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Longitudinal effects of cognitive behavioral therapy for depression on the neural correlates of emotion regulation

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ABSTRACT

Cognitive behavioral therapy (CBT) is effective for a substantial minority of patients suffering from major depressive disorder (MDD), but its mechanism of action at the neural level is not known. As core techniques of CBT seek to enhance emotion regulation, we scanned 31 MDD participants prior to 14 sessions of CBT using functional magnetic resonance imaging (fMRI) and a task in which participants engaged in a voluntary emotion regulation strategy while recalling negative autobiographical memories. Eighteen healthy controls were also scanned. Twenty-three MDD participants completed post-treatment fMRI scanning, and 12 healthy volunteers completed repeat scanning without intervention. Better treatment outcome was associated with longitudinal enhancement of the emotion regulation-dependent BOLD contrast within subgenual anterior cingulate, medial prefrontal cortex, and lingual gyrus. Baseline emotion regulation-dependent BOLD contrast did not predict treatment outcome or differ between MDD and control groups. CBT response may be mediated by enhanced downregulation of neural activity during emotion regulation; brain regions identified overlap with those found using a similar task in a normative sample, and include regions related to self-referential and emotion processing. Future studies should seek to determine specificity of this downregulation to CBT, and evaluate it as a treatment target in MDD.

1. Introduction

Major depressive disorder (MDD) is predicted to become the leading cause of disability by 2030 (Mathers et al., 2008). While treatment with evidence-based cognitive-behavioral therapy (CBT) for depression produces remission in a minority of patients (DeRubeis et al., 2005; Elkin et al., 1989; Luty et al., 2007), with comparable efficacy to other first-line antidepressant treatments (DeRubeis et al., 1999; Dobson et al., 2008; Trivedi et al., 2006), these treatments leave many depressed patients with significant symptoms and impaired functioning despite vigorous treatment. Treatment selection for MDD involves trial-and-error, due to the lack of known clinically useful moderators of treatment outcome. Task-based functional magnetic resonance imaging (fMRI) has been used to investigate neural predictors of treatment outcome with CBT for MDD and to map longitudinal changes produced by CBT in depression (Chuang et al., 2016; Forbes et al., 2010; Franklin et al., 2016; Fu et al., 2008; Ritchey et al., 2011; Siegle et al., 2006; Thompson et al., 2015; Yoshimura et al., 2013), largely by examining the neural correlates of tasks that elicit negative affect.

Deficits in emotion regulation may contribute to depression risk (Hopfinger et al., 2016) and psychopathology. In fMRI studies of emotion regulation, differences in blood-oxygen-level dependent (BOLD) activity and connectivity have been identified in depression (Heller et al., 2009; Johnstone et al., 2007). A key goal of CBT for depression is to develop improved capacities for voluntary regulation of emotion, accomplished through techniques including cognitive restructuring, behavioral activation, and behavioral experiments (Beck, 1995). Indeed, recent evidence suggests that both in-person inpatient CBT for depression (Forkmann et al., 2014) as well a computer-based CBT intervention (Morris et al., 2015) lead to improvements in a form

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of emotion regulation, cognitive reappraisal, and that improvement in reappraisal correlates with reduction in depression severity (Forkmann et al., 2014). We therefore sought to examine the neural correlates of emotion regulation as a predictor of treatment outcome with CBT for depression, and to examine the relationship of longitudinal changes in such emotion regulation-related activity to treatment outcome.

Negative autobiographical memories are particularly salient stimuli for emotion regulation tasks in depression due to their personal relevance, in contrast to other standardized stimuli. Kross et al. developed a fMRI paradigm in which participants recall a series of emotionally negative autobiographical memories and are instructed to either respond naturally ("feel" condition), or regulate their emotional responses in two other conditions ("analyze" and "accept" conditions) (Kross et al., 2009). The analyze strategy was designed as a memory analog of cognitive reappraisal strategies used in previous fMRI studies (Ochsner et al., 2002, 2004; Ray et al., 2005; Wager et al., 2008). During both regulation strategies, healthy volunteers showed reduced activity in brain regions associated with self-referential and affective processing, including subgenual anterior cingulate cortex, medial prefrontal cortex, and lingual gyrus.

We used a modified version of this task to examine the neural correlates of voluntary emotion regulation in a group of individuals with current MDD, both before and after a course of CBT for depression. As the "analyze" condition maps closely onto the core CBT technique of cognitive restructuring, it was selected as the regulation strategy for this study (Beck, 1995). A comparison group of healthy volunteers performed this fMRI task at comparable time-points without a treatment intervention. Given the observed suppression of activity during emotion regulation previously observed in a normal sample, we hypothesized: 1) the magnitude of emotion regulation-dependent BOLD signal reduction (i.e. "feel" > "analyze" contrast) would increase longitudinally as a function of better treatment outcome with CBT; 2) the magnitude of emotion regulation-dependent BOLD reduction at baseline would be correlated with better treatment outcome; and 3) healthy volunteers would show greater emotion regulation-dependent BOLD reduction in relevant brain regions than MDD participants. We conducted whole-brain voxelwise analyses as well as analyses at the region-of-interest (ROI) level, examining regions associated with emotion regulation of negative autobiographical memories in previous work (subgenual cingulate, dorsomedial prefrontal cortex, and lingual gyrus) (Kross et al., 2009).

2. Methods

2.1. Sample

Participants were recruited using online and print advertisements as well as through referrals from surrounding clinics and gave written informed consent prior to research participation. MDD inclusion criteria included: 1) Age18-60; 2) A DSM-IV diagnosis of MDD in a current major depressive episode (MDE) as assessed using the Structured Clinical Interview (SCID) for DSM-IV (First et al., 1995); 3) 17-item Hamilton Rating Scale for Depression (HRSD) score ≥ 16 (Hamilton, 1960); 4) Lack of significant benefit from any current psychiatric medications and ability to tolerate washout (if applicable); 5) Capacity to provide informed consent. MDD exclusion criteria included: 1) Unstable medical conditions; 2) alcohol or substance use disorder within the past 6 months; 3) Other current or past major psychiatric disorders including bipolar disorder; comorbid anxiety and personality disorders were allowed and are described in Table 1; 4) Pregnancy, currently lactating, planning to conceive during the course of study participation or abortion in the past two months; 5) Dementia; 6) A neurological disease or prior head trauma with evidence of cognitive impairment; 7) A first-degree family history of schizophrenia if the subject is less than 33 years old (to exclude possible prodromal phase of schizophrenia); 8) Contraindication to CBT as primary treatment for depression, including prior non-response to an adequate trial of CBT, active psychosis, or severe suicidal ideation including a plan. Healthy control inclusion criteria included: 1) Age 18–60; 2) Lack of current or past DSM-IV Axis-I diagnosis as assessed by the SCID; 3) Capacity to provide informed consent. Healthy control exclusion criteria included items 1,2,4,5 from the MDD exclusion criteria plus first-degree relative with history of major depression, schizophrenia, schizoaffective disorder, or suicide attempt, or two or more first-degree relatives with a history of substance dependence.

2.2. Clinical procedures and treatment

BDI (primary, (Beck et al., 1961)) and 17-item HRDS (secondary, (Hamilton, 1960)) scores were used as measures of pre- and post-treatment depression severity (BDI scores obtained at every session, HRDS scores every fourth session). Following baseline MRI scanning, 14 sessions of CBT for depression were administered over 12 weeks according to a treatment manual (Beck, 1979). Core techniques employed included cognitive-restructuring through the use of dysfunctional thought records; behavioral activation following initial activity monitoring approaches; behavioral experiments as a means to examine negative automatic predictions; and some work to identify and modify more deeply held patterns of negative thinking about oneself, one's life, and one's future ("intermediate beliefs" and "core beliefs." Forty-five-minute sessions occurred as close as possible to twice-weekly for two weeks, then weekly thereafter. Study therapists were M.D.- or Ph.D.-level therapists with extensive training and experience conducting CBT, including training at the Beck Institute for Cognitive Behavioral Therapy. Therapists met weekly for peer supervision. Sessions were audiotaped, and adherence to CBT principles was assessed on at least one session per patient by the Beck Institute using the Cognitive Therapy Rating Scale (mean CTRS = 42.7 ± 5.9) (Young and Beck, 1980). A post-treatment MRI scan was performed at the conclusion of CBT. For healthy volunteers, the fMRI task was repeated at a comparable time-point without a treatment intervention.

Participant flow through the study is depicted in Fig. 1. For the participants that did not complete 14 sessions of CBT, last observation carried forward was applied, using the last BDI measurement obtained before dropout or medication augmentation. Two participants who did not complete CBT monotherapy due to clinical worsening, for whom medication was added to augment CBT, had timepoint 2 scans performed immediately prior to medication augmentation (following sessions 9 and 11 respectively); other CBT non-completers were only included in analyses related to time 1 MRI data. Of the 31 depressed participants included in the analysis, 14 were antidepressant-naive, 15 were unmedicated at enrollment but had a history of prior antidepressant use, and 2 were on an ineffective antidepressant medication at enrollment and completed a 3-week washout prior to scanning and treatment.

2.3. Image acquisition

MRI scans were acquired on two 3T SignaHDx scanners (General Electric Medical Systems, Milwaukee, WI), one at The New York State Psychiatric Institute and one at Weill Cornell Medical College, using the same 8-channel head coil. Scan site was included as a covariate in all analyses. T1-weighted MRI scans were acquired using the following parameters: TR = ~ 6 ms, TE = minimum 2400 ms, flip angle = 8, FOV = 25.6 × 25.6 cm, slice thickness = 1 mm, number of slices = 178, matrix size = 256 × 256 pixels. For functional scanning during the memories task, an Echo Planar Imaging (EPI) acquisition was obtained for each of four runs using the following parameters: TR = 2000 ms, TE = 26 ms, flip angle = 77, FOV = 22.4 × 22.4 cm, slice thickness = 3.5 mm, spacing = 3.5 mm, number of slices = 32, matrix size = 64 × 64 pixels, number of volumes = 115.