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Current State of fMRI Neurofeedback for Psychiatric Disorders

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Introduction

In this review, the definition, approach, and implementation of neurofeedback as an intervention for psychiatric illness is described, with a particular focus on major depressive disorder (MDD). We conclude with a discussion of the potential for neurofeedback to become part of the treatment options available for patients with MDD.

We define neurofeedback as a form of biofeedback in which a person sees and learns to control a display that represents their own brain activity. This review will focus on functional magnetic resonance imaging (fMRI) neurofeedback. In the case of fMRI neurofeedback, participants receive feedback regarding the blood-oxygen-level dependent (BOLD) activity from a region (or several regions) in their own brain.[1] BOLD activity is an indirect measurement of neuronal activity.[2]

Typical Neurofeedback Design

Figure 1 shows the setup of a typical neurofeedback design. The participant is placed in the fMRI machine (Figure 1a). Then a region or a set of regions is defined and localized in the participant's brain (Figure 1b). While the participant is performing a task, their data is processed in real time using neurofeedback software (Figure 1c). Many individuals custom-design their real-time software, but there are commercial products available (Turbo-BrainVoyager; Brain Innovation, the Netherlands). Processing usually includes motion correction and spatial smoothing. The average signal from the region(s) of interest is computed and then presented to participants through a visual display, which they are instructed to change the level of. A dynamic thermometer is most commonly displayed (Figure 1d). However, there are many types of displays that have been used, ranging from the simple thermometer[3] to complex virtual reality displays where, for example, a virtual hospital waiting room starts out loud and chaotic and

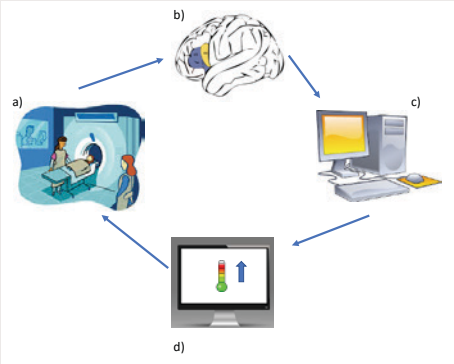

Figure 1. Real-time fMRI neurofeedback setup.

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quiets down as the participant gains control over the signal.[4] Feedback provided in other modalities (e.g., auditory[5]) is rare.

The success of neurofeedback in a clinical context is defined here as: 1) a significant increase in activity over the course of the study; 2) the ability to maintain the desired activity level during a transfer run during which participants engage in the same task as during training but without the neurofeedback information presented; and 3) that there is some clinically significant change in symptoms or behavior. Furthermore, a correlation between success and clinical change provides strong support that the mechanism targeted during neurofeedback is causally related to the pathology of the disorder studied.

While other technologies, such as electroencephalogram (EEG), may also be used to provide neurofeedback, fMRI has the advantage over these other methods by precisely localizing and modulating relevant brain structures.[6] EEG cannot be used to measure activity in deep structures (such as the amygdala),[7] which have been implicated in the pathology of mental illness.[8]

Decades of neuroimaging research has identified regions and networks in the brain that function abnormally in various mental illnesses. Neurofeedback takes advantage of this research by directly modulating these regions in patients. The potential therapeutic impact of fMRI neurofeedback has been examined for MDD,[9-13] obsessive compulsive disorder (OCD),[14,15] schizophrenia,[16-19] addiction,[3,20,21] attention deficit hyperactivity disorder (ADHD),[22,23] and post-traumatic stress disorder (PTSD).[24-27] Table 1 provides an overview of the clinical applications of neurofeedback to date. The current paper focuses on neurofeedback for MDD.

MDD is the leading cause of disability in the United States,[31] with the toll on the U.S. society and economy estimated at $210 billion.[32] Up to two-thirds of patients who seek standard pharmacological and/or psychological interventions will not respond, while only one-half of patients who do will achieve sustained remission.[33] Therefore, there is a need to develop novel therapeutics for MDD and to improve the effectiveness of noninvasive treatments.

Healthy individuals can learn to control hemodynamic activity in a variety of brain regions implicated in emotional processing, including the insula, amygdala, and ventrolateral prefrontal cortex (PFC) using negative memories and imagery;[34] anterior insula using positive and

Study	Disorder	Brain Region	Regulation Instructions	Control Condition	Outcome
Linden et al (2012) (9)	MDD	Brain areas active while viewing positive pictures	Increase activity	Mental rehearsal outside of the scanner	Decreased depressive symptoms
Young et al (2014) (10)	MDD	Amygdala	Increase activity	Alternate region of interest	Decreased state anxiety and increased state happiness
Young et al (2017) (11)	MDD	Amygdala	Increase activity	Alternate region of interest	Decreased depressive symptoms
Hamilton et al (2016) (12)	MDD	Salience network	Decrease activity	Yoked sham	Decreased emotional response to negative scenes and self-descriptive adjectives
Mehler et al (2018) (13)	MDD	Brain areas active while viewing positive pictures	Increase activity	Alternate region of interest	Decreased depressive symptoms in both groups
Gerin et al (2016) (24)	PTSD	Amygdala	Decrease activity	None	Decreased symptoms
Nicholson et al (2017) (25)	PTSD	Amygdala	Decrease activity	None	Decreased dissociative symptoms
Zotev et al (2018) (26)	PTSD	Amygdala	Increase activity	Alternate region of interest	Decreased symptoms in both groups
Zweerings et al (2018) (27)	PTSD	ACC	Decrease activity	None	Decreased intrusion and avoidance scores, increased positive affect
Ruiz et al (2013) (16)	Schizophrenia	Insula	Increase activity	None	Increased recognition of disgust facial expressions
Cordes et al (2015) (17)	Schizophrenia	ACC	Increase activity	None	No behavioral/clinical measure
Dyck et al (2016) (18)	Schizophrenia	ACC	Increase activity	None	Reduced auditory verbal hallucinations, increased positive mood
Orlov (2018) (19)	Schizophrenia	STG	Decrease activity	None	Reduced auditory verbal hallucinations
Li et al (2013) (20)	Addiction	ACC, mPFC	Decrease ACC, Increase mPFC	None	Reduced subjective craving to smoke
Hanlon et al (2013) (3)	Addiction	ACC, mPFC	Decrease ACC, Increase mPFC	None	No behavioral/clinical measure
Karch et al (2015) (21)	Addiction	Prefrontal areas active when viewing pictures of alcohol	Decrease activity	Yoked sham	Decreased ratings of craving
Buyukturkoglu et al (2015) (28)	OCD/Anxiety	Insula	Decrease activity	None	Decreased negative valence and disgust ratings for symptom-provoking images
Scheinost et al (2013) (14)	OCD/Anxiety	Orbitofrontal Cortex	Bidirectional	Yoked sham	Decreased contamination anxiety
Zilverstand (2015) (15)	Spider Phobia/Anxiety	Insula and DLPFC	Increase DLPFC Decrease insula	Mental rehearsal inside of the scanner	Decreased ratings of spider fear
Sitaram et al (2014) (29)	Personality Disorder - Psychopathy	Insula	Increase activity	None	No behavioral/clinical measure
Paret et al (2016) (30)	Personality Disorder - Borderline	Amygdala	Decrease activity	None	Decreased dissociative experiences
Alegria et al (2017) (23)	ADHD	Inferior prefrontal gyrus	Increase activity	Alternate region of interest	ADHD symptom reduction, improved sustained attention
Zilverstand (2017) (22)	ADHD	ACC	Increase activity	Mental rehearsal inside of the scanner	Improved cognitive functioning

Table 1: Neurofeedback Studies in Patients

Abbreviations: ACC = anterior cingulate cortex; ADHD = attention deficit hyperactivity disorder; MDD = major depressive disorder; mPFC = medial prefrontal cortex; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder; STG = superior temporal gyrus

negative imagery;[35] anterior cingulate cortex by focusing on or away from painful stimuli;[36] and amygdala using negative imagery[5] or positive autobiographical memories (AM).[37]

Decades of neuroimaging research has identified neural signatures of depression. By using what we have learned with respect to how patients' brains react differently than those of healthy individuals, we can identify certain regions that seem to be particularly important in the onset and maintenance of these disorders. By far, the region that has received the most attention is the amygdala.[8] This region plays a critical role in emotional processing and responding, in neural processing of underlying emotional responses to salient environmental stimuli, in generating fight or flight responses to potential threats, and in generating emotional reactions to ambiguous, appetitive, or novel stimuli.[38-42] Amygdala neurons project to sensory cortical, prefrontal cortical, and other mesiotemporal regions to process environmental information and prompt adaptive behavioral and visceromotor responses.[43] While much attention has been focused on the amygdala's role in processing and responding to negative/fearful emotional stimuli,[40] evidence suggests the amygdala more generally influences the perceived salience of stimuli and events,[42] and that amygdala BOLD activity increases to both positively and negatively valenced emotional stimuli.[41,44-46] Abundant evidence suggests amygdala hemodynamic responses are exaggerated to negative stimuli in MDD.[47,48] However, extant evidence further suggests MDD-associated abnormalities are "doubly dissociated" from healthy individuals by virtue of their greater amygdala response to negative stimuli and attenuated amygdala response to positive stimuli.[45]

Evidence also supports a role of the amygdala in recovery from MDD. Following successful treatment with selective serotonin reuptake inhibitors (SSRIs), the hyperactivation of the amygdala to negative stimuli decreased while activation of the amygdala to positive stimuli increased.[45] Increased amygdala activity to the presentation of positive words and decreased activity in response to negative words were also seen following two weeks of Cognitive Control Therapy.[49] These findings suggest that decreased activation of the amygdala to positive stimuli is clinically significant, and that some antidepressant drugs and cognitive therapies exert their therapeutic effect by normalizing the emotional processing bias. The evidence supporting a role of the amygdala in onset and recovery from MDD, taken together with evidence that the amygdala links the domains of affective experience/response and emotional memory recall, supports using neurofeedback to train patients to regulate their amygdala response to emotional stimuli.

Increasing Response to Positive Stimuli

While there is sufficient evidence to suggest that decreasing the amygdala response to negative stimuli may be effective at relieving depressive symptoms, neurofeedback studies in depression have focused on the attenuated brain activity seen when processing positive information. This is because in MDD, amygdala responsiveness to positive stimuli is correlated inversely with depression severity.[50,51] In patients remitted from MDD, amygdala activity during positive autobiographical memory (AM) recall is indistinguishable from controls.[51] Therefore, the first randomized clinical trial of neurofeedback for MDD focused on increasing the amygdala response to positive stimuli.[11]

Young and colleagues conducted several studies on the ability of patients with MDD to upregulate their amygdala response to positive autobiographical memories and examined changes in mood, symptoms, and processing biases. In an initial study, depressed patients were indeed able to significantly increase their amygdala BOLD activity over the course of the experiment and maintain it during a transfer run. Following a single session, improvements in mood were observed — specifically, participants who received amygdala neurofeedback were happier and less depressed, anxious, and irritable after neurofeedback relative to before neurofeedback and to a control group that received neurofeedback from a parietal region putatively not implicated in emotion regulation or depression, but which could still be regulated with the strategy of recalling positive memories.[10]

Young and colleagues then went on to conduct a double-blind randomized clinical trial.[11] In this trial, participants engaged in two neurofeedback training sessions and completed measures of symptoms and processing biases one week before and after the neurofeedback training. Clinical measures included both self-report (Beck Depression Inventory-II) and clinically administered (Montgomery–Åsberg Depression Rating Scale [MADRS], Hamilton Depression Rating Scale-21 [HDRS]). All ratings significantly decreased in the experimental group both from baseline and relative to the control group. Twelve participants in the experimental group responded to neurofeedback (defined as at least a 50 percent decrease in MADRS score), compared with two participants in the control group. Six participants in the experimental group and one in the control group met criteria for remission at study end (MADRS score > 10), resulting in a number needed to treat of four (95 percent confidence interval, 2–50). This remission rate is similar to rates seen with antidepressant medications[52] and cognitive behavioral therapy.[53] Furthermore, there was a significant relation between the ability to regulate the amygdala and the degree of improvement in clinical symptoms, providing additional support for the causal role between real-time fMRI neurofeedback (rtfMRI-nf) learning and clinical improvement.

Furthermore, autobiographical memory recall was improved and increased processing of positive stimuli was observed.[11,54] It is a well-replicated finding in the literature that patients with MDD have AM deficits, characterized by overgeneral memory recall: defined as decreased recall of specific AM (a memory for an event that occurred at an identifiable time and place and which did not last over 24 hours, e.g., 'I went grocery shopping last Sunday') and increased recall of general, categorical AM (summaries or categories of events without reference to a single episode, e.g., 'I go grocery shopping every weekend').[55] Following two rtfMRI-nf sessions, participants in the experimental group had an increase in the percent of specific memories recalled and a decrease in the percent of overgeneral memories recalled.[11] The effect was predominately attributable to changes in positive memories. Decreased reaction times to identify positive faces and to classify self-referential words as positive was also observed following neurofeedback in the experimental group.[54] Finally, amygdala responses to implicitly presented emotional faces in a Backward Masking task normalized following amygdala neurofeedback training — amygdala activity increased to positive faces and decreased to negative.[54] This finding suggests that training the amygdala response in one direction (upregulate to positive) at least partly generalized to the processing of other types of emotional stimuli in the amygdala, and that patients learned to adaptively regulate their amygdala response rather than to increase it nonspecifically. Additional clinical trials are ongoing (NCT02709161; NCT03428828) to further develop this procedure into a standardized intervention for MDD.

Other researchers have not focused on a specific region, instead training depressed participants to enhance brain activity in the regions found to be active while viewing positive stimuli or recalling positive experiences.[9,13] The theory is to train individuals to make the brain areas they typically recruit during positive experiences even more responsive to positive stimuli. This research has been conducted by Linden and colleagues and has produced mixed results. In their first study, a localizer scan identified which regions were most active while participants viewed positive images, and then participants were trained to increase activity in these regions while engaging in positive imagery strategies. A control group performed the positive imagery without neurofeedback. Depressive symptoms (measured using the HDRS) decreased 29 percent in the experimental group and increased slightly in the control group.[9] However, when the same procedure was repeated with a different control group that upregulated the parahippocampus using positive imagery of scenes, both groups improved to a similar degree (48 percent increase and 59 percent decrease on the HDRS for the experimental and control groups).[13] While regulation success was not associated with clinical change, self-efficacy was. Participants in either group who improved clinically also reported increased self-efficacy, suggesting that it is enhancing feelings of self-efficacy and not gaining control over a particular signal driving the clinical effects observed in these studies. However, the control group in this study actually increased activity in the same regions as the experimental group (in addition to the parahippocampus), so it is possible that both groups' symptoms improved because they both ultimately regulated the same regions. Further research is needed to disentangle the effects of reward and increasing self-efficacy from gaining control over a brain signal.

Decreasing Response to Negative Stimuli

To date, there has been only one study attempting to train participants with MDD to downregulate the brain response to emotional stimuli. Hamilton et al. (2016) trained participants with MDD to downregulate a region within the predefined salience network that was found to be most active when viewing negative pictures.[12] A yoked sham control group was employed where participants saw the signal from a participant in the experimental group instead of their own brain signal. The experimental group showed a significant decrease in emotional ratings of negative pictures and in self-relevance ratings of negative adjectives following neurofeedback that was not observed in the control group. This suggests that downregulating regions involved in emotional processing also may be clinically effective in MDD. It is likely that a combination of upregulation to positive and downregulation to negative stimuli will ultimately be the most effective intervention for MDD, however, this research has yet to be done.

While no group has examined whether depressed patients can downregulate their amygdala response to negative stimuli, this type of neurofeedback has been found to reduce symptoms of PTSD[24,25,56] and borderline personality disorder.[30] Notably, these disorders are characterized by enhanced reactions to negative stimuli; there is little to no evidence that responses to positive stimuli are altered in these populations. Indeed, training participants with PTSD to upregulate their amygdala did not result in significant changes in PTSD symptoms relative to a control group regulating parietal activity.[26]

Issues to Consider When Designing or Evaluating a Neurofeedback Study

Control Task

The selection of a control task for rtfMRI-nf experiments is challenging, and no consensus has yet been reached as to the optimal approach. Studies utilizing out-of-scanner-control conditions,[9] control conditions in which the neurofeedback bar remains static,[57] or no control condition (examining only within subject changes)[58,59] run the substantial risk of false positives as control participants know they are not receiving feedback, and experimenter blinding is impossible. Therefore, improvements evident in the active relative to the control group may be due to experimenter bias or the appeal of a novel, technology-based intervention and not to gaining control over the target region. Placebo control conditions are the most commonly employed in clinical studies — with participants: a) receiving feedback from a brain region other than that targeted in the experimental group, b) receiving yoked sham feedback that shows the brain activity of a previous participant, or c) engaging in the same strategies as the neurofeedback group while undergoing fMRI but receiving no feedback.

When the control group is provided feedback from an alternate region, participants should be able to gain a similar level of control over the trained signal as the experimental group, and any assigned mental strategy used should be the same across groups. This approach controls for psychoeducative effects (the benefit of learning to control a signal) and allows for conclusions as to whether feedback of the target aspect of brain function is necessary to gain control over that aspect. Additionally, it allows for examination of whether changes in mood and behavior in the experimental group are due specifically to the feedback or to a placebo effect. As long as participants are equally successful at regulating the neurofeedback signal, motivation effects are also controlled for. Studies using this design can be challenging to develop as it can be difficult to select a control ROI that is both independent from the target ROI (so that regulating the control ROI does not systematically affect the target ROI's activity), and that can be regulated by participants as easily as the target ROI using the same assigned mental strategy.

Yoked sham neurofeedback is one of the most commonly employed control conditions in neurofeedback studies.[60] The benefits of this control condition include matching the experimental condition on all aspects except gaining control over the experimental ROI signal. Provided that control participants do not detect the noncontingency between their efforts and the resulting signal change, there should be equal motivation and perceived success between the groups. There is concern, however, that participants will detect noncontingency between their efforts and the resulting signal, resulting in negative effects such as frustration and decreased motivation which can become critical confounds. Therefore, in this type of design, monitoring frustration/satisfaction during the study and asking subjects after the study if they believe they had received the experimental intervention (and having them rate how confident they are in that belief) are critical for interpretation of results.

The mental-rehearsal control condition can play a critical role in demonstrating a true neurofeedback effect because it provides the only possibility to control for pure behavioral (e.g., simple mental training) effects. Implementing this control condition inside the MRI

scanner allows the researchers to rule out global, spatially nonspecific (e.g., general-arousal) effects by analyzing the functional brain-imaging data that is obtained during mental rehearsal. While this control condition is helpful in establishing a true neurofeedback effect by controlling for pure behavioral effects, it should ideally be combined with one or more other control conditions.

At some point in intervention development, the comparison of neurofeedback as an add-on to treatment as usual (TAU) is desirable.[61] This design may be particularly useful in scenarios where TAU is widely available and can reveal whether the neurofeedback component is likely to have a clinically significant benefit over available treatments, which is in many respects the core clinical question. Of course, the neurofeedback plus TAU vs. TAU-only comparison does not address any nonspecific effects, which would have to be addressed by comparison with placebo control interventions, and it does not answer the question of whether other interventions, for example those using cheaper biofeedback technology, would have similar effects. To date, no fMRI neurofeedback study has used TAU as a comparison, and this will be an important future direction for researchers.

What to Train

There are two main approaches for selecting a region or set of regions to train for neurofeedback studies. In the *deficit* approach, researchers attempt to train what is abnormal to function normally. This requires knowledge of the pathophysiology of the disorder and key mechanisms underlying change. This is the approach taken by Young and colleagues in their neurofeedback studies.[10,11] The *compensatory* approach trains participants to enhance what they are already using to take over for impaired function. This approach involves a functional localizer scan to identify areas that are active during a specific task that are then selected for training during neurofeedback. This is the approach taken by Linden and colleagues.[9,13] Both approaches have resulted in clinical improvement in patients with MDD.

How Much Training

Studies attempting to train brain regions implicated in emotional processing via rtfMRI-nf in mood-disordered individuals have provided between one to five separate training sessions,[9,12,24,61] yet no examination of dose response or definition of sufficient target engagement has been provided. Determining a sufficient number of rtfMRI-nf sessions is critical for treatment development,[63] and studies are currently underway to examine dosing and duration of neurofeedback effects.

Issues Contributing to Nonresponse

It is estimated that approximately 30 percent of participants will not be able to learn to control a signal across neurofeedback designs.[64] Examination of these subgroups can assist in the development of subsequent randomized trials that minimize the number of non-learners to avoid loss of power and waste of resources by making the neurofeedback task more learnable and/or identifying predictors for patient selection. Young and colleagues have found amygdala regulation success to be related to the duration of the current depressive episode, suggesting that the clinical success of rtfMRI-nf of the amygdala may be dependent upon targeting patients early in the course of their depressive episode.[10,54] Additional research into what contributes to the inability to regulate a signal is warranted.

There are some **disadvantages** of using fMRI for neurofeedback. Individuals with metal implants or who work with metal (i.e., welding) may not receive an fMRI scan. This is because fMRI uses magnetic waves and could cause serious harm to these individuals. Individuals with claustrophobia are also not good candidates for this intervention, as their anxiety at being in the confined space of the fMRI scanner would likely interfere with the intervention. Finally, fMRI is expensive and requires technically trained staff to operate it. For these reasons, fMRI neurofeedback is unlikely to become widely clinically available within the next several years.[63] However, it may be practical for treatment-resistant individuals to receive this intervention prior to more invasive interventions, such as deep brain stimulation. Furthermore, the information gained by researching neurofeedback may lead to more targeted, scalable interventions. While EEG may not be able to measure activity in limbic structures, several groups are attempting to create an EEG signature of amygdala activity by collecting EEG data concurrently with fMRI data and employing machine learning analyses.[56]

Conclusion

Experiments repeatedly demonstrate that real-time fMRI neurofeedback allows individuals to modulate the BOLD signal from various regions in the brain, and that learning to control these signals results in behavioral change and clinical improvement. This evidence suggests that fMRI neurofeedback may develop into a powerful biobehavioral intervention. However, for that to occur, more well-designed randomized clinical trials are needed, as are comparisons to currently available treatments. For many mental illnesses, particularly MDD, neurofeedback is moving beyond the proof-of-concept state and towards robust, replicable, well-controlled designs.

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