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Differences in the neural correlates of affective responses in depressed and healthy women

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ABSTRACT

We aimed to characterize the extent to which there were differences in neural activation between female participants who were diagnosed with or without depression while viewing negative and neutral imagery. The study enrolled 105 medication-free, right-handed female participants between 17 and 63 years who met criteria for current Major Depressive Disorder ($n=47$) or no prior psychiatric diagnoses ($n=58$). All participants completed a clinical assessment and underwent a functional Magnetic Resonance Imaging (fMRI) scan while responding to an implicit affect task that required them to identify the location of ideographs embedded in one of four corners of each valenced image. When unpleasant (termed negative) stimuli were presented, depressed relative to healthy participants showed significantly decreased activation of the left amygdala and right Inferior Parietal Lobe (IPL). When activation was assessed during the negative versus neutral condition, depressed relative to healthy participants showed significantly increased activation in the Anterior Cingulate Cortex (ACC) and the left IPL. Notably, within-group analyses of healthy participants under the negative condition showed that depressive severity was positively correlated with activation in the left amygdala and left IPL. Our findings suggest that depression influences bottom-up and top-down processing of unpleasant information.

1. Introduction

Major Depressive Disorder (MDD) (APA, 2000) is a debilitating disorder with psychiatric morbidity and disease burden (Ustun et al., 2004). Results have shown that depressed, relative to healthy persons, show altered neural activation when responding to tasks that require the automatic processing of emotionally salient stimuli (Phan et al., 2002; Lee et al., 2007; Bylsma et al., 2008; Foland-Ross and Gotlib, 2012; Pechtel et al., 2013; Jaworska et al., 2014). Specifically, studies have shown that depressed participants display either increased (Townsend et al., 2010) or diminished physiological reactivity to negative emotional stimuli (Bylsma et al., 2008). Altered affective reactivity in depressed individuals has been associated with a dysfunctional emotional regulation while completing a goal directed task (Gross, 2002; Goldin et al., 2008; Pechtel et al., 2013).

Results have shown increased amygdala activation in clinically depressed participants while viewing sad (Arnone et al., 2012) and fearful imagery (Sheline et al., 2001). However, studies have documented a decrease of amygdala activation in depressed relative to healthy participants (Siegle et al., 2007; Hamilton et al., 2008), while other studies have shown no group differences (Davidson, 2002; Irwin et al., 2004; Beauregard et al., 2006; Johnstone et al., 2007; Fales et al., 2008). These variable results may stem from methodological artifacts including psychotropic medication use (Harmer, 2013), depression severity (Anand et al., 2005), onset and history of depressive episodes, and analytic strategies (Groenewold et al., 2013).

Moreover, there appears to be a laterality effect of the amygdala in healthy persons suggests different characteristics for the left and right amygdala with emotional processing. Results suggest a specific right-amygdala response to imagery, but not with word stimuli, along with a specific left-amygdala response to both stimulus types, suggesting more global processing with the left amygdala (Baas et al., 2004; Kensington and Schacter, 2006). This is consistent with findings of a relative left-lateralization for language stimuli and right-lateralization for masked stimuli (Costafreda et al., 2008), potentially reflecting the automaticity of the right amygdala and the slower evaluative process associated with the left (Wright et al., 2001; Anand et al., 2005; Siegle et al., 2002,

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2007; Dichter et al., 2009; Foland-Ross and Gotlib, 2012; Groenewold et al., 2013).

Altered amygdala activation during affective processing may be related to activation in the ACC in depression. Results have shown that bottom-up amygdala activity is regulated by the ACC to reduce task interference, particularly in the context of negative emotion (Johnstone et al., 2007; Siegle et al., 2007; Etkin et al., 2011). Depressed participants have exhibited increased activation in the ACC compared to healthy controls during the presentation of negative versus neutral stimuli, which does not appear to be impacted by lateralization of the ACC (Groenewold et al., 2013).

Similar to the ACC, the inferior parietal lobe (IPL) is involved in decreasing emotional responses to stimuli (Seo et al., 2014), with a greater response to positive than neutral stimuli in the right hemisphere, specifically Brodmann Area 40 (Kensinger and Schacter, 2006). Depressed participants have demonstrated greater activation in the IPL during emotion processing tasks compared to healthy controls, suggesting the potential for the down-regulation of other areas of the brain associated with emotion and/or deficits in deactivating this region to inhibit affective reactivity (Muller et al., 2013, 2014).

The objective of the current study was to assess the extent to which participants with and without depression differ in activation in the amygdala, ACC, and IPL in response to viewing negatively valenced information while detecting a target. We also assessed the direction and strength of the association between activation in the aforementioned Regions-Of-Interest (ROIs) and depression severity among participants with and without depression. To account for potential confounds on patterns of neural activation, we recruited a large sample of unmedicated women either with or without current major depression. Our hypotheses were: (1) depressed, relative to healthy, participants will demonstrate significantly increased activation in the amygdala while viewing negative stimuli; (2) depressed, relative to healthy, participants will show significantly increased activation in the ACC while viewing negative stimuli; (3) depressed, relative to healthy, participants will show significantly increased activation in the IPL with negative stimuli; (4) the severity of depression symptoms will correlate with the level of activation in the amygdala, ACC, and IPL during the presentation of negative stimuli in both depressed and healthy participants. Finally, for exploratory purposes, we conducted a whole-brain analysis to identify additional neuroanatomical differences in depressed and healthy participants.

2. Methods

2.1. Participants

The sample consisted of 105 participants between 17 and 63 years and was restricted to women to eliminate the effects of sex as a confounding variable (Gur et al., 1999) and because of the higher prevalence of MDD in women (Ohayon, 2007). We enrolled participants into four age groups to ensure balanced distribution of age and match groups for age. Of the volunteers screened ($N=1578$), 213 participants were invited to the lab. Of these, 132 individuals signed a written consent form, passed a urine toxicology screen, completed the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Axis I Disorders, (SCID) (First et al., 2002), the Structured Clinical Interview for Axis II Disorder Personality Questionnaire (SCID-II PQ; First et al., 1997), and the Inventory of Depressive Symptomatology-Clinician Rated (IDS-C) (Rush et al., 1986). Depressed participants met DSM-IV criteria for current MDD and an IDS-C score ≥ 24, and healthy participants included individuals with no psychiatric history and an IDS-C score ≤ 11. Additionally, depressed participants with comorbid generalized anxiety disorder, panic disorder, social phobia, specific phobia, and anxiety disorder not otherwise specified were included.

Participants were excluded from the study if they had a lifetime history of severe head trauma, neurological conditions, diagnoses of bipolar I or II, psychosis, obsessive-compulsive disorder, post-traumatic stress disorder, substance abuse or dependence within six months of study participation, and personality disorders (i.e., borderline, schizoid, schizotypal, and antisocial). All participants were medically healthy and medication-free, including no washout of medications, and met safety criteria for participating in a functional magnetic resonance imaging (fMRI) scan. Twelve participants (five healthy, seven depressed) were excluded after data collection due to unusable fMRI data (e.g. excessive motion, excessive cut-off of ROIs, equipment failure, etc.). Specifically, one healthy participant was excluded due to excessive motion. Thus, data from a total of 47 depressed and 58 healthy participants ($n=105$) were used for hypothesis testing.

2.2. Procedure

Participants were screened via phone to ensure eligibility criteria. Subsequently, participants were scheduled to complete a clinical assessment at the laboratory followed by a fMRI scan at the Northwestern University Center for Translational Imaging within one week of the initial appointment. Prior to the scan, participants completed a safety checklist, were introduced to the scanner room, and a trained research assistant issued standard instructions for task completion. A professional MRI technician situated the participants in the scanner and operated the equipment. Compensation and debriefing were offered to all participants upon completion.

2.3. Diagnostic and symptom measures

Participants completed (a) the SCID (First et al., 2002) with trained doctoral students who achieved inter-rater reliability kappa coefficients of.83 for the Mood module and.93 for the Anxiety module; (b) the SCID-II PQ (First et al., 1997), a self-report questionnaire used to screen for DSM-IV Axis II diagnoses, including Antisocial, Borderline, Schizotypal, or Schizoid Personality Disorder. Trained research assistants then reviewed positive responses to determine eligibility; and (c) the IDS-C (Rush et al., 2000, 2003), a validated 30-item symptom measure. Cronbach alpha coefficients for the IDS-C were 0.66 for the depressed group and 0.56 for the healthy group.

2.4. Scanner task

2.4.1. Stimuli

Stimuli for this task consisted of 144 pictures, 48 of each valence (positive, neutral, negative) from the International Affective Picture System (IAPS) (Lang et al., 1999, 2008). These pictures ranged in valence with unpleasant content (e.g., car accidents, burn victims), neutral content (e.g., household items), and pleasant content (e.g., appetizing food), with an equal number of social (i.e., including people) and nonsocial scenes. Picture sets were matched for content, visual properties (e.g., luminance, and complexity), and valence.[2]

[2] Valence: Negative $M=2.96$ (SD=0.40), Neutral $M=5.02$ (SD=0.23), Positive $M=7.03$ (SD=0.39). Arousal: Negative $M=5.28$ (SD=0.61), Neutral $M=3.34$ (SD=0.48), Positive $M=5.23$ (SD=0.61). Please contact corresponding author for picture IDs.