

EEG Biomarkers of Antidepressant Response to Real-Time fMRI Neurofeedback

Masaya Misaki^{1,2,3}, Zhiyin Chen^{1,4}, Saampras Ganesan¹, Takakuni Suzuki⁵

¹*Laureate Institute for Brain Research, Tulsa, OK, USA*

²*Oxley College of Health and Natural Sciences, The University of Tulsa, Tulsa, OK, USA*

³*University of Oklahoma College of Medicine School of Community Medicine, Tulsa, OK, USA*

⁴*Department of Electrical and Computer Engineering, The University of Tulsa, Tulsa, OK, US*

⁵*Department of Psychology, The University of Tulsa, Tulsa, OK, USA*

Introduction

The left-amygdala-targeted real-time fMRI neurofeedback (rtfMRI-NF) paradigm, designed to upregulate left amygdala activity during positive autobiographical memory recall, is a promising intervention for major depressive disorder (MDD) [1]. A large-sample analysis of this paradigm [2] showed that antidepressant response was not predicted by the degree of amygdala upregulation alone. Rather, response was associated with distinctive whole-brain activation patterns during training, suggesting that distributed learning-related processes, rather than direct control of the target region, may drive clinical benefit. We hypothesized that these training-related neural dynamics would also be detectable in simultaneously recorded electroencephalography (EEG) and could serve as predictive markers of subsequent antidepressant response.

Methods

Participants: Forty-five individuals with MDD (29 females; age 32 ± 10 y) underwent one session of rtfMRI-NF training as part of a randomized controlled trial [1,3]. During training, participants recalled positive autobiographical memories and received real-time visual feedback on the left amygdala BOLD signal. Simultaneous 32-channel EEG was recorded throughout.

Analysis 1: After preprocessing to remove EEG noise and artifacts, including fMRI scanning-related and ballistocardiogram artifacts, EEG data were decomposed using a continuous wavelet transform (CWT). Spectral power in four frequency bands (delta, 0.5-4 Hz; theta, 4-8 Hz; alpha, 8-13 Hz; beta, 13-30 Hz) during neurofeedback blocks was z-score normalized relative to the immediately preceding rest period. For each frequency band and channel, a linear mixed-effects model tested associations between normalized power and 1-week change in Montgomery-Åsberg Depression Rating Scale (MADRS) score, controlling for age, sex, and baseline MADRS.

Analysis 2: We quantified EEG-NF coupling to assess whether changes in the neurofeedback signal were associated with EEG dynamics following feedback. Specifically, at each time point t in the 1.5-s post-feedback window, we calculated the Euclidean distance between CWT amplitude vectors at consecutive time points across all 32 channels: $d(t) = \|a_b(t+1) - a_b(t)\|_2$, where $a_b(t)$ is the vector of per-channel CWT amplitudes for frequency band b . The mean $d(t)$ over the window summarized moment-to-moment amplitude changes after each feedback event. For each participant, regression of this measure on the concurrent NF signal change yielded a band-specific EEG-NF coupling coefficient, quantifying the extent to which post-feedback EEG dynamics varied with feedback signal changes. This coefficient was then tested in relation to antidepressant improvement across participants, controlling for age, sex, and baseline MADRS.

Results

Delta-band power during neurofeedback blocks was significantly associated with antidepressant improvement across a centroparietal-temporal cluster of 10 channels (Cz, C4, CP5, CP6, P3, P4, T8, P8, FC6, FCz; FDR $q < 0.05$), with higher delta power corresponding to less improvement. Figure 1A shows the relationship between mean normalized delta-band power during neurofeedback blocks and percent MADRS reduction from baseline to 1 week after NF training. No other frequency band showed significant effects.

NF-EEG coupling was significantly associated with antidepressant outcomes in the theta and alpha bands (FDR $q = 0.031$ and $q = 0.010$, respectively), with stronger coupling corresponding to greater clinical improvement (Figure 1B).

Conclusions

Elevated block-level delta power during neurofeedback blocks predicted poorer antidepressant outcomes and may reflect reduced engagement or inattention during the positive memory task. In contrast, stronger NF-EEG coupling in theta and alpha predicted greater improvement, suggesting that feedback-related modulation of these rhythms may reflect cognitive updating and effortful regulation during positive memory-based self-regulation. These two EEG measures parallel the components identified in the fMRI analysis by Misaki et al. [2]: block-level brain activity during training and moment-to-moment responsiveness to individual feedback events. The convergence across modalities supports the interpretation that training-related neural engagement, rather than amygdala upregulation alone, carries predictive information about antidepressant response. Simultaneously recorded EEG can capture meaningful indices of neurofeedback learning quality, suggesting that EEG may serve as a predictive biomarker of antidepressant response to amygdala-targeted rtfMRI-NF training.

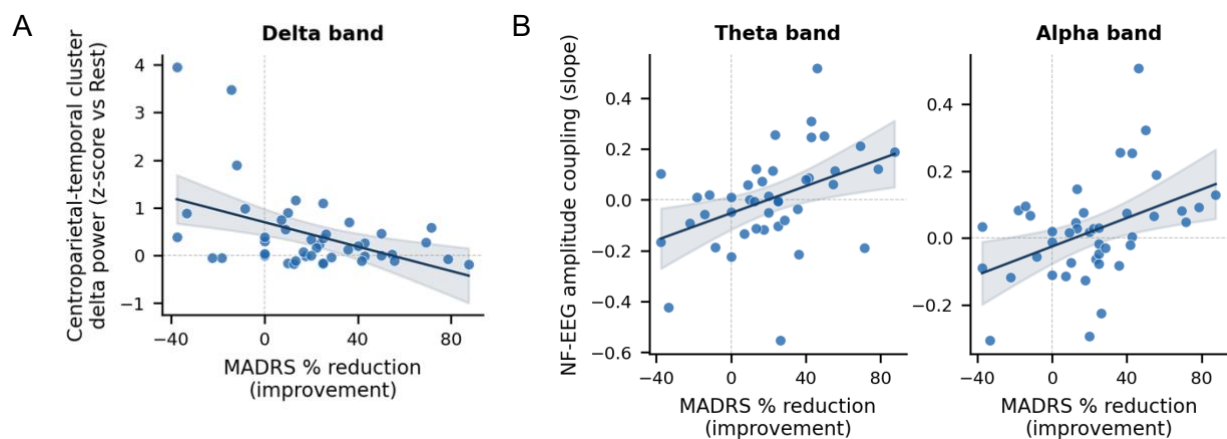


Figure 1. A) Centroparietal-temporal cluster delta power during neurofeedback blocks (z-score relative to rest) vs. antidepressant improvement from baseline to 1 week after NF training. Higher delta power was associated with less improvement ($t[39] = 3.017$, $p = 0.004$, $r^2 = 0.233$). Regression line with 95% CI. B) NF-EEG coupling coefficient vs. antidepressant improvement from baseline to 1 week after NF training for theta and alpha bands. Stronger coupling was associated with greater improvement (theta: $t[39] = 2.693$, $p = 0.010$, $r^2 = 0.186$; alpha: $t[39] = 3.376$, $p = 0.002$, $r^2 = 0.186$). Regression line with 95% CI.

References

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