2016

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Recommended Citation

Albaugh, Matthew D.; Ducharme, Simon; Karama, Sherif; Watts, Richard; Lewis, John D.; Orr, Catherine; Nguyen, Tuong-Vi; McKinstry, Robert C.; Botteron, Kelly N.; Evans, Alan C.; Hudziak, James J.; and The Brain Development Cooperative Group, "Anxious/depressed symptoms are related to microstructural maturation of white matter in typically developing youths." Development and Psychopathology. 1-8. (2016).
https://digitalcommons.wustl.edu/open_access_pubs/5125

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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 imagings) 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 studies have examined the degree to which mood and anxiety symptoms are associated with age-related changes in white matter pathways. Utilizing a large sample of typically developing youths, the aim of the present study is to test the degree to which subclinical mood and anxiety symptoms are associated with age-related changes in white matter microstructure.

The advent of diffusion tensor imaging (DTI) has allowed for the assessment of age-related changes in white matter microstructure among developing youths and young adults (Basser & Pierpaoli, 1996; Makris et al., 1997; Mukherjee et al., 2001; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). With regard to white matter microstructure, evidence indicates that fractional anisotropy (FA) largely reflects the packing density of axons, axonal diameter, as well as degree of myelination within white matter pathways (Beaulieu, 2002). In general, studies investigating white matter development across childhood and adolescence have reported widespread FA increases in white matter pathways (Cascio, Gerig, & Piven, 2007; Lebel et al., 2012; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Schmithorst, Wilke, Dardzinski, & Holland, 2002; Snook, Paulson, Roy, Phillips, & Beaulieu, 2005). Such age-related FA increases in cerebral white matter are postulated to reflect increasing microstructural integrity, and presumed functional maturation, of cerebral fiber pathways. Age-related FA increases within specific white matter pathways have been found to be uniquely associated with aspects of cognitive performance among typically developing

6- to 17-year-olds (Mabbott, Noseworthy, Bouffet, Laughlin, & Rockel, 2006).

In recent years, numerous structural neuroimaging studies have mapped age-related changes in brain structure, including in gray matter structures such as the cerebral cortex, to particular behavioral phenotypes (Giedd et al., 2008; Shaw et al., 2007, 2011). Specifically, aspects of cerebral cortical thickness development have been tied to intelligence, attention-deficit/hyperactivity disorder, as well as subclinical attention problems in healthy, typically developing youths (Ducharme et al., 2012; Shaw et al., 2006, 2007, 2011). Such findings raise the possibility that trajectories of anatomic brain development, or brain morphometric change across time, are meaningful endophenotypes when studying brain–behavior relations among children and adolescents (Giedd et al., 2008).

Members of our group have recently reported that subclinical anxious/depressed (A/D) problems among typically developing youths are associated with reduced rates of age-related cortical thinning within the ventromedial prefrontal cortex (vmPFC; Ducharme et al., 2014). This finding is intriguing given that the vmPFC has been implicated in top-down modulation of the amygdalae in both animal and human functional imaging studies (Phelps, Delgado, Nearing, & LeDoux, 2004; Quirk & Beer, 2006; Quirk, Garcia, & Gonzalez-Lima, 2006; Quirk, Likhtik, Pelletier, & Pare, 2003). It is possible that delayed cortical thickness development in the vmPFC may reflect altered maturation of neural systems involved in the regulation of negative affect. Very recently, Newman et al. (2015) reported that higher anxiety in children was characterized by delayed expansion of the vmPFC and an altered trajectory of global age-related cortical thinning. Similar to Ducharme et al. (2014), the authors of this study utilized dimensional measures of anxiety in a large sample of typically developing youths (Newman et al., 2015). Taken together, findings from these studies suggest that anxious/depressed symptomology is tied to indices of cortical maturation in typically developing youths.

Prior research indicates that age-related changes in both cortical thickness and FA are, to some degree, underpinned by a common biological mechanism (Kochunov et al., 2011). Given close links between cerebral cortical maturation and microstructural development of white matter (Kochunov et al., 2011), it is possible that anxious/depressed symptoms may be tied to age-related changes in white matter, particularly in white matter pathways such as the uncinate fasciculus, cingulum bundle, inferior and superior longitudinal fasciculus, and anterior thalamic radiation, which have been linked to anxious temperament in healthy adults (Kim & Whalen, 2009; Westlye, Bjornebekk, Grydeland, Fjell, & Walhovd, 2011). Utilizing a large cohort of typically developing youths, we hypothesized that subclinical anxious/depressed symptoms would be associated with age-related FA changes in white matter pathways previously implicated in the pathophysiology of mood and anxiety symptoms. Based on literature outlined above, we further hypothesized that anxious/depressed 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

events; abnormality on neurological examination; gestational age at birth less than 37 weeks or greater than 42 weeks; and intrauterine exposure to substances known or highly suspected to alter brain structure or function (for further information, see Evans, 2006). Structural MRI and behavioral data were stored and analyzed within a database at the Data Coordinating Center of the Montreal Neurological Institute, McGill University.

Child Behavior Checklist (CBCL)

The CBCL, one of the most extensively used instruments for assessing child psychopathology and competence worldwide, asks parents to report on specific behaviors exhibited by their child within the previous 6 months (Achenbach, 1991; Achenbach & Rescorla, 2001). In the present study, CBCL A/D scores were utilized as a dimension measure of internalizing symptoms in this cohort of healthy children. Items on the CBCL A/D syndrome scale include "Too fearful or anxious," "Worries," "Nervous, highstrung, or tense," and "Feels too guilty." The CBCL A/D syndrome scale demonstrates excellent psychometric properties. The test–retest reliability is high for A/D ($r = .82$, Cronbach $\alpha = 0.84$; Achenbach & Rescorla, 2001). Further, the stability of A/D is high, with Pearson rs 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 $3 \times 3 \times 3 \text{ mm}^3$ 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 $0 = no\ issue$, $1 = minor$, $2 = moderate$, or $3 = severe$. 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 $0 = perfect$, $1 = minor\ problem$, $2 = moderate\ problem$, or $3 = major\ problem$. 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*

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

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:

$$\text{Mean FA} = \text{intercept} + d_1 + \beta_1(\text{Age}) + \beta_2(\text{ICV})$$
$$+ \beta_3(\text{Gender}) + \beta_4(\text{Scanner}) + \beta_5(\text{CBCL A/D})$$
$$+ \beta_6(\text{Age} \times \text{CBCL A/D}) + e,$$

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 × CBCL A/D interaction term.

Given that the Age × 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 × 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×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×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×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).

Table 2. *Demographic information*

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

Note: CBCL A/D, Child Behavior Checklist anxious/depressed.

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 symptoms were associated with the rate of microstructural development within a number of white matter pathways. Specifically, 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.

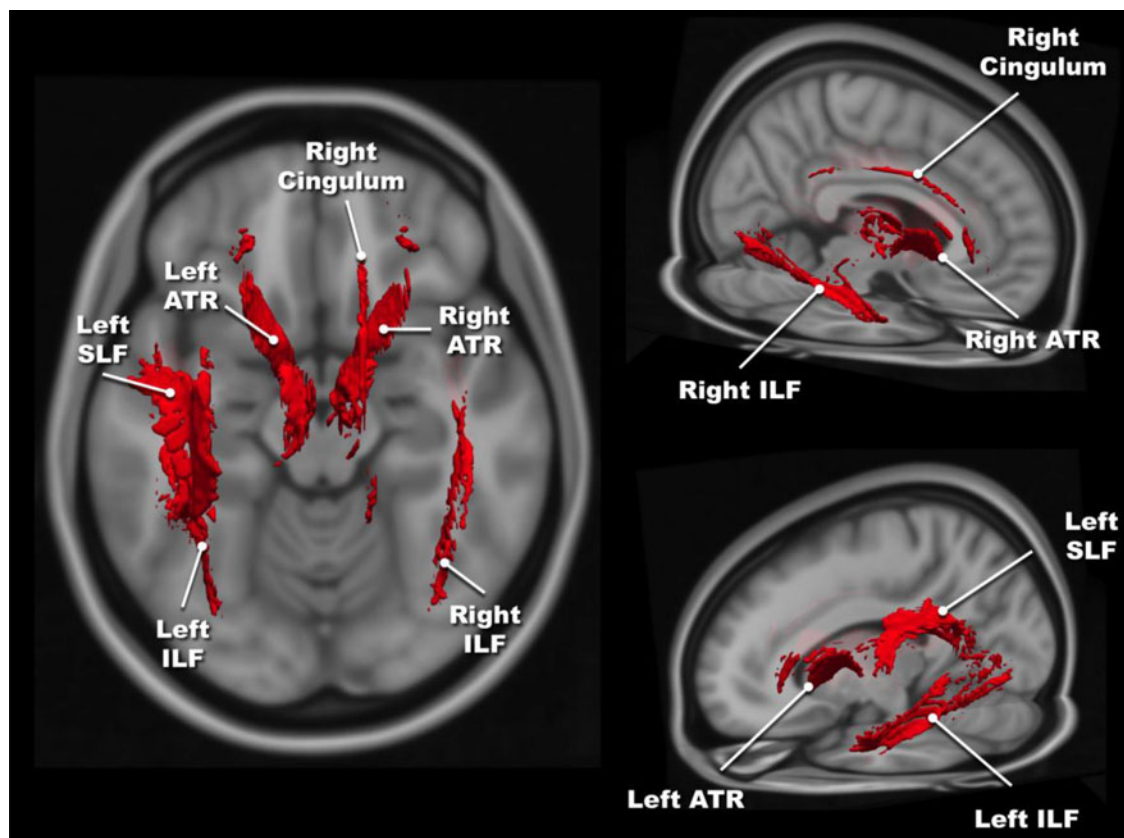**Figure 1.** (Color online) Tracts in which mean fractional anisotropy is associated with an Age × Anxious/Depressed interaction. Three-dimensional rendering of white matter tracts in which Child Behavior Checklist anxious/depressed scores qualified age-related increases in mean fractional anisotropy. Tracts are displayed overlaid upon the Montreal Neurological Institute 152 1-mm brain template.

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

Tract	*t*	*p*
Left SLF	−3.589	.0004[a]
Left ILF	−3.241	.001[a]
Right cingulum	−3.087	.002[a]
Left ant. thal.	−2.775	.006[a]
Right ant. thal.	−2.722	.007[a]
Right ILF	−2.67	.008[a]
Left cingulum	−2.388	.018
Left CST	−1.846	.067
Right SLF	−1.84	.068
Forceps major	−1.682	.094
Forceps minor	−1.632	.104
Right CST	−0.977	.33
Right uncinate	−0.791	.43
Left uncinate	−0.13	.897

Note: SLF, Superior longitudinal fasciculus; ILF, inferior longitudinal fasciculi; ant. thal., anterior thalamic radiation; CST, corticospinal tract.
[a]Significance at the Bonferroni-corrected threshold ($p <$ .0154).

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 fronto-parietal 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, Kavcic, 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-
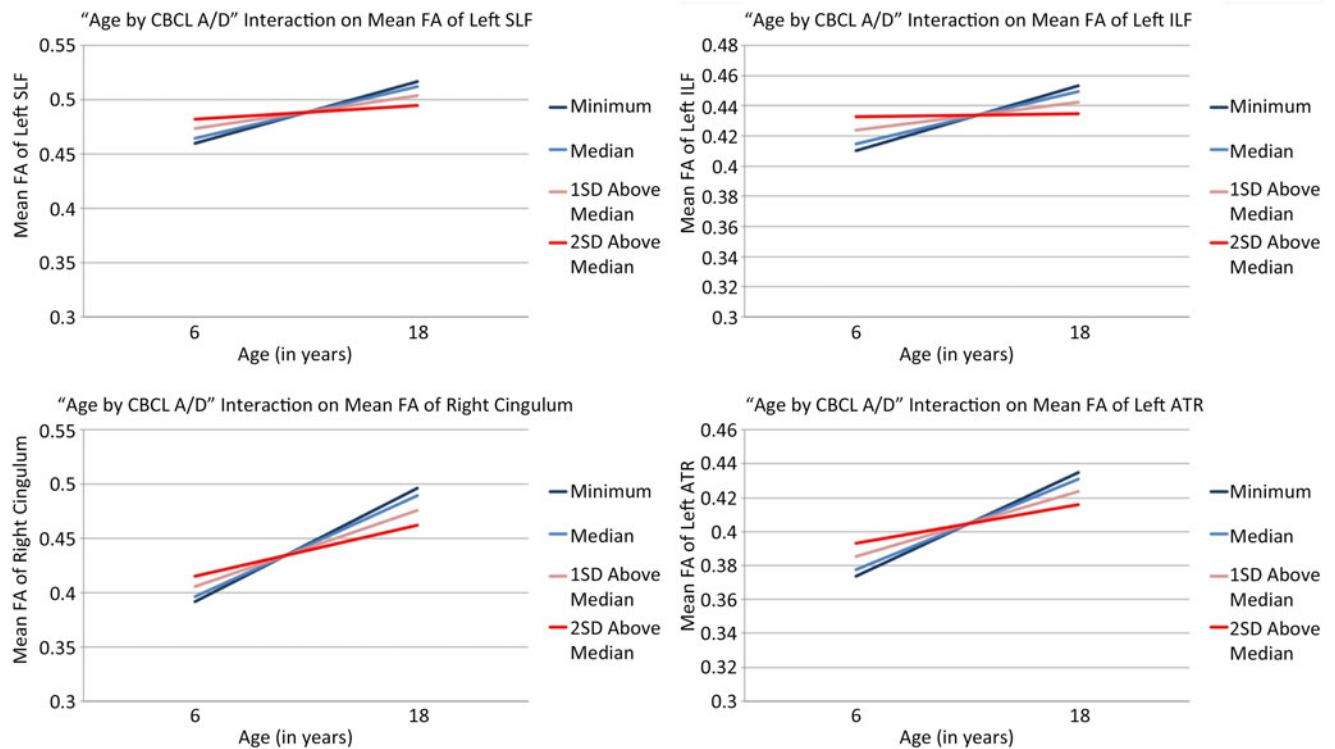
Figure 2. (Color online) Decomposition of Age × Anxious/Depressed interaction. Results for post-hoc simple slopes tests characterizing the statistical relation between age and mean fractional anisotropy of tracts at varying levels of Child Behavior Checklist anxious/depressed scores (i.e., minimum, median, 1 *SD* above median, and 2 *SD* above median).

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

Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist 4–18 and 1991 Profile*. Burlington VT: University of Vermont, Department of Psychiatry.

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA School-Age Forms & Profiles*. Burlington VT: University of Vermont, Research Center for Children, Youth and Families.

Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance B*, *111*, 209–219. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8661285

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system—A technical review. *NMR in Biomedicine*, *15*, 435–455. doi:10.1002/nbm.782

Cascio, C. J., Gerig, G., & Piven, J. (2007). Diffusion tensor imaging: Application to the study of the developing brain. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*, 213–223. doi:10.1097/01.chi.0000246064.93200.e8

Colman, I., Jones, P. B., Kuh, D., Weeks, M., Naicker, K., Richards, M., et al. (2014). Early development, stress and depression across the life course: Pathways to depression in a national British birth cohort. *Psychological Medicine*, *44*, 2845–2854. doi:10.1017/S0033291714000385

Diggle, P. (2002). *Analysis of longitudinal data* (2nd ed.). Oxford: Oxford University Press.

Ducharme, S., Albaugh, M. D., Hudziak, J. J., Botteron, K. N., Nguyen, T. V., Truong, C., et al. (2014). Anxious/depressed symptoms are linked to right ventromedial prefrontal cortical thickness maturation in healthy children and young adults. *Cerebral Cortex*, *24*, 2941–2950. doi:10.1093/cercor/bht151

Ducharme, S., Hudziak, J., Botteron, K., Albaugh, M., Nguyen, T., Karama, S., et al. (2012). Decreased regional cortical thickness and thinning rate are associated with inattention symptoms in healthy children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*, 18–27.

Evans, A. C. (2006). The NIH MRI study of normal brain development. *NeuroImage*, *30*, 184–202. doi:10.1016/j.neuroimage.2005.09.068

Giedd, J. N., Lenroot, R. K., Shaw, P., Lalonde, F., Celano, M., White, S., et al. (2008). Trajectories of anatomic brain development as a phenotype. *Novartis Foundation Symposium Journal*, *289*, 101–112; discussion 112–108, 193–105. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18497098

Hudziak, J. J., Achenbach, T. M., Althoff, R. R., & Pine, D. S. (2007). A dimensional approach to developmental psychopathology. *International Journal of Methods in Psychiatric Research*, *16*(Suppl. 1), S16–S23. doi:10.1002/mpr.217

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., et al. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*, 748–751. doi:10.1176/appi.ajp.2010.09091379

Kim, M. J., & Whalen, P. J. (2009). The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. *Journal of Neuroscience*, *29*, 11614–11618. doi:10.1523/jneurosci.2335-09.2009

Kochunov, P., Glahn, D. C., Lancaster, J., Thompson, P. M., Kochunov, V., Rogers, B., et al. (2011). Fractional anisotropy of cerebral white matter and thickness of cortical gray matter across the lifespan. *NeuroImage*, *58*, 41–49. doi:10.1016/j.neuroimage.2011.05.050

Lai, C. H., & Wu, Y. T. (2014). Alterations in white matter micro-integrity of the superior longitudinal fasciculus and anterior thalamic radiation of young adult patients with depression. *Psychological Medicine*, *44*, 2825–2832. doi:10.1017/S0033291714000440

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. doi:10.1016/j.neuroimage.2011.11.094

Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *NeuroImage*, *40*, 1044–1055. doi:10.1016/j.neuroimage.2007.12.053

Mabbott, D. J., Noseworthy, M., Bouffet, E., Laughlin, S., & Rockel, C. (2006). White matter growth as a mechanism of cognitive development in children. *NeuroImage*, *33*, 936–946. doi:10.1016/j.neuroimage.2006.07.024

Makris, N., Worth, A. J., Sorensen, A. G., Papadimitriou, G. M., Wu, O., Reese, T. G., et al. (1997). Morphometry of in vivo human white matter association pathways with diffusion-weighted magnetic resonance imaging. *Annals of Neurology*, *42*, 951–962. doi:10.1002/ana.410420617

Mukherjee, P., Miller, J. H., Shimony, J. S., Conturo, T. E., Lee, B. C., Almli, C. R., et al. (2001). Normal brain maturation during childhood: Developmental trends characterized with diffusion-tensor MR imaging. *Radiology*, *221*, 349–358. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11687675

Murphy, M. L., & Frodl, T. (2011). Meta-analysis of diffusion tensor imaging studies shows altered fractional anisotropy occurring in distinct brain areas in association with depression. *Biology of Mood and Anxiety Disorders*, *1*, 3. doi:10.1186/2045-5380-1-3

Newman, E., Thompson, W. K., Bartsch, H., Hagler, D. J. Jr., Chen, C. H., Brown, T. T., et al. (2015). Anxiety is related to indices of cortical maturation in typically developing children and adolescents. *Brain Structure and Function*. Advance online publication. doi:10.1007/s00429-015-1085-9

Ni, H., Kavcic, V., Zhu, T., Ekholm, S., & Zhong, J. (2006). Effects of number of diffusion gradient directions on derived diffusion tensor imaging indices in human brain. *American Journal of Neuroradiology*, *27*, 1776–1781. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16971635

North, C. R., Wild, T. C., Zwaigenbaum, L., & Colman, I. (2013). Early neurodevelopment and self-reported adolescent symptoms of depression and anxiety in a National Canadian Cohort Study. *PLOS ONE*, *8*, e56804. doi:10.1371/journal.pone.0056804

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron*, *43*, 897–905. doi:10.1016/j.neuron.2004.08.042

Pierpaoli, C., Jezzard, P., Basser, P. J., Barnett, A., & Di Chiro, G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology*, *201*, 637–648. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8939209

Pierpaoli, C., Walker, L., Irfanoglu, M. O., Barnett, A., Basser, P., Chang, L.-C., et al. (2010). *TORTOISE: An integrated software package for processing of diffusion MRI data*. Paper presented at the ISMRM 18th annual meeting, Stockholm.

Quirk, G. J., & Beer, J. S. (2006). Prefrontal involvement in the regulation of emotion: Convergence of rat and human studies. *Current Opinion in Neurobiology*, *16*, 723–727. doi:10.1016/j.conb.2006.07.004

Quirk, G. J., Garcia, R., & Gonzalez-Lima, F. (2006). Prefrontal mechanisms in extinction of conditioned fear. *Biological Psychiatry*, *60*, 337–343. doi:10.1016/j.biopsych.2006.03.010

Quirk, G. J., Likhtik, E., Pelletier, J. G., & Pare, D. (2003). Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *Journal of Neuroscience*, *23*, 8800–8807. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14507980

Rohde, G. K., Barnett, A. S., Basser, P. J., Marenco, S., & Pierpaoli, C. (2004). Comprehensive approach for correction of motion and distortion in diffusion-weighted MRI. *Magnetic Resonance in Medicine*, *51*, 103–114. doi:10.1002/mrm.10677

Rueckert, D., Sonoda, L. I., Hayes, C., Hill, D. L., Leach, M. O., & Hawkes, D. J. (1999). Nonrigid registration using free-form deformations: Application to breast MR images. *IEEE Transactions on Medical Imaging*, *18*, 712–721. doi:10.1109/42.796284

Schmithorst, V. J., Wilke, M., Dardzinski, B. J., & Holland, S. K. (2002). Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: A cross-sectional diffusion-tensor MR imaging study. *Radiology*, *222*, 212–218. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11756728

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D., et al. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences*, *104*, 19649–19654. doi:10.1073/pnas.0707741104

Shaw, P., Gilliam, M., Liverpool, M., Weddle, C., Malek, M., Sharp, W., et al. (2011). Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: Support for a dimensional view of attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *168*, 143–151. doi:10.1176/appi.ajp.2010.10030385

Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N., et al. (2006). Intellectual ability and cortical development in children and adolescents. *Nature*, *440*, 676–679.

Singer, J. D., & Willett, J. B. (2003). *Applied longitudinal data analysis: Modeling change and event occurrence*. Oxford: Oxford University Press.

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., et al. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, *31*, 1487–1505. doi:10.1016/j.neuroimage.2006.02.024

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(Suppl. 1), S208–S219. doi:10.1016/j.neuroimage.2004.07.051

Snook, L., Paulson, L. A., Roy, D., Phillips, L., & Beaulieu, C. (2005). Diffusion tensor imaging of neurodevelopment in children and young adults. *NeuroImage*, *26*, 1164–1173. doi:10.1016/j.neuroimage.2005.03.016

Takao, H., Hayashi, N., Inano, S., & Ohtomo, K. (2011). Effect of head size on diffusion tensor imaging. *NeuroImage*, *57*, 958–967. doi:10.1016/j.neuroimage.2011.05.019

Waber, D. P., De Moor, C., Forbes, P. W., Almli, C. R., Botteron, K. N., Leonard, G., et al. (2007). The NIH MRI study of normal brain development: Performance of a population based sample of healthy children aged 6 to 18 years on a neuropsychological battery. *Journal of the International Neuropsychology Society*, *13*, 729–746. doi:10.1017/S1355617707070841

Walker, L., Chang, L. C., Nayak, A., Irfanoglu, M. O., Botteron, K. N., McCracken, J., et al. (2015). The diffusion tensor imaging (DTI) component of the NIH MRI study of normal brain development (PedsDTI). *NeuroImage*. Advance online publication. doi:10.1016/j.neuroimage.2015.05.083

Walker, L., Chang, L. C., Nayak, A., Irfanoglu, M. O., Botteron, K. N., McCracken, J., et al. (2016). The diffusion tensor imaging (DTI) component of the NIH MRI study of normal brain development (PedsDTI). *NeuroImage*, *124*(Pt. B), 1125–1130. doi:10.1016/j.neuroimage.2015.05.083

Walker, L., Curry, M., Nayak, A., Lange, N., & Pierpaoli, C. (2013). A framework for the analysis of phantom data in multicenter diffusion tensor imaging studies. *Human Brain Mapping*, *34*, 2439–2454. doi:10.1002/hbm.22081

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. *Archives of General Psychiatry*, *68*, 369–377. doi:10.1001/archgenpsychiatry.2011.2468/4/369

Wu, M., Chang, L. C., Walker, L., Lemaitre, H., Barnett, A. S., Marenco, S., et al. (2008). Comparison of EPI distortion correction methods in diffusion tensor MRI using a novel framework. *Medical Image Computing and Computer-Assisted Intervention*, *11*(Pt. 2), 321–329. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18982621