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Resilience to Risk for Psychopathology: The Role of White Matter Microstructural Development in Adolescence

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ABSTRACT

BACKGROUND: One major risk factor for the development of psychopathology is a family history of psychopathology (FHP). Cross-sectional studies have shown that FHP is associated with alterations in white matter microstructure in adolescents without current psychopathology; however, whether these associations persist throughout adolescence, particularly in those who remain resilient to developing psychopathology, is unclear.

METHODS: Sixty-six adolescents underwent diffusion-weighted imaging at baseline (12–16 years of age) and at one or two follow-up visits (142 total scans). Adolescents' parents completed a modified Family History Assessment Module to calculate FHP density (FHPD) based on familial alcohol use, substance use, and major depressive, generalized anxiety, substance-induced mood, and antisocial personality disorders. The relationship between FHPD and white matter microstructural development was examined using multilevel modeling.

RESULTS: FHPD was associated with significant alterations in white matter microstructure at baseline; in the bilateral superior corona radiata and left superior longitudinal fasciculus, these effects were transient (FHPD was associated with altered white matter microstructure only in early adolescence), while effects in the posterior limb of the internal capsule were persistent. Associations between FHPD and white matter microstructure in the body of the corpus callosum emerged later in adolescence.

CONCLUSIONS: This prospective, longitudinal study provides novel information indicating that the association between FHP and white matter microstructure previously observed in adolescents is transient in most regions but may persist into late adolescence in other regions, despite current resilience to developing psychopathology. Future studies are necessary to determine if these persistent alterations are associated with onset of psychopathology later in life.

Keywords: Adolescence, Family history, Fractional anisotropy, Longitudinal, MRI, Psychopathology

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Adolescence is marked by more frequent emergence of psychopathology (particularly anxiety, mood, behavioral, and substance use disorders) than in adulthood, with half of lifetime cases of psychopathology beginning by 14 years of age, and three quarters by 24 years of age (1). A national survey of over 10,000 adolescents (13–18 years of age) noted that 12% of teens experience a major depressive episode, 32% an anxiety disorder, 22% a behavioral disorder (including oppositional defiant and conduct disorders), and 11% a substance abuse disorder (2). Given the prevalence of these developmental psychopathologies in adolescence, investigations into risk markers of emergent psychopathology during this time are important for targeted prevention efforts.

One significant risk factor for developing psychopathology is the presence of family history of psychopathology (FHP). Having familial history of major depressive, anxiety, alcohol use, or substance use disorder is associated with a two- to fivefold increase in developing that disorder (3–6). A familial history of one disorder may also increase risk for developing other disorders. For example, familial alcohol use disorder is associated with an increased risk for antisocial personality, anxiety, mood, and other substance use disorders (6). With such high comorbidity, it has been suggested that FHP is a nonspecific predictor of adolescent psychopathology (7).

Neuroimaging studies have attempted to identify neural biomarkers of FHP in adolescents free from psychopathology. Markers of typical neurodevelopment in adolescence include widespread increases in fractional anisotropy (FA) and decreases in mean diffusivity (MD), measures of white matter microstructure, with age (8–11). Greater FA and lower MD during adolescence has been associated with developing executive functioning, including lower impulsivity (12), greater inhibitory control (13), and greater working memory capacity (14). Previous studies have demonstrated that adolescents with family history of depression (15), alcoholism (16), and substance use (17) have lower FA than those without family

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history, in regions of the brain associated with maturation of these executive functions (12–14). However, these cross-sectional studies fail to examine the persistence of these microstructural differences in adolescents who remain free of psychopathology (i.e., are currently displaying resilience to the increased risk). That is, it is possible that at-risk adolescents who do not develop psychopathology may demonstrate maturation of white matter microstructure to the point where FHP is no longer associated with neurobiological alterations. Such a finding would provide neurobiological support for studies that have identified protective factors associated with resilience to risk of developing psychopathology in adolescence [e.g., (18)], and those that suggest that a higher degree of FHP is associated with greater executive control in adolescents who remain resilient [e.g., (19)].

This study examined the development of FA and MD in adolescents with varying degrees of FHP, including alcohol use, substance use, and major depressive, anxiety, substance-induced mood, and antisocial personality disorders (all psychopathologies that often emerge during adolescence). Previous neuroimaging studies have grouped participants based on psychopathology for a single disorder and compared them with those without FHP. However, the degree of comorbidity of familial disorders in these studies is unclear. Further, convergent neurobiological findings in studies assessing the effects of FHP (15–17) may suggest FHP as a nonspecific predictor of white matter microstructural alterations. While previous studies in adults have demonstrated utility of a combined FHP measure [e.g., (20)], this has yet to be applied to studies of neurodevelopment. Thus, to improve effect sizes, power, and measurement reliability (21), and to investigate the nonspecific effects of FHP, the current study utilized a combined, continuous FHP density (FHPD), based on the number and degree of relatives with one or more disorders. This, in conjunction with the multilevel modeling framework, allowed for the investigation of both transient and persistent associations between FHPD and white matter microstructural development during adolescence. Based on previous findings, we hypothesized widespread reductions in FA with increased FHPD, particularly in the superior corona radiata, cingulum, and superior longitudinal fasciculus, regions of convergence between multiple studies of familial psychopathology (15–17). Further, as previous studies suggest that a greater degree of FHPD is associated with behavioral improvements in those that remain resilient (19), we hypothesized that the association between FHPD and FA would dissipate with age, as adolescents continue to remain free of personal psychopathology.

METHODS AND MATERIALS

Participants

Recruitment and Exclusionary Criteria. Healthy adolescents, 12 to 16 years of age at baseline (n = 66), were recruited from the local community as part of an ongoing longitudinal study on neurodevelopment (22,23), approved by the Oregon Health & Science University Institutional Review Board. Adolescents and their parents provided written assent and consent, respectively, followed by a comprehensive screening interview to determine study eligibility (see Supplement for details).

Family History Assessment. The Family History Assessment Module (24) was used to calculate a family history density for the following disorders: alcohol use, substance use, generalized anxiety, major depressive, substance-induced mood, and antisocial personality. These densities were based on the number of adolescents' relatives with the respective disorder(s); parents contributed 0.5 each, grandparents 0.25 each, and aunts and uncles a weighted ratio of 0.25 divided by the number of their siblings, with higher densities indicating greater prevalence of familial history. Family history densities for the six disorders were combined to create an FHPD.

Participant Characteristics. Additional demographic information, including socioeconomic status and general intelligence (IQ), were also obtained during baseline sessions (see Supplement for details).

Follow-ups and Assessment for Personal Psychopathology. Following recruitment and collection of baseline neuroimaging measures (see below), quarterly follow-up phone interviews were conducted with youths to assess substance use [90-day Timeline Followback (25)]. Additionally, the Diagnostic Interview Schedule for Children (DISC) Predictive Scales (26) was administered yearly to screen symptoms of psychopathology using the following subscales: social phobia, separation anxiety disorder, agoraphobia, panic attacks, generalized anxiety disorder, obsessive-compulsive disorder, eating disorder, major depressive disorder, mania/hypomania, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder. Individuals that exceeded diagnosis cutoffs on the DISC Predictive Scales completed the National Institute of Mental Health DISC to confirm diagnosis (26). To investigate the association between FHPD and white matter microstructural development, without the confound of personal psychopathology, this study included only adolescents who remained free of current and past positive diagnosis on the DISC and/or the DISC Predictive Scales and remained largely drug and alcohol-naïve (not exceeding initial eligibility thresholds—see Supplement for details). Furthermore, adolescents completed one or two additional imaging sessions at varying intervals, 1 to 6 years after baseline, resulting in a total of 142 neuroimaging visits (Supplemental Figure S1).

Image Acquisition

During all visits, participants were scanned on a 3T Siemens MAGNETOM Tim Trio (Siemens, Erlangen, Germany) with a 12-channel head coil. Diffusion-weighted images (DWIs) were collected using a whole-brain, high-angular resolution, echo-planar imaging sequence (repetition time = 9100 ms, echo time = 88 ms, field of view = 256 mm^2, slices = 72, slice thickness = 2 mm). Gradient encoding pulses were applied in 30 directions (b-value = 1000 s/mm^2), with six additional images collected with a b-value of 0 s/mm^2. Participants received either three (n = 99; scan time = 16 minutes 52 seconds) or two (n = 43; scan time = 11 minutes 24 seconds) identical DWI runs during each imaging session. A diffusion field map was also acquired (repetition time = 790 ms, echo time 1 = 5.19 ms, echo time 2 = 7.65 ms, flip angle = 6°, field of view = 240 mm^2, slices = 72, slice thickness = 2 mm, scan time = 3 minutes 13 seconds) to correct DWIs for eddy current–induced field distortions.

Image Processing

Quality Assessment and Volume Censoring. Before image processing, all DWI runs underwent strict visual inspection for motion and scanner-related artifacts (27). Briefly, for each run, all 36 volumes were examined and classified into one of three categories based on the number of volumes containing artifact: 1) poor if seven or more volumes (>20%) contained artifact; 2) good if one to six volumes contained artifact; and 3) excellent if no volumes contain artifacts. Furthermore, four image quality assurance metrics (temporal signal-to-noise ratio, mean voxel outlier count, maximum voxel outlier count, and mean relative motion) were obtained for each DWI run. The number of runs classified into these three categories was in line with previous studies (27), and quality assurance metrics were shown to differ significantly between all three categories of data quality (see Supplement and Supplemental Table S1). As inclusion of poor data has been shown to result in significantly altered diffusion metrics (27), volumes deemed to contain motion or scanner-related artifact were censored for subjects with good and poor data, however; if the same direction or volume was removed from all DWI runs within a single imaging session, that entire scan was excluded from further analyses (see Supplement for details). Based on this procedure, 10 scans were excluded, resulting in a final sample of 65 individuals with 132 total scans. While volume censoring resulted in the improvement of several quality assurance measures, these measures were also associated with both age and sex (see Supplement for details), and thus were tested as covariates in post hoc analyses.

Diffusion Metrics. DWI processing used a combination of FSL (version 5.0.9) and AFNI (version 17.1.03), and included correction for eddy current distortion, intensity inhomogeneities, head motion, and subsequent adjustment of the gradient table. After identifying the eigenvalues of each diffusion tensor ($\lambda1$, $\lambda2$, $\lambda3$) for every voxel, these eigenvalues were used to calculate the following diffusion metrics: FA, MD, radial diffusivity (RD), and axial diffusivity (AD) (see Supplement for more details).

Image Registration. Advanced Normalization Tools algorithms (28) were used to register participants' FA maps to standard space, before group-level analysis, using procedures outlined previously (29). Following data erosion, all FA maps for an individual subject were registered to an unbiased within-subject template (30). Then, a study-specific template was created using the within-subject templates of all individuals and transformed to Montreal Neurological Institute space. Finally, a Gaussian blur (sigma = 1 mm) was applied to all FA images (31). MD, AD, and RD maps were registered to standard space using the same procedure (see Supplement for details).

Group-Level Analyses

Voxelwise analyses were carried out for FA and MD using AFNI's 3dLME (32), and were fit using maximum likelihood estimation, to allow for direct comparison, in a voxelwise manner, of models with different fixed effects structures (33). The following four models were tested within the entire white matter mask (mean FA >0.3): intercept-only (FA/MD ~ 1), linear growth (FA/MD ~ Age), main effects (FA/MD ~ Age + FHPD), and interaction (FA/MD ~ Age × FHPD). The latter two models allowed for identification of separate regions where there were either transient (interaction model) or persistent (main-effects model) associations between FA/MD and FHPD, respectively (see Supplement for details).

To compare the overall fit of these models, a deviance map was created using the log-likelihood values, estimated voxelwise for each model, based on the following equation: deviance = $-2 \times$ (log likelihood$_{\text{current model}}$ – log likelihood$_{\text{saturated model}}$). A voxelwise threshold ($p < .05$) was then applied to these deviance maps using the χ^2 and degrees-of-freedom difference between the two models (33). To correct for multiple comparisons, AFNI's 3dClustsim (34) was employed using the spatial autocorrelation function parameters (35) obtained from the residuals of the current model ($\alpha < .05$). First, we identified brain regions where FA/MD showed significant development with age by comparing the fit of the intercept-only model and the linear growth model (voxel $\chi^2_1 > 3.841$; FA cluster size >1424 voxels, MD cluster size >1775). Next, to address our hypothesis, that the association between FHPD and FA/MD is transient and dissipates with age, we compared the linear growth model to the interaction model (voxel $\chi^2_2 > 5.991$; FA cluster size >1440 voxels, MD cluster size >1750). Finally, to account for the fact that FHPD may be persistently associated with FA/MD across adolescence, despite current resilience to psychopathology, we compared the linear growth model to the main-effects model (voxel $\chi^2_1 > 3.841$; FA cluster size >1437 voxels, MD cluster size >1714).

By comparing a taxonomy of models, we ensured that our final fixed effects were interpreted only in regions of the brain where the final model(s) serve as the best-fitting model when compared with a reduced model (i.e., linear growth model) and null model (intercept-only model). This method is statistically superior to previous developmental imaging studies, which simply interpret the fixed effects of whole-brain multilevel models, without comparing them with a potentially more parsimonious, alternative, or null model, a practice that has been traditionally discouraged in multilevel modeling approaches (33,36). All post hoc analyses were carried out using R version 3.4.2 (R Development Core Team, Vienna, Austria), and included assessment of AD [diffusion along the primary eigenvector, thought to be a measure of axonal integrity (37)] and RD (diffusion along the secondary, or perpendicular eigenvectors, thought to be a measure of myelin integrity) in all significant clusters, as well as the inclusion of sex and QA measures as covariates, when necessary (see Supplement for details).

RESULTS

Participant Characteristics

The final DWI sample consisted of 65 adolescents (Table 1) with a high comorbidity of familial disorders (75% of individuals had a family history of ≥2 disorders) and FHPD that ranged from 0 to 6.75 (Table 1 and Supplemental Figure S2). FHPD (as well as family history density for each individual disorder) did not correlate with socioeconomic status or IQ, did not differ significantly between male and female adolescents or individuals with and without subclinical levels of psychopathology, and did not vary as a function of age.

FA/MD Development (FA/MD ∼ Age)

There was a single widespread cluster of 277,098 voxels (Figure 1A, violet) for FA, and 302,863 voxels (Figure 2A, violet) for MD, where a linear growth model provided a significantly better fit than an intercept-only model. In these regions, there was a significant increase in FA ($B = 0.007$, $\beta = .676$, $p < .001$) and decline in MD ($B = -4.44 \times 10^{-6}$, $\beta = -.405$, $p < .001$) with age. Underlying these changes were significant declines in both AD and RD with age (see Supplement for details).

Transient and Emergent Associations Between FHPD and FA/MD Development (FA/MD ∼ FHPD × Age)

The interaction models proved to be the best fitting model in several regions (Tables 2 and 3). In the left superior corona radiata (SCR) (Figure 1A, green; 2369 voxels), right SCR (Figure 1A, blue; 1639 voxels), and left superior longitudinal fasciculus (SLF) (Figure 1A, orange; 1800 voxels), greater FHPD was associated with lower FA at baseline (14 years of age [all $B \geq -0.004$, $\beta \geq -.297$, $p < .05$]), but greater increases in FA with age (all $B = 0.002$, $\beta \geq .139$, $p < .01$), resulting in no association between FHPD and FA by 18 years of age (Figure 1B–D). Greater FHPD was also associated with lower AD and greater RD at baseline as well as less significant declines in AD and greater declines in RD, with age, in these regions (see Supplement and Supplemental Tables S3 and S5). In the right SCR (Figure 2A, orange; 3939 voxels), greater FHPD was associated with lower MD at baseline (14 years of age [$B = -6.71 \times 10^{-6}$, $\beta = -.444$, $p < .001$]), but less significant declines in MD with age ($B = 2.30 \times 10^{-6}$, $\beta = .280$, $p < .001$), resulting in no association between FHPD and MD by 18 years of age (Figure 2B). In this region, FHPD was also associated with lower AD at baseline and less significant declines in AD and RD with age (see Supplement and Supplemental Tables S4 and S6). Last, in the body of the corpus callosum (bCC) (Figure 2A, red; 2649 voxels), FHPD was not associated with MD at baseline, but higher FHPD was associated with less significant increases in MD with age ($B = -6.70 \times 10^{-6}$, $\beta = -.160$, $p < .01$), such that by 18 years of age, greater FHPD was associated with lower MD ($B = -3.77 \times 10^{-5}$, $\beta = -.488$, $p < .001$) (Figure 2C). In this region, greater FHPD was also associated with less significant increases in AD and RD with age (see Supplement and Supplemental Tables S4 and S6).

Table 1. Participant Characteristics

Characteristic	Value
Sex, Male/Female	32/33
Ethnicity	
American Indian/Alaskan Native	1
Asian	2
Hispanic/Latino (of any race)	4
White	51
More than one race	7
IQ	111.03 ± 9.73
Socioeconomic Status	30.48 ± 13.74
Family History Assessment Module Densities	
Family history of psychopathology	1.33 ± 1.31
Alcohol use disorder	0.44 ± 0.36
Substance use disorder	0.21 ± 0.32
Major depressive disorder	0.36 ± 0.41
Generalized anxiety disorer	0.20 ± 0.36
Substance-induced mood disorder	0.05 ± 0.19
Antisocial personality disorder	0.06 ± 0.17

Values are *n* or mean ± SD. Socioeconomic status was measured using the Hollingshead Index of Social Position, and IQ was measured using the Wechsler Abbreviated Scale of Intelligence (see Supplement).

Persistent Associations Between FHPD and FA/MD Development (FA/MD ∼ FHPD + Age)

The main-effects model proved to be the best-fitting model in only one region (Table 2). In the posterior limb of the left internal capsule (PIC) (2328 voxels) (Figure 2A, red), greater FHPD was associated with lower FA ($B = -0.008$, $\beta = -.313$, $p < .001$), and lower AD and greater RD (see Supplement and Supplemental Tables S3 and S5), throughout adolescence (Figure 2E).

Additional Covariates

DWI quality assurance metrics were not associated with FA or MD, and did not result in significant model improvement, with one exception: lower temporal signal-to-noise ratio was associated with greater MD in the bCC. Furthermore, when sex was included as a predictor, results demonstrated sex-specific effects in the development of MD, but not associations with FHPD (see Supplement and Supplemental Tables S2).

DISCUSSION

The goal of this study was to investigate both transient and persistent associations between FHP and the development of white matter microstructure in adolescence. To our knowledge, this is the first study to use both a nonspecific measure of FHP and longitudinal statistical modeling to look at the association between degree of FHP and white matter microstructural development. Further, this study utilized a unique sample of individuals—those who have no psychopathology despite FHP risk. Our findings largely demonstrate transient associations between FHPD and white matter microstructural development in those who remain resilient to the increased risk of FHP on the emergence of personal psychopathology during adolescence.

As hypothesized, in the left and right SCR, and the SLF, adolescents with a higher FHPD demonstrated alterations in white matter microstructure (lower FA, MD, and AD and greater RD) at baseline, but greater changes with age, such that the effect of FHPD was nonsignificant by 18 years of age. This finding agrees with previous cross-sectional reports of lower FA in the SCR and SLF in early adolescence in

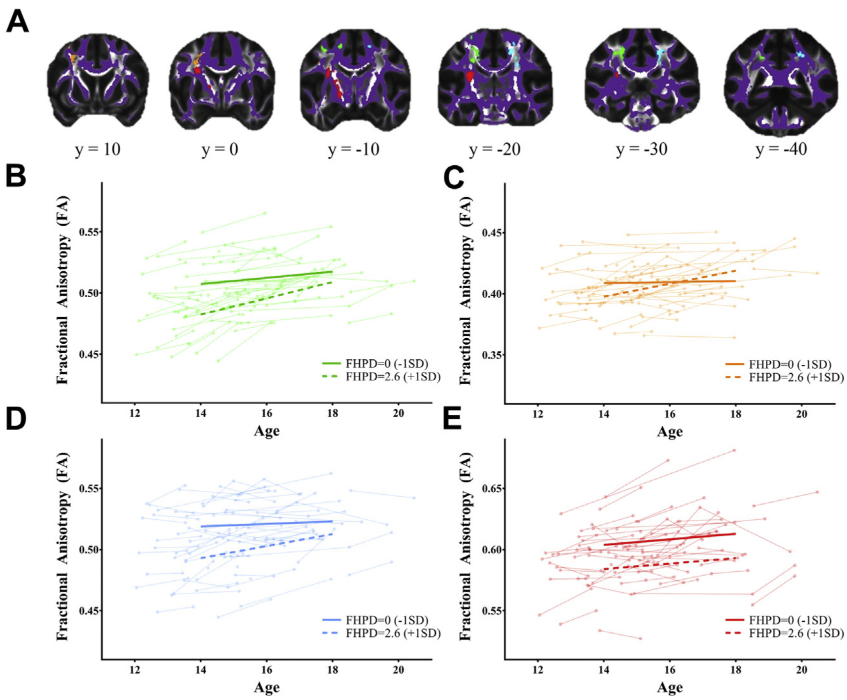

Figure 1. Regions showing significant effects of age and family history of psychopathology density (FHPD) on the development of fractional anisotropy (FA). **(A)** There was a single widespread cluster (violet) where the linear age model provided the best-fitting model; three clusters in the left superior corona radiata (green), superior longitudinal fasciculus (orange), and right superior corona radiata (blue) where a model including the interaction between FHPD and age provided the best fitting model; and one cluster in the left posterior limb of the internal capsule (red) where a model including only the main effects of age and FHPD resulted in the best-fitting model. **(B–E)** Lines for a prototypical individual falling 1 SD above (FHPD = 2.6) and below (FHPD = 0) the group mean for FHPD are overlaid on top of individual measures of FA in all regions where FHPD was significantly associated with FA.

those with a family history of substance use (12.9 ± 1.0 years) (17) and alcoholism (11–15 years of age) (16), and extends these findings by demonstrating that with age these associations dissipate. Lower FA and AD in the SCR and SLF has been associated with various psychopathologies during adolescence, including conduct disorder (38,39), depression (40), and substance use (41), and has also been associated with poor inhibitory control (13,42), a behavioral feature of many types of psychopathology (43–45). This suggests that while a reduction in FA or AD is associated with greater FHPD, as well as with psychopathology, adolescents who remain resilient to this increased risk show marked improvements in white matter microstructural development with age, potentially closing this vulnerable window. Further, though the association between greater FHPD and reduced MD at baseline in the SCR is surprising, as lower MD is often thought to reflect greater overall maturation, it was also accompanied by lower AD (diffusion along the primary eigenvalue), which may suggest the potential presence of additional crossing fibers in those with higher FHPD. While the presence of crossing fibers at the intersection of the SCR and the corpus callosum has been demonstrated (46), diffusion tractography will be necessary to explore this finding further.

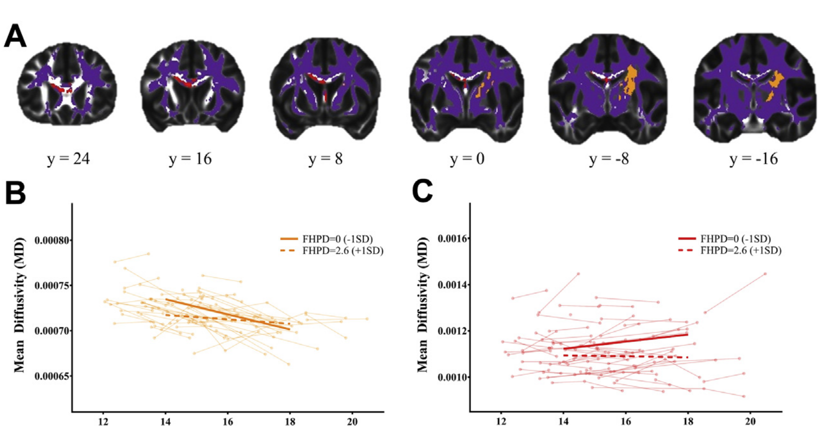

Figure 2. Regions showing significant effects of age and family history of psychopathology density (FHPD) on the development of mean diffusivity (MD). **(A)** There was a single widespread cluster (violet) where the linear age model provided the best fitting model, and two clusters in the right superior corona radiata (orange) and body of the corpus callosum (red) where a model including the interaction between FHPD and age provided the best-fitting model. **(B, C)** Lines for a prototypical individual falling one standard deviation above (FHPD = 2.6) and below (FHPD = 0) the group mean for FHPD are overlaid on top of individual measures of MD in all regions where FHPD was significantly associated with MD.

Table 2. Multilevel Model Parameter Estimates for FA

	Fixed Effect				Variance Component		Psuedo-R^2 Statistic			Goodness of Fit		
	Intercept	FHPD	Age	Age × FHPD	Residual	Intercept	Total	Error	Intercept	Deviance	AIC	BIC
Left Superior Corona Radiata/Precentral Gyrus/Postcentral Gyrus												
FA ∼ 1	0.501 (0.003)[c]				8.87×10^{-5}	4.61×10^{-4}				−699.7	−693.7	−685.1
FA ∼ Age	0.495 (0.003)[c]		0.004 (0.001)[c]		4.43×10^{-5}	4.65×10^{-4}	.087	.500		−748.7	−740.7	−729.1
FA ∼ Age + FHPD	0.504 (0.004)[c]	−0.006 (0.002)[b]	0.004 (0.001)[c]		4.44×10^{-5}	3.90×10^{-4}	.226	.499	.162	−759.9	−749.5	−735.1
FA ∼ Age × FHPD[d]	0.507 (0.004)[c]	−0.010 (0.002)[c]	0.003 (0.001)[c]	0.002 (4.35×10^{-4})[c]	3.50×10^{-5}	3.79×10^{-4}	.250	.605	.186	−772.2	−760.2	−742.9
Left Superior Longitudinal Fasciculus/Middle Frontal Gyrus White Matter												
FA ∼ 1	0.407 (0.002)[c]				5.39×10^{-5}	2.99×10^{-5}				−761.6	−755.6	−746.9
FA ∼ Age	0.404 (0.002)[c]		0.002 (4.90×10^{4})[c]		3.94×10^{-5}	2.84×10^{-4}	.090	.269		−787.4	−779.4	−767.8
FA ∼ Age + FHPD	0.405 (0.003)[c]	−0.001 (0.002)	0.003 (4.92×10^{4})[c]		3.94×10^{-5}	2.83×10^{-4}	.090	.270	.003	−787.6	−777.6	−763.2
FA ∼ Age × FHPD[d]	0.409 (0.004)[c]	−0.004 (0.002)[a]	0.001 (3.95×10^{-4})	0.002 (3.81×10^{-4})[b]	2.93×10^{-5}	2.78×10^{-4}	.130	.457	.019	−809.7	−797.7	−780.4
Right Superior Corona Radiata/Precentral Gyrus												
FA ∼ 1	0.510 (0.003)[c]				7.12×10^{-5}	5.91×10^{-4}				−700.5	−694.5	−685.9
FA ∼ Age	0.506 (0.003)[c]		0.003 (0.001)[c]		5.51×10^{-5}	5.74×10^{-4}	.054	.226		−720.5	−712.5	−701.0
FA ∼ Age + FHPD	0.516 (0.004)[c]	−0.007 (0.002)[b]	0.003 (0.001)[c]		5.52×10^{-5}	4.85×10^{-4}	.198	.225	.154	−730.7	−720.7	−706.3
FA ∼ Age × FHPD[d]	0.519 (0.004)[c]	−0.010 (0.002)[c]	0.001 (0.001)	0.002 (4.88×10^{-4})[b]	4.77×10^{-5}	4.95×10^{-4}	.181	.330	.137	−739.7	−727.7	−710.4
Left Posterior Limb of the Internal Capsule												
FA ∼ 1	0.598 (0.003)[c]				1.11×10^{-4}	4.67×10^{-4}				−682.7	−676.7	−668.1
FA ∼ Age	0.594 (0.003)[c]		0.004 (0.001)[c]		8.32×10^{-4}	4.54×10^{-4}	.062	.248		−705.4	−697.4	−685.8
FA ∼ Age + FHPD[d]	0.604 (0.004)[c]	−0.008 (0.002)[c]	0.004 (0.001)[c]		8.33×10^{-5}	3.55×10^{-4}	.239	.247	.217	−719.6	−709.6	−695.2
FA ∼ Age × FHPD	0.604 (0.004)[c]	−0.007 (0.002)[b]	0.004 (0.001)[c]	-1.11×10^{4} (6.02×10^{-4})	8.33×10^{-5}	3.55×10^{-4}	.239	.247	.218	−719.7	−707.7	−690.4

Values are presented as *B* (SE).

AIC, Akaike information criterion; BIC, Bayesian information criterion; FA, fractional anisotropy; FHPD, family history of psychopathology density.

[a] $p < .05$.

[b] $p < .01$.

[c] $p < .001$.

[d] The final, most parsimonious model.

Table 3. Multilevel Model Parameter Estimates for MD

	Fixed Effect				Variance Component		Psuedo-R^2 Statistic			Goodness of Fit		
	Intercept	FHPD	Age	Age × FHPD	Residual	Intercept	Total	Error	Intercept	Deviance	AIC	BIC
Right Superior Corona Radiata/Posterior Limb of the Internal Capsule												
MD ~ 1	7.19×10^{-4} (2.00×10^{-6})[c]				2.67×10^{-10}	1.23×10^{-10}				−2492.6	−2486.6	−2477.9
MD ~ Age	7.26×10^{-4} (2.17×10^{-6})[c]		-5.46×10^{-6} (8.28×10^{-7})[c]		1.75×10^{-10}	1.39×10^{-10}	.201	.345		−2529.2	−2521.2	−2509.7
MD ~ Age + FHPD	7.29×10^{-4} (2.83×10^{-6})[c]	-2.41×10^{-6} (1.42×10^{-6})	-5.35×10^{-6} (8.25×10^{-7})[c]		1.76×10^{-10}	1.28×10^{-10}	.227	.341	.079	−2532.1	−2522.1	−2507.7
MD ~ Age × FHPD[d]	7.35×10^{-4} (3.17×10^{-6})[c]	-6.71×10^{-6} (1.87×10^{-6})[c]	-8.37×10^{-6} (1.14×10^{-6})[c]	2.30×10^{-6} (6.49×10^{-7})[c]	1.49×10^{-10}	1.39×10^{-10}	.269	.442	.000	−2544.1	−2532.1	−2514.8
Body of the Corpus Callosum/Fornix												
MD ~ 1	0.001 (1.21×10^{-5})[c]				1.15×10^{-9}	8.82×10^{-9}				−2161.9	−2155.9	−2147.2
MD ~ Age	0.001 (1.27×10^{-5})[c]		7.21×10^{-6} (2.49×10^{-6})[b]		9.96×10^{-10}	9.17×10^{-9}	.010	.134		−2184.8	−2161.6	−2150.1
MD ~ Age + FHPD	0.001 (1.70×10^{-5})[c]	-2.34×10^{-5} (9.01×10^{-6})[a]	7.27×10^{-6} (2.49×10^{-6})[b]		9.96×10^{-10}	8.24×10^{-9}	.075	.134	.101	−2176.2	−2166.2	−2151.8
MD ~ Age × FHPD[d]	0.001 (1.73×10^{-5})[c]	-1.09×10^{-5} (9.67×10^{-6})	1.53×10^{-5} (3.45×10^{-6})[c]	-6.70×10^{-6} (2.10×10^{-6})[b]	8.97×10^{-10}	7.87×10^{-9}	.118	.220	.142	−2186.3	−2174.3	−2157.0

Values are presented as *B* (SE).

AIC, Akaike information criterion; BIC, Bayesian information criterion; FHPD, family history of psychopathology density; MD, mean diffusivity.

[a] $p < .05$.

[b] $p < .01$.

[c] $p < .001$.

[d] The final, most parsimonious model.

Further, we identified two regions that provide additional information about the association between FHPD and white matter microstructural development. In the left PIC, greater FHPD was associated with persistently lower FA and AD, and greater RD, throughout adolescence. This is consistent with previous cross-sectional findings that demonstrated lower FA in adolescents with a family history of alcoholism in anterior regions of the internal capsule (16), and suggests that these effects may extend posteriorly. Meanwhile, in the bCC, associations between FHPD and MD appear to manifest during adolescence, such that higher FHPD is associated with less change in MD (as well as in AD and RD) with age, with no association being observed at baseline. This finding also fits with prior research, which has demonstrated lower FA values in the corpus callosum of adults with a family history of substance use (17), with our findings suggesting that other white matter microstructural measurements may be similarly affected.

In adolescence, reduced FA in the PIC has been associated with depression (47), conduct disorder (38,48), generalized anxiety disorder (49), and substance use (50), and reduced RD and FA in the corpus callosum has been associated with conduct disorder (38) and depression (47). Additionally, lower FA in these regions has been associated with greater impulsivity (12) and poorer inhibition (51) during adolescence—again, behaviors that are often associated with various manifestations of psychopathology (43–45). Thus, it is possible that the emergent and persistent alterations in white matter microstructure observed in resilient adolescents indicate that some adolescents may emerge into psychopathology later in life. Consistent with this hypothesis, lower FA in the PIC has been associated with late- compared with early-onset depression in adults (52), while lower FA in the bCC has been observed in adults with late-onset panic disorder, when compared with control subjects (53). Our longitudinal findings extend these cross-sectional reports in adults and suggest that these white matter abnormalities may be present earlier in life. Additional time points are necessary to determine if adolescents in our sample develop psychopathology later in adulthood.

While our findings provide novel insight into the development white matter microstructure in adolescents with FHP, they are not without limitations. First, while all adolescents in this analysis currently remain free from personal psychopathology, this does not preclude the possibility that individuals might still develop psychopathology. In fact, some of our findings may suggest that our sample is particularly vulnerable to developing late-onset psychopathological disorders. Despite over half our sample's having reached late adolescence, this must be considered when weighing the long-term resilience of our sample. Similarly, without a full understanding of white matter development in individuals with personal psychopathology, it is unclear whether the transient effects observed would persist in individuals that do go on to develop psychopathology, although the large body of literature demonstrating white matter microstructural impairments in those with personal psychopathology, in regions found in this study, helps corroborate this conclusion (38–41,47–50). Second, while several studies suggest that FA and MD change nonlinearly across adolescence (9,54), with only two time points of neuroimaging data for most subjects we did not have power to model nonlinear changes. Third, given the sample size (particularly the low number of individuals with a family history of substance-induced mood and antisocial personality disorders), as well as the high degree of comorbidity of several familial disorders, we were not capable of looking at the effects of family history of individual disorders. Fourth, while greater FA and AD and lower MD and RD are considered to be markers of structural maturation during adolescence, it does not rule out the possibility that a portion of these microstructural alterations may be attributable to changes in crossing fiber tracts, which may cloud interpretation of our findings. Fifth, while age effects were robust (Figures 1 and 2) and similar to those in recent consortium-based studies (8), newer DWI sequences, capable of obtaining more accurate measures of white matter microstructure, will be necessary to confirm. Sixth, while previous studies suggest sex differences in the rate of white matter maturation (55), post hoc analyses failed to reveal any sex-specific associations with FHPD. Future studies, in a larger sample, will be necessary to model the three-way interaction among sex, age, and FHPD in a voxelwise manner. Last, the demographics of this sample (largely white non-Hispanic, with a high socioeconomic status and IQ) represent an unfortunate sampling bias, which has been recently shown to potentially confound developmental neuroimaging findings (56). Future studies will be necessary to confirm the generalizability of these findings to other demographics.

In conclusion, our findings extend previous cross-sectional studies demonstrating reduced FA in adolescents with FHP and suggest that many associations between FHP and white matter microstructure dissipate by late adolescence/early adulthood. These findings suggest that some of the protective factors previously associated with FHP (18,19) may be associated with underling structural improvements during this sensitive period of brain development. Further, we provide evidence that some of the microstructural features previously shown to be associated with late-onset psychopathology in adults may also be associated with FHP-related abnormalities in adolescents. Future studies will be necessary to confirm this notion; however, this provides encouraging information for those seeking to develop prevention strategies that may be best targeted toward adolescents, who are still undergoing continued neurodevelopment and are thus more amenable to intervention.

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REFERENCES

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE (2005): Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62:593–602.
2. Merikangas KR, He JP, Burstein M, Swanson SA, Avenevoli S, Cui L, *et al.* (2010): Lifetime Prevalence of Mental Disorders in U.S. Adolescents: Results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry 49:980–989.
3. Williamson DE, Birmaher B, Axelson DA, Ryan ND, Dahl RE (2004): First episode of depression in children at low and high familial risk for depression. J Am Acad Child Adolesc Psychiatry 43:291–297.
4. Merikangas KR, Dierker LC, Szatmari P (1998): Psychopathology among offspring of parents with substance abuse and/or anxiety disorders: A high-risk study. J Child Psychol Psychiatry 39:711–720.
5. Merikangas KR, Avenevoli S (2000): Implications of genetic epidemiology for the prevention of substance use disorders. Addict Behav 25:807–820.
6. Nurnberger JI Jr., Wiegand R, Bucholz K, O'Connor S, Meyer ET, Reich T, *et al.* (2004): A family study of alcohol dependence: Coaggregation of multiple disorders in relatives of alcohol-dependentprobands. Arch Gen Psychiatry 61:1246–1256.
7. McLaughlin KA, Gadermann AM, Hwang I, Sampson NA, Al-Hamzawi A, Andrade LH, *et al.* (2012): Parent psychopathology and offspring mental disorders: Results from the WHO World Mental Health Surveys. Br J Psychiatry 200:290–299.
8. Pfefferbaum A, Rohlfing T, Pohl KM, Lane B, Chu W, Kwon D, *et al.* (2016): Adolescent development of cortical and white matter structure in the NCANDA sample: Role of sex, ethnicity, puberty, and alcohol drinking. Cereb Cortex 26:4101–4121.
9. Lebel C, Beaulieu C (2011): Longitudinal development of human brain wiring continues from childhood into adulthood. J Neurosci 31:10937–10947.
10. Barnea-Goraly N, Menon V, Eckert M, Tamm L, Bammer R, Karchemskiy A, *et al.* (2005): White matter development during childhood and adolescence: A cross-sectional diffusion tensor imaging study. Cereb Cortex 15:1848–1854.
11. Giorgio A, Watkins KE, Chadwick M, James S, Winmill L, Douaud G, *et al.* (2010): Longitudinal changes in grey and white matter during adolescence. Neuroimage 49:94–103.
12. Olson EA, Collins PF, Hooper CJ, Muetzel R, Lim KO, Luciana M (2009): White matter integrity predicts delay discounting behavior in 9- to 23-year-olds: A diffusion tensor imaging study. J Cogn Neurosci 21:1406–1421.
13. Seghete KLM, Herting MM, Nagel BJ (2013): White matter microstructure correlates of inhibition and task-switching in adolescents. Brain Res 1527:15–28.
14. Nagy Z, Westerberg H, Klingberg T (2004): Maturation of white matter is associated with the development of cognitive functions during childhood. J Cogn Neurosci 16:1227–1233.
15. Huang H, Fan X, Williamson DE, Rao U (2011): White matter changes in healthy adolescents at familial risk for unipolar depression: A diffusion tensor imaging study. Neuropsychopharmacology 36:684–691.
16. Herting MM, Schwartz D, Mitchell SH, Nagel BJ (2010): Delay discounting behavior and white matter microstructure abnormalities in youth with a family history of alcoholism. Alcohol Clin Exp Res 34:1590–1602.
17. Acheson A, Wijtenburg SA, Rowland LM, Winkler AM, Gaston F, Mathias CW, *et al.* (2014): Assessment of whole brain white matter integrity in youths and young adults with a family history of substance-use disorders. Human Brain Mapp 35:5401–5413.
18. Collishaw S, Hammerton G, Mahedy L, Sellers R, Owen MJ, Craddock N, *et al.* (2016): Mental health resilience in the adolescent offspring of parents with depression: A prospective longitudinal study. Lancet Psychiatry 3:49–57.
19. Jones SA, Steele JS, Nagel BJ (2017): Binge drinking and family history of alcoholism are associated with an altered developmental trajectory of impulsive choice across adolescence. Addiction 112:1184–1192.
20. Finn PR, Sharkansky EJ, Viken R, West TL, Sandy J, Bufferd GM (1997): Heterogeneity in the families of sons of alcoholics: The impact of familial vulnerability type on offspring characteristics. J Abnorm Psychol 106:26.
21. MacCallum RC, Zhang S, Preacher KJ, Rucker DD (2002): On the practice of dichotomization of quantitative variables. Psychol Methods 7:19.
22. Cservenka A, Nagel BJ (2012): Risky decision-making: An FMRI study of youth at high risk for alcoholism. Alcohol Clin Exp Res 36:604–615.
23. Cservenka A, Casimo K, Fair DA, Nagel BJ (2014): Resting state functional connectivity of the nucleus accumbens in youth with a family history of alcoholism. Psychiatry research 221:210–219.
24. Rice JP, Reich T, Bucholz KK, Neuman RJ, Fishman R, Rochberg N, *et al.* (1995): Comparison of direct interview and family history diagnoses of alcohol dependence. Alcohol Clin Exp Res 19:1018–1023.
25. Sobell LC, Brown J, Leo GI, Sobell MB (1996): The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. Drug Alcohol Depend 42:49–54.
26. Lucas CP, Zhang H, Fisher PW, Shaffer D, Regier DA, Narrow WE, *et al.* (2001): The DISC Predictive Scales (DPS): Efficiently screening for diagnoses. J Am Acad Child Adolesc Psychiatry 40:443–449.
27. Roalf DR, Quarmley M, Elliott MA, Satterthwaite TD, Vandekar SN, Ruparel K, *et al.* (2016): The impact of quality assurance assessment on diffusion tensor imaging outcomes in a large-scale population-based cohort. Neuroimage 125:903–919.
28. Avants BB, Epstein CL, Grossman M, Gee JC (2008): Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. Med Image Anal 12:26–41.
29. Schwarz CG, Reid RI, Gunter JL, Senjem ML, Przybelski SA, Zuk SM, *et al.* (2014): Improved DTI registration allows voxel-based analysis that outperforms tract-based spatial statistics. Neuroimage 94:65–78.
30. Avants B, Gee JC (2004): Geodesic estimation for large deformation anatomical shape averaging and interpolation. Neuroimage 23:S139–S150.
31. Ashburner J, Friston KJ (2000): Voxel-based morphometry—The methods. Neuroimage 11:805–821.
32. Chen G, Saad ZS, Britton JC, Pine DS, Cox RW (2013): Linear mixed-effects modeling approach to FMRI group analysis. Neuroimage 73:176–190.
33. Singer JD, Willett JB (2003): Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. London: Oxford University Press.
34. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995): Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. Magn Reson Med 33:636–647.
35. Cox RW, Chen G, Glen DR, Reynolds RC, Taylor PA (2017): FMRI clustering in AFNI: False-positive rates redux. Brain Connect 7:152–171.
36. Bliese PD, Ployhart RE (2002): Growth modeling using random coefficient models: Model building, testing, and illustrations. Organ Res Methods 5:362–387.
37. Alexander AL, Lee JE, Lazar M, Field AS (2007): Diffusion tensor imaging of the brain. Neurotherapeutics 4:316–329.
38. Puzzo I, Seunarine K, Sully K, Darekar A, Clark C, Sonuga-Barke EJS, Fairchild G (2018): Altered white-matter microstructure in conduct

disorder is specifically associated with elevated callous-unemotional traits. J Abnorm Child Psychol 46:1451–1466.
39. Haney-Caron E, Caprihan A, Stevens MC (2014): DTI-measured white matter abnormalities in adolescents with conduct disorder. J Psychiatr Res 48:111–120.
40. LeWinn KZ, Connolly CG, Wu J, Drahos M, Hoeft F, Ho TC, *et al.* (2014): White matter correlates of adolescent depression: Structural evidence for frontolimbic disconnectivity. J Am Acad Child Asolesc Psychiatry 53:899–909, 909.e1-e7.
41. Jacobus J, McQueeny T, Bava S, Schweinsburg BC, Frank LR, Yang TT, *et al.* (2009): White matter integrity in adolescents with histories of marijuana use and binge drinking. Neurotoxicol Teratol 31:349–355.
42. Tamnes CK, Fjell AM, Westlye LT, Østby Y, Walhovd KB (2012): Becoming consistent: Developmental reductions in intraindividual variability in reaction time are related to white matter integrity. J Neurosci 32:972–982.
43. Nigg JT, Wong MM, Martel MM, Jester JM, Puttler LI, Glass JM, *et al.* (2006): Poor response inhibition as a predictor of problem drinking and illicit drug use in adolescents at risk for alcoholism and other substance use disorders. J Am Acad Child Adolesc Psychiatry 45:468–475.
44. Kyte ZA, Goodyer IM, Sahakian BJ (2005): Selected executive skills in adolescents with recent first episode major depression. J Child Psychol Psychiatry 46:995–1005.
45. Chamberlain SR, Derbyshire KL, Leppink EW, Grant JE (2016): Neurocognitive deficits associated with antisocial personality disorder in non-treatment-seeking young adults. J Am Acad Psychiatry Law 44:218–225.
46. Wiegell MR, Larsson HB, Wedeen VJ (2000): Fiber crossing in human brain depicted with diffusion tensor MR imaging. Radiology 217:897–903.
47. Bessette KL, Nave AM, Caprihan A, Stevens MC (2014): White matter abnormalities in adolescents with major depressive disorder. Brain Imaging Behav 8:531–541.
48. Sarkar S, Dell'Acqua F, Froudist Walsh S, Blackwood N, Scott S, Craig MC, *et al.* (2016): A whole-brain investigation of white matter microstructure in adolescents with conduct disorder. PLoS One 11:e0155475.
49. Liao M, Yang F, Zhang Y, He Z, Su L, Li L (2014): White matter abnormalities in adolescents with generalized anxiety disorder: A diffusion tensor imaging study. BMC Psychiatry 14:41.
50. Zorlu N, Angelique Di Biase M, Kalayci CC, Zalesky A, Bagci B, Oguz N, *et al.* (2016): Abnormal white matter integrity in synthetic cannabinoid users. Eur Neuropsychopharmacol 26:1818–1825.
51. Treit S, Chen Z, Rasmussen C, Beaulieu C (2014): White matter correlates of cognitive inhibition during development: A diffusion tensor imaging study. Neuroscience 276:87–97.
52. Cheng Y, Xu J, Yu H, Nie B, Li N, Luo C, *et al.* (2014): Delineation of early and later adult onset depression by diffusion tensor imaging. PLoS One 9:e112307.
53. Lai CH, Wu YT (2013): Fronto-occipital fasciculus, corpus callosum and superior longitudinal fasciculus tract alterations of first-episode, medication-naive and late-onset panic disorder patients. J Affect Disord 146:378–382.
54. 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.
55. Simmonds DJ, Hallquist MN, Asato M, Luna B (2014): Developmental stages and sex differences of white matter and behavioral development through adolescence: A longitudinal diffusion tensor imaging (DTI) study. Neuroimage 92:356–368.
56. LeWinn KZ, Sheridan MA, Keyes KM, Hamilton A, McLaughlin KA (2017): Sample composition alters associations between age and brain structure. Nat Commun 8:874.