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Cortico-amygdalar maturational coupling is associated with depressive symptom trajectories during adolescence

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ABSTRACT

Background: Adolescence is characterized by increasing prevalence of depressive symptomatology, along with significant structural brain development. While much research has examined focal abnormalities in gray matter structure underlying depression, we employed a structural coupling approach to examine whether longitudinal associations between amygdala and cortical development (referred to as maturational coupling) was related to concurrent changes in depressive symptomatology during adolescence.

Method: 166 participants underwent up to three MRI scans (367 scans) between 11 and 20 years of age. Depressive symptoms were measured at three coinciding time points using the Center for Epidemiological Studies-Depression scale. Linear mixed models were employed to identify whether change in amygdala volume was related to development of cortical thickness, and if maturational coupling of these regions was related to changes in depressive symptomatology.

Results: Positive maturational coupling was identified between the right amygdala and (predominantly anterior) prefrontal cortex, as well as parts of the temporal cortices. Greater positive coupling of these regions was associated with reductions in depressive symptoms over time.

Conclusions: Findings highlight significant associations between cortico-amygdalar maturational coupling and the emergence of depressive symptoms during adolescence, suggesting that synchronous development of these regions might support more adaptive affect regulation and functioning.

Introduction

Adolescence is characterized by a dramatic rise in the incidence of depression – the leading cause of disability during the second decade of life in developed countries (World Health Organization, 2014). Future mental health trajectories are often shaped during this time, with the experience of a depressive symptom during adolescence increasing the likelihood of future disorder onset (Costello and Maughan, 2015). Research has investigated the neurobiological underpinnings of depression, identifying structural abnormalities in the amygdala, subgenual anterior cingulate cortex (ACC), and various regions of the prefrontal cortex (Dohm et al., 2016; Kerestes et al., 2014; Miller et al., 2015; Singh and Gotlib, 2014). However, given documented maturation of both subcortical and prefrontal regions during adolescence (Dennis and Brotman, 2003; Goddings et al., 2014; Mutlu et al., 2013; Raznahan et al., 2011b; Tamnes et al., 2010; Vijayakumar et al., 2016), it can also be speculated that coordinated development of these regions may help support adaptive functioning, while aberrations to this pattern may result in poorer regulatory capacities that have enduring effects on mental health.

Indeed, it is widely theorized that depression emerges from the development of, and interaction between two broadly defined brain systems that work in concert – the subcortical system that supports affect generation and reactivity, and the prefrontal cortex that is involved in the cognitive regulation of affective states (Badcock et al., 2017; Carver et al., 2008; Heller, 2016; Pfeifer and Allen, 2012; Siegle et al., 2007). Within the subcortical system, the amygdala is the most consistently implicated region in depression, with its extensive functional and anatomical connectivity highlighting the central role this region plays in emotional processing, learning and motivation (Mears

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and Pollard, 2016). As such, it is important to characterize coordinated development of the amygdala and PFC regions and understand how this may relate to the emergence of depressive symptomatology.

In comparison to traditional focal approaches, analyses investigating associations between brain regions have the potential to reveal more about cognitive and affective processes characterized by distributed neural activity (Evans, 2013). Within the structural neuroimaging field, this has resulted in a surge of studies on structural *covariance* or *coupling* of gray matter (i.e., how structural properties, such as volume or thickness, of different regions correlate with each other; Alexander-Bloch et al., 2013b; Zielinski et al., 2010). This is frequently hypothesized to arise from coordinated neurobiological development through mutually trophic effects mediated by underlying axonal connections (i.e., Hebbian principals of "neurons that fire together wire together"; Hebb, 1949). Indeed, past investigations have also documented patterns of maturational coupling (i.e., patterns of correlated change) across the cortical mantle (Lerch et al., 2006; Raznahan et al., 2011a). However, coupling of subcortical and cortical structures may be particularly relevant to understanding associations between neurodevelopment and depression, as described above.

Only two studies have investigated normative structural coupling between subcortical and cortical structures. Albaugh and colleagues (2013) identified negative coupling between the amygdala and prefrontal structures. While they examined longitudinal data, no age-related effects were found (i.e., the relationship between amygdala volume and cortex thickness remained constant at any given time from 5-to-23 years of age). However, they did not investigate whether *change in amygdala structure* over time was related to *change in cortical structures*. To our knowledge, Walhovd and colleagues (2015) are the only authors to examine this question, showing that development of the hippocampus and basal ganglia were both positively related to cortical development, with greater subcortical reductions being related to greater cortical reductions. Each subcortical structure also exhibited unique coupling with largely non-overlapping cortical areas. Such an investigation is yet to be undertaken on cortico-*amygdalar* coupling.

In light of research supporting the importance of functional maturational coupling of the cortex and amygdala in affective processes (Gee et al., 2013), along with research implicating structural brain development in depression (Ducharme et al., 2014; Whittle et al., 2014), it can be hypothesized that similar associations may be present in relation to maturational coupling of structure. Initial research into the functional relevance of structural covariance networks focused on cognitive functions (Lee et al., 2013; Raznahan et al., 2014), but one recent study investigated associations with behavioral problems. Ameis et al. (2014) found amygdala-orbitofrontal cortex (OFC) coupling varied as a function of externalizing problems in adolescents, with a lack of coupling being associated with higher levels of problems. However there has been no research examining how *maturational coupling* may relate to internalizing symptoms and associated psychopathology.

Therefore, the current study characterized cortico-amygdalar maturational coupling during adolescence, and subsequently investigated whether this pattern of coupling was related to concurrent changes in depressive symptomatology. We focused on the amygdala given its prominent role in affective processing and prior research implicating functional and structural abnormalities in this region with depression (Kerestes et al., 2014; Singh and Gotlib, 2014). The research question was addressed in a community sample of adolescents examined longitudinally from 11-to-20 years of age, with up to three brain scans obtained per individual, as well as concurrent assessment of depressive symptoms. While structural correlates of depressive symptomatology have previously been examined in this sample (Whittle et al., 2014, 2011), this is the initial investigation into structural coupling. We first examined maturational cortico-amygdalar coupling, and given prior findings by Walhovd et al. (2015), hypothesized positive associations between change in amygdala volume and change in cortical thickness, particularly within regions implicated in modulating amygdala function (i.e., dorsolateral, dorsomedial and ventromedial PFC (dlPFC, dmPFC, vmPFC), OFC, and inferior parietal cortices; Arnsten and Rubia, 2012; Burnett et al., 2011; Rempel-Clower, 2007). We subsequently examined whether these patterns of cortico-amygdalar maturational coupling were related to changes in depressive symptomatology. Although exploratory in nature, we hypothesized that adolescents with positive coupling (particularly greater correlated reductions in the size of the amygdala and associated cortical regions) would experience reductions in symptoms over time. In order to examine the specificity of findings to depression, particularly given the predominant role of the amygdala in anxiety (Blackford and Pine, 2012), we also investigated whether maturational coupling was related to changes in anxiety symptoms.

Methodology

Participants

The current sample was derived from a larger longitudinal cohort enrolled in the Orygen Adolescent Development Study (OADS), conducted in Melbourne, Australia. Students (N=2453) in the final year of primary school were recruited from schools to participate in an initial screening phase, which involved completion of the Early Adolescent Temperament Questionnaire-Revised (EATQR; Capaldi and Rothbart, 1992). Based on scores, a smaller sample of 415 students were selected by over-sampling adolescents at the extreme ends of the distribution for temperamental factors of Effortful Control and Negative Emotionality to maximize inter-individual differences in psychological well-being (an equal number of participants were invited to participate from the following standard deviation ranges above and below mean: i) 0–1 ii) 1–2 iii) 2–2.5 and iv) greater than 2.5, to emphasize distribution at the tails).

245 adolescents agreed to participate in the broader ADS. Of this sample, a number of adolescents declined participation in the Magnetic Resonance Imaging (MRI) assessments, resulting in 177 participants completing MRI scans at one to three time points when they were aged approximately 13 (time 1: T1), 17 (time 2: T2) and 19 (time 3: T3) years. Based on visual inspection of FreeSurfer processed MRI data (see below for details) by a researcher trained in neuroanatomy, nine participants were excluded due to poor image quality. Two additional participants with full scale IQ less than 70, as assessed by the Wechsler Intelligence Scale of Children – Version IV (Wechsler, 2003), were excluded from analyses. Following exclusions, 166 participants (n=86 males) aged 11-to-20 years were available for analyses. While this sample had greater variance on temperamental distributions compared to the school-screening sample (due to the sampling strategy, see Table S1), it also exhibited normal distribution on Effortful Control and Negative Emotionality based on the Kolmogorov-Smirnoff test ($p > 0.05$) and did not present with skewness or kurtosis (estimate/standard error $< \pm 2$).

Seventy-three participants had three scans, 55 had two scans and 38 had one scan. Table 1 provides a breakdown of the number of participants at each time point, and demographic and cognitive characteristics. Males and females did not differ on any of these variables ($p > 0.05$). The final sample also did not differ from the initial school-screening sample (N=2453) on socioeconomic disadvantage ($t_{(2439)}=21.292$; p=0.197) or sex (Pearson's $\chi^2=2.245$; p=0.691). Twenty-eight participants of the final sample met criteria for past or current psychiatric disorder at T1, and an additional 28 and 19 participants met criteria at T2 and T3, respectively, as assessed by the Schedule for Affective Disorder and Schizophrenia for School-Aged Children: Present and Lifetime Version (Kaufman and Schweder, 2004). Refer to supplementary material (Table S2) for further detail on administration and reliability of KSADS interviews. Table 2 provides further detail on psychiatric diagnoses. The prevalence of psycho-