) The standard mathematical procedures used in the characterization of mTBI EEGs should be expanded to incorporate newer methods of analysis including non-linear dynamical analysis, complexity measures, analysis of causal interactions, graph theory, and information dynamics. (4) Reports of high specificity in qEEG evaluations of TBI must be interpreted with care. High specificities have been reported in carefully constructed clinical studies in which healthy controls were compared against a carefully selected TBI population. The published literature indicates, however, that similar abnormalities in qEEG measures are observed in other neuropsychiatric disorders. While it may be possible to distinguish a clinical patient from a healthy control participant with this technology, these measures are unlikely to discriminate between, for example, major depressive disorder, bipolar disorder, or TBI. The specificities observed in these clinical studies may well be lost in real world clinical practice. (5) The absence of specificity does not preclude clinical utility. The possibility of use as a longitudinal measure of treatment response remains. However, efficacy as a longitudinal clinical measure does require acceptable test-retest reliability. To date, very few test-retest reliability studies have been published with qEEG data obtained from TBI patients or from healthy controls. This is a particular concern because high variability is a known characteristic of the injured central nervous system.

Rosenfeld, V. W., Rutledge, D. N., & Stern, J. M. (2015). Polysomnography with quantitative EEG in patients with and without fibromyalgia. Journal of clinical neurophysiology: official publication of the American Electroencephalographic Society, 32(2), 164–170. https://doi.org/10.1097/WNP.0000000000000134. Purpose: Characterize the polysomnographic (PSG) and quantitative EEG (qEEG) features of fibromyalgia and determine whether fibromyalgia patients differ in these measures when compared with a control sleep disorder population. Methods: All undergoing all-night PSG for evaluation of a sleep disorder were evaluated for fibromyalgia. The PSGs were interpreted for routine sleep measures, and qEEG was performed to measure the delta and alpha frequency power during non-rapid eye movement sleep. Measures and qEEG were analyzed according to fibromyalgia diagnosis. Setting: Community-based sleep medicine center. Patients: All patients undergoing PSG over a 2-year period. Interventions: None. Results: Of the 385 patients in the study population, 133 had fibromyalgia according to American College of Rheumatology criteria. The population's average Epworth Sleepiness Score was 10.5, the average sleep efficiency was 78%, and the Periodic Limb Movement disorder prevalence was 15%. None of these sleep measures differed significantly between the fibromyalgia and non-fibromyalgia groups. Obstructive sleep apnea was present in 45% of the fibromyalgia group. Significant differences were present in the qEEG ratio of delta to alpha frequency power, which was 95% specific for fibromyalgia when ≤1. A qEEG ratio ≤10.5 was 85% sensitive for fibromyalgia, and a qEEG ratio >10.5 had an 89% negative predictive value for fibromyalgia. Among patients with fibromyalgia who were not taking a benzodiazepine or benzodiazepine agonist, a qEEG ratio ≤10.5 was 84% specific and had a 78% positive predictive value. Conclusions: Sleep disorders identified by routine PSG, including obstructive sleep apnea, are common in fibromyalgia, but periodic leg movement disorder and poor sleep efficiency are not. A qEEG low delta/alpha ratio during non-rapid eye movement sleep can differentiate patients with fibromyalgia from others who are referred for PSG. Consideration of benzodiazepine and benzodiazepine agonist use is important when interpreting the delta/alpha ratio.

Sansevere, A. J., Hahn, C. D., & Abend, N. S. (2019). Conventional and quantitative EEG in status epilepticus. Seizure, 68, 38–45. https://doi.org/10.1016/j.seizure.2018.09.011. Purpose: To summarize the use of continuous electroencephalographic monitoring (cEEG) in the diagnosis and management of pediatric convulsive status epilepticus (CSE) and subsequent non-convulsive seizures (NCS) with a focus on available guidelines and infrastructure. In addition, we provide an overview of quantitative EEG (QEEG) for the identification of NCS in critically ill children. Methods: We performed a review of the medical literature on the use of cEEG and QEEG in pediatric CSE. This included published guideline, consensus statements, and literature focused on the use of cEEG and QEEG to detect NCS.
Results: cEEG monitoring is recommended for prompt recognition of ongoing seizures that may be subtle, masked by pharmacologic paralysis, and or converted from convulsive seizures to NCS after administration of anti-seizure medications. Evidence indicating that high seizure burden is associated with worse outcome has motivated prompt recognition and management of NCS. The American Clinical Neurophysiology Society's consensus statement recommends a minimum of 24 h to exclude electrographic seizures, while the Neurocritical Care Society's guideline suggests 48 h in patients that are comatose. The use of QEEG amongst electroencephalographers and critical care medicine providers is increasing for NCS detection in critically ill children. The sensitivity and specificity of QEEG to detect NCS ranges from 65 to 83% and 65-92%, respectively. Conclusion: The use of cEEG is important to the diagnosis and treatment of NCS or subtle clinical seizures after pediatric CSE. QEEG allows cEEG data to be reviewed and interpreted quickly and is a useful tool for detection of NCS after CSE.

Saroka, K. S., & Persinger, M. A. (2013). Potential production of Hughlings Jackson's "parasitic consciousness" by physiologically-patterned weak transcerebral magnetic fields: QEEG and source localization. Epilepsy & behavior: E&B, 28(3), 395–407. https://doi.org/10.1016/j.yebeh.2013.05.023. Exotic experiences such as the sensing of another consciousness or the detachment of consciousness from the body are occasionally reported by individuals with partial seizures from a temporal lobe focus. The experiences display the characteristics of Hughlings Jackson's "parasitic consciousness". We have hypothesized that these experiences are encouraged by slight discrepancies in hemispheric activity that can be simulated by application of weak, physiologically-patterned magnetic fields across the cerebral hemispheres. Electroencephalographic and Low Resolution Electromagnetic Tomography (sLORETA) data revealed altered activity bands within specific regions within the cerebral cortices during these experiences. The clear

changes in power of brain activity were discerned after consistent durations of exposure to specifically patterned weak magnetic fields. Millisecond range point durations were required. The technology may be useful to explore the subjective components associated with complex partial seizures.

Schmitt, S., & Dichter, M. A. (2015). Electrophysiologic recordings in traumatic brain injury. Handbook of clinical neurology, 127, 319–339. https://doi.org/10.1016/B978-0-444-52892-6.00021-0. Following a traumatic brain injury (TBI), the brain undergoes numerous electrophysiologic changes. The most common techniques used to evaluate these changes include electroencepalography (EEG) and evoked potentials. In animals, EEGs immediately following TBI can show either diffuse slowing or voltage attenuation, or high voltage spiking. Following a TBI, many animals display evidence of hippocampal excitability and a reduced seizure threshold. Some mice subjected to severe TBI via a fluid percussion injury will eventually develop seizures, which provides a useful potential model for studying the neurophysiology of epileptogenesis. In humans, the EEG changes associated with mild TBI are relatively subtle and may be challenging to distinguish from EEG changes seen in other conditions. Quantitative EEG (QEEG) may enhance the ability to detect post-traumatic electrophysiologic changes following a mild TBI. Some types of evoked potential (EP) and event related potential (ERP) can also be used to detect post-traumatic changes following a mild TBI. Continuous EEG monitoring (cEEG) following moderate and severe TBI is useful in detecting the presence of seizures and status epilepticus acutely following an injury, although some seizures may only be detectable using intracranial monitoring. CEEG can also be helpful for assessing prognosis after moderate or severe TBI. EPs, particularly somatosensory evoked potentials, can also be useful in assessing prognosis following severe TBI. The role for newer technologies such as magnetoencephalography and bispectral analysis (BIS) in the evaluation of patients with TBI remains unclear.

Simkin, D. R., Thatcher, R. W., & Lubar, J. (2014). Quantitative EEG and neurofeedback in children and adolescents: anxiety disorders, depressive disorders, comorbid addiction and attention-deficit/hyperactivity disorder, and brain injury. Child and adolescent psychiatric clinics of North America, 23(3), 427–464. https://doi.org/10.1016/j.chc.2014.03.001. This article explores the science surrounding neurofeedback. Both surface neurofeedback (using 2-4 electrodes) and newer interventions, such as real-time z-score neurofeedback (electroencephalogram [EEG] biofeedback) and low-resolution electromagnetic tomography neurofeedback, are reviewed. The limited literature on neurofeedback research in children and adolescents is discussed regarding treatment of anxiety, mood, addiction (with comorbid attention-deficit/hyperactivity disorder), and traumatic brain injury. Future potential applications, the use of quantitative EEG for determining which patients will be responsive to medications, the role of randomized controlled studies in neurofeedback research, and sensible clinical guidelines are considered.

Smailovic, U., & Jelic, V. (2019). Neurophysiological Markers of Alzheimer's Disease: Quantitative EEG Approach. Neurology and therapy, 8(Suppl 2), 37–55. https://doi.org/10.1007/s40120-019-00169-0. Currently established and employed biomarkers of Alzheimer's disease (AD) predominantly mirror AD-associated molecular and structural brain changes. While they are necessary for identifying disease-specific neuropathology, they lack a clear and robust relationship with the clinical presentation of dementia; they can be altered in healthy individuals, while they often inadequately mirror the degree of cognitive and functional deficits in affected subjects. There is growing evidence that synaptic loss and dysfunction are early events during the trajectory of AD pathogenesis that best correlate with the clinical symptoms, suggesting measures of brain functional deficits as candidate early markers of AD. Resting-state electroencephalography (EEG) is a widely available and noninvasive diagnostic method that provides direct insight into brain synaptic activity in real time. Quantitative EEG (qEEG) analysis additionally provides information on physiologically meaningful frequency components, dynamic alterations and topography of EEG signal generators, i.e. neuronal signaling. Numerous studies have shown that qEEG measures can detect disruptions in activity, topographical distribution and synchronization of neuronal (synaptic) activity such as generalized EEG slowing, reduced global synchronization and anteriorization of neuronal generators of fast-frequency resting-state EEG activity in patients along the AD continuum. Moreover, qEEG measures appear to correlate well with surrogate markers of AD neuropathology and discriminate between different types of dementia, making them promising low-cost and noninvasive markers of AD. Future large-scale longitudinal clinical studies are needed to elucidate the diagnostic and prognostic potential of qEEG measures as early functional markers of AD on an individual subject level.

Song, Y., Zang, D. W., Jin, Y. Y., Wang, Z. J., Ni, H. Y., Yin, J. Z., & Ji, D. X. (2015). Background rhythm frequency and theta power of quantitative EEG analysis: predictive biomarkers for cognitive impairment post-cerebral infarcts. Clinical EEG and neuroscience, 46(2), 142–146. https://doi.org/10.1177/1550059413517492. In clinical settings, cerebral infarct is a common disease of older adults, which usually increases the risk of cognitive impairment. This study aims to assess the quantitative electroencephalography (qEEG) as a predictive biomarker for the development of cognitive impairment, post-cerebral infarcts, in subjects from the Department of Neurology. They underwent biennial EEG recording. Cerebral infarct subjects, with follow-up cognitive evaluation, were analyzed for qEEG measures of background rhythm frequency (BRF) and relative δ, θ, α, and β band power. The relationship between cognitive impairment and qEEG, and other possible predictors, was assessed by Cox regression. The results showed that the risk hazard of developing cognitive impairment was 14 times higher for those with low BRF than for those with high BRF ($P < .001$). Hazard ratio (HR) was also significant for more than median θ band power (HR = 5, P = .002) compared with less than median θ band power. The HRs for δ, α, and β bands were equal to the baseline demographic, and clinical characteristics were not significantly different. In conclusion, qEEG measures of BRF, and relative power in θ band, are potential predictive biomarkers for cognitive impairment in patients with cerebral infarcts. These biomarkers might be valuable in early prediction of cognitive impairment in patients with cerebral infarcts.

Thatcher RW, Biver CJ, Soler EP, Lubar J, Koberda JL (2020) New Advances in Electrical Neuroimaging, Brain Networks and Neurofeedback Protocols. J Neurol Neurobiol 6(3): dx.doi.org/10.16966/2379-7150.168. Human EEG biofeedback (neurofeedback) started in the 1940s [1] using 1 EEG recording channel, then to 4 channels in the 1990s. New advancements in electrical Neuroimaging expanded EEG biofeedback to 19 channels using Low Resolution Electromagnetic Tomography (LORETA) three-dimensional current sources of the EEG [2]. In 2004-2006 the concept of a "real-time" comparison of the EEG to a healthy reference database was developed and tested using surface EEG z-score neurofeedback based on a statistical bell curve called "real-time" z-scores. The "real-time" or "live" normative reference database comparison was developed to help reduce the uncertainty of what threshold to select to activate a feedback signal and to unify all EEG measures to a single value, i.e., the distance from the mean of an age matched reference sample. In 2009 LORETA z-score neurofeedback further increased the specificity by targeting brain network hubs referred to as Brodmann areas. A symptom check list program to help link symptoms to dysregulation of brain networks based on fMRI and PET and neurology was created in 2009. The symptom checklist and NIH based networks linking symptoms to brain networks grew out of the human brain mapping program starting in 1990 which is continuing today. A goal is to increase specificity of EEG biofeedback by targeting brain network hubs and connections between hubs likely linked to the patient's symptoms. New advancements in electrical neuroimaging introduced in 2017 provide increased resolution of three-dimensional source localization with 12,700 voxels using swLORETA with the capacity to conduct cerebellar neurofeedback and neurofeedback of subcortical brain hubs such as the thalamus, amygdala and habenula. Future applications of swLORETA z-score neurofeedback represents another example of the transfer of knowledge gained by the human brain mapping initiatives to further aid in helping people with cognition problems as well as balance problems and parkinsonism. A brief review of the past, present and future predictions of z-score neurofeedback are discussed with special emphasis on new developments that point toward a bright and enlightened future in the field of EEG biofeedback.

Thatcher, R. & Lubar, J. (2008). ***History of the scientific standards of QEEG normative databases.*** **Published in: Introduction to QEEG and Neurofeedback: Advanced Theory and Applications. Eds: Budzynski, T., Budzynski, H., Evans, J. & Abarbanel, A. Academic Press, San Diego, CA.** The nearly 40 year history of quantitative EEG (QEEG) normative databases are reviewed with special emphasis on the implementation of scientific and statistical
standards. Differences between normative databases and standard control studies are discussed. The application of scientific and statistical standards such as peer reviewed publications, inclusion/exclusion criteria, number of subjects per age group, Gaussian tests for normality, cross-validation tests, amplifier matching, clinical correlations and FDA registration are presented in a historical context. A check list of "Gold Standards" for the evaluation of QEEG normative databases is presented in which the more checks then the higher the scientific and statistical standards for a given normative database. The goal of the paper is to provide an historical perspective and brief review of QEEG normative databases in order to encourage both users and authors of normative databases to strive for standardization.

Trujillo, P., Mastropietro, A., Scano, A., Chiavenna, A., Mrakic-Sposta, S., Caimmi, M., Molteni, F., & Rizzo, G. (2017). Quantitative EEG for Predicting Upper Limb Motor Recovery in Chronic Stroke Robot-Assisted Rehabilitation. IEEE transactions on neural systems and rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society, 25(7), 1058–1067. https://doi.org/10.1109/TNSRE.2017.2678161. Stroke is a leading cause for adult disability, which in many cases causes motor deficits. Despite the developments in motor rehabilitation techniques, recovery of upper limb functions after stroke is limited and heterogeneous in terms of outcomes, and knowledge of important factors that may affect the outcome of the therapy is necessary to make a reasonable prediction for individual patients. In this paper, we assessed the relationship between quantitative electroencephalographic (QEEG) measures and the motor outcome in chronic stroke patients that underwent a robot-assisted rehabilitation program to evaluate the utility of QEEG indices to predict motor recovery. For this purpose, we acquired resting-state electroencephalographic signals from which the power ratio index (PRI), delta/alpha ratio, and brain symmetry index were calculated. The outcome of the motor rehabilitation was evaluated using upper limb section of the Fugl-Meyer Assessment. We found that PRI was significantly correlated with the motor recovery, suggesting that this index may provide useful information to predict the rehabilitation outcome.

Wang, Q. & Sourina, O. (2013). Real-time mental arithmetic task recognition from EEG signals. IEEE Trans Neural Syst Rehabil Eng:21(). 225-32. Electroencephalography (EEG)-based monitoring the state of the user's brain functioning and giving her/him the visual/audio/tactile feedback is called neurofeedback technique, and it could allow the user to train the corresponding brain functions. It could provide an alternative way of treatment for some psychological disorders such as attention deficit hyperactivity disorder (ADHD), where concentration function deficit exists, autism spectrum disorder (ASD), or dyscalculia where the difficulty in learning and comprehending the arithmetic exists. In this paper, a novel method for multifractal analysis of EEG signals named generalized Higuchi fractal dimension spectrum (GHFDS) as roposed and applied in mental arithmetic task recognition from EEG signals. Other features such as power spectrum density (PSD), autoregressive model (AR), and statistical features were analyzed as well. The usage of the proposed fractal dimension spectrum of EEG signal in combination with other features improved the mental arithmetic task recognition accuracy in both multi-channel and one-channel subject-dependent algorithms up to 97.87% and 84.15% correspondingly. Based on the channel ranking, four channels were chosen which gave the accuracy up to 97.11%. Reliable real-time neurofeedback system could be implemented based on the algorithms proposed in this paper.

Wickering E, Gaspard N, Zafar S, Moura VJ, Biswal S, Bechek S, O'Connor K, Rosenthal ES, Westover MB. (2016). Automation of Classical QEEG Trending Methods for Early Detection of Delayed Cerebral Ischemia: More Work to Do. J Clin Neurophysiol. 2016 Jun;33(3):227-34. doi: 10.1097/WNP.0000000000000278. PMID: 27258446; PMCID: PMC4894333. The purpose of this study is to evaluate automated implementations of continuous EEG monitoring-based detection of delayed cerebral ischemia based on methods used in classical retrospective studies. We studied 95 patients with either Fisher 3 or Hunt Hess 4 to 5 aneurysmal subarachnoid hemorrhage who were admitted to the Neurosciences ICU and underwent continuous EEG monitoring. We implemented several variations of two classical algorithms for automated detection of delayed cerebral ischemia based on decreases in alpha-delta ratio and relative alpha variability. Of 95 patients, 43 (45%) developed delayed cerebral ischemia. Our automated implementation of the classical alpha-delta ratio-based trending method resulted in a sensitivity and specificity (Se,Sp) of (80,27)%, compared with the values of (100,76)% reported in the classic study using similar methods in a nonautomated fashion. Our automated implementation of the classical relative alpha variability-based trending method yielded (Se,Sp) values of (65,43)%, compared with (100,46)% reported in the classic study using nonautomated analysis. Our findings suggest that improved methods to detect decreases in alpha-delta ratio and relative alpha variability are needed before an automated EEG-based early delayed cerebral ischemia detection system is ready for clinical use.

Widge, A. S., Bilge, M. T., Montana, R., Chang, W., Rodriguez, C. I., Deckersbach, T., Carpenter, L. L., Kalin, N. H., & Nemeroff, C. B. (2019). Electroencephalographic Biomarkers for Treatment Response Prediction in Major Depressive Illness: A Meta-Analysis. The American journal of psychiatry, 176(1), 44–56. https://doi.org/10.1176/appi.ajp.2018.17121358. Objective:

Reducing unsuccessful treatment trials could improve depression treatment. Quantitative EEG (QEEG) may predict treatment response and is being commercially marketed for this purpose. The authors sought to quantify the reliability of QEEG for response prediction in depressive illness and to identify methodological limitations of the available evidence. Method: The authors conducted a meta-analysis of diagnostic accuracy for QEEG in depressive illness, based on articles published between January 2000 and November 2017. The review included all articles that used QEEG to predict response during a major depressive episode, regardless of patient population, treatment, or QEEG marker. The primary meta-analytic outcome was the accuracy for predicting response to depression treatment, expressed as sensitivity, specificity, and the logarithm of the diagnostic odds ratio. Raters also judged each article on indicators of good research practice. Results: In 76 articles reporting 81 biomarkers, the meta-analytic estimates showed a sensitivity of 0.72 (95% CI=0.67-0.76) and a specificity of 0.68 (95% CI=0.63-0.73). The logarithm of the diagnostic odds ratio was 1.89 (95% CI=1.56-2.21), and the area under the receiver operator curve was 0.76 (95% CI=0.71-0.80). No specific QEEG biomarker or specific treatment showed greater predictive power than the all-studies estimate in a meta-regression. Funnel plot analysis suggested substantial publication bias. Most studies did not use ideal practices. Conclusions: QEEG does not appear to be clinically reliable for predicting depression treatment response, as the literature is limited by underreporting of negative results, a lack of out-of-sample validation, and insufficient direct replication of previous findings. Until these limitations are remedied, QEEG is not recommended for guiding selection of psychiatric treatment.

SLEEP DISORDERS

Arns, M., Kenemans, JL. (2012). Neurofeedback in ADHD and insomnia: Vigilance stabilization through sleep spindles and circadian networks. Neuroscience Biobehavioral Review. In this review article an overview of the history and current status of neurofeedback for the treatment of ADHD and insomnia is provided. Recent insights suggest a central role of circadian phase delay, resulting in sleep onset insomnia (SOI) in a sub-group of ADHD patients. Chronobiological treatments, such as melatonin and early morning bright light, affect the suprachiasmatic nucleus. This nucleus has been shown to project to the noradrenergic locus coeruleus (LC) thereby explaining the vigilance stabilizing effects of such treatments in ADHD. It is hypothesized that both Sensori-Motor Rhythm (SMR) and Slow-Cortical Potential (SCP) neurofeedback impact on the sleep spindle circuitry resulting in increased sleep spindle density, normalization of SOI and thereby affect the noradrenergic LC, resulting in vigilance stabilization. After SOI is normalized, improvements on ADHD symptoms will occur with a delayed onset of effect. Therefore, clinical trials investigating new treatments in ADHD should include assessments at follow-up as their primary endpoint rather than assessments at outtake. Furthermore, an implication requiring further study is that neurofeedback could be stopped when SOI is normalized, which might result in fewer sessions.

Bell, J. S. (1979). The use of EEG theta biofeedback in the treatment of a patient with sleep-onset insomnia. *Biofeedback & Self Regulation*, 4(3), 229-236. In this report, the treatment of a 42-year-old female with a complaint of chronic sleep-onset insomnia is described. Following the unsuccessful use of relaxation training, treatment consisted of 11 sessions of EEG theta rhythm (4--7 Hz) biofeedback. Theta density and five sleepindices were monitored throughout baseline, placebo, and treatment sessions. A significant increase in theta density was accompanied by reports of a decrease in sleep latency and an increase in total sleep time. This improvement was maintained after withdrawal of medication and at 3-month follow-up.

Berner, I., Schabus, M., Wienerroither, T., & Klimesch, W. (2006). The significance of sigma neurofeedback training on sleep spindles and aspects of declarative memory. *Applied Psychophysiology & Biofeedback,* 31(2), 97-114. The functional significance of sleep spindles for overnight memory consolidation and general learning aptitude as well as the effect of four 10-minute sessions of spindle frequency (11.6-16 Hz, sigma) neurofeedback-training on subsequent sleep spindle activity and overnight performance change was investigated. Before sleep, subjects were trained on a paired-associate word list task after having received either neurofeedback training (NFT) or pseudofeedback training (PFT). Although NFT had no significant impact on subsequent spindle activity and behavioral outcomes, there was a trend for enhanced sigma band-power during NREM (stage 2 to 4) sleep after NFT as compared to PFT. Furthermore, a significant positive correlation between spindle activity during slow wave sleep (in the first night half) and overall memory performance was revealed. The results support the view that the considerable inter-individual variance in sleep spindle activity can at least be partly explained by differences in the ability to acquire new declarative information. We conclude that the short NFT before sleep was not sufficient to efficiently enhance phasic spindle activity and/or to influence memory processing. NFT was, however, successful in increasing sigma power, presumably because sigma NFT effects become more easily evident in actually trained frequency bands than in associated phasic spindle activity.

Coursey RD, Frankel BL, Gaarder KR, Mott DE. (1980). A comparison of relaxation techniques with electrosleep therapy for chronic, sleep-onset insomnia a sleep-EEG study. Biofeedback and Self-Regulation. Mar;5(1):57-73.
Two methods of relaxation therapy, electromyograph biofeedback and autogenic training, were compared to a nonrelaxation treatment, electrosleep therapy, in reducing sleep latency among 22 chronic, sleep-onset insomniacs. While none of the electrosleep patients improved on all-night laboratory electroencephalographic sleep records or daily home sleep logs, approximately one-half of the relaxation-treated patients showed marked improvement, which was sustained over a 1-month follow-up period. Although some sleep and treatment variables differentiated relaxation therapy responders from nonresponders, external stress appeared to be the most salient factor. Successful and unsuccessful patients could not be differentiated on any of the psychological variables studied.

Fedotchev A, Radchenko G, Zemlianaia A. (2018). On one approach to health protection: Music of the brain. J Integr Neurosci. 2018;17(3-4):309-315. doi: 10.3233/JIN-170053. PMID: 29060941. This review presents the current status of a method for prevention and timely correction of human functional disturbances that was first proposed by Russian neurologist Ya.I. Levin in 1998 and further developed by the authors. The approach is named "Music of the Brain" and is based on musical or music-like stimulation organized in strict accordance with the biopotentials of a patient's brain. Initial studies on the music of the brain approach were analyzed, and its limitations were noted. To enhance the efficiency and usability of the approach, several combinations of music therapy with neurofeedback technique - musical neurofeedback - were developed. Enhanced efficiency of the approach has been shown for correction of functional disturbances during pregnancy and for elimination of stress-induced states in high technology specialists. The use and advantages of musical neurofeedback technology for increasing human cognitive activity, correcting sleep disturbances and treatment of disorders of attention were verified. After further development and testing the approach may be suited for a wide range of therapeutic and rehabilitation procedures in the protection of public health.

Hammer, BU., Colbert, AP., Brown, KA., Llioi, EC. (2011). Neurofeedback for insomnia: a pilot study of Z-score SMR and individualized protocols. Applied Psychophysiology and Biofeedback, 36(4): 251-264. Insomnia is an epidemic in the US. Neurofeedback (NFB) is a little used, psychophysiological treatment with demonstrated usefulness for treating insomnia. Our objective was to assess whether two distinct Z-Score NFB protocols, a modified sensorimotor (SMR) protocol and a sequential, quantitative EEG (sQEEG)-guided, individually designed (IND) protocol, would alleviate sleep and associated daytime dysfunctions of participants with insomnia. Both protocols used instantaneous Z scores to determine reward condition administered when awake. Twelve adults with insomnia, free of other mental and uncontrolled physical illnesses, were randomly assigned to the SMR or IND group. Eight completed this randomized, parallel group, single-blind study. Both groups received fifteen 20-min sessions of Z-Score NFB. Pre-post assessments included sQEEG, mental health, quality of life, and insomnia status. ANOVA yielded significant post-treatment improvement for the combined group on all primary insomnia scores: Insomnia Severity Index (ISI $p<.005$), Pittsburgh Sleep Quality Inventory (PSQI $p<.0001$), PSQI Sleep Efficiency ($p<.007$), and Quality of Life Inventory ($p<.02$). Binomial tests of baseline EEGs indicated a significant proportion of excessively high levels of Delta and Beta power ($p<.001$) which were lowered post-treatment (paired z-tests $p<.001$). Baseline EEGs showed excessive sleepiness and hyperarousal, which improved post-treatment. Both Z-Score NFB groups improved in sleep and daytime functioning. Post-treatment, all participants were normal sleepers. Because there were no significant differences in the findings between the two groups, our future large scale studies will utilize the less burdensome to administer Z-Score SMR protocol.

Hoedlmoser, K., Pecherstorfer, T., Gruber, E., Anderer, P., Doppelmayr, M., Klimesch, W., & Schabus, M. (2008). Instrumental conditioning of human sensorimotor rhythm (12-15 Hz) and its impact on sleep as well as declarative learning. *Sleep*, 31(10), 1401-1408. Study Objectives: To test whether instrumental conditioning f sensorimotor rhythm (SMR; 12-15 Hz) has an impact on sleep parameters as well as declarative memory performance in humans. DESIGN: Randomized, parallel group design. SETTING: 10 instrumental conditioning sessions, pre- and post-treatment investigation including sleep evaluations. PARTICIPANTS: 27 healthy subjects (13 male) Interventions: SMR-conditioning (experimental group) or randomized-frequency conditioning (control group); declarative memory task before and after a 90-min nap. MEASUREMENT AND RESULTS: The experimental group was trained to enhance the amplitude of their SMR-frequency range, whereas the control group participated in a randomized-frequency conditioning program (i.e., every session a different 3-Hz frequency bin between 7 and 20 Hz). During pre- and post-treatment the subjects had to attend the sleep laboratory to take a 90-min nap (2:00-3:30 pm) and to perform a declarative memory task before and after sleep. The experimental design was successful in conditioning an increase in relative 12-15 Hz amplitude within 10 sessions ($d = 0.7$). Increased SMR activity was also expressed during subsequent sleep by eliciting positive changes in different sleep parameters (sleep spindle number [$d = 0.6$], sleep onset latency [$d = 0.7$]); additionally, this increased 12-15 Hz amplitude was associated with enhancement in retrieval score computed at immediate cued recall ($d = 0.9$). CONCLUSION: Relative SMR amplitude increased over 10 instrumental conditioning sessions (in the experimental group only) and this "shaping of one's own brain activity" improved

subsequent declarative learning and facilitated the expression of 12-15 Hz spindle oscillations during sleep. Most interestingly, these electrophysiological changes were accompanied by a shortened sleep onset latency.

Kinreich, S., Podipsky, I., Jamshy, S., Intrator, N. & Hendler, T. (2014). Neural dynamics necessary and sufficient for transition into pre-sleep induced by EEG neurofeedback. NeuroImage: Aug15(97). 19-28. The transition from being fully awake to pre-sleep occurs daily just before falling asleep; thus its disturbance might be detrimental. Yet, the neuronal correlates of the transition remain unclear, mainly due to the difficulty in capturing its inherent dynamics. We used an EEG theta/alpha neurofeedback to rapidly induce the transition into pre-sleep and simultaneous fMRI to reveal state-dependent neural activity. The relaxed mental state was verified by the corresponding enhancement in the parasympathetic response. Neurofeedback sessions were categorized as successful or unsuccessful, based on the known EEG signature of theta power increases over alpha, temporally marked as a distinct "crossover" point. The fMRI activation was considered before and after this point. During successful transition into pre-sleep the period before the crossover was signified by alpha modulation that corresponded to decreased fMRI activity mainly in sensory gating related regions (e.g. medial thalamus). In parallel, although not sufficient for the transition, theta modulation corresponded with increased activity in limbic and autonomic control regions (e.g. hippocampus, cerebellum vermis, respectively). The post-crossover period was designated by alpha modulation further corresponding to reduced fMRI activity within the anterior salience network (e.g. anterior cingulate cortex, anterior insula), and in contrast theta modulation corresponded to the increased variance in the posterior salience network (e.g. posterior insula, posterior cingulate cortex). Our findings portray multi-level neural dynamics underlying the mental transition from awake to pre-sleep. To initiate the transition, decreased activity was required in external monitoring regions, and to sustain the transition, opposition between the anterior and posterior parts of the salience network was needed, reflecting shifting from extra- to intrapersonal based processing, respectively.

Ninias, M., Kober, SE., Witte, M., Koschutnig, K. & Neuper, C. (2015) Brain volumetry and self-regulation of brain activity relevant for neurofeedback. Biological Psychology. http://dx.doi.org/10.1016/j.biopsycho.2015.07.009. Neurofeedback is a technique to learn to control brain signals by means of real time feedback. In the present study, the individual ability to learn two EEG neurofeedback protocols – sensorimotor rhythm and gamma rhythm – was related to structural properties of the brain. The volumes in the anterior insula bilaterally, left thalamus, right frontal operculum, right putamen, right middle frontal gyrus, and right lingual gyrus predicted the outcomes of sensorimotor rhythm training. Gray matter volumes in the supplementary motor area and left middle frontal gyrus predicted the outcomes of gamma rhythm training. These findings combined with further evidence from the literature are compatible with the existence of a more general self-control network, which through self-referential and self-control processes regulates neurofeedback learning.

Pérez-Elvira, R., Carrobles, J. A., López Bote, D. J., & Oltra-Cucarella, J. (2019). Efficacy of Live Z-Score neurofeedback training for chronic insomnia: A single-case study. NeuroRegulation, 6(2), 93–101. https://doi.org/10.15540/nr.6.2.93. Insomnia is the most common sleep disorder in the general population. Pharmacological treatments have shown efficacy in the short term, yet the symptoms return once the treatment has been withdrawn. In the search for treatment options with long-lasting effects, neurofeedback (NF) has arisen as a therapeutic option. Neurofeedback is the application of operant conditioning to brain activity. The aim of this work is to show the effectiveness of Live Z-Score NF training (LZT), a paradigm within the field of NF, in a case of insomnia. Participants: A 32-year-old male with chronic insomnia since his adolescence. Methods: Thirty 35-min sessions of qEEG-guided LZT using patient's highly preferred feedback. The main outcomes of this study were the patient's qEEG metrics and a visual analog scale of sleep quality throughout the intervention. Results: qEEG-guided LZT showed an improvement of 90.63% of the patient's qEEG metrics and an 82.55% relief of the clinical symptoms after 30 NF sessions. Conclusions: Although more research is needed to establish that NF based on Live Z-Score is effective for insomnia, our results suggest that NF might be a therapeutic alternative for the treatment of insomnia.

Reiner, M., Rozengurt, R. & Barnea, A. (2014). Better than sleep: Theta neurofeedback training accelerates memory consolidation. Biological Psychology:Jan;95(45). 45-53. Consistent empirical results showed that both night and day sleep enhanced memory consolidation. In this study we explore processes of consolidation of memory during awake hours. Since theta oscillations

have been shown to play a central role in exchange of information, we hypothesized that elevated theta during awake hours will enhance memory consolidation. We used a neurofeedback protocol, to enhance the relative power of theta or beta oscillations. Participants trained on a tapping task, were divided into three groups: neurofeedback theta; neurofeedback beta; control. We found a significant improvement in performance in the theta group, relative to the beta and control groups, immediately after neurofeedback. Performance was further improved after night sleep in all groups, with a significant advantage favoring the theta group. Theta power during training was correlated with the level of improvement, indicating a clear relationship between memory consolidation, and theta neurofeedback.

Sollfrank, T., Ramsay, A., Perdikis, S., Williamson, J., Murray-Smith, R., Leeb, R., Millan, JdR. & Kubler, A. (2015). The effects of multimodal and enriched feedback on SMR-BCI performance. Clinical Neurophysiology: 127(1). 490-498. Objective: This study investigated the effect of multimodal (visual and auditory) continuous feedback with information about the uncertainty of the input signal on motor imagery based BCI performance. A liquid floating through a visualization of a funnel (funnel feedback) provided enriched visual or enriched multimodal feedback. Methods: In a between subject design 30 healthy SMR-BCI naive participants were provided with either conventional bar feedback (CB), or visual funnel feedback (UF), or multimodal (visual and auditory) funnel feedback (MF). Subjects were required to imagine left and right hand movement and were trained to control the SMR based BCI for five sessions on separate days. Results: Feedback accuracy varied largely between participants. The MF feedback lead to a significantly better performance in session 1 as compared to the CB feedback and could significantly enhance motivation and minimize frustration in BCI use across the five training sessions. Conclusion: The present study demonstrates that the BCI funnel feedback allows participants to modulate sensorimotor EEG rhythms. Participants were able to control the BCI with the funnel feedback with better performance during the initial session and less frustration compared to the CB feedback. Significance: The multimodal funnel feedback provides an alternative to the conventional cursorbar feedback for training subjects to modulate their sensorimotor rhythms.

Schabus, M., Heib DP., Lechinger J., Griessenberger H., Klimesch W., Pawlizki A., Kunz AB., Sterman BM. & Hoedlmoser K. (2014). Enhancing sleep quality and memory in insomnia using instrumental sensorimotor rhythm conditioning. Biological Psychology Jan;95. 126-134. EEG recordings over the sensorimotor cortex show a prominent oscillatory pattern in a frequency range between 12 and 15 Hz (sensorimotor rhythm, SMR) under quiet but alert wakefulness. This frequency range is also abundant during sleep, and overlaps with the sleep spindle frequency band. In the present pilot study we tested whether instrumental conditioning of SMR during wakefulness can enhance sleep and cognitive performance in insomnia. Twenty-four subjects with clinical symptoms of primary insomnia were tested in a counterbalanced within-subjects-design. Each patient participated in a SMR- as well as a sham-conditioning training block. Polysomnographic sleep recordings were scheduled before and after the training blocks. Results indicate a significant increase of 12-15 Hz activity over the course of ten SMR training sessions. Concomitantly, the number of awakenings decreased and slow-wave sleep as well as subjective sleep quality increased. Interestingly, SMR-training enhancement was also found to be associated with overnight memory consolidation and sleep spindle changes indicating a beneficial cognitive effect of the SMR training protocol for SMR "responders" (16 out of 24 participants). Although results are promising it has to be concluded that current results are of a preliminary nature and await further proof before SMR-training can be promoted as a non-pharmacological approach for improving sleep quality and memory performance.

Sterman, MB., Shouse, MN. (1980). Quantitative analysis of training, sleep EEG and clinical response to EEG operant conditioning in epileptics. Electroencephalography and Clinical Neurophysiology, 49(5-6): 558-579. This report is a follow-up to a previous paper which described seizure rate changes with central cortical EEG feedback training in 8 poorly controlled epileptic subjects. Data examined here include associated training compliance and performance, sleep EEG spectra, clinical EEG and anticonvulsant blood levels. The study employed a double-cross-over, single blind ABA design applied to two subgroups of epileptic patients. Both groups had in common two training periods (A1, A2) in which either 12--15 c/sec (subgroup I, n = 4) or 18--23 c/sec (subgroup II, n = 4) was reinforced in the absence of 6--9 c/sec, movement or epileptiform discharge, and one training period (B) in which 6--9 c/sec was reinforced in the absence of 12--15 or 18--23 c/sec as well as movement and epileptiform discharge. Training

periods occurred primarily in the home and lasted 3 months. Compliance with training instructions and response acquisition were demonstrated. Overall anticonvulsant blood levels were low and unrelated to EEG or seizure changes. Clinical EEG findings corresponded to sleep EEG and seizure rate outcomes. Power spectral analysis of sampled non-REM sleep from all-night EEG recordings obtained after each training phase indicated contingency specific changes which were limited to sensorimotor recordings in subgroup I and corresponded to the pattern of seizure rate changes in this group. EEG changes were also limited to sensorimotor cortex in subgroup II, but were linear and paralleled a progressive decrease in seizure rate. Both groups, however, showed the same pattern of EEG changes with seizure reductions; low and high frequencies were reduced and intermediate, rhythmic frequencies increased. Correlational analysis confirmed this relationship. The pattern, duration and topographic specificity of these changes suggested a normalization of sensorimotor EEG substrates related to the EEG feedback training.

Sterman MB. (1977). Sensorimotor EEG operant conditioning: experimental and clinical effects. ***The Pavlovian Journal of Biological Science*****. Apr-Jun;12(2):63-92.** (No abstract available.)

SUBSTANCE ABUSE AND ADDICTION DISORDERS

Arani, FD., Rostami, R., Nostratabadi, M. (2012). Effectiveness of neurofeedback training as a treatment for opioid-dependent patients. *Clinical EEG and Neuroscience*:41(3). 170-177. Neurofeedback (NF) training has been employed as a therapeutic method in substance-dependence disorder over the last three decades. The purpose of the present study was to examine the effectiveness of this method on improvement of comorbid neuro-psychological syndromes in opioid-dependence disorder. Psychopathological and craving dimensions and brain activity signals of 20 opioid dependent patients were measured using Symptom Checklist-90-Revised (SCL-90-R), Heroin Craving Questionnaire (HCQ), and Quantitative Electroencephalography (QEEG). All the patients were undergoing pharmacotherapy. They were assigned to two groups that were matched based on SCL-90-R scores, education and age. The experimental group received 30 sessions of NF training in addition to their medicine. The control group received only the usual pharmacotherapy. The probable changes were monitored by reappraisal of all the patients after the treatment. We hypothesized that patients in the experimental group would show more reduction in their comorbid syndromes. The Multivariate Analysis of Covariance (MANCOVA) showed that the experimental group, in comparison with control group, showed significantly more improvement in all three outcome measures. In the SCL-90-R, improvement was noted with the hypochondriacs, obsession, interpersonal sensitivity, aggression, psychosis, and general symptomatic indexes. In the HCQ, improvement was found in the anticipation of positive outcome, desire to use substance, and total average score. Finally, the QEEG showed positive changes in frontal, central and parietal delta, frontal and central theta, parietal alpha and frontal and central Sensory Motor Rhythm (SMR) amplitudes. This study suggests that NF can be used as a therapeutic method to ameliorate abnormalities related to opioid-dependence disorders. The results emphasize the importance of neuropsychological interventions in treatment of substance-dependence disorders.

Burkett, V. S., Cummins, J. M., Dickson, R. M., & Skolnick, M. (2005). An open clinical trial utilizing real-time EEG operant conditioning as an adjunctive therapy in the treatment of crack cocaine dependence. *Journal of Neurotherapy*, 9(2), 27-48. Electroencephalographic (EEG) biofeedback has been employed in substance use disorder (SUD) over the last three decades. The SUD is a complex series of disorders with frequent comorbidities and EEG abnormalities of several types. EEG biofeedback has been employed in conjunction with other therapies and may be useful in enhancing certain outcomes of therapy. Based on published clinical studies and employing efficacy criteria adapted by the Association for Applied Psychophysiology and Biofeedback and the International Society for Neurofeedback and Research, alpha theta training—either alone for alcoholism or in combination with beta training for stimulant and mixed substance abuse and combined with residential treatment programs, is probably efficacious. Considerations of further research design taking these factors into account are discussed and descriptions of contemporary research are given.

Callaway, T.G., Bodenhamer-Davis, E. (2008). Long-term follow-up of a clinical replication of the Peniston Protocol for chemical dependency. *Journal of Neurotherapy* 12(4), 243 – 259. *Introduction*. This study is a long-term follow-up of an early replication of the Peniston EEG biofeedback (EEG-BFB) Protocol for chemical dependency (Peniston & Kulkosky, 1989, 1990). *Method*. This clinical trial included 16 chemically dependent adult participants treated with the Peniston Protocol in a university outpatient clinic between 1993 and 1995. Ten participants were probationers classified as high risk for rearrest. Treatment effects were assessed using pre/posttreatment measures (Beck Depression Inventory, Minnesota Multiphasic Personality Inventory-2) and long-term follow-up of abstinence and rearrest rates. Probationer rearrest rates were compared to an equivalent probation sample ($n = 24$) that did not receive EEG-BFB. *Results*. Initial Beck Depression Inventory scores indicated mild/moderate depression but were significantly reduced posttreatment to within normal limits. Substantial differences were noted posttreatment on 7 Minnesota Multiphasic Personality Inventory-2 clinical scales suggesting less psychopathology following treatment. Long-term (74–98 months) follow-up indicated that 81.3% ($n = 13$) participants were abstinent. Rearrest rates and probation revocations for the probationer subgroup were lower than the

comparison group (40% vs. 79.16%). *Conclusion*. This study provides evidence of the durability of Peniston Protocol results over time but has the usual limitations of a clinical trial with a small sample, nonrandomized, and uncontrolled design. Implications for further research are discussed including the relevance of recent modifications to the Peniston Protocol and qEEG–based protocols in treating substance abuse.

Cannon, R., Lubar, J., Sokhadze, E., & Baldwin, D. (2008). LORETA Neurofeedback for addiction and the possible neurophysiology of psychological processes influenced: A Case Study and region of interest (ROI) analysis of LNFB in right anterior cingulate cortex (ACC). ***Journal of Neurotherapy*****,12(4), 227-242.** Introduction. This case study explores the efficacy of low-resolution electromagnetic tomographic (LORETA) neurofeedback (LNFB) in the right anterior cingulate cortex (ACC) as a method for addiction treatment and examines the frequency specific effects of this training in eight other regions of the cortex identified as playing an important role in substance use disorders. Methods. This case study was completed with one right-handed, 28-year-old female participant with 3 years of continuous abstinence from polysubstance abuse; her drugs of choice were heroin and alcohol, and she reported an 8-year history of alcohol abuse and a 4-year history of heroin use (IV). She completed 25 sessions of LNFB training in which she increased 14–18 Hz activity in the right ACC. We utilized electrophysiological measures to assess the increase or decrease in eight regions of interest (ROI): the right hippocampus, the right amygdaloid complex, the right orbitofrontal cortex (OFC), the right occipital lobe, the right insular cortex, the right uncus, and two regions in the left prefrontal cortex and compared them using complex linear mixed model and partial correlation procedures. Results. The data indicate significant associations between these limbic and cortical regions. The linear increase in the right ACC was in the desired direction; however, this will require more than 25 sessions to reach significance. The effects of training in the right ACC show significant increase and decrease for all frequencies in specific regions of interest. Conclusion. This is the first study of its kind to explore the relationship between these nine ROI as influenced by LNFB in the right ACC. The data suggest that these regions may play an intricate role in behaviors and characteristics involved in addiction; specific changes in the alpha frequency in limbic regions and increases in associations between regions in the theta frequency may influence personality and other behaviors associated with addictive traits. This case study illustrates the possible neural mechanisms involved in the negative self-reference associated with addiction even after a significant period of abstinence and possibly offers insight into antecedents to the onset of substance use disorders.

Cabrera EA, Wiers CE, Lindgren E, Miller G, Volkow ND, Wang GJ. Neuroimaging the Effectiveness of Substance Use Disorder Treatments. J Neuroimmune Pharmacol. 2016 Sep;11(3):408-33. doi: 10.1007/s11481-016-9680-y. Epub 2016 May 16. PMID: 27184387. Neuroimaging techniques to measure the function and biochemistry of the human brain such as positron emission tomography (PET), proton magnetic resonance spectroscopy ((1)H MRS), and functional magnetic resonance imaging (fMRI), are powerful tools for assessing neurobiological mechanisms underlying the response to treatments in substance use disorders. Here, we review the neuroimaging literature on pharmacological and behavioral treatment in substance use disorder. We focus on neural effects of medications that reduce craving (e.g., naltrexone, bupropion hydrochloride, baclofen, methadone, varenicline) and that improve cognitive control (e.g., modafinil, N-acetylcysteine), of behavioral treatments for substance use disorders (e.g., cognitive bias modification training, virtual reality, motivational interventions) and neuromodulatory interventions such as neurofeedback and transcranial magnetic stimulation. A consistent finding for the effectiveness of therapeutic interventions identifies the improvement of executive control networks and the dampening of limbic activation, highlighting their values as targets for therapeutic interventions in substance use disorders.

Casanova, M., Baryth, J., El-Baz, A., Tasman, A., Sears, L., & Sokhadze, E. (2012). Repetitive transcranial magnetic stimulation (rTMS) modulates event-related potential (ERP) indices of attention in autism. ***Translational Neuroscience*****, 3(2) 170-180.** In our previous study on individuals with autism spectrum disorder (ASD) (Sokhadze et al., Appl Psychophysiol Biofeedback 34:37-51, 2009a) we reported abnormalities

in the attention-orienting frontal event-related potentials (ERP) and the sustained-attention centro-parietal ERPs in a visual oddball experiment. These results suggest that individuals with autism over-process information needed for the successful differentiation of target

and novel stimuli. In the present study we examine the effects of low-frequency, repetitive Transcranial Magnetic Stimulation (rTMS) on novelty processing as well as behavior and social functioning in 13 individuals with ASD. Our hypothesis was that low-frequency rTMS application to dorsolateral prefrontal cortex (DLFPC) would result in an alteration of the cortical excitatory/inhibitory balance through the activation of inhibitory GABAergic double bouquet interneurons. We expected to find post-TMS differences in amplitude and latency of early and late ERP components. The results of our current study validate the use of low-frequency rTMS as a modulatory tool that altered the disrupted ratio of cortical excitation to inhibition in autism. After rTMS the parieto-occipital P50 amplitude decreased to novel distracters but not to targets; also the amplitude and latency to targets increased for the frontal P50 while decreasing to non-target stimuli. Low-frequency rTMS minimized early cortical responses to irrelevant stimuli and increased responses to relevant stimuli. Improved selectivity in early cortical responses lead to better stimulus differentiation at later-stage responses as was made evident by our P3b and P3a component findings. These results indicate a significant change in early, middle-latency and late ERP components at the frontal, centro-parietal, and parieto-occipital regions of interest in response to target and distracter stimuli as a result of rTMS treatment. Overall, our preliminary results show that rTMS may prove to be an important research tool or treatment modality in addressing the stimulus hypersensitivity characteristic of autism spectrum disorders.

Clemans, Z., El-Baz, A., Hollifield, M., & Sokhadze, E. (2012). Single trial time-frequency analysis of error processing in PTSD. *Neuroscience Letters*. E-publication. http://dx.doi.org/10.1016/j.neulet.2012.07.051. Error processing studies in psychology and psychiatry are relatively common. Event-related potentials (ERPs) are often used as measures of error processing, two such response-locked ERPs being the error-related negativity (ERN) and the error-related positivity (Pe). The ERN and Pe occur following committed error in reaction time tasks as low frequency (4-8 Hz) electroencephalographic (EEG) oscillations registered at the midline fronto-central sites. We created an alternative method for analyzing error processing using time-frequency analysis in the form of a wavelet transform. A study was conducted in which subjects with PTSD and healthy control completed a forced-choice task. Single trial EEG data from errors in the task were processed using a continuous wavelet transform. Coefficients from the transform that corresponded to the theta range were averaged to isolate a theta waveform in the time-frequency domain. Measures called the time-frequency ERN and Pe were obtained from these waveforms for five different channels and then averaged to obtain a single time-frequency ERN and Pe for each error trial. A comparison of the amplitude and latency for the time-frequency ERN and Pe between the PTSD and control group was performed. A significant group effect was found on the amplitude of both measures. These results indicate that the developed single trial time-frequency error analysis method is suitable for examining error processing in PTSD and possibly other psychiatric disorders.

deBeus, R. J. (2007). Quantitative electroencephalography-guided versus Scott/Peniston neurofeedback with substance abuse outpatients: A pilot study. *Applied Psychophysiology and Biofeedback*, 35(4), 146-151. Electroencephalographic (EEG) biofeedback has been employed in substance use disorder (SUD) over the last three decades. The SUD is a complex series of disorders with frequent comorbidities and EEG abnormalities of several types. EEG biofeedback has been employed in conjunction with other therapies and may be useful in enhancing certain outcomes of therapy. Based on published clinical studies and employing efficacy criteria adapted by the Association for Applied Psychophysiology and Biofeedback and the International Society for Neurofeedback and Research, alpha theta training—either alone for alcoholism or in combination with beta training for stimulant and mixed substance abuse and combined with residential treatment programs, is probably efficacious. Considerations of further research design taking these factors into account are discussed and descriptions of contemporary research are given.

Dehghani-Arani F, Rostami R & Nadali H. (2013). Neurofeedback training for opiate addiction: improvement of mental health and craving. Appl Psychophysiol Biofeedback. 2013 Jun;38(2):133-41. doi: 10.1007/s10484-013-9218-5. Psychological improvements in patients with substance use disorders have been reported after neurofeedback treatment. However, neurofeedback has not been commonly accepted as a treatment for substance dependence. This study was carried out to examine the effectiveness of this therapeutic method for opiate dependence disorder. The specific aim was to investigate whether treatment leads to any changes in mental health and substance craving. In this experimental study with a pre-post test design, 20 opiate dependent patients undergoing Methadone or Buprenorphine maintenance treatment were examined and matched and randomized into two groups. While both experimental and control groups received their usual maintenance treatment, the experimental group received 30 sessions of neurofeedback treatment in

addition. The neurofeedback treatment consisted of sensory motor rhythm training on Cz, followed by an alpha-theta protocol on Pz. Data from the general health questionnaire and a heroin craving questionnaire were collected before and after treatment. Multivariate analysis of covariance showed that the experimental group achieved improvement in somatic symptoms, depression, and total score in general mental health; and in anticipation of positive outcome, desire to use opioid, and relief from withdrawal of craving in comparison with the control group. The study supports the effectiveness of neurofeedback training as a therapeutic method in opiate dependence disorder, in supplement to pharmacotherapy.

Fahrion, S. L., Walters, E. D., Coyne, L., & Allen, T. (1992). Alterations in EEG amplitude, personality factors and brain electrical mapping after alpha theta brainwave training: A controlled case study of an alcoholic in recovery. ***Alcoholism: Clinical & Experimental Research*****, 16, 547-552.** A controlled case study was conducted of effects of EEG alpha and theta brainwave training with a recovering alcoholic patient who experienced craving and fear of relapse after 18 months of abstinence. Training consisted of six sessions of thermal biofeedback to increase central nervous system (CNS) relaxation. Effects were documented with pretreatment and post-treatment personality testing, 20-channel digitized EEG evaluations both under relaxed conditions and under stress, minute-by-minute physiologic recordings of autonomic and EEG data during each training session, blood pressure, and heart rate indications taken both during relaxation and under stress, and by clinical observation. Results replicated those of a previous controlled study with chronic alcoholic patients not abstinent prior to treatment. New findings include post-treatment indications of more relaxed CNS functioning under stress, and of reduced autonomic activation both during relaxation and under stress. Brain-mapping indications of anxiety associated with painful cold-pressor stimulation were seen only in the pretest readings; at post-test the brain map indicated pain-associated EEG activity in the contralateral somatosensory area, but no apparent anxiety-associated EEG activity. At 4 months post-treatment the patient's wife and colleagues report the patient appears to function in a more relaxed way under the impact of stress, and he reports no longer experiencing craving for alcohol. Overall, support is provided for the possibility that alpha and theta brainwave training may be a useful intervention for the abstinent alcoholic experiencing stress-related craving and fear of relapse.

Faridi, A., Taremian, F., Thatcher, R. W., Dadashi, M., Moloodi, R. (2020). Comparison of LORETA Z score Neurofeedback and Cognitive Rehabilitation in terms of their Effectiveness in Reducing Craving in Opioid Addicts. Basic and Clinical Neuroscience. Just Accepted publication Oct. 3, 2020. Doi: http://dx.doi.org/10.32598/bcn.12.1.1946.1 DOI: http://dx.doi.org/10.32598/bcn.12.1.1946.1. Background: Previous studies have shown that conventional neurofeedback and cognitive modification treatments have led to numerous psychological improvements in patients suffering from substance use disorders. However, effectiveness of LORETA (Low-Resolution Brain Electromagnetic Tomography) Z score neurofeedback (LZNFB) and Cognitive rehabilitation therapy on reducing of opium craving has yet to be investigated. Thus, aim of the present study was to compare effectiveness of LZNFB and Cognitive rehabilitation therapy with methadone maintenance treatment (MMT) in reduction of opium craving in patients with opioid use disorder. Methods: Thirty patients with opioid use disorder undergoing MMT were randomly assigned into three groups: LZNFB with MMT, Cognitive rehabilitation with MMT (as experimental groups), and MMT alone Control group. The LZNFB and Cognitive rehabilitation groups received 20 and 15 sessions of treatment, respectively. The three groups were assessed using a number of questionnaires as well as Dot-Probe Task at pre-test, post-test, and one-month follow-up. Results: The results showed that both experimental groups accomplished significantly greater reduction in opium craving than MMT alone group at post-test and follow up ($P<0.05$). The LZNFB with MMT group showed higher decrease in opioid craving than the Cognitive rehabilitation with MMT group. In addition, Cognitive rehabilitation group experienced greater improvement on attentional bias towards craving cues than LZNFB with MMT group at post-test and follow up. Finally, LZNFB with MMT group and Cognitive rehabilitation with MMT group got higher scores on the recovery assessment scale than MMT alone group at post-test and follow up. According to results of this study, LZNFB training is more effective than Cognitive Rehabilitation in decreasing of craving and improving quality of life in addiction to opioids. Conclusion: The findings of the current study provided preliminary support for the effectiveness of LZNFB and Cognitive rehabilitation on reduction of opium craving, improvement of attentional bias towards craving cues and quality of life among Iranian opioids use patients.

Goldberg, R. J., et al. (1976). Alpha conditioning as an adjunct treatment for drug dependence: Part I. *International Journal of Addiction*, 11, 1085-1089. The effects of alpha conditioning on the habits of four methadone-maintained patients were assessed. All four learned some control over alpha activity in the 5-week, 10-session training period. The most striking results, however, related to the subjects' substitution of self-initiated mental states associated with alpha for previously used drug-seeking or self-medicating methods of coping with everyday problem situations. All four subjects reported a decrease in illicit drug usage and an increased feeling of self-control. Verification of improvement in adjustment and drug abuse was shown by counseling reports and narcotic screens from the maintenance program.

Gross, E., El-Baz, A. S., Sokhadze, G. E., Sears, L., Casanova, M. F., & Sokhadze, E. M. (2012). Induced EEG gamma oscillation alignment improves differentiation between autism and ADHD group responses in facial categorization task. *Journal of Neurotherapy*, 16, 78-91. Children diagnosed with an autism spectrum disorder (ASD) often lack the ability to recognize and properly respond to emotional stimuli. Emotional deficits also characterize children with attention deficit/hyperactivity disorder (ADHD), in addition to exhibiting limited attention span. These abnormalities may effect a difference in the induced EEG gamma wave burst (35–45 Hz) peaked approximately 300–400 ms following an emotional stimulus. Because induced gamma oscillations are not fixed at a definite point in time poststimulus, analysis of averaged EEG data with traditional methods may result in an attenuated gamma burst power. We used a data alignment technique to improve the averaged data, making it a better representation of the individual induced EEG gamma oscillations. A study was designed to test the response of a subject to emotional stimuli, presented in the form of emotional facial expression images. In a four-part experiment, the subjects were instructed to identify gender in the first two blocks of the test, followed by differentiating between basic emotions in the final two blocks (i.e., anger vs. disgust). EEG data were collected from ASD ($n = 10$), ADHD ($n = 9$), and control ($n = 11$) subjects via a 128-channel EGI system, and processed through a continuous wavelet transform and bandpass filter to isolate the gamma frequencies. A custom MATLAB code was used to align the data from individual trials between 200 and 600 ms poststimulus, EEG site, and condition by maximizing the Pearson product–moment correlation coefficient between trials. The gamma power for the 400-ms window of maximum induced gamma burst was then calculated and compared between subject groups. Condition (anger/disgust recognition, gender recognition) × Alignment × Group (ADHD, ASD, Controls) interaction was significant at most of parietal topographies (e.g., P3-P4, P7-P8). These interactions were better manifested in the aligned data set. Our results show that alignment of the induced gamma oscillations improves sensitivity of this measure in differentiation of EEG responses to emotional facial stimuli in ADHD and ASD.

Hanlon CA., Hartwell KJ., Canterberry M., Li X., Owens M., Lematty T., Prisciandaro JJ., Borckardt J., Brady KT. & George MS. (2013). Reduction of cue-induced craving through real time neurofeedback in nicotine users: The role of region of interest selection and multiple visits. Psychiatry Res. 2013 Jul 30;213(1):79-81. doi: 10.1016/j.pscychresns.2013.03.003. This multi-visit, real-time functional magnetic resonance imaging feedback study demonstrates that treatment-seeking smokers can effectively modulate their behavioral and brain responses to smoking cues. They are more effective at decreasing activity in functionally defined regions involved in "craving" (e.g. ventral anterior cingulate cortex [vACC]) rather than increasing activity in regions involved in "resisting" (e.g. dorsal medial prefrontal cortex [dmPFC]).

Horrell, T., El-Baz, A., Baruth, J., Tasman, A., Sokhadze, G., Stewart, C., & *Sokhadze, E.* (2010). Neurofeedback effects on evoked and induced EEG gamma band reactivity to drug -related cues in cocaine addiction. *Journal of Neurotherapy*, 14(3), 195-216. Introduction. Preoccupation with drug and drug-related items is a typical characteristic of cocaine addicted individuals. It has been shown in multiple accounts that prolonged drug use has a profound effect on the EEG recordings of drug addicts when compared to controls during cue reactivity tests. Cue reactivity refers to a phenomenon in which individuals with a history of drug abuse exhibit excessive psychophysiological responses to cues associated with their drug of choice. One of the aims of this pilot study was to determine the presence of an attentional bias to preferentially process drug-related cues using evoked and induced gamma reactivity measures in cocaine addicts before and after biobehavioral treatment based on neurofeedback. Another aim was to show that central sensorimotor rhythm (SMR) amplitude increase and frontal theta control is possible in an experimental outpatient drug users group over 12

neurofeedback sessions. Method. Ten current cocaine abusers participated in this pilot research study using neurofeedback combined with Motivational Interviewing sessions. Eight of them completed all planned pre- and postneurofeedback cue reactivity tests with event-related EEG recording and clinical evaluations. Cue reactivity test represented a visual oddball task with images from the International Affective Picture System and drug-related pictures. Evoked and induced gamma responses to target and nontarget drug cues were analyzed using wavelet analysis. Results. Outpatient participants with cocaine addiction completed the biobehavioral intervention and successfully increased SMR while keeping theta practically unchanged in 12 sessions of neurofeedback training. The addition of Motivational Interviewing helped retain patients in the study. Clinical evaluations immediately after completion of the treatment showed decreased self-reports on depression and stress scores, and urine tests collaborated reports of decreased use of cocaine and marijuana. Effects of neurofeedback resulted in a lower EEG gamma reactivity to drug-related images in a postneurofeedback cue reactivity test. In particular, evoked gamma showed decreases in power to nontarget and to a lesser extent target drug-related cues at all topographies (left, right, frontal, parietal, medial, inferior), whereas induced gamma power decreased globally to both target and nontarget drug cues. Our findings supported our hypothesis that gamma band cue reactivity measures are sufficiently sensitive functional outcomes of neurofeedback treatment. Both evoked and induced gamma measures were found capable to detect changes in responsiveness to both target and nontarget drug cues. Conclusion. Our study emphasizes the utility of cognitive neuroscience methods based on EEG gamma band measures for the assessment of the functional outcomes of neurofeedback-based biobehavioral interventions for cocaine use disorders. This approach may have significant potential for identifying both physiological and clinical markers of treatment progress. The results confirmed our prediction that EEG changes achieved with neurofeedback training will be accompanied by positive EEG outcomes in a cue reactivity and clinical improvements.

Keith, JR., Ragpay, L., Theodore, D., Schwartz, JM & Ross, JL. (2014). An assessment of an automated EEG biofeedback system for attention deficits in a substance use disorders residential treatment setting. Psychology of Addiction Behaviors: Sept 2014 Early e-pub. Attention deficits are prevalent among individuals with substance use disorders and may interfere with recovery. The present study evaluated the effectiveness of an automated electroencephalogram (EEG) biofeedback system in recovering illicit substance users who had attention deficits upon admission to a comprehensive residential treatment facility. All participants (n = 95) received group, family, and individual counseling. Participants were randomly assigned to 1 of 3 groups that either received 15 sessions of automated EEG biofeedback (AEB), 15 sessions of clinician guided EEG biofeedback (CEB), or 15 additional therapy sessions (AT). For the AEB and CEB groups, operant contingencies reinforced EEG frequencies in the 15-18 Hz (β) and 12-15 Hz (sensorimotor rhythm, "SMR") ranges and reduce low frequencies in the 1-12 Hz (Δ, θ, and α) and 22-30 Hz (high β) ranges. The Test of Variables of Attention (TOVA), a "Go-NoGo" task, was the outcome measure. Attention scores did not change on any TOVA measure in the AT group. Reaction time variability, omission errors, commission errors, and d' improved significantly (all p values < .01) in the AEB and CEB groups. AEB and CEB did not differ significantly from each other on any measure. The results demonstrate that automated neurofeedback can effectively improve attention in recovering illicit substance users in the context of a comprehensive residential substance abuse treatment facility.

Kelly, M. J. (1997). Native Americans, neurofeedback, and substance abuse theory: Three year outcome of alpha/theta neurofeedback training in the treatment of problem drinking among Dine' (Navajo) people. *Journal of Neurotherapy,* 2(3), 24-60. This three year follow-up study presents the treatment outcomes of 19 Dine' (Navajo) clients who completed a culturally sensitive, alpha/theta neurofeedback training program. In an attempt to both replicate the earlier positive studies of Peniston (1989) and to determine if neurofeedback skills would significantly decrease both alcohol consumption and other behavioral indicators of substance abuse, these participants received an average of 40 culturally modified neurofeedback training sessions. This training was adjunctive to their normal 33 day residential treatment. According to DSM-IV criteria for substance abuse, 4 (21%) participants now meet criteria for "sustained full remission", 12 (63%) for "sustained partial remission", and 3 (16%) still remain "dependent" (American Psychiatric Association, 1994). The majority of participants also showed a significant increase in "level of functioning" as measured by the DSM-IV Axis V GAF. Subjective reports from participants indicated that their original neurofeedback training had been both enjoyable and self-empowering; an experience generally different from their usual treatment routine of talk-therapy and education. This internal training also appeared to naturally stimulate significant, but subtle, spiritual experiences and to be naturally compatible with traditional Navajo

cultural and medicine-ways. At the three-year follow-up interview, participants typically voiced that these experiences, and their corresponding insights, had been helpful both in their ability to cope and in their sobriety. From an outside perspective, experienced nurses also reported unexpected behavioral improvements during the participant's initial training. Additionally, administrators and physicians generally found the objective feedback and verification quality of neurofeedback protocols compatible with their own beliefs. An attempt has also been made to conceptualize the outcome analysis of this study within both a culturally specific and universal socio/bio/ environmental context.

Lackner, N., Unterrainer, H. F., Skliris, D., Wood, G., Wallner-Liebmann, S. J., Neuper, C., & Gruzelier, J. H. (2016). The Effectiveness of Visual Short-Time Neurofeedback on Brain Activity and Clinical Characteristics in Alcohol Use Disorders: Practical Issues and Results. Clinical EEG and neuroscience, 47(3), 188–195. https://doi.org/10.1177/1550059415605686. The present study was carried out to examine the efficacy of alpha/theta neurofeedback (NF) with a new visual paradigm in a cohort of alcohol use disordered (AUD) patients (n = 25) treated in an Austrian therapeutic community center. The experimental study design focused on changes in absolute and relative resting EEG band power as well as in clinical variables, including depression (Beck Depresion Inventory [BDI-V]), psychiatric symptoms (Brief Symptom Inventory [BSI], coping (Freiburg Questionnaire on Coping with Illness [FKV-lis]), psychotherapy motivation (Therapy Motivation Questionnaire [FPTM-23]), sense of coherence (Sense of Coherence Scale [SOC-13]), posttraumatic growth (Posttraumatic Growth Inventory [PPR]), and alcohol cravings (Alcohol Craving Questionnaire [ACQ]). For measuring training effects, participants were randomly allocated to 2 groups: an experimental group (EG, n = 13) and a control group (CG, n = 12). Patients in EG received 12 sessions of visual NF training over a period of 6 weeks to enhance alpha (8-12 Hz) and theta (4-7 Hz) frequency band power in addition to the standard treatment program of the rehabilitation center. Participants in CG received no additional NF intervention. The multivariate analysis of covariance (MANCOVA) showed a change by trend in absolute alpha and theta power in the EG. Even though no MANCOVA effects were found in the clinical scales, AUD patients reported increasing control of their brain activity during the course of NF. However, changes in several clinical scales (BDI-V, BSI, FKV-lis, PPR) from pre- to posttest were observed only in the EG contrary to the CG. The findings of this pilot study provide first evidence for the practicality and effectiveness of visual short-term NF as an additive intervention in the therapeutic community.

Lamontague, Y., Hand, I., Annable, L., et al. (1975). Physiological and psychological effects of alpha and EMG feedback training with college drug users: A pilot study. *Canadian Psychiatric Association Journal*, 20, 337-349. Twenty-four volunteer college students who were regular drug users were randomly allocated to three training groups of equal size: alpha feedback, EMG feedback and a yoked control group. The subjects were unaware of which feedback condition they received and were asked to practice at home during a six-month follow-up period in order to achieve a relaxed state similar to that experienced during training. No group was successful in retaining gains made in their alpha levels during each session, but the EMG group significantly reduced their muscular activity during training and retained the improvement during follow-up. The alpha and yoked groups did not greatly improve their EMG during training but at follow-up achieved the same levels as the EMG group. There was evidence to suggest that a reduction in drug use among light and medium users was maintained during follow-up. Significant and lasting improvements were made by each group in the duration and quality of their sleep and anxiety levels were reduced.

Luigjes J, Segrave R, de Joode N, Figee M, Denys D. (2019) Efficacy of Invasive and Non-Invasive Brain Modulation Interventions for Addiction. Neuropsychol Rev. 2019 Mar;29(1):116-138. doi: 10.1007/s11065-018-9393-5. Epub 2018 Dec 7. PMID: 30536145; PMCID: PMC6499746. It is important to find new treatments for addiction due to high relapse rates despite current interventions and due to expansion of the field with non-substance related addictive behaviors. Neuromodulation may provide a new type of treatment for addiction since it can directly target abnormalities in neurocircuits. We review literature on five neuromodulation techniques investigated for efficacy in substance related and behavioral addictions: transcranial direct current stimulation (tDCS), (repetitive) transcranial magnetic stimulation (rTMS), EEG, fMRI neurofeedback and deep brain stimulation (DBS) and additionally report on effects of these interventions on addiction-related cognitive processes. While rTMS and tDCS, mostly applied at the dorsolateral prefrontal cortex, show reductions in immediate craving for various addictive substances, placebo-responses are high and long-term outcomes are understudied. The lack in well-designed EEG-neurofeedback studies despite decades of investigation impedes conclusions

about its efficacy. Studies investigating fMRI neurofeedback are new and show initial promising effects on craving, but future trials are needed to investigate long-term and behavioral effects. Case studies report prolonged abstinence of opioids or alcohol with ventral striatal DBS but difficulties with patient inclusion may hinder larger, controlled trials. DBS in neuropsychiatric patients modulates brain circuits involved in reward processing, extinction and negative-reinforcement that are also relevant for addiction. To establish the potential of neuromodulation for addiction, more randomized controlled trials are needed that also investigate treatment duration required for long-term abstinence and potential synergy with other addiction interventions. Finally, future advancement may be expected from tailoring neuromodulation techniques to specific patient (neurocognitive) profiles.

Markiewcz R. (2017) The use of EEG Biofeedback/Neurofeedback in psychiatric rehabilitation. Psychiatr Pol. 2017 Dec 30;51(6):1095-1106. English, Polish. doi: 10.12740/PP/68919. Epub 2017 Dec 30. PMID: 29432505. The aim of the systematic review was to evaluate the use of EEG Biofeedback/Neurofeedback in patients treated for mental disorders. The review covered publications analyzing influences and effects of therapy in patients receiving psychiatric treatment based on EEG Biofeedback/Neurofeedback. Selection of publications was made by searching PubMed and Scopus databases. 328 records concerning applications of the presented method were identified in total, including 84 records for patients diagnosed with mental disorders. The analysis of studies indicates that EEG Biofeedback/Neurofeedback is used for treatment of neurological, somatic and mental disorders. Its psychiatric applications for clinically diagnosed disorders include treatmentof depression, anorexia, dyslexia, dysgraphia, ADD, ADHD, schizophrenia, abuse of substances, neuroses, PTSD, and Alzheimer's disease. Research results imply that the neuromodulating effect of the therapy positively influences cognitive processes, mood, and anxiety levels. Positive effects of EEG Biofeedback confirm usefulness of this method as a main or auxiliary method in treatment of people with mental disorders. On the basis of conducted studies, it is worthwhile to consider inclusion of this method into the comprehensive neurorehabilitation activities.

Pandria N, Kovatsi L, Vivas AB, Bamidis PD. (2016). Resting-state Abnormalities in Heroin-dependent Individuals. Neuroscience. 2018 May 15;378:113-145. doi: 10.1016/j.neuroscience.2016.11.018. Epub 2016 Nov 21. PMID: 27884551. Drug addiction is a major health problem worldwide. Recent neuroimaging studies have shed light into the underlying mechanisms of drug addiction as well as its consequences to the human brain. The most vulnerable, to heroin addiction, brain regions have been reported to be specific prefrontal, parietal, occipital, and temporal regions, as well as, some subcortical regions. The brain regions involved are usually linked with reward, motivation/drive, memory/learning, inhibition as well as emotional control and seem to form circuits that interact with each other. So, along with neuroimaging studies, recent advances in resting-state dynamics might allow further assessments upon the multilayer complexity of addiction. In the current manuscript, we comprehensively review and discuss existing resting-state neuroimaging findings classified into three overlapping and interconnected groups: functional connectivity alterations, structural deficits and abnormal topological properties. Moreover, behavioral traits of heroin-addicted individuals as well as the limitations of the currently available studies are also reviewed. Finally, in need of a contemporary therapy a multimodal therapeutic approach is suggested using classical treatment practices along with current neurotechonologies, such as neurofeedback and goal-oriented video-games.

Passini, F., Watson, C. G., Dehnel, L., Herder, J., & Watkins, B. (1977). Alpha wave biofeedback training therapy in alcoholics. *Journal of Clinical Psychology*, 33(1), 292-299. This investigation evaluated the therapeutic efficacy of alpha-wave biofeedback treatment for alcoholics. Twenty-five Ss were compared to a matched control group before and after administration of a 3-week alpha-wave biofeedback regimen on a wide variety of criteria that included State-Trait Anxiety, the MMPI, Multiple Affect Adjective Check List, Zuckerman's Sensation Seeking Scale, Watson's Anhedonia Scale, the Brief Psychiatric Rating Scale, and baseline alpha. The experimental Ss received 10 hour-long alpha training sessions. The experimentals showed more improvement than did controls on alpha production and two anxiety measure. Contradictory results appeared on two suspicion/paranoia measures. Alpha training appeared useful in the treatment of anxiety, but not other problems. However, the absence of significant correlations between amount of change on alpha and the anxiety measures suggests that the improvement may be due to a placebo effect.

Peniston, E. G., & Kulkosky, P. J. (1989). Alpha-theta brainwave training and beta-endorphin levels in alcoholics. Alcohol: Clinical & Experimental Research, 13(2), 271-279. An alpha-theta brainwave-biofeedback training program was applied as a novel

treatment technique for chronic alcoholics. Following a temperature-biofeedback pretraining phase, experimental subjects completed 15 30-min sessions of alpha-theta biofeedback training. Compared to a nonalcoholic control group and a traditionally treated alcoholic control group, alcoholics receiving brainwave training (BWT) showed significant increases in percentages of EEG record in alpha and theta rhythms, and increased alpha rhythm amplitudes. Alcoholics receiving BWT showed a gradual increase in alpha and theta brain rhythms across the 15 experimental sessions. These experimentally treated alcoholics showed sharp reductions in self-assessed depression (Beck's Depression Inventory) compared to the control groups. Alcoholics receiving standard medical treatment (abstinence, group psychotherapy, antidepressants) showed a significant elevation in serum beta-endorphin levels at the conclusion of the experiment. This neuropeptide is an index of stress and a stimulant of caloric (e.g., ethanol) intake. Application of brainwave treatment, a relaxation therapy, appears to counteract the increase in circulating beta-endorphin levels seen in the control group of alcoholics. 13-month follow-up data indicate sustained prevention of relapse in alcoholics that completed alpha-theta brainwave training.

Ross S. M. (2013). Neurofeedback: an integrative treatment of substance use disorders. Holistic nursing practice, 27(4), 246–250. https://doi.org/10.1097/HNP.0b013e3182971b7c. Substance use disorders are exceedingly complicated as is the treatment. To increase positive outcomes, an understanding of all facets, bio/psycho/social/spiritual, economic, and interdisciplinary aspects, are essential to successful treatment. Neurofeedback has been applied successfully as an integrative treatment of SUDs for more than 30 years. Highlighted research that includes the Peniston Alpha-Theta protocol and Scott-Kaiser modifications of the Peniston protocol has shown that SUD treatment when combined with conventional treatment has the potential to improve measurable parameters and significantly increase positive outcomes.

Saxby, E., & Peniston, E. G. (1995). Alpha-theta brainwave neurofeedback training: An effective treatment for male and female alcoholics with depressive symptoms. Journal of Clinical Psychology, 51(5), 685-693. This was an experimental study of 14 alcoholic outpatients using the Peniston and Kulkosky (1989, 1991) brainwave treatment protocol for alcohol abuse. After temperature biofeedback pretraining, experimental subjects completed 20 40-minute sessions of alpha-theta brainwave neurofeedback training (BWNT). Experimentally treated alcoholics with depressive syndrome showed sharp reductions in self-assessed depression (Beck's Depression Inventory). On the Millon Clinical Multiaxial Inventory-I, the experimental subjects showed significant decreases on the BR scores: schizoid, avoidant, dependent, histrionic, passive-aggression, schizotypal, borderline, anxiety, somatoform, hypomanic, dysthmic, alcohol abuse, drug abuse, psychotic thinking, and psychotic depression. Twenty-one-month follow-up data indicated sustained prevention of relapse in alcoholics who completed BWNT.

Saxby, E., & Peniston, E. G. (1995). Alpha-theta brainwave neurofeedback training: an effective treatment for male and female alcoholics with depressive symptoms. Journal of clinical psychology, 51(5), 685–693. https://doi.org/10.1002/1097-4679(199509)51:5<685::aid-jclp2270510514>3.0.co;2-k. This was an experimental study of 14 alcoholic outpatients using the Peniston and Kulkosky (1989, 1991) brainwave treatment protocol for alcohol abuse. After temperature biofeedback pretraining, experimental subjects completed 20 40-minute sessions of alpha-theta brainwave neurofeedback training (BWNT). Experimentally treated alcoholics with depressive syndrome showed sharp reductions in self-assessed depression (Beck's Depression Inventory). On the Millon Clinical Multiaxial Inventory-I, the experimental subjects showed significant decreases on the BR scores: schizoid, avoidant, dependent, histrionic, passive-aggression, schizotypal, borderline, anxiety, somatoform, hypomanic, dysthmic, alcohol abuse, drug abuse, psychotic thinking, and psychotic depression. Twenty-one-month follow-up data indicated sustained prevention of relapse in alcoholics who completed BWNT.

Scott, W. C., Kaiser, D., Othmer, S., & Sideroff, S. I. (2005). Effects of an EEG biofeedback protocol on a mixed substance abusing population. The American journal of drug and alcohol abuse, 31(3), 455–469. https://doi.org/10.1081/ada-200056807. This study examined whether an EEG biofeedback protocol could improve outcome measures for a mixed substance abusing inpatient population. Method: One hundred twenty-one volunteers undergoing an inpatient substance abuse program were randomly assigned to the EEG biofeedback or control group. EEG biofeedback included training in Beta and SMR to address attentional variables, followed by an alpha-theta protocol. Subjects received a total of 40 to 50 biofeedback sessions. The control group received additional time in

treatment equivalent to experimental procedure time. The Test of Variables of Attention (TOVA), and MMPI, were administered with both tester and subject blind as to group placement to obtain unbiased baseline data. Treatment retention and abstinence rates as well as psychometric and cognitive measures were compared. Results: Experimental subjects remained in treatment significantly longer than the control group ($p < 0.005$). Of the experimental subjects completing the protocol, 77% were abstinent at 12 months, compared to 44% for the controls. Experimental subjects demonstrated significant improvement on the TOVA ($p < .005$) after an average of 13 beta-SMR sessions. Following alpha-theta training, significant differences were noted on 5 of the 10 MMPI-2 scales at the $p < .005$ level. Conclusions: This protocol enhanced treatment retention, variables of attention, and abstinence rates one year following treatment.

Simkin, DR., Thatcher, RW. & Lubar, J. (2014). Quantitative EEGB and Neurofeedback in Children and adolescents: Anxiety disorders, depressive disorders, comorbid addiction and attention-deficit/hyperactivity disorder and brain injury. ***Child and Adolescent Psychiatric Clinics of North America*****:23(3). 427-464.** This article explores the science surrounding neurofeedback. Both surface neurofeedback (using 2-4 electrodes) and newer interventions, such as real-time z-score neurofeedback (electroencephalogram [EEG] biofeedback) and low-resolution electromagnetic tomography neurofeedback, are reviewed. The limited literature on neurofeedback research in children and adolescents is discussed regarding treatment of anxiety, mood, addiction (with comorbid attention-deficit/hyperactivity disorder), and traumatic brain injury. Future potential applications, the use of quantitative EEG for determining which patients will be responsive to medications, the role of randomized controlled studies in neurofeedback research, and sensible clinical guidelines are considered.

Sokhadze, T.M., Cannon, R., & Trudeau, D.L. (2008). EEG biofeedback as a treatment for substance use disorders: Review, rating of efficacy and recommendations for future research, ***Applied Psychophysiology & Biofeedback*****, 33(1), 1-28.** Electroencephalographic (EEG) biofeedback has been employed in substance use disorder (SUD) over the last three decades. The SUD is a complex series of disorders with frequent comorbidities and EEG abnormalities of several types. EEG biofeedback has been employed in conjunction with other therapies and may be useful in enhancing certain outcomes of therapy. Based on published clinical studies and employing efficacy criteria adapted by the Association for Applied Psychophysiology and Biofeedback and the International Society for Neurofeedback and Research, alpha theta training-either alone for alcoholism or in combination with beta training for stimulant and mixed substance abuse and combined with residential treatment programs, is probably efficacious. Considerations of further research design taking these factors into account are discussed and descriptions of contemporary research are given.

Sokhadze, E., Stewart, C., Hollifield, M., El-Baz, A.., Singh, S., & Tasman, A. (2008). Attentional bias to stress-related pictorial cues in cocaine addiction comorbid with PTSD. ***Journal of Neurotherapy*****,12(4), 205-225.** Cocaine addiction places a specific burden on mental health services through its comorbidity with other psychiatric disorders. Treatment of patients with cocaine abuse is more complicated when addiction is co-occurring with PTSD. This study used dense-array event-related potential (ERP) technique to investigate whether the patients with this form of dual diagnosis display excessive reactivity to both trauma and drug cues as compared to neutral cues. Cue reactivity refers to a phenomenon in which individuals with a history of drug dependence exhibit verbal, physiological, and behavioral responses to cues associated with their preferred substance of abuse. This study explores ERP differences associated with cue-related responses to both drug and trauma cues in a three-category oddball task using neutral, drug-, and trauma-related pictorial stimuli. The study was conducted on 14 cocaine dependent subjects, 11 subjects with cocaine dependence comorbid with PTSD, and 9 age- and gender-matched control subjects. A 128-channel Electrical Geodesics EEG system was used to record ERP during the visual three-category oddball task with three categories (neutral, drug, stress) of affective pictures. Patients with cocaine dependence and PTSD, as compared to patients with only cocaine addiction and control subjects, showed excessive cue reactivity to both drug- and trauma-related visual stimuli. Most profound differences were found in the amplitude and latency of frontal P3a, and centro-parietal P3b ERP components. Group differences were found as well between patients with cocaine abuse (both addiction-only and dual diagnosis groups) vs. controls on most ERP measures for drug-related cues. We propose that the employed ERP cue reactivity variables could be used as valuable functional outcome measures in dually diagnosed drug addicts undergoing behavioral treatment.

Sokhadze, E., Stewart, C. M., Tasman, A., Daniels, R., & Trudeau, D. (2011). Review of rationale for neurofeedback application in adolescent substance abusers with comorbid disruptive behavioral disorders. *Journal of Neurotherapy*, 15, 232-261. Neurofeedback is a type of operant conditioning in which an individual modifies the frequency, amplitude, or other characteristic of his or her own brain activity as measured by EEG. Neurofeedback-training-based neurotherapy is one of the potentially efficacious nonpharmacological treatment options for substance use disorders (SUD) in adults, but it is also a very promising as a treatment modality for adolescents, especially those with stimulant abuse and attention and conduct problems. There is practically no literature on the use of neurofeedback in adolescent drug abusers. Treatment of attention-deficit/hyperactivity disorder (ADHD) with neurofeedback has already gained substantial empirical support in recent years. Short-term effects were shown to be comparable to those of stimulant medication at the behavioral and neuropsychological level, leading to significant decreases of inattention, hyperactivity, and impulsivity. In addition, neurofeedback results in concomitant improvement and normalizations of neurophysiological patterns assessed with EEG, event-related potentials (ERPs), and fMRI. Neurofeedback techniques may be of special interest for adolescent medicine because of the high comorbidity of SUD and ADHD in adolescents. ADHD is often comorbid with other disruptive behavioral disorders such as conduct disorder and oppositional defiant disorder. Techniques that combine classic ADHD neurofeedback approaches with behavioral addiction treatment hold special interest for adolescents with dual diagnosis. They are medication free and thus both minimize opportunities for prescribed medication misuse and diversions and are free of medication side effects. Furthermore, neurofeedback directly acts on the specific brain activity that are known to be altered in SUD and ADHD. By providing low-risk and medication-free therapy for both ADHD and SUD, neurofeedback is an option for practitioners reluctant to prescribe controlled substances to ADHD adolescents at risk for substance abuse.

Sokhadze, E., Baruth, J., Sears, L., Sokhadze, G. E., El-Baz, A., Williams, E., Klapheke, R., & Casanova, M. F. (2012). Event related potentials study of attention regulation during illusory figure categorization task in ADHD, autism spectrum disorders, and typical children. *Journal of Neurotherapy*,16, 12-31. Autism spectrum disorders (ASD) and attention deficit/hyperactivity disorder (ADHD) are very common developmental disorder that share some similar symptoms of social, emotional, and attentional deficits. This study is aimed to help understand the differences and similarities of these deficits using analysis of dense-array event-related potentials (ERP) during an illusory figure recognition task. Although ADHD and ASD seem very distinct, they have been shown to share some similarities in their symptoms. Our hypothesis was that children with ASD will show less pronounced differences in ERP responses to target and nontarget stimuli as compared to typical children and, to a lesser extent, ADHD. Participants were children with ASD (N=16), ADHD (N=16), and controls (N=16). EEG was collected using a 128-channel EEG system. The task involved the recognition of a specific illusory shape, in this case a square or triangle, created by three or four inducer disks. There were no between-group differences in reaction time (RT) to target stimuli, but both ASD and ADHD committed more errors; specifically, the ASD group had statistically higher commission error rate than controls. Posterror RT in ASD group was exhibited in a posterror speeding rather than corrective RT slowing typical for the controls. The ASD group also demonstrated an attenuated error-related negativity as compared to ADHD and controls. The fronto-central P200, N200, and P300 were enhanced and less differentiated in response to target and nontarget figures in the ASD group. The same ERP components were marked by more prolonged latencies in the ADHD group as compared to both ASD and typical controls. The findings are interpreted according to the "minicolumnar" hypothesis proposing existence of neuropathological differences in ASD and ADHD, specifically minicolumnar number/width morphometry spectrum differences. In autism, a model of local hyperconnectivity and long-range hypoconnectivity explains many of the behavioral and cognitive deficits present in the condition, whereas the inverse arrangement of local hypoconnectivity and long-range hyperconnectivity in ADHD explains some deficits typical for this disorder. The current ERP study supports the proposed suggestion that some between-group differences could be manifested in the frontal ERP indices of executive functions during performance on an illusory figure categorization task.

Stewart JL, May AC, Paulus MP. (2019) Bouncing back: Brain rehabilitation amid opioid and stimulant epidemics. Neuroimage Clin. 2019;24:102068. doi: 10.1016/j.nicl.2019.102068. Epub 2019 Nov 5. PMID: 31795056; PMCID: PMC6978215. Recent methamphetamine and opioid use epidemics are a major public health concern. Chronic stimulant and opioid use are characterized by significant psychosocial, physical and mental health costs, repeated relapse, and heightened risk of early death. Neuroimaging research highlights deficits in brain processes and circuitry that are linked to responsivity to drug cues over natural rewards as well as suboptimal

goal-directed decision-making. Despite the need for interventions, little is known about (1) how the brain changes with prolonged abstinence or as a function of various treatments; and (2) how symptoms change as a result of neuromodulation. This review focuses on the question: What do we know about changes in brain function during recovery from opioids and stimulants such as methamphetamine and cocaine? We provide a detailed overview and critique of published research employing a wide array of neuroimaging methods - functional and structural magnetic resonance imaging, electroencephalography, event-related potentials, diffusion tensor imaging, and multiple brain stimulation technologies along with neurofeedback - to track or induce changes in drug craving, abstinence, and treatment success in stimulant and opioid users. Despite the surge of methamphetamine and opioid use in recent years, most of the research on neuroimaging techniques for recovery focuses on cocaine use. This review highlights two main findings: (1) interventions can lead to improvements in brain function, particularly in frontal regions implicated in goal-directed behavior and cognitive control, paired with reduced drug urges/craving; and (2) the targeting of striatal mechanisms implicated in drug reward may not be as cost-effective as prefrontal mechanisms, given that deep brain stimulation methods require surgery and months of intervention to produce effects. Overall, more studies are needed to replicate and confirm findings, particularly for individuals with opioid and methamphetamine use disorders.

Trudeau, D. L. (2005). Applicability of brain wave biofeedback to substance use disorder in adolescents. Child & Adolescent Psychiatric Clinics of North America, 14(1), 125-136. Neurofeedback treatment for addictions in adults is probably efficacious, and several reported approaches are described with their indications. Neurofeedback is promising as a treatment modality for adolescents, especially those with stimulant abuse and attention and conduct problems. It is attractive as a medication-free, neurophysiologic, and self-actualizing treatment for a substance-based, brain-impaired and self-defeating disorder. More research, beginning with case reporting, is needed to assess use and efficacy in adolescents.

Watson, C. G., Herder, J., & Passini, F. T. (1978). Alpha biofeedback therapy in alcoholics: An 18-month follow-up. Journal of Clinical Psychology, 34(3), 765-769. In an earlier study on patients with alcohol problems, an experimental group given 10 hour-long alpha biofeedback training sessions showed greater improvement on State and Trait Anxiety scores than did a control sample. In the present study an 18-month follow-up was done on those Ss. The differences between the experimentals and controls in State and Trait Anxiety after 18 months were essentially identical to the differences between them immediately after treatment, which indicates that alpha training had long-range therapeutic effects. A difference between the groups on the Alcohol Rehabilitation Follow up Questionnaire also suggested that alpha training may have been associated with some reduction in alcohol consumption as well.

Yamaguchi T, Tazaki M. (2016). Neurofeedback therapy for alcohol use disorder. Nihon Arukoru Yakubutsu Igakkai Zasshi. 2016 Aug;51(2):91-100. English, Japanese. PMID: 30462384. Neurofeedback is a therapeutic learning process that provides visual and auditory feedback to an individual about his or her brainwaves in order to teach self-regulation of brain function. Currently, neurofeedback therapy has been attempted to apply to various psychiatric disorders and certain therapeutic effects have been shown. The advantage of incorporating neurofeedback therapy to the conventional treatments is 1) the action on the central nervous system can be expected. by directly reinforcing EEG, 2) on the premise of neural plasticity, without ongoing intervention, long-term therapeutic effect can be expected, 3) except rare temporary headache, no significant side effects are reported, 4) compared to other psychotherapies, neurofeedback is expected to have a therapeutic effect within a relatively short period of time. The present paper outlines neurofeedback therapy in the treatment of alcohol dependence and points out the new direction and remaining issues in neurofeedback therapy.

Zilverstand A, Parvaz MA, Moeller SJ, Goldstein RZ. (2015). Cognitive interventions for addiction medicine: Understanding the underlying neurobiological mechanisms. Prog Brain Res. 2016;224:285-304. doi: 10.1016/bs.pbr.2015.07.019. Epub 2015 Nov 14. PMID: 26822363; PMCID: PMC5206794. Neuroimaging provides a tool for investigating the neurobiological mechanisms of cognitive interventions in addiction. The aim of this review was to describe the brain circuits that are recruited during cognitive interventions, examining differences between various treatment modalities while highlighting core mechanisms, in drug addicted individuals. Based on a systematic Medline search we reviewed neuroimaging studies on cognitive behavioral therapy, cognitive inhibition of craving, motivational interventions, emotion regulation, mindfulness, and neurofeedback training in addiction. Across intervention modalities, common results included the normalization of aberrant activity in the brain's reward circuitry, and the recruitment and strengthening of

the brain's inhibitory control network. Results suggest that different cognitive interventions act, at least partly, through recruitment of a common inhibitory control network as a core mechanism. This implies potential transfer effects between training modalities. Overall, results confirm that chronically hypoactive prefrontal regions implicated in cognitive control in addiction can be normalized through cognitive means.