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

Madsen, Kathrine Skak; Jernigan, Terry L.; Vestergaard, Martin; Mortensen, Erik Lykke; Baare, William F. C.

*Published in:*
Neuropsychologia

*DOI:*
10.1016/j.neuropsychologia.2018.04.010

*Publication date:*
2019

*Document version*
Publisher's PDF, also known as Version of record

Neuropsychologia 114 (2018) 1–10

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

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

Kathrine Skak Madsen[a,b,c,*], Terry L. Jernigan[a,b,d], Martin Vestergaard[a], Erik Lykke Mortensen[b,e], William F.C. Baaré[a,b]

[a] Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, MR-Research Department, Section 714, Copenhagen University Hospital Hvidovre, Kettegaard Allé 30, 2650 Hvidovre, Denmark
[b] Center for Integrated Molecular Brain Imaging, Copenhagen, Denmark
[c] Institute of Technology, Metropolitan University College, Copenhagen, Denmark
[d] Center for Human Development, University of California San Diego, La Jolla, United States
[e] Institute of Public Health and Center for Healthy Aging, University of Copenhagen, Copenhagen, Denmark

ARTICLE INFO

*Keywords:*
Diffusion tensor imaging
Laterality
Negative emotionality
Personality
Gender differences
Sex differences

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

* Corresponding author at: Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, MR-Research Department, Section 714, Copenhagen University Hospital Hvidovre, Kettegaard Allé 30, 2650 Hvidovre, Denmark.
*E-mail address:* Kathrine@drcmr.dk (K.S. Madsen).

https://doi.org/10.1016/j.neuropsychologia.2018.04.010
Received 7 September 2017; Received in revised form 6 April 2018; Accepted 8 April 2018
Available online 11 April 2018

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

11–15 year-olds (SDQ DAWBA DK, 2017), all participants had a SDQ total difficulties score within the normal range (≤11 in girls, ≤13 in boys), except for two girls, who had slightly elevated scores (12–15 for girls, corresponding to the 20% highest scores), but below clinical thresholds.

The data included in the present study consisted of data from 62 (38 girls, 24 boys) of the 73 children and adolescents assessed in the 6th HUBU assessment, in which personality assessments and MRI were conducted. Data from the remaining 11 participants (seven girls, four boys) were excluded from the present study because of not being scanned due to metallic dental braces (n = 3), incidental clinical findings on the MRI scans (n = 2), no personality data acquired due to time constraints in the behavioural testing session (n = 4), or poor MR-image quality (n = 2). In addition to the 63 participants from the 6th HUBU assessment, we included 10 children and adolescents (seven girls, three boys) from the 8th HUBU assessment, who either had not participated in the 6th HUBU assessment (n = 5) or who did not have all relevant data acquired in the 6th HUBU assessment (n = 5).

### 2.2. Personality assessment

An adapted Danish version of the 81-item Junior Eysenck Personality Questionnaire (J-EPQ) (Eysenck and Eysenck, 1975; Nyborg et al., 1982) was administered on the same day as the MR-scanning. The J-EPQ measures three major dimensions of personality, i.e. neuroticism (negative emotionality), extraversion and psychoticism (tough mindedness). Here, we focused on the neuroticism scale, which consists of 20 items. The questionnaire was read out loud, and the participants were asked to indicate how well each item described their personality. In the original J-EPQ version, participants have to answer each item with a "Yes" or a "No". In the present study, we extended the rating scale to include four possible answers: Strongly agree / Agree / Disagree / Strongly disagree, which were scored on a 0–3 point scale, in order to get more detailed estimates of the personality traits. The neuroticism scale using either of the rating scales showed good to excellent internal consistency (Cronbach's alpha for the 2-point scale (α = .857) and the adapted 4-point scale (α = .904)).

### 2.3. Image acquisition

All subjects were scanned using a 3 T Siemens Magnetom Trio MR scanner (Siemens, Erlangen, Germany) with an eight-channel head coil (Invivo, FL, USA). All acquired scans were aligned parallel to the anterior commissure–posterior commissure line. T1-weighted images of the whole head were acquired using a 3D MPRAGE sequence (TR = 1550 ms, TE = 3.04 ms, matrix 256 × 256, 192 sagittal slices, 1 × 1 × 1 $mm^3$ voxels, acquisition time = 6:38). T2-weighted images of the whole head were acquired using a 3D turbo spin echo sequence (TR = 3000 ms, TE = 354 ms, FOV = 282 × 216, matrix = 256 × 196, 192 sagittal slices, 1.1 × 1.1 × 1.1 $mm^3$ voxels, acquisition time = 8:29). Whole brain diffusion-weighted (DW) images were acquired using a twice-refocused balanced spin echo sequence that minimized eddy current distortion (Reese et al., 2003). Ten non-DW images (b = 0) and 61 DW images (b = 1200 s/$mm^2$), encoded along independent collinear diffusion gradient orientations, were acquired (TR = 8200 ms, TE = 100 ms, FOV = 220 × 220, matrix = 96 × 96, GRAPPA: factor = 2, 48 lines, 61 transverse slices with no gap, 2.3 × 2.3 × 2.3 $mm^3$ voxels, acquisition time = 9:50). A gradient echo field map was acquired to correct $B_0$ field distortions (TR = 530 ms, TE[1] = 5.19 ms and TE[2] = 7.65 ms, FOV = 256 × 256; matrix = 128 × 128, 47 transverse slices with no gap, voxel size = 2 × 2 × 3 $mm^3$, acquisition time = 2:18).

### 2.4. Image preprocessing

Raw images were visually inspected to ascertain data quality. Images were preprocessed using pipelines implemented in Matlab, using mainly SPM8 (Wellcome Department of Cognitive Neurology, University College London, UK) routines. T1-weighted and T2-weighted images were corrected for spatial distortions due to non-linearity in the gradient system of the scanner (Jovicich et al., 2006). The T2-image was coregistered (no reslicing), using a 6-parameter mutual information rigid transformation to the T1-image, which was registered into MNI orientation (no scaling). In the DWI analysis, each subject's mean b0 image was coregistered (no reslicing), to the brain-masked T2-image, after which all DW images were coregistered (no reslicing) to the mean b0 image. Next, all coregistered images were corrected for geometric distortions using a voxel displacement map based on both the acquired $B_0$ field map (Andersson et al., 2001) and the scanner specific gradient non-linearities (Jovicich et al., 2006). Finally, all images were resliced using trilinear interpolation. Note that this procedure involves only one reslicing step. The diffusion gradient orientations were adjusted to account for any rotation applied during registration. The diffusion tensor was fitted using a least-squared-fit by non-linear optimization employing a Levenburg-Marquardt algorithm (Jones and Basser, 2004) implemented in Camino (Cook et al., 2006), and constrained to be positive definite by fitting its Cholesky decomposition. Fractional anisotropy (FA) as well as diffusivity parallel (axial diffusivity, $\lambda_{||} = \lambda 1$) and perpendicular (radial diffusivity, $\lambda\perp = (\lambda 2 + \lambda 3) / 2$) to the principal diffusion direction were calculated. A brain mask based on the mean b0 image was applied to the FA and diffusivity images.

### 2.5. Inter-subject spatial normalization of fibre tracts

In the present study, we extracted FA and diffusivity measures from regions-of-interest (ROIs) to test specific hypotheses and to determine the anatomical specificity of observed associations (see below). Spatial normalization and alignment of fibre tracts across subjects were achieved using the Tract-Based Spatial Statistics (TBSS) module (Smith et al., 2006), part of FSL 4.1.4 (Smith et al., 2004). At first, all subjects' FA images were aligned into a common space using the non-linear registration tool FNIRT (Andersson et al., 2001). A study-specific target, the group's most representative FA image, was then identified after non-linearly registering each subject's FA image to every other subject's FA image. Next, the target FA image was aligned to MNI space using affine registration and subsequently the entire aligned dataset was transformed into 1 mm3 MNI space. A cross-subject mean FA image was created and thinned to create a mean FA skeleton, representing the centres of all tracts common to the group. The mean FA skeleton was thresholded at FA > .25, and contained 130,934 1 $mm^3$ interpolated isotropic voxels, corresponding to approximately 39% of the voxels with FA above .25. Each subject's aligned FA image was then projected onto the mean skeleton by locating the highest local FA value in the direction perpendicular to the skeleton tracts and assigning this value to the skeleton. In addition, the nonlinear warps, and skeleton projections were applied to the $\lambda_{||}$ and $\lambda\perp$ data.

### 2.6. Regions-of-interest

To test our hypotheses, mean FA, $\lambda_{||}$ and $\lambda\perp$ values were extracted from left and right sided ROIs in the cingulum, uncinate fasciculus and in the white matter underlying the ventromedial prefrontal cortex ($vmPFC_{WM}$). The ROIs are depicted in Fig. 1. ROIs were manually drawn onto the mean skeleton overlaid on the mean FA image using FSLview. The skeleton segments representing the cingulum were clearly distinguishable from all other skeleton segments. Cingulum ROIs included all skeleton segments within the body of the cingulum, and excluded segments intersecting the cingulum but diverging from the main body of the tract. Right and left cingulum ROIs contained 883 and 973 voxels, respectively. Uncinate fasciculus ROIs were delineated using the JHU White-Matter Tractography Atlas (Hua et al., 2008) implemented in FSLview for guidance. Only central uncinate fasciculus

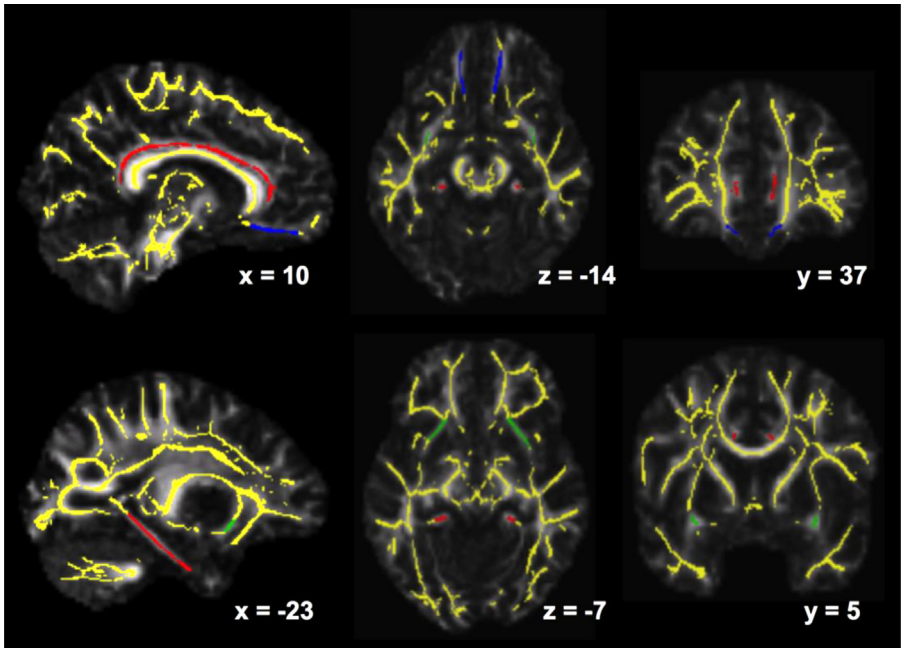


**Fig. 1.** Regions-of-interest in the cingulum bundle (red), uncinate fasciculus (green) and in the white matter underlying the ventromedial prefrontal cortex (blue), and the TBSS skeleton (yellow) overlaid on the target fractional anisotropy (FA) map. Axial (z), coronal (y) and sagittal (x) views of the ROIs with the corresponding MNI coordinates for each slice.

segments were included, while segments extending towards the temporal pole, the inferior frontal gyrus and orbitofrontal cortex were excluded. Right and left uncinate fasciculus ROIs included 422 and 375 voxels, respectively. Finally, $vmPFC_{WM}$ ROIs were drawn, which included the skeleton segments in the white matter underlying the right and left vmPFC, while excluding segments in the frontal pole. The $vmPFC_{WM}$ ROIs extended from MNI-coordinates y = 53 to Y = 27. The right and left $vmPFC_{WM}$ ROIs contained 292 and 215 voxels, respectively. To assess the anatomical specificity of observed associations, right (66,303 voxels) and left (64,265 voxels) hemispheric skeleton ROIs were delineated using the mid-sagittal plane (not included in either of hemispheric ROIs).

### 2.7. Left-right asymmetry measures

ROI diffusion parameter asymmetries were calculated as the difference between left and right ROI values expressed as a percentage of the bilateral mean:

((2*(Left – Right)) / (Left + Right))*100

### 2.8. Statistical analyses

Statistical analyses were performed in SPSS20. Two-tailed *t*-tests were used to compare left and right ROI values (paired samples), and sex differences in neuroticism and parent's average years of education (independent samples). Multiple linear regression was used to examine age, sex and handedness effects on ROI FA values or ROI FA asymmetries. Multiple linear regression models predicting neuroticism were used to test our hypotheses. Shapiro-Wilk tests showed that the residuals from all the main regression analyses did not significantly deviate from the normal distribution. All other assumptions for linear regression were fulfilled. A p-value below .05 was considered significant.

Based on our previous findings in adults, our major hypothesis was that neuroticism would be associated with cingulum FA asymmetry. To test our primary hypothesis, cingulum FA asymmetry, sex by cingulum FA asymmetry and age by cingulum FA asymmetry, controlling for age, sex and the interaction age by sex, were entered in a multiple linear regression model predicting neuroticism. Our secondary hypotheses tested if neuroticism was also associated with $vmPFC_{WM}$ and uncinate fasciculus FA asymmetries, which were tested using the same analysis strategy as the one for cingulum FA asymmetry (Model A). To follow-up on sex by ROI FA asymmetry effects, boys and girls were analysed separately, using age, ROI FA asymmetry, and age by ROI FA asymmetry as predictors of neuroticism (Model B). Model A and B are summarised below:

Model A:

$$Y = \beta_0 + \beta_1 X_{age} + \beta_2 X_{sex} + \beta_3 X_{ROI} + \beta_4 X_{age} X_{sex} + \beta_5 X_{age} X_{ROI} + \beta_4 X_{sex} X_{ROI} + \varepsilon$$

Model B:

$$Y = \beta_0 + \beta_1 X_{age} + \beta_2 X_{ROI} + \beta_3 X_{age} X_{ROI} + \varepsilon$$

In these equations, $Y$ corresponds to the neuroticism score, ROI corresponds to the ROI FA asymmetry measures, and $\varepsilon$ is the error term.

Planned follow-up analyses assessed 1) the anatomical specificity of observed effects by including global white matter hemispheric FA asymmetry as an additional covariate in Model B, 2) whether the observed effects might be driven by differences in handedness by including handedness as an additional covariate in model B, and 3) the contribution of the left and right ROIs to observed asymmetry effects by analysing left and right ROIs both simultaneously and separately. Based on our results in girls, a post hoc analysis was conducted, in which neuroticism was modelled with cingulum and $vmPFC_{WM}$ FA asymmetry simultaneously to assess if their effects were additive. Finally, to further explore the nature of observed FA findings, $\lambda_{||}$ and $\lambda\perp$ were investigated, since higher FA can be due to increased $\lambda_{||}$ and/or decreased $\lambda\perp$. This was tested by replacing the ROI FA variables with either $\lambda_{||}$ or $\lambda\perp$ in the models where the ROI FAs were significant.

## 3. Results

### 3.1. Descriptive statistics

Neuroticism and ROI FA values are presented in Table 1. The mean neuroticism score from the 2-point rating scale is displayed in Table 1 to allow for comparisons between the present cohort and other cohorts. However, only the neuroticism score from the 4-point rating scale was

**Table 1**
Descriptive statistics. Mean ± standard deviation for age, parent average years of education, SDQ – total difficulties score, neuroticism and region-of-interest fractional anisotropy (FA) values for girls and boys.

| | Girls (N = 45) | Boys (N = 27) |
|---|---|---|
| Age | 12.67 ± 1.74 | 12.66 ± 1.59 |
| Handedness (right / left) | 40 / 5 | 24 / 3 |
| Parents' average years of education | 14.09 ± 1.98 | 13.32 ± 1.68 |
| SDQ – total difficulties score | 4.70 ± 3.15 | 4.64 ± 4.01 |
| Neuroticism (4-point scale) | 29.0 ± 10.2 | 22.6 ± 10.7 |
| Neuroticism (2-point scale) | 10.1 ± 4.6 | 7.6 ± 4.8 |
| Cingulum FA asymmetry | 3.93 ± 3.08 | 4.27 ± 2.85 |
| $VmPFC_{WM}$ FA asymmetry | 5.44 ± 8.16 | 4.66 ± 7.48 |
| Uncinate fasciculus FA asymmetry | 2.06 ± 3.96 | 1.77 ± 3.67 |
| Left cingulum FA | .544 ± .027 | .551 ± .033 |
| Right cingulum FA | .523 ± .026 | .528 ± .032 |
| Left $vmPFC_{WM}$ FA | .391 ± .029 | .395 ± .034 |
| Right $vmPFC_{WM}$ FA | .370 ± .028 | .377 ± .030 |
| Left uncinate fasciculus FA | .508 ± .029 | .511 ± .030 |
| Right uncinate fasciculus FA | .497 ± .027 | .503 ± .034 |

*Abbreviations: SDQ = Strength and Difficulties Questionnaire, $VmPFC_{WM}$ = white matter underlying the ventromedial prefrontal cortex.*

used in the statistical analyses. Girls had significantly higher neuroticism scores than boys ($t = 2.479$, $p = .014$, Cohen's $d = .612$), while parents' average years of education did not significantly differ between girls and boys ($t = -1.674$, $p = .099$, Cohen's $d = .416$). For each of the ROI pairs, FA was significantly higher in the left than the right ROI ($ts \geq 4.304$, $ps < .00005$). FA increased with age in all ROIs ($\beta s = .132 - .253$, $p = .108 - .272$), except the right $vmPFC_{WM}$ ($\beta = .053$, $p = .661$). However, the increase in ROI FA was only significant for the left cingulum ($\beta = .253$, $p = .034$). There were no significant age effects in FA asymmetry for any of the ROIs ($\beta s \leq .214$, $ps \geq .072$). Furthermore, there were no significant sex ($\beta s \leq -.113$, $ps \geq .335$) or handedness ($\beta s \leq -.182$, $ps \geq .126$) effects on ROI FA or ROI FA asymmetry.

### 3.2. Neuroticism and FA: whole group analyses

In the main models predicting neuroticism scores, we did not observe any significant main effects of ROI FA asymmetry ($ps \geq .361$) or age ($ps \geq .23$), but there was a main effect of sex with girls having higher neuroticism scores than boys ($p = .011 - .094$). Moreover, we observed a significant sex by cingulum FA asymmetry interaction effect ($\beta = .353$, $p = .003$). We did not observe a significant sex by $vmPFC_{WM}$ FA asymmetry ($\beta = .669$, $p = .116$) or sex by uncinate fasciculus FA asymmetry interaction effects ($\beta = -.362$, $p = .401$). Nor did we observe any significant age by sex interaction effects ($ps > .19$), or age by ROI FA asymmetry interaction effects ($ps > .15$).

### 3.3. Neuroticism and FA: analyses of boys and girls separately

Subsequent analyses of boys and girls separately showed that neuroticism was significantly and positively associated with cingulum FA asymmetry in girls, and negatively associated with cingulum FA asymmetry in boys (Table 2, Model 1; Fig. 2a and b). In boys, a significant age by cingulum FA asymmetry interaction effect was also observed (Table 2, Model 1; Fig. 3b). The cingulum FA asymmetry effect remained significant in both girls and boys when hemispheric FA asymmetry was included in the models (Table 2, Model 1a), indicating anatomical specificity. Furthermore, in girls, neuroticism was also significantly and positively associated with $vmPFC_{WM}$ FA asymmetry (Table 2, Model 2), and this relationship also remained significant with hemispheric FA asymmetry in the models (Table 2, Model 2 and 2a; Fig. 2c). No significant relationship was observed between neuroticism and $vmPFC_{WM}$ FA asymmetry for boys (Table 2, Model 2, Fig. 2d), or with uncinate FA asymmetry for any of the sexes ($ps \geq .383$). Including handedness as an additional covariate did not change the results of any of the above analyses.

### 3.4. Neuroticism and FA: contribution of left and right ROI FA

Follow-up analyses, modelling left and right cingulum FA as simultaneous predictors of neuroticism, showed that neuroticism was negatively associated with right and positively associated with left cingulum FA in girls, and visa versa in boys (Table 3, Model 4). Moreover, in girls, a similar effect to that of cingulum was observed for left and right $vmPFC_{WM}$ FA (Table 3, Model 5). Notably, when modelled individually, neither left nor right ROI FA were significantly associated with neuroticism (Table 3, Model 4a, 4b, 5a and 5b), indicating that it is the relationship between the left and right ROIs that exhibited associations with neuroticism, and not the left or right ROIs individually.

### 3.5. Post hoc analyses

To investigate if the observed associations between neuroticism and cingulum and $vmPFC_{WM}$ FA asymmetry in girls were additive, the two ROI measures were modelled simultaneously. When modelled simultaneously, both cingulum ($\beta = .446$, $p = .003$) and $vmPFC_{WM}$ ($\beta = .485$, $p = .0006$) FA asymmetry were significantly associated with neuroticism, in a model also including age ($\beta = .091$, $p = .52$), and the interactions age by cingulum FA asymmetry ($\beta = -.206$, $p = .15$) and age by $vmPFC_{WM}$ FA asymmetry ($\beta = .296$, $p = .042$), suggesting that the two asymmetry measures independently contribute to neuroticism.

Further exploration of the nature of the observed FA asymmetry effects revealed that in girls, the ROI $\lambda\perp$ asymmetries (cingulum: $\beta = -.311$, $p = .057$; $vmPFC_{WM}$: $\beta = -.322$, $p = .034$), but not the ROI $\lambda_{||}$ asymmetries ($\beta < .15$, $p > .35$), were associated with neuroticism. In boys, neither cingulum $\lambda\perp$ asymmetry ($\beta = .23$, $p = .23$), nor cingulum $\lambda_{||}$ asymmetry ($\beta = -.16$, $p = .43$) was associated with neuroticism.

## 4. Discussion

The present study examined associations between neuroticism and microstructural asymmetry of fronto-limbic white matter tracts in typically-developing children and adolescents aged 10–15 years. Specifically, higher neuroticism scores were associated with decreased left relative to right cingulum FA in boys, and increased left relative to right cingulum FA in girls. This relationship became stronger with increasing age in boys, but not in girls. Furthermore, higher neuroticism was associated with increased left relative to right FA of the $vmPFC_{WM}$ in girls, but not in boys. When modelled simultaneously, both cingulum and $vmPFC_{WM}$ FA asymmetry were significantly associated with neuroticism in girls, suggesting that the two measures of asymmetry independently contributed to neuroticism. The observed associations were mediated by the *relationship* between left and right white matter fibre tract FA and were *not* driven by FA in either the left or right fibre tract individually. Furthermore, including a hemispheric white matter FA asymmetry measure in the models did not change the ROI asymmetry effects, indicating that the effects are likely to be anatomically specific and not linked to general hemispheric white matter FA asymmetry.

We have previously observed that higher neuroticism scores correlated with higher right relative to left cingulum FA in healthy adults (Madsen et al., 2012). Some additional previous studies, mainly in adults, have reported on negative emotionality traits being related to left-right asymmetry. A fMRI study of negative emotional vs. neutral faces observed that neuroticism was positively associated with right amygdala – right dorsomedial PFC functional connectivity, and negatively correlated with left amygdala – right anterior cingulate connectivity (Cremers et al., 2010). The significance of brain asymmetry is not fully clear, however it has been suggested that laterality provides

**Table 2**
Results from the main models predicting neuroticism for boys and girls separately.

| Dependent variable: Neuroticism | | ROI FA asymmetry | | Age | | Age by ROI FA asymmetry | | Hemispheric FA asymmetry | |
|---|---|---|---|---|---|---|---|---|---|
| Model | $r^2$ | β | p | β | p | β | p | β | p |
| Cingulum - boys | | | | | | | | | |
| 1 | .309 | − .401 | **.037** | − .159 | .381 | − .388 | **.039** | | |
| 1a | .405 | − .426 | **.022** | − .197 | .259 | − .455 | **.015** | − .320 | .073 |
| Cingulum - Girls | | | | | | | | | |
| 1 | .125 | .373 | **.026** | .020 | .895 | − .087 | .588 | | |
| 1a | .136 | .385 | **.024** | .031 | .841 | − .082 | .611 | − .106 | .480 |
| $VmPFC_{WM}$ - Girls | | | | | | | | | |
| 2 | .222 | .436 | **.003** | .157 | .309 | .254 | .106 | | |
| 2a | .227 | .438 | **.003** | .164 | .295 | .251 | .114 | − .071 | .614 |
| $VmPFC_{WM}$ - Boys | | | | | | | | | |
| 2 | .091 | − .070 | .745 | − .369 | .159 | − .206 | .443 | | |

Each row represents a separate regression model predicting neuroticism with ROI FA asymmetry for either the cingulum or $vmPFC_{WM}$. Models 1 and 2 included ROI FA asymmetry, age, and age by ROI FA asymmetry. Models 1a and 2a additionally included hemispheric white matter FA asymmetry. Abbreviations: FA = fractional anisotropy, ROI = region-of-interest, $VmPFC_{WM}$ = white matter underlying the ventromedial prefrontal cortex.

efficiency benefits, diminish redundancies linked to duplication of function, and decreases conflicts between the hemispheres (Lindell, 2013). Brain asymmetries have been described for several cognitive functions and behaviours, including emotional processing and approach/withdrawal behaviour (Grimshaw and Carmel, 2014; Lindell, 2013). The left hemisphere has been associated with positive affect, motivation to approach and/or inhibition of negative distractors, while the right hemisphere has been associated with negative affect, motivation to withdraw and/or inhibition of positive distractors. Lower left relative to right frontal activity has been associated with withdrawal-related traits and negative affect, while lower right relative to left frontal activity has been linked with approach-related traits and positive affect (Grimshaw and Carmel, 2014; Lindell, 2013; Nusslock et al., 2015). In the present study, we found that neuroticism was associated

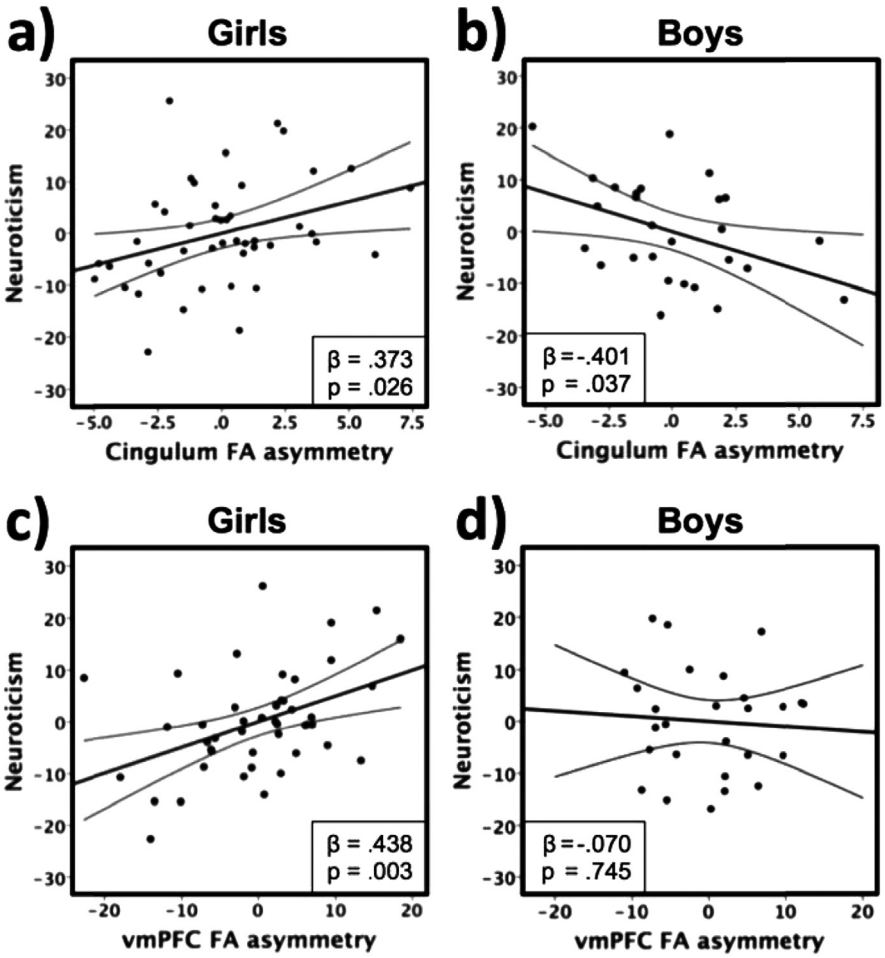


**Fig. 2.** Partial regression plots of neuroticism as a function of fractional anisotropy (FA) left-right asymmetry of the cingulum bundle in girls (a) and boys (b), and of the white matter underlying the ventromedial prefrontal cortex (vmPFC) in girls (c) and boys (d), adjusted for age and age by ROI FA asymmetry. Note the residuals are plotted. The standardized regression coefficients (β) and the significance level (p) are displayed within each partial regression plot.

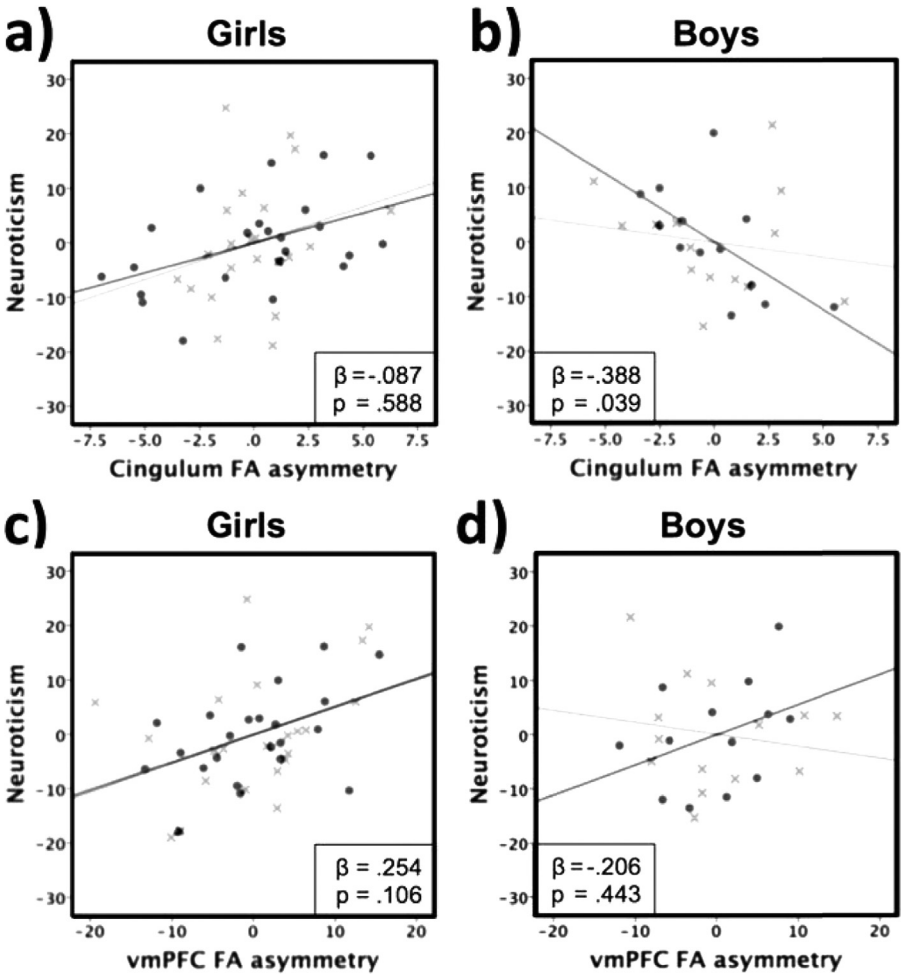


**Fig. 3.** Partial regression plots of neuroticism by left-right ROI fractional anisotropy (FA) asymmetry of the cingulum bundle in girls (a) and boys (b), and of the white matter underlying the ventromedial prefrontal cortex (vmPFC) in girls (c) and boys (d), adjusted for age. The plots visualise the youngest half (x) and the oldest half (•) of the girls (left) or boys (right) split by the median years of age (girls: 12.44 years, boys: 12.67 years) to secure two age groups of similar size. In girls, the association between neuroticism and ROI FA asymmetry did not appear to significantly differ with age (a, c) In boys, the association between neuroticism and cingulum FA asymmetry became stronger with age (d), while the relationship between neuroticism and vmPFC FA asymmetry did not significantly differ with age (b). The standardized regression coefficients (β) and the significance level (p) of the age by ROI FA asymmetry interaction (Model 1 and 2 in Table 2) are displayed within each partial regression plot. Note the residuals are plotted.

**Table 3**
Follow-up analyses assessing the relative contribution of fractional anisotropy (FA) in left and right regions-of-interest (ROIs) on neuroticism for boys and girls separately.

| | | Left ROI FA | | Right ROI FA | | Age | | Age by left ROI FA | | Age by right ROI FA | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Model | $r^2$ | β | p | β | p | β | p | β | p | β | p |
| Cingulum - Boys | | | | | | | | | | | |
| 4 | .337 | − .806 | .055 | .891 | **.039** | − .141 | .456 | − 1.265 | .063 | 1.448 | **.036** |
| 4a | .079 | − .021 | .918 | | | − .256 | .217 | .109 | .591 | | |
| 4b | .123 | | | .137 | .501 | − .220 | .283 | | | .204 | .309 |
| Cingulum - Girls | | | | | | | | | | | |
| 4 | .168 | .520 | .066 | − .720 | **.014** | .121 | .490 | − .044 | .868 | .299 | .300 |
| 4a | .025 | − .019 | .921 | | | .108 | .557 | .136 | .418 | | |
| 4b | .087 | | | − .335 | .080 | .231 | .175 | | | .247 | .163 |
| $VmPFC_{WM}$ - Girls | | | | | | | | | | | |
| 5 | .187 | .382 | **.025** | − .326 | **.046** | .079 | .611 | − .033 | .837 | .159 | .335 |
| 5a | .076 | .262 | .102 | | | .033 | .833 | .019 | .903 | | |
| 5b | .073 | | | − .184 | .232 | .156 | .324 | | | .192 | .224 |

ROI FA asymmetry for either the cingulum or the white matter underlying the ventromedial prefrontal cortex ($vmPFC_{WM}$). Each row represents a separate regression model predicting neuroticism either by modelling the left and right ROIs simultaneously (Models 3 and 4), or the left (models 4a and 5a) or right (models 4b and 5b) ROI individually. All models included age, and age by ROI FA asymmetry.

with relative differences between the left and the right ROIs and *not* with left or right ROIs' FA magnitude. Since the left and right hemispheres have been associated with differences in affect and approach/avoidance behaviour, is seems plausible that the balance between the left and the right ROIs may play an important role for trait neuroticism which reflects different negative-emotion related behaviours and tendencies.

Asymmetries of fronto-limbic structures and fibre tracts have also been related to affective and stress-related disorders (Kim et al., 2006; Nusslock et al., 2011). One study reported that individuals with post-traumatic stress disorder (PTSD) had lower FA of the left cingulum compared to controls. In addition, on average the PTSD group had higher FA of the right relative to the left cingulum, while the control group had higher FA of the left relative to the right cingulum (Kim et al., 2006). While MRI studies on hemispheric asymmetry in mood, anxiety and stress are sparse, the role of frontal cortical activity

asymmetry has been investigated for more than 30 years using electroencephalography (EEG), though with inconsistent findings (Nusslock et al., 2015; Thibodeau et al., 2006; van der Vinne et al., 2017). Nevertheless, the most recent meta-analysis study reported a significant age-by-sex-by-depression severity interaction effect on frontal alpha asymmetry. This effect was mainly driven by an opposite sex effect in the population over the age of 53 years, in which severely depressed females had greater left than right cortical frontal alpha activity, while severely depressed males had greater right than left cortical alpha activity (van der Vinne et al., 2017). Of note, the direction of the opposite sex effects reported in van der Vinne et al. (2017) are similar to those observed in the present study. Moreover, a prospective study of young adults found that decreased left relative to right frontal resting EEG activity was associated with greater probability for having a depressive episode during a 3-year follow-up period (Nusslock et al., 2011). As higher neuroticism scores as well as frontal alpha asymmetry have been associated with an increased risk of developing affective disorders (Kendler et al., 2006, 2004; Nusslock et al., 2011, 2015), we suggest that cingulum and $vmPFC_{WM}$ microstructural asymmetries may be brain structural markers for a predisposition or risk for developing affective disorders. Future studies, including prospective studies, are needed to address if and how fronto-limbic microstructural asymmetries predispose or increase risk of developing affective disorders in healthy as well as clinical cohorts. Further studies should also investigate the possible link between structural and frontal cortical activity asymmetries in negative emotionality and affective disorders.

In the present study, we report on sex differences in the association between neuroticism scores and left-right cingulum microstructural asymmetry. Our observation in boys that higher neuroticism scores were associated with decreased left relative to right cingulum FA is comparable to what we previously found in healthy adults (Madsen et al., 2012). While we hypothesized that there might be sex differences in the neural correlates of neuroticism, we did not expect to find that females would exhibit an opposite asymmetry effect, i.e. higher neuroticism scores associated with increased left relative to right cingulum FA. Some other studies have reported of sex differences in the neural correlates of negative emotionality traits. One study of 16–17 year-old adolescents observed that neuroticism was associated with the bilateral volume and left cortical thickness of the subgenual anterior cingulate cortex and that this relationship was positive in girls, but negative in boys (Blankstein et al., 2009). Another study found that higher harm avoidance scores were significantly associated with larger amygdala volume in young female adults, but not in young male adults (Iidaka et al., 2006). Summarised, both these studies reported that negative emotionality trait scores were positively associated with left-sided structures in females, while negative or no associations with left-sided structures were observed in males. The results of the present study concurs, to some extend, with these previous findings, in that neuroticism scores were positively associated with FA in the left relative to the right cingulum and $vmPFC_{WM}$ in females and negatively associated with left relative to right cingulum FA in males. It is unknown what might underlie the observed sex differences in the relationship between neuroticism and fronto-limbic white matter asymmetries. One possible factor is differences in sex hormones. There is evidence that sex hormones affect functional brain asymmetries (Hausmann, 2017). Frontal alpha asymmetry have been observed to differ across the menstrual cycle in high vs. low neuroticism females, suggesting that changing female sex hormone levels affect frontal alpha asymmetry differently in women with high vs. low neuroticism scores (Huang et al., 2015). There is also some evidence that sex hormones affect structural brain asymmetries. Peripubertal testosterone levels have been observed to affect cortical thickness differently in boys and girls, with testosterone affecting cortical thickness in the left hemisphere more than the right hemisphere in boys, and the right hemisphere more than the left hemisphere in girls (Nguyen et al., 2013). Future studies are needed to elucidate to which extent sex hormones may play a role in the observed sex differences between neuroticism and fronto-limbic white matter asymmetries. The present study highlights that it is important to examine sex differences when investigating neural correlates of negative emotionality traits.

To further explore the nature of the observed FA effects, we examined the $\lambda_{||}$ and $\lambda\perp$, as these diffusivity measures may provide additional information about the underlying tissue microstructure. In girls, the ROI $\lambda\perp$ asymmetries, but not the ROI $\lambda_{||}$ asymmetries, were significantly associated with neuroticism scores. In boys, neither cingulum $\lambda\perp$ asymmetry, nor cingulum $\lambda_{||}$ asymmetry were significantly associated with neuroticism. However, since cingulum $\lambda\perp$ asymmetry exhibited a weak positive and cingulum $\lambda_{||}$ asymmetry a week negative association with neuroticism, differences in both $\lambda_{||}$ and $\lambda\perp$ may contribute to the observed associations with FA asymmetry in boys. Though the interpretation of differences in diffusion parameters is not straightforward, previous studies suggest that $\lambda\perp$ may be more sensitive to changes in axonal density, myelination and extracellular volume fraction (Beaulieu, 2009; Schwartz et al., 2005). The perpendicular apparent diffusion coefficient has been reported to be positively correlated with axonal spacing and extracellular volume fraction, and negatively correlated with axonal number and myelination in the cervical spinal cord in rats (Schwartz et al., 2005). The observed $\lambda\perp$ asymmetry effects may, thus, be related to asymmetry in axonal density, organization and/or myelination of the cingulum and $vmPFC_{WM}$. However, axonal organization may also contribute to differences in $\lambda\perp$ (Beaulieu, 2009; Schwartz et al., 2005). Finally, the size of the fibre bundle may also play a role, in that increased partial volume effects may reduce FA in smaller fibre bundles (Vos et al., 2011). The present cingulum and $vmPFC_{WM}$ findings could therefore be affected by the structural properties intrinsic to the fibre tracts or to the size of the fibre tracts, which could affect the underlying diffusivities differently.

The current study has some potential limitations. The study included almost twice as many girls as boys, which might have prevented us from detecting effect sizes in boys similar to those observed in girls. However, notably the observed association between higher neuroticism scores and decreased left relative to right cingulum FA in boys corroborates our previous findings in healthy adults, of which approximately two thirds were male (Madsen et al., 2012). The fact that we found associations between neuroticism and cingulum microstructural asymmetry in two independent, albeit non-comparable cohorts, suggests that this relationship is not a chance finding. The main objective of the present study was to examine whether the association between neuroticism and cingulum microstructural asymmetry, previously observed in adults, was already present in children and adolescents aged 10–15 years, or whether such a relationship would emerge during this age period. While we observed that the neuroticism – cingulum asymmetry association was already present and independent of age in girls, we also observed that in boys the association became stronger with age. However, given the relatively small sample size of males, it is not possible to conclude whether the association emerges during the age range of the present study, or whether it merely becomes stronger. In order to establish whether the observed relationships arise during childhood, future studies need to include larger sample sizes as well as expand the age range to include younger children. Furthermore, we used chronological age to account for possible neurodevelopmental differences in children and adolescents of different ages. However, the included age range of 10–15 years is also the period in human development in which puberty typically occurs. There is accumulating evidence that individual differences in pubertal development are associated with neurodevelopmental differences or changes in white matter microstructure, above and beyond chronological age, that may differ between boys and girls (Herting et al., 2017, 2012). Therefore, future studies should include measures of pubertal development, as it would allow for a more fine-grained characterization of the nature and timing of the observed associations between neuroticism and cingulum FA asymmetry.

## 5. Conclusion

The present study corroborates our previous results in adults, highlighting that fronto-limbic white matter microstructural asymmetry may play an important role in neuroticism. Moreover, the present results extend our previous study, by suggesting that there are sex differences in the neural correlates of neuroticism. The neurobiological significance of these sex differences is unclear, and future studies are necessary to elucidate the significance of such differences between boys and girls in greater detail. Further, as neuroticism is a risk factor for anxiety and mood disorders, which exhibit sex differences in prevalence, future studies also need to elucidate whether sex differences in the neural correlates of negative emotionality traits might be associated with the sex differences observed in the prevalence of anxiety and mood disorders.

## Acknowledgements

The authors thank the children and their parents for their participation in the HUBU study.

## Funding

This work was supported by the Danish Council of Independent Research Council | Medical Sciences (09–060166 and 0602–02099B), the Lundbeck Foundation (R32-A3161) and the Lundbeck Foundation Center of Excellence grant to The Center for Integrated Molecular Brain Imaging.

## References

Andersson, J.L., Hutton, C., Ashburner, J., Turner, R., Friston, K., 2001. Modeling geometric deformations in EPI time series. Neuroimage 13, 903–919.

Angstmann, S., Madsen, K.S., Skimminge, A., Jernigan, T.L., Baare, W.F., Siebner, H.R., 2016. Microstructural asymmetry of the corticospinal tracts predicts right-left differences in circle drawing skill in right-handed adolescents. Brain Struct. Funct. 221, 4475–4489. http://dx.doi.org/10.1007/s00429-015-1178-5.

Beaulieu, C., 2009. The biological basis of diffusion anisotropy. In: Johansen-Berg, H., Behrens, T.E.J. (Eds.), Diffusion MRI: From Quantitative Measurement to In-vivo Neuroantomy. Elsevier, London, pp. 105–126.

Belcher, A.M., Volkow, N.D., Moeller, F.G., Ferre, S., 2014. Personality traits and vulnerability or resilience to substance use disorders. Trends Cogn. Sci. 18, 211–217. http://dx.doi.org/10.1016/j.tics.2014.01.010.

Bienvenu, O.J., Nestadt, G., Samuels, J.F., Costa, P.T., Howard, W.T., Eaton, W.W., 2001. Phobic, panic, and major depressive disorders and the five-factor model of personality. J. Nerv. Ment. Dis. 189, 154–161.

Bienvenu, O.J., Samuels, J.F., Costa, P.T., Reti, I.M., Eaton, W.W., Nestadt, G., 2004. Anxiety and depressive disorders and the five-factor model of personality: a higher- and lower-order personality trait investigation in a community sample. Depress. Anxiety 20, 92–97. http://dx.doi.org/10.1002/da.20026.

Bjornebekk, A., Fjell, A.M., Walhovd, K.B., Grydeland, H., Torgersen, S., Westlye, L.T., 2013. Neuronal correlates of the five factor model (FFM) of human personality: multimodal imaging in a large healthy sample. Neuroimage 65, 194–208. http://dx.doi.org/10.1016/j.neuroimage.2012.10.009.

Blankstein, U., Chen, J.Y., Mincic, A.M., McGrath, P.A., Davis, K.D., 2009. The complex minds of teenagers: neuroanatomy of personality differs between sexes. Neuropsychologia 47, 599–603 (doi: S0028-3932)(08)(00418-1)(pii) (10.1016/j.neuropsychologia.2008.10.014).

Clewett, D., Bachman, S., Mather, M., 2014. Age-related reduced prefrontal-amygdala structural connectivity is associated with lower trait anxiety. Neuropsychology 28, 631–642. http://dx.doi.org/10.1037/neu0000060.

Cook, P.A., Bai, Y., Nedjati-Gilani, S., Seunarine, K.K., Hall, M.G., Parker, G.J., Alexander, D.C., 2006. Camino: Open-Source Diffusion-MRI Reconstruction and Processing. In: Proceedings of the 14th Scientific Meeting of the International Society for Magnetic Resonance in Medicine, Seattle, WA, USA, 2759.

Cremers, H.R., Demenescu, L.R., Aleman, A., Renken, R., van Tol, M.J., van der Wee, N.J., Veltman, D.J., Roelofs, K., 2010. Neuroticism modulates amygdala-prefrontal connectivity in response to negative emotional facial expressions. Neuroimage 49, 963–970 (doi: S1053-8119)(09)(00902-1)(pii) (10.1016/j.neuroimage.2009.08.023).

Eden, A.S., Schreiber, J., Anwander, A., Keuper, K., Laeger, I., Zwanzger, P., Zwitserlood, P., Kugel, H., Dobel, C., 2015. Emotion regulation and trait anxiety are predicted by the microstructure of fibers between amygdala and prefrontal cortex. J. Neurosci. 35, 6020–6027. http://dx.doi.org/10.1523/JNEUROSCI.3659-14.2015.

Eluvathingal, T.J., Hasan, K.M., Kramer, L., Fletcher, J.M., Ewing-Cobbs, L., 2007. Quantitative diffusion tensor tractography of association and projection fibers in normally developing children and adolescents. Cereb. Cortex 17, 2760–2768.

Eysenck, H.J., Eysenck, S.B.G., 1975. Manual of the Eysenck Personality Questionnaire (Adult and Junior). Hodder & Stoughton, pp. 1–19.

Goodwin, R.D., Gotlib, I.H., 2004. Gender differences in depression: the role of personality factors. Psychiatry Res. 126, 135–142. http://dx.doi.org/10.1016/j.psychres.2003.12.024.

Grimshaw, G.M., Carmel, D., 2014. An asymmetric inhibition model of hemispheric differences in emotional processing. Front. Psychol. 5, 489. http://dx.doi.org/10.3389/fpsyg.2014.00489.

Hansell, N.K., Wright, M.J., Medland, S.E., Davenport, T.A., Wray, N.R., Martin, N.G., Hickie, I.B., 2012. Genetic co-morbidity between neuroticism, anxiety/depression and somatic distress in a population sample of adolescent and young adult twins. Psychol. Med. 42, 1249–1260. http://dx.doi.org/10.1017/S0033291711002431.

Hausmann, M., 2017. Why sex hormones matter for neuroscience: a very short review on sex, sex hormones, and functional brain asymmetries. J. Neurosci. Res. 95, 40–49. http://dx.doi.org/10.1002/jnr.23857.

Herting, M.M., Kim, R., Uban, K.A., Kan, E., Binley, A., Sowell, E.R., 2017. Longitudinal changes in pubertal maturation and white matter microstructure. Psychoneuroendocrinology 81, 70–79. http://dx.doi.org/10.1016/j.psyneuen.2017.03.017.

Herting, M.M., Maxwell, E.C., Irvine, C., Nagel, B.J., 2012. The impact of sex, puberty, and hormones on white matter microstructure in adolescents. Cereb. Cortex 22, 1979–1992. http://dx.doi.org/10.1093/cercor/bhr246.

Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D.S., Calabresi, P.A., Pekar, J.J., van Zijl, P.C., Mori, S., 2008. Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. Neuroimage 39, 336–347 (doi: S1053-8119)(07)(00688-X)(pii) (10.1016/j.neuroimage.2007.07.053).

Huang, Y., Zhou, R., Cui, H., Wu, M., Wang, Q., Zhao, Y., Liu, Y., 2015. Variations in resting frontal alpha asymmetry between high- and low-neuroticism females across the menstrual cycle. Psychophysiology 52, 182–191. http://dx.doi.org/10.1111/psyp.12301.

Iidaka, T., Matsumoto, A., Ozaki, N., Suzuki, T., Iwata, N., Yamamoto, Y., Okada, T., Sadato, N., 2006. Volume of left amygdala subregion predicted temperamental trait of harm avoidance in female young subjects. A voxel-based morphometry study. Brain Res. 1125, 85–93 (S0006-8993)(06)(02722-3)(pii)(10.1016/j.brainres.2006.09.015).

Jang, K.L., Livesley, W.J., Vernon, P.A., 1996. Heritability of the big five personality dimensions and their facets: a twin study. J. Pers. 64, 577–591.

Jernigan, T.L., Baare, W.F., Stiles, J., Madsen, K.S., 2011. Postnatal brain development Structural imaging of dynamic neurodevelopmental processes. Prog. Brain Res. 189, 77–92 (doi: B978-0-444-53884-0.00019-1)(pii)(10.1016/B978-0-444-53884-0.00019-1).

Jones, D.K., Basser, P.J., 2004. "Squashing peanuts and smashing pumpkins": how noise distorts diffusion-weighted MR data. Magn. Reson. Med. 52, 979–993. http://dx.doi.org/10.1002/mrm.20283.

Jovicich, J., Czanner, S., Greve, D., Haley, E., van der Kouwe, A., Gollub, R., Kennedy, D., Schmitt, F., Brown, G., Macfall, J., Fischl, B., Dale, A., 2006. Reliability in multi-site structural MRIstudies: effects of gradient non-linearity correction on phantom and human data. Neuroimage 30, 436–443 (doi: S1053-8119)(05)(00729-9)(pii)(10.1016/j.neuroimage.2005.09.046).

Kendler, K.S., Gatz, M., Gardner, C.O., Pedersen, N.L., 2006. Personality and major depression: a Swedish longitudinal, population-based twin study. Arch. Gen. Psychiatry 63, 1113–1120 (doi: 63/10/1113)(pii)(10.1001/archpsyc.63.10.1113).

Kendler, K.S., Kuhn, J., Prescott, C.A., 2004. The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. Am. J. Psychiatry 161, 631–636.

Kim, S.J., Jeong, D.U., Sim, M.E., Bae, S.C., Chung, A., Kim, M.J., Chang, K.H., Ryu, J., Renshaw, P.F., Lyoo, I.K., 2006. Asymmetrically altered integrity of cingulum bundle in posttraumatic stress disorder. Neuropsychobiology 54, 120–125 (doi: 000098262)(pii)(10.1159/000098262).

Klarborg, B., Skak Madsen, K., Vestergaard, M., Skimminge, A., Jernigan, T.L., Baare, W.F., 2012. Sustained attention is associated with right superior longitudinal fasciculus and superior parietal white matter microstructure in children. Hum. Brain Mapp. http://dx.doi.org/10.1002/hbm.22139.

Lebel, C., Beaulieu, C., 2011. Longitudinal development of human brain wiring continues from childhood into adulthood. J. Neurosci. 31, 10937–10947 (doi: 31/30/10937)(pii)(10.1523/JNEUROSCI.5302-10.2011).

Lebel, C., Gee, M., Camicioli, R., Wieler, M., Martin, W., Beaulieu, C., 2012. Diffusion tensor imaging of white matter tract evolution over the lifespan. Neuroimage 60, 340–352. http://dx.doi.org/10.1016/j.neuroimage.2011.11.094.

Lewis, G.J., Panizzon, M.S., Eyler, L., Fennema-Notestine, C., Chen, C.H., Neale, M.C., Jernigan, T.L., Lyons, M.J., Dale, A.M., Kremen, W.S., Franz, C.E., 2014. Heritable influences on amygdala and orbitofrontal cortex contribute to genetic variation in core dimensions of personality. Neuroimage 103, 309–315. http://dx.doi.org/10.1016/j.neuroimage.2014.09.043.

Lindell, A.K., 2013. Continuities in emotion lateralization in human and non-human primates. Front Hum. Neurosci. 7, 464. http://dx.doi.org/10.3389/fnhum.2013.00464.

Madsen, K.S., Baare, W.F., Skimminge, A., Vestergaard, M., Siebner, H.R., Jernigan, T.L., 2011. Brain microstructural correlates of visuospatial choice reaction time in children. Neuroimage 58, 1090–1100. http://dx.doi.org/10.1016/j.neuroimage.2011.07.032.

Madsen, K.S., Baare, W.F., Vestergaard, M., Skimminge, A., Ejersbo, L.R., Ramsoy, T.Z., Gerlach, C., Akeson, P., Paulson, O.B., Jernigan, T.L., 2010. Response inhibition is associated with white matter microstructure in children. Neuropsychologia 48, 854–862 (doi: S0028-3932)(09)(00431-X)(pii)(10.1016/

j.neuropsychologia.2009.11.001).
Madsen, K.S., Jernigan, T.L., Iversen, P., Frokjaer, V.G., Mortensen, E.L., Knudsen, G.M., Baare, W.F., 2012. Cortisol awakening response and negative emotionality linked to asymmetry in major limbic fibre bundle architecture. Psychiatry Res. 201, 63–72 (doi: S0925-4927)(11)(00272-1)(pii)(10.1016/j.pscychresns.2011.07.015).
McIntosh, A.M., Bastin, M.E., Luciano, M., Maniega, S.M., Del, C.V.H.M., Royle, N.A., Hall, J., Murray, C., Lawrie, S.M., Starr, J.M., Wardlaw, J.M., Deary, I.J., 2013. Neuroticism, depressive symptoms and white-matter integrity in the Lothian Birth Cohort 1936. Psychol. Med. 43, 1197–1206. http://dx.doi.org/10.1017/S003329171200150X.
Mincic, A.M., 2015. Neuroanatomical correlates of negative emotionality-related traits: a systematic review and meta-analysis. *Neuropsychologia*, NSYD1500049. http://dx.doi.org/10.1016/j.neuropsychologia.2015.08.007.
Modi, S., Trivedi, R., Singh, K., Kumar, P., Rathore, R.K., Tripathi, R.P., Khushu, S., 2013. Individual differences in trait anxiety are associated with white matter tract integrity in fornix and uncinate fasciculus: preliminary evidence from a DTI based tractography study. Behav. Brain Res. 238, 188–192. http://dx.doi.org/10.1016/j.bbr.2012.10.007.
Montag, C., Reuter, M., Weber, B., Markett, S., Schoene-Bake, J.C., 2012. Individual differences in trait anxiety are associated with white matter tract integrity in the left temporal lobe in healthy males but not females. Neuroscience 217, 77–83. http://dx.doi.org/10.1016/j.neuroscience.2012.05.017.
Newman, E., Thompson, W.K., Bartsch, H., Hagler Jr., D.J., Chen, C.H., Brown, T.T., Kuperman, J.M., McCabe, C., Chung, Y., Libiger, O., Akshoomoff, N., Bloss, C.S., Casey, B.J., Chang, L., Ernst, T.M., Frazier, J.A., Gruen, J.R., Kennedy, D.N., Murray, S.S., Sowell, E.R., Schork, N., Kenet, T., Kaufmann, W.E., Mostofsky, S., Amaral, D.G., Dale, A.M., Jernigan, T.L., 2016. Anxiety is related to indices of cortical maturation in typically developing children and adolescents. Brain Struct. Funct. 221, 3013–3025. http://dx.doi.org/10.1007/s00429-015-1085-9.
Nguyen, T.V., McCracken, J., Ducharme, S., Botteron, K.N., Mahabir, M., Johnson, W., Israel, M., Evans, A.C., Karama, S., Brain Development Cooperative, G., 2013. Testosterone-related cortical maturation across childhood and adolescence. Cereb. Cortex 23, 1424–1432. http://dx.doi.org/10.1093/cercor/bhs125.
Niclasen, J., Teasdale, T.W., Andersen, A.M., Skovgaard, A.M., Elberling, H., Obel, C., 2012. Psychometric properties of the Danish Strength and Difficulties Questionnaire: the SDQ assessed for more than 70,000 raters in four different cohorts. PLoS One 7, e32025. http://dx.doi.org/10.1371/journal.pone.0032025.
Nusslock, R., Shackman, A.J., Harmon-Jones, E., Alloy, L.B., Coan, J.A., Abramson, L.Y., 2011. Cognitive vulnerability and frontal brain asymmetry: common predictors of first prospective depressive episode. J. Abnorm. Psychol. 120, 497–503. http://dx.doi.org/10.1037/a0022940.
Nusslock, R., Walden, K., Harmon-Jones, E., 2015. Asymmetrical frontal cortical activity associated with differential risk for mood and anxiety disorder symptoms: an RDoC perspective. Int. J. Psychophysiol. 98, 249–261. http://dx.doi.org/10.1016/j.ijpsycho.2015.06.004.
Nyborg, H., Eysenck, S.B.G., Kroll, N., 1982. Cross-cultural comparison of personality in Danish and English children. Scand. J. Psychol. 23, 291–297. http://dx.doi.org/10.1111/j.1467-9450.1982.tb00443.x.
Omura, K., Todd Constable, R., Canli, T., 2005. Amygdala gray matter concentration is associated with extraversion and neuroticism. Neuroreport 16, 1905–1908 (doi: 00001756-200511280-00007)(pii).
Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence? Nat. Rev. Neurosci. 9, 947–957 (doi: nrn2513)(pii)(10.1038/nrn2513).
Reese, T.G., Heid, O., Weisskoff, R.M., Wedeen, V.J., 2003. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. Magn. Reson. Med. 49, 177–182.
Rive, M.M., van Rooijen, G., Veltman, D.J., Phillips, M.L., Schene, A.H., Ruhe, H.G., 2013. Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. Neurosci. Biobehav. Rev. 37, 2529–2553. http://dx.doi.org/10.1016/j.neubiorev.2013.07.018.
Schmahmann, J.D., Pandya, D.N., 2006. Fiber Pathways of the Brain. Oxford University Press, Oxford, UK.
Schwartz, E.D., Cooper, E.T., Fan, Y., Jawad, A.F., Chin, C.L., Nissanov, J., Hackney, D.B., 2005. MRI diffusion coefficients in spinal cord correlate with axon morphometry. Neuroreport 16, 73–76.
SDQ DAWBA DK, 2017. Danish norms from webpage assessed February 26, 2018: http://sdq-dawba.dk/wp-content/uploads/2017/10/Forel%C3%B8bige-SDQ-normer-okt.-17.docx.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487–1505.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M., Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 (Suppl 1), S208–S219.
Sutin, A.R., Evans, M.K., Zonderman, A.B., 2013. Personality traits and illicit substances: the moderating role of poverty. Drug Alcohol Depend. 131, 247–251. http://dx.doi.org/10.1016/j.drugalcdep.2012.10.020.
Taddei, M., Tettamanti, M., Zanoni, A., Cappa, S., Battaglia, M., 2012. Brain white matter organisation in adolescence is related to childhood cerebral responses to facial expressions and harm avoidance. Neuroimage 61, 1394–1401. http://dx.doi.org/10.1016/j.neuroimage.2012.03.062.
Thibodeau, R., Jorgensen, R.S., Kim, S., 2006. Depression, anxiety, and resting frontal EEG asymmetry: a meta-analytic review. J. Abnorm. Psychol. 115, 715–729. http://dx.doi.org/10.1037/0021-843X.115.4.715.
van der Vinne, N., Vollebregt, M.A., van Putten, M., Arns, M., 2017. Frontal alpha asymmetry as a diagnostic marker in depression: fact or fiction? A meta-analysis. Neuroimage Clin. 16, 79–87. http://dx.doi.org/10.1016/j.nicl.2017.07.006.
Vestergaard, M., Madsen, K.S., Baare, W.F., Skimminge, A., Ejersbo, L.R., Ramsoy, T.Z., Gerlach, C., Akeson, P., Paulson, O.B., Jernigan, T.L., 2011. White matter microstructure in superior longitudinal fasciculus associated with spatial working memory performance in children. J. Cogn. Neurosci. 23, 2135–2146. http://dx.doi.org/10.1162/jocn.2010.21592.
Vos, S.B., Jones, D.K., Viergever, M.A., Leemans, A., 2011. Partial volume effect as a hidden covariate in DTI analyses. Neuroimage.
Westlye, L.T., Bjornebekk, A., Grydeland, H., Fjell, A.M., Walhovd, K.B., 2011. Linking an anxiety-related personality trait to brain white matter microstructure: diffusion tensor imaging and harm avoidance. Arch. Gen. Psychiatry 68, 369–377. http://dx.doi.org/10.1001/archgenpsychiatry.2011.24.
Wright, C.I., Williams, D., Feczko, E., Barrett, L.F., Dickerson, B.C., Schwartz, C.E., Wedig, M.M., 2006. Neuroanatomical correlates of extraversion and neuroticism. Cereb. Cortex 16, 1809–1819 (doi: bhj118)(pii)(10.1093/cercor/bhj118).