Anxious/depressed symptoms are related to microstructural maturation of white matter in typically developing youths

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Anxious/depressed symptoms are related to microstructural maturation of white matter in typically developing youths

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Abstract

There are multiple recent reports of an association between anxious/depressed (A/D) symptomatology and the rate of cerebral cortical thickness maturation in typically developing youths. We investigated the degree to which anxious/depressed symptoms are tied to age-related microstructural changes in cerebral fiber pathways. The participants were part of the NIH MRI Study of Normal Brain Development. Child Behavior Checklist A/D scores and diffusion imaging were available for 175 youths (84 males, 91 females; 241 magnetic resonance imagerings) at up to three visits. The participants ranged from 5.7 to 18.4 years of age at the time of the scan. Alignment of fractional anisotropy data was implemented using FSL/Tract-Based Spatial Statistics, and linear mixed model regression was carried out using SPSS. Child Behavior Checklist A/D was associated with the rate of microstructural development in several white matter pathways, including the bilateral anterior thalamic radiation, bilateral inferior longitudinal fasciculus, left superior longitudinal fasciculus, and right cingulum. Across these pathways, greater age-related fractional anisotropy increases were observed at lower levels of A/D. The results suggest that subclinical A/D symptoms are associated with the rate of microstructural development within several white matter pathways that have been implicated in affect regulation, as well as mood and anxiety psychopathology.

Although numerous neuroimaging studies have investigated functional and structural correlates of mood and anxiety symptoms, few have investigated the extent to which such symptoms are related to brain morphometric changes across time in the developing human brain (Ducharme et al., 2014; Newman et al., 2015). Furthermore, no previous stud-
pressed symptoms would be associated with a reduced rate of microstructural development.

Methods

Sampling and recruitment

The NIH MRI Study of Normal Brain Development is a large, multisite project that provides a normative database to study relations between healthy brain maturation and behavior (Evans, 2006). Subjects were recruited throughout the United States utilizing a population-based sampling method aimed at minimizing selection bias (Waber et al., 2007). Using available US Census 2000 data, a representative, typically developing sample was recruited at six pediatric study centers. The six pediatric centers consisted of Children’s Hospital (Boston), Children’s Hospital Medical Center (Cincinnati, Illinois), University of Texas Houston Medical School (Houston, Texas), University of California Los Angeles Neuropsychiatric Institute and Hospital (Los Angeles), Children’s Hospital of Philadelphia (Philadelphia, Pennsylvania) and Washington University (St. Louis, Missouri). Recruitment was monitored throughout the study, ensuring that enrollment across all pediatric centers was demographically representative with regard to age, gender, ethnicity, and socioeconomic status (full demographic features of subjects are provided in Evans, 2006). Specifically, census data were used to define low-, medium-, and high-income categories for families in the overall population, as well as to determine the expected distribution of race/ethnicity within each of the income categories. Race/ethnicity by income categories were distributed across the study’s planned age distribution. Regionally specific targets were subsequently created for each pediatric study center based on postal code census data. Subjects were not recruited through convenience volunteer methods, but were obtained and then screened through targeted mailings. An institutional review board approved the study and informed consent was obtained from parents, as well as child assent. The Objective 1 database (release 4.0) used in this study included 431 healthy youths, and upon enrollment (i.e., first study visit), ages ranged from 4.5 years to 18.25 years. The study followed a longitudinal design such that participants underwent magnetic resonance imaging brain scanning and behavioral testing on three separate visits, occurring at roughly 2-year intervals.

Given that the aim of the NIH MRI Study of Normal Brain Development was to study healthy, typically developing children, stringent exclusion criteria were utilized including meeting criteria for a current or past Axis I disorder on structured parent or child interview (Diagnostic Interview for Children and Adolescents; exceptions included simple phobia, social phobia, adjustment disorder, oppositional defiant disorder, enuresis, encopresis, or nicotine dependency); having one or more first-degree relatives with a lifetime history of Axis I psychiatric disorder; family history of inherited neurological disorder or mental retardation due to nontraumatic
Anxious/depressed white matter development

Anxiety symptoms were assessed as part of the CBCL. A major problem was defined as a score of 70 or below, whereas minor problems were rated as 71-79, and no issue was rated as 80 and above. The CBCL A/D syndrome scale demonstrates excellent psychometric properties. The test–retest reliability is high for A/D ($r = .82$, Cronbach $\alpha = .84$; Achenbach & Rescorla, 2001). Further, the stability of A/D is high, with Pearson $r$ of .68 and .56 reported for 12- and 24-month intervals, respectively (Achenbach & Rescorla, 2001). Subjects in the present study possessed $T$ scores of 70 or below, and thus none of the subjects obtained clinically significant scores.

**DTI and quality control procedures**

Preprocessed and quality-controlled FA data are publicly available, and were downloaded directly from the NIH Normal Brain Development website (http://pediatricmri.nih.gov; Walker et al., 2015). The DTI protocol for the NIH Normal Brain Development study has been detailed in previous reports (Evans, 2006; Walker et al., 2015; Walker, Curry, Nayak, Lange, & Pierpaoli, 2013), as well as in documentation freely available online (http://ndar.nih.gov/data_from_labs.html). In summary, DTI data were collected at five of the six participating centers using a 1.5-T Siemens scanner (three sites) or GE scanner (two sites). DTI protocol implemented a spin echo planar imaging (EPI) sequence with minimum repetition time $= 3$ s, minimum achievable echo time with full echo acquisition, axial slices (i.e., perpendicular to the z axis of the magnet, not oblique), field of view, matrix, and slice thickness adjusted to yield $3 \times 3 \times 3$ mm$^3$ voxels. Acquisitions consisted of 48–60 contiguous slices, $b$ values of 0 and 1000 s mm$^{-2}$ with six diffusion directions, repeated four times without averaging, $4 \times (1 \times b = 0 \text{ s mm}^{-2} + 6 \times b = 1000 \text{ s mm}^{-2})$, resulting in a total of 28 volumes. Resultant images were reconstructed at their native resolution (without use of zero filling or interpolation). The publicly available TORTOISE processing pipeline was used to prepare the diffusion data (Pierpaoli et al., 2010). Processing steps included: eddy current distortion and motion correction (Rohde, Barnett, Basser, Marenco, & Pierpaoli, 2004); susceptibility-induced EPI distortion correction (Wu et al., 2008) using T2W image as a target for registration; and rigid reorientation into a common final space defined by the registered T2W image.

Information pertaining to NIH Normal Brain Development DTI quality control can be found online (http://ndar.nih.gov/data_from_labs.html) and is provided here for the reader’s reference. All diffusion imaging underwent rigorous quality assessment in terms of adherence to study protocol, as well as image quality. Each acquisition was rated on the following imaging parameters: brain coverage (top of the brain); brain coverage (bottom of the brain); severity of ghosting artifact; artifacts affecting signal, such as spike noise, radiofrequency artifacts, or reconstruction artifacts; motion resulting in signal dropout; occurrence of motion within volume (interleave misregistration, and severity of eddy current distortions; severity of susceptibility induced EPI distortion; and the pervasiveness of cardiac pulsation. For each of the above categories, data were rated as $0 = \text{no issue}$, $1 = \text{minor}$, $2 = \text{moderate}$, or $3 = \text{severe}$. Raters were blind to subjects’ behavioral data, including A/D scores. Finally, the raw corrected data (i.e., after processing with the TORTOISE pipeline) were assessed on the following criteria: quality of motion and eddy distortion correction; quality of susceptibility-induced EPI distortion correction; and visual assessment of overall and regional (e.g., frontal, parietal, etc.) quality of tensor-derived quantities. For each of these categories, data were rated as $0 = \text{perfect}$, $1 = \text{minor problem}$, $2 = \text{moderate problem}$, or $3 = \text{major problem}$. Although postprocessing techniques were applied in an attempt to correct for all artifacts and distortions, a number of data sets were ultimately rejected. These data sets were removed from the database with the aim of ensuring a standard level of quality. The Normal Brain Development study was organized into two objectives. Objective 1 included participants aged 4.5 years and older at enrollment, whereas Objective 2 included participants who were younger than 4.5 years of age at enrollment. Including both Objective 1 and Objective 2 data, a total of 878 diffusion scans were acquired as part of the larger NIH study (Walker et al., 2016). A total of 498 diffusion scans (from 274 unique subjects) were included in the database, with the total number of rejected acquisitions equaling 380 (43.3% of total number of acquisitions; Walker et al., 2016). Data in the present study were only from the Objective 1 cohort. Reasons for rejection of diffusion data for the Objective 1 cohort are enumerated in Table 1. Deviations from the imaging acquisition protocol accounted for more than 85% of rejections. Thus, the overwhelming majority of rejections were independent of participant characteristics and, instead, an unfortunate reflection of data sets being acquired with inconsistent voxel sizes.

**Statistical analyses**

Registration of subjects’ FA data was performed using the Tract-Based Spatial Statistics stream, which is part of the FSL software package (Smith et al., 2004, 2006). All sub-
Table 1. Reason for rejection of diffusion data for the Objective 1 cohort

<table>
<thead>
<tr>
<th>Reason for Rejection</th>
<th>DTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motion with or without protocol errors</td>
<td>11</td>
</tr>
<tr>
<td>Artifacts (spike noise, ghosting, etc.)</td>
<td>31</td>
</tr>
<tr>
<td>Artifacts combined with protocol errors</td>
<td>17</td>
</tr>
<tr>
<td>Uncorrectable eddy current distortions combined with protocol errors</td>
<td>92</td>
</tr>
<tr>
<td>Incorrect image matrix size/resolution</td>
<td>76</td>
</tr>
<tr>
<td>Other protocol errors (including incomplete acquisition)</td>
<td>67</td>
</tr>
<tr>
<td>Total</td>
<td>294</td>
</tr>
</tbody>
</table>

Note: DTI, Diffusion tensor imaging.

...jects’ FA data were aligned into Montreal Neurological Institute 152 space using the nonlinear registration tool FNIRT, which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was created and thinned in order to produce a mean FA skeleton. To test the hypothesis that CBCL A/D symptoms are associated with microstructural development of fiber pathways, tracts of interest were defined using the Johns Hopkins University white matter tractography atlas (probability threshold of 25%). For each available diffusion scan, average FA values were obtained for 14 white matter tracts. These tracts included the left and right superior longitudinal fasciculus, inferior longitudinal fasciculus, anterior thalamic radiation, cingulum bundle, uncinate fasciculus, corticospinal tract, as well as forceps major and forceps minor. Using FSL, mean FA values for all white matter pathways were calculated for all subjects at all time points.

Mean FA values were subsequently imported into the statistical software package, IBM SPSS Statistics 21 (SPSS Inc., Chicago). To test our hypothesis, linear mixed-effects models were employed within SPSS. Mixed-effects models provide a way in which to analyze unbalanced longitudinal data, while maximizing statistical power (i.e., utilizing all available data; Diggle, 2002; Shaw et al., 2011; Singer & Willett, 2003). Using a first-order autoregressive model, subject ID was entered as a random effect in order to account for within-individual dependence. Age, intracranial volume (ICV), gender, and scanner were statistically controlled for in analyses. ICV was included as a covariate based on research indicating that diffusion metrics such as FA are influenced by head size (Takao, Hayashi, Inano, & Ohtomo, 2011). In order to test the degree to which CBCL A/D moderates the relationship between age and microstructural organization, the following model was run for each of the 14 tracts:

\[
\text{Mean FA} = \text{intercept} + d_1(\text{Age}) + \beta_2(\text{ICV}) + \beta_3(\text{Gender}) + \beta_4(\text{Scanner}) + \beta_5(\text{CBCL A/D}) + \beta_6(\text{Age} \times \text{CBCL A/D}) + e,
\]

where \(d_1\) represents the random effect of subject ID and \(e\) corresponds to residual error. Given our a priori hypothesis, we were primarily interested in the significance of the Age \(\times\) CBCL A/D interaction term.

Given that the Age \(\times\) CBCL A/D interaction was being tested in 14 different tracts, our threshold for statistical significance was adjusted accordingly. A Bonferroni adjustment resulted in a corrected significance threshold of \(p \leq .0154\), accounting for the average correlation in mean FA values across the 14 white matter tracts (\(r = .553\)).

Results

Demographics

A total of 175 subjects (91 females, 84 males; 241 scans) were analyzed in the present study. Of the 175 subjects, 118 subjects had imaging and behavioral data available for only one visit, and 57 subjects had data available at two or more visits. At time of scan, subjects ranged from 5.7 to 18.4 years of age, with a mean age of 12.4 years (SD = 3.2 years; see online-only supplementary Figure S.1). The mean CBCL A/D raw score was 1.7 (SD = 1.9). Preliminary analyses revealed that CBCL A/D score was not significantly associated with study site, gender, or age. Further, there was no evidence of a Gender \(\times\) Age interaction on CBCL A/D scores in this sample. Demographic information for the present sample as well as the larger Normal Brain Development study is shown in Table 2. Participants in the current sample were older relative to the larger NIH Normal Brain Development cohort (\(t = 2.13, p = .03\)), but did not differ with regard to CBCL A/D score (\(t = 0.36, p = .72\)). Further, when compared to the larger sample, the present sample did not differ with regard to race (\(\chi^2 = 2.14, p = .83\)) or gender (\(\chi^2 = 0.00, p = 1.00\)).

Diffusion imaging

As a first step, models were run without the Age \(\times\) CBCL A/D interaction term. Across all tracts, there was no main association between CBCL A/D and mean FA while controlling for the effects of age, gender, ICV, and scanner site. However, the Age \(\times\) CBCL A/D interaction was significantly associated with mean FA in six white matter tracts: the left superior longitudinal fasciculus (SLF), left and right anterior thalamic radiation, left and right inferior longitudinal fasciculi, and the right cingulum bundle (Figure 1). Results are summarized in Table 3. The results were not meaningfully altered when quality control ratings of motion artifact were entered as a covariate.

The Age \(\times\) CBCL A/D interaction on FA was subsequently decomposed using simple slope tests. Across all significant tracts, greater age-related FA increases were observed at lower levels of A/D (Figure 2; an example of a scatterplot with raw diffusion data is provided in online-only supplemental Figure S.2).
Discussion

To the best of our knowledge, this is the first study to report an association between age-related changes in white matter microstructure and anxious/depressed symptoms among healthy, typically developing youths. As hypothesized, anxious/depressed symptomatology was associated with reduced rates of age-related increases in FA within bilateral anterior thalamic radiation, bilateral inferior longitudinal fasciculi, the left SLF, and right cingulum. Controlling for quality control variables, including motion artifact, did not meaningfully alter our results. Taken together, these results support the notion of anxious/depressed symptoms in children and adolescents being tied to neurodevelopment, not only at the level of the cortex (Ducharme et al., 2014; Newman et al., 2015), but also at the level of the cerebral white matter.

Table 2. Demographic information

<table>
<thead>
<tr>
<th></th>
<th>Larger Cohort (N = 431)</th>
<th>Current Sample (N = 175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>M = 11.8 years, SD = 4.1 years, 1,074 time points</td>
<td>M = 12.4 years, SD = 3.2 years, 241 time points</td>
</tr>
<tr>
<td>Gender</td>
<td>52% Female (224), 48% male (207)</td>
<td>52% Female (91), 48% male (84)</td>
</tr>
<tr>
<td>Race</td>
<td>African American/Black 9.28%</td>
<td>African American/Black 9.30%</td>
</tr>
<tr>
<td></td>
<td>American Indian or Alaskan Native 0.23%</td>
<td>American Indian or Alaskan Native 0.58%</td>
</tr>
<tr>
<td></td>
<td>Asian 1.62%</td>
<td>Asian 1.74%</td>
</tr>
<tr>
<td></td>
<td>White 81.44%</td>
<td>White 83.14%</td>
</tr>
<tr>
<td></td>
<td>Not provided 6.73%</td>
<td>Not provided 4.65%</td>
</tr>
<tr>
<td></td>
<td>Mixed 0.70%</td>
<td>Mixed 0.58%</td>
</tr>
<tr>
<td>Household income</td>
<td>Median income bracket = 7.00 ($50,000–$75,000)</td>
<td>Median income bracket = 7.00 ($50,000–$75,000)</td>
</tr>
<tr>
<td>CBCL A/D raw score</td>
<td>M = 1.61, SD = 1.95, based on 913 observations</td>
<td>M = 1.66, SD = 1.89, based on 241 observations</td>
</tr>
</tbody>
</table>

Note: CBCL A/D, Child Behavior Checklist anxious/depressed.
With the advent of advanced structural neuroimaging analyses, certain forms of developmental psychopathology have been tied to structural brain development. In recent years, for example, neuroimaging studies of cerebral cortical morphology have provided compelling evidence that attention-deficit/hyperactivity disorder symptoms are associated with lagging cortical development, particularly within the frontoparietal areas of the cortex (Ducharme et al., 2012; Shaw et al., 2007, 2011). Despite such findings, few studies have examined the relationship between internalizing symptoms and structural brain development. Two recent studies, studying large samples of typically developing youths, have provided support for anxiety symptomatology being related to indices of cerebral cortical maturation (Ducharme et al., 2014; Newman et al., 2015). A possible link between anxious/depressed symptoms and delayed brain maturation is further supported by clinical observations, such as mood and anxiety symptoms in adolescence being associated with delayed attainment of early developmental milestones (Colman et al., 2014; North, Wild, Zwaigenbaum, & Colman, 2013). It is reasonable that such behavioral delays are underpinned by protracted maturation of brain circuitry.

It is noteworthy that previous neuroimaging studies have reported associations between FA and internalizing symptoms among older, healthy participants (Kim & Whalen, 2009; Westlye et al., 2011). In a large study of 263 healthy adults, Westlye et al. (2011) reported that harm avoidance, an anxiety-related personality trait and risk factor for mood and anxiety psychopathology, was negatively associated with FA in the bilateral anterior thalamic radiations, cingulum bundle, inferior longitudinal fasciculus, superior longitudinal fasciculus, as well as several other white matter pathways (Westlye et al., 2011). The white matter regions in which Westlye et al. (2011) revealed negative associations between harm avoidance and FA overlap with areas in which we found associations between FA and an Age × CBCL A/D interaction. It is possible that the reduced rate of age-related FA increases among youths with higher A/D scores (reported in the present study) may underpin the negative association between FA and anxiety symptoms reported in adults.

It is interesting that results from the present study also show some degree of overlap with imaging studies of clinically significant mood and anxiety symptoms. Young adults with major depressive disorder have been found to possess reduced FA in the left SLF and right anterior thalamic radiation when compared to healthy age-matched controls (Lai & Wu, 2014). In a meta-analysis of diffusion imaging studies on major depressive disorder, reduced FA in the left SLF was revealed as a stable finding across studies (Murphy & Frodl, 2011). These findings suggest that, to some extent, clinical and subclinical forms of internalizing psychopathology may share common neural substrates. As a result, present findings also dovetail with the notion of certain forms of developmental psychopathology representing dimensional, quantitative traits that fall along continua (Hudziak, Achenbach, Althoff, & Pine, 2007).

This study possesses a number of limitations that must be considered. The diffusion data used in this study possessed low angular resolution. It would have been advantageous to acquire 24 unique, nonredundant, noncollinear diffusion directions and 4 b = 0 volumes (given that the present study collected 28 volumes). Unfortunately, this was not the standard at the time the study was launched: high angular resolution diffusion was not available in a form that could be implemented on both GE and Siemens scanners. As a result, we are unable to implement fiber-tracking methods that would allow for more precise anatomical investigation. That being said, previous research indicates that, when taking a region of interest approach, FA values are not significantly different when data are acquired at 6, 21, and 31 diffusion-encoded gradient directions (Ni, Kavic, Zhu, Ekholm, & Zhong, 2006). Although we have attempted to control for confounds such as motion artifact, we cannot rule out the possibility that the quality of our diffusion data may have influenced our results. Future studies are needed to replicate our findings, using higher resolution data acquired with a greater number of diffusion directions. Another methodological limitation is the high percentage of diffusion scans that deviated from the imaging acquisition protocol. As a result, it is possible that the sample used in the present study was not representative of the larger NIH Normal Brain Development sample. That being said, youths in the present study did not differ with regard to racial background, median household income, gender, or anxious/depressed score when compared to the larger study sample.

This study possesses a number of methodological strengths. In particular, we utilized a large sample of typically developing youths who were extensively screened for clinically significant psychiatric problems, as well as for family history of psychiatric mood or anxiety disorders. Furthermore, in order to charac-

### Table 3. Significance of Age × Anxious/Depressed interaction on mean fractional anisotropy

<table>
<thead>
<tr>
<th>Tract</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left SLF</td>
<td>-3.589</td>
<td>.0004&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Left ILF</td>
<td>-3.241</td>
<td>.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Right cingulum</td>
<td>-3.087</td>
<td>.002&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Left ant. thal.</td>
<td>-2.775</td>
<td>.006&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Right ant. thal.</td>
<td>-2.722</td>
<td>.007&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Right ILF</td>
<td>-2.67</td>
<td>.008&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Left cingulum</td>
<td>-2.388</td>
<td>.018</td>
</tr>
<tr>
<td>Left CST</td>
<td>-1.846</td>
<td>.067</td>
</tr>
<tr>
<td>Right SLF</td>
<td>-1.84</td>
<td>.068</td>
</tr>
<tr>
<td>Forceps major</td>
<td>-1.682</td>
<td>.094</td>
</tr>
<tr>
<td>Forceps minor</td>
<td>-1.632</td>
<td>.104</td>
</tr>
<tr>
<td>Right CST</td>
<td>-0.977</td>
<td>.33</td>
</tr>
<tr>
<td>Right uncinate</td>
<td>-0.791</td>
<td>.43</td>
</tr>
<tr>
<td>Left uncinate</td>
<td>-0.13</td>
<td>.897</td>
</tr>
</tbody>
</table>

Note: SLF, Superior longitudinal fasciculus; ILF, inferior longitudinal fasciculi; ant. thal., anterior thalamic radiation; CST, corticospinal tract.

<sup>a</sup>Significance at the Bonferroni-corrected threshold (p < .0154).
terize subclinical internalizing problems in these healthy youths, we used quantitative, empirically based assessment measures of emotional and behavioral problems. This work strongly resonates with the research domain criteria initiative, emphasizing the importance of neurodevelopmental research focusing on evidence-based dimensional constructs in typically developing youths (Insel et al., 2010).

In conclusion, this is the first report of an association between anxious/depressed symptoms and white matter microstructural development. These results seemingly complement our group’s previous report of anxious/depressed symptoms being linked to a reduced rate of cortical thickness maturation within the prefrontal cortex. Future longitudinal neuroimaging studies are needed to characterize putative relationships between internalizing symptoms and trajectories of neurodevelopment.

Supplementary Material
To view the supplementary material for this article, please visit http://dx.doi.org/10.1017/S0954579416000444.

References


