Psychiatry Research: Neuroimaging 212 (2013) 99–107

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression

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ARTICLE INFO

Article history:
Received 27 August 2012
Received in revised form
7 January 2013
Accepted 10 January 2013

Keywords:
Emotion regulation
Major depressive disorder
Default mode network
Memory
Functional magnetic resonance imaging (fMRI)

ABSTRACT

Functional magnetic resonance imaging (fMRI) was used to examine cognitive regulation of negative emotion in 12 unmedicated patients with major depressive disorder (MDD) and 24 controls. The participants used reappraisal to increase (*real* condition) and reduce (*photo* condition) the personal relevance of negative and neutral pictures during fMRI as valence ratings were collected; passive viewing (*look* condition) served as a baseline. Reappraisal was not strongly affected by MDD. Ratings indicated that both groups successfully reappraised negative emotional experience. Both groups also showed better memory for negative vs. neutral pictures 2 weeks later. Across groups, increased brain activation was observed on negative/*real* vs. negative/*look* and negative/*photo* trials in left dorsolateral prefrontal cortex (DLPFC), rostral anterior cingulate, left parietal cortex, caudate, and right amygdala. Depressive severity was inversely correlated with activation modulation in the left DLPFC, right amygdala, and right cerebellum during negative reappraisal. The lack of group differences suggests that depressed adults can modulate the brain activation and subjective experience elicited by negative pictures when given clear instructions. However, the negative relationship between depression severity and effects of reappraisal on brain activation indicates that group differences may be detectable in larger samples of more severely depressed participants.

1. Introduction

Anhedonia and excessive sadness are cardinal symptoms of major depressive disorder (MDD) (American Psychiatric Association, 2000). Emotional context insensitivity research demonstrates that these symptoms flatten the emotional landscape (Rottenberg, 2005; Rottenberg et al., 2005). In one study, healthy controls and depressed adults viewed amusing, sad, and neutral films (Rottenberg et al., 2005). Controls showed predictable changes in self-reported sadness and happiness, but the depressed group showed heightened sadness regardless of which film was presented. While blunted reactivity to positive stimuli in depression is widely known, it is noteworthy that depressed participants did not show increased sadness when viewing sad films (Rottenberg et al., 2005), a result linked to more severe depression and worse psychosocial function (Rottenberg et al., 2002). This finding indicates that depression truncates the range of negative emotional experience, which has clinical implications.

Emotional context insensitivity may have consequences for emotion regulation. Reappraisal—re-interpreting stimuli to modify their meaning—can modulate negative emotional experience (Ochsner et al., 2004) and supports successful interpersonal functioning (Gross and John, 2003). Furthermore, reappraisal does not impair explicit memory and may improve it, in contrast to the negative effects on memory associated with expressive suppression (Dillon et al., 2007; Hayes et al., 2010; Richards and Gross, 2000). Thus, reappraisal is widely considered an effective emotion-regulation technique. Because depression restricts the range of emotional reactions, it may also limit the ability to reappraise emotional responses once they arise.

Behavioral support for this hypothesis is mixed. Studies in remitted depression (Ehring et al., 2010; Kanske et al., 2012) reported found that instructed reappraisal reduced negative emotional experience. However, the use of remitted samples may have decreased the likelihood of detecting depression effects. Indeed, compared to controls, an unmedicated MDD sample reported greater difficulty in cognitively reducing sadness, and the level of difficulty was correlated with depressive severity (Beauregard et al., 2006). Thus, reappraisal of negative emotional experience may be impaired in acute, unmedicated depression.

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http://dx.doi.org/10.1016/j.pscychresns.2013.01.001

The neuroimaging literature is also mixed. One functional magnetic resonance imaging (fMRI) study found that medicated depressed adults could cognitively reduce amygdala activation elicited by negative pictures, although the degree of amygdala modulation was negatively correlated with depressive severity (Erk et al., 2010a). This contrasts with reports of blunted reappraisal effects on amygdala activation in both remitted (Kanske et al., 2012) and unmedicated depressed samples (Beauregard et al., 2006). Another study found no amygdala modulation during reappraisal in controls or unmedicated depressed adults (Johnstone et al., 2007), but observed right prefrontal cortex (PFC) hyperactivation in the depressed group. This is difficult to interpret, because another study reported right dorsolateral prefrontal cortex (DLPFC) hypoactivation during reappraisal in medicated depression (Erk et al., 2010a). Overall, effects of depression on reappraisal are not well understood.

In light of this mixed evidence, we conducted an fMRI study of reappraisal in MDD. To maximize sensitivity to depression effects, we recruited an unmedicated sample experiencing a current major depressive episode and compared them to healthy controls. Participants reappraised their responses to negative and neutral pictures and provided trial-by-trial valence ratings to permit investigation of subjective experience. The primary hypothesis was that depressed participants would not be able to cognitively increase or reduce their negative emotional responses, as measured by valence ratings and brain activation.

The alternative hypothesis was that depression would have minimal effects on reappraisal because of the use of detailed instructions and cues. This prediction was motivated by a prior study in remitted students, which found no effects of depression on instructed reappraisal (Ehring et al., 2010). Importantly, this study also reported that the remitted group spontaneously engaged in an ineffective emotion-regulation strategy (expressive suppression). This suggests that the remitted participants were able to reappraise effectively because they were given clear instructions and cues, and may not have done so otherwise.

We also examined explicit memory. Two weeks after the fMRI session, participants completed a recognition memory test for the negative and neutral pictures presented in the scanner. In controls, high confidence memory responses are typically more accurate for arousing vs. neutral material, an effect linked to amygdala activation at encoding (Canli et al., 2000; Dolcos et al., 2004). A prior study in a mostly medicated sample suggested that this mechanism is hyperactive in depression (Hamilton and Gotlib, 2008). Thus, we performed a subsequent memory analysis to test whether the MDD group showed stronger amygdala activation than controls during successful encoding of negative pictures. We also investigated whether memory was sensitive to reappraisal.

2. Methods

2.1. Procedures

2.1.1. Participants

Participants comprised 27 controls and 14 depressed individuals. Data from three controls and one depressed participant were excluded due to excessive head motion (>4 mm or degrees incremental). A depressed participant with amygdala activation 5 SDs below the MDD mean was removed, leaving 24 controls and 12 depressed participants. Valence ratings were not recorded for one depressed participant. Twenty-two controls and all depressed participants completed a memory test 2 weeks later. Consent was obtained, consistent with an IRB-approved protocol. Participants were paid (MRI: $25/h; memory: $10/h) and debriefed.

2.1.2. Stimulus selection

Three sets of 144 pictures (72 negative, 72 neutral) were used in the MRI session, as distracters in the memory test, and in an electroencephalography session following the memory test (data not presented). Assignment of picture sets to sessions was counterbalanced. Negative pictures included images from the International Affective Picture System (IAPS) (Lang et al., 2005) and the Internet depicting threatening animals, violence, drug use, accidents, painful medical procedures, poverty, and old age. Neutral pictures depicted people engaged in mundane activities.

2.1.3. Stimulus validation

Nine laboratory members (5 females) rated the pictures for valence (1=negative, 9=positive) and arousal (1=calm, 9=excited). *Gender* × *Set* × *Picture Type* analyses of variance (ANOVAs) revealed only effects of *Picture Type* for valence (negative: 2.62 ± 0.60; neutral: 5.55 ± 0.47; $F(1, 3)=171.58$, $p=0.001$) and arousal (negative: 6.96 ± 0.31; neutral: 4.14 ± 0.80; $F(1, 3)=47.55$, $p=0.006$). Thus, the pictures elicited the intended emotional responses in both genders.

2.1.4. Diagnostic interview

Eligibility was established using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (First et al., 2002). Depressed participants were unmedicated, met criteria for MDD, and had no history of psychosis. Comorbidity was mainly confined to anxiety disorders (see *Results*). Past psychotropic medication was allowed (no use in the preceding 2 weeks for benzodiazepines, 6 weeks for selective serotonin reuptake inhibitors, 6 months for dopaminergic drugs). Two depressed participants were attending psychotherapy sessions once or twice monthly; the other depressed participants were not in therapy. Five depressed participants reported past psychotherapy of varying duration (1 month or less, $n=2$; 2 years or less, $n=2$; unclear, $n=1$). Controls reported no current or past Axis I diagnosis. Participants were 19–63 years old and right-handed. None presented with neurological conditions or significant medical history, or met criteria for lifetime substance dependence or substance abuse in the last year.

2.1.5. Reappraisal task

The task was designed to modulate emotional experience and minimize demand characteristics. Trials included a cue word (“REAL”, “LOOK”, or “PHOTO”; duration: 1 s), a jittered inter-stimulus interval (ISI: 3–5 s), a negative or neutral picture (6 s), a second ISI (1.5–3 s), and a rating screen (3 s). The rating screen displayed self-assessment manikins (Lang et al., 2005) corresponding to five levels on a valence scale (1=negative, 3=neutral, 5=positive). Participants pressed a button to rate their emotional state at trial end. A fixation cross was presented during the ISIs and inter-trial interval (2–11 s). Participants completed 12 practice trials after the interview and in the scanner to ensure comprehension. During scanning, they completed six blocks of 24 trials. Optimal trial sequences were determined with optseq (Dale, 1999).

The cues were explained after the interview and at the outset of the MRI session. To maximize experimental control, we constrained the reappraisal technique by emphasizing self-focused reappraisal rather than situation-focused reappraisal, in which participants reinterpret negative situations in order to envision more positive outcomes (Ochsner et al., 2004). Specifically, in response to the *real* cue, participants were asked to mentally place themselves in scenes as though they were happening now, and vividly imagine all the sensations that would be experienced. This was intended to intensify negative emotional experience. By contrast, the *photo* cue was designed to dampen responses to negative pictures by increasing the sense of psychological distance (Kross and Ayduk, 2008). Thus, in response to the *photo* cue, participants were told to imagine that scenes were old, posed photographs being viewed from a distance. In response to the *look* cue, participants viewed pictures without controlling their responses. The instructions emphasized imagery rather than emotion regulation to limit demand characteristics[1].

The task was programmed in E-Prime (Psychology Software Tools, Inc; Sharpsburg, PA). Behavioral data were analyzed with SPSS version 19.0.0 software (IBM; Armonk, NY).

2.1.6. Questionnaires

To assess depressive and anxious symptoms, habitual use of emotion-regulation strategies, and mental imagery, the following self-report measures were administered after scanning: the Beck Depression Inventory-II (BDI-II: Beck et al., 1996), Emotion Regulation Questionnaire (ERQ: Gross and John, 2003), Mood and Anxiety Symptom Questionnaire (MASQ: Watson et al., 1995), Ruminative Responses Scale (RRS: Nolen-Hoeksema and Morrow, 1991; Treynor et al., 2003), and Vividness of Visual Imagery Questionnaire (VVIQ: Marks, 1973). The Wechsler Test of Adult Reading (WTAR: Green et al., 2008; Psychological Corporation, 2001) provided an IQ estimate.

[1] See Supplementary Material for verbatim instructions.