White matter integrity and functional connectivity in adolescents with a parental history of substance use disorder

Xiaofu He¹,a,b,1,* , Diana V. Rodriguez-Moreno²,a,b,1,** , Yael M. Cycowicz¹,a,b , Keely Cheslack-Postava²,a,b , Huilan Tang²,b , Zhishun Wang²,a,b , Lawrence V. Amse³,a,b , Megan Ryan²,b , Lupo Geronazzo-Alman²,a,b , George J. Musa³,a,b,c , Adam Bisaga²,a,b , Christina W. Hoven¹,a,b,c

¹Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, 10032, USA
²The New York State Psychiatric Institute, New York, NY, 10032, USA
³Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, 10032, USA

Abstract

A family history (FH+) of substance use disorder (SUD) increases an adolescent’s risk for substance use initiation and progression. Greater impulsivity and reward seeking behavior is known to be associated with such risk. At the neurological level, dysfunction of cortico-striatal and cortico-limbic pathways have been proposed as contributors to the increased SUD risk in adolescents with FH+. In addition, disadvantaged environments have been associated with atypical brain connectivity and higher SUD risk. However, it remains unclear if this increased risk is manifested in structural and functional brain abnormalities prior to regular drug use. To examine this, we employed complementary imaging of structural and functional connectivity of 60 FH+ and 55 FH− minority adolescents, all from families with low socio-economic status. We acquired diffusion tensor-imaging (DTI) and resting state fMRI data across the whole brain. Structural connectivity was examined by measuring fractional anisotropy (FA) using DTI, to indicate integrity of the white matter tracts. Functional connectivity within and between resting state networks was assessed by the correlation of blood-oxygen-level-dependent (BOLD) signal between intra and inter-network nodes. Psychological measures of impulsivity and reward seeking were also obtained with standardized measures, the BIS-11 and the BIS/BAS, and their association with FA and functional connectivity was evaluated. We found no differences in white matter integrity between the groups. Compared to FH−, FH + adolescents showed significantly greater
functional connectivity between posterior regions of the Default Mode Network (DMN) and the Fronto-Parietal Network (FPN). While psychological measures of reward seeking behavior did not differ between the FH+ and FH− groups, impulsivity, assessed by the BIS-11, was significantly higher for FH+. However, we did not find significant differences between the FH+ and FH− groups when comparing associations of BIS-11 scores and white matter integrity or functional connectivity measures. The stronger inter-network functional connectivity between the DMN and FPN in FH + adolescents suggests that transmitted risk for SUD may be related to large-scale brain dynamics. The lack of structural differences support the importance of early prevention efforts for FH + adolescents, before initiation of drug use, allowing for healthy brain development.

Keywords
Substance use disorder (SUD) risk; Family history (FH) of SUD; Adolescent substance naive; Diffusion tensor imaging (DTI); Resting state fMRI; Impulsivity

1. Introduction

Family history (FH+) of substance use disorder (SUD) is considered among the most prominent risk factors that increases adolescents’ vulnerability for substance use (Benegal et al., 2007; Biederman et al., 2000; Zimić and Jukić, 2012). Familial transmission of SUD risk likely occurs through both genetic and environmental mechanisms (Bjork et al., 2017; Egervari et al., 2018; Yu and McClellan, 2016; Zimić and Jukić, 2012), and includes the transmission of behavioral traits, such as impulsivity, risk-seeking and emotional dysregulation, all of which contribute to early drug experimentation (Ersche et al., 2012; Squeglia et al., 2014; Vanyukov et al., 2009). In addition, disadvantaged family and social environments are known to impair children’s brain maturation (Dufford et al., 2020; Ursache et al., 2016), for review see (Noble and Giebler, 2020) and development of emotional and cognitive abilities, which can result in risky behaviors, including substance use (Hicks et al., 2014; Tobler et al., 2013). Dysfunction in multiple brain regions involved in executive functions, cognitive control, and reward processing (Haber and Knutson, 2010; Shoal and Giancola, 2001; Tarter et al., 2003; Wong et al., 2006), are likely to underlie behaviors that increases risk of SUD in adolescents. Indeed, developmental models (Casey and Jones, 2010) point to immature connectivity across regions of cortico-striatal and cortico-limbic circuits as neurological substrates of adolescents’ increased risk for SUD. Furthermore, whole brain models indicate that broader patterns of connectivity across multiple distributed networks, beyond cortico-striatal and cortico-limbic circuits, underlie differences in impulsivity in adolescents with and without FH+ (Davis et al., 2013; Herting et al., 2010; Holla et al., 2017). Therefore, studying pre-existing differences in functional and structural connectivity between FH+ and FH− young adolescents from disadvantage environments prior to their regular substance use is an important opportunity for potentially identifying biomarkers of SUD vulnerability.

Studies of anatomical connectivity examining white matter integrity, as measured by fractional anisotropy (FA), support the notion that there are widespread alterations in white matter integrity in tracts connecting regions of the fronto-striatal and fronto-limbic networks.
in FH+, compared to FH− substance-naïve adolescents. However, there are discrepancies in the presence and direction of previously identified FA differences in FH + compared to FH− adolescents. For example, FH + teens, compared to FH− teens, show lower FA values in fronto-cortical tracts of the anterior corona radiate (ACR), in fronto-striatal tracts of the superior longitudinal fasciculus (SLF), as well as in parieto-cortical tracts of the posterior corona radiate (PCR) (Acheson et al., 2014). Squeglia et al. (2014) reported that FH + teens have higher FA in many association fibers and inter-hemispheric white matter tracts, including the SLF and inferior longitudinal fasciculus (ILF), right anterior limb of internal capsule (ALIC) containing frontal-thalamic tracts, and left PCR. Other studies report some white matter tracts with higher FA and other tracts with lower FA. For example, FH + youth show significantly lower FA in left ALIC, ACR, SLF and ILF, but higher FA in the left superior PCR (Herting et al., 2010). In contrast, Hulvershorn et al. (2018) observed no differences in FA between FH+ and FH− youth. There are several possible reasons for these inconsistencies, including variabilities among samples and increased risk for SUD due to factors other than FH. In particular, those studies did not match socio-economic status (SES) of the FH+ and FH− groups, had small sample size, or focused on FH + teens from non-disadvantaged environments. Recent evidence has suggested that white matter variations among children can be detected based on differences in SES or income alone ((Dufford et al., 2020; Ursache et al., 2016) for review see (Noble and Giebler, 2020)). For example, Dufford et al. (2020) reported a significant prospective positive association between childhood income-to-need ratio and white matter organization in the bilateral uncinate fasciculus, bilateral cingulum bundle, bilateral SLF, and corpus callosum. A large study of 1082 children and adolescents reported that higher integrity of multiple white tracts was associated with better executive task performance among the participants from higher SES families, but not from the lowest SES families (Ursache et al., 2016). Those studies, therefore, suggest the need to control for SES to avoid misinterpreting white matter differences due to factors other than FH status. Thus, in this study, we assessed white matter alteration due to family SUD risk among FH + compared with FH− adolescents in a unique sample derived from the same disadvantaged socioeconomic and social environment that differed only in family history of SUD.

Very few studies have examined intrinsic (resting state) functional connectivity in FH + compared to FH− adolescents before regular substance use. Such studies have focused almost exclusively on the connectivity of reward pathways. For example, FH + compared to FH− teens showed reduced connectivity between the nucleus acumbens and inferior frontal gyrus and postcentral regions, which are associated with reward and executive functions (Cservenka et al., 2014). A study comparing FH + youth who reported alcohol consumption to FH + youth who did not report such consumption, showed reduced connectivity in frontal-striatal pathways (Martz et al., 2019). Furthermore, functional connectivity approaches have investigated intra-network connectivity beyond the striatal and limbic circuits, as well as inter-network connectivity during the resting state. For example, Holla and colleagues (Holla et al., 2017) observed diminished intra-network connectivity in FH + substance-naïve adolescents within fronto-parietal (FPN) and cingulo-operculum (CO) cognitive control networks, as well as in sensorimotor (SN) and cerebellar (CER) networks. In contrast, Vaidya and colleagues (Vaidya et al., 2019), using independent component
analysis, observed decreased connectivity only within the SN in FH+ compared to FH− adolescents, but found no association between inter-network connectivity and FH status. As with white matter integrity studies, differences in SES of FH+ and FH− groups, based on small sample sizes, and/or the inclusion of non-disadvantage samples could have led to the inconsistencies of results across those brain resting state studies. Despite reported discrepancies in resting state connectivity changes with FH status, these studies suggest that widespread functional connectivity alterations are present in drug-naïve FH+ youth. The studies mentioned above focused on alcohol use disorder (AUD), however, alterations in intrinsic connectivity have also been observed in top-down control and limbic/reward systems in SU individuals. Thus, it is not clear if these changes are due to FH status or substance use per se (Krmpotich et al., 2013; Ma et al., 2010; Weissman et al., 2015). We hypothesize that intrinsic connectivity differences within and between neural systems involved in cognitive control and reward processing underlie the FH risk for SUD. Therefore, we assessed functional white matter integrity in our sample with the expectation that FH+ substance-naïve adolescents would show connectivity alterations, especially in the FPN regions.

It has been proposed that the strength of structural connectivity between brain regions is robustly related to functional connectivity strength. However, functional connectivity strength does not automatically imply similar strength of structural connectivity, since one or more intermediary regions could mediate the strength of that functional path (Damoiseaux and Greicius, 2009; Honey et al., 2009). In that sense, structural abnormalities better predict functional abnormalities than the converse. Therefore, information about both functional and structural connectivity could potentially contribute to a better understanding of connectivity-related dysfunction that might be present in FH+ youth. Also, only a few studies have examined both functional connectivity and white matter integrity differences between FH+ and FH− subjects. Wetherill and colleagues did not find a correspondence between resting functional connectivity and white matter integrity in the FPN. Specifically, there was decreased resting functional connectivity between the posterior parietal cortex (PPC) and the dorsolateral prefrontal cortex (DLPFC) in FH+, compared to FH− youth, but no differences in FA values, suggesting that functional connectivity differences were not dependent on white matter integrity differences in those neuronal paths (Wetherill et al., 2012). In contrast, Herting and colleagues observed decreases in both functional and white matter integrity in ALIC and left SLF connecting anterior PFC and contralateral cerebellar regions in FH+ subjects compared to FH− (Herting et al., 2010). Both studies focused on youth with and without FH of AUD. To the best of our knowledge, no other study has investigated functional and structural connectivity in adolescents with and without FH of SUD. Consequently, we investigated both resting state functional connectivity and white matter integrity in our substance naïve FH+ and FH− adolescents.

Increased risk for SUD has been associated with heightened impulsivity. Trait impulsivity is a predisposition for seeking immediate rewards without adequate regard for subsequent negative consequences. Impulsivity can be assessed with psychometrically validated questionnaires, including the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) that assesses attentional, motor, and non-planning impulsiveness, while the Behavioral Inhibition and Behavioral Activation Scale (BIS/BAS) (Carver and White, 1994) assesses...
avoidance of negative experiences and reward seeking. A whole-brain resting state study of young adults found that highly impulsive individuals, as measured by the BIS-11, showed decreased connectivity in the cortico-striatal pathways compared to less impulsive individuals (Davis et al., 2013). Impulsivity can also be assessed with behavioral tasks that measure inhibitory control in the face of reward stimuli. Ersche (Ersche et al., 2012) observed that smaller FA in the right inferior frontal gyrus was associated with lower performance on an inhibitory control task in FH+ individuals compared to controls. Hulvershorn et al. (2018) observed a positive correlation between FA in ACR and IFL and a behavioral index of SUD risk transmission in both FH+ and FH− groups combined. In contrast, neither performance on a delay discounting task, another index of impulsivity (Herting et al., 2010), nor performance on a cognitive inhibition task, were associated with FA (Squeglia et al., 2014). The negative findings in these studies were obtained using small samples matched for SES, whereas Hulvershon’s study, which reported associations of impulsivity scores with FA, did not match the groups for SES. In our previous study of well-matched, low SES minority adolescent groups with and without family history of SUD, we found that increased impulsive choices on a delay discounting task among the FH+ adolescents was not associated with differences in brain activation of cognitive control or reward processing networks (Rodriguez-Moreno et al., 2021). Thus, using the same sample of young adolescents with similarly disadvantaged backgrounds, we sought to investigate whether measures of behavioral impulsivity were associated with structural or resting state connectivity changes in reward and executive control networks.

In summary, the goal of this study was to compare structural and functional connectivity across FH+ and FH− adolescents from well-matched family and social environments, to elucidate if there are brain characteristics associated with the increased risk for SUD conferred by FH+ status prior to regular substance use. We hypothesized that FH+ adolescents will show an anomalous pattern of white matter integrity in fronto-limbic and fronto-parietal neurocircuits, which are presumed to be associated with reward processing, cognitive control and emotion regulation. Differences in intra-network functional connectivity of FPN, SN and CER, and in inter-network connectivity among them, were expected between groups. We also expected that differences in white matter integrity would be paralleled by differences in resting state functional connectivity. In addition, we hypothesized that if there were differences in impulsive and reward seeking behaviors between FH+ and FH, it would be associated with connectivity differences between these groups. Because drug use is known to affect this connectivity, examining inter- and intra-network connectivity in FH+ adolescents before they start regular use of substances, is critical to assessing whether familial risk contributes to drug use, initiation and progression, and ultimately for identifying prevention targets.

2. Methods and materials

2.1. Participants

One hundred and fifteen low-income, urban, minority adolescents participated in this connectivity study. Adolescents were recruited from a previous epidemiological investigation were classified as FH+ if a biological parent had past year or lifetime drug
or alcohol abuse or dependence based on the Composite International Diagnostic Interview (CIDI) (Akesson et al., 2012). The distribution of substance use disorder among the FH+ parents were as following: 14 SUD, 21 AUD and 25 both SUD and AUD. Due to time constraints, a few participants did not complete every measure of the MRI scan. DTI scans were obtained from 53 FH+ and 54 FH− adolescents, and resting state fMRI scans were obtained from 59 FH+ and 55 FH− adolescents. Resting state fMRI data were examined in 54 FH+ and 51 FH− adolescents; we excluded 6 participants with excessive head motion, 1 with severe artifacts in the T1, and 2 with abnormal radiologic reports. For the DTI analysis, we excluded 2 participants that did not pass quality control (He et al., 2014) and 2 adolescents with abnormal radiologic reports. The study received approval from the IRB of the New York State Psychiatric Institute. All youth participants signed an assent form and the parent signed a consent form for their child’s participation.

2.2. Psychological measures
All participants were administered the BIS-11 and BIS/BAS to assess impulsivity and approach/avoidance behaviors.

2.3. MRI data acquisition
MRI data were acquired on a GE Discovery 3.0 T whole body scanner (GE Medical Systems, Waukesha, Wisconsin). Diffusion data were obtained along 64 non-collinear spatial directions using a single-shot spin echo planar imaging sequence (TR/TE = 9000 ms/90 ms, flip angle = 90°, field of view = 19.2 × 19.2 cm, matrix size = 96 × 96 (machine-interpolated to 128 × 128 for post-processing), b value = 1000 s/mm², and five baseline images at b = 0 s/mm², slice thickness = 2 mm without gap, and an in-plane resolution of 1.5 mm, and single excitation per image). The DTI scan lasted 10 min and 21 s. We also acquired brief spin echo EPI images (in the opposite phase encoding direction) for estimating inhomogeneity of the main magnetic field (Holland et al., 2010).

A single 6-min resting-state fMRI scan was acquired for each subject using axial echo planar imaging sequence (TR/TE = 2000 ms/25 ms, flip angle = 77°, field of view = 19.2 × 19.2 cm, matrix size = 64 × 64, slice thickness = 3 mm without gap, an in-plane resolution of 3 mm, and single excitation per image). We also acquired a sagittal T1-weighted image using a 3-dimensional BRAVO sequence (inversion time = 450 ms, flip angle = 12°, matrix size = 256 × 256, in-plane resolution of 1 mm, field of view = 25 × 25 cm, slice thickness = 1 mm without gap, and 176 slices in oblique plane) for co-registration during resting-state fMRI data pre-processing.

2.4. DTI data processing and analysis
DTI images were processed using the FMRIB Software Library (FSL)5.0.11 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (Smith et al., 2004). FMRIB’s Diffusion Toolbox (FDT) was used for preprocessing steps including inhomogeneity distortion correction, eddy correction, within-volume (slice-to-volume) movement correction, brain segmentation, tensor estimation, and calculation of fractional anisotropy (FA). Specifically, FSL toolbox “top-up” (Andersson et al., 2003) was used to correct inhomogeneity distortions for both DWI and fMRI data. Eddy currents, which induce stretches and shears in the diffusion
weighted images (DWI), were corrected using FDT toolbox, and brain extraction was carried out with Brain Extraction Tool (BET) (Smith, 2002) in order to delete non-brain tissues from an image of the whole head. Within-volume movement correction was done in FSL tool “Eddy” (J. L. R. Andersson et al., 2017). A diffusion tensor model was fitted at each voxel using DTIFIT and FA measures were derived from the fitted diffusion tensors. Data quality was assessed by visually checking the color-encoded FA images, where X-component of a direction was mapped to red, Y- and Z-components were mapped to green and blue respectively, in order to exclude those participants which had motion-corrupted DTI data (X. He et al., 2014).

Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) were used to prepare the data for statistical analysis. First, all subjects’ FA images were aligned to a 1x1x1mm standard space by running the nonlinear registration. The FMRIB58_FA standard-space image was used as the target image for registration (Smith et al., 2006) and the aligned FA images from each participant were then averaged to create a mean FA image. A mean FA skeleton image was generated by using a thinned group mean FA images, representing the centers of all white matter tracts common to the group. The FA threshold for the skeleton was set to 0.20 to exclude grey matter regions from the analyses. Each participant’s aligned FA images were then projected onto the skeleton, which was then used for statistical analyses. The Johns Hopkins University (JHU) white matter tractography atlas (Mori et al., 2008; Wakana et al., 2007) was used to quantify mean FA for all white matter tracts.

2.5. Processing of resting state fMRI data

Standard resting state fMRI data preprocessing procedures and first-level analyses were performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) and CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012), including motion realignment, slice-timing correction and spatial normalization of functional images to the Montreal Neurological Institute (MNI) space, MNI152. The functional images were resampled at 2 mm$^3$, and smoothed using a Gaussian smoothing kernel with 8 mm$^3$ full-width at half maximum (FWHM). Linear regression was used to remove confounding factors of blood-oxygen-level-dependent (BOLD) signal variation, including six head motion parameters, white matter (WM), cerebrospinal fluid (CSF) signals and outlier scans. Outlier scans were detected using Artifact Detection Tools (ART) (included in the CONN toolbox), and were defined as scans with composite motion (combined translational and rotational displacements) greater than 2 mm or 2°, or if the global mean signal was greater than 9 SD. If the percentage of outlier scans was ≥20%, we excluded that subject from further analysis.

2.6. Statistical analyses of DTI and resting-state fMRI data

2.6.1. DTI data—We compared FA between FH− and FH + using a voxel-wise statistical analysis implemented on TBSS (Jenkinson et al., 2012). For this purpose, we used FSL Randomize (version 2.9, (Nichols and Holmes, 2002)) permutation-based nonparametric inference, with n = 10,000 iteration, and correction of multiple comparisons with TFCE (FWE-corrected p < 0.05) (Smith and Nichols, 2009). We also used a General Linear Model (GLM) to model mean FA of all white matter tracts using Group as regressor, and age and sex as covariates of no interest. We reported the results for the FH+ and FH− comparison...
under $p < 0.05$, which was corrected for multiple comparisons using FDR, as well as exploratory analysis at a more lenient level (uncorrected $p < 0.05$) to reveal differences across groups approaching significance.

2.6.2. Resting-state fMRI data—We compared functional connectivity of brain regions within and between resting state networks using a region-of-interest analyses in Conn toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012). Specifically, we examined the DMN, FPN, and SN networks. We selected these networks to investigate their functional connectivity based on our prior hypothesis that these networks constituted neural circuits related to the transmission of SUD from parent to offspring.

2.6.3. Associations of DTI and resting-state data with psychological measures—We conducted a GLM analysis, with age and sex as covariates, to examine associations between FA and neuropsychological measures for those white matter tracts that were different between groups (FH + vs. FH−). Similarly, we conducted a GLM analysis, with age and sex as covariates, to analyze the association between functional resting-state connectivity and neuropsychological measures for those pathways that showed group differences. Both analyses were implemented on SAS 9.4 (SAS Institute Inc., Cary, NC) and results under $p < 0.05$ are reported here.

2.6.4. DTI and resting-state comparisons across high/low behavioral scores and FH status—To further examine associations between levels of psychological measures, we stratified our FH+ and FH− groups according to their psychological scores. For each psychological measure, we defined those who were 1 Standard Deviation above the mean of total score as “high” whereas the other adolescents were defined as “low”. Using this categorization resulted in a 2x2 factorial design with 4 subgroups: FH+/high; FH+/low; FH−/High; and FH−/low. We ran several ANOVAs to assess whether there were differences in structural or functional connectivity between FH x high/low BIS-11, BAS or BIS groups.

3. Results

3.1. Participants

Demographic characteristics did not differ between FH+ and FH− groups (Table 1). Indeed, the FH− and FH + samples were well matched on race/ethnicity, mostly Black and Hispanic, with both groups having similar low socio-economic status. BIS-11 attentional impulsiveness was higher for FH + than FH− adolescents ($p = 0.04$). BIS/BAS scores did not differ between the groups, thus, we focused on BIS-11 scores for examining the correlation between white matter integrity and functional connectivity.

3.2. White matter integrity - Structural connectivity

FA values for FH+ were greater than for FH− ($p < 0.05$, uncorrected) in the ALIC ($t = 1.99$, $p = 0.049$), ACR ($t = 2.02$, $p = 0.046$), inferior cerebellar peduncle (ICP) ($t = 2.01$, $p = 0.045$), superior cerebellar peduncle (SCP) ($t = 2.19$, $p = 0.031$) and cerebral peduncle ($t = 2.02$, $p = 0.046$) (See Fig. 1). However, none of these differences survived statistical correction for multiple comparisons. Moreover, there was no voxel-based TBSS group
difference on FA of the projected skeleton (FWE-corrected p < 0.05) when a permutation test was performed.

3.3. Resting state - Functional connectivity

There was significantly greater functional connectivity in the FH + than the FH− group between resting state networks. We observed increased connectivity between the left lateral parietal (LP) cortex of the DMN and the right posterior parietal cortex (PPC) of the FPN, and between the posterior cingulate cortex (PCC) of the DMN and right PPC of the FPN (p < 0.05, FDR-corrected) (See Fig. 2). No significant differences in functional connectivity were observed within any of the DMN, FPN, and SN resting state networks.

3.4. Correlations between structural and functional connectivity strength and BIS-11

Only BIS-11 scores differed between the FH groups, so we examined the association of BIS-11 scores with connectivity results that survived multiple comparison correction. No statistically significant (p < 0.05) results were observed in correlation analyses of the BIS-11 attentional impulsiveness score with either structural or functional connectivity, for either the FH + group, the FH− group, or the combined groups.

3.5. Association between high/low behavioral scores and FH status in relation to structural and functional connectivity

The ANOVAs for the structural connectivity did not yield any significant associations after correction for multiple comparisons, with the FH x high/low groups for any of the 3 behavioral measures.

The ANOVAs for the functional connectivity yielded significant associations of the FH x high/low groups (interactions) after correction for multiple comparisons (0.05/6 = 0.00833) for each of the 3 behavioral measures as shown in Table 2.

Post-hoc tests reveal that for BIS-11, the connectivity strength of LP (L) – PPC (R) and PCC-PPC (R) differs for the FH+/high impuslivity and FH−/low impulsivity and between FH−/high impulsivity and FH−/Low impulsivity scores. These results indicate that the strength of the connectivity values of the LP (L)-PCC and PCC-PPC (R) of the low impulsive participants of the FH− groups differs from the high impulsivity participants regardless of FH status.

Post-hoc tests revealed that for the BAS total score, the strength of connectivity of LP (L) – PPC (R) and PCC-PPC (R), differs between the FH+/low and the FH−/low BAS scores. Similarly, post-hoc tests for the BIS score and the connectivity strength of the LP (L) – PPC (R) and PCC-PPC (R), reveal a difference between the FH+/low and the FH−/low BIS scores. These results indicate that the FH status groups differed in their association of functional connectivity among those with low BIS or BAS scores. However, the power to detect differences between high score participants was limited, as we had fewer participants within high score categories.
4. Discussion

The goal of this study was to examine differences in brain structural and functional connectivity between adolescents with and without a FH of SUD, from similar disadvantaged backgrounds. Our investigation of white matter integrity, however, did not find differences between groups after multiple comparisons correction, indicating that there were no detectable white matter alterations that differentiated FH+/FH−, at least that could be related to familial transmission of risk for SUD. This differs from previous DTI studies that report decreases or increases in white matter integrity of tracts associated with reward and control pathways.

With respect to functional connectivity, we found group differences in inter-network connectivity between posterior regions of the DMN and FPN. These findings did not support any of our initial hypotheses that the differences in intra- or inter-connectivity would be in systems associated with reward seeking and impulsivity. While these differences in functional connectivity are unlike those previously reported, our results support the notion that wide-range connectivity may be a sensitive marker of FH + status and, thus, potentially, SUD risk, in these low SES, drug-naïve adolescents.

Structural connectivity differences between FH+ and FH− groups in prior studies were mostly reported in cortico-striatal and cortico-limbic tracts. Our lack of significant differences in white matter integrity was similar to that reported by Hulverston (Hulvershorn et al., 2018). However, in our study, comparisons that yielded uncorrected significant differences between our FH groups were found in the fronto-cortical pathways of the ACR, the frontal-thalamic fibers of ALIC and the fronto-cerebellar pathways of the SCP and ICP, suggesting that subtle differences between groups may exist. The ACR, together with the ALIC, are part of the limbic-thalamo-cortical circuitry associated with top-down cognitive and emotional control systems (Catani et al., 2002; Sanjuan et al., 2013; Tadayonnejad and Ajilore, 2014; Williamson et al., 2013). Differences in ACR have been associated with FH of SUD (Acheson et al., 2014), FH of AUD (Herting et al., 2010), liability index of family transmission (Hulvershorn et al., 2018) and also the effects of drug use (Huang et al., 2020; McQueeny et al., 2009). Furthermore, it has been suggested that the involvement of frontopontine fibers, which project from the frontal lobe to the cerebellum via ALIC, SCP, and ICP tracts (Dum and Strick, 2003; Schmahmann & Pandya, 1995, 1997), may underlie the impaired executive function in youth with FH of AUD (Herting et al., 2010) and in active adolescent drug users (Bava et al., 2009; Bora et al., 2012; Jacobsen et al., 2007; Unterrainer et al., 2017). These reports are consistent with some of our uncorrected findings, and confirm the expected differences in executive control and reward systems in FH + adolescents compared to FH−.

However, as mentioned, the previously reported white matter integrity differences between FH+ and FH− were contradictory, with some studies observing decreases and others increases in FA values. Notably, most studies found decreases of FA values, corresponding to decrease in white matter integrity, as observed in FH+ compared to FH− children and young adults (Acheson et al., 2014). Decreases in white matter integrity are hypothesized to underlie the diminished frontal control which characterizes impulsive and risky behaviors,
typically observed in FH+. Nonetheless, some studies have reported increased FA in drug-naïve FH+ adolescents, similar to those seen in healthy adults. Squeglia interpreted the increased FA as an earlier maturation of white matter tracts accompanied by an earlier tendency toward inappropriate behavioral exploration and risky behaviors (Clark et al., 2005; Squeglia et al., 2014). Thus, the increased FA values of our uncorrected results are in line with this later interpretation.

Several reasons could account for the lack of corrected significant differences in FA between groups in the present study. First, unlike many studies on FH of SUD, our FH+ and FH− participants were carefully matched in all aspects except their FH status (as reported in Table 1). Some of the previous studies did not match the groups for variables such as parental education and/or socioeconomic status (Ryan et al., 2016; Vaidya et al., 2019), group differences that could have partially been the source of their observed structural differences. Second, the psychological impulsivity profiles of our two adolescent groups were very similar, with marginally significant differences reported only in the BIS-11 attentional scale but no differences in the BIS/BAS. Furthermore, there were no differences in structural connectivity between the FH status and high/low score groups for any of the 3 behavioral measures. This suggests that structural connectivity across FH groups could not be differentiated based on behavioral measures. As previously mentioned, the observed structural differences in earlier studies could have been, at least in part, due to consistent differences in impulsivity (Acheson et al., 2014), rather than in FH status per se. Third, smaller sample investigations, such as those previously reported, may have their findings accounted for by the particularities of their samples, whereas our larger sample was more likely to be representative of low SES, FH+ adolescents at risk for SUD. Based on Cohen’s d we have 80% power to detect an effect size of 0.79 between the two FH groups. However, we observed a moderate effect size of 0.39–0.42 in the 5 tracts between the groups. Therefore, our null results are not due to lack of overall power, but to lack of power in detecting small effect sizes, given that our FH groups are very similar. Finally, our sample included FH of both drug and alcohol use disorder. Therefore, if white matter alterations due to FH are drug-specific, as may be the case for FH+ of AUD (Herting et al., 2010), then the heterogeneity of our sample may have prevented us from detecting such differences. However, giving the effect of drugs and alcohol in some of the same regions of limbic and fronto striatal circuits (Abrahao et al., 2017; Koob and Volkow, 2016), we expect at least a partially overlapping neural circuit involved in the familial transmission of SUD risk.

As for functional connectivity, we found stronger interactions between the PCC of the DMN, and between the PPC of the FPN resting state networks in the FH+ group, which has not been previously reported. The DMN is typically more active at rest and is related to stimulus-independent, self-generated thoughts that occur while maintaining a broad attentional state (Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001). In contrast, FPN is active in goal-directed tasks when attention is targeted towards external stimuli (Corbetta and Shulman, 2002), and exerts top-down cognitive and attentional control (He et al., 2007; Nelson et al., 2010; Rosazza and Minati, 2011). The interaction between these networks has been shown to control executive functions, including cognitive flexibility, attention, and working memory (Bray et al., 2015; Chadick and Gazzaley, 2011;
Fornito et al., 2012). Increased coupling between DMN and FPN is seen, for example, in risk-prone individuals during emotion seeking behaviors (Baltruschat et al., 2020), and among heroin users compared to healthy controls (Li et al., 2013). In addition, DMN shows flexible interactions between regions, whereas the FPN is characterized by persistent stable connections (Hellyer et al., 2014). Therefore, the increased connectivity between these networks in FH + adolescents may facilitate a faster engagement of FPN for goal-directed attention tasks, as well as promote faster processing of stimuli in a way that may be related to impulsive or reward seeking behaviors. This is supported by our previous report of increased impulsive reward seeking among the FH + group as measured in a delayed discounting task (Rodriguez-Moreno et al., 2021). In addition, the connectivity strength between these networks was higher for the FH + than the FH– group, but only for “low” subgroups of three psychological measures (impulsivity, approach, and inhibition behaviors). These results further suggest that variation in these behaviors may be associated with differential coupling between DMN and FPN according to FH status. Importantly, resting state fMRI results provide evidence for associations between functional connectivity strength and behavioral measures but cannot indicate the directionality of the association.

Future studies are required to determine if the changes in functional connectivity are the cause or the consequence of differences in the behavioral phenotypes of drug naïve adolescents. Importantly, these findings suggest that early targeted interventions could be used to regulate impulsive behavior in FH + adolescents.

Our results are also in contrast with previous investigations that only observed intra-network connectivity changes between FH+ and FH– teens (Herting et al., 2010; Holla et al., 2017; Vaidya et al., 2019). These differences may be partially due to differences in sample characteristics, as discussed above, as well as differences in analytic methods (i.e., correlations, independent component analysis or graph theories to investigate whole-brain connectivity). Based on the general relationship between functional and structural connectivity, we hypothesized that white matter integrity differences between groups would be associated with functional connectivity differences. However, similar to the findings of Wetherill et al. (Wetherill et al., 2012), white matter integrity did not differ across FH+ and FH– groups, thus the observed differences in functional connectivity most probably reflect dynamic changes of brain function rather than white matter fiber abnormalities.

Understanding brain changes that correspond to the progression from being a substance naïve individual to one with SUD is very important. Our data on naïve adolescents do not show a clear indication of early structural changes, while studies of adolescents and adults with SUD show extensive changes in structural and functional connectivity (Hudkins et al., 2012; Moeller and Paulus, 2018; Rakesh et al., 2021). Our results argue against significant early changes in brain network architecture due to FH status per se that would lead to SUD, rather it points more to the fact that structural brain changes occur as a result of the drug use. However, some studies, especially those that investigated AUD, reported white matter brain differences prior to alcohol use, possibly suggesting a unique familial contribution to AUD risk (Herting et al., 2010). While our sample of FH + parents includes a large proportion of parents with AUD, we still did not find difference between groups. Further investigations, such as the ongoing NIDA funded ABCD Study, following a very large cohort of substance naïve individuals and charting the progression and development of SUD, are necessary to
increase understanding of the contribution of familial and environmental factors to SUD risk.

In conclusion, our findings suggest that altered functional inter-network connectivity, but not intra-network connectivity, might be related to the known increased risk for SUD in FH + adolescents. Specifically, stronger functional connectivity between posterior brain regions of the DMN and FPN in FH + supports the notion that increased risk for SUD is related to alterations of whole brain interactions. In addition, no white matter differences were associated with changes of functional connectivity, suggesting that FH + risk is due to network dynamics rather than white matter tract impairments.

Importantly, these results suggest that FH status in our young cohort has not yet resulted in detectable impairments in brain structure, adding weight to the idea that early interventions could be effective in preventing progression to SUD. Longitudinal studies are needed to distinguish the contributions of familial history to differences in brain structure and function, from those changes that are due to drug use itself, and to facilitate the development of innovative prevention/intervention programs for at-risk youth to prevent progression to SUD.

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Highlights:

- Adolescents with a family history (FH+) are known to be at a greater risk for substance use disorder (SUD)
- White matter integrity assessed with DTI did not differ between FH+ and FH− groups
- There were no intra-network connectivity differences in cortico-striatum and cortico-limbic systems between FH+ and FH− groups
- Default Mode Network (DMN)/Fronto-Parietal Network (FPN) inter-network connectivity was different between FH+ and FH− teens
- Associations of impulsivity or reward seeking with white matter integrity or connectivity did not differ between groups
- Neither impulsivity nor reward seeking were associated with white matter integrity or connectivity in either group
Fig. 1. White matter integrity structural connectivity.
Five white matter tracts of the right hemisphere had greater FA values in the FH + group compared with the FH− group for uncorrected (p < 0.05) but not significant when corrected (p > 0.05). Those tracts are overlaid on the mean FA skeleton (green) on MNI152 T1 image space. Results are displayed in neurological orientation. Bar graphs show the mean FA value of each tract in both FH− and FH + groups. ALIC: anterior limb of internal capsule, ACR: Anterior corona radiate; ICP: Inferior cerebellar peduncle; SCP: Superior cerebellar peduncle.
Fig. 2. Resting state functional connectivity.

a) Schematic representation of resting state functional connectivity between the Default Mode Network (DMN; blue circles) and Fronto-Parietal Network (FPN; red circles). Red lines indicate greater functional connectivity in FH+ group compared with FH− group. Results are displayed in neurological orientation. 

b) Mean functional connectivity strength between left LP in the DMN and right PPC in the FPN (p corrected for false discovery rate<0.05). 

c) Mean functional connectivity strength between PCC in the DMN and right PPC in the FPN (p corrected for false discovery rate<0.05). PFC: prefrontal cortex; MPFC: medial PFC; PCC: posterior cingulate cortex; LP: lateral parietal cortex; PPC: posterior parietal cortex.
Table 1
Demographics and psychological measures (N = 115).

|                          | FH+ (N=60) | FH− (N=55) | Statistic | df | P   |
|--------------------------|------------|------------|-----------|----|-----|
| Age (years)              |            |            |           |    |     |
|                          | Mean (SD)  | Mean (SD)  | T         | df | P   |
|                          | 15.17 (1.33) | 14.99 (1.31) | −0.73 | 113 | 0.46 |
| Sex                      |            |            |           |    |     |
| Female                   | 28 (%)     | 28 (%)     | 0.21     | 1  | 0.65|
| SES (household income)^a |            |            |           |    |     |
| <$15K                    | 19 (33.93) | 19 (37.20) | 0.68     | 2  | 0.71|
| $15–50K                  | 26 (46.3)  | 25 (49.02) |          |    |     |
| >$50K                    | 11 (19.64) | 7 (13.73)  |          |    |     |
| Race/Ethnicity           |            |            |           |    |     |
| Hispanic                 | 35 (58.33) | 35 (63.64) | 0.34     | 2  | 0.84|
| Black                    | 16 (26.67) | 13 (23.64) |          |    |     |
| Other                    | 9 (15.00)  | 7 (12.73)  |          |    |     |
| BIS-11                   |            |            |           |    |     |
| Attentional impulsiveness| 16.60 (3.20)| 15.41 (2.72) | −2.11 | 112 | 0.04|
| Motor impulsiveness      | 21.75 (4.23)| 20.97 (3.73) | −0.93 | 110 | 0.30|
| Non-planning impulsiveness| 28.07 (5.20)| 26.91 (4.67) | −0.91 | 112 | 0.22|
| BIS/BAS                  |            |            |           |    |     |
| BAS Drive                | 10.32 (2.34)| 10.66 (1.88) | 0.84 | 111 | 0.40|
| BAS Fun seeking          | 11.10 (1.78)| 11.23 (1.44) | 0.42 | 110 | 0.67|
| BAS Reward responsiveness| 15.70 (2.15)| 15.71 (1.80) | 0.03 | 112 | 0.97|
| BIS score                | 18.03 (3.00)| 18.00 (1.98) | −0.05 | 111 | 0.96|

^aData missing for 8 households.
Table 2

Differences between FH+/FH− groups in the association between DMN and FPN functional connectivity strength and high/low psychological scores (ANOVA, with Bonferroni multiple comparisons correction p = 0.05/6 = 0.00833).

|                | LP (L)—PPC (R) | PCC—PPC (R) |
|----------------|-----------------|--------------|
|                | F value  | p-value | F value  | p-value |
| BIS-11         | 6.06    | 0.0008  | 6.56    | 0.0004  |
| BAS total      | 4.74    | 0.004   | 5.26    | 0.002   |
| BIS            | 4.83    | 0.004   | 5.36    | 0.002   |

Abbreviations: LP (L): left lateral parietal; PPC (R): right posterior parietal cortex; PCC: posterior cingulate cortex.