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White matter integrity in alcohol-naive youth with a family history of alcohol use disorders

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Abstract

Background—Understanding pre-existing neural vulnerabilities found in youth who are family history positive (FHP) for alcohol use disorders could help inform preventative interventions created to delay initiation age and escalation of heavy drinking. The goal of this study was to compare indices of white matter integrity using diffusion tensor imaging (DTI) between FHP and family history negative (FHN) youth using a sample of 94 alcohol-naive adolescents and to examine if differences were associated with global and domain-specific cognitive functioning.

Method—Participants were 48 FHP and 46 FHN demographically matched, healthy, substance-naive 12- to 14-year-olds (54% female) recruited from local middle schools. Participants completed a neuropsychological test battery and magnetic resonance imaging session, including DTI.

Results—FHP youth had *higher* fractional anisotropy and axial diffusivity, and *lower* radial and mean diffusivity, than FHN youth in 19 clusters spanning projection, association and interhemispheric white matter tracts. Findings were replicated after controlling for age, gender, socio-economic status, grade and pubertal development. Groups did not differ significantly on global or domain-specific neuropsychological test scores.

Conclusions—FHP teens showed higher white matter integrity, but similar cognitive functioning, to FHN youth. More mature neural features could be related to more precocious behaviors, such as substance use initiation, in FHP youth. Future research exploring white matter maturation before and after substance use initiation will help elucidate the neuro-developmental trajectories in youth at risk for substance use disorders, to inform preventive efforts and better understand the sequelae of adolescent alcohol and drug use.

Keywords

Adolescence; diffusion tensor imaging; family history; neuropsychological functioning; structural connectivity; substance use disorders; white matter integrity

Introduction

Youth with a positive family history of alcohol use disorders (family history positive; FHP) are at increased risk for a number of negative outcomes, including initiation of alcohol use at an earlier age (Hill & Yuan, 1999; McGue *et al.* 2001), development of alcohol-related problems and alcohol use disorders (Milberger *et al.* 1999; Elliott *et al.* 2012) and other drug involvement (Elliott *et al.* 2012), when compared with family history negative (FHN) youth. Recent findings suggest that these consequences, which carry hefty individual and societal burdens, could be due to underlying neural traits that exist before youth initiate substance use. Understanding pre-existing vulnerabilities in FHP youth could help inform interventions and preventative techniques to delay initiation age and the escalation of heavy drinking.

Several behavioral and neural differences have been found between FHP and FHN youth, prior to the initiation of drinking. Neuropsychological studies have shown that alcohol-naïve FHP children tend to perform worse on tasks of attention (Tarter *et al.* 1989; Ozkaragoz *et al.* 1997; Corral *et al.* 1999), visuospatial functioning (Ozkaragoz *et al.* 1997; Corral *et al.* 1999), memory (Ozkaragoz *et al.* 1997) and executive functioning (Giancola *et al.* 1993; Harden & Pihl, 1995; Corral *et al.* 2003) than FHN youth, with these cognitive deficits persisting into young adulthood (Lovallo *et al.* 2006; Acheson *et al.* 2011).

Aberrations in neural development may help explain behavioral differences observed between FHP and FHN youth. During adolescence, overall gray matter tends to reduce while white matter increases. Gray matter maturation typically follows an inverted U-shaped pattern, with increases in gray matter until early adolescence (roughly peaking at age 11–13 years), followed by decreased volume into early adulthood (Huttenlocher, 1990; Sowell *et al.* 1999; Giedd, 2004; Gogtay *et al.* 2004; Giedd *et al.* 2009). In contrast, white matter continues to increase linearly, well into early adulthood (Giedd, 2004; Lenroot & Giedd, 2006; Bava *et al.* 2010; Yap *et al.* 2013). Increased white matter volume is believed to be related to progressive myelination of axons during adolescence, and is associated with greater connectivity between brain regions (Pfefferbaum *et al.* 1994, Sowell *et al.* 2004; Jernigan & Gamst, 2005; Hüppi & Dubois, 2006), smoother and more efficient communication between frontal–subcortical brain regions (Luna & Sweeney, 2004) and improved cognitive performance (Bava *et al.* 2010).

Recent research has suggested that structural and functional neural abnormalities related to gray and white matter may underlie behavioral deficits found in FHP youth. Functional magnetic resonance imaging (fMRI) studies have demonstrated that FHP youth show aberrations in prefrontal brain activation during tasks of spatial (Spadoni *et al.* 2008; Mackiewicz Seghete *et al.* 2013) and verbal (Cservenka *et al.* 2012) working memory, risky decision making (Cservenka & Nagel, 2012) and inhibition (Schweinsburg *et al.* 2004; Silveri *et al.* 2011). Abnormalities in frontal, parietal and cerebellar functional connectivity have also been found in FHP youth (Herting *et al.* 2011; Wetherill *et al.* 2012).

White matter integrity findings have been less clear. Fractional anisotropy (FA) is a measure of white matter integrity derived from diffusion tensor imaging (DTI) that reflects white

matter coherence by indexing the diffusion of water molecules in brain structures (Basser & Pierpaoli, 1996; Le Bihan *et al.* 2001). Additional measures of white matter integrity obtained during DTI include: mean diffusivity (MD), a measure of the overall magnitude of diffusional motion; radial diffusivity (RD), a quantification of the magnitude of diffusion perpendicular to the main fiber axis; and axial diffusivity (AD), the magnitude of diffusion parallel to the fiber axis (Lebel *et al.* 2012). High FA suggests strong fiber regularity and organization, but values may also reflect myelination and structural characteristics of the axon, while low MD values reflect greater white matter density (Schmithorst *et al.* 2002; Roberts & Schwartz, 2007). Increases in FA and decreases in MD typically occur in white matter during adolescence (Giorgio *et al.* 2008), which are often associated with decreases in RD. Alcohol-naïve FHP youth have shown both higher FA (left posterior superior corona radiata/centrum semiovale) and lower FA (right anterior superior corona radiata, left superior longitudinal fasciculus, right extreme capsule, left inferior longitudinal fasciculus, left anterior limb of the internal capsule, and right optic radiation) compared with FHN youth (Herting *et al.* 2010), while other studies have shown no differences between groups (Wetherill *et al.* 2012).

A growing number of studies have shown greater FA in frontal white matter tracts in at-risk adolescents when compared with controls, including youth who meet criteria for attention deficit/hyperactivity disorder (ADHD) (Li *et al.* 2010) and conduct disorder (Sarkar *et al.* 2013), as well as teens who engage in more dangerous and risky behaviors (Berns *et al.* 2009). Increases in white matter integrity observed during adolescence (Bava *et al.* 2010; Yap *et al.* 2013), particularly in frontal regions, may begin earlier in high-risk youth, increasing their likelihood of engaging in sensation-seeking behaviors at an earlier age.

Alcohol consumption has been associated with lower white matter integrity in chronic alcoholic adults (Pfefferbaum *et al.* 2006a,b) and binge-drinking teens (McQueeney *et al.* 2009). In addition, the interaction of FHP and retrospective history of alcohol exposure has been associated with decreased white matter integrity (Hill *et al.* 2013). On the other hand, teens with alcohol use disorders have shown higher FA values similar to the studies on at-risk youth above (De Bellis *et al.* 2008). Given the data on post-consumption white matter, it is important to characterize the white matter status of individuals at risk for alcohol problems to better understand the influence of consumption on white matter development. Therefore, the goal of this study was to observe white matter integrity differences between FHP and FHN youth using a relatively large ($N=94$) sample of alcohol-naïve adolescents, and to examine if differences were associated with global and domain-specific cognitive functioning.

Method

Participants

Participants were 94 healthy 12- to 14-year-olds (54% female) recruited through flyers sent to households of students attending San Diego area public middle schools (Squeglia *et al.* 2009b, 2013b). Extensive screening and background information were obtained from the youth, their biological parent, and one other parent or close relative. The study protocol was

executed in accordance with the standards approved by the University of California, San Diego Human Research Protections Program.

Exclusionary criteria included: any neurological or Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) Axis I disorder (APA, 1994), determined by the National Institute of Mental Health Diagnostic Interview Schedule for Children—version 4.0 (Shaffer *et al.* 2000); any history of head trauma or loss of consciousness (>2 min); history of chronic medical illness; learning disability or mental retardation; use of medications potentially affecting the brain; premature birth (i.e. born prior to 35th gestational week); any suggestion of prenatal alcohol (>2 drinks during a given week) or illicit drug exposure; experience with alcohol or drugs, defined as >2 total days in their life on which drinking had occurred, or >1 drink consumed on an occasion; 1 lifetime experiences with marijuana and any use in the past 3 months; 1 lifetime cigarette use; and any history of other intoxicant use (Squeglia *et al.* 2009b, 2012; Wetherill *et al.* 2013); contraindication to MRI (e.g. braces); inadequate comprehension of English; non-correctable sensory problems; and clinically abnormal brain anatomy as determined by neuroradiologist review. The final sample included 94 adolescents who were typically in the 7th grade, with modal family socio-economic status in the Hollingshead 11–15 range (Hollingshead, 1965), and commonly with high average estimated intelligence quotient and school grades (see Table 1). Of the 94 participants, two had had one drink on one occasion, while one participant had had one drink on two separate occasions, leaving this a mostly substance-naïve sample.

Measures

Family history—The Family History Assessment Module (Rice *et al.* 1995) ascertained familial alcohol use disorders in first- and second-degree relatives, as self-reports have been found to be a reliable way to determine familial alcohol or substance use (Andreasen *et al.* 1986), and are valid predictors of alcohol use vulnerability and future dependence (Stoltenberg *et al.* 1988). Family history information was collected from the youth, one biological parent, and the other parent or (in <7% of cases) another close relative. Informants were asked if any of the youth's parents, aunts, uncles and/or grandparents ever had any problems due to alcohol, such as social, academic or occupational problems; alcohol-related arrests; negative health consequences; previous treatment for alcohol-related disorders; or if they were frequently intoxicated. Using these criteria to diagnose FHP is more conservative than other classification schemes, valuing specificity (98%) over sensitivity (39%), resulting in fewer false positives of alcohol use disorders diagnoses (Rice *et al.* 1995). Informants' responses were compiled, and if any of the relatives endorsed two or more of the criteria, the youth was classified as FHP for an alcohol use disorder. FHP youth ($n=48$) had one first- or second-degree relative with a history of alcohol use disorder, and FHN youth ($n=46$) had no alcohol use disorder in any first-or second-degree relative. Additionally, family history density scores were calculated by adding 0.5 for each biological parent and 0.25 per biological grandparent (Zucker *et al.* 1994) endorsed by either youth or parent as having alcohol use disorders. FH density scores ranged from 0 to 1.75 in the current sample.

Socio-economic status—Socio-economic background information (i.e. educational attainment, occupation and salary of each parent) was obtained from parents and converted to a Hollingshead Index of Social Position score (Hollingshead, 1965).

Pubertal development—The Pubertal Development Scale (Petersen *et al.* 1988) is a reliable and valid five-item self-report measure of pubertal maturation.

Neurocognition—A 180-min neuropsychological battery was administered by trained, reliable psychometrists within 1 week of scanning to assess cognitive functioning on six cognitive domains related to adolescent alcohol use (Squeglia *et al.* 2009a, in press; Jacobus & Tapert, 2013): short-term memory; sustained attention; verbal learning and memory; visuospatial functioning; spatial planning and problem solving; and inhibition-interference. Domains were determined by a factor analysis of the Z scores of the 24 total neuropsychological test variables ascertained (Squeglia *et al.* 2013a). Short-term memory was comprised of: Wechsler Intelligence Scale for Children, third edition (WISC-III; Wechsler, 1991) Digit Span, digit forward and digit backward raw scores; and Wechsler Adult Intelligence Scale, fourth edition (Wechsler, 2008) Letter–Number sequencing raw scores. Sustained attention consisted of: Digit Vigilance Test (Lewis, 1995) total time (s); WISC-III Coding raw score; and Delis–Kaplan Executive Function System (D-KEFS; Delis *et al.* 2001) Trails Conditions 1, 2, 3 and 4 (i.e. Visual Scanning, Number Sequencing, Letter Sequencing, Letter–Number Switching) time to complete (s). Verbal learning and memory consisted of California Verbal Learning Test–Children’s version (List A Total 1–5 raw, List A Trial 5 raw, Short Delay Free and Cued Recall raw, and Long Delay Free and Cued Recall raw scores; Delis *et al.* 1994). Visuospatial functioning was comprised of: Rey–Osterrieth Complex Figure Copy and 30-min Delay Accuracy scores (Rey & Osterrieth, 1993); Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) Block Design raw scores; and Hooper Visual Organization Test (Hooper, 1958) raw total score. Spatial planning and problem solving included: the WISC-III Mazes total score; WASI Matrix Reasoning total score; and D-KEFS Towers total achievement score. Cognitive inhibition-interference was comprised of D-KEFS Color–Word Interference Conditions 3 and 4 time to complete (s). All timed raw scores (i.e. Digit Vigilance, Trails, Color–Word Interference) were reversed-coded so that longer times corresponded to poorer performance. An overall Global Functioning score was calculated by averaging all subtest Z scores together.

MRI acquisition—Participants were imaged in a 3 T General Electric Excite MR system with an eight-channel phase-array head coil (General Electric Medical Systems, USA). A scout scan ensured good head placement and whole-brain coverage. High angular resolution diffusion images (Frank, 2001) were collected along 61 non-collinear directions determined by the electrostatic repulsion model which minimizes bias in measurements by sampling with approximately uniform distribution on a sphere (Jones *et al.* 1999), in addition to a reference image with no diffusion weighting ($b=0$). The diffusion encoding scheme consisted of a single-shot dual spin echo excitation optimized for minimum echo time (TE) and reduction of eddy current artifacts (Reese *et al.* 2003). The following sequence parameters were applied: TE=93 ms, repetition time (TR)=10900 ms, field of view=240 mm, matrix=128×128, 34 contiguous slices, 3 mm slice thickness, b -value=1500s/mm², one

average. Two field maps were collected for un-warping to correct for signal loss and geometric distortion due to B0 field inhomogeneities (Jezzard & Balaban, 1995; Andersson & Skare, 2002). Total scan time including field maps was 16 min 2 s.

Data processing—Datasets were visually inspected slice by slice for each subject and all valid datasets were corrected for head motion, eddy current distortion and signal loss using FSL tools (FMRIB Software Library, UK; Smith *et al.* 2004), and 48 participants (not described in this study) were removed from the analysis due to motion artifact. Specifically, image acquisitions for each direction were merged into a single four-dimensional file and aligned to the first volume using affine registration with six degrees of freedom and Fourier interpolation to correct for motion (FLIRT-FMRIB's Linear Image Registration Tool; Jenkinson *et al.* 2002). Each of the 61 direction files were then registered to the B0 image using a six-parameter registration in two dimensions to minimize eddy current distortions (FDT-FMRIB's Diffusion Tool-box 2.0; Behrens *et al.* 2003). Next, phase unwrapping (PRELUDE-Phase Region Expanding Labeler for Unwrapping Discrete Estimates; Jenkinson, 2003) and regularization [FUGUE-FMRIB's Utility for Geometrically Unwarping EPIs (echo planar images); Jenkinson & Smith, 2001] of field maps were conducted for quantifying field distortions. Resulting measurements were translated into voxel shifts, effectively assigning image intensities to correct voxel locations.

For this study, FA was calculated using FMRIB's Diffusion Toolbox (Behrens *et al.* 2003). Diffusion indices were examined with tract-based spatial statistics (Smith *et al.* 2006), and involved the following steps. To achieve initial alignment, FA maps were registered to an averaged FA template (FMRIB-58) in Montreal Neurological Institute (MNI)-152 standard space using an affine-only registration. This was followed by a nonlinear transformation into 1-mm cubic voxel dimensions (FNIRT-FMRIB's Non-linear Registration Tool). Data were examined for laterality, orientation and cross-subject anatomical alignment. Next, transformed images were averaged across subjects to create a mean FA image, from which a white matter skeleton was derived, representing tracts common to all subjects. Individual transformed FA images were then projected onto the skeleton. To minimize partial-volume effects and areas of high inter-subject variability, values were thresholded at FA >0.2 (Smith *et al.* 2007). Data from each point on the skeleton formed the basis of voxel-wise statistical comparisons. Within clusters where FA values differed between FHP and FHN youth, average MD, RD and AD values were extracted using the same process as the FA analysis described above to further clarify the microstructural properties of white matter found to differ between groups.

Data analyses—Voxel-wise statistics on skeleton space FA data were carried out in AFNI (<http://afni.nimh.nih.gov/afni/>) using independent-samples *t* tests. Correction for multiple comparisons was achieved through a combination of individual voxel probability and cluster size thresholding using Monte Carlo simulation (Ward, 2000) for type I error control. Consistent with previous findings (Jacobus *et al.* 2013a), clusters $\geq 21 \mu l$ (21 contiguous $1 \times 1 \times 1$ mm voxels) with an individual voxel effect of $\alpha < 0.001$ were interpreted, yielding a brain-wise $\alpha < 0.01$ of finding such a cluster under the null hypothesis. Anatomical

identification of tract structures was confirmed using white matter atlases (Wakana *et al.* 2004; Mori *et al.* 2008).

FHP and FHN groups were compared on demographic and cognitive functioning (both global and domain-specific) variables using a two-tailed Student's *t* test in SPSS (Rel. 18.0.0. 2009; IBM, USA). A 3d *t* test++ in AFNI (Cox, 1996; Ward, 2000) determined group differences between FHP and FHN youth on FA, as well as MD, RD and AD within the regions that significantly differed in regards to FA. For FHP youth, Pearson's *r* correlations were run between cognitive domains and FA values in the regions that differed between FHP and FHN youth; because of the exploratory nature of these correlations, α levels were set at 0.01.

Results

Demographics

FHP ($n=48$) and FHN ($n=46$) youth were matched at the group level on age, gender, race, socio-economic status, years of education, pubertal development, academic achievement, externalizing symptoms and verbal intelligence (see Table 1). FHP and FHN groups did not differ significantly on any demographic variable, or any item on the Pubertal Development Scale.

White matter

FHP youth ($n=48$) had higher FA than FHN youth ($n=46$) in 19 clusters, spanning projection, association and interhemispheric white matter tracts. Findings were confirmed after controlling for age, gender, socioeconomic status, grade and pubertal development. These 19 regions included: the left inferior longitudinal fasciculus (Cohen's $d=0.76$, 0.87 and 0.81), right inferior longitudinal fasciculus ($d=0.78$), body of the corpus callosum ($d=0.72$ and 0.83), left superior longitudinal fasciculus ($d=0.92$, 0.79 and 0.72), right superior longitudinal fasciculus ($d=0.94$, 0.81 and 0.84), left sagittal stratum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) ($d=0.88$), right anterior limb of the internal capsule ($d=0.88$), right anterior thalamic radiation ($d=0.86$), left posterior corona radiata ($d=0.64$), right external capsule ($d=0.79$), left forceps major ($d=0.92$) and right forceps minor ($d=0.71$) (see Table 2 and Fig. 1). Within these 19 clusters, FHP youth had lower MD (in nine out of 19 regions), higher AD (in five out of 19 regions) and lower RD (in all 19 regions) compared with FHN youth (see Table 2). Relationships between family history density scores and diffusion indices did not reach statistical significance (p 's<0.01).

Neurocognition

FHP and FHN groups did not differ on global or domain-specific neuropsychological test scores (p 's> 0.44; see Table 3). For FHP youth ($n=48$), FA in the 19 white matter tracts of interest did not relate to global or domain-specific neuropsychological test scores (p 's>0.01).

Discussion

The aim of this study was to understand white matter and cognitive functioning as they relate to family history of alcohol use disorders (i.e. FHP) in a relatively large sample of alcohol-naïve adolescents. Despite having similar demographic backgrounds, age, pubertal development and neurocognitive performance, FHP youth had higher FA and AD, and lower MD and RD, than FHN youth in 19 different white matter fibers, spanning association, projection and interhemispheric tracts connecting diffusely distributed regions throughout the brain. The findings across regions were highly consistent, with no tracts showing lower FA or AD, or higher MD and RD, in FHP compared with FHN youth, and the observed effect sizes were quite large (Cohen's d 0.64 to 0.94). This suggests higher white matter integrity in these tracts among substance-naïve early adolescents with familial alcohol use disorders.

The white matter tracts that differed between FHP and FHN youth connect several cortical and subcortical regions that undergo significant neuro-development during adolescence (Jellison *et al.* 2004; Barnea-Goraly *et al.* 2005). These white matter tracts included the superior longitudinal fasciculus, a massive bundle of association fibers connecting the frontal, temporal, parietal and occipital regions of the brain, as well as the inferior longitudinal fasciculus, which connects temporal and occipital regions. Several projection fibers, connecting subcortical (e.g. thalamic, basal ganglia) to frontal brain regions, were also found to have higher white matter integrity in FHP youth. White matter development in these regions is important for the improvement of a number of cognitive skills during adolescence, including attention, memory, executive functioning and motor skills (Barnea-Goraly *et al.* 2005). To that end, white matter abnormalities in these regions may help explain cognitive and behavioral differences found in FHP youth during adolescence.

Our findings are in contrast to some preliminary findings that suggest that FHP youth have lower (Herting *et al.* 2010) or equivalent (Wetherill *et al.* 2012) white matter integrity compared with FHN youth. However, our results are consistent with the growing research showing higher FA in youth who engaged in high rates of dangerous behaviors (Berns *et al.* 2009), as well as youth diagnosed with conduct disorder (Sarkar *et al.* 2013) and ADHD (Li *et al.* 2010). Increases in white matter coherence and organization observed during adolescence (Bava *et al.* 2010; Yap *et al.* 2013) may begin earlier in youth who engage or are more likely to engage (as is the case with FHP youth) in risk-taking behaviors. On one hand, this accelerated maturation may be viewed as advantageous, as it could be related to earlier autonomy, behavioral exploration and prosocial behaviors. Alternatively, this early maturation could be viewed as 'vulnerability' for youth, increasing their likelihood of engaging in sensation-seeking behaviors at an earlier age. Our findings add to the emergent literature suggesting that these neurodevelopmentally precocious youth may have a tendency to initiate and escalate risk-taking behaviors when compared with their peers. This could lead to either positive or negative risk taking, depending on other environmental and peer influences.

For the FHP youth, higher FA was not related to better scores on cognitive testing, suggesting that more mature neural features do not necessarily indicate better cognitive

functioning. These more developed white matter features may be influencing risk-taking behaviors specifically more than general cognition.

Despite alcohol-naïve FHP youth showing greater white matter coherence, this advantage, or possible vulnerability, attenuates after youth initiate heavy substance use during adolescence. Specifically, previous studies have consistently found that heavy substance-using teens show decreasing FA compared with their non-using counterparts after alcohol and marijuana initiation (McQueeney *et al.* 2009; Bava *et al.* 2013; Jacobus *et al.* 2013a,b), suggesting that these higher FA levels are not maintained once heavy substance use begins. These findings are consistent with fMRI studies that show that more mature neural response patterns appear to be a risk factor for future initiation of substance use, with advantages decreasing after alcohol use initiation (Squeglia *et al.* 2012; Wetherill *et al.* 2013). Importantly, these alcohol-related aberrations in brain structure and function are during a time when healthy non-using adolescents tend to show increasing white matter coherence and more mature neural processing (Giorgio *et al.* 2008; Schmithorst & Yuan, 2010; Stiles & Jernigan, 2010; Tamnes *et al.* 2010; Lebel *et al.* 2012). In sum, while more mature neural markers may predate substance use, advantages appear to reduce post-initiation.

Some limitations exist. Youth in this sample were alcohol-naïve, high-functioning adolescents from high socio-economic status backgrounds, with no psychological, medical or behavioral issues who were performing well academically. In general, they were performing above average on all neurocognitive domains (see Table 3) and were within the average range in terms of externalizing behaviors (Table 1). Therefore, these youth were quite high functioning, and findings may not generalize to youth with co-occurring psychopathology or who have experienced significant traumatic life events that may typically be associated with positive family histories of alcohol use disorders. The current findings are cross-sectional; longitudinal studies are needed to understand the neural trajectory of white matter development in FHP youth and how development differs in youth at risk for developing substance-related problems.

Conclusions

In sum, we found that FHP teens have higher white matter integrity, but similar cognitive functioning, to FHN youth. More mature neural features could be related to more precocious behaviors, such as substance use initiation, in FHP youth. Future research exploring white matter maturation before and after substance use initiation will help elucidate the neurodevelopmental trajectories present in FHP youth, and could be used to inform preventive efforts.

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References

- Acheson A, Vincent AS, Sorocco KH, Lohvallo WR. Greater discounting of delayed rewards in young adults with family histories of alcohol and drug use disorders: studies from the Oklahoma family health patterns project. *Alcoholism: Clinical and Experimental Research*. 2011; 35:1607–1613.
- Andersson JL, Skare S. A model-based method for retrospective correction of geometric distortions in diffusion-weighted EPI. *NeuroImage*. 2002; 16:177–199. [PubMed: 11969328]
- Andreasen NC, Rice J, Endicott J, Reich T, Coryell W. The family history approach to diagnosis. How useful is it? *Archives of General Psychiatry*. 1986; 43:421–429. [PubMed: 3964020]
- APA. *Diagnostic and Statistical Manual of Mental Disorders*. 4. American Psychiatric Association; Washington, DC: 1994. (DSM-IV)
- Barnea-Goraly N, Menon V, Eckert M, Tamm L, Bammer R, Karchemskiy A, Dant CC, Reiss AL. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cerebral Cortex*. 2005; 15:1848–1854. [PubMed: 15758200]
- Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance, Series B*. 1996; 111:209–219. [PubMed: 8661285]
- Bava S, Jacobus J, Thayer RE, Tapert SF. Longitudinal changes in white matter integrity among adolescent substance users. *Alcoholism: Clinical and Experimental Research*. 2013; 37:E181–E189.
- Bava S, Thayer R, Jacobus J, Ward M, Jernigan TL, Tapert SF. Longitudinal characterization of white matter maturation during adolescence. *Brain Research*. 2010; 1327:38–46. [PubMed: 20206151]
- Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, Matthews PM, Brady JM, Smith SM. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magnetic Resonance in Medicine*. 2003; 50:1077–1088. [PubMed: 14587019]
- Berns GS, Moore S, Capra CM. Adolescent engagement in dangerous behaviors is associated with increased white matter maturity of frontal cortex. *PLoS ONE*. 2009; 4:e6773. [PubMed: 19707512]
- Corral M, Holguín SR, Cadaveira F. Neuro-psychological characteristics of young children from high-density alcoholism families: a three-year follow-up. *Journal of Studies on Alcohol*. 2003; 64:195–199. [PubMed: 12713192]
- Corral MM, Holguín SR, Cadaveira F. Neuropsychological characteristics in children of alcoholics: familial density. *Journal of Studies on Alcohol*. 1999; 60:509–513. [PubMed: 10463807]
- Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*. 1996; 29:162–173. [PubMed: 8812068]
- Cservenka A, Herting MM, Nagel BJ. Atypical frontal lobe activity during verbal working memory in youth with a family history of alcoholism. *Drug and Alcohol Dependence*. 2012; 123:98–104. [PubMed: 22088655]
- Cservenka A, Nagel BJ. Risky decision-making: an fMRI study of youth at high risk for alcoholism. *Alcoholism: Clinical and Experimental Research*. 2012; 36:604–615.
- De Bellis MD, Van Voorhees E, Hooper SR, Gibling N, Nelson L, Hege SG, Payne ME, MacFall J. Diffusion tensor measures of the corpus callosum in adolescents with adolescent onset alcohol use disorders. *Alcoholism: Clinical and Experimental Research*. 2008; 32:395–404.
- Delis, DC.; Kaplan, E.; Kramer, JH. *The Delis–Kaplan Executive Function System: Examiner’s Manual*. The Psychological Corporation; San Antonio, TX: 2001.
- Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. *Manual for the California Verbal Learning Test–Children’s Version*. The Psychological Corporation; San Antonio, TX: 1994.

- Elliott JC, Carey KB, Bonafide KE. Does family history of alcohol problems influence college and university drinking or substance use? A meta-analytical review. *Addiction*. 2012; 107:1774–1785. [PubMed: 22452451]
- Frank LR. Anisotropy in high angular resolution diffusion-weighted MRI. *Magnetic Resonance in Medicine*. 2001; 45:935–939. [PubMed: 11378869]
- Giancola PR, Peterson JB, Pihl RO. Risk for alcoholism, antisocial behavior, and response perseveration. *Journal of Clinical Psychology*. 1993; 49:423–428. [PubMed: 8315046]
- Giedd JN. Structural magnetic resonance imaging of the adolescent brain. *Annals of the New York Academy of Sciences*. 2004; 1021:77–85. [PubMed: 15251877]
- Giedd JN, Lalonde FM, Celano MJ, White SL, Wallace GL, Lee NR, Lenroot RK. Anatomical brain magnetic resonance imaging of typically developing children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2009; 48:465–470. [PubMed: 19395901]
- Giorgio A, Watkins KE, Douaud G, James AC, James S, De Stefano N, Matthews PM, Smith SM, Johansen-Berg H. Changes in white matter microstructure during adolescence. *NeuroImage*. 2008; 39:52–61. [PubMed: 17919933]
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF III, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM. Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences USA*. 2004; 101:8174–8179.
- Harden PW, Pihl RO. Cognitive function, cardiovascular reactivity, and behavior in boys at high risk for alcoholism. *Journal of Abnormal Psychology*. 1995; 104:94–103. [PubMed: 7897058]
- Herting MM, Fair D, Nagel BJ. Altered fronto-cerebellar connectivity in alcohol-naïve youth with a family history of alcoholism. *NeuroImage*. 2011; 54:2582–2589. [PubMed: 20970506]
- Herting MM, Schwartz D, Mitchell SH, Nagel BJ. Delay discounting behavior and white matter microstructure abnormalities in youth with a family history of alcoholism. *Alcoholism: Clinical and Experimental Research*. 2010; 34:1590–1602.
- Hill SY, Terwilliger R, McDermott M. White matter microstructure, alcohol exposure, and familial risk for alcohol dependence. *Psychiatry Research*. 2013; 212:43–53. [PubMed: 23473988]
- Hill SY, Yuan H. Familial density of alcoholism and onset of adolescent drinking. *Journal of Studies on Alcohol*. 1999; 60:7–17. [PubMed: 10096304]
- Hollingshead, AB. Two-Factor Index of Social Position. Yale University Press; New Haven, CT: 1965.
- Hooper, HE. The Hooper Visual Organization Test Manual. Western Psychological Services; Los Angeles: 1958.
- Hüppi PS, Dubois J. Diffusion tensor imaging of brain development. *Seminars in Fetal and Neonatal Medicine*. 2006; 11:489–497. [PubMed: 16962837]
- Huttenlocher PR. Morphometric study of human cerebral cortex development. *Neuropsychologia*. 1990; 28:517–527. [PubMed: 2203993]
- Jacobus J, Squeglia LM, Bava S, Tapert SF. White matter characterization of adolescent binge drinking with and without co-occurring marijuana use: a 3-year investigation. *Psychiatry Research*. 2013a; 214:374–381. [PubMed: 24139957]
- Jacobus J, Tapert SF. Neurotoxic effects of alcohol in adolescence. *Annual Review of Clinical Psychology*. 2013; 9:703–721.
- Jacobus J, Thayer RE, Trim RS, Bava S, Frank LR, Tapert SF. White matter integrity, substance use, and risk taking in adolescence. *Psychology of Addictive Behaviors*. 2013b; 27:431–442. [PubMed: 22564204]
- Jellison BJ, Field AS, Medow J, Lazar M, Salamat MS, Alexander AL. Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. *American Journal of Neuroradiology*. 2004; 25:356–369. [PubMed: 15037456]
- Jenkinson M. Fast, automated, N-dimensional phase-unwrapping algorithm. *Magnetic Resonance in Medicine*. 2003; 49:193–197. [PubMed: 12509838]
- Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*. 2002; 17:825–841. [PubMed: 12377157]

- Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*. 2001; 5:143–156. [PubMed: 11516708]
- Jernigan TL, Gamst AC. Changes in volume with age—consistency and interpretation of observed effects. *Neurobiology of Aging*. 2005; 26:1271–1278. [PubMed: 16006011]
- Jezzard P, Balaban RS. Correction for geometric distortion in echo planar images from B0 field variations. *Magnetic Resonance in Medicine*. 1995; 34:65–73. [PubMed: 7674900]
- Jones DK, Horsfield MA, Simmons A. Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. *Magnetic Resonance in Medicine*. 1999; 42:515–525. [PubMed: 10467296]
- Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriat H. Diffusion tensor imaging: concepts and applications. *Journal of Magnetic Resonance Imaging*. 2001; 13:534–546. [PubMed: 11276097]
- Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C. Diffusion tensor imaging of white matter tract evolution over the lifespan. *NeuroImage*. 2012; 60:340–352. [PubMed: 22178809]
- Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. *Neuroscience and Biobehavioral Reviews*. 2006; 30:718–729. [PubMed: 16887188]
- Lewis, RF. Digit Vigilance Test. Psychological Assessment Resources; Odessa, FL: 1995.
- Li Q, Sun J, Guo L, Zang Y, Feng Z, Huang X, Yang H, Lv Y, Huang M, Gong Q. Increased fractional anisotropy in white matter of the right frontal region in children with attention-deficit/hyperactivity disorder: a diffusion tensor imaging study. *Neuroendocrinology Letters*. 2010; 31:747–753. [PubMed: 21196923]
- Lovallo WR, Yechiam E, Sorocco KH, Vincent AS, Collins FL. Working memory and decision-making biases in young adults with a family history of alcoholism: studies from the Oklahoma Family Health Patterns Project. *Alcoholism: Clinical and Experimental Research*. 2006; 30:763–773.
- Luna B, Sweeney JA. The emergence of collaborative brain function: fMRI studies of the development of response inhibition. *Annals of the New York Academy of Sciences*. 2004; 1021:296–309. [PubMed: 15251900]
- Mackiewicz Seghete KL, Cservenka A, Herting MM, Nagel BJ. Atypical spatial working memory and task-general brain activity in adolescents with a family history of alcoholism. *Alcoholism: Clinical and Experimental Research*. 2013; 37:390–398.
- McGue M, Iacono WG, Legrand LN, Elkins I. Origins and consequences of age at first drink. II. Familial risk and heritability. *Alcoholism: Clinical and Experimental Research*. 2001; 25:1166–1173.
- McQueeney T, Schweinsburg BC, Schweinsburg AD, Jacobus J, Bava S, Frank LR, Tapert SF. Altered white matter integrity in adolescent binge drinkers. *Alcoholism: Clinical and Experimental Research*. 2009; 33:1278–1285.
- Milberger S, Faraone SV, Biederman J, Chu MP, Feighner JA. Substance use disorders in high-risk adolescent offspring. *American Journal on Addiction*. 1999; 8:211–219.
- Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, Hua K, Faria AV, Mahmood A, Woods R, Toga AW, Pike GB, Neto PR, Evans A, Zhang J, Huang H, Miller MI, van Zijl P, Mazziotta J. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *NeuroImage*. 2008; 40:570–582. [PubMed: 18255316]
- Ozkaragoz T, Satz P, Noble EP. Neuropsychological functioning in sons of active alcoholic, recovering alcoholic, and social drinking fathers. *Alcohol*. 1997; 14:31–37. [PubMed: 9014021]
- Petersen AC, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: reliability, validity, and initial norms. *Journal of Youth and Adolescence*. 1988; 17:117–133. [PubMed: 24277579]
- Pfefferbaum A, Adalsteinsson E, Sullivan EV. Dysmorphology and microstructural degradation of the corpus callosum: interaction of age and alcoholism. *Neurobiology of Aging*. 2006a; 27:994–1009. [PubMed: 15964101]

- Pfefferbaum A, Adalsteinsson E, Sullivan EV. Supratentorial profile of white matter microstructural integrity in recovering alcoholic men and women. *Biological Psychiatry*. 2006b; 59:364–372. [PubMed: 16125148]
- Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Archives of Neurology*. 1994; 51:874–887. [PubMed: 8080387]
- Reese TG, Heid O, Weisskoff RM, Wedeen VJ. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. *Magnetic Resonance in Medicine*. 2003; 49:177–182. [PubMed: 12509835]
- Rey, A.; Osterrieth, PA. Translations of excerpts from Andre Rey's "Psychological examination of traumatic encephalopathy" and P.A. Osterrieth's "The complex figure copy test". In: Corwin, J.; Bylsma, FW., editors. *Clinical Neuropsychologist*. Vol. 7. 1993. p. 3-21.
- Rice JP, Reich T, Bucholz KK, Neuman RJ, Fishman R, Rochberg N, Hesselbrock VM, Nurnberger JII, Schuckit MA, Begleiter H. Comparison of direct interview and family history diagnoses of alcohol dependence. *Alcoholism: Clinical and Experimental Research*. 1995; 19:1018–1023.
- Roberts TP, Schwartz ES. Principles and implementation of diffusion-weighted and diffusion tensor imaging. *Pediatric Radiology*. 2007; 37:739–748. [PubMed: 17598100]
- Sarkar S, Craig MC, Catani M, Dell'acqua F, Fahy T, Deeley Q, Murphy DG. Frontotemporal white-matter microstructural abnormalities in adolescents with conduct disorder: a diffusion tensor imaging study. *Psychological Medicine*. 2013; 43:401–411. [PubMed: 22617495]
- Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study. *Radiology*. 2002; 222:212–218. [PubMed: 11756728]
- Schmithorst VJ, Yuan W. White matter development during adolescence as shown by diffusion MRI. *Brain and Cognition*. 2010; 72:16–25. [PubMed: 19628324]
- Schweinsburg AD, Paulus MP, Barlett VC, Killeen LA, Caldwell LC, Pulido C, Brown SA, Tapert SF. An fMRI study of response inhibition in youths with a family history of alcoholism. *Annals of the New York Academy of Sciences*. 2004; 1021:391–394. [PubMed: 15251915]
- Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. NIMH Diagnostic Interview Schedule for Children Version IV (NIMH DISC-IV): description, differences from previous versions, and reliability of some common diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2000; 39:28–38. [PubMed: 10638065]
- Silveri MM, Rogowska J, McCaffrey A, Yurgelun-Todd DA. Adolescents at risk for alcohol abuse demonstrate altered frontal lobe activation during Stroop performance. *Alcoholism: Clinical and Experimental Research*. 2011; 35:218–228.
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage*. 2006; 31:1487–1505. [PubMed: 16624579]
- Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*. 2004; 23:S208–S219. [PubMed: 15501092]
- Smith SM, Johansen-Berg H, Jenkinson M, Rueckert D, Nichols TE, Miller KL, Robson MD, Jones DK, Klein JC, Bartsch AJ, Behrens TE. Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. *Nature Protocols*. 2007; 2:499–503.
- Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. *In vivo* evidence for post adolescent brain maturation in frontal and striatal regions. *Nature Neuroscience*. 1999; 2:859–861.
- Sowell ER, Thompson PM, Leonard CM, Welcome SE, Kan E, Toga AW. Longitudinal mapping of cortical thickness and brain growth in normal children. *Journal of Neuroscience*. 2004; 24:8223–8231. [PubMed: 15385605]
- Spadoni AD, Norman AL, Schweinsburg AD, Tapert SF. Effects of family history of alcohol use disorders on spatial working memory BOLD response in adolescents. *Alcoholism: Clinical and Experimental Research*. 2008; 32:1135–1145.

- Squeglia LM, Jacobus J, Brumback T, Meloy MJ, Tapert SF. White matter integrity in alcohol-naïve youth with a family history of alcohol use disorders. *Psychological Medicine*. (in press).
- Squeglia LM, Jacobus J, Sorg SF, Jernigan TL, Tapert SF. Early adolescent cortical thinning is related to better neuropsychological performance. *Journal of the International Neuropsychological Society*. 2013a; 19:962–970. [PubMed: 23947395]
- Squeglia LM, Jacobus J, Tapert SF. The influence of substance use on adolescent brain development. *Clinical EEG and Neuroscience*. 2009a; 40:31–38. [PubMed: 19278130]
- Squeglia LM, McKenna BS, Jacobus J, Castro N, Sorg SF, Tapert SF. BOLD response to working memory not related to cortical thickness during early adolescence. *Brain Research*. 2013b; 1537:59–68. [PubMed: 24012876]
- Squeglia LM, Pulido C, Wetherill RR, Jacobus J, Brown GG, Tapert SF. Brain response to working memory over three years of adolescence: influence of initiating heavy drinking. *Journal of Studies on Alcohol and Drugs*. 2012; 73:749–760. [PubMed: 22846239]
- Squeglia LM, Spadoni AD, Infante MA, Myers MG, Tapert SF. Initiating moderate to heavy alcohol use predicts changes in neuropsychological functioning for adolescent girls and boys. *Psychology of Addictive Behaviors*. 2009b; 23:715–722. [PubMed: 20025379]
- Stiles J, Jernigan TL. The basics of brain development. *Neuropsychology Review*. 2010; 20:327–348. [PubMed: 21042938]
- Stoltenberg SF, Mudd SA, Blow FC, Hill EM. Evaluating measures of family history of alcoholism: density *versus* dichotomy. *Addiction*. 1988; 93:1511–1520. [PubMed: 9926555]
- Tamnes CK, Ostby Y, Fjell AM, Westlye LT, Due-Tønnessen P, Walhovd KB. Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. *Cerebral Cortex*. 2010; 20:534–548. [PubMed: 19520764]
- Tarter RE, Jacob T, Bremer DL. Specific cognitive impairment in sons of early onset alcoholics. *Alcoholism: Clinical and Experimental Research*. 1989; 13:786–789.
- Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, Mori S. Fiber tract-based atlas of human white matter anatomy. *Radiology*. 2004; 230:77–87. [PubMed: 14645885]
- Ward, BD. [Accessed 15 June 2013] Simultaneous inference for fMRI data. 2000. (<http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>)
- Wechsler, D. Wechsler Intelligence Scale for Children. 3. Psychological Corporation; New York: 1991.
- Wechsler, D. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation; San Antonio, TX: 1999.
- Wechsler, D. Wechsler Adult Intelligence Scale. 4. Pearson; San Antonio, TX: 2008.
- Wetherill RR, Bava S, Thompson WK, Boucquey V, Pulido C, Yang TT, Tapert SF. Frontoparietal connectivity in substance-naïve youth with and without a family history of alcoholism. *Brain Research*. 2012; 1432:66–73. [PubMed: 22138427]
- Wetherill RR, Squeglia LM, Yang TT, Tapert SF. A longitudinal examination of adolescent response inhibition: neural differences before and after the initiation of heavy drinking. *Psychopharmacology*. 2013; 230:663–671. [PubMed: 23832422]
- Yap QJ, Teh I, Fusar-Poli P, Sum MY, Kuswanto C, Sim K. Tracking cerebral white matter changes across the lifespan: insights from diffusion tensor imaging studies. *Journal of Neural Transmission*. 2013; 120:1369–1395. [PubMed: 23328950]
- Zucker RA, Ellis DA, Fitzgerald HE. Developmental evidence for at least two alcoholisms: I. Biopsychosocial variation among pathways into symptomatic difficulty. *Annals of the New York Academy of Sciences*. 1994; 708:134–146. [PubMed: 8154674]

Fig. 1.

White matter clusters that showed significant group differences in fractional anisotropy (FA) between family history positive (FHP; $n=48$) and family history negative (FHN; $n=46$) youth (21 voxels; $p's > 0.001$), depicted in red. In all regions examined (highlighted in red), FHP youth show higher FA than FHN teens. R, Right; L, left.

Table 1Demographic information for 94 alcohol-naïve adolescents^a

	FHN (<i>n</i> =46)	FHP (<i>n</i> =48)
Age, years ^b	13.49 (0.63)	13.65 (0.71)
Gender, % females	61	48
Race, % Caucasian ^c	78	64
FHAM positive diagnoses, 2 criteria endorsed, <i>n</i>		
Biological parents	0	11
Aunts/uncles	0	21
Grandparents	0	27
Family history density score	0.00 (0.00)	0.34 (0.39)
Lifetime alcohol use occasions ^d	0.00 (0.00)	0.08 (0.35)
Hollingshead Index of Social Position score ^e	20.43 (11.74)	25.38 (15.69)
Duration of education, years	6.80 (0.78)	7.04 (0.77)
Pubertal Development Scale – females	2.10 (0.46)	2.28 (0.57)
Pubertal Development Scale – males	2.97 (0.62)	3.25 (0.64)
Grade point average ^f	3.62 (0.47)	3.54 (0.59)
Child Behavior Checklist externalizing symptoms, T score	39.51 (6.59)	41.15 (7.72)
WASI-IV vocabulary, T score	57.58 (8.10)	57.94 (7.86)

Data are given as mean (standard deviation).

FHN, Family history negative; FHP, family history positive; FHAM, Family History Assessment Module; WASI-IV, Wechsler Abbreviated Scale of Intelligence – 4th edition.

^aThere were no group differences on any demographic variable.

^bAge range 12–14 years.

^cFor the full sample, race was 71% Caucasian, 19% multi-racial, 5% Asian, 2% Black, and 2% Hawaiian/Pacific islander.

^dRange 0–2 days.

^eHigher scores indicate lower socio-economic status.

^fGrade point averages were self-reported.

Table 2

Demonstration of significant group differences in FA between FHP ($n=48$) and FHN ($n=46$) youth (21 voxels; $p's > 0.001$) in 19 white matter clusters^a

Cluster	Anatomical region	Volume, μ l	MNI coordinates ^b			FHN FA: mean (S.D.)	FHP FA: mean (S.D.)	Effect size ^c
			x	y	z			
1	L inferior longitudinal fasciculus ^d	57	-46.1	-16.4	-19.6	0.47 (0.05)	0.51 (0.06)	0.76
2	Body of corpus callosum ^{d,e}	51	-15.0	13.0	29.7	0.54 (0.04)	0.57 (0.05)	0.72
3	L superior longitudinal fasciculus ^{d,e}	48	-35.2	-1.3	33.1	0.35 (0.04)	0.39 (0.04)	0.92
4	L sagittal stratum ^{d,f}	41	-38.1	-9.2	-17.2	0.44 (0.04)	0.47 (0.03)	0.88
5	R anterior limb of internal capsule ^{d,e}	41	19.6	18.9	1.3	0.42 (0.04)	0.45 (0.04)	0.88
6	R anterior thalamic radiation ^{d,e}	38	8.8	-15.0	9.4	0.27 (0.02)	0.28 (0.02)	0.86
7	R superior longitudinal fasciculus ^{d,f}	36	51.8	-28.4	-12.1	0.40 (0.04)	0.44 (0.04)	0.94
8	R superior longitudinal fasciculus ^{d,e}	35	39.9	-11.6	28.9	0.53 (0.05)	0.57 (0.04)	0.81
9	L inferior longitudinal fasciculus ^{d,e}	34	-47.0	-33.3	-10.2	0.49 (0.04)	0.52 (0.04)	0.87
10	R superior longitudinal fasciculus ^{d,e}	29	28.2	-9.0	44.0	0.41 (0.04)	0.45 (0.04)	0.84
11	L posterior corona radiata ^d	28	-26.0	-24.4	25.8	0.55 (0.03)	0.58 (0.04)	0.64
12	L inferior longitudinal fasciculus ^{d,e}	24	-32.7	-80.4	-4.9	0.32 (0.04)	0.36 (0.05)	0.81
13	L superior longitudinal fasciculus ^d	24	-42.3	-40.9	7.8	0.53 (0.04)	0.56 (0.04)	0.79
14	L forceps major ^{d,f}	24	-15.0	-73.2	15.0	0.25 (0.04)	0.29 (0.05)	0.92
15	R inferior longitudinal fasciculus ^d	22	55.1	-19.3	-15.7	0.28 (0.05)	0.31 (0.05)	0.78
16	Body of corpus callosum ^d	22	-12.8	-4.4	32.4	0.66 (0.04)	0.69 (0.04)	0.83
17	R external capsule ^{d,e}	21	30.7	-15.1	12.5	0.49 (0.03)	0.51 (0.03)	0.79
18	R forceps minor ^{d,f}	21	20.5	42.7	19.2	0.47 (0.05)	0.51 (0.05)	0.71
19	L superior longitudinal fasciculus ^{d,f}	21	-43.0	-8.4	25.6	0.45 (0.04)	0.48 (0.05)	0.72

FA, Fractional anisotropy; FHP, family history positive; FHN, family history negative; MNI, Montreal Neurological Institute; S.D., standard deviation; L, left; R, right; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity.

^aIn all regions, FHP youth showed higher FA than FHN teens. Regions are listed in order by largest to smallest volume.

^bCoordinates of the center of mass.

^c Cohen's *d* effect sizes computed from means and S.D.s.

^d Within this region, there was lower RD in FHP compared with FHN youth (note: no regions showed higher RD in FHP group compared with FHN); p 's < 0.01.

^e Within this region, there was lower MD in FHP compared with FHN youth (note: no regions showed higher MD in FHP group compared with FHN); p 's < 0.05.

^f Within this region, there was higher AD in FHP compared with FHN youth (note: no regions showed lower AD in FHP group compared with FHN); p 's < 0.02.

Table 3Neuropsychological test scores by domain and individual test^a

	FHN (n=46)	FHP (n=48)	Group differences: <i>p</i>
Global neuropsychological functioning, Z score	0.12 (0.52)	0.06 (0.47)	0.45
Short-term memory, Z score	0.23 (0.77)	0.11 (0.76)	0.60
WISC-III digit span forward, total raw score	10.24 (1.09)	10.09 (1.90)	0.69
WISC-III digit span backward, total raw score	6.44 (1.88)	6.28 (1.84)	0.67
WAIS-IV letter–number sequencing, raw score	10.71 (1.66)	10.34 (1.87)	0.32
Sustained attention, Z score	0.11 (0.77)	0.04 (0.63)	0.88
Digit Vigilance Test total time, s	224.27 (62.06)	222.13 (41.23)	0.85
WISC-III coding, raw score	63.02 (12.30)	60.83 (10.68)	0.36
D-KEFS trails condition 1 total time, s	23.67 (7.20)	23.40 (5.21)	0.83
D-KEFS trails condition 2 total time, s	29.98 (12.84)	31.52 (8.89)	0.50
D-KEFS trails condition 3 total time, s	30.80 (10.93)	31.40 (7.30)	0.76
D-KEFS trails condition 4 total time, s	69.67 (22.07)	75.50 (25.96)	0.25
Verbal learning and memory, Z score	0.04 (0.95)	0.01 (0.80)	0.44
CVLT-C list A total 1–5, total words	55.16 (8.92)	55.54 (6.80)	0.82
CVLT-C trial 5, total words	12.56 (1.91)	12.87 (1.54)	0.39
CVLT-C short delay free recall, total words	11.74 (2.02)	11.57 (2.62)	0.72
CVLT-C short delay cued recall, total words	12.09 (1.81)	11.80 (1.93)	0.47
CVLT-C long delay free recall, total words	12.07 (1.96)	12.02 (1.72)	0.91
CVLT-C long delay cued recall, total words	12.48 (1.90)	12.17 (1.58)	0.41
Visuospatial functioning, Z score	0.18 (0.64)	0.07 (0.73)	0.95
Rey-O complex figure copy accuracy, total			
Rey-O complex figure delay accuracy, total	18.52 (4.94)	17.61 (4.65)	0.37
WASI block design, total	47.42 (12.50)	44.94 (13.68)	0.37
Hooper Visual Organization Test, raw total score	25.14 (2.29)	25.12 (2.33)	0.96
Spatial planning and problem solving, Z score	0.09 (0.62)	0.09 (0.72)	0.56
WISC-III mazes, total score	22.76 (3.33)	23.57 (3.25)	0.24
WASI matrix reasoning, total score	27.41 (2.81)	27.21 (3.72)	0.78
D-KEFS towers, total achievement score	17.20 (2.24)	16.94 (2.80)	0.62
Inhibition-interference, Z score	0.25 (0.79)	0.15 (0.77)	0.59
D-KEFS color–word interference condition 3 total time, s	57.09 (13.03)	57.38 (10.75)	0.91
D-KEFS color–word interference condition 4 total time, s	62.15 (11.64)	64.56 (14.35)	0.38

Data are given as mean (standard deviation).

FHN, Family history negative; FHP, family history positive; WISC-III, Wechsler Intelligence Scale for Children – 3rd edition; WAIS-IV, Wechsler Adult Intelligence Scale – 4th edition; D-KEFS, Delis–Kaplan Executive Function System; CVLT-C, California Verbal Learning Test–Children's version; Rey-O, Rey–Osterrieth; WASI, Wechsler Abbreviated Scale of Intelligence.

^aNo cognitive domain or individual test differed between the FHN and FHP groups.