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Research paper

White matter microstructure in boys with persistent depressive disorder

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ABSTRACT

Background: Persistent depressive symptoms in children and adolescents are considered a risk factor for the development of major depressive disorder (MDD) later in life. Previous research has shown alterations in white matter microstructure in pediatric MDD but discrepancies exist as to the specific tracts affected. The current study aimed to improve upon previous methodology and address the question whether previous findings of lower fractional anisotropy (FA) replicate in a sample of children with persistent depressive disorder characterized by mild but more chronic symptoms of depression.

Methods: White matter microstructure was examined in 25 boys with persistent depressive disorder and 25 typically developing children. Tract specific analysis implemented with the Diffusion Tensor Imaging - ToolKit (DTI-TK) was used to probe fractional anisotropy (FA) in eleven major white matter tracts.

Results: Clusters within the left uncinate, inferior fronto-occipital and cerebrospinal tracts showed lower FA in the clinical group. FA in the left uncinate showed a negative association with self-reported symptoms of depression.

Conclusions: The results demonstrate lower FA in several white matter tracts in children with persistent depressive disorder. These findings support the contention that early onset depression is associated with altered white matter microstructure, which may contribute to the maintenance and recurrence of symptoms.

1. Introduction

Major depressive disorder (MDD) is one of the leading mental health problems in adults with an estimated worldwide lifetime prevalence of 11.2% (Kessler et al., 2015). Many cases of adult MDD begin in adolescence and risk factors for depression may occur even earlier (Kennard et al., 2006; Kovacs and Lopez-Duran, 2010). Adolescence is marked by continued changes in brain maturation and a rise in depressive symptoms during adolescence has often been associated with these changes (e.g., Davey et al., 2008; Foland-Ross et al., 2015; Schmaal et al., 2015).

Grey and white matter exhibit differential developmental patterns with the former showing an overall decrease and the latter an overall increase in volume from late childhood to early adulthood (Mills and Tamnes, 2014). While these measures focus on the macrostructure of the tissue, it is also possible to examine changes in the white matter microstructure using diffusion weighted imaging. White matter restricts the movement of water molecules, which is greater along the long axis of a fibre than across it. Common metrics used to describe these properties are fractional anisotropy (FA) and mean diffusivity (MD). In addition, axonal (AD) and radial diffusivity (RD) corresponding to movement along and across fibre bundles respectively can also be determined. FA is frequently reported in studies of white matter microstructure and lower FA is often interpreted as a reduction in myelination but it may equally correspond to differences in axon diameter, fibre bundle density, crossing fiber, myelin thickness or the cytoskeleton (Chanraud et al., 2010; Jones et al., 2013; Winston, 2012).

Global white matter FA shows a gradual increase throughout childhood and adolescence with associated decreases in MD and RD (Mills and Tamnes, 2014). However, regional differences have been observed with fiber connecting frontal and temporal cortices (Colby et al., 2011; Lebel and Beaulieu, 2011; Tamnes et al., 2010) including the cingulum and uncinate fasciculi, which develop at a slower rate than some of the other fiber (Lebel et al., 2012; Olson et al., 2015; Westlye et al., 2010). Environmental stressor or genetic predisposition may differentially affect the development of white matter pathways and concomitant changes may relate to the development of depressive symptoms (Ladouceur et al., 2012).

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To date there have been only few investigations into white matter microstructure in pediatric depressive disorders and there is little consistency across results. Tracts that have been reported by more than two studies include the cingulum, the uncinate fasciuli and the inferior fronto-occipital fasciculi (Aghajani et al., 2013; Bessette et al., 2014; Cullen et al., 2010; Henderson et al., 2013; LeWinn et al., 2014). Changes in the microstructure of the corpus callosum have also been reported by several studies but vary in the exact location with differences reported in the genu (Bessette et al., 2014; LeWinn et al., 2014) as well as the body (Aghajani et al., 2013; Bessette et al., 2014; LeWinn et al., 2014). Generally, lower FA is observed in these fibre bundles in the clinical group but increased FA has also been reported (Aghajani et al., 2013; Henderson et al., 2013). In addition to the above findings, a whole range of other fibre bundles have been reported by individual studies that have not yet been replicated (e.g., Bessette et al., 2014).

In a review of structural and functional neuroimaging studies of pediatric MDD, Hulvershorn et al. (2011) propose that at least some of the alterations in brain structure and function may predate psychopathology. Support comes from a study that examined a group of adolescents with a parental history of depression that reported lower FA in the left cingulum, the splenium of the corpus callosum, the uncinate, superior longitudinal and inferior fronto-occipital fasciculi (Huang, Fan et al., 2011). However, the study only included a small sample size (18 high-risk youth and 13 controls) and has not yet been replicated. While Huang et al. (2011) did not find correlations with symptoms, other studies have found associations between FA in the uncinate and trait anxiety in healthy individuals (Kim and Whalen, 2009; Montag et al., 2012); thus it is not clear whether lower FA precedes symptom onset or simply reflects symptom severity. Although the function of the uncinate is still largely unknown several previous studies have implicated its role in reversal learning, reward processing and long-term memory retrieval (Olson et al., 2015). The latter two are often impaired in MDD suggesting that white matter microstructure in the uncinate may be altered.

Beyond the uncinate Henderson et al. (2013) showed that irritability was associated with lower FA in the sagittal striatum, anterior corona radiata, and tracts leading to prefrontal and temporal cortices while anhedonic symptoms were associated with structural alterations in the anterior limb of the internal capsule and projection fiber to the orbitofrontal cortex. White matter associations with other symptoms that often coexist with depressive disorders such as low self-esteem, hopelessness and attention difficulties have not been examined in children and adolescents with depressive disorders.

Most investigations thus far have employed the tract based spatial statistics (TBSS) procedure (Smith et al., 2006) that projects volumetric data onto a white matter skeleton. While this has advantages to other methods such as voxel-based morphometry, TBSS has limited anatomical specificity and fails to take into account orientation information in the diffusion data (Bach et al., 2014). In addition, previous methods most commonly report values averaged across tracts and do not provide location specific information within tracts. Yet, a recent study has shown that there is considerable variation within tracts as they mature (Chen et al., 2016). To improve upon previous shortcomings the current study used full tensor information for improved registration and employed tract specific analysis to localize any white matter differences within tracts. Our aim was to investigate white matter microstructural differences between a sample of boys with persistent depressive disorder and matched typically developing children. Studying a group of children characterized by chronic but mild symptoms may contribute to a better understanding of whether persistency of symptoms may impact on brain structure to a greater degree than severity of symptoms. In addition, these children are at increased risk of developing a major depressive episode (Klein et al., 2000) and information about underlying neurobiology may help in identifying risk factors that may potentially be the target of early interventions. In line with previous findings in pediatric depression we expected lower FA in white matter fibre tracts in the clinical group, particularly the uncinate fasciculi and the inferior-fronto-occipital fasiculi. We also predicted to find an association between depressive symptoms and FA in the left uncinate fasciculus.

2. Method

2.1. Participants

A total of 50 male young people aged nine to sixteen years participated in this study. 25 met DSM-V diagnostic criteria for persistent depressive disorder (DSM-IV dysthymic disorder) and were recruited from a pediatric psychiatric outpatient clinic at The Royal Children's Hospital, Melbourne, Australia. Our previous study using functional magnetic resonance imaging (fMRI) (Vilgis et al., 2014) included 10 of the 25 patients with DD and 10 of the 25 typically developing children. Diagnoses were assessed categorically using the Anxiety Disorders Interview Schedule (ADIS) (parent and child version) (Silverman and Albano, 1996) and dimensionally with the Child Behavior Checklist (CBCL) (Achenbach and Edelbrock, 1983). Young people also completed the Children's Depression Inventory (CDI) (Kovacs, 1992). Of the 25 boys that met diagnostic criteria for persistent depressive disorder thirteen also met criteria for generalized anxiety disorder, nine for separation anxiety disorder and seven for social phobia as rated by their caregiver on the ADIS. Eleven also met diagnostic criteria for oppositional defiant disorder (ODD) and five for conduct disorder (CD). Persistent depressive disorder can be diagnosed based on primarily irritable mood, which has been shown to contribute to greater disruptive behavior disorder symptoms (Harrington et al., 2001). Therefore, a diagnosis of comorbid CD and/or ODD was allowed for inclusion in the current study. Furthermore, the clinical presentations of ‘pure’ and comorbid depressive and conduct disorders have been found to be very similar unlike comorbid Attention-deficit/hyperactivity disorder (ADHD) and depression (Angold et al., 1999; Ezpeleta et al., 2006). Hence, a diagnosis of ADHD was an exclusion criterion for the current study. Typically developing children (TD) were recruited from local schools and matched for age to the clinical group. They completed the same semi-structured clinical interviews and questionnaires as the clinical participants. Participants were included if they were male, right-handed as assessed using a subtest of the Scored Developmental Neurological Examination (Taylor et al., 1986a, 1986b) and with a full-scale IQ above 70 as assessed by the Wechsler Intelligence Scale for Children (WISC-IV). Maternal education was measured with the Parental Account of Childhood Symptoms (PACS) (Taylor et al., 1986a). Exclusion criteria were the presence of an intellectual disability, learning disorder or known neurological or endocrine condition. Participants were also excluded if they had a previous diagnosis for an Autistic Spectrum Disorder, Bipolar Disorder or Psychotic Disorders. All participants were medication-naïve except for one clinical participant who was treated with fluoxetine. The study was approved by The Royal Children's Hospital Human Research Ethics Committee and all participants and their parents provided written informed consent. Table 1 lists demographic and clinical variables for both groups.

2.2. Image acquisition

Data were acquired on a 3-Tesla Siemens Tim Trio MRI scanner (Siemens, Erlangen, Germany), at The Royal Children's Hospital Melbourne. Diffusion-weighted echoplanar images (EPI) for 30 children (15 clinical matched to 15 TD on age) were acquired along 30 diffusion gradient directions for acquisition of 58 axial slices through the whole brain with in-plane resolution of 2.30 × 2.30 mm (b value of 1000 s/mm^2, TR = 7293 ms, TE = 87 ms, 90° flip angle, number of averages = 1, matrix size = 98 × 98, slice thickness = 2.3 mm, spacing between slices = 2.3 mm). Diffusion-weighted EPI of the remaining 20 children (10 clinical matched to 10 TD on age) were acquired on the