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Assessment of whole brain white matter integrity in youths and young adults with a family history of substance use disorders

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Abstract

Individuals with a family history of substance use disorders (FH+) are at a greater risk of developing substance use disorders than their peers with no such family histories (FH−) and this vulnerability is proportional to the number of affected relatives (FH density). The risk for developing substance use disorders peaks during adolescence to early adulthood in the general population, and that is thought to be related to delayed maturation of frontocortical and frontostriatal functional circuits. We hypothesized that FH+ youth and young adults have impaired myelination of frontocortical and frontostriatal white matter tracts. We examined fractional anisotropy (FA) data in 80 FH+ and 34 FH− youths (12.9±1.0 years) and in 25 FH+ and 30 FH− young adults (24.3±3.4 years). FH+ youths had lower FA values in both frontocortical and frontostriatal tracts as well as parietocortical tracts including the anterior, superior and posterior corona radiata and the superior frontal-occipital fasciculus. Moreover, FA values in these tracts were negatively correlated with FH density. FH+ adults had lower FA values in two frontocortical tracts: the genu of the corpus callosum and anterior corona radiata and also significant negative correlations between FA and FH density in these same tracts. In both groups, lower FA values corresponded to higher radial diffusivity suggesting reduced axonal myelination. We interpreted

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our findings as evidence for impaired myelination of frontal white matter that was proportional to FH density. Our data suggest that deficits may partially resolve with age, paralleling an age-related decline in risk for developing substance use disorders.

Keywords

Frontal white matter; family history; risk; diffusion tensor imaging; substance use

Introduction

Youths and young adults with a family history of alcohol and/or other drug use disorders (FH+) are at a greater risk for developing substance use disorders compared to their peers with no such history (FH−) (Finn, et al., 1990; Lieb, et al., 2002; McCaul, et al., 1990; Merikangas, et al., 1998). Moreover, their risk of developing substance use disorders is proportional to the number of biological parents and grandparents with substance use disorders (FH density) (Dawson, et al., 1992; Stoltenberg, et al., 1998). This increased risk has a genetic basis as demonstrated by twin, adoption, cross-fostering, and pedigree analysis studies (Cloninger, et al., 1981; Merikangas, 1990; Reich, et al., 1998; Slutske, et al., 2002), and is associated with a phenotypic pattern of “behavioral undercontrol” characterized by increased sensation seeking, risk-taking, aggressiveness, and antisocial behaviors (Sher, et al., 2004; Sher and Trull, 1994; Tarter, et al., 2003). Likewise, FH+ individuals show deficits in executive functioning, impulse control, decision-making, and attention (Acheson, et al., 2011a; Acheson, et al., 2011b; Corral, et al., 2003; Deckel, 1999; Lovallo, et al., 2006; Stevens, et al., 2003) and altered activity in frontocortical and frontostriatal regions (Acheson, et al., 2009; Cservenka, et al., 2012; Glahn, et al., 2007; Heitzeg, et al., 2010; Schweinsburg, et al., 2004; Silveri, et al., 2011). These findings suggest FH+ individuals have impairments in frontocortical and frontostriatal functioning, although specific mechanisms underlying this impairment and as well as potential relationships to risk for substance use disorders remain elusive.

The risk of developing a substance use disorder in FH+ individuals peaks during adolescence and early adulthood, similar to trends observed in general population (McGorry, et al., 2011). It has been hypothesized that this increased vulnerability in adolescence and early adulthood in the general population is driven at least in part by the relatively slow maturation of frontocortical and frontostriatal tracts (Blakemore and Robbins, 2012; Ernst and Fudge, 2009; Somerville and Casey, 2010), which not reach peak myelination levels until an individual is in their 30’s or 40’s, compared to the motor and sensory tracts that reach peak maturity in their teens or early 20’s (Kochunov, et al., 2011b; Kochunov, et al., 2012; Sowell ER, et al., 2003; Westlye, et al., 2010). This delayed maturation of frontocortical and frontostriatal tracts is thought to lead to poor inhibition of reward-seeking and risk-taking behavior, including propensity towards problem substance use (Blakemore and Robbins, 2012; Ernst and Fudge, 2009; Somerville and Casey, 2010). Plausibly, individuals more prone towards engaging in problem substance use in adolescence and early adulthood may have even more delayed or impaired frontocortical and frontostriatal white matter development during this period.

It is therefore plausible that FH+ individuals have delayed or impaired development of frontocortical and frontostriatal white matter relative to their peers and this contributes to the propensity towards problem substance use and other excessive reward seeking and risk taking behaviors. Consistent with this hypothesis, FH+ adolescents appear to show reduced myelination of frontocortical and frontostriatal pathways compared to FH− adolescents (Herting, et al., 2010). However, this study had a small sample size (13 FH+ and 14 FH−) and was not sufficiently powered to examine additional relationships within the FH+ group, such as the impact of FH density. In addition, it is not clear whether FH+ related deficits in forebrain white matter persist past adolescence or are resolved during later development. To address these questions, we examined integrity of cerebral white matter in two large and well-characterized cohorts of FH+ youths and adults. These cohorts were collected as part of two independent study protocols and procedural differences prevented us from combing the cohorts. However, examining the two cohorts allows us to make initial observations about the possible course of FH+ related white matter deficits from preadolescence to early adulthood.

We estimated myelination levels using diffusion tensor imaging (DTI) to index fractional anisotropy (FA) of water diffusion. FA describes the directional selectivity of the random diffusion of water molecules (Basser, 1994; Conturo, et al., 1996; Pierpaoli and Basser, 1996; Ulug, et al., 1995). Higher FA values (maximum theoretical value is 1.0) are observed along heavily myelinated white matter tracts. The structure of the axonal cell membranes and myelin sheath hinders the diffusion of water molecules in all directions except along the fiber tract, therefore producing highly anisotropic water diffusion (Pierpaoli and Basser, 1996). The absolute white matter FA values are sensitive to a variety of parameters including regional myelination levels, the degree of intra-voxel fiber crossing, axonal density and average axonal diameter (Beaulieu, 2002). However, changes in regional FA values during normal maturation and aging are shown to be predominantly due to changes in axonal myelination and can therefore be used as indirect measurement of myelin level (Budde, et al., 2007; Madler, et al., 2008; Song, et al., 2003; Song, et al., 2005). Several recent studies used FA of cerebral white matter to study heterocronicity of cerebral myelination and showed that the FA values of frontocortical and frontostriatal white matter tracts increase rapidly during the adolescence and suggest their peak myelination level is not reached until the an individual is in their twenties or thirties (Hasan, et al., 2009a; Hasan, et al., 2009b; Kochunov, et al., 2011b; Kochunov, et al., 2012; McLaughlin, et al., 2007).

In the present study, we tested two hypotheses. First, we hypothesized that FH+ individuals have impaired myelination of frontocortical and frontostriatal axonal tracts, as evidenced by the lower FA values. Second, we hypothesized that the degree of deficit in white matter integrity would be proportional to the FH density. We compared FA values in both cohorts across fourteen major white tracts and specifically in frontocortical tracts such as the anterior corona radiata and frontostriatal tracts such as the superior frontooccipital fasciculus.

Methods

Overview

We examined whole brain DTI data from two independent cohorts of FH+ and FH− individuals. The first cohort consisted of preadolescent to early adolescent youths and the second cohort consisted of young adults. Imaging data for both cohorts were collected using the same scanner and RF coil with similar high angular resolution DTI protocols and analyzed using identical procedures. Our statistical approach consisted of first comparing FH group differences across whole-brain average FA and regional values. Next, we examined correlations between FA and FH density. All analyses were repeated after controlling for possible demographic confounding variables. Finally, we also examined regional differences in the axial and radial diffusivities in secondary analyses. Reduced FA values can be caused by increased intravoxel crossing and tortuosity or twisting of white matter fibers rather than simply decreased myelination (Beaulieu, 2002). However, parallel results with radial but not axial diffusivity would suggest FA differences are caused by differences in diffusivity across the axonal membranes, specifically implicating altered axonal myelination.

Youth cohort

Participants—Thirty-four FH− and 80 FH+ youths (10 to 14 years old, average age = 12.9±1.0) were recruited from a cohort of 386 volunteers in a community based ongoing longitudinal study of adolescent development and substance use involvement in youths at elevated risk for substance use disorders (Ryan, et al., Under Review). FH+ youths were deliberately oversampled to ensure a range in substance outcomes in the longitudinal portion of the study. Estimated intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI; Psychological Corporation, 1999). Family socioeconomic status was measured using the Four Factor Index of Socioeconomic Status (FFISS; Hollingshead, 1975). Psychiatric symptoms and diagnoses was assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman, et al., 1997) administered by trained research assistants and reviewed by a staff psychiatrist board-certified in child and adolescent psychiatry. Externalizing and internalizing symptoms for all participants were assessed from parent or guardian reports on the Child Behavior Checklist (Achenbach, 2001). Exclusion criteria included: regular substance use (defined as substance use at least once per month for 6 consecutive months; Clark, et al., 2005), positive breath alcohol or urine drug test at time of screening, low IQ (< 70), implantable metallic devices or braces, or physical or developmental disabilities that would interfere with the subject's ability to understand or complete study requirements. Oppositional defiant disorder, conduct disorder, attention deficit/hyperactivity disorder, dysthymia or anxiety disorders were not exclusionary for FH+ in the youth cohort because these disorders are commonly comorbid with problem substance use (Iacono, et al., 2008). All participants signed consent forms approved by the Institutional Review Board of The University of Texas Health Science Center at San Antonio approved the study procedures. Privacy was further protected by a Certificate of Confidentiality from the Department of Health and Human Services.

Family history of substance use disorders—Family history classification for the youth cohort was established using the Family History Assessment Module (Rice, et al., 1995) based on parent report. All FH+ participants had a biological father with a past or present substance use disorder. Most FH+ youths (79%) had a father with an alcohol use disorder history, and 64% had a father with history of alcohol and other drug use disorders. Some FH+ youths (31%) had a biological mother with substance use disorder histories. Some (18%) had a mother with an alcohol use disorder history and 11% had a mother with history of alcohol and other drug use disorders. The most common other drug use disorders among parents were cannabis and stimulant use disorders. A family history density score (FH density) was calculated by counting the number of biological parents and grandparents meeting criteria for any substance use disorder. Affected grandparents had similar alcohol and other drug use disorder histories as affected parents. Scores ranged from 0 (FH− participants) to a possible 6 (FH+ participants with both parents and all grandparents affected).

Collection and Processing of Magnetic Resonance Imaging Data—All MRI procedures were performed at the Research Imaging Institute, University of Texas Health Science Center at San Antonio using Siemens Tim Trio 3T MR system (Erlangen, Germany) equipped with a multichannel head coil using a protocol described elsewhere (Wijtenburg, et al., 2012). A single-shot, echo-planar, single refocusing spin-echo sequence was used to acquire diffusion-weighted data with a spatial resolution of 1.7×1.7×3.0 mm. The sequence parameters were: TE/TR=83/7000 ms, FOV=200 mm, two diffusion weighing values b=0 and 700 s/mm^2 and five b=0 (non-diffusion weighted) images, 64 isotropically distributed diffusion-weighted directions, and axial slice orientation with 50 slices and no gaps. The number of directions, b=0 images, and the magnitude of the b values were calculated using an optimization technique that maximizes the contrast to noise ratio based on the average diffusivity of the cerebral white matter and the T_2 relaxation times (Jones, et al., 1999). In addition, high-resolution T1-weighted data were collected using an optimized protocol described previously (Kochunov, et al., 2006).

Image processing—DTI data was processed using a tract-based spatial statistics method, distributed as a part of FMRIB Software Library (FSL) package (Smith, et al., 2006) as described elsewhere (Kochunov, et al., 2011b). The population-based, 3D, DTI cerebral white matter tract atlas developed at Johns Hopkins University and distributed with the FSL package (Wakana, et al., 2004) was used to calculate population average FA values along the spatial course of fourteen, major white matter tracts (Table 2, Figure 1) as described elsewhere (Kochunov, et al., 2011a; Kochunov, et al., 2012). Briefly, The Johns Hopkins University atlas was non-linearly aligned to the minimal deformation target brain and image containing labels for individual tracts was transferred to the minimal deformation target brain space using nearest-neighbor interpolation. Per-tract average values were calculated by averaging the values along the tracts in both hemispheres. The overall average FA values were calculated by averaging values for the entire white matter skeleton.

Adult Cohort

Participants—Thirty FH− and 25 FH+ young adults (18 to 30 years old, average age = 24.3±3.4 years) were recruited from a larger cohort of 450 volunteers participating in a community based ongoing study examining behavioral and physiological characteristics of healthy young adults at elevated risk of alcohol and other substance use disorders (Lovallo, et al., 2013). Estimated intelligence (Shipley mental age) was determined from the vocabulary score on the Revised Shipley Institute of Living Scale (Zachary, 1986). SES was measured using the Hollingshead scale (Hollingshead, 1975) with updated occupational categories and was based on the primary occupation of the main breadwinner in the household in which the participant grew up. Psychological functioning was assessed using the computerized version of the Diagnostic Interview Schedule-IV (DIS-IV; Bucholz, et al., 1994) and the Beck Depression Inventory II (BDI; Beck, et al., 1996). Antisocial traits were quantified with the Sociability scale of the California Personality Inventory (CPI-So; Gough, 1994), a 46-item self-report measure of norm abiding and pro-social behaviors. Alcohol and drug use were assessed through the Cahalan Drinking Habits Questionnaire (Cahalan and Cisin, 1968), the Alcohol Use Disorders Identification Test (Barbor, et al., 1992), and a drug use questionnaire (Saunders, et al., 2008). Exclusion criteria included: a history of alcohol or drug dependence, substance abuse or depression within the past 2 months, a history of any other DSM-IV-TR (APA, 2000) Axis I disorder, failing a urine drug screen or breath-alcohol test on days of testing, or physical or developmental disabilities that would interfere with the subject's ability to understand or complete study requirements. All participants signed consent forms approved by the Institutional Review Boards of the University of Oklahoma Health Sciences Center and the Veterans Affairs Medical Center in Oklahoma City, OK and at the University of Texas Health Sciences Center, San Antonio, TX and were paid for their participation. Privacy was further protected by a Certificate of Confidentiality from the Department of Health and Human Services.

Family history of substance use disorders—Family history classification for the adult cohort was established using the Family History Research Diagnostic Criteria (Andreasen, et al., 1977; Zimmerman, et al., 1988) and confirmed by parent report for all subjects. Almost all had FH+ adults (80%) had a father with substance use disorder histories. Most (72%) had a father with an alcohol use disorder history, and 28% had a father with history of alcohol and other drug use disorders. Some FH+ adults (42%) had a biological mother with substance use disorder histories. Some (31%) had a mother with an alcohol use disorder history and 23% had a mother with history of alcohol and other drug use disorders. Information on the type of other drug use disorders was not recorded. Affected grandparents had similar alcohol and other drug use disorder histories as affected parents. FH density was calculated as in the youth cohort, with scores ranging from 0 to 6.

Diffusion tensor imaging and data processing—All imaging was also performed on the same scanner and the same sequence controls parameters. The only difference was that 55 isotropically distributed diffusion-weighted directions were used instead of 64, in the interest of shorter scan time. The adult cohort DTI data were processed identically to the youth cohort DTI data.

Statistics—FA values averaged for the whole brain and regional white matter measurements were compared between FH+ and FH− individuals in both cohorts using independent sample t-tests. In addition, we examined linear correlations between regional FA values and FH density in both groups separately. We then replicated these same analyses examining radial and axial diffusivity in place of FA. If the FH differences are driven by differences in myelination, we would expect parallel results with radial but not axial diffusivity.

Binary logistic regressions were used to test for significant relationships between FH group and FA tracts while controlling for socioeconomic status and the presence of externalizing and internalizing disorders. In these analyses FH group was the dependent variable, and the predictors were identified as those tracts that significantly differentiated groups in the preceding t-test comparisons after Bonferroni correction. The regressions were conducted using individual models rather than multivariate because FA in all these tracts was significantly correlated with one another. A similar approach was used with linear regressions to predict FH density.

Results

Youth Cohort

Participant Characteristics—Demographic data for the youth cohort are summarized in Table 1. The FH+ and FH− groups did not differ in age, race, or ethnicity or drug use. However, FH+ participants had lower IQ, socioeconomic status, and had more externalizing and internalizing problems.

Imaging findings—FA data were discarded from 5 FH− females, 3 FH+ females, and 2 FH+ males, due to movement artifacts (a spatial shift of over 3 mm between consecutive imaging frames). Post-hoc analyses demonstrated no significant differences in the average motion between FH+ and FH− individuals (average motion per TR = 0.41±0.11mm vs. 0.42±0.12mm, $p = 0.95$, for FH+ and FH− subjects, respectively).

FH+ youths had significantly lower FA values in frontocortical and frontostriatal tracts including the anterior and superior corona radiata and superior frontal-occipital fasciculus (all $p < 0.05$ with Bonferroni correction, Table 2). Similarly, FH density was significantly and negatively correlated with FA values primarily in the same tracts, indicating that progressively lower FA values were seen in individuals with more parents and grandparents with substance use disorders (Table 2, Figure 1, Figure 1S). Similar deficits were observed in parietocortical tracts including the posterior corona radiata. These FA differences remained significant after excluding youths with externalizing and internalizing disorders (Table 1S). Post-hoc analyses indicate that reduced FA in FH+ individuals due to elevations in the radial diffusivity (Table 2S). FH+ subjects also showed some modest reductions in axial diffusivity but most were not significant after controlling for multiple comparisons (Table 3S, see supplement).

FA values of the anterior and superior corona radiata were independent predictors of FH group after controlling for socioeconomic status and the presence of externalizing and

internalizing disorders (Table 3). Anterior corona radiata FA correctly classified 80% of the sample (57% of FH− and 89% of FH+), and FA in the superior corona radiata correctly classified 79% of the sample (57% of FH− and 88% of FH+). Similarly, FA in the anterior, superior, and posterior corona radiata, thalamic radiation, and superior frontal-occipital fasciculus all were significant predictors of density of family history of substance use disorders, even after controlling for socioeconomic status and the presence of externalizing and internalizing disorders.

Adult Cohort

Participant Characteristics—The FH+ and FH− groups did not differ in age, estimated intelligence, race, or ethnicity, but FH+ participants had a significantly lower socioeconomic status (Table 4).

Imaging findings—No data from adults had to be excluded due to excessive movement and there were no difference in the average motion between FH+ and FH− individuals (average motion per TR = 0.39±0.13mm vs. 0.38±0.12mm, p = 0.95, for FH+ and FH− subjects respectively). FH+ adults had lower FA values only in frontocortical tracts, specifically the genu of the corpus callosum and anterior corona radiata, and FH density was significantly negatively correlated with FA values in these same tracts (Table 5, Figure 1, Figure 2S). Similar to the youth cohort, radial diffusivity was elevated in the frontocorticol tracts in the FH+ cohort (Table 4S). There were no significant group differences in the axial diffusivity (Table 5S). In addition, we observed a significant correlation between FH density and thalamic radiation axial diffusivity.

Anterior corona radiata FA was a significant predictor of FH density, even after controlling for socioeconomic status (standardized $\beta = -.363$; $t = -2.89$; $p = .006$, $R^2 = .200$).

Discussion

Our study demonstrated significantly reduced fractional anisotropy (FA) of cerebral white matter in both the youth and young adult FH+ individuals. FH+ youth had lower FA in frontocortical and frontostriatial tracts, and the degree of impairment was proportional to the number of affected parents and grandparents, an empirical risk factor for developing substance use disorder (Dawson, et al., 1992; Stoltenberg, et al., 1998). FH+ youth also had reduced FA in parietocortical tracts, and FA was negatively correlated with FH density in these same tracts. In FH+ adults, FA was decreased only in frontocortical tracts, and FA was negatively correlated to FH density in these tracts as well. Analyses of radial and axial diffusivities indicate the reduced FA values in FH+ individuals were caused by higher radial diffusivity (across the axonal membranes), specifically implicating reduced axonal myelination. Our findings in adolescent cohort provide strong support for the hypothesis that adolescent FH+ individuals may experience altered or delayed development of frontal white matter. Our findings in young adults suggests that white matter deficits may partially be resolved by early adulthood, paralleling a decline in the risk for developing substance use disorders from adolescence to adulthood.

Our findings replicate and extend the previous study that identified FA deficits in a small sample of FH+ youths (Herting, et al., 2010). We replicated the findings of lower FA values in frontal white matter of FH+ in both youth and adult cohorts. We also replicated the earlier study's finding of lower parietocortical FA in FH+ youth but did not observe this in FH+ adults. Moreover, we demonstrated that FA deficits were proportional to FH density in both youths and young adults. Similarly, others have reported reduced frontal as well as parietal FA values in individuals with substance use disorders (Chung, et al., 2007; Lim, et al., 2008; Lin, et al., 2012; Liu, et al., 2010; Ma, et al., 2009; McQueeny, et al., 2009; Romero, et al., 2010; Upadhyay, et al., 2010). Collectively, these findings suggest that impaired integrity of the frontal white matter may be a neurobiological phenotype associated with having a family history of substance use disorders. Furthermore, these findings demonstrate that white matter deficits in FH+ individuals are present before and may potentially contribute to the development of substance use disorders. Longitudinal studies will be needed to directly evaluate this hypothesis, and we are prospectively following youth cohort to investigate these issues. In fact, our cohort was chosen to oversample the FH+ youths and include those with externalizing and internalizing conditions to increase the likelihood of observing a range of substance use outcomes.

Further, our study demonstrated the reduced FA values in FH+ individuals generally corresponded with increased radial but not axial diffusivity, suggesting that reduced axonal myelination is the likely biological mechanism behind our FA findings. Methodologically, the absolute FA values are only indirect measurements of axonal myelination as FA is also sensitive to factors such as the axonal diameter, intra-voxel changes in fiber orientation and others (Budde, et al., 2007; Song, et al., 2003; Song, et al., 2005). Radial diffusivity is a measure of a restricted diffusivity across the axonal walls. Biologically, this measure indexes the permeability of axonal membranes and therefore serves as an indirect estimate of axonal myelination level. Furthermore, studies in animal models where levels of myelination were carefully manipulated showed that changes in the radial diffusivity (e.g., diffusivity across the axonal membranes) was responsible for changes in FA values (Budde, et al., 2007; Gao, et al., 2009; Song, et al., 2003; Song, et al., 2005). Consistent with this rational, radial diffusivity values for the tracts that showed significantly lower FA in FH+ group were also significantly and positively correlated with the FH density. This was in contrast with the axial diffusivity measurements for the same areas that showed sporadic, weaker relationships with FH group status and FH density.

The regional pattern of group-wise FA differences are consistent with the heterochronisity of cerebral myelination trends, first reported by Fleschsig (1901), however the biological basis of our findings cannot be fully understood because the biology of the regional heterochronicity during normal cerebral myelination is not well known. The pattern of regional differences between FH+ youth and their FH− peers pointed specifically at the frontocortical and frontostriatal tracts as well as parietocortical tracts that carry multimodal, associative and projection fibers with no group differences for the FA values of the sensory and motor tracts. Microscopy studies show that oligodendrocytes that myelinate associative tracts are morphological distinct from these that myelinate motor and sensory tracts (Pfefferbaum, et al., 2000; Sullivan, et al., 2001; Wood P. and Bunger RP., 1984). The former type of oligodendrocytes produce far fewer myelin layers per axon (less myelin) and

have reduced rates of myelin turn over and slower rates of myelin repair than the glia located in the primary sensory and motor tracts (Hof, et al., 1990; Lamantia and Rakic, 1990; Wakana, et al., 2004). Recent studies indicate there is strong genetic control over normal cerebral myelination process (Kanchibhotla, et al., 2013). Therefore, a plausible explanation for our findings is the genotype-by-age interactions that affect cerebral development that may be regionally specific. Recently advanced gene-by-environment interaction analysis demonstrated that genes influence neurocognitive traits and white matter coherence as a function of age from young adulthood to old age (Glahn, et al., 2013). In another example, polymorphisms in the *TP53*, a gene central to DNA repair were specifically associated with deficits in the multimodal, frontal matter integrity WM (Molina, et al., 2011). The specific genes that exert risk for developing alcohol and other substance use disorders are unknown but this risk has a strong genetic basis (Cloninger, et al., 1981; Merikangas, 1990; Reich, et al., 1998; Slutske, et al., 2002). Therefore, our findings may help future genetic and genotype-by-age studies to choose quantitative endophenotypes to get measurements closely linked with the neurobiology of this disorder.

The white matter deficits in FH+ adolescents were more pervasive and included frontocorotical, frontostriatal, and parietocortical tracts compared to FH+ adults where FA deficits were confined to frontocortical tracts. This difference is unlikely to be brought about by the procedural differences as imaging data for both cohorts were collected on the same scanner and RF coil using very similar protocols and analyzed using identical procedures. Similarly, the youth cohort findings were not the result of including individuals externalizing and internalizing disorders since the same findings were observed after excluding these individuals. In fact, this may suggest that the decreased frontocortical, frontostriatal, and parietocortical white matter in FH + individuals may be caused by delays in the normal maturation of these tracts during development. This also implies that many FH + individuals eventually reach normal myelination levels at adulthood, at least in some tracts. A relatively limited window of impaired white matter development in adolescence through early adulthood in FH+ individuals would parallel the enhanced risk for developing substance use disorders during this period (McGorry, et al., 2011), and may plausibly contribute to in the initiation and progression of substance use disorders. However, larger cross sectional studies, including a broader age range of participants, and prospective studies following FH+ youth into adulthood are needed to test this hypothesis.

Our study has both strengths and limitations. Strengths include the use of two independent, well-characterized, large sample study cohorts tested with nearly identical DTI protocols. It is unlikely that the findings were a consequence of substance use as the adult cohort was free of substance use disorders and none of the youth cohort had any history of regular substance use or and most had not even having tried alcohol or other drugs. Limitations include a lack of prospective data on substance use outcomes, although the youth cohort is currently being followed longitudinally. Although the results suggest some white matter impairments observed in FH+ youths may be resolved by adulthood, we were not able to directly compare findings across the cohorts and specifically test for age effects due to the slight differences in the DTI protocol. Additionally our youth cohort was predominantly Hispanic, while our adult cohort was predominantly non-Hispanic with relatively fewer males. Finally, it possible that by not testing FH+ adults with substance use disorders we

may have restricted the adult cohort to individuals less predisposed to substance use disorders, although non-affected FH+ individuals may still have inherited risk factors (Cloninger, et al., 1981), similar to other complex genetic disorders where individuals may have inherited predisposing factors without ultimately becoming afflicted themselves (Falconer, 1965; Falconer, 1967). Thus it possible that factors other than development may have contributed to the different findings between the two cohorts. Finally, reduced FA values can be caused by increased intravoxel crossing and tortuosity or twisting of white matter fibers (Beaulieu, 2002). However, in this study, we consider altered myelination to be the likely culprit for reduced FA values because of the parallel findings with radial, but not axial, diffusivity.

Conclusions

In the present study, we observed impairments in frontocortical, frontostriatal and parietocortical white matter in FH+ youths that were robustly associated with FH density, before initiation of any regular drug or alcohol use, and obtained similar FA findings limited to frontocortical white matter in a young adult cohort. Our findings suggest that FH+ youths have impaired development of frontal and parietal white matter that may at least partially resolve by early adulthood, potentially paralleling their increased risk for substance use disorder development in adolescence through early adulthood. However, additional cross-sectional and longitudinal studies will be needed to directly investigate this possibility as well as examine relationships with frontal white matter deficits and the initiation and progression of substance use disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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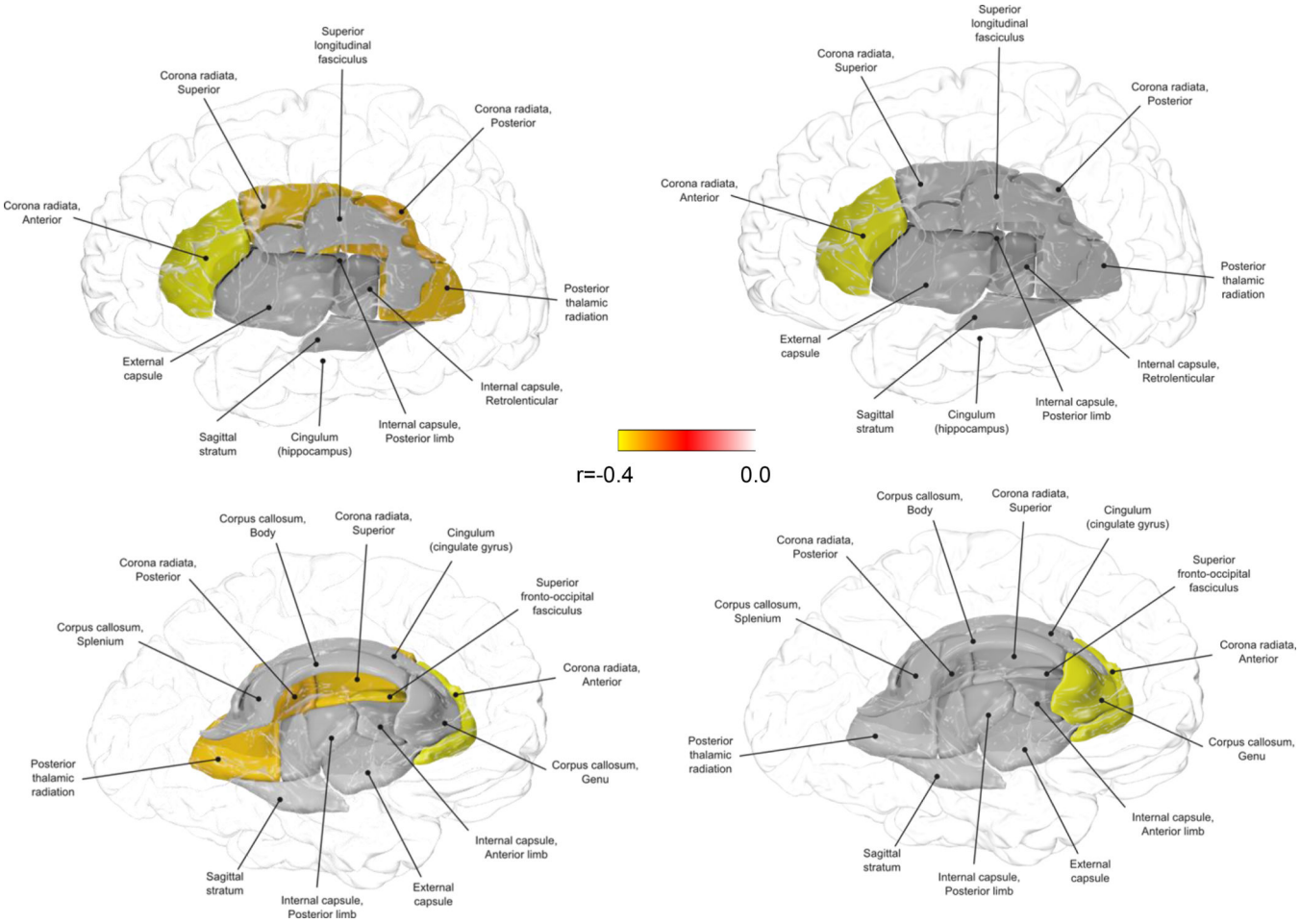

Figure 1.

Significant correlation coefficients ($p \leq .05$, corrected) between regional FA values and FH density (number of parents and grandparents with substance use disorders) are color-coded for individual white matter tracts is shown for the youth cohort (left) and young adult cohort (right). Lateral (top) and medial (bottom) projections are shown.

Table 1

Demographic Information for the Youth Cohort

	FH− (n=34)		FH+ (n=80)	
	Mean	***(SD)***	**Mean**	***(SD)***
Age	12.9	(1.1)	12.9	(1.2)
Wechsler Abbreviated Scale of Intelligence	102.8	(12.2)	96.3	(12.5)*
Four Factor Index of Socioeconomic Status	43.6	(10.2)	34.0	(12.6)*
CBCL Externalizing Problems	2.0	(2.6)	7.4	(7.6)*
CBCL Internalizing Problems	2.9	(4.0)	6.4	(6.2)*
	Number	*(%)*	Number	*(%)*
Gender				
Male	19	(56)	39	(49)
Female	15	(44)	41	(51)
Race				
African-American	1	(3)	11	(14)
Caucasian	32	(94)	67	(84)
Other	1	(3)	2	(3)
Ethnicity				
Hispanic/Latino	29	(85)	63	(79)
Non-Hispanic/Latino	5	(15)	17	(21)
Externalizing Disorders				
Attention Deficit Hyperactivity Disorder	0	(0)	16	(20)
Conduct Disorder	0	(0)	3	(4)
Oppositional Defiant Disorder	0	(0)	10	(13)
Internalizing Disorders				
Generalized Anxiety Disorder	0	(0)	7	(9)
Separation Anxiety Disorder	0	(0)	2	(3)
Specific Phobia	0	(0)	7	(9)
Lifetime alcohol & drug use (n. ever used)				
Alcohol	1	(3)	6	(8)
Marijuana	0	(0)	4	(5)
Tobacco	1	(3)	2	(3)
Other	0	(0)	0	(0)

* $p<0.05$

FH+= family history of substance use disorders (SUDs); FH− = no family history of SUDs; CBCL= Child Behavior Checklist (48).

Table 2

Youth Cohort Fractional Anisotropy (FA) Values

	FH− (n=30)	FH+ (n=75)	Significance of group-wise t-test	FH Density Correlation	
Tract	**Mean (± SD)**		***p***	***r***	***p***
Corpus Callosum					
Genu	.763(.035)	.746 (.027)	.009	−.196	.044
Body	.664 (.033)	.656 (.040)	.314	−.145	.139
Splenium	.771 (.022)	.763 (.024)	.121	−.167	.087
Internal Capsule	.635 (.017)	.625 (.019)	.013	−.182	.063
Corona Radiata					
Anterior	.479 (.019)	.463 (.018)	$1.8 \cdot 10^{-5}$ *	−.404	$1.8 \cdot 10^{-5}$ *
Superior	.517 (.015)	.504 (.019)	.001 *	−.332	$5.1 \cdot 10^{-4}$ *
Posterior	.528 (.017)	.515 (.021)	.001 *	−.307	$8.7 \cdot 10^{-4}$ *
Posterior Thalamic Radiation	.637 (.026)	.623 (.027)	.020	−.320	.001 *
Sagital Striatum	.574 (.031)	.563 (.026)	.076	−.175	.074
External Capsule	.494 (.017)	.489 (.017)	.202	−.070	.479
Cingulum	.623 (.028)	.611 (.028)	.043	−.152	.122
Superior Longitudinal Fasciculus	.514 (.019)	.505 (.022)	.043	−.135	.170
Frontal-occipital Fasciculus					
Superior	.543 (.0278)	.523 (.027)	.002 *	−.342	$3.6 \cdot 10^{-4}$ *
Inferior	.523 (.038)	.522 (.040)	.872	.012	.905

Uncorrected *p* values reported.

* indicates $p \leq .05$ with Bonferroni correction ($p \leq .004$).

Table 3

Regression Analyses for Youth Cohort

	Family History Binary Logistic Regression				Family Density Linear Regression			
	Wald	***p***	***OR* 95% *CI***	**Nagelkerke R^2**	**Standardized β**	***t***	***p***	**R^2**
Tract								
Corona Radiata								
Anterior	10.12	.001	.995 (.993–.998)	.394	−.350	−4.10	<.001	.281
Superior	9.63	.002	.995 (.992–.998)	.395	−.345	−4.01	<.001	.280
Posterior	--	--	--	--	−.268	−3.04	.003	.232
Thalamic Radiation	--	--	--	--	−.334	−3.93	<.001	.273
Superior Frontal-occipital Fasciculus	--	--	--	--	−.347	−4.12	<.001	.282

Table 4

Demographic Information in the Adult Cohort

	FH− (n=30)		FH+ (n=25)	
	Mean	***(SD)***	**Mean**	***(SD)***
Age	24.5	(2.7)	24.1	(4.2)
Shipley Vocabulary score	31	(4.3)	30	(4.2)
Hollingshead & Redlich Socioeconomic Status score	49	(13)	40	(15) *
California Personality Inventory Sociability Scale score	32.1	(4.0)	30.2	(4.3)
Beck Depression Inventory score	4.0	(5.7)	4.7	(5.3)
Age at First Drink	17	(2.9)	15	(4.0)
Drinks per month	35.4	(46.6)	19.8	(29.1)
	Number	*(%)*	Number	*(%)*
Gender				
Male	13	(43)	7	(28)
Female	17	(57)	18	(72)
Race *				
African-American	0	(0)	7	(28)
Caucasian	27	(90)	18	(72)
Other	3	(10)	0	(0)
Ethnicity				
Hispanic/Latino	3	(10)	4	(16)
Non-Hispanic/Latino	27	(90)	21	(84)
Tobacco smoker	1	(3)	1	(4)
Past alcohol abuse	3	(11)	1	(4)
Past other substance use disorders	0	(0)	0	(0)
Lifetime illicit drug use (n ever used)				
Marijuana	13	(4)	14	(5)
Other drug use	6	(20)	8	(32)

* $p<0.05$

Table 5

Adult Cohort

	FH− (n=30)	FH+ (n=25)	Significance of group-wise t-test	FH Density Correlation	
Tract	**Mean (± SD)**		***p***	***r***	***p***
Corpus Callosum					
Genu	.767 (.029)	.739 (.054)	.017	−.399	.003*
Body	.685 (.040)	.679 (.048)	.586	−.125	.365
Splenium	.780 (.023)	.779 (.029)	.850	−.005	.969
Internal Capsule	.626 (.023)	.629 (.027)	.673	.101	.461
Corona Radiata					
Anterior	.539 (.023)	.518 (.033)	.010	−.397	.003*
Superior	.510 (.022)	.507 (.026)	.729	−.110	.425
Posterior	.517 (.023)	517 (.021)	.964	−.029	.832
Posterior Thalamic Radiation	.620 (.027)	.620 (.015)	.955	−.018	.895
Sagital Striatum	.574 (.029)	.573 (.027)	.869	.098	.477
External Capsule	.498 (.021)	.496 (.024)	.807	−.041	.764
Cingulum	.637 (.035)	.633 (.031)	.652	−.133	.334
Superior Longitudinal Fasciculus	.511 (.025)	.511 (.019)	.938	−.132	.338
Frontal-occipital Fasciculus					
Superior	.573 (.042)	.572 (.043)	.923	−.120	.382
Inferior	.492 (.045)	.495 (.056)	.865	.030	.827

Uncorrected *p* values reported.

* indicates $p \leq .05$ with Bonferroni correction ($p \leq .004$).