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Neuroticism is linked to microstructural left-right asymmetry of fronto-limbic fibre tracts in adolescents with opposite effects in boys and girls

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ABSTRACT

Neuroticism is a fundamental personality trait that reflects a tendency to experience heightened negative affect and susceptibility to stress. Negative emotionality has been associated with fronto-limbic brain structures and connecting fibre tracts. The major fibre tracts connecting the frontal and limbic brain regions are the cingulum bundle and uncinate fasciculus. We previously found that healthy adults with higher neuroticism scores had decreased left relative to right fractional anisotropy (FA) of the cingulum. Both cingulum and uncinate fasciculus FA increases throughout childhood and into early adulthood. Since adolescence is associated with an increased incidence of anxiety and mood disorders, for which neuroticism is a known risk factor, the question arises whether the association between neuroticism and fronto-limbic white matter microstructure asymmetry is already present in children and adolescents or whether such relationship emerges during this age period. To address this question, we assessed 72 typically-developing 10-to-15 year-olds with diffusion-weighted imaging on a 3 T magnetic resonance scanner. Neuroticism was assessed with the Junior Eysenck Personality Questionnaire. FA and parallel and perpendicular diffusivity measures were extracted for cingulum, uncinate fasciculus as well as the white matter underlying the ventromedial prefrontal cortex. Higher neuroticism scores were associated with decreased left relative to right cingulum FA in boys, while in girls, higher neuroticism scores were associated with increased left relative to right cingulum and ventromedial prefrontal white matter FA, indicating that there are sex differences in the neural correlates of neuroticism. Our findings suggest that the link between neuroticism and frontal-limbic white matter microstructure asymmetry likely predates early adolescence. Future studies need to elucidate the significance of the observed sex differences in the neural correlates of neuroticism.

1. Introduction

Adolescence is associated with an increased incidence of neuropsychiatric disorders, such as anxiety, mood and substance use disorders (for review see (Paus et al., 2008)), for which neuroticism is a known risk factor (Belcher et al., 2014; Bienvenu et al., 2001; Kendler et al., 2006; Sutin et al., 2013). Neuroticism is a fundamental personality trait that reflects an individual's tendency to experience negative emotionality, such as anger, anxiety, guilt, sadness and worry, and a higher susceptibility to stress. High neuroticism scores have been linked to mood and anxiety disorders, such as phobias, panic disorder, and major depression (Bienvenu et al., 2001, 2004), and prospective studies show that high neuroticism scores increase the risk of developing major depression (Kendler et al., 2006, 2004). Females have higher neuroticism scores as well as higher prevalence of anxiety and mood disorders than males (Goodwin and Gotlib, 2004; Paus et al., 2008). The latter change from an equal female-male prevalence before puberty to a 2:1 female-male prevalence after puberty (Paus et al., 2008). Neuroticism shows substantial heritability (Hansell et al., 2012; Jang et al., 1996; Kendler et al., 2006), as well as substantial genetic correlation with symptoms of anxiety/depression in adolescents (Hansell et al., 2012) and major depression in adults (Kendler et al., 2006). Thus, neuroticism

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and a predisposition for anxiety/depression may result from shared genetic factors. Moreover, negative emotionality also exhibits a positive genetic link with medial orbitofrontal cortex thickness, suggesting that the latter may partly mediate the observed heritability of negative emotionality traits (Lewis et al., 2014).

Findings from structural magnetic resonance imaging (MRI) studies on the neural correlates of negative emotionality-related traits in mainly healthy adult volunteers, as well as in volunteers with disorders such as major depression, have implicated frontal and limbic brain structures, such as the orbitofrontal cortex, ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex, and the amygdala (Mincic, 2015; Omura et al., 2005; Rive et al., 2013; Wright et al., 2006). A recent meta-analysis study of the structural neural correlates of negative emotionality traits reported that negative emotionality was positively associated with left amygdala volume and negatively associated with left orbitofrontal cortex volume (Mincic, 2015). In a large cohort of youths aged 7–20 years, higher anxiety scores were associated with smaller vmPFC surface area adjusted for total area, as well as overall thinner cortex (Newman et al., 2016). Interestingly, these associations diminished with age, suggesting that youths with higher anxiety scores may have delayed expansion of the vmPFC and an altered global cortical thinning trajectory. Moreover, a study of 16–17 year-old healthy adolescents observed opposite sex effects of the neural correlates of neuroticism, in that neuroticism was positively correlated with subgenual anterior cingulate cortex grey matter volume and cortical thickness in females, but negatively in males (Blankstein et al., 2009). Frontal brain regions, including the anterior cingulate and dorsomedial prefrontal cortex, as well as the orbitofrontal cortex and vmPFC are connected to medial temporal lobe structures, such as the amygdala and hippocampus, by two major white matter tracts, respectively, the cingulum bundle and uncinate fasciculus (Schmahmann and Pandya, 2006). Diffusion-weighted imaging (DWI), which is sensitive to the diffusion of water molecules, allows for measurements of the microstructural properties of white matter fibre tracts. In white matter, cellular structures, such as the axonal membranes and surrounding myelin sheaths, hinder diffusion of water in the direction perpendicular relative to parallel to a fibre bundle, thereby causing diffusion anisotropy (Beaulieu, 2009). By fitting a diffusion tensor to each voxel of the DWI data, measures, such as fractional anisotropy (FA), and parallel (axial, $\lambda_{||}$) and perpendicular (radial, $\lambda\perp$) diffusivity, can be extracted. FA reflects the degree of diffusion directionality, which can be influenced by microstructural properties, such as axonal density, diameter, organization, and myelination (Beaulieu, 2009; Schwartz et al., 2005). DWI studies investigating the white matter correlates of negative emotionality-related traits in predominantly healthy adult populations have provided inconsistent results showing global as well as region-specific associations (Mincic, 2015). Globally, higher neuroticism and harm avoidance scores have been associated with widespread lower white matter FA (Bjornebekk et al., 2013; Westlye et al., 2011). Regionally, higher negative emotionality trait scores have been associated with both lower (Eden et al., 2015) and higher FA (Clewett et al., 2014) of fibres connecting the right amygdala and vmPFC. Moreover, higher negative emotionality has been linked to lower FA of the right (Taddei et al., 2012) and bilateral (McIntosh et al., 2013) uncinate fasciculus, as well as higher FA of the left uncinate fasciculus (Modi et al., 2013). Furthermore, higher negative emotionality scores have been linked to higher FA in the left uncinate fasciculus, cingulum, superior longitudinal fasciculus and inferior fronto-occipital fasciculus in males, but not in females (Montag et al., 2012). The above findings suggest that brain asymmetry may play a role in negative emotionality-related traits. In line with this hypothesis, we previously found in healthy adults that higher neuroticism scores were associated with higher FA of the right relative to the left cingulum. (Madsen et al., 2012). Notably, the association with neuroticism was not driven by the absolute FA values of the left or right cingulum, but by the relative difference between left and right cingulum FA. Even though research findings do not provide a clear picture, individual differences in fronto-limbic fibre tracts appear to play an important role for negative emotionality traits. Moreover, associations between negative emotionality traits and white matter microstructure may differ between brain hemispheres as well as between sexes.

Currently, most studies investigating the neuroanatomical correlates of negative emotionality have examined adults. However, disorders such as anxiety and major depression often debut in adolescence, a period in human life characterized by ongoing brain maturation that continues well into early adulthood (Jernigan et al., 2011). Maturational increases in FA, reflecting a disproportionate decrease in $\lambda\perp$ relative to $\lambda_{||}$, have been observed in multiple white matter locations throughout childhood, adolescence and young adulthood, possibly due to ongoing myelination, and/or increased axonal diameter and density (Eluvathingal et al., 2007; Lebel and Beaulieu, 2011; Lebel et al., 2012). Notably, the cingulum bundle and the uncinate fasciculus show a protracted maturation into late adolescence and early adulthood (Lebel and Beaulieu, 2011; Lebel et al., 2012). In the present study, we examined whether the relationship between neuroticism and cingulum FA asymmetry, which we previously observed in healthy adults, is already present in typically-developing children and adolescents aged 10–15 years, or whether such relationship emerges during this age range. Additionally, we investigated the relationship between neuroticism and FA asymmetry of the uncinate fasciculus and the white matter underlying the vmPFC. Furthermore, we examined to what extent the observed relationships might change with age or differ between sexes. Finally, to explore the nature of observed FA findings, we examined the ROI $\lambda_{||}$ and $\lambda\perp$ asymmetries in post hoc analyses, since higher FA can be due to increased $\lambda_{||}$ and/or decreased $\lambda\perp$.

2. Methods and materials

2.1. Participants

The present study included 72 typically-developing children and adolescents (45 girls, 27 boys) aged 10.1–15.5 years (mean ± standard deviation = 12.7 ± 1.7), who all were enrolled in the longitudinal HUBU ("*Hjernens Udvikling hos Børn og Unge*" – in English: Brain maturation in children and adolescents) project designed to trace developmental changes, in which 95 typically-developing children (55 girls, 40 boys) aged seven to 13 years and their families had been recruited from three elementary schools in the Copenhagen suburban area in 2007. All children and adolescents who volunteered for the HUBU project were included, except for those with any known history of neurological or psychiatric disorders or significant brain injury, according to parent reports. Participants in the HUBU cohort have been assessed up to 12 times, with six months intervals for the first 10 assessments. Prior to participation and after receiving oral and written explanation about the study aims and procedures, all children assented to partake in the study and informed written consent was obtained from the parents of all subjects. The study was approved by the Ethical Committees of the Capital Region of Denmark (H-KF-01–131/03) and conducted in accordance with the Declaration of Helsinki. Previous publications on baseline data investigated the relationship between higher-order cognitive functions or motor function and grey and white matter microstructure (Angstmann et al., 2016; Klarborg et al., 2012; Madsen et al., 2011, 2010; Vestergaard et al., 2011).

The included 72 children and adolescents were of primarily Caucasian descent (96%). Sixty-four participants were right-handed and eight participants were left-handed as assessed by the Edinburgh Handedness Inventory. To screen participants for psychopathology, parents filled in the Danish version of Strength and Difficulties Questionnaire (SDQ) (Niclasen et al., 2012) in the 3rd HUBU assessment conducted 1.5–2.5 years before the 6th and the 8th HUBU assessment. SDQ data was available for 66 (44 girls, 22 boys) of the 72 participants included in the present study. Based on Danish norms for