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Neural activation during cognitive reappraisal in girls at high risk for depression

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ABSTRACT

Objective: Although emotion dysregulation, one of the core features of depression, has long been thought to be a vulnerability factor for major depressive disorder (MDD), surprisingly few functional magnetic resonance imaging (fMRI) studies have investigated neural correlates of emotion regulation strategies in unaffected high risk individuals.

Method: Sixteen high risk (RSK) young women and fifteen matched low risk controls (CTL) were scanned using fMRI while performing an emotion regulation task. During this task, participants were instructed to reappraise their negative emotions elicited by International Affective Picture System images (IAPS). In addition, Difficulties in Emotion Regulation Strategies Scale (DERS) was used to assess participants' emotion dysregulation levels.

Results: Both RSK and CTL individuals show increased amygdala activation in response to negative emotional stimuli, however no difference was found between groups in using cognitive reappraisal strategies and functions of brain regions implicated in cognitive reappraisal. Interestingly, our psychometric test results indicate that high risk individuals are characterised by lower perceived emotional clarity (EC).

Conclusion: Results of the current study suggest depression vulnerability may not be linked to the effectiveness of cognitive reappraisal. Alternatively, lower EC may be a vulnerability factor for depression.

1. Introduction

Major Depressive Disorder (MDD) is among the most prevalent mental disorders that cause marked impairment in social and occupational functioning, and quality of life (APA, 2013). It is estimated that 150 million people worldwide are affected with MDD at any moment in time, and one in every five women and one in every eight men experience a MDD episode during their lifetime (Kessler et al., 1994; Wang et al., 2007). In addition, depression is frequently comorbid with other psychiatric and medical disorders (APA, 2013). Most importantly, 15% of depressed patients eventually die by suicide (Simon and VonKorff, 1998).

Although effective treatments are available, it has been estimated that, even under optimal conditions, current treatments (e.g. medications and psychotherapy) can reduce only about one third of the disease burden associated with MDD (Andrews and Wilkinson, 2002; Chisholm et al., 2004). A plausible way of reducing disease burden of MDD might be reducing the number of new cases. This can be done by prevention rather than treatment, as recent studies have consistently shown that intervention in high risk individuals can reduce later transition to depression (van Zoonen et al., 2014). Therefore, it is important to identify and use prevention strategies for individuals who are at high risk of depression before they have experienced a depressive episode.

Although there are some well known vulnerability factors for the development of depression such as age, gender, adverse childhood experiences, neuroticism, and family history of MDD not all people with these risk factors will go on to develop a depressive episode. The challenge is to predict those individuals most likely to make this transition, because there are currently no tests or biological markers that can assist in making early diagnosis of this disorder. There is thus a pressing need to identify neurobiological markers that can identify those high risk subjects who are most likely to become depressive, so

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that clinical resources could be focused on this subgroup. Insight in this process may aid to understand the neural underpinnings of the onset of MDD, which is vital to improve treatment and prevention strategies.

Emotion dysregulation is one of the core features of MDD (Gotlib and Joormann, 2010). In addition, previous research has suggested that MDD may result from the inability to down regulate negative emotions through cognitive emotion regulation strategies such as reappraisal, acceptance, or problem-solving (Billings and Moos, 1981; D'Zurilla et al., 1998; Nolen-Hoeksema, 2012). Among them cognitive reappraisal is by far the most studied emotion regulation strategy through functional neuroimaging methods in both healthy individuals and depressed patients. Therefore, neural correlates of reappraisal in unaffected high risk individuals may provide more insight in biological risk markers of MDD. However, no study to date has examined neural correlates of cognitive reappraisal in unaffected high risk individuals relative to low risk controls.

During cognitive reappraisal, one attempts to reinterpret an emotion-eliciting situation in a way that alters its meaning and reduces its emotional impact (Gross, 2002). Available data suggests that the beneficial effects of reappraisal are provided through the interactions between the amygdala and regions of the prefrontal cortex (Buhle et al., 2014). The dorsolateral prefrontal cortex (DLPFC), which relates to executive control of cognitive functions, is among the most consistently activated prefrontal cortex region in neuroimaging studies of reappraisal (Kalisch, 2009; Ochsner and Gross, 2005). The other important brain region in cognitive emotion regulation, the amygdala, is involved in the evaluation of and response to emotional stimuli (LeDoux, 2000; Zald, 2003).

In healthy controls, investigators have found reasonably consistent associations between exposure to negative stimuli and increased amygdala activation (Costafreda et al., 2008). This increased amygdala activation elicited by exposure to negative stimuli is significantly reduced during reappraisal. Modulation of amygdala activation is accomplished by the increased activation of DLPFC (Ochsner and Gross, 2008). In other words, the functional coupling between DLPFC and amygdala may reflect the effectiveness of reappraisal.

With respect to depression, the main brain regions implicated in reappraisal, amygdala and DLPFC, appear to be dysfunctional. It has been reported that compared to healthy controls, depressed patients show greater amygdala activation when exposure to negative emotional stimuli (Hamilton and Gotlib, 2008). Studies of both resting-state brain perfusion and glucose metabolism have consistently revealed lower levels of DLPFC activation in depressed patients than healthy controls (Biver et al., 1994). In addition, neuroimaging studies of cognitive reappraisal have reported reduced DLPFC activation, decreased capacity to reduce amygdala activation, and reduced DLPFC-amygdala coupling in response to negative stimuli in depressed patients (Erk et al., 2010; Greening et al., 2014).

In recent years, researchers have begun to explore the extent to which these abnormalities are present in high risk individuals. Results of these studies are intriguing. For example similar to depressed patients, high risk individuals show greater amygdala activation in response to negative stimuli than the controls (Chan et al., 2009; Levesque et al., 2011; Monk et al., 2008; Wolfensberger et al., 2008). In addition, it has also been reported that relative to controls, high risk individuals have diminished activation of the DLPFC in response to the presentation of fearful faces (Mannie et al., 2011) and attempt to ameliorate sad mood by recalling positive memories (Joormann et al., 2012). Although these findings suggest that altered limbic and prefrontal functioning precedes long before a depressive episode and serves as a neurobiological marker for depression vulnerability, it is clear that empirical evidence for an emotion dysregulation view of depression vulnerability is still limited and further investigation is warranted.

The aim of this present study was to extend our understanding of neurobiological markers for depression vulnerability. Based on the literature described above, we conducted an fMRI study of cognitive reappraisal and hypothesized that high risk individuals, relative to low risk controls, would report more difficulties in using reappraisal strategies and show greater activation in the amygdala in response to negative stimuli, and less activation in prefrontal cortex regions during ameliorating of negative affect.

Young daughters of mothers with recurrent MDD were identified as the high risk group of our study. The rationale behind this choice comes from following studies: 1) MDD generally peaks in the early adulthood period and females experience depression 1.5- to 3-fold higher rates than men (Kessler et al., 2003); 2) Offspring of parents with MDD face a three times greater risk for MDD than offspring without such a family history (Weissman et al., 2006); 3) Maternal depression is particularly associated with depression in offspring by age 24 (Klein et al., 2005); 4) Daughters of depressed mothers are more vulnerable to depression than sons (Davies and Windle, 1997). Taken together, young women with mothers suffering from recurrent MDD appear to be one of the most favourable high risk populations in order to investigate neurobiological markers for depression vulnerability.

2. Material and methods

2.1. Participants

Forty two right-handed girls between the ages of 18 and 24 years with no past or current DMS-IV axis I disorder participated in the study. Twenty two girls had biological mothers suffering from recurrent MDD (high risk group [RSK]), and 20 girls had biological mothers with no history of any axis I disorder (low risk group/control [CTL]).

Eleven participants (6 RSK and 5 CTL) were subsequently excluded for high mood scores and/or excessive movement in the MRI scanner, leaving a total of 31 participants who completed the study.

High risk participants were recruited among daughters of female patients with recurrent MDD attending both Ege University School of Medicine's psychiatric outpatient clinic and other local psychiatric outpatient clinics in Izmir. Depressed patients were diagnosed by a consultant psychiatrist and did not have any psychiatric comorbidity. The healthy control subjects were volunteers via advertisements posted in numerous locations within the local community.

Participants eligibility for the study was evaluated by a psychiatrist using following self- and observer-rated scales: Structured clinical interviews for DSM-IV (SCID)-I (Spitzer et al., 1992), Hamilton Depression Rating Scale for Depression (HDRS) (Hamilton, 1969), State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). All participants scored within normal range (0–8) for healthy individuals on the HDRS. The mean scores of both groups were well below the clinical cut-off point (> 8) for depression. In addition, the Difficulties in Emotion Regulation Scale (DERS) (Gratz and Roemer, 2004) was used to assess participants' emotion dysregulation levels. The DERS is a brief, 36-item self-report questionnaire designed to assess multiple aspects of emotional dysregulation. Higher scores suggest greater problems with emotion regulation.

Handedness was determined by the Edinburg Handedness Inventory (Oldfield, 1971). Written informed consent was obtained from all subjects subsequent to a detailed description of the study. The study design, approved by the local ethics committee of the Ege University School of Medicine, was prepared in accordance with the ethical standards laid down in the Declaration of Helsinki. All participants were paid for their participation in the study.

The exclusion criteria of the study were as follows: left handed, current pregnancy, a current or past psychiatric or neurological disease, a previous or present head injury, a current medical disease influencing the central nervous system, inability to read and see stimuli presented on the screen, any contradictions to magnetic resonance imaging (i.e. metal in the body or claustrophobia).