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Limbic Activity Modulation Guided by Functional Magnetic Resonance Imaging–Inspired Electroencephalography Improves Implicit Emotion Regulation

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ABSTRACT

The amygdala has a pivotal role in processing traumatic stress; hence, gaining control over its activity could facilitate adaptive mechanism and recovery. To date, amygdala volitional regulation could be obtained only via real-time functional magnetic resonance imaging (fMRI), a highly inaccessible procedure. The current article presents high-impact neurobehavioral implications of a novel imaging approach that enables bedside monitoring of amygdala activity using fMRI-inspired electroencephalography (EEG), hereafter termed amygdala-electrical fingerprint (amyg-EFP). Simultaneous EEG/fMRI indicated that the amyg-EFP reliably predicts amygdala-blood oxygen level–dependent activity. Implementing the amyg-EFP in neurofeedback demonstrated that learned downregulation of the amyg-EFP facilitated volitional downregulation of amygdala-blood oxygen level–dependent activity via real-time fMRI and manifested as reduced amygdala reactivity to visual stimuli. Behavioral evidence further emphasized the therapeutic potential of this approach by showing improved implicit emotion regulation following amyg-EFP neurofeedback. Additional EFP models denoting different brain regions could provide a library of localized activity for low-cost and highly accessible brain-based diagnosis and treatment.

Keywords: Amygdala, Brain-computer interface, EEG neurofeedback, Machine learning, Real-time fMRI, Stress

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Neurocognitive models of stress-related psychopathologies point to downregulation of amygdala activity as a key mechanism in emotion regulation (1), an essential feature in the effective recovery from traumatic stress (2). Therefore, learning to regulate one's own amygdala activity may diminish detrimental and facilitate adaptive stress coping mechanisms (3). Obtaining volitional regulation of the amygdala was thus far possible only via online closed-loop training (i.e., neurofeedback [NF]) guided by real-time functional magnetic resonance imaging (fMRI) (4–6). Such learned regulation was indeed demonstrated to result in reduced stress- (7) and depression-related (8) symptoms. Despite these seemingly promising findings, the clinical utility of fMRI-based interventions is considerably limited due to immobility, high cost, and extensive physical requirements of the scanning procedure (9). Electroencephalography (EEG), on the other hand, is a relatively inexpensive and mobile brain imaging technique that can be easily implemented at any location. Nonetheless, the clinical benefit of EEG-NF, particularly for affective disturbances such as depression and posttraumatic stress disorder, remains dubious (10,11), possibly due to poor spatial resolution, which hampers the targeting of deep limbic areas such as the amygdala (12). The current study conducted a first-of-its-kind investigation of the neurobehavioral implications of a novel imaging approach that allows for the bedside monitoring of amygdala activity using fMRI-inspired EEG, hereafter termed amygdala-electrical fingerprint (amyg-EFP).

The amyg-EFP was recently developed in our laboratory by applying advanced machine learning algorithms on EEG data acquired simultaneously with fMRI. This resulted in a new individually fitted EEG model of weighted coefficients that can be used to probe localized blood oxygen level–dependent (BOLD) activity of a predefined region (13). However, this approach still required prior fMRI scanning for each subject, precluding its widespread use and easy application. The current work reached beyond the initial computational study and tested a new one-class model of the amyg-EFP that is valid across different individuals and thus could be used without prior fMRI (Figure 1; Supplemental Figure S1). The current study further aimed to portray the translational potential of this novel approach in treating human traumatic stress while considering its underlying process. To this end, we performed three NF experiments comparing volitional regulation of the amyg-EFP with either EFP-sham or no-treatment

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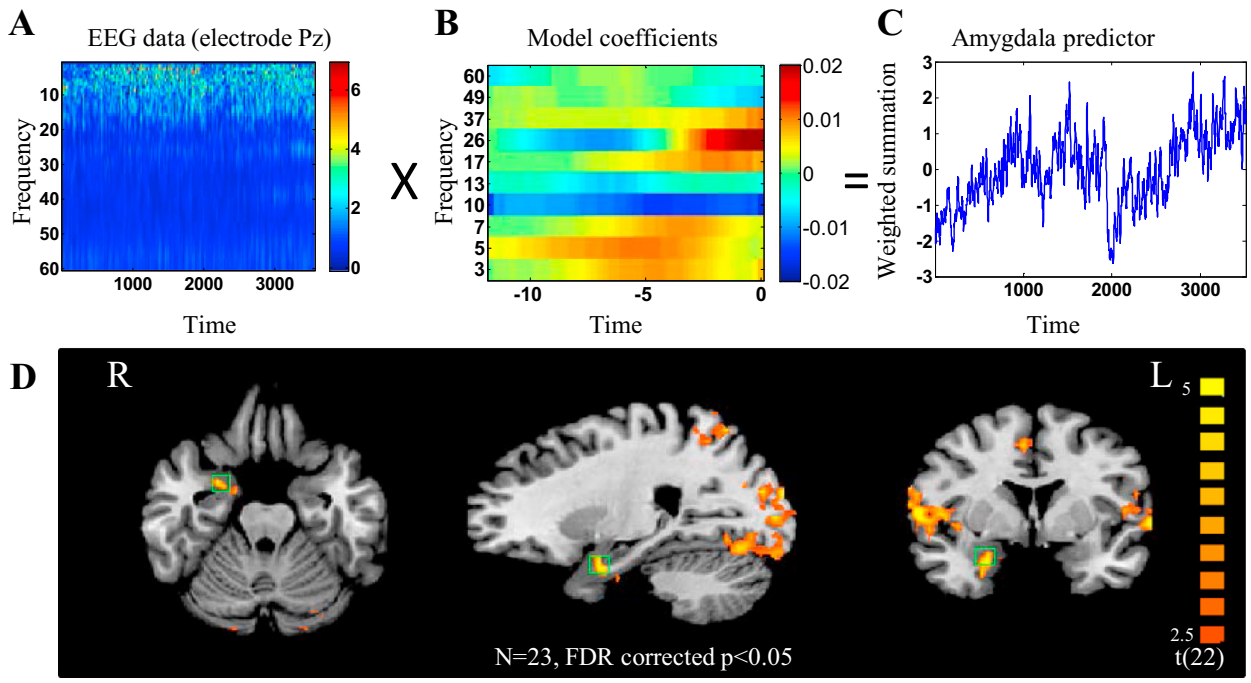

Figure 1. The amygdala-electrical fingerprint (amyg-EFP) prediction model. The recorded electroencephalography (EEG) data **(A)** are multiplied by the common model coefficient matrix **(B)** to produce the predictor of the right amygdala blood oxygen level-dependent (BOLD) activity **(C). (A)** The EEG data used for the model are a time/frequency matrix recorded from electrode Pz including all frequency bands in a time window of 12 seconds. **(B)** The common model coefficients matrix. [CH] × [FQ] × [Delay] × [Time]. Functional magnetic resonance imaging-BOLD activity at time *T* can be predicted by the EEG using the frequency intensity *FQ* of electrode *CH* in delay *D* from *T*. In our case, *CH* includes a selected single electrode (Pz). **(C)** The predicted right amygdala BOLD activity time course. Further details regarding the construction process of the amyg-EFP is available in the Supplement. **(D)** Experiment 1 whole-brain amyg-EFP correlates. Correlation maps obtained from whole-brain random effects general liner model analysis using as a predictor the amyg-EFP during neurofeedback are shown in axial, sagittal, and coronal views (left to right). The area that was used originally (on a different group) to develop the amyg-EFP model is marked by a green square. See Supplemental Table S1 for whole-brain peak correlates in more regions. FDR, false discovery rate; L, left; R, right.

control subjects. Simultaneous EEG/fMRI recordings conducted in the first experiment validated the amyg-EFP as a reliable predictor of amygdala fMRI-BOLD activity. In a second experiment, we further examined the relation between the amyg-EFP and the amygdala-BOLD using a prospective design, conducting fMRI before and after training to downregulate the amyg-EFP outside the scanner. This experiment demonstrated a causal link between learned downregulation via amyg-EFP NF and a subsequent improved ability to regulate amygdala-BOLD activity via fMRI-NF. Moreover, this learned skill manifested as reduced reactivity of the amygdala in response to provoking visual stimuli, possibly indicating an adaptive acquired plasticity. Lastly, the third experiment pointed to the clinical potential of this novel approach by showing improved implicit emotion regulation following amyg-EFP NF.

METHODS AND MATERIALS

All experiments and data analysis were conducted at the Functional Brain Center, Wohl Institute for Advanced Imaging, Tel-Aviv Sourasky Medical Center and were approved by the Sourasky ethics review board. Participants gave written informed consent, were healthy, and had normal hearing and normal or corrected-to-normal vision. Each group in each experiment contained different individuals (total $n = 82$).

Experiment 1

Twenty-four participants were randomly assigned either to the EFP-test ($n = 15$; aged 22–29) or to the EFP-sham ($n = 9$; aged 23–29) group in a single-blind manner. Participants were simultaneously scanned by EEG/fMRI during five consecutive blocks, each lasting 7 minutes. The EFP-test group received continuous auditory feedback driven by their amyg-EFP amplitude changes, calculated online every 3 seconds (14). The EFP-sham group received auditory feedback unrelated to their amyg-EFP signal. In the first rest block, participants were given no specific instructions and received no auditory feedback. In the subsequent four NF blocks, participants were instructed to lower the volume of an auditory stimulus by exercising mental strategies. Instructions were intentionally unspecific, allowing individuals to adopt the mental strategy that they subjectively found most efficient (15). See the Supplement for online calculation of amyg-EFP amplitude and feedback generation.

Experiment 2

Eighteen participants were randomly assigned either to the EFP-test ($n = 9$; aged 23–29) or to the EFP-sham group ($n = 9$; aged: 22–29) in a single-blind manner. The prospective design of experiment 2 included three separate sessions (pretraining/training/posttraining) (Supplemental Figure S2).

Participants' baseline ability to volitionally regulate amygdala-BOLD activity was measured pretraining by conducting a two-block session (60 seconds each) of amygdala-targeted fMRI-NF (amyg-fMRI NF) (Supplemental Figure S3). This two-block duration was previously found insufficient to facilitate fMRI-NF learning (16). At the training session (5 to 7 days later), participants were randomly assigned to either EFP-test or EFP-sham. The amyg-EFP NF took place outside the MRI scanner and consisted of six blocks (rest block and five NF blocks; 5 minutes each). At posttraining (24 to 48 hours after training), participants underwent a full-length five-block session of amyg-fMRI NF. The amyg-fMRI NF followed a commonly used design (16) and was applied as a test to verify that by learning to regulate the amygdala, as measured by EEG alone (i.e., amyg-EFP), participants actually learned to regulate amygdala-BOLD activity as measured by real-time fMRI. Therefore, during amyg-fMRI NF (pretraining and posttraining), feedback for both groups was driven by amygdala activity. The only difference between the groups was during the training session, in which the EFP-test group received online feedback driven by the amyg-EFP and the EFP-sham group received feedback unrelated to their own brain activity. Before and after all NF sessions, participants performed a backward masking task while being scanned by fMRI. Four subjects (two EFP-test; two EFP-sham) were unable to meet the experiment schedule and were excluded from the analysis. The final analysis included 14 subjects.

Backward Masking

Participants were instructed to identify backward-masked photographs of either a person or an object presented for either 33 ms or 83 ms. Admon *et al.* (17) found that high amygdala reactivity to short presentation (33 ms) among a priori healthy individuals predicted more stress symptoms following trauma. One EFP-sham subject did not participate and was excluded from the analysis.

Experiment 3

Forty participants were randomly assigned to the EFP-test (n = 16, aged: 22–33), EFP-sham (n = 12; aged 23–32), or no-treatment (n = 12; aged 23–34) group. Amygdala-related behavioral modifications were tested based on a well-established association between performance in an emotional conflict Stroop task and downregulation of amygdala activity (18). All groups performed two sessions of this task with a 1-hour break between sessions. During the break, the EFP-test group underwent amyg-EFP NF, the EFP-sham group underwent sham-NF, and the no-treatment group had no particular task. NF in experiment 3 was performed using a visual scenario with the fMRI-NF design of experiment 2 (Supplemental Figure S3). Participants in the EFP-test and EFP-sham groups had no knowledge of their assignment. During the emotional conflict task, participants viewed fearful or happy facial expressions with superimposed congruent or incongruent words (happy\fear) and were asked to identify the emotional expression while ignoring the words. Emotional adaptation is measured by the difference in response times between the low-conflict (two consecutive incongruent stimuli [ii]) and high-conflict (incongruent stimulus following congruent stimuli [ci]) conditions. A low score (ii−ci) indicates better implicit emotion regulation (18).

RESULTS

Experiment 1: The Amyg-EFP Neural Validity

The simultaneous EEG/fMRI recordings indicated that the amyg-EFP reliably predicted amygdala fMRI-BOLD activity. A whole-brain random effects general liner model analysis using the amyg-EFP signal for all participants (i.e., EFP-test and EFP-sham) as a regressor revealed that the amyg-EFP signal correlated with the BOLD activity of the right amygdala (peak Talairach coordinates: x = 23, y = −2; z = −17; false discovery rate-corrected $p < .05$, n = 23) (Figure 1D). Remarkably, the amyg-EFP signal in this study correlated with amygdala-BOLD activity in the region of interest (ROI) used to develop the model (peak coordinates: x = 20, y = −5; z = −17). Importantly, the analysis revealed no differences between the EFP-test and EFP-sham groups in the BOLD correlates of the amyg-EFP. As anticipated, the amyg-EFP also correlated with activity in additional brain regions, including premotor, somatosensory, and associative visual cortexes (Supplemental Table S1). An additional whole-brain analysis, using conventional EEG markers of general arousal (alpha and theta) as regressors, verified that the amyg-EFP is a unique marker providing valuable information of limbic subcortical activity beyond what could be obtained using conventional EEG (Supplemental Figure S4).

Analysis of amyg-EFP signal modulations during NF relative to rest indicated that, as hypothesized, the EFP-test group responded differently than the EFP-sham group (Supplemental Figure S5). A two-way repeated measures analysis of variance revealed a group (EFP-test/EFP-sham) by condition (rest/NF) interaction ($F_{1,22}$ = 4.34, $p < .05$). Planned comparisons (19) further showed that while the EFP-test group downregulated the amyg-EFP signal during NF relative to rest ($F_{1,22}$ = 5.8, $p < .03$; rest [mean ± SD] = .04 ± .05; NF = −.34 ± .71), the EFP-sham group did not ($F_{1,22}$ = .59, $p > .45$; rest = .01 ± .09; NF = .16 ± .37) (see Supplemental Figure S6 for changes in all EEG frequencies). Also consistent with our assumptions, changes in amyg-EFP correlated with changes in amygdala-BOLD activity during NF relative to rest (r = .47, $p < .03$), with participants who significantly reduced amyg-EFP amplitude during NF relative to rest also exhibiting a simultaneous reduction in amygdala-BOLD activity (t_9 = −2.24, $p < .05$; mean NF relative to rest = −.06 ± .08). Importantly, this reduction was not observed in other, nontargeted brain areas (Supplement).

Experiment 2: Neural Effects of Amyg-EFP NF

Similar to the first experiment, only the EFP-test group learned to downregulate the amyg-EFP during NF at the training session (Supplemental Figure S7). To test whether this learned amyg-EFP regulation led to improved downregulation of amygdala-BOLD activity, we performed an ROI analysis on the amygdala functional cluster used for the initial amyg-EFP model development. We compared the amygdala-BOLD activity observed during fMRI-NF before amyg-EFP NF (pretraining) with that observed during fMRI-NF posttraining. As

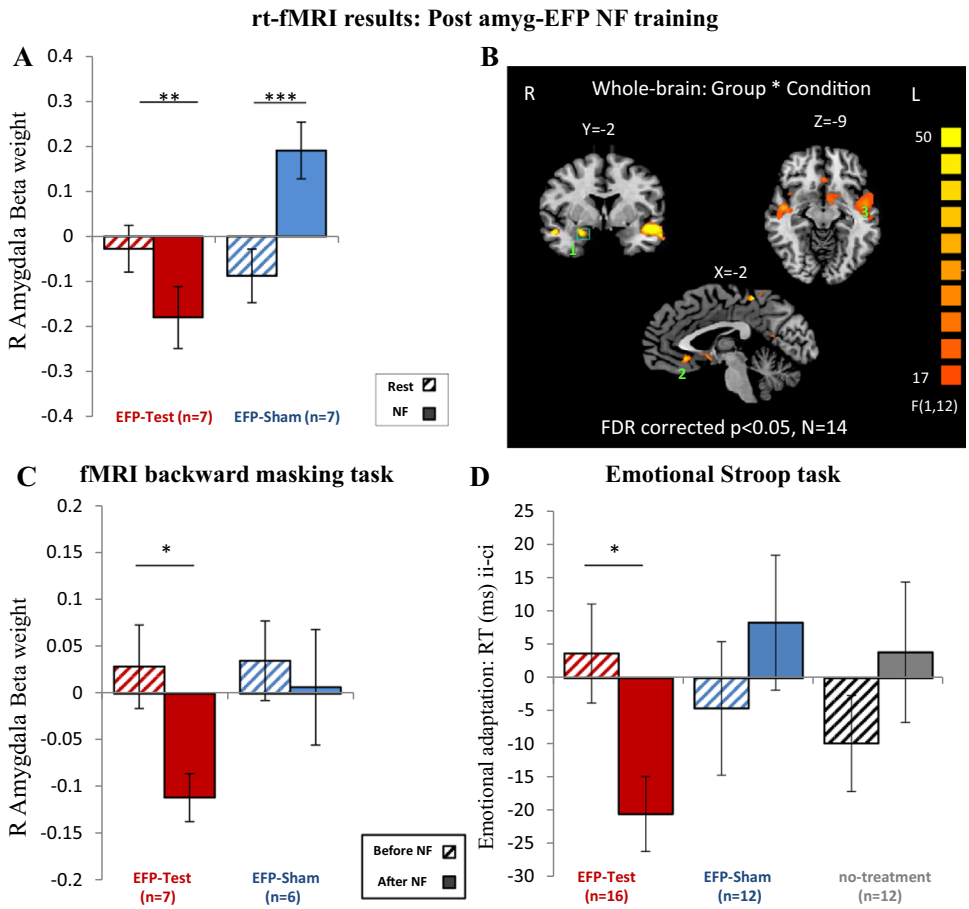

Figure 2. Amygdala-electrical fingerprint (amyg-EFP) neurofeedback (NF) outcome measures. **(A)** Experiment 2, posttraining real-time functional magnetic resonance imaging (rt-fMRI) results. The group × condition interaction ($F_{1,12}$ = 64.7, p < .001) shows that, as expected, following amyg-EFP NF training, only the EFP-test group (red bars) was able to downregulate amygdala activity during NF (solid fill) relative to rest (dashed fill). The EFP-sham group, in contrast, showed increased amygdala activity during NF relative to rest. Before amyg-EFP NF training, neither the EFP-test nor the EFP-sham groups were successful in downregulating amygdala blood oxygen level-dependent activity during NF relative to rest (all p > .2). **(B)** Coronal, axial, and sagittal views of blood oxygen level-dependent activity interaction map (group [test/sham] × condition [NF/rest]) obtained by whole-brain random effects general liner model analysis (n = 14) conducted on the post amyg-EFP NF training rt-fMRI. The green square (1) indicates the amygdala region of interest (ROI) for which the amyg-EFP model was originally developed. Note that the same ROI was targeted in the fMRI-NF. The whole-brain activation maps show that frontal and temporal areas were involved in the downregulation of amygdala activity (2—subgenual anterior cingulate cortex, 3—posterior insula). **(C)** Experiment 2, backward masking. Changes in mean amygdala peak activation for EFP-test and EFP-sham groups obtained in response to stimuli presented for 33 ms during the backward masking task before NF training (dashed fill) and following NF training (solid fill). Average beta (peak activation) were extracted from the ROI that was targeted in the fMRI NF training. Only the EFP-test group showed reduced amygdala reactivity after the NF training. The EFP-sham group showed no significant changes between time points. **(D)** Experiment 3 reaction times (RT) (ms) in the emotional conflict task with relation to NF training. A low score indicates higher emotional adaptation (Y-axis) and thus better emotion regulation. A significant interaction ($F_{2,37}$ = 4.45, p < .02) was found between group (EFP-test/EFP-sham/no-treatment) and time (before NF/after NF) showing that after NF (solid fill) only the EFP-test group (red) exhibited improved emotion regulation relative to before NF training (dashed fill). *p < 05; **p < .01; ***p < .001. ci, congruent stimulus followed by an incongruent stimulus; FDR, false discovery rate; ii, two consecutive incongruent stimuli; L, left; R, right.

expected, following amyg-EFP NF, only the EFP-test group exhibited improved downregulation of amygdala fMRI-BOLD activity relative to pretraining. A triple group (EFP-test/EFP-sham) by time point (pretraining/posttraining) by condition (rest/NF) interaction ($F_{1,12}$ = 18.66, p < .001) indicated that as expected, before amyg-EFP NF neither the EFP-test nor the EFP-sham groups were able to reduce amygdala activity during amyg-fMRI NF (all p > .2). In contrast, Figure 2A shows a group × condition interaction ($F_{1,12}$ = 62.29, p < .001), indicating that after amyg-EFP NF, only the EFP-test group successfully reduced amygdala-BOLD activity during NF relative to rest ($F_{1,12}$ = 15.67, p < .002; rest = −.027 ± .27, NF = −.18 ± .36). Surprisingly, posttraining amygdala activity of the EFP-sham group increased during fMRI-NF relative to rest ($p_{Bonferroni}$ < .001, rest = −.09 ± .32, NF = .19 ± .33). To further explore other brain regions that also might have been modulated along the amygdala, whole-brain random effects general liner model analysis was conducted on the group × condition interaction effect at the posttraining session. This analysis revealed that several temporal and prefrontal regions reacted similarly to the amygdala (Figure 2B; Supplemental Table S2). Follow-up analysis testing the training effect (NF < rest) within each group further revealed areas, such as the dorsal anterior cingulate cortex and presupplementary motor area, that might have been involved in amygdala downregulation (Supplemental Tables S3 and S4).

The neural effect of the NF training was further assessed by conducting an ROI analysis on the amygdala weighted beta during viewing of backward-masked stimuli before and after all NF sessions. Figure 2C shows that as hypothesized, following amyg-EFP NF, only the EFP-test group showed reduced reactivity of the amygdala relative to before training (EFP-test: $F_{1,11}$ = 4.90, p < .05; pretraining = .03 ± .12; posttraining = −.11 ± .07; EFP-sham: $F_{1,11}$ = .17, p > .68; pretraining = .03 ± .10; posttraining = .01 ± .15). Pretraining,

no differences were found between the groups ($F_{1,11} = .01$, $p > .92$). However, the analysis of variance did not reveal a significant group × time point interaction ($F_{1,11} = 1.44$, $p > .25$), preventing a definite dissociation between the groups.

Experiment 3: Behavioral Effect of Amyg-EFP NF

Similar to the first two experiments (Supplemental Figures S5 and S7), a group × condition interaction ($F_{1,26} = 4.78$, $p < .04$) revealed that only the EFP-test group learned to volitionally downregulate the amyg-EFP (EFP-test: $F_{1,26} = 11.28$, $p < .003$; rest = −.33 ± 1.29, NF = −.62 ± 1.23; EFP-sham: $F_{1,26} = .01$, $p > .98$; rest = −.62 ± .68, NF = −.62 ± .60). As hypothesized, following amyg-EFP NF, the EFP-test group showed improved implicit emotion regulation, while the EFP-sham and the no-treatment groups did not. A group × time point interaction ($F_{2,37} = 4.45$, $p < .02$) (Figure 2D) indicated that following NF, only the EFP-test group showed a lower emotional adaptation score relative to before NF (EFP-test: $F_{1,37} = 6.18$, $p < .02$; before = 3.72 ± 30.66; after = −20.43 ± 23.26; EFP-sham: $F_{1,37} = 1.31$, $p > .25$; before = −4.54 ± 25.06; after = 8.34 ± 36.57; no-treatment: $F_{1,33} = 1.49$, $p > .23$; before = −9.79 ± 34.78; after = 3.88 ± 35.17). Pretraining, no differences were found between the groups (all $p > .28$).

DISCUSSION

The current work demonstrated a novel, mobile, and low-cost method for local neuromodulation of deeply located limbic activity. Simultaneous EEG\fMRI indicated that the amyg-EFP model reliably predicts fMRI-BOLD activity in the amygdala ROI, for which it was originally developed (Figure 1D). Prospective fMRI scanning convincingly showed that learned amyg-EFP downregulation is causally related to improved downregulation of amygdala-BOLD activity via fMRI-NF and to reduced amygdala reactivity to visual stimuli (Figure 2). Behavioral evidence demonstrated the positive effect of amyg-EFP NF on implicit emotion regulation, pointing to the therapeutic potential of this new approach (Figure 2D).

Pushing the Spatial Limits of EEG

Source estimation of EEG is considered an ill-posed problem (20). This problem becomes even more detrimental when aiming to locate sources in deep subcortical regions. The EFP model introduced a novel data-driven approach to enable the prediction of fMRI-BOLD activity using only EEG (13). However, when forsaking a priori hypotheses, this data-driven method also suffers from a higher risk of false discovery. By conducting simultaneous EEG/fMRI on a new sample, the current study validated that the amyg-EFP can indeed predict amygdala-BOLD activity (Figure 1D). The fact that this prediction is included in the ROI used to develop the model is both reassuring and remarkable. Our results do not imply, however, that amygdala-BOLD activity is the sole origin of the amyg-EFP signal, and we do not claim to directly measure amygdala neuronal activity from scalp electrodes. Rather, the additional BOLD correlates of the amyg-EFP revealed by the whole-brain analysis (Figure 1D; Supplemental Table S1) suggest that the amyg-EFP reflects the activity of a network of regions, including areas of the limbic and salience systems in which the amygdala is considered a major hub (21). This claim is further supported by the results of the fMRI-NF showing that as expected, additional brain regions were involved in successful amygdala downregulation (Figure 2B; Supplemental Table S2). These regions, including the posterior insula and subgenual anterior cingulate cortex, were previously associated with salience processing (22) and affect regulation (23), respectively. This result once again coincides with the notion that amygdala downregulation requires the recruitment of a widely distributed neural system that possibly involves multiple levels of regulation (24). Further research could optimize the specificity of the amyg-EFP by recording EEG simultaneously with amygdala targeted fMRI-NF. Integrating intracranial electrical measurements could further enhance the model specificity and overcome the current models' base toward low frequencies (Figure 1B) resulting from the fact that slow frequencies are more prominent when recording scalp-EEG. Such research could also enable the development of additional EFP models denoting other limbic regions and provide a library of localized activation reflecting multiple processes for mobile and highly accessible brain-based diagnosis and treatment.

Therapeutic Implications of the EFP Approach

The results of the current study showing that participants are able to learn downregulation of the amygdala in a single session are consistent with previous fMRI-NF studies (25,26). However, the neural effect of amygdala-targeted NF was thus far mainly estimated on the basis of observed neural changes during an actual fMRI-NF session or, alternatively, using subsequent resting-state fMRI (7,8,25–27). In the current study, we have gone farther by training participants with amyg-EFP NF guided by auditory feedback outside the MRI scanner and subsequently tested their performance in a different context using fMRI-NF with visual feedback (Supplemental Figure S2). Our findings indicate that training in one modality and context can be transferred to a completely different context and even a different modality, as long as the same localized brain activity is targeted (Figure 2A; Supplemental Figure S7). In addition, beyond previous studies, we tested whether this learned amygdala regulation could facilitate adaptive response in an entirely different fMRI task. Our results indicate an acquired plasticity of the amygdala by showing that learned regulation via NF was later transferred to a greater reduction in amygdala reactivity in response to backward masked stimuli (Figure 2C). Lastly, while the behavioral effects of amygdala-targeted NF were previously examined using explicit measurements such as self-report questionnaires, our work exhibits implicit behavioral modifications in a task known to involve amygdala activity (18). Relative to the control groups, following amyg-EFP NF, participants exhibited a greater improvement of implicit emotion regulation, as indicated by the change in performance on the emotional conflict task (Figure 2D). Failure to implicitly regulate emotions was previously associated with stress-related psychopathologies (28). Taken together, these results demonstrate the potential of amyg-EFP NF to affect both neural processes

and behavioral manifestations of emotion regulation in healthy individuals. Such acquired regulation may facilitate adaptive mechanisms of coping with stress, hence reducing vulnerability to its consequences. However, these assumptions must be further investigated using multiple NF sessions, testing its effect before and after real-life trauma.

One might argue that the relatively weak statistical effect found for the reduced amygdala reactivity in the backward masking (Figure 2C) limits the conclusions that may be drawn. Readers should bear in mind, however, that this effect was tested on a healthy population of normal baseline performance. Testing these effects on a clinical population with abnormal amygdala activity at baseline should presumably result in stronger effects. Moreover, testing the effects of explicit regulation training such as NF on implicit regulation skills is also assumed to produce weaker effects. As such, the finding of both implicit neural and behavioral transfer effects after a relatively short training period is quite impressive.

The introduction of an EEG-based method for amygdala activity modulation holds great clinical potential. Showing that the learned skill of amygdala downregulation could facilitate adaptive neural plasticity and manifest as improved emotion regulation further demonstrates the huge clinical implications of this novel method. The future development of additional EFP models denoting different brain regions could provide a library of localized activity for mobile and low-cost brain-based diagnosis and treatment. Implementing the amyg-EFP model in NF, the current study clearly demonstrates the prospects of such approaches. EFP-NF holds the potential to reach anyone anywhere, in the form of home-stationed bedside treatment for recent trauma patients or stress resilience training for trauma prone individuals.

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TH and JNK conceived and designed the study. JNK, AC, and AO-B collected the data. GJ, SK, LI, IK, and JNK programmed the real-time imaging Paradigm and data analysis methods. YMH and NI conceptualized and constructed the EFP model. JNK, GG, IK, AC, and AG analyzed the data. AG and AE designed the emotional conflict task. JNK and TH wrote the manuscript. YMH, GG, AC, SK, LI, AE, AG, and NI read and commented on the manuscript.

The authors report no biomedical financial interests or potential conflicts of interest.

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