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Research paper

Attention bias in older women with remitted depression is associated with enhanced amygdala activity and functional connectivity

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ABSTRACT

Background: Cognitive bias is a common characteristic of major depressive disorder (MDD) and is posited to remain during remission and contribute to recurrence risk. Attention bias may be related to enhanced amygdala activity or altered amygdala functional connectivity in depression. The current study examined attention bias, brain activity for emotional images, and functional connectivity in post-menopausal women with and without a history of major depression.

Methods: Attention bias for emotionally valenced images was examined in 33 postmenopausal women with (n=12) and without (n=21) a history of major depression using an emotion dot probe task during fMRI. Group differences in amygdala activity and functional connectivity were assessed using fMRI and examined for correlations to attention performance.

Results: Women with a history of MDD showed greater attentional bias for negative images and greater activity in brain areas including the amygdala for both positive and negative images (pcorr < 0.001) than women without a history of MDD. In all participants, amygdala activity for negative images was correlated with attention facilitation for emotional images. Women with a history of MDD had significantly greater functional connectivity between the amygdala and hippocampal complex. In all participants amygdala–hippocampal connectivity was positively correlated with attention facilitation for negative images.

Limitations: Small sample with unbalanced groups.

Conclusions: These findings provide evidence for negative attentional bias in euthymic, remitted depressed individuals. Activity and functional connectivity in limbic and attention networks may provide a neurobiological basis for continued cognitive bias in remitted depression.

1. Introduction

Major depressive disorder (MDD) is a complex disorder that impacts multiple systems in the brain and alters emotional and cognitive processes that are integral to healthy daily functioning and quality of life. The incidence and prevalence of MDD in women is 2–3 times higher than in men (Kessler et al., 2003). In men new onset rates and 12 month prevalence of MDD remain fairly constant from puberty to old age, but increase in women at puberty and remain higher than men until menopause (Kessler et al., 2005; Kessler, 2003). Although new-onset MDD in women generally declines in following the menopause transition, women with previous depressive episodes remain at high risk for recurrence (Freeman et al., 2014). Identifying trait-like factors that remain during remission may help identify novel targets for treatments and interventions aimed at reducing depression recurrence in these women.

Cognitive bias for negative emotional information may contribute to mood disorder risk. Beck's model posits that greater attention or memory for negative events contributes to the development, maintenance, and recurrence of depression by influencing schemas about the self and the world (Beck, 2005; Beck and Haigh, 2014). Consistent with this cognitive model depressed and dysthymic individuals show enhanced memory (Hallion and Ruscio, 2011) and attention (Duque and Vazquez, 2015; Isaac et al., 2014; Sears et al., 2011; Wiens and Syrjänen, 2013) for negative information. Attention bias may present as enhanced initial orientation of attention to emotionally-valenced stimuli or difficulty disengaging from stimuli that have captured attention. Previous studies of attention bias in currently depressed

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and at-risk individuals have demonstrated difficulty disengaging attention from emotionally-valenced stimuli (Gotlib et al., 2004; Joormann et al., 2007). Studies examining biased attentional orientation toward emotional-stimuli have provided inconsistent results, however orientation can be affected by stimulus type and duration and many studies have used stimuli better suited to assess attention bias related to anxiety than depression (Gotlib and Joormann, 2010).

A causative link between cognitive bias and mood is suggested by the finding that modulating attention bias also affects anxiety and depressive symptoms (Hallion and Ruscio, 2011). Experimentally, attention bias modification has been shown to be able to both decrease depressive symptoms (by reducing negative bias) and increase depressive symptoms (by increasing negative bias) (Hallion and Ruscio, 2011), indicating that bias in attention may contribute directly to depressive symptoms rather than being a consequence of depressed mood.

An important component of the cognitive model of depression is that cognitive bias is not only related to current mood-state or stress but also to mood-independent cognitive schemas and altered cognitive processing of emotional information that remain during remission and euthymia (Beck and Haigh, 2014; Sears et al., 2011). Mood-congruent cognitive biases have been reliably found in currently depressed individuals and are associated with the severity of depressive symptoms (Gaddy and Ingram, 2014). Cognitive bias in euthymic, remitted depressed individuals may indicate a trait cognitive vulnerability for depression (Joormann and Gotlib, 2007; Sears et al., 2011) that contributes to the high risk of recurrence (Keller and Berndt, 2002; Kessler et al., 2003; Solomon et al., 1997).

Brain activity or functional connectivity differences that remain in remission may represent a neurobiological basis for continued cognitive biases and vulnerability to depression. Altered activity in fronto-limbic circuits has been associated with attention bias, negative mood, and rumination in currently depressed individuals. De Raedt and Koster (2010) posit a model of depression vulnerability in which decreased dorsal prefrontal activity and increased amygdala activity contributes to negative mood and risk for future depressive episodes (De Raedt and Koster, 2010). This model is supported by studies demonstrating that both currently depressed (Arnone et al., 2012), and at risk populations (Zhong et al., 2011) show greater amygdala activity to negative emotional stimuli than never depressed healthy controls. Attention bias for negative information in remitted depressed individuals may be related to greater amygdala responses for negative stimuli and altered functional connectivity.

To assess attention bias in euthymic post-menopausal women with remitted depression we examined performance and functional brain activity in participants with and without a history of depression during an emotion dot probe (EDP) task. We used fMRI during the EDP task to examine brain activity associated with differences in attentional bias for emotionally-valenced images. We examined resting-state functional connectivity before the EDP task to assess differences in intrinsic amygdala functional connections to other brain areas between the groups. This intrinsic functional connectivity, measured before the task and in the absence of negative-mood induction, may represent stable, trait-like differences in amygdala function (unrelated to task or mood). Altered functional interaction between brain regions responsible for emotional processing may predispose processing of negative emotional information in women with past MDD history despite being euthymic and reveal a neurobiological basis for cognitive vulnerability to depression recurrence in these women.

We hypothesized that participants with a history of MDD would show attention bias for negative images that would not be seen in participants without a history of MDD, and that attention bias would be associated with greater amygdala activity for negative images and altered amygdala functional connectivity.

2. Methods

2.1. Participants

Thirty three right handed postmenopausal women between the ages of 45–75 were included in this study (Past MDD: n=12; No MDD: n=21). Participants were recruited for a larger study examining the effects of estradiol replacement on stress responding in postmenopausal women with and without a history of depression. Participants were recruited through notices in local media and direct mailings which described the study as having a focus on cognition after menopause. Potential participants completed a screening visit before approval for study inclusion. The results reported here include data from all women who completed baseline study visits (pre-estradiol treatment). No participants received estradiol treatment prior to or during participation in the procedures described here. None of the participants were taking ovarian hormones and were at least one year without such treatment. This study was approved by the Vanderbilt University Institutional Review Board and informed consent was obtained from all participants.

2.2. Cognitive screening

All participants were cognitively assessed using: the Wechsler Abbreviated Scale of Intelligence (WASI-II) (Wechsler, 2013), the Mini Mental State Exam (MMSE) (Folstein et al., 1975), Mattis Dementia Rating Scale (DRS-2) (Mattis, 1988), Brief Cognitive Rating Scale, and the Global Deterioration Scale (GDS) (Reisberg et al., 1982). Participants were required to have a GDS score of 1–2 and a MMSE score of greater than 25. No participant scored below 123 on the Mattis scale or below 90 on the WASI; participants were of average or above intelligence with no evidence of dementia or mild cognitive impairment.

2.3. MDD history screening

Participants were screened for current and past depression, mania and dysthymia using the partial Structured Clinical Interview for DSM-IV-TR (SCID) (Spitzer et al., 1992). Participants were excluded for a history of premenstrual dysphoric disorder, or any axis I diagnosis (current or past) other than MDD.

Criteria for never depressed participants were: no current or past episodes that met SCID criteria for MDD, dysthymia, or mania, a current score less than 7 on the Beck Depression Inventory (BDI), and less than 15 on Beck Anxiety Inventory (BAI) (Beck, 1978).

Criteria for prior history of MDD were: at least one episode, in the last ten years that met criteria for MDD on the SCID, no MDD episodes in the last year, current BDI score less than 7, and current BAI less than 15.

2.4. Emotion dot probe (EDP) task

The EDP task is a spatial attention task that measures attention bias (Kimonis et al., 2006; Muñoz Centifanti et al., 2013). The EDP task used in this study was a picture variant using images from the International Affective Pictures System (IAPS) (Lang et al., 2008) and included neutral, positive, and negative (threat and distress) images (Fig. 1). Trials of the EDP consisted of a fixation cross presented in the middle of the screen, followed by a brief presentation (500 ms) of a picture pair with one image each on the right and left of the screen. After the picture presentation, a target (asterisk) appeared either on the right or left of the screen (replacing one of the images) and the participant was instructed to indicate by finger button press the side of the screen on which the target appeared as quickly as possible (available response duration was 1750 ms). The time between the target's appearance and the subject's response was used for the