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Effects of salience-network-node neurofeedback training on affective biases in major depressive disorder

J. Paul Hamilton [a,*], Gary H. Glover [b], Epifanio Bagarinao [c], Catie Chang [d], Sean Mackey [c], Matthew D. Sacchet [e], Ian H. Gotlib [f]

[a] Center for Social and Affective Neuroscience, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden
[b] Department of Radiology, Stanford University, Stanford, CA, USA
[c] Department of Anesthesiology, Stanford University, Stanford, CA, USA
[d] Advanced MRI Section, Laboratory of Functional and Molecular Imaging, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA
[e] Neurosciences Program, Stanford University, Stanford, CA, USA
[f] Department of Psychology, Stanford University, Stanford, CA, USA

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ABSTRACT

Neural models of major depressive disorder (MDD) posit that over-response of components of the brain's salience network (SN) to negative stimuli plays a crucial role in the pathophysiology of MDD. In the present proof-of-concept study, we tested this formulation directly by examining the affective consequences of training depressed persons to down-regulate response of SN nodes to negative material. Ten participants in the real neurofeedback group saw, and attempted to learn to down-regulate, activity from an empirically identified node of the SN. Ten other participants engaged in an equivalent procedure with the exception that they saw SN-node neurofeedback indices from participants in the real neurofeedback group. Before and after scanning, all participants completed tasks assessing emotional responses to negative scenes and to negative and positive self-descriptive adjectives. Compared to participants in the sham-neurofeedback group, from pre- to post-training, participants in the real-neurofeedback group showed a greater decrease in SN-node response to negative stimuli, a greater decrease in self-reported emotional response to negative scenes, and a greater decrease in self-reported emotional response to negative self-descriptive adjectives. Our findings provide support for a neural formulation in which the SN plays a primary role in contributing to negative cognitive biases in MDD.

1. Introduction

Over the last two decades, neuroimaging investigations of Major Depressive Disorder (MDD) have been instrumental in increasing our understanding of this prevalent and debilitating condition (Kessler and Wang, 2009). Sufficient data have now accumulated from functional neuroimaging investigations of depression that, through meta-analytic integration, we have been able to identify the neural abnormalities that have been found most reliably to characterize this disorder. Specifically, in a recent meta-analysis of studies using task-based functional magnetic resonance imaging (FMRI), we found reliably increased response in fronto-insular cortex, amygdala, and dorsal anterior cingulate cortex (dACC) to negative stimuli relative to neutral stimuli; importantly, we did not observe this pattern with respect to response to positive relative to neutral stimuli in MDD (Hamilton et al., 2012). Based on these findings, we presented a neural account of the well-documented heightened response to negative stimuli in MDD, which has been hypothesized to play a significant role in the etiology and maintenance of this disorder (Beck, 1976; Gotlib and Joormann, 2010). In this formulation, we posit that through monosynaptic projections to the amygdala, dACC, and fronto-insular cortex (Jones and Burton, 1976; Mufson and Mesulam, 1984; Padmala et al., 2010), heightened baseline activity in the pulvinar nucleus in depression (Hamilton et al., 2012) potentiates response of these primary limbic nodes to affective information.

In this model, fronto-insular cortex, dACC, and amygdala — primary nodes in the brain's salience network (SN), which is postulated to undergird perception of and response to personally relevant stimuli (SN; Seeley et al., 2007) — play a crucial role in biasing the processing of negative information in MDD. This and similar formulations proposed by clinical neuroscientists (e.g., Menon, 2011) are difficult to test directly using traditional

* Corresponding author.
E-mail address: paul.hamilton@liu.se (J.P. Hamilton).

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functional neuroimaging paradigms, which typically identify only neural *correlates* of cognitive or emotional activity. Given this limitation of traditional FMRI paradigms in making causal attributions, in the present study we used an FMRI-based neurofeedback system that allows individuals to see and learn to modulate regional brain responses. The implementation of this method permits investigators to examine the effects on behavior of modulating neural activation (Weiskopf et al., 2004), as opposed to the more typical examination of the effects on the brain of manipulating behavior. Such FMRI neurofeedback systems have now been used successfully to teach healthy individuals to volitionally alter response in sensorimotor (DeCharms et al., 2004), and limbic regions (Caria et al., 2007; Hamilton et al., 2011), and to reduce the experience of pain (deCharms et al., 2005).

Recent studies using FMRI neurofeedback in MDD have explored the therapeutic utility of this method in depression. A seminal, non-placebo-controlled study showed that it is possible to teach depressed persons to increase idiographic neural activity associated with positive affect and, in doing so, decrease depressive symptomatology (Linden et al., 2012). Another recent study showed that teaching depressed persons to increase amygdala activity during recall of happy autobiographical memories increases happiness and decreases anxiety in MDD (Young et al., 2014). While not controlling for placebo effects, these studies have provided strong preliminary support for the clinical efficacy of FMRI neurofeedback paradigms.

In the current proof-of-concept study, we take a different perspective relative to previous, clinically oriented work by using FMRI neurofeedback as a tool to test and develop neural models of MDD. For this study, we constructed an experimental paradigm for testing the role of SN node over-response in producing the negative affective biases implicated reliably in MDD. In designing this study, we reasoned that if the SN plays a crucial role in producing negative affective biases in MDD, then teaching depressed persons to decrease responding in SN nodes to negative affective information should decrease affective responding to negative but not positive information. If, on the other hand, learned down-modulation of SN response to negative information has no effect on response to negative information, the hypothesis that the SN plays a critical role in negative affective biases in MDD will be disconfirmed.

To measure the effects of SN-node neurofeedback training (NFT), we assessed responses to both negative and positive stimuli before and after a regimen of NFT. In order to determine effects on affective functioning attributable to NFT as distinct from placebo effects, we also included a group of depressed participants who received sham NFT; that is, the neurofeedback they received was not veridical but, instead, was feedback from other depressed participants who had received real neurofeedback. We predicted, first, that receiving real NFT would lead to successful down-modulation of SN node response; thus, we predicted that, compared with depressed participants who received sham NFT, depressed participants who received real NFT would show reduced response of their most reactive SN node to negative stimuli following NFT. Further, and in accord with the model we present above, we predicted that, relative to their sham NFT counterparts, depressed persons who received real SN NFT would also exhibit reduced affective responding to negative affective challenge. Finally, given that the SN has been conceptualized as part of a negative valence system (Insel et al., 2010) in MDD (Hamilton et al., 2012), we predicted that the effects of real NFT would not generalize to affective responses to positive stimuli.

2. Methods and materials

2.1. Participants

Twenty-two adults diagnosed with MDD initially participated in this study. All participants met criteria for a DSM-IV diagnosis of MDD based on their responses to the Structured Clinical Interview for DSM (SCID; First et al., 2001), administered by trained diagnostic interviewers. Depressed individuals with a current comorbid diagnosis of any Axis-I disorder other than Social Anxiety Disorder (SAD) were not included in the study. Given that we were comparing two groups of depressed participants (real versus sham NFT), we included depressed individuals who were taking antidepressant medication in this study because we would not be confounding medication status with psychiatric diagnosis and, importantly, because this would bolster the generalizability of our findings to the general population of depressed persons, over half of whom take psychotropic medications (Pratt et al., 2011). At the end of the interview session, all participants completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1979) and the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988). The BDI-II and PANAS are frequently used and well validated self-report measures of the severity of depressive symptoms and levels of positive and negative affect, respectively. All stages of the research presented here were carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

To assess cognitive, behavioral, and neural effects of NFT, we assigned participants to one of two groups: REAL, in which participants saw real-time neural response data from a component of their own SN, and SHAM, in which participants saw, in the context of an otherwise equivalent neurofeedback procedure, neural response data from participants in the REAL group instead of their own neural data. We elected to use a sham NFT control group—as opposed to a control group seeing neurofeedback from a control region not implicated in depression—because this form of experimental control is the only way to ensure that the positive and negative reinforcement provided from neurofeedback, and the potential effects of this feedback on subsequent task performance, were precisely controlled. Importantly, two researchers were involved in NFT scanning: one who interacted with participants and was blind to group assignment and one that ran the NFT interface and who was not blind to group assignment. Further, in keeping with the objective of this study was to investigate the role of the SN in the pathophysiology of MDD, we focused only on the effects of learned modulation of this network.

Given pilot data indicating that 5 out of 6 individuals were successful in using neurofeedback to learn how to control neural response, we first ran 12 participants through the REAL neurofeedback protocol and identified 10 who were successful in using NFT to learn to regulate responding of a functionally defined SN-node (we include performance data for the two non-learners in a supplement to this article). Even though we excluded only a small proportion of our recruited REAL NFT sample, to ensure that this process did not bias our sample (i.e., that selecting successful neuromodulators did not inadvertently also select for factors such as age or severity of depression that might affect performance), we selected and ran through the SHAM NFT protocol depressed individuals who were matched to participants from the REAL group with respect to age, education, medication, symptom severity, and comorbidity with SAD. Importantly, all participants provided consent for participation in the NFT procedure knowing that there would be a chance that they would see sham neurofeedback.

2.2. Neurofeedback scanning protocol

2.2.1. Overview

Participants were first shown the neurofeedback interface and neuromodulation task outside of the scanner. In addition, before and after scanning, participants completed two computer-based tasks (described below) to assess response to affective challenge. After entering the scanner, participants underwent a functional-localizer/pre-training assessment scan, three NFT scans, and a post-training assessment scan. Finally, following scanning and assessment, all participants were interviewed about whether they believed the NFT signal was real and, for exploratory purposes, what technique they used to control the NFT signal.

2.2.2. Pre- and post-scanning assessments

To assess changes in affective responding due to NFT, participants completed, both before and after training, an out-of-scanner picture-rating task in which they viewed and rated on a scale of 1–9 the intensity of 15 novel, negatively valenced pictures from the International Affective Picture System (IAPS; Lang and Greenwald, 1993). We used a total of 78 novel, negative IAPS pictures (mean intensity: 4.18; SE: 0.17; mean arousal: 5.11; SE: 0.15) for the behavioral testing and scanning portions of the study (15 for each rating task, 15 for each of the pre- and post-training scans, and 6 for each of three NFT scans). To ensure their appropriateness for use with depressed participants, the negative pictures were all rated by two trained clinicians on a 1–9 scale as reflecting higher levels of sadness than of fear or disgust (mean sadness: 7.5; mean fear: 2.5; mean disgust: 2.0). In addition, before and after NFT, participants completed a brief version of the self-referent encoding