GrayMatters Health

Clinical Publications Portfolio

GrayMatters Health and its core technology has been extensively researched with peer-reviewed articles in prestigious medical journals.
These publications form the clinical foundation of Prism.

Note: The term Amygdala Electrical Finger-Print (AmygEFP) in clinical publications is now referred to as the EEG-fMRI-Pattern (EFP) biomarker.

Clinical

Fruchter E, Goldenthal N, Adler LA, Gross R, Harel EV, Deutsch L, Nacasch N, Grinapol S, Amital D, Voigt JD, Marmar CR. Amygdala-derived-EEG-fMRI-pattern neurofeedback for the treatment of chronic post-traumatic stress disorder. A prospective, multicenter, multinational study evaluating clinical efficacy. Psychiatry Research, Volume 333, 2024.

A prospective, single arm, multisite, multinational, open label trial assessing the safety and efficacy of a novel amygdala-derived neurofeedback treatment, designated Amygdala-Derived-EFP, for chronic PTSD.

Participants, including veterans and civilians, underwent screening, training, 15 neurofeedback sessions over 8 weeks and; baseline, termination (8 weeks) and 3 month post treatment assessments with validated measures. The primary endpoint was more than 50 % of the participants demonstrating a Minimally Clinically Important Difference (MCID) defined as a 6-point reduction, on the Clinician Administered PTSD Scale (CAPS-5) total score at 3 months. Secondary measures included the PCL-5, ERQ, PHQ-9, and CGI.

The primary endpoint was met, with a CAPS-5 MCID response rate of 66.7 %. The average reduction in CAPS-5 total scores at 3 month follow up was 13.5 points, more than twice the MCID. Changes from baseline in CAPS-5, PCL-5, PHQ-9 scores at 8 weeks and the 3 month follow-up demonstrated statistically significant improvements in response and; demonstrated effect sizes ranging from 0.46 to 1.07. Adverse events were mild and resolved after treatment.

This study builds on prior research demonstrating similar outcomes using amygdala-derived neurofeedback. Positive attributes of this therapy include monitoring by non-physician personnel, affordability, accessibility, and tolerability.

Fruchtman-Steinbok T, Keynan JN, Cohen A, Jaljuli I, Mermelstein S, Drori G, Routledge E, Krasnoshtein M, Playle R, Linden DEJ, Hendler T. Amygdala electrical-finger-print (AmygEFP) NeuroFeedback guided by individually-tailored Trauma script for post-traumatic stress disorder: Proof-of-concept. Neuroimage Clin. 2021;32:102859.

Demonstrating the feasibility of amygdala-EFP neurofeedback for PTSD treatment, by reducing PTSD symptoms and improving amygdala self-regulation.

The amygdala brain region is involved in emotional processing, and its dysregulation is associated with PTSD. Therefore, if a person could learn to self-regulate activity of this brain region, it could help alleviate their symptoms. Such 'brain training' is accomplished by neurofeedback, in which the amygdala activity is recorded, analyzed in real-time and presented as feedback to the trainee. A major limitation in the scalability of this procedure for clinical use is that measurement of deep brain activity in the amygdala requires fMRI scanning. To overcome this limitation, an amygdala model, termed amygdala-EFP biomarker, was developed. It uses simultaneous EEG-fMRI recordings, training a machine-learning model to predict amygdala fMRI signals based on the EEG signals. The resulting amygdala EFP is implemented in EEG-based neurofeedback, without the need for patient MRI scanning.

In this randomized clinical trial, 59 patients were assigned either to amygdala-EFP neurofeedback (with two alternative feedback interfaces) or to no-neurofeedback control groups. Patients who trained with amygdala-EFP neurofeedback with 8-week protocol demonstrated greater reduction in PTSD symptoms (CAPS-5 questionnaire score) and improved fMRI down-regulation of the amygdala, compared to the control. Clinical improvement was preserved at 3- and 6-months following completion of the training, as measured via self-reported symptom severity (PCL questionnaire score). This demonstrates the potential benefit of amygdala-EFP neurofeedback training for PTSD treatment.

Fine NB, Helpman L, Bardin Armon D, Gurevitch G, Sheppes G, Seligman Z, Hendler T, Bloch M. Limbic Amygdala-related EEG Neuro-Feedback as an add-on Therapy for treatment-resistant Childhood Sexual Abuse PTSD: Feasibility Study. Psychiatry Clin Neurosci 2023 Aug 24.

Testing the feasibility of amygdala-EFP neurofeedback to augment psychotherapy for complex PTSD from childhood sexual abuse (CSA).

This randomized controlled study tested the effects of self-neuromodulation training in 55 women with treatment-resistant CSA-PTSD during ongoing trauma-focused psychotherapy. Participants were randomly assigned to 10 sessions of adjunctive neurofeedback (test) or psychotherapy-only (control) groups. Participants in the neurofeedback group successfully learned to down-regulate the amygdala-EFP signal.

Long-term PTSD symptoms (PCL-5 scores) significantly decreased in the neurofeedback group, compared with the control group.

Moreover, the neurofeedback group continued to show symptom improvement over time, as measured by PCL-5 at 3- and 6-month follow-up, showing durability of amygdala-based neurofeedback for this PTSD population.

Keynan JN, 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. Electrical fingerprint of the amygdala guides neurofeedback training for stress resilience. Nat Hum Behav. 2019 Jan;3(1):63-73.

Demonstrating the effects of amygdala-EFP neurofeedback on emotional resilience and amygdala self-regulation during ongoing intensive and stressful military training.

This study tested the ability of amygdala-EFP neurofeedback training to improve emotional resilience under stressful ongoing life conditions. In a double-blind experiment, 180 healthy individuals undergoing a stressful military training program were randomly assigned to either test or control conditions. During a 4-week long experimental scheme, test participants trained on amygdala-EFP neurofeedback, whereas control participants either trained on alpha/theta neurofeedback or no neurofeedback.

Emotional resilience, as measured via a psychological questionnaire of alexithymia and by a behavioral emotional-regulation test, improved after amygdala-EFP neurofeedback, but not after alpha/theta neurofeedback, and was worsened in participants who did not receive any form of feedback. Furthermore, in an fMRI scan performed after training, only participants who were trained with amygdala-EFP neurofeedback were able to down-regulate their amygdala activity. As compared with no neurofeedback, amygdala-EFP neurofeedback also resulted in higher co-activation of the amygdala together with another brain region involved in emotional regulation: the ventro-medial prefrontal cortex (vmPFC). These results demonstrate the beneficial effects of amygdala-EFP neurofeedback on emotional resilience during stress exposure.

Neurofeedback

Voigt JD, Mosier M, Tendler A. Systematic review and meta-analysis of neurofeedback and its effect on posttraumatic stress disorder. Frontiers in Psychiatry 21 March 2024

A meta-analysis of neurofeedback for treating PTSD that includes fMRI informed EEG NF.

Neurofeedback (NF) technologies in the treatment of posttraumatic stress disorder (PTSD) have evolved over the years. Prior systematic reviews and meta-analyses on randomized controlled trials (RCTs) have shown promising results using electroencephalogram (EEG) NF for PTSD but used traditional EEG NF technologies and with very small numbers of patients. This meta-analysis is an update to include several RCTS (using newer forms of deep brain feedback—functional magnetic resonance imaging [fMRI] NF and fMRI informed EEG NF).

Systematic literature review was conducted using the electronic databases PubMed Central, Cochrane CENTRAL, and EBSCO/CINAHL and used the following search terms: [(neurofeedback AND random*) AND trial] AND PTSD.
Results from all studies identified favored neurofeedback's effect on reducing PTSD symptoms including BDI pretest–posttest [mean difference (MD): 8.30 (95% CI: 3.09 to 13.52; P = 0.002; I2 = 0%)]; BDI pretest–follow-up (MD: 8.75 (95% CI: 3.53 to 13.97; P < 0.00001; I2 = 0%); CAPS-5 pretest–posttest [MD: 7.01 (95% CI: 1.36 to 12.66; P = 0.02; I2 = 86%)]; CAPS-5 pretest–follow-up (MD: 10 (95% CI: 1.29 to 21.29; P = 0.006; I2 = 77%); PCL-5 pretest–posttest (MD: 7.14 (95% CI: 3.08 to 11.2; P = 0.0006; I2 = 0%); PCL-5 pretest–follow-up (MD: 14.95 (95% CI: 7.95 to 21.96; P < 0.0001; I2 = 0%). GRADE assessments of CAPS, PCL, and BDI demonstrated a moderate/high level in the quality of the evidence that NF has a positive clinical effect for treating PTSD.

Goldway N, Jalon I, Keynan JN, Hellrung L, Horstmann A, Paret C, Hendler T. Feasibility and utility of amygdala neurofeedback. Neurosci Biobehav Rev. 2022 Jul;138:104694.

A review of research studies that tested the effects of amygdala-neurofeedback (using either fMRI or amygdala-EFP) on the ability to self-regulate the amygdala.

This is a meta-analysis of 33 studies, in which amygdala neurofeedback was accomplished either in an EEG setting measuring the amygdala-EFP signal, or in an fMRI setting measuring amygdala activity. Overall, amygdala neurofeedback resulted in (1) increased regulation (relative to baseline), (2) improved self-regulation following multiple training sessions, and (3) improved clinical symptoms following multiple training sessions. The article further analyzes aspects of study design that contribute to neurofeedback efficacy. An additional re-analysis of fMRI studies further revealed that when the amygdala is down-regulated by neurofeedback, the activity reduction in the amygdala is associated with a reduction in activity of other brain regions including the insula, prefrontal cortex, and para-hippocampal cortex.

Lubianiker N, Goldway N, Fruchtman-Steinbok T, Paret C, Keynan JN, Singer N, Cohen A, Kadosh KC, Linden DEJ, Hendler T. Process-based framework for precise neuromodulation. Nat Hum Behav. 2019 May;3(5):436-445

The authors put forward the concept of process-based NF by targeting specific dysfunctional mental processes and paving the way for precise and personalized neuromodulation.

Three aspects of neurofeedback training and testing are addressed: (1) Neural targeting – the part of the brain that we want to influence with neurofeedback. The authors propose moving from an approach that targets a single brain region, to targeting a mental process, which involves a network of multiple brain regions often activated in synchrony. For example, emotional regulation involves limbic regions [such as the amygdala], together with other brain regions [such as the insula and prefrontal cortex]. Even in single-region neurofeedback targeting, effects usually extend beyond the target region, to other brain regions; (2) Feedback interface – the interactive setup and manner in which the feedback is presented.

The authors propose designing a feedback interface that systematically targets the mental process we want to influence, by creating a contextual setting in which this mental process is typically expressed or triggered [such as an enjoyable setting to target reward processing, or a stressful setting to target emotional regulation]; (3) Neurofeedback specificity – the combination of test, control and placebo conditions by which we try to isolate the effects of a specific neurofeedback method. The authors propose designing randomized clinical trials combining multiple control conditions to allow better inference.

Cohen A, Keynan JN, Jackont G, Green N, Rashap I, Shani O, Charles F, Cavazza M, Hendler T, Raz G. Multi-modal Virtual Scenario Enhances Neurofeedback Learning. Front Robot AI, 2016 Aug 31; 3:52.

Introducing a gamified neurofeedback interface and its benefits for amygdala-EFP training.

The study introduces a novel neurofeedback interface, depicting an animated audiovisual scenario of a hospital waiting room. The level of stress in the waiting room is modulated by the neural signal. When amygdala-EFP increases, the animated characters crowd the reception area, and the room becomes noisier. The participants' goal is to reduce their amygdala-EFP signal, causing the characters to quiet down and go back to their seats. Training with the animated scenario improved participants' ability to self-regulate their amygdala-EFP significantly better than when training with a simple 2D thermometer feedback interface (a bar image that fills up and changes color as signal increases). This demonstrates the benefits of neurofeedback training with a gamified interface.

EFP Biomarker

Keynan JN, Meir-Hasson Y, Gilam G, Cohen A, Jackont G, Kinreich S, Ikar L, Or-Borichev A, Etkin A, Gyurak A, Klovatch I, Intrator N, Hendler T. Limbic Activity Modulation Guided by Functional Magnetic Resonance Imaging-Inspired Electroencephalography Improves Implicit Emotion Regulation. Biol Psychiatry. 2016 Sep 15;80(6):490-496.

Demonstrating the effects of amygdala-EFP neurofeedback training on the ability to self-regulate amygdala activity and on emotional reactivity.

The amygdala EFP was developed with the intention of establishing, in the long run, a scalable method for training emotional regulation. Specifically, it is aimed to reduce emotional reactivity related to an over-active amygdala. Following the development of the amygdala EFP, which provided an EEG-based biomarker of amygdala activity, the innovation was tested in a neurofeedback procedure termed amygdala-EFPNF. Three questions were addressed: (1) Does amygdala -EFP-NF increase one's ability to down-regulate their own amygdala activity? (2) Does amygdala -EFP-NF reduce one's reactivity of the amygdala in response to emotional images? (3) Does amygdala -EFP-NF improve one's behavioral emotional regulation?

The study used a combination of fMRI, EEG and behavioral measurements to test, and successfully demonstrate, the effectiveness of amygdala -EFP NF in accomplishing all three objectives. Thus, the amygdala-EFP not only probes amygdala-related activity but also causally influences it when implemented in a neurofeedback procedure.

Meir-Hasson Y, Kinreich S, Podlipsky I, Hendler T, Intrator N. An EEG Finger-Print of fMRI deep regional activation. Neuroimage. 2014 Nov 15;102 Pt 1:128-141.

Introducing the EEG finger-print (EFP); a computational model that tracks the activity of deep brain regions via EEG, thereby reducing the need for fMRI scanning.

Traditional EEG neurofeedback paradigms, such as alpha/theta sampling, provide low spatial accuracy, which makes deep brain regions, such as the amygdala, largely inaccessible. The EFP model was developed in order to overcome this limitation, by using simultaneous EEG-fMRI recordings. It exploits the high spatial resolution imaging enabled by fMRI, and incorporates advanced signal processing and machine learning methods of EEG signals. Thereby, the model learns to predict a brain region's activity as measured with the fMRI, based on the signals recorded in EEG. An amygdala-EFP model successfully predicted the amygdala's fMRI signal from a single EEG electrode. Moreover, it provided better prediction of amygdala activity than the traditional alpha/theta EEG sampling. Thus, the EFP is proposed as a more targeted biomarker of neural activity, which can be applied in EEG-based neurofeedback and other brain-guided procedures.

Meir-Hasson Y, Keynan JN, Kinreich S, Jackont G, Cohen A, Podlipsky-Klovatch I, Hendler T, Intrator N. One-Class FMRI-Inspired EEG Model for Self-Regulation Training. PLoS One. 2016 May 10;11(5):e0154968.

Applying an EFP-neurofeedback procedure to train amygdala down-regulation in participants that did not undergo fMRI.

The amygdala brain region is involved in emotional processing, and its dysregulation is associated with emotional dysfunction. Therefore, if we could teach a person to self-regulate their activity of this brain region, it may alleviate their symptoms. Such neural-regulation training is accomplished via neurofeedback, in which the amygdala activity is recorded, analyzed in real time and presented as feedback to the trainee. A major limitation in the scalability of this procedure for clinical use is that measurement of such deep brain activity requires fMRI scanning. To remove this limitation, an amygdala EFP was developed for use in an EEG-only neurofeedback procedure. The article describes the innovative computational methods that were used to achieve an effective common model for amygdala EFP. The model was developed from simultaneous EEG-fMRI recordings in one group of participants, and tested in EEG-only neurofeedback in a new group of participants. Participants in the new group learned to substantially reduce their amygdala EFP signal if they had been trained with true feedback, but not if they had been trained with sham feedback. This shows that amygdala EFP can be implemented in EEG-based neurofeedback without the need for patient MRI scanning.

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