Study Protocol

Official Title: Effects of Amygdala Neurofeedback on Depressive Symptoms and Processing Biases

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Scientific Background

Real-time functional magnetic resonance imaging (rtfMRI), in which blood oxygen-level dependent (BOLD) fMRI data processing and display are performed concomitant with image acquisition (Cox et al., 1995) has enabled rtfMRI neurofeedback (rtfMRI-nf), allowing a person to see and regulate the fMRI signal from their own brain (deCharms, 2008). rtfMRI-nf has the advantage over other biofeedback methods (such as EEG) of precisely localizing neurophysiological activation, and allowing focal investigation of relationships between cognitive-behavioral functions and neuroplasticity changes in deep brain structures (deCharms et al., 2004; Weiskopf et al., 2007). Recent studies provide evidence of the utility of rtfMRI-nf in psychiatric populations (Ruiz et al., 2011; Linden et al., 2012; Young et al., 2014). Our proposal focuses on attenuated positive emotional processing in major depressive disorder (MDD). Cognitive theories of MDD are predicated on the idea that perception and cognition are biased by negative emotions (Roiser et al., 2012), and abundant evidence suggests left amygdala hemodynamic responses are exaggerated to negative stimuli in MDD (Sheline et al., 2001; Drevets et al., 2002; Siegle et al., 2002; Fu et al., 2004). 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 (Victor et al., 2010), including positive autobiographical memories (Young et al, 2016). Dr. Young's previous work has shown that it is possible to restore the normative positive processing bias evinced in healthy individuals to MDD patients via the use of rtfMRI-nf (Young et al., 2014). This research suggests that low amygdala automatic reactivity to positive stimuli is associated with reduced recruitment of attentional resources that cause emotional stimuli to be rendered salient and something worth expending effort recalling, suggesting neurocognitive techniques increasing positive processing conceivably hold therapeutic potential in the clinical management of MDD.

Neurofeedback combines biological and cognitive treatment principles in a way that differentiates it from both traditional biofeedback and cognitive therapy. It provides the additional benefit of enhancing the patent's perception of self-efficacy, which is considered an important principle in cognitive restructuring (Bandura, 1997). A fundamental component of cognitive-behavioral treatment of MDD involves the restructuring of thought and emotional processing towards affectively positive and away from affectively negative thoughts, feelings, and memories (Beck, 1993). Newer cognitive therapies specifically target positive affect and increasing patients' ability to sustain positive affect over time (McMakin et al., 2011). The continued focus on improving positive affect as a component of cognitive therapy provides a clear rationale to train MDD patients to more effectively access positive autobiographical memories in the generation of positive mood. The rtfMRI-nf procedure for MDD may provide clinicians with a tool to optimize cognitive therapy. It is a well-established finding in the literature that CBT is associated with better outcome when patients experience 'sudden gains' during the first third of treatment. A sudden gain is defined as a change in Beck Depression Inventory (BDI) score in one between session interval that is at least 7 points and at least 25% of the previous score (Tang & DeRubies, 1999; Kelly et al., 2005). While the neurophysiological mechanism underlying this phenomenon has not to our knowledge been investigated it has been established that these gains can occur in the absence of overt cognitive changes (Kelly et al., 2005). Patients who experience a sudden gain during the first third of treatment are more likely to be classified as treatment responders (Kelly et al., 2005), and experience better outcomes, with

patients experiencing sudden gains remaining less depressed than other patients after the end of treatment (Tang & DeRubeis, 1999; Tang et al., 2002; Tang et al., 2007). Therefore, increasing the number of patients experience sudden gains during the first third of CBT has the potential to improve long-term outcomes of CBT and provides a strong rationale for augmenting CBT with early interventions that decrease depressive symptoms, such as our amygdala rtfMRI-nf protocol.

Study Objectives

The objective of the proposed research is to determine whether augmenting standard cognitive-behavioral therapy (CBT) with real-time fMRI neurofeedback aimed at increasing the amygdala's hemodynamic response to positive autobiographical memory recall will result in greater efficacy and a shorter time course to symptom improvement.

Specific Aim: In patients with major depressive disorder, determine whether the time course of symptom improvement and overall efficacy of cognitive-behavioral therapy (CBT) can be improved by augmenting it with real-time fMRI amygdala neurofeedback (rtfMRI-nf) regarding amygdala activity.

Hypothesis: Because our rtfMRI-nf procedure utilizes principles of CBT including restructuring emotional processing towards the positive, and because we have observed large changes in depression ratings over the course of 3 weeks in those receiving amygdala rtfMRI-nf, we hypothesize augmenting a course of CBT with two amygdala rtfMRI-nf sessions aimed at increasing the amygdala's response to positive autobiographical memories during the first month of therapy will result in a greater decrease in depressive symptoms (as measured by the primary outcome measure BDI-II and the secondary outcome measure PROMISE depression rating) compared to those who receive rtfMRI-nf from a parietal control region putatively not involved in emotional processing.

Study Design & Methods

We will assess the efficacy of augmenting cognitive behavioral therapy with real-time fMRI neurofeedback in depressed adults. This is an experimental longitudinal design where participants will be followed weekly for 10 weeks after being randomized under double-blind conditions to receive 2 sessions of neurofeedback from the amygdala (experimental group) or a parietal region serving as an active control. Procedures involve a battery of self-report measures, fMRI and psychophysiological indices (eye tracking, heart rate, respiration, electroencephalography). Following the neurofeedback procedure, participants will receive 10 weeks of CBT at no cost to them. Two hundred and forty participants will be screened, and 60 will complete the research activities.

Eligibility Criteria

i) right-handed adults (ages 18 – 55) with a primary diagnosis of MDD according to diagnostic criteria DSM-IV-TR for recurrent MDD who are currently depressed will be recruited to participate
ii) must be able to give written informed consent prior to participation
iii) Do not have a clinically significant or unstable cardiovascular, pulmonary, endocrine, neurological, gastrointestinal illness or unstable medical disorder
iv) Do not meet DSM-IV criteria for alcohol and/or substance dependence (other than nicotine) within 12 months prior to screening
v) Do not have a history of traumatic brain injury
vi) Are able to complete MRI scan; do not have claustrophobia or general MRI exclusions (e.g., shrapnel inside body)
vii) are not currently pregnant or breast feeding
viii) are able to complete questionnaires written in English
ix) Are not currently (within 3 weeks of testing) using any anticonvulsants, stimulants, benzodiazepines, beta-blockers, or other medications (except antidepressants and antipsychotics) likely to influence cerebral blood flow. Effective medications will not be discontinued for the purposes of the study.
x) Do not have a DSM-IV-TR diagnosis of psychotic or organic mental disorder, bipolar I or II disorder. We will record the presence of co-morbid anxiety disorders, but will not exclude MDD participants with such disorders so long as the anxiety disorder is not the primary/dominant diagnosis
xi) Do not have any eye problems or difficulties in corrected vision.
xii) are willing to temporarily discontinue therapy to participate in the study

Statistical Considerations

To examine change in BDI score (primary outcome) and PROMIS (secondary outcome), a linear mixed effects model with the fixed factors of Visit(1, 2, 3, 4) and Group(Experimental, Control) was used. The neurofeedback training effect was evaluated via linear mixed effects model with the fixed factors of Run(Baseline, Practice, Run1, Run2, Run3, Transfer), Visit(2, 3), region-of-interest(Amygdala, Intraparietal), and Group(Experimental, Control) for regional percent signal change.

Power analysis used in estimating sample size in fMRI studies suggests for a liberal threshold of $p<0.05$, 16 participants are required to achieve 80% power at the single voxel level for typical activations between groups (Desmond et al., 2002) Mumford & Nichols, 2008). Proof-of concept studies comparing CBT for MDD augmented with antidepressant medication have found statistical differences on clinical measures (including HDRS and BDI) with 20 participants per group (Rush et al., 1977; Blackburn et al., 1981; Lynch et al., 2003; Huijbers et al., 2012). Therefore, during the R00 phase, we plan to include 30 participants per group to allow for larger drop out rates (at least 33%) due to the increased number of study visits required for the CBT component.