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Reduced fronto-amygdalar connectivity in adolescence is associated with increased depression symptoms over time

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ABSTRACT

Depression is common among adolescents, affecting greater than 12% of youth in a given year. Studies have shown aberrant amygdala connectivity in depressed adolescents, compared with controls; however, no studies have examined whether these abnormalities precede and heighten risk for depressive symptom expression. This study used resting state functional connectivity (RSFC) magnetic resonance imaging to examine neurobiological markers of escalating depression symptoms in adolescents (ages 12–16 years; free from psychopathology at baseline). Of a large sample of adolescents, 18 showed ≥ 1 S.D. increase in depression scale t-scores over time ("escalators"; time to escalation ranging from 6 to 54 months in follow up) and were matched and compared to 19 youth showing stable CDI scores over time ("controls"). Whole-brain analyses on baseline RSFC data using an amygdala seed region-of-interest (ROI) showed that controls had greater RSFC, relative to escalators, between the right amygdala and left inferior frontal and supramarginal gyrus and right mid-cingulate cortex. Additionally, relative to escalators, control youth had less RSFC between the left amygdala and cerebellum. Findings suggest a possible neurobiological marker of increasing depressive symptoms during adolescence, characterized in part by reduced fronto-limbic connectivity, suggesting a premorbid deficiency in top-down emotional regulation.

1. Introduction

Adolescence is a developmental period characterized by social, physical, hormonal, and neural changes (Casey et al., 2008; Luciana, 2013). These diverse changes, and their different developmental timelines, are thought to create a unique vulnerability to psychopathology that is specific to this time in life (Blakemore and Choudhury, 2006; Casey et al., 2008; Konrad et al., 2013; Ladouceur et al., 2012). One such example is an increased incidence of depression. Major depressive disorder (MDD) is common among adolescents, affecting over 12% of youth in a given year (SAMSHA, 2015). Furthermore, adolescent-onset MDD is associated with more severe and chronic depression across the lifespan, as well increased suicide rates (Zisook et al., 2007), the latter of which is the second leading cause of mortality among those aged 10–24 years (Heron, 2016). Given the dramatic increase in rates of MDD that occurs during the adolescent years (Hankin et al., 1998), identifying potential neurobiological biomarkers and underpinnings of risk for MDD is crucial for ultimately informing prevention efforts.

The prefrontal cortex and limbic system both undergo major neurodevelopment and reorganization during adolescence, which affects the ways in which adolescents assess, process, and evaluate both risk and emotion (Heller and Casey, 2016; Steinberg, 2005). The amygdala, a key brain structure within the limbic system, detects and responds to threats and aids in the formulation of emotional responses (Baxter and Murray, 2002; LeDoux, 2003; Ochsner et al., 2012) and responds differentially to emotional stimuli in adolescents when compared to adults (Casey, 2015). The prefrontal cortex (PFC) is one of the last brain regions to develop and is broadly responsible for higher order cognitive functions, including planning and cognitive control (Blakemore and Choudhury, 2006; Fuster, 2001). The PFC also plays a major role in emotional behavior when working in tandem with the limbic system (Fuster, 2001). More specifically, the functionally connected circuits of the amygdala and PFC have been shown to be the principal neural correlates of emotional regulation and processing (Ochsner et al., 2002; Ochsner and Gross, 2005), circuitry showing developmental change during adolescence (Gabard-Durnam et al., 2014).

Grounded in existing knowledge of emotional neural circuitry and

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associated developmental changes in the brain, several neuroimaging studies have investigated the neural correlates of depression in adolescent populations. Utilizing task-based functional magnetic resonance imaging (fMRI), these studies have reported abnormal amygdala activation, including both hyper- and hypo-active amygdala response to emotional stimuli in un-medicated depressed adolescents, as well as regions of atypical PFC brain response, during emotion processing tasks (Henje Blom et al., 2015; for review, see Hulvershorn et al., 2011; Kerestes et al., 2014). In addition to task-based fMRI studies of adolescent depression implicating regional abnormalities in amygdala and PFC functioning, more recently, studies have begun to examine resting state functional connectivity of the amygdala in depressed adolescents. Resting state functional connectivity (RSFC) magnetic resonance imaging allows the examination of functional connections in the brain, in the absence of external task demands, by correlating temporally synchronous spontaneous blood-oxygen-level dependent (BOLD) activity (Fox and Raichle, 2007; van den Heuvel and Hulshoff Pol, 2010). Though widespread differences in functional connectivity have been observed between depressed adolescents and controls using this technique (Bebko et al., 2015; Connolly et al., 2017; Pannekoek et al., 2014; Rzepa and McCabe, 2016; Sacchet et al., 2016), several studies have demonstrated fronto-amygdalar hypo-connectivity in adolescents with MDD compared to healthy controls, including reduced RSFC between the right amygdala and the left frontal pole and right anterior cingulate cortex (Pannekoek et al., 2014) and between the right amygdala and ventromedial and bilateral dorsolateral PFC (Connolly et al., 2017). Another study examining children with MDD, with and without maternal MDD, showed reduced RSFC between the amygdala and bilateral dorsolateral PFC in both groups compared to controls (Luking et al., 2011). Thus, aberrant fronto-amygdalar RSFC may be a neural substrate of altered emotional processing, either as a function of the depressed state or as an etiological risk factor leading to depressive symptomatology, given the role of this circuitry in emotional regulation. Examining premorbid functional connectivity between the amygdala and prefrontal regions in adolescents who later show an increase in depression symptoms could provide unique insight into the neural correlates of developmental risk for psychopathology, specifically adolescent-onset MDD.

While a few studies have examined amygdala task-related brain response (Swartz et al., 2015) and RSFC (Luking et al., 2011) in at-risk children and adolescents with familial depression, and one study showed increased subgenual anterior cingulate cortex to amygdala RSFC in adolescents who develop depression (Davey et al., 2015), to our knowledge, no studies have examined whether atypical neural features entirely precede depressive symptom expression. The present study addresses this gap by using RSFC to examine potential neurobiological connectivity markers of later escalating depression symptoms in an adolescent sample. Based on previous findings of abnormalities in functional connectivity of the limbic system in depressed adolescents (Bebko et al., 2015; Connolly et al., 2017; Pannekoek et al., 2014), we compared baseline whole-brain, seed-based amygdala RSFC of youth who showed a significant increase in depression symptoms over time to that of well-matched youth who showed a stable mood presentation. We hypothesized weaker premorbid fronto-amygdalar functional connectivity in those adolescents who later showed an increase in depressive symptoms. This investigation is crucial to identifying potential neurobiological markers of adolescent-onset depressive symptom expression.

2. Method

2.1. Study participants

Adolescents, ages 12–16 years, were recruited through the community as part of a larger, ongoing longitudinal study of adolescent neurodevelopment (Alarcon et al., 2015; Cservenka et al., 2014; Cservenka and Nagel, 2012). Following informed consent and assent, all youth and a parent/legal guardian completed separate comprehensive screening interviews to assess eligibility. Exclusionary criteria at baseline included major medical conditions or injury affecting central nervous system functioning, prenatal exposure to drugs or alcohol, personal alcohol/drug use (> 10 lifetime alcoholic drinks or > 2 drinks per occasion, > 10 lifetime uses of marijuana, any other drug use, or > 4 cigarettes per day), as assessed by the Brief Lifetime version of the Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998), current diagnoses of DSM-IV Axis I psychiatric disorder (including learning disability) as assessed by the computerized NIMH Diagnostic Interview Schedule for Children - Predictive Scales (DISC-PS-4.32b) (Lucas et al., 2001; Shaffer et al., 2000), report of psychotic disorder in a biological parent as assessed by the Family History Assessment Module (Rice et al., 1995), current use of psychotropic medication, left handedness, and MRI contraindications.

After establishing eligibility, youth were administered a baseline battery of neuropsychological assessments and questionnaires. This battery included the two-subtest form of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) to assess intellectual functioning, the Childhood Depression Inventory (CDI) (Kovacs, 1985) to assess current (past two weeks) depression symptoms and severity, and the State Anxiety Subscale from the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) to assess state anxiety at the time of the baseline scan. Socioeconomic status was estimated using parent-report via the Hollingshead Index of Social Position (Hollingshead, 1957). Pubertal development was assessed through self-report using the Pubertal Development Scale (Petersen et al., 1988). Following baseline study visits, youth were contacted every three months and administered quarterly follow-up telephone interviews. During these telephone interviews, youth were asked to complete the CDI and the CDDR (Brown et al., 1998) to assess recent (past 90 days) alcohol, drug, and tobacco use.

Based on these quarterly telephone interviews of approximately 175 participants, youth who showed ≥ 10-point increase in depression t-scores (one standard deviation) from baseline, as assessed by the CDI, were included in the sample (escalators; n = 18, females = 10). Although a full diagnostic assessment of MDD was not completed, 7 escalator youth had an intermediate or positive diagnosis on the DISC MDD module at some point during the follow-up period. Escalators showed this increase in depression scores at varying times throughout follow up, ranging from 6 months to 54 months. These youth were carefully matched and compared to youth from the larger sample who showed stable CDI scores over time (controls; n = 19, females = 11). Specifically, escalators and controls were matched on baseline CDI scores, age, sex, puberty, IQ, time in follow up, and alcohol and drug use at baseline. All procedures were approved by the Oregon Health & Science University (OHSU) Institutional Review Board.

2.2. MRI data acquisition

Youth were scanned at baseline on a Siemens Tim Trio 3.0 T MRI scanner at the Advanced Imaging Research Center at OHSU. One high-resolution T1-weighted anatomical image was acquired for co-registration of functional data (repetition time (TR) = 2300 ms, echo time (TE) = 3.58 ms, orientation = sagittal, 256 × 256 matrix, resolution 13 mm, 9:14 min). Resting state functional MRI (fMRI) data were acquired with two blood-oxygen level dependent (BOLD)-weighted images (TR = 2500 ms, TE = 30 ms, flip angle = 90°, field of view = 240 mm^2, slices = 36, slice thickness = 3.8 mm, resolution = 3.75 × 3.75 × 3.8 mm, 4:17 min/run), during which participants were instructed to stay still and fixate on a white cross in the center of a black screen. Lying in a supine position on the scanner bed, youth were able to view visual stimuli with a mirror mounted on a 12-channel head coil reflecting a projection from the head of the scanner. Afterwards, youth confirmed wakefulness during resting state scans.