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Altered fronto-cerebellar connectivity in alcohol-naïve youth with a family history of alcoholism

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Abstract

Fronto-cerebellar connections are thought to be involved in higher-order cognitive functioning. It is suspected that damage to this network may contribute to cognitive deficits in chronic alcoholics. However, it remains to be elucidated if fronto-cerebellar circuitry is altered in high-risk individuals even prior to alcohol use onset. The current study used functional connectivity MRI (fcMRI) to examine fronto-cerebellar circuitry in 13 alcohol-naïve, at-risk youth with a family history of alcoholism (FH+) and 14 age-matched controls. In addition, we examined how white matter microstructure, as evidenced by fractional anisotropy (FA) related to fcMRI. FH+ youth showed significantly reduced functional connectivity between bilateral anterior prefrontal cortices and contralateral cerebellar seed regions compared to controls. We found that this reduction in connectivity significantly correlated with reduced FA in the anterior limb of the internal capsule and the superior longitudinal fasciculus. Taken together, our findings reflect associated aberrant functional and structural connectivity in substance-naïve FH+ adolescents, perhaps suggesting an identifiable neurophenotypic precursor to substance use. Given the role of frontal and cerebellar brain regions in subserving executive functioning, the presence of premorbid abnormalities in fronto-cerebellar circuitry may heighten the risk for developing an alcohol use disorder in FH+ youth through atypical control processing.

Keywords

alcohol; fMRI; adolescence; functional connectivity; cerebellum; at-risk

1.1 Introduction

The onset of alcohol use typically occurs during adolescence (Bates and Labouvie, 1997). By the 12th grade, 72% of teens have used alcohol (Johnston et al., 2007), accompanied by a sharp increase in alcohol use disorders (AUD) observed across the adolescent years (Chung et al., 2002). While effort has been directed toward understanding the neurotoxic effects of

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alcohol, it is equally important to identify potential neurobiological markers that may underlie risk for alcohol abuse.

Here, we examined the brain circuitry of an at-risk population prior to substance use. Specifically, we examined youth with a family history of alcoholism (FH+). FH+ adolescents often begin using at younger ages (McGue et al., 2001), have greater severity of use (Chassin et al., 2004), and have higher incidence of AUD than the general population (Milberger et al., 1999). Even when alcohol-naïve, FH+ youth perform worse on a variety of neuropsychological tests (Tapert and Brown, 2000) and show poorer postural control compared to their peers (Hill et al., 2000).

Emerging research has shown structural and functional brain abnormalities in high-risk youth, prior to alcohol use. Specifically, non-using FH+ youth have altered white matter microstructure (Herting et al., 2010), larger cerebellums (Hill et al., 2007), and atypical task-related prefrontal cortex activity (Schweinsburg et al., 2004) compared to controls. Notably, these types of abnormalities not only occur in FH+ adolescents prior to use, but also appear in adult patients with AUD. For example, adult alcoholics have atypical white matter microstructure in frontal and limbic pathways (Yeh et al., 2009), abnormal glucose metabolism in frontal and cerebellar regions (Adams et al., 1993; Martin et al., 1992), and altered task-related activity in the left prefrontal cortex and the right lateral cerebellum (Petersen et al., 1989). Taken together, these data suggest common abnormalities in fronto-cerebellar circuitry between adult alcoholics and FH+ youth prior to alcohol use, and may reflect a neural vulnerability for AUD (Tessner and Hill, 2009).

Thus, the goal of this study was to examine fronto-cerebellar circuitry in FH+ youth and age-matched controls without a family history of alcoholism (FH-). We did this by combining two complementary methods – functional connectivity MRI (fcMRI) and diffusion tensor imaging (DTI). fcMRI measures low-frequency (0.1 Hz) correlated blood oxygen level dependent signal fluctuations between a particular seed region and all other voxels in the brain. Voxels significantly correlated with the seed region are considered “functionally connected” (Biswal et al., 1995; Hampson et al., 2002). DTI is a technique that allows for in vivo quantification of white matter coherence and directionality as measured by fractional anisotropy (FA), a value which reflects axonal and myelin fiber integrity (Basser, 1995). Therefore, we first focused on examining fcMRI in defined fronto-cerebellar brain regions (see Table 1), previously shown to be important for generalized task-level control processing (Dosenbach et al., 2006). Next, we related these findings to the underlying neural substrate by examining fcMRI results in relation to white matter regions, previously identified as atypical in FH+ youth (Herting et al., 2010). Because fronto-cerebellar systems are disrupted in adult alcoholics (Adams et al., 1993; Martin et al., 1992; Petersen et al., 1989; Sullivan et al., 2003), and because portions of this circuit have been shown to be atypical in FH+ youth (Hill et al., 2007; Schweinsburg et al., 2004), we hypothesized that FH+ youth would show weaker fronto-cerebellar connectivity than their FH- peers, as indicated by fcMRI analyses. Furthermore, we hypothesized that weaker fronto-cerebellar connectivity would be related to aberrant white matter microstructure.

1.2 Methods and Materials

1.2.1 Participants

Participants included 13 FH+ (6 females) and 14 FH- (7 females) substance naïve youth, ages 11 to 15 years, and were a subset of a larger sample previously published (Herting et al., 2010). All participants were recruited and underwent comprehensive screening interviews as part of an ongoing study of adolescent neurodevelopment. Briefly, following written consent and assent in accordance with the local Institutional Review Board, separate

structured telephone interviews were conducted with youth and parents. Interviews consisted of the Diagnostic Interview Schedule for Children Predictive Scales (DISC-PS-4.32b) (Hoven et al., 2005; Lucas et al., 2001), the Family History Assessment Module (FHAM) (Rice et al., 1995), the Brief Lifetime version of the Customary Drinking and Drug Use Record (Brown et al., 1998), and the Structured Clinical Interview (SCI) (Brown et al., 1994). Exclusionary criteria for youth included the inability of a parent to provide family history information, lifetime history of a diagnosed DSM-IV psychiatric disorder, history of any alcohol or substance use (including cigarettes), neurological illness or head trauma, serious medical problems, mental retardation or learning disability, prenatal exposure to drugs or alcohol, reported history of psychotic disorders in biological parents (i.e. bipolar I or schizophrenia), left-handedness, irremovable metal, and pregnancy.

1.2.2 Classification of Family History Alcohol and Substance Use/Dependence

Dichotomizing individuals based on first, or first and second degree relatives with an AUD, has been shown to be a robust measure of substance abuse vulnerability (Stoltenberg et al., 1998). Thus, the FHAM was used to assess DSM-IV criteria for AUD in first and second degree relatives during telephone interview. Based on this information, youth were categorized as either FH+ or FH-. Youth were considered FH+ if a history of AUD was reported for one, or both, biological parents, or two or more second-degree relatives on the maternal or paternal side of the family; youth were considered FH- if a total absence of AUD among relatives was reported.

1.2.3 Participant Characteristics

To provide an estimate of overall intellectual functioning, youth were administered the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Pubertal maturation was assessed using the Pubertal Development Scale (Petersen et al., 1988). The Edinburgh Handedness Inventory was used to verify right-handedness (Oldfield, 1971). Socioeconomic status (SES) was assessed by administering the Hollingshead Index of Social Position (ISP) to parents as part of the telephone interview, a measure which is based on occupation and educational attainment of each parent (Hollingshead, 1975).

1.2.4 Imaging Acquisition

All subjects were scanned on a 3.0 Tesla Siemens Magnetom Tim Trio system (Siemens Medical Solutions, Erlangen, Germany) with a twelve channel head coil. Whole-brain, high-resolution structural anatomical images were acquired in the sagittal plane using a T₁ weighted MPRAGE scanning sequence (TI = 900ms, Flip Angle = 10 degrees, TE = 3.58 ms, TR = 2300 ms, acquisition matrix = 256×240, slice thickness = 1.1mm). Diffusion weighted images were acquired oblique to the AC-PC, using a high-angular resolution echo planar sequence (TR = 9500ms, TE = 95 ms, FOV = 240 mm², 72 slices, slice thickness = 2mm). The entire DTI sequence consisted of four averages of 72 axial slices, covering the whole brain, acquired with a b-value of 1000s/mm² along 20 diffusion directions (3 b=0 images/average). Whole-brain functional magnetic resonance imaging (fMRI) was acquired in the axial plane, oblique to the AC-PC, using a T2*-weighted echo planar blood oxygen level dependent (BOLD) sequence (TR = 2000 ms, TE = 30 ms, FOV = 240 mm, flip-angle = 90°, 33 slices no gap, slice thickness = 3.75mm). Data from two block-design and one event-related design task were included in the fMRI analyses (See Table 2). Specifically, the block-design tasks included modified versions of the counting stroop (Bush et al., 2006) and the emotional counting stroop (Whalen et al., 2006), as well as a masked emotional faces task (Whalen et al., 1998). The event-related task was a reward-based decision making task (Paulus et al., 2003). For all three tasks, stimuli were back-projected on a screen that participants viewed via a mirror attached to the head coil, and if required, responses were made using an MRI compatible mechanical button box. No verbal responses were necessary.

for any of the tasks. Subjects were asked to perform a variety of cognitive functions across these tasks, including cognitive inhibition, implicit and explicit facial perception and, and reward-based decision making (See Table 2).

1.2.5 fMRI Data Preprocessing

In order to reduce artifacts, functional images underwent a series of preprocessing steps (Miezin et al., 2000). These processes included 1) removal of a central spike, 2) slice-timing correction, 3) correction for head movement within and across task runs, and 4) within-run intensity normalization to a whole brain mode value of 1000. Only data with less than 1.5 mm root mean squared (RMS) of within-run motion, across 6 motion parameters, were included in further analyses (differences in movement between groups was not statistically significant: $t(25) = -1.78$, $p = .098$). For each individual, functional data were transformed into standard Talairach coordinates (Talairach and Tournoux, 1988) and resampled into 3 mm³ voxels. Functional datasets from each task were then concatenated to make a single timeseries dataset for each participant, which was used in all further preprocessing and data analysis. Examining functional connectivity patterns collapsed across multiple tasks has been done previously (Andrews-Hanna et al., 2007; Casey et al., 2007; Fair et al., 2007b), and is thought to represent inherent brain connectivity patterns above and beyond any specific task effect.

1.2.6 fcMRI Correlation Preprocessing

Additional processing steps were used to reduce variance unlikely to reflect neuronal activity (e.g. heart rate and respiration), as previously established (Fox et al., 2005). First, spatial smoothing (6mm full width at half maximum), and a temporal band-pass filter ($0.009 \text{ Hz} < f < 0.08 \text{ Hz}$) were applied to the data. Next, regression analyses were used to regress out the six parameters obtained by motion correction, the averaged whole brain signal, ventricular signal averaged from the ventricular region-of-interest (ROI), and white matter signal averaged from the white matter ROI, as well as the first order derivative terms for the whole brain, ventricular, and white matter signals.

1.2.7 Voxelwise & Pairwise Correlation Analyses

Four seed regions (12 mm diameter spheres), previously identified as important for task control (Dosenbach et al., 2006), were chosen for analysis. The coordinates for these seed regions can be found in Table 1, and included bilateral anterior prefrontal cortex (aPFC) and bilateral lateral cerebellar regions. For all subjects, BOLD timecourses were extracted for both lateral cerebellar seed regions, and correlation maps were generated by computing correlation coefficients between the seed region timecourse and the timecourse for all other brain voxels, creating a correlation matrix. Next, a Fisher z transformation was applied to the correlation coefficients to improve normality for subsequent analyses. For both groups, one sample t -tests were performed to provide group-level correlation maps for each seed. Two-sample t -tests were used to examine quantitative group differences in functional connectivity. To correct for multiple comparisons, a Monte Carlo simulation was performed, with results requiring 35 contiguous voxels exceeding a z -score of 2.5 necessary for cluster significance at an $\alpha < .05$. Caret software (Van Essen et al., 2001) was used to visualize and generate images.

In addition to voxelwise correlation analyses, pairwise correlations were conducted between BOLD timeseries in each of the four predefined seed regions. Again, a Fisher r to z transformation was applied to the correlation coefficients to improve normality prior to direct comparison of pairwise correlations using two-sample, two-tailed t -tests.

1.2.8 DTI Preprocessing and Analyses

DTI was not collected for one FH+ youth due to a technical error. Details of the DTI protocol and analyses have been reported previously on a larger sample, which includes all participants used for the current analyses (Herting et al., 2010). Briefly, image preprocessing included correction of magnetic field inhomogeneities, head motion, aligning of the 4 diffusion runs, and skull removal using FMRIB tools from FSL (Jenkinson, 2003; Jenkinson et al., 2002; Smith, 2002). AFNI (Cox, 1996) was used to calculate fractional anisotropy (FA) for each voxel. Next, Tract Based Spatial Statistics (TBSS) version 1.2 (Smith et al., 2006; Smith et al., 2007) was used to 1) co-align each subject's FA image, 2) create a white matter skeleton, representing only the major tracts common across all subjects, and 3) project each subject's FA image onto the skeleton for subsequent voxelwise analyses. To examine mean FA between FH+ and FH- youth, voxelwise independent sample *t*-tests were performed on the FA white matter skeleton (Cox, 1996). To correct for multiple comparisons, a Monte Carlo simulation (Cox, 1996) was performed, and 23 contiguous voxels exceeding a *t*-threshold of 2.75, $p < .01$, (cluster volume $\geq 23 \mu\text{L}$, clusterwise $\alpha < .01$) were necessary for statistical significance.

The authors, however, acknowledge that the TBSS technique has a number of limitations. Specifically, TBSS is limited in its ability to accurately measure FA values in regions where there is a high number of crossing tracts, and skeleton contiguity is not enforced at junctions (Smith et al., 2006). Therefore, voxelwise statistics are also difficult to interpret in these regions. In addition, TBSS is sensitive to outliers. Thus, follow-up ROI based analyses were also performed to verify results (See Herting et al., 2010 for full details).

1.2.9 Task Related BOLD Signal in Seed Regions

To determine if task-related differences between the two groups accounted for group differences detected in functional connectivity, exploratory post-hoc analyses were performed examining task-related BOLD signal in the 4 pre-defined seed regions. Briefly, images were blurred with a full width at half maximum of 6 mm and analyzed using Analysis of Functional NeuroImages (AFNI) (Cox, 1996). For each task, the time series data from each subject was deconvolved with a reference vector representing the task design, in light of the delayed hemodynamic response, while covarying for motion and linear trends. The fit coefficients (β), were then derived from fitting the time series data to the task model. Using the center of mass coordinates for seed regions employed in the voxelwise connectivity analyses (see Table 1), 10mm diameter spheres were created. Each spherical ROI was then applied to each subject's BOLD data for all tasks to examine the average fit of the model in each of the four seed regions. These averages were exported to SPSS. One-sample *t*-tests were performed for each group to determine if significant activation was seen in any of the four seed region ROIs, while independent *t*-tests were used to examine the fit of the model for each ROI between groups.

1.2.10 Structural and Functional Connectivity Analyses

We have previously shown differences in structural connectivity between FH+ and FH- youth, as measured by FA, which utilized a larger sample that included the current subsample of participants (Herting et al., 2010). Excluding regions susceptible to partial volume effects (the inferior longitudinal fasciculus and the parietal superior corona radiata), the results from this first study showed that FH+ youth had significantly lower FA in 6 white matter clusters, including a cluster in the right optic radiation, right extreme capsule, left superior longitudinal fasciculus, left anterior limb of the internal capsule, and two clusters in the right anterior superior corona radiata. Thus, we specifically wanted to examine how FA in these previously reported 6 regions showing group differences may relate to functional connectivity differences seen in these youth. To accomplish this, mean FA values were

extracted from the significant between-group FA clusters for each individual. Of the significant FA clusters, only the 6 clusters that were independent of partial volume effects were used for further analyses (Herting et al., 2010). A Pearson's correlation was then performed, across all subjects, to examine the relationship between FA in each of the 6 TBSS clusters and the z-transformed pairwise correlation coefficients between the four predefined seed regions. Balancing the number of comparisons being made and the somewhat preliminary nature of this study, correlations with a $p < .01$ were considered significant.

1.3 Results

1.3.1 Demographics

Participant demographic information is presented in Table 3. One subject did not have IQ data, due to a technical error. FH+ youth did not significantly differ from controls on age [$t(25) = .14, p = .88$], pubertal status [$t(25) = .08, p = .94$], SES [$t(25) = -1.35, p = .19$], IQ [$t(24) = .72, p = .47$], or grade point average (GPA) [$t(25) = 1.86, p = .07$]. Notably, performance on all fMRI tasks was comparable between FH+ and FH- youth (Table 3). Furthermore, when performance scores for all tasks were converted into Z-scores and averaged across tasks, FH+ and FH- youth did differ in overall performance [FH- Z-score = .11 (.35), FH+ Z-score = -.13 (.44); $t(25) = 1.58, p = .13$].

1.3.2 FH+ youth show altered fronto-cerebellar connectivity

To examine fronto-cerebellar circuitry in FH- and FH+ youth, fcMRI maps were created using both right and left lateral cerebellar seed regions for each group (Figure 1a). FH- youth showed functional connections, demonstrated by positive correlations in the BOLD timeseries, between right and left lateral cerebellar seed regions and contralateral anterior prefrontal cortices. These findings are consistent with known neuroanatomy, in which fronto-pontine fibers decussate at the brainstem before making connections with the contralateral cerebellum (see Kelly and Strick, 2003; Schmahmann and Pandya, 1997 and Discussion). FH+ youth, however, showed little to no functional connectivity between the cerebellar seeds and their opposing anterior prefrontal cortices (Figure 1a). Direct statistical comparisons of fcMRI group maps confirmed these results (Figure 1b). Other differences were also noted in the direct comparison. Reduced lateral cerebellar connectivity for FH+ youth was additionally observed with the cingulate gyrus, bilateral cuneus, and contralateral putamen and insula (Table 4).

Pairwise correlations between BOLD timeseries in each of the four predefined seed regions were also performed as a secondary method to examine fronto-cerebellar connectivity between the groups. Similar to voxelwise functional connectivity, FH+ youth had significantly weaker correlations between BOLD timeseries for both lateral cerebellum seed regions and the contralateral aPFC compared to FH- youth (Figure 2) [Right lateral cerebellum & Left aPFC: $t(25) = 2.45, p = .022$; Left lateral cerebellum & Right aPFC $t(25) = 2.45, p = .021$]. However, FH+ youth had a stronger correlation between BOLD patterns in the left and right lateral cerebellar regions compared to FH- youth [$t(25) = -2.22, p = .04$].

1.3.3 Altered fronto-cerebellar circuitry was independent of task-specific activation

To determine if group differences in fronto-cerebellar circuitry were influenced by task-specific patterns of activation, task-related BOLD signal was examined in the aPFC and cerebellar regions. Results showed that, overall, all four seed regions showed minor task-related activation across the tasks (Supplementary Table 1). Importantly, the model fit was not significantly different between FH+ and FH- youth for all four seed regions and across all three tasks. The exception to this finding was that FH+ youth showed greater activation

than FH- youth in the left aPFC during one block condition during the emotional stroop task (Supplementary Table 1). As a whole, these findings are important, because they strongly suggest that group differences in functional connectivity were not simply due to differences in brain activation related to the tasks used in our fcMRI analyses. Rather, our findings reflect an inherent difference in intrinsic brain connectivity in FH+ youth. Similar findings have been reported elsewhere (Andrews-Hanna et al., 2007).

1.3.4 Fronto-cerebellar connectivity is related to structural connectivity in FH+ and FH- youth

Given our previous findings showing differences in structural connectivity between FH+ and FH- youth, we sought to determine the relationship between structural and functional connectivity in these youth. Therefore, we performed correlational analyses between FA in these 6 predefined clusters of group difference and fronto-cerebellar correlation coefficients across all subjects. These results can be seen in Table 5. FA in the left anterior limb of the internal capsule was positively correlated with functional connectivity between the left aPFC and the right lateral cerebellum [$r(26) = .505, p = .009$] (Figure 3a). In addition, higher FA in the left superior longitudinal fasciculus was significantly associated with stronger functional connectivity between the right aPFC and contralateral cerebellum [$r(26) = .616, p = .001$] (Figure 3b). Importantly, significant relationships were not seen between the connectivity findings and FA in other regions that are not likely related to fronto-cerebellar connectivity, such as the anterior superior corona radiata and the optic radiations, reflecting localization of these relationships to fronto-cerebellar pathways.

1.4 Discussion

The current study examined fronto-cerebellar circuitry in youth at high risk for developing an AUD compared to control youth. FH+ participants demonstrated reduced functional connectivity between bilateral lateral cerebellar regions and contralateral anterior prefrontal cortices compared to FH- age-matched controls. In addition, lower FA in white matter regions positioned along known fronto-cerebellar anatomical tracts was significantly associated with reduced functional connectivity.

A compelling aspect to the current findings is that contralateral functional connectivity patterns were identified between the frontal lobes and the cerebellum. As such, we start the discussion with background regarding the known neuroanatomy of fronto-cerebellar connectivity. While the cerebellum was traditionally believed to be associated with motor function, recent research suggests that the cerebellum also forms parallel closed-loop circuits with the frontal lobes (Dum and Strick, 2003; Jones, 1985; Kelly and Strick, 2003), contributing to higher-order cognitive behavior (Paulesu et al., 1993; Petersen et al., 1989; Schmahmann and Sherman, 1998). Indeed, anatomical studies in non-human primates have shown that the frontal lobes project via the cerebral peduncle and pontine nuclei to the cerebellum. In return, efferent projections from the cerebellum project to the contralateral thalamus, and then to the cortex, including prefrontal regions (Dum and Strick, 2003; Jones, 1985; Kelly and Strick, 2003; Middleton and Strick, 2001).

Investigations of resting-state functional connectivity in humans have revealed related findings. For example, fcMRI studies involving distinct regions of the posterior neocerebellum have identified functional connections with prefrontal and parietal cortices, including the superior and middle frontal gyrus, as well as the frontal pole (Habas et al., 2009; O'Reilly et al., 2010). These connectivity results also show contralateral fronto-cerebellar organization (Habas et al., 2009; O'Reilly et al., 2010), mirroring the fact that white matter fibers decussate and cross over to the contralateral hemisphere between the cerebellum and the cerebral cortex (Kelly and Strick, 2003). Consistent with these findings,

our results showed that distinct contralateral functional connectivity between the lateral cerebellum and the prefrontal cortex exists in healthy adolescents, and that this connectivity is atypical in FH+ youth. Furthermore, we found that fronto-cerebellar connectivity significantly correlated with structural connectivity (FA) in the anterior limb of the internal capsule and the left superior longitudinal fasciculus. Notably, the anterior limb of the internal capsule carries the aforementioned fronto-pontine fibers that project from the frontal lobe to the cerebellum (Schmahmann and Pandya, 1995, 1997), whereas the superior longitudinal fasciculus has projections into the frontal cortex around the Sylvian fissure (Wakana et al., 2004).

The pattern of functional connectivity between the lateral cerebellum and the prefrontal cortex was weaker in FH+ youth compared to FH- youth. Notably, both groups were matched on demographic variables, and were only different with regard to family history of alcoholism. Additionally, both groups showed comparable behavior on all fMRI tasks used in this study. Thus, while impairments in cerebellar and frontal lobe functioning in adult alcoholism are well-established (Sullivan et al., 2002; For a complete review see Sullivan et al., 2003), the current findings show disrupted fronto-cerebellar connectivity, prior to alcohol use. These results support previous speculation that cerebello-thalamic-cortical systems may be vulnerable in high-risk youth with a family history of AUD (Tessner and Hill, 2009).

Several lines of research provide rationale for how atypical fronto-cerebellar functional connectivity may confer vulnerability for alcoholism. Converging evidence from lesion studies and neuroimaging show that cortico-cerebellar circuits are important for numerous high-order cognitive functions, including attention (Allen et al., 1997), executive control (Schmahmann and Sherman, 1998), and working memory (Paulesu et al., 1993). Based on these associations, premorbid dysfunction in fronto-cerebellar connectivity in FH+ individuals may contribute to the wide array of behavioral deficits previously reported in these youth (Corral et al., 1999; Schweinsburg et al., 2004; Tapert and Brown, 2000). If aberrant fronto-cerebellar circuitry in FH+ youth is associated with impaired executive functioning, this may facilitate early onset alcohol use through poor decision making and increased risk-taking relative to FH- peers. Furthermore, aberrant fronto-cerebellar functional connectivity in FH+ youth may reflect an overall developmental delay, as long range functional connections, such as those between the cerebellum and the cerebral cortex, emerge across development (Fair et al., 2009; Fair et al., 2007a). This possibility is further supported by the fact that 1) FH+ youth have lower FA values, indicative of less myelination or axonal caliber, in a variety of brain regions (Herting et al., 2010); and 2) that in the current study, weaker functional connectivity was shown to associate with lower FA in tracts that are aberrant in FH+ youth that carry fibers between the frontal lobes and cerebellum (e.g. the anterior limb of the internal capsule). Although functional connectivity data are based on correlational analyses and do not necessarily reflect structural connectivity, the current findings suggest that the two may in fact be related in FH+ youth. It is possible that FH+ may have a delay in structural connectivity and myelination which could contribute to impairments in establishing intact fronto-cerebellar functioning relative to their peers. Future research is needed to clarify the how delayed structural and functional connectivity may independently, as well as concurrently impact executive functioning and decision-making capabilities in these youth. Furthermore, it will be important to determine if relatively immature brain connectivity in FH+ youth render them especially vulnerable to the neurotoxic and cognitive effects of alcohol compared to their lower risk peers.

While our results show strong evidence that the fronto-cerebellar system is altered in FH+ youth, there are a number of potential limitations that need to be addressed. First, while our data are suggestive that atypical connectivity may be a precursor to excessive alcohol use,

they are not determinative. Thus, longitudinal data will be necessary to begin to directly examine if weaker fronto-cerebellar connectivity predicts alcohol use in high-risk FH+ youth, and how this atypical connectivity relates to the typical developmental trajectory (Fair et al., 2009; Fair et al., 2007a). In addition, it should be noted that in the current study a single informant was interviewed to assess family history, and although significant group differences were seen, research has shown that increasing the number of informants leads to an increased ability of detecting family history of alcoholism (Andreasen et al., 1986). Additionally, the current study examined fronto-cerebellar connectivity across multiple tasks, including both block and event-related fMRI task design. While previous research has shown that examining functional correlations across tasks is useful (Andrews-Hanna et al., 2007; Casey et al., 2007; Fair et al., 2007b), and that functional correlation patterns across multiple tasks are likely to be consistent above and beyond any specific task effect, this is still an ongoing discussion for the field. Particularly, our post-hoc analyses showed that overall BOLD signal did not differ between the groups in any of the predefined seed regions for any of the tasks. Thus, it is unlikely that the current results are due solely to any one particular task activation pattern per se, but rather, our findings reflect an overall deficit in intrinsic fronto-cerebellar circuitry independent of task activity. Nonetheless, in the future it will be important to confirm these findings using pure resting state fMRI to observe how it might differ from the current approach.

In conclusion, this study demonstrated that although frontal-cerebellar connectivity is present by adolescence, it is significantly weaker in youth with a family history of alcoholism, which may reflect a neuromaturational delay in this at-risk group. While atypical fronto-cerebellar functioning and circuitry is apparent in adult alcoholics and has been thought to be associated with the neurotoxic effects of alcohol (Adams et al., 1993; Martin et al., 1992; Petersen et al., 1989; Pfefferbaum et al., 1997; Sullivan et al., 2002), our results show that abnormalities exist in these circuits in FH+ youth, prior to alcohol use onset. Thus, these findings may point to an important biological marker of risk for AUD. Elucidating how structural and functional differences in this circuitry lead to increased risk, and prospectively relate to the emergence of alcohol use, is crucial in furthering our understanding of AUD etiology and developing targeted intervention and prevention strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research Highlights

- Contralateral fronto-cerebellar functional connectivity exists in developing youth.
- Youth at high-risk for alcoholism show aberrant fronto-cerebellar connectivity.
- Aberrant fronto-cerebellar functional connectivity relates to structural connectivity.
- Fronto-cerebellar circuitry may be a distinct vulnerability marker for at-risk youth.

Figure 1.

Functional connectivity for the right and left lateral cerebellar seed regions of FH- and FH+ youths. a.) Axial view of individual group positive z-maps resulting for the left and right lateral cerebellum seed regions, respectively. Note: FH- show contralateral aPFC connectivity with the cerebellum, whereas this connectivity is absent in FH+ youth (circled regions). b.) Direct between group comparisons for the right and left lateral cerebellar seed regions. FH- > FH+ cerebellar connectivity with the contralateral aPFC (circled regions). Images corrected for multiple comparisons ($p < .05$).

b.

Correlation Coefficient (<i>r</i>)	FH-	FH+	<i>p</i> -value
Right Lateral Cerebellum & Left aPFC	.19	.10	.022
Left Lateral Cerebellum & Right aPFC	.18	.05	.021
Right & Left Lateral Cerebellum	.30	.42	.04

Figure 2.

Between group pairwise correlations for bilateral lateral cerebellar and aPFC seed regions.
a.) Visual depiction of group differences overlaid on top of a semi-transparent axial brain b.) Individual group correlation coefficients between seed regions.

Figure 3.

Relationship between structural and functional connectivity. a.) Relationship between FA in the left anterior limb of the internal capsule (alic) and left aPFC fronto-cerebellar connectivity. b.) Relationship between FA in the left superior longitudinal fasciculus (slf) and right aPFC fronto-cerebellar connectivity. FA images are in MNI standardized space, and red ROIs reflect cluster location. Scatter plot insets: squares = FH-individuals; circles = FH+; black line = total fit; small dotted line = fit of FH- data; large dotted line = fit of FH+ data.

Table 1

Seed regions (from Dosenbach et al., 2006). Coordinates are in standard Talairach space.

Seed Region		Coordinates x, y, z	Functional Network
Lateral Cerebellum	Left	-32, -66, -29	Cerebellar
	Right	31, -61, -29	
Anterior Prefrontal Cortex (aPFC)	Left	-28, 51, 15	Fronto-parietal
	Right	27, 50, 23	

Table 2

Experimental details for tasks included in analyses. A single standard imaging protocol was used to acquire all data (See Methods). TR = repetition time.

	1	2	3
Task Condition	Stroop (Counting ^a & Emotional ^b)	Explicit and Implicit Face Perception ^c	Reward-Based Decision Making ^d
fMRI Task Design	Block	Block	Event-Related
Stimuli	Words	Faces	Images
Stimuli	Visual	Visual	Visual
Response	Button Press	None	Button Press
# Subjects (# FH+)	27 (13)	25 (12)	26 (12)
TR Length (s)	2	2	2
Task Run Length (# of TRs)	128	78	256
# of Task Runs	3	2	1

^a Adapted from Bush *et al.*, 2006

^b Adapted from Whalen *et al.*, 2006

^c Adapted from Whalen *et al.*, 1998

^d Paulus *et al.*, 2003

TR = repetition time.

Table 3

Demographic and performance data for subjects by family history group. All values are means and standard deviations, unless otherwise noted.

	FH- (n=14)	FH+ (n=13)	<i>t</i>-value	<i>p</i>-value
<u>Demographics</u>				
Female (n)	7	6		
Age	13.6 (1.6)	13.5 (1.3)	<i>t</i> (25) = .14	.88
Pubertal maturation ^a	2.6 (.8)	2.6 (.7)	<i>t</i> (25) = .08	.94
Caucasian (%)	92.9	84.6		
Full scale IQ ^b	119 (11) ^d	116 (9.4)	<i>t</i> (24) = .72	.47
GPA	3.7 (.3)	3.4 (.4)	<i>t</i> (25) = 1.86	.07
SES ^c	21.9 (11)	28 (13.3)	<i>t</i> (25) = -1.35	.19
<u>Task Performance</u>				
Stroop (% Accuracy)				
Counting	88.8 (8.8)	85.2 (7.9)	<i>t</i> (25) = 1.12	.27
Emotional Counting	94.8 (3.2)	87.0 (22.2)	<i>t</i> (25) = 1.30	.20
Face Perception (# of faces remembered)				
Explicit	4.4 (.9)	4 (.9)	<i>t</i> (22) = 1.07	.30 ^e
Implicit	0.38 (.8)	0.2 (.6)	<i>t</i> (22) = .71	.49 ^e
Reward-Based Decision Making (% Choices Made)				
Risky	53.2 (12.1)	49.9 (19.4)	<i>t</i> (24) = .53	.60
Safe	46.2 (11.9)	49.9 (19.2)	<i>t</i> (24) = -.60	.55

^a Pubertal Development Scale

^b WASI

^c Hollingshead Index of Social Position (ISP)

^{d, e} Denotes one subject missing data due to collection error

Table 4

Additional regions showing group differences in functional connectivity with the lateral cerebellum. All regions reflect weaker functional connectivity in FH+ compared to FH- youth for both the left and right lateral cerebellum. Coordinates are based on standard Talairach space.

	Brodmann's Area	Voxels	x	y	z
Left lateral cerebellum					
Superior frontal Gyrus	10	60	21	50	24
Middle Frontal Gyrus	10	46	-37	44	12
	9	43	44	11	34
Cingulate Gyrus	23	34	4	-23	27
Culmen		65	-1	-33	-25
Pyramis		36	14	-79	-27
Right lateral cerebellum					
Middle Frontal Gyrus	9	73	-32	29	31
	9	43	-26	37	27
	10	73	-31	47	19
Middle Temporal Gyrus	21	36	52	-12	-18
Cingulate Gyrus	24	73	-3	13	27
Cuneus	19	58	-9	-84	37
	19	40	12	-78	35
	18	35	9	-74	25
Putamen		64	-26	-7	6
Insula		53	-41	7	2
Uvula		73	-9	-81	-33
		54	0	-64	-27
Pyramis		53	14	-64	-29

	Brodmann's Area	Voxels	x	y	z
Tuber		28	-35	-74	-30

Table 5

Relationships between FA and fronto-cerebellar connectivity. Correlation coefficients reflecting the relationship between FA in each of the 6 TBSS clusters and the z-transformed pairwise correlation coefficients between the aPFC and contralateral cerebellar regions among all subjects. Cluster coordinates are in standard MNI space.

FA clusters x, y, z	Left aPFC to Right lateral cerebellum	Right aPFC to Left lateral cerebellum
Right <i>scr</i>		
20, 13, 40	-.003	.09
20, 32, 25	.23	.39
Left <i>slf</i>		
-41, -4, 24	.37	.616
Right <i>ec/cs</i>		
29, 13, -6	.331	.457
Left <i>alic</i>		
-19, 13, 6	.505	.303
Right <i>or</i>		
27, -76, 7	.11	.25

Bold values reflect significance at $p < .01$.

scr = superior corona radiata; *slf* = superior longitudinal fasciculus; *ec/cs* = extreme capsule/centrum semiovale; *alic* = anterior limb of the internal capsule; *or* = optic radiation.