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Neural substrates of negativity bias in women with and without major depression☆

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ABSTRACT

Background: The functional localization of negativity bias, an influential index of emotion information processing, has yet to be identified.
Method: Depressed ($n = 47$) and healthy participants ($n = 58$) completed a clinical interview for DSM-IV Axis I disorders, symptom checklists, a behavioral task to measure negativity bias, and then viewed positive and negative images of social and nonsocial scenes during an event-related fMRI task. Two subsamples of participants with high (i.e., 75%; $n = 26$) and low (i.e., 25%; $n = 26$) negativity bias scores were as included in subsequent analyses to examine neural differences.
Results: Depressed participants with a higher, relative to lower, negative bias showed significantly greater neural activation in the left inferior frontal gyrus.
Conclusion: High negativity bias evokes a distinctive pattern of brain activation in the frontal cortex of depressed participants. Increased activation occurred in the left inferior frontal gyrus, related to Brodmann area 44, which is associated with language and semantic processing, response inhibition, and cognitive reappraisal. This finding may reflect an abnormality in integrative emotional processing rather than processing of individual emotional dimensions in depressed participants with negativity bias.

1. Introduction

In daily life, people are confronted by appetitive and aversive stimuli, often simultaneously. The capacity to differentiate unpleasant from pleasant stimuli and to respond adaptively is therefore essential. Preferential processing of negative relative to positive information develops early in the lifespan for humans (Vaish, Grossmann, & Woodwar, 2008), which presumably evolved as a defensive mechanism. Negative stimuli evoke a more pronounced and rapid (automatic) response than equally extreme and arousing positive stimuli (Baumeister, Bratslavsky, Finkenauer, & Vohs, 2001; Cacioppo, Gardner, & Berntson, 1997; Delplanque, Silvert, Hot, & Sequeira, 2005; Goldsmith & Dhar, 2013; Huang & Luo, 2006; Kisley, Wood, & Burrows, 2007) – a distinction that has been termed negativity bias (Larsen, Norris, McGraw, Hawkley, & Cacioppo, 2009). Negativity bias has been associated with underlying physiological correlates, such as a larger late positive evoked potential (Ito & Cacioppo, 2000; Ito, Larsen, Smith, & Cacioppo, 1998; Smith et al., 2006) and increased corrugator activity (Neta, Norris, & Whalen, 2009). Negativity bias can also be measured in behavioral tasks across several modalities (e.g., visual, auditory) and types of stimuli (e.g., pictures, words; (Larsen et al., 2009; Norris, Larsen, Crawford, & Cacioppo, 2011)). Finally, negativity bias has been differentially associated with specific serotonin receptor genes (Ashare, Norris, Wileyto, Cacioppo, & Strasser, 2013), suggesting that it may be influenced by the functioning of the serotonin transporter.

Neuroimaging data have suggested that negativity bias is associated with activation of specific brain regions. In a seminal study using positron emission tomography (PET), Jung et al. (2006) identified neuroanatomical regions that were selectively activated when processing negative information in healthy participants. In the neg-

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ativity bias condition, which required integrative processing of both negative and positive information, there was significant activation in the right frontal pole, the left middle frontal gyrus, and left inferior frontal gyrus. Analyses designed to identify unique regions of activation indicated that only the middle frontal gyrus (i.e., dorsolateral prefrontal cortex) was activated during the negativity bias condition (integrative processing of positive and negative information), whereas activation in the ventromedial prefrontal, limbic, and subcortical regions were associated with the processing of univalent conditions (positive or negative information). From a behavioral perspective, Jung et al. (2006) findings demonstrated that participants took longer to respond and were more likely to endorse feeling negative (i.e., to label their subjective emotion produced by the stimuli as negative) during the negativity bias condition compared with the single valence conditions, which suggests that the processing of bivalent stimuli (both positive and negative) requires more effort than processing of unipolar valence (positive or negative) (Jung et al., 2006).

Enhanced negativity bias has been identified as a characteristic of depressed individuals (Roiser, Elliott, & Sahakian, 2012). This finding is consistent with research that shows neuroanatomical differences in the processing of negative information in depression (Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013). However, it is possible that negativity bias is uninfluenced by depressive state as negativity bias can occur without the experience of negative emotions (Dong, Zhou, Zhao, & Lu, 2011). Given that negativity bias has been associated with the activation of specific brain regions in healthy adults (Vaish et al., 2008) and negativity bias may be amplified among depressed individuals (Gollan et al., 2015), we hypothesized that the activation of such brain regions may also be enhanced in depressed individuals. This study, therefore, tests the reproducibility of Jung's findings on healthy and depressed participants guided by the a-priori ROIs from Jung's study. Further, because there is under review no prior data examining the neural substrates of negativity bias on depressed participants, this study was designed to investigate the neural substrates of high and low levels of negativity bias drawn from a larger sample of depressed and healthy participants. This approach builds upon yet-to-be published data in this lab examining predictors of treatment response for depression, wherein, those with high negativity bias at baseline showed an accelerated treatment response at 16 weeks of treatment, suggesting that high negativity bias is an important distinction that warrants additional study.

In this study, depressed and healthy participants completed a behavioral task outside of the scanner, as well as a task during functional brain imaging, which permitted a behavioral and a functional neuroanatomical analysis of negativity bias. We examined the functional neuroanatomical correlates of negativity bias using an event-related functional magnetic resonance imaging (fMRI) paradigm among depressed and healthy participants with low and high expression of negativity bias (i.e., low and high NB). Based on an evaluative space model of negativity bias (Cacioppo et al., 1997), the fMRI negativity bias condition was created by subtracting the activation when participants viewed positive stimuli from the activation when participants viewed negative stimuli. We tested specific hypotheses related to regions-of-interest (ROIs) previously observed to be associated with negativity bias (Jung et al., 2006) that aligned with significant areas of activation during the negativity bias condition in healthy participants that resulted from a whole-brain analysis. Further, we extended the ROI approach to compare diagnosis and negativity bias. Given the prior findings of Jung et al. (2006), we hypothesized that in the subregions of the frontal gyrus: (Vaish et al., 2008) participants with higher NB would show increased activation during the negativity bias condition; (Cacioppo et al., 1997) relative to healthy participants, depressed participants would show increased activation during the negativity bias condition; and (Delplanque et al., 2005) depressed participants with high NB would exhibit higher levels of activation than depressed participants with low NB and healthy participants with high or low NB. Of note, we chose to enroll only women in this study because the genetic correlates of negativity bias may differ in males and females (Ashare et al., 2013), females have a higher incidence of depression (Kessler, Chiu, Demler, Merikangas, & Walters, 2005), and to reduce the effect of sex-related variation in patterns of brain activation (Zaidi, 2010).

2. Methods and materials

2.1. Participants

Participants included females aged 17–63 years, including participants diagnosed with current major depressive disorder (MDD) per the structured clinical interview for the DSM-IV Axis I Disorders, (SCID; (First, Spitzer, Gibbon, & Williams, 2002)) and a score $\geq$24 on the Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C) (Rush et al., 2003, 1986a), indicating that MDD participants were experiencing at least moderate depression severity at the time of study. In turn, healthy participants were enrolled with no lifetime psychiatric diagnoses (per the SCID) and a score $\leq$11 on the IDS-C. To enroll, participants had to be medically healthy, and unmedicated with no recent wash out. Participants were excluded if they had a history of severe head trauma, neurological conditions, lifetime diagnoses of bipolar I or II, psychosis, obsessive–compulsive disorder, posttraumatic stress disorder, borderline, schizoid, schizotypal, or antisocial personality disorders, or current substance abuse/dependence. Participants were also later excluded for poor imaging data (e.g., participants with excessive motion, defined as >3 mm within each run). The final sample included 47 depressed participants and 58 healthy participants.

2.2. Procedure

Participants were screened via phone to determine eligibility and then invited to the laboratory. Participants signed the written consent form, passed a toxicology urine screen, and completed clinical interviews and questionnaires. Participants completed a functional magnetic resonance imaging (fMRI) scan at the Northwestern University Center for Translational Imaging within a week, on average, of their first assessment. Participants completed a safety checklist prior to entering the scanner room. A professional MRI technician operated the equipment while a research assistant issued instructions. Compensation and debriefing were offered upon study completion.

2.3. Diagnostic and symptom measures

Trained clinical psychology Ph.D. students conducted SCID and IDS-C interviews. The SCID is a semi-structured interview of DSM-IV Axis I diagnoses and has adequate inter-rater reliability with reported kappa values ranging between .70 and 1.00 (First, Spitzer, Gibbon, & Williams, 1997). Evaluators were trained with SCID training tapes (Spitzer, Williams, Gibbon, & First, 1989) and tracked with weekly supervision to prevent rater drift. Inter-rater agreement estimations for this study yielded kappa coefficients of .83 for the Mood module and .93 for the Anxiety module. The IDS-C, a 30-item clinician-rated measure of DSM-IV symptoms, has strong psychometric properties (Rush et al., 2003, 1986b). Cronbach alphas for the IDS-C in our sample were .66 for the depressed group and .56 for the healthy group.