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FMRI BOLD responses to negative stimuli in the prefrontal cortex are dependent on levels of recent negative life stress in major depressive disorder

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Abstract

It is poorly understood how stressors modulate neurobiological mechanisms that may contribute to the heterogeneity of Major Depressive Disorder (MDD). Unmedicated patients diagnosed with MDD ($n = 15$) and individually matched healthy controls ($n = 15$) completed stress questionnaires and were studied with functional magnetic resonance imaging while viewing emotional words. Significant effects of recent negative life stressors, but not early life stress/trauma, were observed on regional blood oxygen level dependent activity during presentation of negative words in patients with MDD. No significant effects of stress on brain activation to negative words were found in controls. In MDD patients, positive correlations were found bilaterally in orbitofrontal areas 11/47/12m, which are involved in representing negatively-valenced stimuli. Negative correlations were also found in the right ventrolateral prefrontal area 45, subgenual cingulate area 25, and nucleus accumbens, all of which are implicated in the pathophysiology of MDD. Negative memory bias was additionally positively associated with recent negative life stress and negatively associated with subgenual cingulate activation, suggesting a mechanism by which stress may contribute to these abnormalities. The severity of recent negative life stressors is an important modifier of neurobiological and cognitive function in MDD and may help explain heterogeneity in the disorder.

Keywords

orbital; subgenual; ventrolateral; accumbens; memory; depression

1. Introduction

Stressful life events can precipitate, maintain, and exacerbate major depressive disorder (MDD) (Kessler, 1997; Kendler et al., 1999; Paykel, 2003; Hammen, 2005). Although it is clear that past and current life experiences contribute to MDD in genetically predisposed individuals (Monroe and Simons 1991; Kendler et al., 1995; Caspi et al., 2003), the biological link between stress and MDD is not known.

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It is well established that early life trauma significantly increases the likelihood of developing MDD in adulthood (reviewed by Heim and Nemeroff, 2001). Early life exposure to physical or emotional abuse is correlated with greater emotional reactivity (Cummings et al., 1994; Heim et al., 2000; Pollack and Sinha, 2002), which is in turn associated with the risk for developing mood and anxiety disorders (Pine et al., 2001). Physiological consequences to early life trauma include sensitization of the hypothalamic-pituitary-adrenal axis (Ladd et al., 2000; Heim and Nemeroff, 2001; Pryce et al., 2005), and structural brain changes (Lyons et al., 2001; Vythilingam et al., 2002; Teicher et al., 2004; Cohen et al., 2006). However, no studies have examined the neural responses to emotional stimuli in adults with MDD as a function of early life stress. In one fMRI study, healthy adults who grew up with harsh parenting showed lower amygdala activity while viewing fearful or angry faces, suggesting desensitization of fear responsive regions (Taylor et al., 2006).

A robust relationship has also been drawn between recent stressful life events and the onset and exacerbation of MDD (Kendler et al., 1999; Scher et al., 2005). A prevailing cognitive theory is that emotional biases or distortions of stressful life events contribute to the development and maintenance of MDD (Beck, 1979; Scher et al., 2005). Recent studies have found greater cognitive changes in patients with a major stressor compared to patients without a major stressor (Monroe et al., 2007), and that depressed individuals selectively attend to and remember negatively-valenced information (Leppänen, 2006; Hamilton and Gotlib, 2008). In this study, it is predicted that depressed individuals with higher levels of stress will have greater memory bias for negatively-valenced words. To date, there has been no investigation of the neural correlates of emotional reactivity or negative memory bias as a function of recent life stress in MDD.

The present study was designed to examine the relationship of early and recent negative life stress to regional brain activity in subjects with and without MDD. During fMRI, volunteers were exposed to emotional words, which have been shown to detect functional brain abnormalities in MDD (Siegle et al., 2002; Canli et al., 2004). It was hypothesized that stressors (whether early or recent) would contribute to the variability of responses in emotion regulatory regions in MDD (e.g., orbitofrontal, ventrolateral, and subgenual cingulate cortex, nucleus accumbens, amygdala).

2. Methods

2.1 Subjects

23 patients diagnosed with MDD (8 male, 15 female; mean age, 41.26 ± 11.67) and 20 healthy controls (7 male, 13 female; mean age, 40.55 ± 10.35) were recruited via newspaper advertisements, campus fliers, and word of mouth in local treatment clinics. Written informed consent was obtained and study protocols were approved by the Institutional Review Board of the University of Michigan Medical School. Patients with MDD underwent the Structured Clinical Interview for Depression (SCID-IV) diagnostic interview (First et al., 1995), scored > 15 (mean score, 19.41 ± 2.63) on the 17-item Hamilton Depression Rating Scale, had no other current or past diagnosis, and were unmedicated for at least six months at the time of the study (mean duration of illness, 25.46 ± 35.88 months; range, 1.5 to 132 months). Controls were screened for active medical illness and for psychiatric disorders using the SCID-IV non-patient version. Control subjects had no personal or family history of psychiatric disorders. None of the subjects were taking psychotropic medications, including hormones or hormonal contraception in women. Pregnancy tests were confirmed negative prior to scanning. Urine drug screens were also obtained in all subjects immediately prior to scanning.

2.2 Questionnaires

The Childhood Trauma Questionnaire (CTQ) is a 25-item inventory that provides a brief, reliable, and valid measure of childhood abuse and neglect (Bernstein et al., 1994). Summary scores were used for group comparisons and regression with fMRI activation.

The Moos Life Events Scale (MLES) is a 36-item inventory of life stress experienced within the last 12 months (Moos et al., 1990). Each event was assigned a life-change unit weighting (Holmes and Rahe, 1967), and the total scores for negative life events (15 items) were used for group comparisons and regression with fMRI activation.

2.3 Emotion Word Stimulus Task

During the fMRI scan, blocks of positive, negative, and neutral words were presented using the integrated functional imaging system (IFIS; Psychology Software Tools, Pittsburgh, USA), which uses a LCD video display in the bore of the MR scanner and a fiber optic response collection keypad device. Subjects were instructed to read the word silently and press a button on the keypad using their right index finger to indicate that they understood the word. Words were selected from the Affective Norms for English Words (ANEW) list, which provides a normative emotional rating for a large number of words in the English language (Bradley and Lang, 1999). The words in the ANEW list were rated on the dimensions of valence and arousal on a scale of 1 (negative valence; low arousal) to 9 (positive valence; high arousal). For the present study, we chose negative words with an average valence rating of less than 3, neutral words with valence ratings between 4.5 and 5.5 and positive words with a valence rating greater than 7. Standard deviations for all valence ratings were less than 2 and arousal ratings were greater than 3. Word length ranged from 3 to 11 letters (mean number of letters, 6.04 ± 1.64).

Words were presented one at a time (3 seconds, followed by one second cross-hair orientation) in blocks of six or nine words of the same valence. There were five runs of six blocks each, counterbalanced using the Latin Squares design, with two blocks from each condition (positive, negative, neutral). Non-active, rest blocks of 6 or 18 seconds were interspersed between each block.

Following the scan, memory recall and recognition were administered without prior warning to evaluate implicit recall and recognition memory performance, using percent word recall and recognition respectively. Greater bias for remembering negative words (negative memory bias relative to neutral words) was expected in the MDD group compared to the control group. Negative memory bias was determined by subtracting percent recall or recognition of neutral words from percent recall or recognition of negative words.

The emotional words task was chosen over other emotional probes (i.e. faces, pictures) to test the hypothesis that cognitive distortions are affected by stressful experiences in MDD. Emotional words may require more cognitive processing effort (i.e. memory, associations), which may be more subtly influenced by life stress. In contrast sad faces, for example, may elicit more reflexive responses, involving subcortical structures such as the amygdala (Leppänen, 2006).

2.4 fMRI data acquisition

Whole brain scans were performed using a 3.0 Tesla GE Signa scanner (Milwaukee, WI, USA) using a standard radio frequency coil. BOLD contrasts were acquired using a T2*-weighted pulse sequence (repetition time, 2000 ms; echo time, 30 ms; flip angle, 90°; field of view, 24 cm, 64×64 matrix; 1 voxel, $3.75 \times 3.75 \times 4$ mm), with single-shot combined spiral in/out acquisition (Glover and Law, 2001), which has been shown to reduce signal

dropout near sinuses. The entire volume of brain (30 slices) was acquired at each repetition time. A high resolution T1-weighted pulse sequence was acquired to provide anatomical localization [three-dimensional spoiled gradient recalled echo (3-DSPGR); repetition time, 24 ms; echo time, 5 ms; flip angle, 45°; field of view, 24 cm, 256 × 256 matrix; slice thickness, 1.5 mm].

2.5 fMRI data analysis

BOLD contrasts were slice time corrected, realigned, smoothed with an $8 \times 8 \times 8$ Gaussian filter, and analyzed with Statistical Parametric Mapping v.2 (SPM2) (Wellcome Institute of Cognitive Neurology, London, UK). Contrast t maps for each participant were derived using a primary subtraction of negative word blocks minus neutral word blocks (Neg-Neut), normalized with linear and non-linear warping to standard space (Montreal Neurological Institute, Quebec, CA), and smoothed with an $3 \times 3 \times 2$ Gaussian filter to reduce residual interindividual anatomical variability. Interindividual, random-effects analyses were performed using SPM2. Subdivisions of the OFC were identified using the scheme of Ongür and colleagues (2003) and mapped onto standard space (Kringelbach and Rolls, 2004). Brain regions previously shown to exhibit abnormal activity in MDD were examined as *a priori* hypothesized regions, which included the orbitofrontal cortex (OFC) (Drevets, 2007), ventrolateral prefrontal cortex (VLPFC) (Lévesque et al., 2004; Johnstone et al., 2007; Langenecker et al., 2007; Wager et al., 2008; Keedwell et al., 2009), subgenual cingulate (Drevets et al., 1997; Mayberg et al., 2000; Keedwell et al., 2009), nucleus accumbens (Pizzagalli et al., 2009), and amygdala (Whalen et al., 2002). Activation in these regions was considered statistically significant if they survived small volume correction (10 mm sphere, $P < 0.01$, corrected). Activation outside of these regions was considered statistically significant at $P < 0.05$ after family-wise error correction. Scores for CTQ and MLES were entered as regressors in a second-level analysis for BOLD Neg-Neut signal within SPM2. Areas of significant activation were extracted using MarsBaR region of interest (ROI) toolbox (version 0.38) (Brett et al., 2002) for SPM, and analyzed with SPSS statistical software (version 16.0, Chicago, IL, USA) to confirm the findings from the SPM analyses, plot the data, and rule out the presence of outliers using the Tukey box plot, where an outlier is defined as a score greater than 1.5 interquartile lengths from the first or third quartile.

3. Results

Compared to healthy controls, patients with MDD reported significantly higher levels of childhood trauma ($t_{36} = 3.60$, $P = 0.0009$, two-tailed) and recent negative life stress ($t_{32} = 3.94$, $P = 0.0004$, two-tailed) (Fig. 1).

15 patients and 13 controls completed all three measures (CTQ, MLES, and fMRI scan). In this sample, fMRI voxel-by-voxel analyses revealed that MLES but not CTQ contributed significantly to BOLD Neg-Neut signal. Therefore, MLES was examined alone with BOLD Neg-Neut signal in a simple correlation. In this analysis, two additional controls who completed MLES (but not CTQ) and fMRI scan were added, for a total of 15 patients and 15 controls, which yielded the main results in this report. Without considering MLES or CTQ, patients and controls did not differ in BOLD Neg-Neut signal.

In patients with MDD ($n = 15$), a whole-brain analysis revealed a significant positive correlation between MLES scores and BOLD Neg-Neut signal in OFC (Fig. 2; Table 1). Spearman's rank correlation performed with the extracted data yielded r values for left OFC ($r = 0.75$, $P = 0.001$) and right OFC ($r = 0.74$, $P = 0.002$). In healthy controls ($n = 15$), BOLD Neg-Neut signal was not significantly associated with CTQ or MLES scores in voxel-by-voxel SPM2 whole-brain analysis or ROI analyses with data extracted from the regions identified in MDD subjects. Furthermore, the number of recent life events was not

correlated with the Hamilton Depression Rating Scale in MDD subjects, suggesting that BOLD signals were not related to depression severity, although the range of scores on this scale was relatively limited.

A significant negative correlation was found between MLES and BOLD Neg-Neut signal in right inferior frontal gyrus [VLPFC; Brodmann Area (BA) 45] (Fig. 3; Table 1) ($r = -0.54$, $P = 0.04$). In addition, MLES and BOLD Neg-Neut signal were inversely correlated in a region that spanned bilateral subgenual cingulate (BA 25) and NAcc (Fig. 4; Table 1) in MDD volunteers. This cluster was subdivided using the MarsBaR ROI toolbox into left and right subgenual cingulate (left, $r = -0.60$, $P = 0.02$; right, $r = -0.55$, $P = 0.03$), and left and right NAcc (left, $r = -0.51$, $P = 0.05$; right, $r = -0.66$, $P = 0.008$) (Table 1). No significant relationship was found between MLES and BOLD Neg-Neut signal in the amygdala.

For all the above ROIs, additional analyses were performed to examine MLES relationships with Neg-Rest and Neut-Rest separately to assess whether the relationships were in fact related to reactivity to negative words rather than neutral words. For Neg-Rest, significant positive correlations were found between MLES and OFC activity (left: $r = 0.70$, $P = 0.003$; right: $r = 0.51$, $P = 0.05$), and a negative correlation was found with right NAcc activity ($r = -0.64$, $P = 0.01$). Negative correlations were also obtained for the right VLPFC ($r = -0.163$, $P = 0.56$), left NAcc ($r = -0.40$, $P = 0.14$), and subgenual cingulate (left: $r = -0.45$, $P = 0.09$; right: $r = -0.46$, $P = 0.09$) – however, these did not reach statistical significance. No significant relationships were observed between MLES and Neut-Rest contrasts, confirming that the correlations observed in the Neg-Neut contrast were related to brain activity while viewing negative words, not to an effect of neutral words.

Compared to controls, patients with MDD had greater negative recognition memory bias, as initially hypothesized ($t_{29} = 1.87$, $P = 0.04$, one-tailed). No group differences were found for negative recall memory bias or false positives for either recall or recognition. In patients with MDD, negative recognition memory bias was positively correlated with MLES scores ($r = 0.72$, $P = 0.002$) (Fig. 5A), and negatively correlated with BOLD Neg-Neut activity in right subgenual cingulate ($r = -0.61$, $P = 0.02$) (Fig. 5B); negative correlations approached statistical significance in the left subgenual cingulate ($r = -0.49$, $P = 0.06$) and right VLPFC ($r = -0.50$, $P = 0.06$). In healthy controls, no significant correlations were found between negative recall or recognition memory bias and MLES, CTQ, or BOLD Neg-Neut signal.

These data suggest that the severity of recent negative life stressors is an important modifier of neurobiological and cognitive memory biases in MDD.

4. Discussion

The present work found variability in neural response to emotional stimuli in unmedicated participants diagnosed with MDD, as a function of recent negative life stressors. Localized positive relationships were found between levels of recent negative life stress and identical bilateral locations in OFC. Converging evidence suggests that central and lateral parts of OFC including 11l and 47/12m are specifically involved in representing the emotional impact of anticipated negative outcomes (Kringelbach and Rolls, 2004). In the present study, recent negative life stress in the context of MDD may have exacerbated negative associations to negative words, therefore preferentially activating these areas of OFC. In patients with MDD and related disorders, OFC has also been found to be ineffective in downregulating amygdala activity during effortful reappraisal of negative stimuli (Johnstone et al., 2007). It is also of interest that in MDD, OFC was the only brain region with activity in response to viewing negative words that was positively associated with negative life stress. It is possible that OFC does not habituate to stressors and a dysfunction in this region

is associated with MDD. In a study of rats using chronic audiogenic stress, OFC was the only observed brain region to display higher c-fos mRNA induction (Campeau et al., 2002).

Negative associations were found between right VLPFC activity in response to negative words and recent negative life stress in MDD. Right VLPFC is involved in the reappraisal and cognitive control of emotions in healthy individuals (Lévesque et al., 2004; Johnstone et al., 2007; Wager et al., 2008). Our recent work has illustrated hyperactivation in patients with MDD within this same region for regulation in a cognitive control task, which was designed to be devoid of emotionally-laden stimuli, suggesting a more general regulatory dysfunction in MDD (Langenecker et al., 2007). The present findings show that higher levels of recent negative life stress are associated with hypoactivation in the right VLPFC, suggesting that stress interferes with the cognitive control of emotions in MDD, as indicated by a positive correlation with negative memory bias (Fig. 5A).

Negative associations were found between subgenual cingulate activity in response to negative words and recent negative life stress in MDD. Both subgenual hyper- and hypoactivity have been found at baseline in MDD (Drevets et al., 1997; Mayberg et al., 2000), and viewing sad-neutral faces increases subgenual cingulate activity in MDD to a greater extent than in healthy individuals (Gotlib et al., 2005; Keedwell et al., 2009). However, baseline hypoactivity in this area has also been associated with poor treatment response in MDD (Mayberg et al., 2000), suggesting substantial heterogeneity in the pathophysiology of this disorder. In our study, it is possible that higher levels of recent negative life stress reduce the effort required to generate negative affect, such that the processing of negatively-valenced information becomes more involuntary. In support of this hypothesis, subgenual cingulate activity was negatively associated with negative memory bias (Fig. 5B), and recent negative life stress was positively associated with negative memory bias (Fig. 5A), which may be facilitated by exposure to stress. Furthermore, Schwabe and colleagues (2008) found that cold stress enhanced memory negative words specifically in subjects who released cortisol, suggesting a possible mechanism for stress-facilitated negative memory bias.

The present study also found a negative association between NAcc activity in response to negative words and recent negative life stress in MDD. Although better known for its role in processing reward, NAcc also has a role in processing salient aversive events (Levita et al., 2002). Previous studies have found either no differences or reductions in NAcc activity in MDD compared to controls during a reward task (Knutson et al., 2008; Pizzagalli et al., 2009). It is possible that NAcc response to emotional stimuli is decreased in the face of recent negative life stress in MDD. Both the subgenual cingulate and NAcc receive heavy input from the paraventricular thalamic nucleus, which is involved in the transmission of stress signals from hypothalamus and midbrain (Hsu and Price, 2007, 2009). Thus these two structures may be part of a pathogenic stress circuit in MDD.

A positive relationship between recent negative life stress and negative memory bias in MDD (Fig. 5A) may partly explain the association between stress and abnormal brain responses to negative words. Depressed individuals selectively attend to and remember negatively-valenced information (Leppänen, 2006; Hamilton and Gotlib, 2008), and those with severe life events exhibit greater changes in cognitive biases compared to those without severe life events (Monroe et al., 2007). Greater memory for negative stimuli in MDD may involve activation in the subgenual cingulate (Fig. 5B) which was negatively correlated with negative memory bias scores in the present study.

Childhood trauma, a potent risk factor for MDD, may set the tone for abnormal neural responses to future stressors (Heim et al., 2008). The present study found that levels of

childhood trauma were higher in MDD, but the fMRI data did not show that trauma scores influenced neural responses to emotional stimuli. Most likely, the severity of trauma experienced by most of the subjects in this sample may not have been sufficiently high to translate into neurobiological changes, as has been observed in patients diagnosed with posttraumatic stress disorders (Bremner et al., 2003). It is also possible that even when early trauma was significant, stimuli reminiscent of the specific traumatic event, but not lexical stimuli with less specific emotional content, would be related to neural responses.

Limitations of this study include retrospectively rated scales, which may be subject to recall bias. However, a previous study has shown that subjectively rated CTQ scores were supported by collateral, corroborative information (Bernstein et al., 2003). It has also been shown that reports of early events occurring when individuals are old enough to have knowledge of them are reasonably accurate (Brewin et al., 1993). In addition, the MLES used in this study explicitly asks to report life events within the last 12 months, a relatively short time frame likely to be less susceptible to memory bias. Other limitations include a relatively small sample size, which may have reduced the statistical power to detect changes using whole-brain analyses. As mentioned above, another limitation is that the sample may not have experienced sufficiently high levels of childhood trauma to translate into differences in neurobiological changes.

Items on the MLES are weighted with the Social Readjustment Rating Scale by Holmes and Rahe (1967), one of the most widely used scales for quantifying stressful life events. One major criticism of this scale is that it includes both negative and positive life events to arrive at a stress score. However, the present study used only negative life events, which has been shown to be the only type of life events that affect illness (Miller and Rahe, 1997). More comprehensive measures of life stress have been designed to differentiate between acute and chronic stress, assign context and meaning to stressors, and evaluate perceptions or appraisals of stress (Monroe, 2008). Future studies will consider these measures to replicate and expand this work.

The main findings were the associations between levels recent negative life stress and BOLD Neg-Neut activity in patients with MDD. These associations were found in brain areas known to be involved in MDD (i.e. OFC, VLPFC, subgenual cingulate, NAcc). Since levels of stress differed between patients and controls (see Fig. 1), it would have been difficult to interpret a comparison between MDD and controls as a function of stress with a relatively small sample. Future studies would need larger samples and the incorporation of stress as covariates in the interpretation of neural activation differences between MDD and controls.

In summary, levels of recent negative life stress in patients with MDD are strongly related to variations in the activity of structures responding to negative emotional stimuli. Stressful life events may further affect cognitive-emotional aspects of MDD through the exacerbation of negative memory bias. The findings indicate that the severity of recent negative life stressors is an important modifier of neurobiological function in MDD samples, contributing to the variability in neuroimaging findings, and underscore the importance of monitoring life stressors and their cognitive-emotional impact during the course of study and treatment.

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Fig. 1.

Childhood trauma and recent negative life stress in healthy controls (HC) and patients with major depressive disorder (MDD). Compared to HC, patients with MDD had higher levels of A) childhood trauma ($t_{36} = 3.60$, $P = 0.0009$, two-tailed) and B) recent negative life stress ($t_{32} = 3.94$, $P = 0.0004$, two-tailed). Scores were broadly distributed in both groups.

Fig. 2.

fMRI BOLD activity in response to viewing negative words minus activity to neutral words (Neg-Neut) in patients with MDD. A) The BOLD Neg-Neut signal in the bilateral orbitofrontal cortex (OFC) (shown at four coronal levels) positively associated with levels of recent negative life stress. Solid and dashed lines within the BOLD Neg-Neut signal mark the outer edge of cortex and white matter, respectively. The peak BOLD Neg-Neut signal in left OFC was found in area 11l, extending into 11m and 47/12m. In right OFC, the peak BOLD Neg-Neut signal was found in caudal 11l and 47/12m. B) Positive correlations between BOLD Neg-Neut signal in OFC and levels of recent negative life stress (left OFC, $r = 0.75$, $P = 0.001$; right OFC, $r = 0.74$, $P = 0.002$). Activity in OFC was additionally subjected to small volume correction [left OFC: 10 mm sphere at $-22, 46, -10$; $t(15) = 5.30$, $P < 0.002$, corrected; right OFC: 10 mm sphere at $36, 36, -6$; $t(15) = 4.78$, $P < 0.005$, corrected].

Fig. 3.

A) BOLD Neg-Neut signal in the right ventrolateral prefrontal cortex (VLPFC) negatively associated with levels of recent negative life stress. B) Negative correlation between BOLD Neg-Neut signal in right VLPFC and levels of recent negative life stress (right VLPFC, $r = -0.54$, $P = 0.04$). Activity in VLPFC was additionally subjected to small volume correction [10 mm sphere at 54, 34, 8; $t(15) = 4.75$, $P < 0.006$, corrected].

Fig. 4. BOLD Neg-Neut signals in A) subgenual cingulate and B) nucleus accumbens negatively associated with levels of recent negative life stress. C) Negative correlations between BOLD Neg-Neut signal in subgenual cingulate and levels of recent negative life stress (left subgenual, $r = -0.60$, $P = 0.02$; right subgenual, $r = -0.55$, $P = 0.03$), and D) negative correlations between BOLD Neg-Neut signal in nucleus accumbens and levels of recent negative life stress (left accumbens, $r = -0.51$, $P = 0.05$; right accumbens, $r = -0.66$, $P = 0.008$). Activity in the subgenual/NAcc cluster was additionally subjected to small volume correction [10 mm sphere at 0, 14, -12; $t(15) = 4.64$, $P < 0.006$, corrected].

Fig. 5.

Memory bias for negative words in patients with MDD. A) Negative memory bias was positively correlated with levels of recent negative life stress ($r = 0.72$, $P = 0.002$). B) Negative memory bias was negatively correlated with BOLD activity in the right subgenual cingulate (left, $r = -0.49$, $P = 0.06$; right, $r = -0.61$, $P = 0.02$).

Table 1

Activation foci in response to negative-neutral words in MDD, correlated with levels of recent negative life stress

Location	Brodman's Area	x, y, z (mm)	t	Cluster size	Rho value for extracted ROIs
<u>Positively correlated</u>					
Orbitofrontal cortex (l)	111, 47/12m	-22, 46, -10	5.30***	5240	0.75**
Orbitofrontal cortex (r)	111, 47/12m	36, 36, -6	4.78***	4064	0.74**
<u>Negatively correlated</u>					
ventrolateral (r)	45	54, 34, 8	4.75***	1144	-0.54*
Subgenual/accumbens cluster (cluster subdivided)		0, 14, -12	4.64***	2840	-0.58*
Subgenual cingulate (l)	25	-5, 14, -12	-	856	-0.60*
Subgenual cingulate (r)	25	5, 13, -12	-	1040	-0.55*
Nucleus accumbens (l)		-7, 7, -13	-	328	-0.51*
Nucleus accumbens (r)		10, 6, -14	-	616	-0.66**

Coordinates from Montreal Neurological Institute; ROIs, regions of interest.

*** $P < 0.0005$, uncorrected

* $P < 0.05$

** $P < 0.01$.