Neural correlates of self-perceptions in adolescents with major depressive disorder

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ABSTRACT

Alteration in self-perception is a salient feature in major depression. Hyperactivity of anterior cortical midline regions has been implicated in this phenomenon in depressed adults. Here, we extend this work to depressed adolescents during a developmental time when neuronal circuitry underlying the sense of self matures by using task-based functional magnetic resonance imaging (fMRI) and connectivity analyses. Twenty-three depressed adolescents and 18 healthy controls (HC) viewed positive and negative trait words in a scanner and judged whether each word described them ('self' condition) or was a good trait to have ('general' condition). Self-perception scores were based on participants' endorsements of positive and negative traits during the fMRI task. Depressed adolescents exhibited more negative self-perceptions than HC. Both groups activated cortical midline regions in response to self-judgments compared to general-judgments. However, depressed adolescents recruited the posterior cingulate cortex/precuneus more for positive self-judgments. Additionally, local connectivity of the dorsal medial prefrontal cortex was reduced during self-reflection in depressed adolescents. Our findings highlight differences in self-referential processing network function between depressed and healthy adolescents and support the need for further investigation of brain mechanisms associated with the self, as they may be paramount to understanding the etiology and development of major depressive disorder.

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1. Introduction

Adolescence is a sensitive period of development characterized in part by maturation of neuronal circuitry related to emotional processing and the sense of self (Giedd, 2004; Sebastian et al., 2008). It is during this stage that many psychiatric conditions first emerge, including major depressive disorder (MDD), an illness characterized by feelings of worthlessness and low self-esteem (Manani and Sharma, 2013; Wilburn and Smith, 2005). Adolescent MDD is a major public health concern, associated with severe consequences including suicide, the second leading cause of death in this age group (Perou et al., 2013). Relatedly, longstanding evidence suggests low self-esteem is linked to suicidal behavior (Lewinsohn et al., 1994; Manani and Sharma, 2013; McGee and Williams, 2000; Mitsui et al., 2014; Overholser et al., 1995; Wilburn and Smith, 2005). Thus, research that targets brain mechanisms associated with self-referential processing in depressed adolescents is paramount to understanding the etiology and development of the disorder.

It has been suggested that regions within the 'default mode network' (DMN) are active in the resting brain when thoughts are often introspective and self-reflective but are typically deactivated during more goal-directed tasks (Andrews-Hanna et al., 2010; Raichle et al., 2001). However, this is still a topic of active investigation as the existence of a passive state of brain function and its interaction with task-positive networks is not fully understood. The DMN includes cortical midline structures, such as the medial prefrontal cortex (MPFC), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and precuneus, as well as the inferior parietal cortex, lateral temporal cortex, and hippocampus (Andrews-Hanna et al., 2010; Buckner et al., 2008). While regions within this network have been associated with several cognitive domains such as the memory and attention systems, among others (Broyd et al., 2009;

Buckner et al., 2008), recent work has implicated the DMN in affective cognition due to its connections with brain regions involved in emotion and salience, such as the amygdala and insula (Ho et al., 2014a; Sambataro et al., 2013; Uddin, 2015). For example, the midline core (i.e. MPFC, ACC, PCC, precuneus) has been shown to be activated during self-referential processing in both healthy adults (Andrews-Hanna et al., 2010; Denny et al., 2012; Kelley et al., 2002; Lemogne et al., 2012; Northoff et al., 2006) and adolescents (Pfeifer et al., 2007, 2009). Alterations in these regions may consequently underlie self-referential processing deficits that manifest as low self-esteem and feelings of worthlessness in affective disorders (Ho et al., 2014a).

Currently, studies investigating self-referential processing deficits in depression have focused on adults. Findings appear conflicting, with reports of both increased (Lemogne et al., 2009, 2010; Yoshimura et al., 2010) and decreased (Grimm et al., 2009; Johnson et al., 2009) activation of the MPFC during self-reflection (Nejad et al., 2013). One theory postulates that hyperactivity of anterior cortical midline regions during negative self-reflection contributes to ruminations about the self in depression (Lemogne et al., 2009, 2010, 2012; Yoshimura et al., 2010, 2014). For example, Yoshimura et al. (2010) found that negative thoughts in particular increased activity in the dorsal medial prefrontal cortex (dMPFC) and ventral ACC in depressed adults compared to healthy controls, whereas activity in these areas was similar in both groups for positive self-thoughts (Yoshimura et al., 2010). Johnson et al. (2009) similarly found that the dMPFC was activated in healthy controls and depressed adults in response to positive thoughts like personal hopes and dreams. However, depressed adults showed less deactivation (higher signal) of this region when prompted to have non-self-referential thoughts, suggesting depressed individuals may have difficulty disengaging from negative self-focused ruminations. An alternate theory proposes that cortical midline regions are not necessarily hyperactivated during active self-reflection in depressed adults, but rather that resting-state activity in these regions is abnormally increased (Greicius et al., 2007), which leads to reduced signal changes in these regions during self-reflection tasks and appears as hyperactivity (Grimm et al., 2009; Northoff et al., 2011).

While studies of depressed adults have begun to tease apart the brain regions involved in self-reflection and negative rumination, few have investigated the connectivity of these regions to better understand self-referential processing network function. Task-dependent functional connectivity analyses may help clarify the relationships between regions within this network. Only two studies to date have specifically examined task-dependent connectivity between cortical midline structures during self-referential processing in MDD, and both were also in adults. Lemogne et al. (2009) found increased connectivity between the posterior cingulate cortex and anterior regions of the DMN, including the dMPFC and ACC in depressed patients, while Yoshimura et al. (2010) found increased connectivity between the ACC, MPFC, and amygdala. One caveat of both studies was that patients were treated with psychotropic medications.

Based on the above observations, the current study extends this line of work and examines self-referential processing in psychotropic medication-free adolescents with depression, as well as task-dependent connectivity of cortical midline regions within the DMN during self-referential thought. We hypothesized that adolescents with MDD would exhibit more negative self-perceptions compared to healthy controls—scores that were based on participants' endorsement and rejection of positive and negative trait words in the scanner. Additionally, we predicted depressed adolescents would show increased activity and connectivity of cortical midlines regions (e.g., MPFC, ACC, PCC, precuneus), similarly to depressed adults (Lemogne et al., 2009, 2010, 2012; Yoshimura

et al., 2010, 2014). Furthermore, we expected neural activity and connectivity in these regions to negatively correlate with self-esteem scores.

2. Material and methods

2.1. Participants

The sample consisted of 23 adolescents with MDD and 18 healthy controls (HC), all right-handed and group matched on age and sex. Six individuals were excluded from all fMRI analyses, 5 for excessive motion and 1 for image distortion. The final imaging sample consisted of 20 adolescents with MDD and 15 HC. Depressed adolescents were recruited from the New York University (NYU) Child Study Center, the Bellevue Hospital Center Department of Psychiatry, and through local advertisements. Healthy controls were recruited through local advertisements. An Institutional Review Board (IRB) approved the study, and written informed consent was obtained from participants age 18 and older; those under age 18 provided signed assent and a parent provided signed informed consent.

Participants ranged in age from 12 to 20 years old and did not present with any significant medical or neurological conditions. Participants were screened for pubertal stage using the Tanner Scale (Tanner, 1962) and were all required to be at least a 4. Exclusion criteria included a low IQ (<80), MRI contraindications, a positive urine toxicology test, or a positive pregnancy test in women. Depressed adolescents met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (DSM-IV-TR) criteria for diagnosis of MDD, with a current episode of at least 8 weeks in duration, and a minimum raw score of 36 on the Children's Depression Rating Scale-Revised [CDRS-R; Poznanski et al., 1985]. All participants were free of psychotropic medication for at least seven half-lives of the drug. Furthermore, adolescents with MDD could not have a current diagnosis of post-traumatic stress disorder or an eating disorder, or a current or past DSM-IV-TR diagnosis of bipolar disorder, schizophrenia, pervasive developmental disorder, panic disorder, obsessive-compulsive disorder, conduct disorder, Tourette's disorder, or a substance-related disorder in the past year. Healthy control adolescents did not meet the criteria for any current or past DSM-IV-TR diagnosis and were psychotropic medication-naïve.

2.2. Clinical assessments

A board-certified child/adolescent psychiatrist or clinical psychologist performed psychiatric assessments using the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version [KSADS-PL; Kaufman et al., 1997], a semi-structured interview conducted with both the participant and their parents. Depression severity was assessed using the self-rated Beck Depression Inventory-Second Edition [BDI-II; Beck et al., 1997] and the clinician-rated CDRS-R. Anxiety was assessed using the Multidimensional Anxiety Scale for Children, while suicidality was quantified using the Beck Scale for Suicidal Ideation [BSSI; Beck et al., 1979]. Lastly, IQ was estimated using the Kaufman Brief Intelligence Test (Kaufman and Kaufman, 1990).

2.3. Word task

Similar to past research (Fossati et al., 2003; Yoshimura et al., 2009, 2010, 2014), participants were presented with positive or negative trait adjectives (e.g., positive = calm, intelligent, likeable, kind; negative = obnoxious, messy, greedy, dumb) and had to answer one of three questions: (1) general-judgments ("Is this a good trait?"); (2) self-judgments ("Does this describe you?"); (3)