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Frontoparietal Connectivity in Substance-naïve Youth with and without a Family History of Alcoholism

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Abstract

Frontoparietal connections underlie key executive cognitive functions. Abnormalities in the frontoparietal network have been observed in chronic alcoholics and associated with alcohol-related cognitive deficits. It remains unclear whether neurobiological differences in frontoparietal circuitry exist in substance-naïve youth who are at-risk for alcohol use disorders. This study used functional connectivity magnetic resonance imaging and diffusion tensor imaging to examine frontoparietal connectivity and underlying white matter microstructure in 20 substance-naïve youth with a family history of alcohol dependence and 20 well-matched controls without familial substance use disorders. Youth with a family history of alcohol dependence showed significantly less functional connectivity between posterior parietal and dorsolateral prefrontal seed regions ($p < .05$), as compared to family history negative controls; however, they did not show differences in white matter architecture within tracts subserving frontoparietal circuitry ($p > .34$). Substance-naïve youth with a family history of alcohol dependence show less frontoparietal functional connectivity in the absence of white matter microstructural abnormalities as compared to youth with no familial risk. This may suggest a potential neurobiological marker for the development of substance use disorders.

Keywords

Alcohol; Functional connectivity; Adolescence; Frontoparietal; At-risk

1. Introduction

Alcohol use is common during adolescence, with typical onset of drinking between ages of 15 and 17 (Sartor et al., 2009; Sartor et al., 2007; York et al., 2004). By high school

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graduation, approximately 75% of adolescents have consumed alcohol (Johnston et al., 2010) and nearly 10% meet alcohol use disorder (AUD) criteria (Clark et al., 2004). Youth with a positive family history (FHP) of AUD are at an increased risk for initiating alcohol use at an earlier age and developing drinking problems, compared to youth with no such family history (FHN) (Schuckit, 1985; Trim et al., 2010a). Although neural mechanisms predicting this increased risk remain unclear, the extant literature on adults with AUD provides insight into potential neurobiological differences that may exist prior to alcohol initiation and place FHP youth at risk for AUD (Herting et al., 2010; Reich et al., 1998; Spadoni et al., 2008).

Chronic alcoholism has been associated with structural brain changes (Crews & Nixon, 2009; Pfefferbaum et al., 2009; Chanraud et al., 2010), functional brain alterations (Gilman et al., 2010; Pfefferbaum et al., 2001), and neurocognitive impairments (for review, Sullivan & Pfefferbaum, 2005). Notably, adult alcoholics show deficits in executive cognitive functioning (for reviews, Sullivan and Pfefferbaum, 2005; Oscar-Berman and Marinkovic, 2007), likely reflecting neurotoxic changes in frontoparietal connections. Neuroimaging studies have noted atypical white matter microstructure in frontal and parietal networks (Pfefferbaum et al., 2010) and altered task-related brain activity in the dorsal prefrontal cortex and posterior parietal cortex in adults with AUD (Boettiger et al., 2007). Recent research suggests that the frontoparietal network may be compromised relatively early in the course of heavy drinking, as adolescent heavy drinkers exhibit altered frontoparietal activity (Schweinsburg et al., 2010) and white matter microstructure (McQueeney et al., 2009); however, these frontoparietal abnormalities may predate alcohol use.

Neurobiological markers of vulnerability that exist prior to alcohol initiation have been suggested by neuroimaging, electrophysiological measures, and other neurological findings, (Bauer and Hesselbrock, 1999; Hill et al., 1999; Hill, 2004). Specifically, FHP youth have shown reduced volume of the right orbitofrontal cortex (Hill et al., 2009) and amygdala (Hill et al., 2001); smaller intracranial volume (Gilman et al., 2007); weaker fronto-cerebellar connectivity (Herting et al., 2010); abnormalities in vigilance-related neural activity (Spadoni et al., 2008); and delays in reaching age-appropriate P300 amplitudes (Begleiter et al., 1984; Hill et al., 1999; Polich et al., 1994) and postural control (Hill et al., 2000). Several of these neurobiological differences have suggested abnormalities in frontoparietal circuitry (Hada et al., 2001; Rangaswamy et al., 2004; Spadoni et al., 2008), including the posterior parietal cortex (PPC) and dorsolateral prefrontal cortex (DLPFC), as these areas are involved in inhibitory control, executive control, and decision-making (Lundqvist, 2010). As such, abnormalities in frontoparietal connectivity may contribute to the neurocognitive abnormalities observed among FHP youth and may be a premorbid neurobiological marker for the development of AUDs.

The current study expands on the existing literature by examining frontoparietal network functioning and integrity in substance-naïve FHP youth and matched controls with no family history of alcoholism (FHN), using functional connectivity MRI (fcMRI) and diffusion tensor imaging (DTI). fcMRI encompasses a variety of analytic approaches (Zhou et al., 2009), including the zero-order temporal correlation between the blood oxygen level dependent (BOLD) time series signal of a designated seed region and all other voxels in the brain (Biswal et al., 1995; 1997). These correlations can be used to create a map representing functionally-related neural activity in spatially segregated brain regions (Leopold et al., 2003a, b). Thus, fcMRI measures the degree to which anatomically distinct brain regions form coherent functional networks (Deco et al., 2011).

In contrast, DTI can assess structural networks by quantifying the diffusion of water molecules in neural tissue, indicating white matter structural organization and integrity. We

compared four scalar diffusion measurements: (i) fractional anisotropy (FA), which reflects directional coherence of diffusion motion; (ii) mean diffusivity (MD), quantifying the average magnitude of diffusion motion; (iii) axial diffusivity (AD), reflecting diffusion along the axis of white matter fibers; and (iv) radial diffusivity (RD), indicating diffusion perpendicular to the axis of white matter fibers.

We examined fcMRI and underlying white matter microstructure in specific frontoparietal areas subserving working memory (PPC and DLPFC; Spadoni et al., 2008; Tapert et al., 2004) in substance-naïve FHP and FHN youth. Based on neurobiological and neurobehavioral differences observed in FHP youth, we hypothesized that FHP youth would show weaker frontoparietal connectivity and white matter fiber tract organization and integrity than FHN youth.

2. Results

2.1. Task Performance

FHP youth did not significantly differ from FHN youth on accuracy or reaction time on the visual working memory (VWM) task [e.g., supra-span trial accuracy: $t(35) = 0.09$, $p = .93$; supra-span trial reaction time: $t(35) = -0.14$, $p = .89$].

2.2. Frontoparietal Connectivity

Frontoparietal connectivity in FHP and FHN youth was examined by using fcMRI maps (corrected for multiple comparisons, >24 contiguous voxels each at $p < .05$) representing the correlation between: right PPC to right DLPFC, left PPC to left DLPFC, right PPC to left DLPFC, and left PPC to right DLPFC, plus exploratory analyses examining correlations of the seed regions to all other voxels in the brain, for each subject. Single sample t-tests evaluated the extent to which these correlations differed from zero for each FH group. FHN youth showed positive correlations between BOLD response time series in: right PPC with right PPC [mean $r = .53$, $p < .001$], left PPC with left DLPFC [mean $r = .33$, $p < .001$], right PPC with left DLPFC [mean $r = .24$, $p < .001$], and left PPC with right DLPFC [mean $r = .35$, $p < .001$]. In contrast, the FHP youth exhibited positive correlations between the right PPC and right DLPFC [mean $r = .39$, $p < .001$] and left PPC and right DLPFC [mean $r = .26$, $p < .001$]. Independent samples t-tests compared the groups directly, and FHP youth had significantly weaker zero-order correlations between BOLD response time series for the bilateral PPC seed regions and DLPFC than FHN youth [right PPC and right DLPFC: $t(38) = 2.08$, $p = .04$; right PPC and left DLPFC: $t(38) = 2.14$, $p = .04$; left PPC and left DLPFC: $t(38) = 2.28$, $p = .03$; and left PPC and right DLPFC: $t(38) = 2.04$, $p = .05$]. When examining connectivity between seed regions and other voxels in the brain, FHP youth also showed weaker PPC connectivity with the lingual gyrus, cuneus, fusiform gyrus, inferior temporal gyrus, mammillary body, and insula (see Table 2), as compared to FHN youth.

To evaluate structural connectivity differences between FHP and FHN youth, we compared DTI indices along white matter tracts subserving frontoparietal connections and found no significant differences between groups on FA ($ps > .35$), MD ($ps > .55$), AD ($ps > .66$), or RD ($ps > .34$).

2.3. Frontoparietal Connectivity and Task Performance

Follow-up Pearson's correlation analyses were performed to examine the relationship between the z-transformed PPC and DLPFC correlation coefficients and behavioral performance during the supra-span VWM task. Number of missed responses during the supra-span VWM task was negatively correlated with functional connectivity between the right PPC and left DLPFC [$r(40) = -.42$, $p = .007$]. Further examination within groups

revealed that FHP youth did not exhibit significant correlations between PPC and DLPFC functional connectivity and behavioral performance measures ($ps > .23$); however, number of missed responses during the supra-span VWM task was negatively correlated with PPC and DLPFC functional connectivity among FHP youth [$r(20) = -.63, p = .002$]. Significant correlations were not observed between functional connectivity findings and other measures of behavioral performance, such as accuracy or reaction time.

3. Discussion

The goal of this study was to examine the association between family history of alcohol use disorders and frontoparietal connectivity in substance-naïve youth. Prior research has highlighted neurocognitive and neurobiological abnormalities among FHP youth, and therefore, we predicted that FHP youth would exhibit weaker frontoparietal connectivity and altered white matter fiber tract organization and integrity compared to age-matched FHN youth. FHP youth demonstrated reduced functional connectivity between PPC and DLPFC compared to FHN youth. Frontoparietal circuitry, which includes areas of the dorsal attention network (Corbetta and Schulman, 2002), continues to develop from short-range, local connections to long-range, integrated networks during adolescence and into adulthood (Fair et al., 2007; 2009). Thus, our findings suggest that weaker frontoparietal connectivity among FHP youth may be indicative of a neurodevelopmental delay whereby FHP youth exhibit weaker long-range connections (i.e., correlation between BOLD time series in PPC to DLPFC) than their FHN counterparts. Follow-up correlation analyses revealed that functional connectivity between the PPC and DLPFC was negatively associated with number of missed responses during a supra-span visual working memory task, specifically among substance-naïve FHN youth. As such, stronger functional connectivity among FHN youth improved overall attention during the task and suggests that weaker frontoparietal connectivity among FHP youth may underlie attentional deficits observed among FHP youth (Knopik et al., 2009), placing them at higher risk for developing attention-deficit/hyperactivity disorder (ADHD; Bush, 2011).

Contrary to our hypothesis, FHP youth did not show altered white matter architecture in tracts subserving frontoparietal circuitry, suggesting that myelination alone cannot explain frontoparietal connectivity disparities. Rather, variations or delays in synaptic transmission may account for differences in frontoparietal connectivity. The lack of white matter differences between substance-naïve FHP and FHN youth supports prior cross-sectional studies showing abnormal white matter microstructure in adolescent binge drinkers, which related to hangover symptoms (McQueeney et al., 2009). Escalation to heavy alcohol use and resulting withdrawal symptomatology, as opposed to familial risk, might be one contributing factor to the reduced white matter integrity observed among heavy drinking youth.

Although we found significant connectivity differences between substance-naïve FHP and FHN youth using an event-related task, fMRI analyses can be performed using a range of experimental approaches, including resting state (e.g., Biswal et al., 1995; Buckner et al., 2011; Fair et al., 2007, 2009), task-specific block (e.g., Anand et al., 2005; Koshino et al., 2005), and event-related designs (e.g., Fox et al., 2006; Pompei et al., 2011; Versace et al., 2010). Thus, there are several options to consider when determining fMRI analytic approach. Specifically, resting-state approaches examine connectivity when the subject is not engaged in a specific mental task and usually assume that time series data are stationary, whereas task-specific, event-related designs do not require stationarity and explore connectivity during a cognitive task (Rissman et al., 2004; Zhou et al., 2009). For this study, the results should be interpreted in the context of working memory task demands.

These data should be considered in light of possible limitations. Our relatively small sample size may have precluded detection of white matter anisotropy or diffusivity differences. Similarly, our *a priori* decision to limit analyses to the specified seed regions and selected white matter tracts to minimize Type I error may have increased Type II error, resulting in unidentified differences between groups. We also acknowledge that effect sizes are modest and may be related to sample characteristics, such as moderate density of familial alcohol use disorder density among FHP youth. Since analyses were not longitudinal, we cannot ascertain whether differences in frontoparietal connectivity predicts alcohol use in FHP youth. Future studies will need to examine whether abnormalities in frontoparietal connectivity directly predicts alcohol use disorders. This study is strengthened; however, by examining functional connectivity and white matter microstructure in well-matched, substance-naïve youth, and we were therefore able to rule out several potential confounds. Furthermore, we combined fMRI and DTI methodologies to not only examine neural regions implicated in the development of AUDs but how they are functionally integrated.

The current study demonstrates that substance-naïve youth with a family history of alcohol use disorders show weaker frontoparietal connectivity, which could be a neurobiological marker for alcohol use disorders and is suggestive of a neurodevelopmental delay among FHP youth. Although functional connectivity alterations were evident, substance-naïve youths did not exhibit white matter structural differences in areas underlying frontoparietal circuitry. These findings have important implications for intervention and prevention programs, as it may be possible to increase functional connectivity through cognitive training, such as working memory and attention tasks used in cognitive remediation. Cognitive remediation, specifically restorative approaches, addresses neurocognitive and neurobiological deficits through repeated practice, which encourages the simultaneous firing or excitation of neurons within a network, and consequently, strengthens the connection within the network (Hebb, 1949). Given “Hebb’s Rule” indicating neurons that “fire together, wire together,” we theorize that cognitive training could affect frontoparietal connectivity by encouraging co-activation of neurons in areas underlying working memory and executive cognitive functions like the frontoparietal network. Future studies using a longitudinal approach should examine mediating and moderating factors of frontoparietal connectivity across development and the extent to which differences in frontoparietal connectivity represents a neurobiological marker for the development of alcohol use disorders in youth at risk.

4. Methods

4.1. Participants

Participants were 20 FHP (50% female) and 20 FHN (50% female) 12–14 year-old substance-naïve youth from an ongoing longitudinal neuroimaging study (Bava et al., 2011; Pulido et al., 2009; Spadoni et al., 2008; Squeglia et al., 2009), recruited through flyers mailed to parents of local middle schoolers (Anderson et al., 2005; Schweinsburg et al., 2004). Following consent and assent from all parents and adolescents, separate structured interviews were completed with the youth, one biological parent, and one other parent or close relative, with the Family History Assessment Module (FHAM; Rice et al., 1995), Customary Drinking and Drug Use Record (CDDR; Brown et al., 1998); and Diagnostic Interview Schedule for Children-Version IV (C-DISC-4.0; Shaffer et al., 1996, 2000).

Exclusionary criteria were: parental history of bipolar, psychotic, or antisocial personality disorder; complicated or premature birth (<34 weeks gestation); any indication of *in utero* alcohol, tobacco, or illicit drug exposure; history of neurological or serious medical illness, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV, American Psychiatric Association, 1994) Axis I disorder, traumatic brain injury with loss of

consciousness > 2 min., or learning disabilities; left-handedness; lifetime use of any psychiatric medication; sensory impairments; non-fluency in English; MRI contraindications; more than 6 lifetime alcohol (and no more than 1 drink per drinking occasion) use occasions; and any lifetime tobacco, marijuana, or other illicit drug use. Groups were statistically equivalent on gender, ethnicity, socioeconomic status, IQ, academic grade point averages, age, pubertal development, and body mass index (see Table 1).

4.2. Measures

The Family History Assessment Module (FHAM; Rice et al., 1995) assessed DSM-IV criteria of alcohol and other drug abuse and dependence in first and second degree relatives. Based on FHAM information, youth were categorized as FHP or FHN. FHP youth had at least one biological parent or two or more second degree relatives with a history of alcohol use disorder, and FHN youth had a total absence of familial substance use disorders. Intellectual functioning was assessed with the 4 subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). The Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) provided a level of adolescent psychopathological syndromes (e.g., internalizing and externalizing behaviors). The Hollingshead Index of Social Position assessed socioeconomic status based on occupation and educational attainment of each parent (Hollingshead, 1965). The Pubertal Development Scale assessed pubertal maturation (Petersen et al., 1988). Body mass index of each participant was calculated as weight (lb)/[height (in)]² × 703).

4.3. Image Acquisition

Youth were imaged on a 3.0-Tesla General Electric CXK4 MR system with an 8-channel phase-array head coil (General Electric Medical System, Milwaukee, WI, USA). Participants had very minimal lifetime histories of personal substance use, and no participant had used alcohol or any other intoxicant for the 50 days prior to scanning. Participants were placed comfortably on the scanner table and the head was stabilized with foam cushions (NoMoCo Pillow, La Jolla, CA). Scan sessions involved a 10-second scout scan to assure good head placement and slice selection covering the whole brain, and a sagittally-acquired high-resolution 3d T1-weighted anatomical image (FOV 24 cm, 256 × 256 × 192 matrix, 0.94 × 0.94 × 1 mm voxels, 176 slices; TR=8 ms, TE=3 ms, TI=450 ms, flip angle 12°, 7:19 minutes). Whole-brain echo planar images were collected axially (FOV 24 cm, 64 × 64 matrix, 3.75 × 3.75 × 3.8 mm voxels, TR = 2000 ms, TE = 30 ms, 90° flip angle, 32 slices no gap, slice thickness = 3.8 mm) as an event-related visual working memory (VWM) task was administered (Luck and Vogel, 1997; Tapert et al., 2004; Trim et al., 2010b). The VWM task trials consisted of 2 (easy working memory load), 4 (moderate load), or 6 (supra-span load) colored dots presented for 100 ms at random locations on a gray background that was back-projected onto a screen. After a 1000 ms delay, the subsequent trial (2000 ms) included the same number of dots presented in the same location that were either the same color array or one dot was a different color. For each trial, participants indicated whether the color displays were the same (“press button 1”) or if they differed (“press button 2”). Each trial was followed by a 500 ms timeout. Participants completed 30 trials of each type (2, 4, or 6 dots) presented randomly, in addition to 69 fixation (rest) trials of variable duration to provide an optimized fast-event related sequence (256 repetitions, total task time of 8 minutes, 32 seconds).

Whole brain high angular resolution diffusion images (HARDI; Frank, 2001) were acquired along 61 noncollinear directions including a $b = 0$ reference image (TE/TR = 93/10,900 ms, FOV = 240 mm, matrix = 128 × 128, 34 contiguous slices, 3 mm slice thickness, b -value = 1500 s/mm²). Two field maps were collected for unwarping to correct for signal loss and

geometric distortion due to B0 field inhomogeneities (Andersson and Skare, 2002; Jezzard and Balaban, 1995).

4.4. Data Processing and Analysis

Structural and functional image processing used Analysis of Functional NeuroImages software (AFNI; <http://afni.nimh.nih.gov>; Cox, 1996), FreeSurfer (Fischl et al., 2002), and FMRIB Software Library (FSL; <http://www.fmrib.ox.ac.uk/fsl/index.html>; Smith et al., 2004). Functional connectivity MRI (fcMRI) assessed the temporal correlations between the BOLD time series data of the VWM task in PPC and DLPFC seed regions. FcMRI preprocessing steps were conducted to reduce the influence any non-task effects. Abnormal values were removed (AFNI *3drespike*), and time series data were temporally aligned and coregistered to a stable base volume (AFNI *3dvolreg*). Each participant's anatomical image was segmented with FreeSurfer, to which time series data were aligned. White matter and ventricle masks were defined and eroded by one voxel along each axis, and time series signal from these white matter and ventricle sources was obtained using AFNI's *ANATICOR* pipeline (Jo et al., 2010) and regressed out of the VWM task time series along with motion adjustments made in coregistration (AFNI *3dDeconvolve*). Temporal band-pass filtering ($0.009 \text{ Hz} < f < 0.08 \text{ Hz}$), spatial smoothing at 6 mm full-width at half-maximum, and neuroanatomical standardization were applied using AFNI.

From the resulting time series dataset, seed masks representing regions identified as important for working memory and cognitive control (Paskavitz et al., 2010; Tapert et al., 2001; 2004) were created by depositing 12-mm diameter spheres in each participant's left and right PPC and DLPFC (see Figure 1). 12-mm spheres were used based on the degree of spatial filtering applied and because ROIs of this size have been shown maintain anatomical specificity and signal sensitivity (Marrelec & Fransson, 2011). A BOLD response time series from the supra-span (6-dot) VWM task, averaged across the region for each repetition, was extracted from each of the 4 seed ROIs. Zero-order correlation analyses were then conducted between the time series extracted from the seed ROIs (i.e., correlation between right PPC and right DLPFC; left PPC and left DLPFC; right PPC and left DLPFC; and left PPC and right DLPFC) and then exploratory analyses examined correlations between the seed regions and all other brain voxels (from the whole brain time series dataset) for each subject (AFNI *3dDeconvolve*). Resulting correlation coefficients were normalized using a Fisher z -transform.

For within-group examination of normalized voxelwise correlation values that significantly differed from zero, single sample t -tests were performed (AFNI *3dttest*) for each group. Independent sample t -tests determined significant group differences in time series seed-voxel correlations (AFNI *3dttest*). Correction for multiple comparisons was achieved through a Monte Carlo simulation, indicating only clusters $\geq 648 \mu\text{l}$ (or 24 contiguous voxels) with a z -score > 2.02 would be interpreted, for an overall volume $\alpha = .05$.

DTI data were used to evaluate structural connectivity between PPC and DLPFC regions. White matter integrity was measured with DTI indices FA, MD, AD, and RD in tracts subserving left and right frontoparietal connections, including the superior longitudinal fasciculus and genu of corpus callosum (see Figure 1). DTI data processing (see Bava et al., 2010 for details) included correction for head motion and eddy current distortion, using FSL tools (Smith et al., 2004). Preprocessed images underwent tensor decomposition to derive scalar diffusion indices (i.e., FA, MD, AD, and RD) for each voxel (Le Bihan et al., 2001), and statistical analyses were performed on FA maps using Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) to co-align each subject's FA image, create a mean FA image from which a white matter skeleton was derived, and project individual transformed FA images onto the skeleton. Partial-volume effects and areas of high inter-subject variability

were minimized by thresholding values at 0.2. Values from individuals' nearest relevant tract center were assigned to the skeleton through a perpendicular search for the maximum value within the skeleton. MD, RD, and AD data were analyzed using the same skeleton-projection vectors derived from the FA images (Smith et al., 2007). Voxelwise statistical comparisons were carried out in AFNI using data from each point on the skeleton using independent sample *t*-tests corrected for multiple comparisons and only clusters > 153 μ l with brain-wise $p < .05$ were interpreted.

Associations between functional connectivity between the DLPFC and PPC and behavioral performance during the supra-span VWM task were examined using Pearson's correlation. Correlation analyses were performed across all subjects and within groups using behavioral performance data (i.e., accuracy, reaction time, and number of missed responses) and the z-transformed correlation coefficients between the four seed regions.

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Highlights

- Abnormalities in frontoparietal connectivity predate alcohol initiation.
- Altered frontoparietal connectivity is evident among youth at-risk for AUD.
- Atypical frontoparietal connectivity may be a neurobiological marker for AUD.

Figure 1. Functional connectivity MRI seed regions and white matter tracts of interest. Yellow = functional connectivity seed regions of interest; Red = superior longitudinal fasciculus; Blue = genu of corpus callosum

Figure 2. Between-group comparisons of frontoparietal connectivity (FHP < FHN) for the right and left PPC and dorsolateral prefrontal cortex (DLPFC) seed regions ($p < .05$).

Table 1

Participant characteristics by family history status.

	Family History Negative (<i>n</i> = 20) M (SD) or %	Family History Positive (<i>n</i> = 20) M (SD) or %	<i>p</i> -value
Female (%)	50%	50%	.67
Age	13.5 (0.7)	13.6 (0.6)	.66
Caucasian (%)	83%	80%	.87
Hollingshead socioeconomic status	20.1 (6.7)	20.7 (8.4)	.81
Full Scale IQ	112 (9.1)	112 (12.0)	.67
Grade point average in school	3.7 (0.4)	3.6 (0.4)	.97
CBCL internalizing <i>T</i> -score	40.9 (6.4)	41.2 (6.9)	.89
CBCL externalizing <i>T</i> -score	38.9 (7.1)	40.0 (7.7)	.62
Pubertal Development Scale			
Males	2.2 (0.4)	2.2 (0.1)	1.0
Females	3.0 (1.0)	2.8 (0.9)	.81
Body mass index	18.9 (2.8)	19.6 (2.5)	.40

Abbreviations: CBCL, Child Behavior Checklist

Table 2

Regions showing weaker connectivity with posterior parietal seed regions in FHP compared to FHN youth (clusters ≥ 24 voxels with z -scores > 2.02 ; brain-wise $\alpha = .05$).

	Voxels	Talairach Coordinates		
		x	y	z
<i>Right posterior parietal cortex</i>				
Left lingual gyrus	146	−16	−80	6
Right cuneus	58	4	−88	20
Left insula	37	−38	14	−6
Right fusiform gyrus	35	38	−62	−6
Right inferior temporal gyrus	33	46	−4	−28
<i>Left posterior parietal cortex</i>				
Left lingual gyrus	77	−14	−76	2
Right inferior temporal gyrus	43	46	−4	−28
Left mammillary body	42	−4	−14	−10
Right cuneus	35	4	−86	18