Resting state functional connectivity of the nucleus accumbens in youth with a family history of alcoholism

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Abstract

Adolescents with a family history of alcoholism (FHP) are at heightened risk for developing alcohol use disorders (AUDs). The nucleus accumbens (NAcc), a key brain region for reward processing, is implicated in the development of AUDs. Thus, functional connectivity of the NAcc may be an important marker of risk in FHP youth.

Resting state functional magnetic resonance imaging (rs-fcMRI) was used to examine the intrinsic connectivity of the NAcc in 47 FHP and 50 family history negative (FHN) youth, ages 10–16 years old.

FHP and FHN adolescents showed significant group differences in resting state synchrony between the left NAcc and bilateral inferior frontal gyri and the left postcentral gyrus (PG). Additionally, FHP youth differed from FHN youth in right NAcc functional connectivity with the left orbitofrontal cortex (OFC), left superior temporal gyrus, right cerebellum, left PG, and right occipital cortex. These results indicate that FHP youth have less segregation between the NAcc and executive functioning brain regions, and less integration with reward-related brain areas, such as the OFC. The findings of the current study highlight that premorbid atypical connectivity of appetitive systems, in the absence of heavy alcohol use, may be a risk marker in FHP adolescents.

Keywords

Alcohol; Ventral Striatum; Adolescence; Familial; Risk

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1. Introduction

1.1. Family History of Alcoholism

Adolescents with a family history of alcoholism (FHP) have elevated risk for developing alcohol use disorders (AUDs) compared to youth without a family history (FHN) of AUDs (Dawson et al., 1992; Goodwin et al., 1974; Sher et al., 1991). In an effort to understand psychological and neurobiological factors that contribute to increased vulnerability for alcohol abuse, behavioral and neuroimaging research has focused on identifying markers of risk in FHP youth. As there are various cognitive (Corral et al., 2003; Harden and Pihl, 1995; Poon et al., 2000), neurobiological (Cservenka et al., 2012; Cservenka and Nagel, 2012; Mackiewicz Seghete et al., 2013; Schweinsburg et al., 2004; Silveri et al., 2011), and psychological (Sher, 1991) abnormalities in FHP youth in the *absence* of heavy alcohol consumption, there is likely some heritable risk factor associated with developing an AUD. Given that adolescence is a time of heightened risk for the emergence of alcohol abuse, it is critical to examine functional brain differences between FHP and FHN youth prior to the initiation of any heavy alcohol use. By doing so, FHP-related neurobiological markers can be identified in the absence of alcohol-induced neurotoxicity, and examined during a period of active brain development, when cognitive, affective, and reward-driven systems (Casey and Jones, 2010; Ernst et al., 2006b; Galvan et al., 2006; Somerville and Casey, 2010) may contribute to addiction vulnerability.

1.2. Nucleus Accumbens and Alcohol Use Disorders

Alcoholism is a disorder associated with dysfunctional mesolimbic reward circuitry (see Noble (1996) for review). However, there is a debate as to whether abnormalities in alcoholics' reward-related brain circuitry are a consequence of long-term alcohol abuse, or if these regions show premorbid atypical structure and/or function that contributed to the development of AUDs. The nucleus accumbens (NAcc) is a primary region of reward processing and response (Knutson et al., 2001). Structural changes, functional alterations, and neuroadapations of this region are implicated in heavy alcohol use, across human (Claus et al., 2011; Wu et al., 2010) and animal studies (Alaux-Cantin et al., 2013; Szumlinski et al., 2007). The NAcc, which is part of the mesoscorticolimbic dopamine pathway (Berendse et al., 1992; Nauta et al., 1978), has extensive functional connections to other reward-related regions, including orbitofrontal cortex (OFC), basal ganglia, and the amygdala (Cauda et al., 2011). Thus, understanding functional connectivity of the NAcc is important for identifying atypical reward-related connectivity patterns that may contribute to risk for addiction.

In alcoholics and heavy drinkers, structural studies have found reduced NAcc volume (Makris et al., 2008), while functional magnetic resonance imaging (fMRI) suggests increased blood oxygen level-dependent (BOLD) response in this region in the presence of alcohol-related cues (Claus et al., 2011; Kareken et al., 2004; Myrick et al., 2004; Wrase et al., 2007). Further, also seen in alcoholics (Beck et al., 2009; Wrase et al., 2007), adults and youth with a family history of alcoholism show blunted NAcc response during monetary reward anticipation compared to their FHN peers (Andrews et al., 2011; Yau et al., 2012). Additionally, FHP youth show increased functional connectivity of the NAcc with precuneus, somatosensory, and sensorimotor regions during reward anticipation (Weiland et al., 2013). This suggests that familial risk for alcoholism may be associated with abnormal reward processing, even in the absence of alcohol abuse. However, to our knowledge, there have been no studies published in FHP youth examining functional connectivity of the NAcc, in the absence of task-related demands (i.e., during rest).

1.3. Resting State Functional Connectivity of the Nucleus Accumbens

Resting state functional connectivity magnetic resonance imaging (rs-fcMRI) is a technique that characterizes the synchronous fluctuation of the BOLD timecourse at rest (Biswal et al., 1995). This technique has been used to identify distinct brain networks and the development of their functional connections (Dosenbach et al., 2007; Fair et al., 2007; Fox et al., 2005). Studies of resting state synchrony in healthy individuals indicate that the NAcc shows positive functional connectivity, or integration, with other reward and affect-related regions, such as the OFC, striatum, and amygdala (Barnes et al., 2010; Di Martino et al., 2008). In contrast, the NAcc shows negative functional connectivity, or segregation, with regions implicated in cognitive control, such as dorsolateral prefrontal and inferior parietal cortices (Barnes et al., 2010; Di Martino et al., 2008). Recently, studies in long-term abstinent alcoholics have shown that the NAcc has decreased functional connectivity with limbic regions, including the caudate and the medial dorsal and anterior nuclei of the thalamus, and increased connectivity with executive functioning brain areas, such as the dorsolateral prefrontal cortex and inferior parietal lobule (Camchong et al., 2013a; Camchong et al., 2013b). The authors interpreted these patterns of connectivity as compensatory mechanisms that allowed for continued abstinence, as they were associated with improved neuropsychological performance.

Despite these alterations in resting state synchrony observed in abstinent alcoholics, it is yet unknown whether FHP and FHN youth differ in resting state connectivity of the NAcc. This analysis is critical to differentiating consequences of long-term alcohol use from underlying risk for the development of AUDs. Thus, the goal of the current study was to use rs-fcMRI in a sample of 10–16 year old FHP and FHN youth, who had not used alcohol or other substances heavily. While healthy adults exhibit segregation of ventral striatal and fronto-parietal brain regions (Barnes et al., 2010; Di Martino et al., 2008), FHP youth and young adults have reduced functional response in these same regions (Andrews et al., 2011; Cservenka et al., 2012; Cservenka and Nagel, 2012; Mackiewicz Seghete et al., 2013; Yau et al., 2012). Interestingly, weaker NAcc response in FHP individuals during reward anticipation is related to behavioral impulsivity (Andrews et al., 2011), which could suggest interference between reward and cognitive control brain activity. Thus, we predicted that at-risk youth would have less segregation between these regions, which would suggest less distinct dissociation of reward and cognitive control brain areas. Additionally, the NAcc is typically positively functionally connected to other reward-related brain regions, such as the OFC (Barnes et al., 2010; Di Martino et al., 2008), which is essential for reward learning (Tanabe et al., 2013), and has smaller volume and increased activity to alcohol cues in those with addiction (Claus et al., 2011; Tanabe et al., 2009). Furthermore, individuals at risk for alcoholism show decreased laterality of OFC volume between right and left hemispheres (Hill et al., 2009). Given these OFC abnormalities in substance dependence and risk for alcoholism, we also hypothesized that FHP youth would have less integration between the NAcc and other reward-related brain regions, such as the OFC, suggestive of poorer within-network integration of appetitive brain regions.

2. Materials and Methods

2.1. Participants

Participants, ages 10–16 years, were recruited from the local community. FHP youth were part of an ongoing longitudinal study and matched for demographic characteristics to FHN participants. To determine eligibility, structured interviews were conducted by telephone with the youth and one of their parents [Structured Clinical Interview; (Brown et al., 1994)]. Exclusionary criteria included: lack of information on family history, family history of psychotic disorders, diagnosis of a DSM-IV psychiatric disorder [Diagnostic Interview

Schedule for Children, Predictive Scales (Lucas et al., 2001)], significant lifetime alcohol or substance use (> 10 lifetime alcoholic drinks or > 2 drinks on any single occasion, > 5 uses of marijuana, > 4 cigarettes per day, any other drug use) [Customary Drinking and Drug Use Record; (Brown et al., 1998)], neurological illness, significant head trauma (loss of consciousness > 2 minutes), serious medical conditions, mental retardation or learning disability, prenatal exposure to drugs or alcohol, left-handedness [Edinburgh Handedness Inventory; (Oldfield, 1971)], MRI contraindications, and pregnancy. Written consent and assent were obtained from all youth and their parents in accordance with the Oregon Health & Science University (OHSU) Institutional Review Board.

129 adolescents (62 FHN, 67 FHP), underwent magnetic resonance imaging scanning. After excluding participants with poor nucleus accumbens delineation (n = 5), excessive head movement (n = 24), or data preprocessing errors (n = 3), the final sample included 97 participants (see Table 1 for demographic information).

2.2. Family History of Alcohol Use Disorders

The Family History Assessment Module (Rice et al., 1995) was used with at least one biological parent and the participating youth, to assess the presence of AUDs, as defined by DSM-IV criteria, in first (biological parents) and second degree relatives (biological aunts, uncles, and grandparents). Youth were categorized as FHN or FHP based on this information. FHN youth had no relatives with a history of AUDs. FHP youth had at least one parent or two or more second-degree relatives on the same side of the family with a history of AUDs. For FHP youth, a Family History Density (FHD) score was calculated indicating the degree of familial AUDs: parents contributed 0.5, grandparents 0.25, and aunts and uncles a weighted ratio of 0.25 divided by the number of their siblings. In the FHP group, scores ranged from 0.04 to 1.50. The presence of first or second-degree relatives with AUD is a robust measure of vulnerability to AUDs or other substance abuse (Stoltenberg et al., 1998).

2.3. Participant Characteristics

Intellectual functioning (IQ) was estimated with the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), and academic achievement was estimated with self-reported grade point average (GPA). Socioeconomic status was estimated with the Hollingshead Index of Social Position (Hollingshead, 1957), administered to parents. Pubertal development was evaluated with the self-report Pubertal Development Scale (Petersen et al., 1988) and scores were translated into Tanner Stages (Carskadon and Acebo, 1993). All demographic variables were inspected for normal distribution. Sex and race were analyzed with chi-square tests. Two-sample *t*-tests or Mann-Whitney *U*-tests were used to compare groups on normally and non-normally distributed demographic variables, respectively. Statistical analyses were performed in IBM SPSS statistics for Windows (Corp., Released 2011).

2.4. Imaging Procedures

Participants were scanned in a 3.0 Tesla Siemens Magnetom Tim Trio system (Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head coil, located at OHSU's Advanced Imaging Research Center. 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°, TE = 3.58 ms, TR = 2300 ms, acquisition matrix 256 × 240, resolution 1 × 1 × 1.1 mm). Whole brain resting state functional images were acquired over two runs (TR = 2500 ms, TE = 30 ms, flip angle = 90°, resolution = 3.75 × 3.75 × 3.8 mm, FOV = 240 mm^2, 36 slices, 100 TRs, time of acquisition for each run 4:17). During the resting state scan, participants viewed a white fixation cross, centered on a black

background, projected on a mirror mounted on the head coil. They were instructed to fixate on the cross and remain still.

2.5. Image Processing and Analyses

Previously published, standard image preprocessing steps were used (Costa Dias et al., 2013; Fair et al., 2007; Fair et al., 2012; Mills et al., 2012) to reduce non-neuronal artifacts (Miezin et al., 2000). Preprocessing of images included correction of slice timing from the interleaved acquisition, removal of MR signal offset central spike, and signal normalization to a mode value of 1000. A temporal band-pass filter was applied to remove high frequency (0.009Hz < f < 0.08Hz) signal noise from heart rate and respiration. Additional preprocessing steps included regressing the white matter and ventricular signal from the pre-defined regions of interest (ROIs), regressing the global signal from the whole brain, and regressing the derivatives of the white matter, ventricular, and whole-brain signals. Importantly, no spatial smoothing was applied due to the interest in examining signal in small sub-cortical structures. Anatomical images were transformed to 3 mm^3 Talairach space (Talairach and Tournoux, 1988); functional images were also transformed and then co-registered to the anatomical images. Alignment of the functional and anatomical data was visually inspected.

Because rs-fcMRI is sensitive to head movement, additional preprocessing steps were applied to reduce motion artifact. Specifically, regression of the three translational and three rotational shift directions was first applied. Additionally, variance of signal change from the average signal (DVAR), excluding frames with signal intensities greater than absolutes value of 8, was used to censor frames due to excessive head movement (Fair et al., 2012; Shannon et al., 2011). While the identification of movement frames in the image is similar, this value is higher than previously proposed (Fair et al., 2012; Power et al., 2012) due to the absence of spatial smoothing. The threshold for acceptable frames removed was set at 40%, leaving at least 5 minutes of resting state data for each participant. Youth with greater than 40% of frames removed (9 FHN, 15 FHP) were excluded from further analyses. Furthermore, frame-to-frame displacement (FD) was calculated for each participant's remaining frames (FDi = |Δdix|+|Δdiy|+|Δdiz|+|Δαi|+|Δβi|+|Δγi|), where Δdix = d(i−1)x−dix) (Power et al., 2012). There were no significant group differences in the average percent of frames removed due to motion (FHP = 12.52, SD = 10.57; FHN = 10.97, SD = 10.04; $t = -0.74$, $P = 0.49$), nor in FD (FHP = 0.11, SD = 0.03; FHN = 0.11, SD = 0.03; $t = 0.15$, $P = 0.88$) or DVAR (FHP = 5.91, SD = 0.67; FHN = 5.89, SD = 0.64; $t = 0.15$, $P = 0.88$) remaining mean, after censoring.

Whole-brain seed-based connectivity analysis was used to examine functional connectivity of the NAcc with other areas of the brain. The NAcc was defined for each participant using FMRIB Software Library's FMRIB Integrated Registration and Segmentation Tool, an automated segmentation tool that determines grey and white matter boundaries, using the youth's T1-weighted anatomical image (Patenaude et al., 2011). NAcc ROIs were converted to 3 mm^3 voxels in Talairach space. Each of the ROIs was visually inspected for precision of definition. Four FHP and one FHN youth had poorly anatomically placed ROIs, and were excluded from further analyses. Rs-fcMRI was analyzed by correlating the timecourse of the NAcc BOLD response with all other voxels in the brain, generating a resting state functional connectivity map of the left and right NAcc for each participant. Correlation coefficients (*r* values) were transformed to Fisher *Z* scores to improve normality. In-house software developed at Washington University in St. Louis, was used to generate the following statistical maps. One-sample *t*-tests were performed on the Fisher's *Z* transformed correlation coefficients to examine the functional connectivity patterns of the left and right NAcc for FHP and FHN youth. Next, two-sample t-tests (assuming unequal variance, *P* <

0.05) were performed to examine whole-brain functional connectivity differences between the groups. Monte Carlo simulation was used to avoid Type I error at a voxel threshold of $P < 0.05$, Z 2.25, and a cluster threshold 53 contiguous voxels. Peak Z coordinates for the whole-brain group differences in connectivity were extracted using the following procedure. Twenty mm radius sphere were created around peak Z scores 20 mm apart. These clusters were masked by the Monte Carlo corrected maps.producing three clusters of significant group differences for the left NAcc and five clusters for the right NAcc (Table 2). Thus, voxels that did not pass multiple comparisons correction were eliminated. Correlation coefficients (r values) for each individual were extracted for correlations between left and right nucleus accumbens and the clusters of significant group differences. These were used in hierarchical regressions to control for nuisance variables (section 3.2.3.), as well as to examine family history density relationships with functional connectivity (section 3.2.4.). Finally, results of group differences were surface-mapped onto the PALS-B12 atlas, using Caret software (Van Essen et al., 2001), except for cerebellar group differences, which were displayed in volumetric space and overlaid on a template brain.

3. Results

3.1. Demographics

97 subjects were included in the final analyses of resting state functional connectivity (47 FHP, 50 FHN). Demographic characteristics of the samples are described in Table 1. Participants were well matched on age, sex ratio, race, pubertal stage, and IQ (all $p > 0.05$). However, they differed on SES (FHN = 28.56, SD = 12.37, FHP = 34.60, SD = 14.29, $U = 842$, $Z = -2.41$, $P = 0.016$) and GPA (FHN = 3.62, SD = 0.39, FHP = 3.41, SD = 0.53, $U = 746$, $Z = -2.11$, $P = 0.035$), both of which were higher in the FHN group. For all demographic values, all subjects were within three SD of the mean, except one FHN subject with low SES. Due to the exclusionary criteria put in place, only 7 FHP and 3 FHN youth had ever used alcohol or substances in this sample (Table 1).

3.2. Resting State Functional Connectivity

3.2.1. Nucleus Accumbens Functional Connectivity in FHP and FHN Youth—At a gross level, one-sample t-test maps of each group showed that both FHP and FHN youth had positive functional connectivity (integration) between the NAcc and the basal ganglia, including the caudate and anterior portions of the putamen. Additionally, all youth showed positive functional connectivity between the NAcc and the anterior temporal lobes. Both groups had mostly positive functional connectivity with medial orbitofrontal cortex (except for an area of group differences below, section 3.2.2). FHP and FHN youth showed negative functional connectivity (segregation) from dorsal regions of the prefrontal cortex, as well as from the superior and inferior parietal cortices, regions implicated in higher order executive functioning (Figure 1, Monte Carlo corrected ($Z = 2.25$, $P < 0.05$)).

3.2.2. Group Differences in Nucleus Accumbens Functional Connectivity—Significant group differences in left NAcc functional connectivity were found with the left inferior frontal gyrus (IFG), right IFG, and left postcentral gyrus (PG) (Figure 2 and Table 2). In both the left and right IFG, FHP and FHN youth had negative functional connectivity (segregation) with the left NAcc; however, in FHP youth, there was significantly weaker segregation between these regions. FHN youth showed segregation between the left PG and left NAcc; however, FHP youth showed positive functional connectivity (integration) between these regions.

Significant group differences in right NAcc functional connectivity were found with the left OFC, the left superior temporal gyrus (STG), the left PG, the right occipital cortex, and the

right cerebellum (Figure 3 and Table 2). As expected, FHN youth had positive functional connectivity (integration) between the right NAcc and left OFC, but FHP youth had negative functional connectivity (segregation) between these regions. The right occipital cortex and left STG both showed weaker segregation with the right NAcc in FHP than FHN youth. With the left PG, FHP youth again had an opposite pattern of functional connectivity from FHN youth. This was also true for the right cerebellum, which showed integration with the right NAcc in FHN youth, but segregation in the FHP group. No family history × sex interactions were present in the pairs of ROIs that showed significant group differences in connectivity.

3.2.3. Hierarchical Regressions with GPA and SES—Since GPA and SES were significantly different between the groups, hierarchical regression was performed to see if family history status was still a significant predictor of group differences in resting state functional connectivity, after controlling for these nuisance covariates. SES did not contribute significantly to functional connectivity in any of the areas of left and right NAcc group functional connectivity differences. However, GPA was a significant predictor of functional connectivity between the left NAcc and left IFG ($F(1,88) = 6.52$, $\beta = -0.26$, $t = -2.15$, $P = 0.03$, R^2 change = 0.07), as well as the right NAcc and left STG ($F(1,88) = 4.61$, $\beta = -0.22$, $t = -2.55$, $P = 0.01$, R^2 change = 0.05). When family history status was added to the model, it accounted for significantly more variance in connectivity in these two areas of group differences (left NAcc-left IFG: $F(1,88) = 23.65$, $\beta = 0.55$, $t = 6.62$, $P < 0.001$, R^2 change = 0.28; right NAcc-left STG: $F(1,88) = 14.51$, $\beta = 0.46$, $t = 4.82$, $P < 0.001$, R^2 change = 0.20). Thus, while GPA explained some of the variance in connectivity, family history status was a significantly better predictor (as seen by the significant F change of the P-values reported above) of resting state functional connectivity in these regions.

3.2.4. Nucleus Accumbens Functional Connectivity and Family History Density of Alcoholism—In FHP youth, FHD was significantly related to functional connectivity between the right NAcc and the cluster in the right occipital cortex in which significant group differences in connectivity were observed ($R^2 = 0.09$, $\beta = 0.29$, $t = 2.01$, $P = 0.045$; Figure 4). Here, greater FHD was associated with less segregation between the right NAcc and right occipital cortex. Additionally, there was a trend-level association between FHD and connectivity between the right NAcc and right cerebellum ($R^2 = 0.07$, $\beta = -0.13$, $t = -1.83$, $P = 0.07$; Figure 4). Specifically, in this cluster, higher FHD was related to less positive functional connectivity (less integration) between the right NAcc and right cerebellum.

3.2.5. Nucleus Accumbens Functional Connectivity and Relationships with Sensation Seeking and Impulsivity—In addition to familial history of alcoholism, personality features, such as sensation seeking and impulsivity, may be important risk markers for adolescent alcohol use. Thus, we examined whether there were significant group differences on the Zuckerman-Kuhlman Impulsive Sensation Seeking questionnaire (Zuckerman et al., 1993), as well as behavior on a computerized delay discounting task (Mitchell, 1999). Next, we examined whether scores from these measures correlated with group differences in connectivity. Eighty-nine of the 97 participants had sensation seeking scores in our sample. Eight FHN participants, included from another study, were not administered this questionnaire. FHP youth had significantly higher sensation seeking levels than FHN youth, $t = 2.78$, $p = 0.007$ (Table 1). Higher sensation seekers had less segregation between the left NAcc and left IFG at trend-level ($R^2 = 0.04$, $\beta = 0.20$, $t = 1.86$, $p = 0.067$).

Seventy-eight participants in our sample were administered the delay discounting task. We chose to examine log [k] as our measure of impulsivity, as it reflects the preference of

smaller immediate rewards over larger delayed rewards. There were no significant group differences in mean log [k]: FHP (n = 46) = −4.65, FHN (n = 31) = −5.60, t = 1.32, p = 0.19 (one outlier excluded from analysis). There was one trend level relationship between log [k] and right NAcc-right PG connectivity (R^2 = 0.05, β = −0.21, t = −1.88, p = 0.065), such that greater discounting was associated with more negative functional connectivity between these regions.

4. Discussion

The goal of this study was to investigate differences in resting state synchrony of the NAcc between FHP and FHN youth, since intrinsic connectivity of this brain region may be an important neurobiological marker of AUD risk. As hypothesized, there was significantly less segregation between the NAcc and regions of the fronto-parietal network in FHP youth, which could suggest poorer dissociation of cognitive control and reward networks. There was also less integration of the right NAcc and left OFC in FHP youth, which was consistent with our prediction that at-risk youth would have reduced synchrony between the NAcc and other reward-related structures, suggesting poorer integration of appetitive brain regions. In addition, FHP youth showed opposite patterns of functional connectivity with bilateral NAcc and the left PG, and had less segregation between the right NAcc and left STG and right OCC. Interestingly, FHP youth showed segregation between the right NAcc and right cerebellum, while these two regions were positively connected in FHN youth.

4.1. Nucleus Accumbens Resting State Connectivity and Risk for Alcoholism

The findings in the current study present a novel profile of familial history risk associated with atypical patterns of reward network connectivity. As adult studies of ventral striatal resting state functional connectivity have shown (Barnes et al., 2010; Di Martino et al., 2008), the typical pattern of NAcc positive functional connectivity is integration with other limbic structures, such as the OFC or ventromedial prefrontal cortex (PFC), which have extensive structural (Nakano et al., 1999) and functional (Cauda et al., 2011) connections with the NAcc. Thus, the segregated pattern of connectivity between these regions in FHP youth appears to be atypical and may increase vulnerability towards alcohol abuse.

Additionally, it is important to examine parallels between rs-fcMRI and task-related fMRI, since resting state connectivity closely corresponds to task-related fMRI BOLD signal and behavioral performance (Fox et al., 2007; Smith et al., 2009). Parallel findings from these two techniques may provide important and complementary information about these brain networks. For example, research in alcoholics has shown that poor reward-related decision-making is linked to deficits in ventromedial PFC functioning (Bechara et al., 2001), which could reflect dissociation of subcortical and prefrontal pathways needed for adaptive decision-making that leads to heightened reward-driven behavior. Furthermore, the OFC is a critical brain region for reward-related valuation (Elliott et al., 2008; Peters and Buchel, 2009), and learning (Galvan et al., 2005). Neuroimaging studies suggest that both the NAcc and OFC show heightened activity during the processing of rewards (Spicer et al., 2007). Thus, improper feedback between the OFC to the NAcc, due to weak functional integration between these structures, could lead to atypical reward valuation, possibly increasing the likelihood for bottom-up driven and potentially risky behavior in FHP youth. Recently, substance-dependent individuals performing the Iowa Gambling Task, had reduced prediction error BOLD response in both the OFC and ventral striatum compared with healthy controls. The authors argued that disrupted trial-to-trial prediction error signaling from the NAcc to the OFC could account for these findings (Tanabe et al., 2013). Thus, if FHP youth have preexisting weaker resting state synchrony between the NAcc and OFC than FHN adolescents, they could be more vulnerable to poor reward-related decisions.

FHP youth also showed weaker segregation between the left NAcc and bilateral IFG, a brain area implicated in executive functioning (Somerville et al., 2011; Tamm et al., 2002) that is negatively correlated with NAcc BOLD activity in healthy adults (Cauda et al., 2011). Thus, reduced negative functional connectivity between reward and cognitive processing brain regions in FHP youth may be indicative of atypical dissociation of brain networks, since healthy brain development is associated with both within-network integration and between-network segregation (Fair et al., 2007). Response inhibition, which is a key function of inferior frontal gyri (Tamm et al., 2002), could be less effective during heated situations, if it is more weakly dissociated from reward-related brain areas. Tasks that recruit both executive and reward networks, such as those that require reward-related decision-making, are needed to examine behavioral relationships with NAcc and frontal lobe connectivity in these youth.

While not originally hypothesized, it is also noteworthy that FHP and FHN adolescents differed in right NAcc and right cerebellum connectivity, with FHN youth showing positive functional connectivity between these structures, and FHP youth showing anti-correlated synchrony. Atypical cerebellar structure is implicated in both alcoholism (De Bellis et al., 2005) and risk for AUDs (Hill et al., 2007; Hill et al., 2011). Additionally, we have previously found atypical cerebellar activity during risky decision-making in FHP youth (Cservenka and Nagel, 2012), and a negative association between FHD of alcoholism and cerebellar response during spatial working memory (Mackiewicz Seghete et al., 2013). Further, FHP adolescents have reduced fronto-cerebellar connectivity compared with their peers (Herting et al., 2011), which is also present in adults with AUDs (Rogers et al., 2012), suggesting that there may be a heritable component to alterations in cerebellar functioning and connectivity. Based on the current findings, other cerebellar functional connections may also be aberrant in FHP youth. Even though direct structural connections between the NAcc and cerebellum are unknown, it is possible that third party brain regions are responsible for the coactivation patterns observed (Cauda et al., 2011). Additionally, FHD showed a trend-level relationship between right NAcc and right cerebellum connectivity, suggesting that familial loading of alcoholism could affect intrinsic connectivity profiles. Further work is needed to understand how particular cerebellar lobules may differ in resting state connectivity with the NAcc in at-risk youth to understand of the specificity of these findings.

Interestingly, the patterns of negative functional connectivity in FHN youth between the right NAcc and left STG, right NAcc and left OCC, and bilateral NAcc and left PG, correspond to what has been seen in healthy adults (Di Martino et al., 2008). Thus, reduced segregation between brain structures with widespread functionality also represents an atypical connectivity profile in FHP youth. This could indicate that reward network dissociation from the rest of the brain is aberrant and may lead to abnormal signaling among functionally distinct brain regions, suggesting not one, but multiple pathways of risk. A similar finding was reported by Weiland et al. (2013), who found that during reward anticipation in task-related fMRI, FHP youth had positive functional connectivity with the PG, opposite from what was observed in FHN youth. The PG is implicated in orientation of visual attention (Corbetta, 1998), and while speculative, weaker dissociation of reward-related systems and the PG could increase attention to appetitive stimuli in FHP youth. Future work should investigate similarities between task-related and resting state functional connectivity findings in FHP youth.

Finally, while not significant, there were two trend-level relationships between sensation seeking and left NAcc connectivity, as well as impulsivity and right NAcc connectivity across the entire participant sample. FHP youth who had less segregation between the left NAcc and left IFG compared with their peers were also higher sensation seekers. Thus, this correlation may be partly driven by both higher sensation seeking and reduced segregation

of these brain regions in FHP compared with FHN youth. Nonetheless, sensation seeking may be another critical endophenotype for alcoholism-related risk and an important correlate of resting state synchrony. Further, greater preference for smaller immediate vs. larger delayed rewards was related to more negative connectivity between the right NAcc and left PG, the connectivity pattern present in FHN youth. Thus, some patterns of intrinsic connectivity may confer protection or resilience in FHP youth who had positive connectivity between these regions, a pattern that related to less discounting behavior.

4.2. Limitations

While this is the first study examining resting state functional connectivity of the NAcc in FHP youth, there are some limitations that should be noted. First, the brain regions that showed significant group differences in left and right NAcc connectivity were not identical between the two seed regions. The right NAcc differences were more varied, and included the OFC, somatosensory, visual, temporal, and cerebellar brain regions. There is some literature to suggest that the right NAcc and right hemisphere is more affected in AUDs (Makris et al., 2008; Oscar-Berman and Bowirrat, 2005), and thus could be a region in FHP adolescents that shows more altered connectivity than the left NAcc. However, future work is needed to replicate these differences.

Second, since this study was a cross-sectional examination of NAcc functional connectivity, cause-and-effect relationships between connectivity and alcohol use cannot be inferred. Longitudinal investigations will be important to understand if any of the connectivity differences seen in the current analysis are predictive of future alcohol abuse, as well as determine the effect of alcohol-induced neurotoxicity on reward network connectivity.

Third, due to the sensitivity of rs-fcMRI to excessive head movement, 15 FHP and 9 FHN youth were excluded from the sample. Exclusion of these participants may have resulted in removal of variance in youth of interest, particularly given that more participants were excluded from the FHP sample. For example, head movement may relate to symptoms of inattentiveness or impulsive personality, as it is often a significant challenge for fMRI studies in children with attention-deficit hyperactivity disorder (Epstein et al., 2007; Fair et al., 2012). Since those characteristics further confer risk for alcohol use during adolescence (Ernst et al., 2006a; Jester et al., 2008), it is likely that some adolescents at high risk were not included in this dataset.

Finally, it should be noted that since youth with psychiatric disorders were excluded from this study, not all alcoholism-related risk factors, including clinically diagnosed externalizing or internalizing disorders, were present in this sample, and thus the level of risk in our participants was likely reduced. However, by examining familial alcoholism in the absence of psychopathology, our findings may help guide prevention strategies aimed specifically at intergenerational transmission of AUDs.

4.3. Conclusions

Compared to FHN youth, FHP youth had significantly weaker segregation of the NAcc and cortical executive control regions, suggesting poorer dissociation of appetitive and cognitive systems. FHP youth also had weaker synchrony between the NAcc and OFC, indicating poorer integration of the reward network. The aberrant pattern of NAcc connectivity seen in FHP youth may represent a risk factor for developing AUDs, as it could lead to improper reward learning, due to weaker integration with the OFC, and interference with cognitive control, as a function of its reduced segregation from brain areas associated with executive processes. Future work should characterize resting state synchrony of other brain regions implicated in the development of AUDs to have a better understanding of intrinsic

connectivity patterns that could be heritable risk factors in FHP individuals, and thereby increase vulnerability for alcohol abuse.

Acknowledgments

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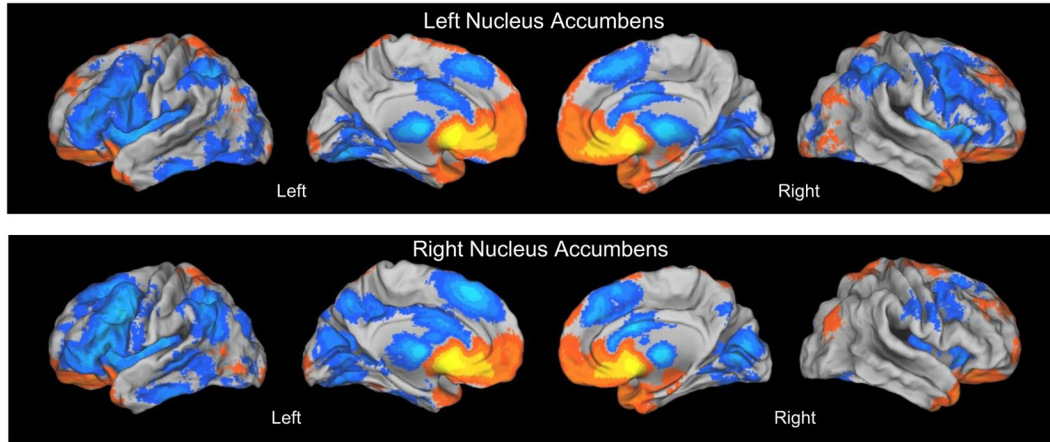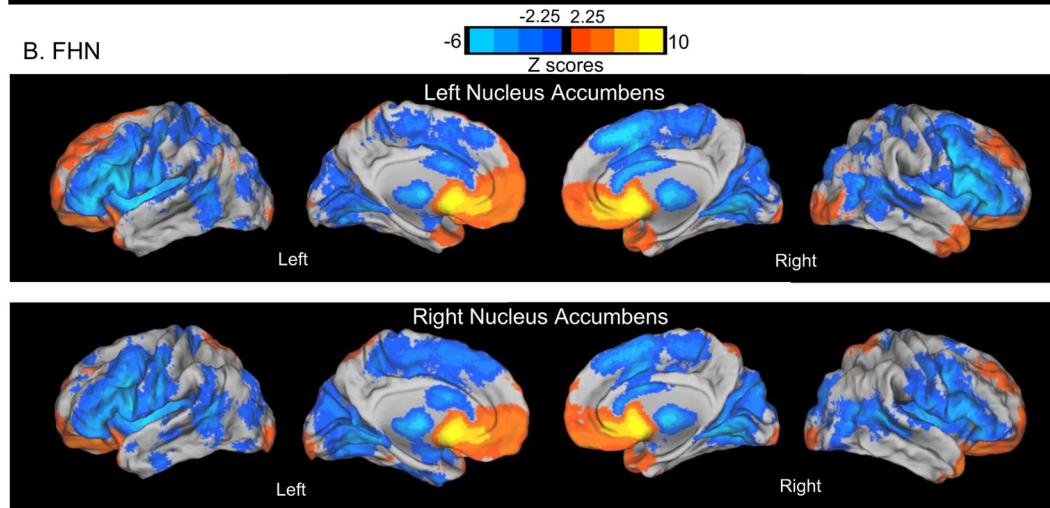
Figure 1.
Left and Right Nucleus Accumbens Functional Connectivity in FHP and FHN Youth
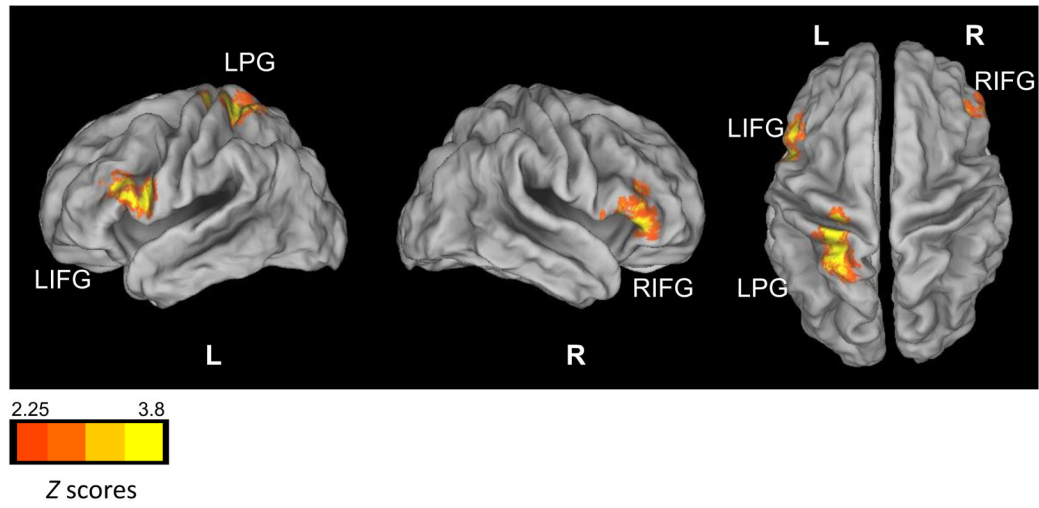
Figure 2.
Group Differences in Left Nucleus Accumbens Resting State Functional Connectivity
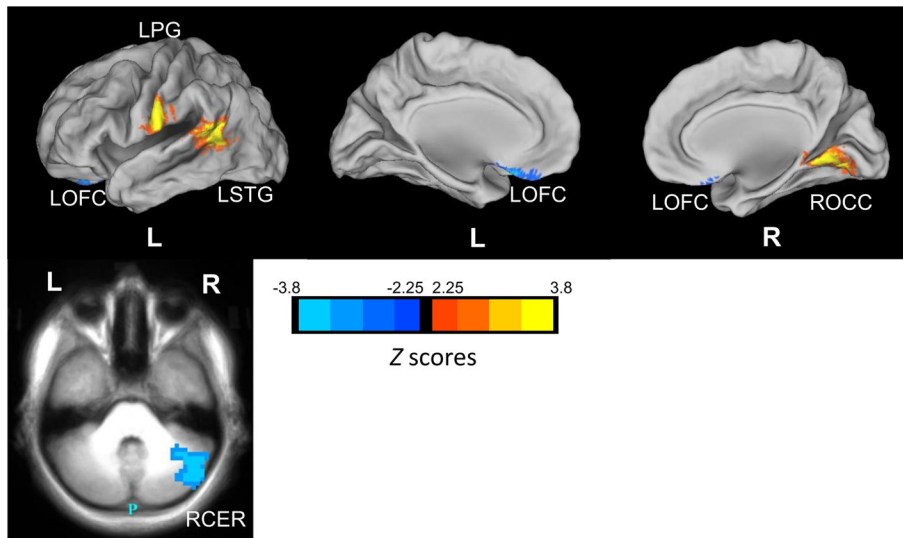
Figure 3.
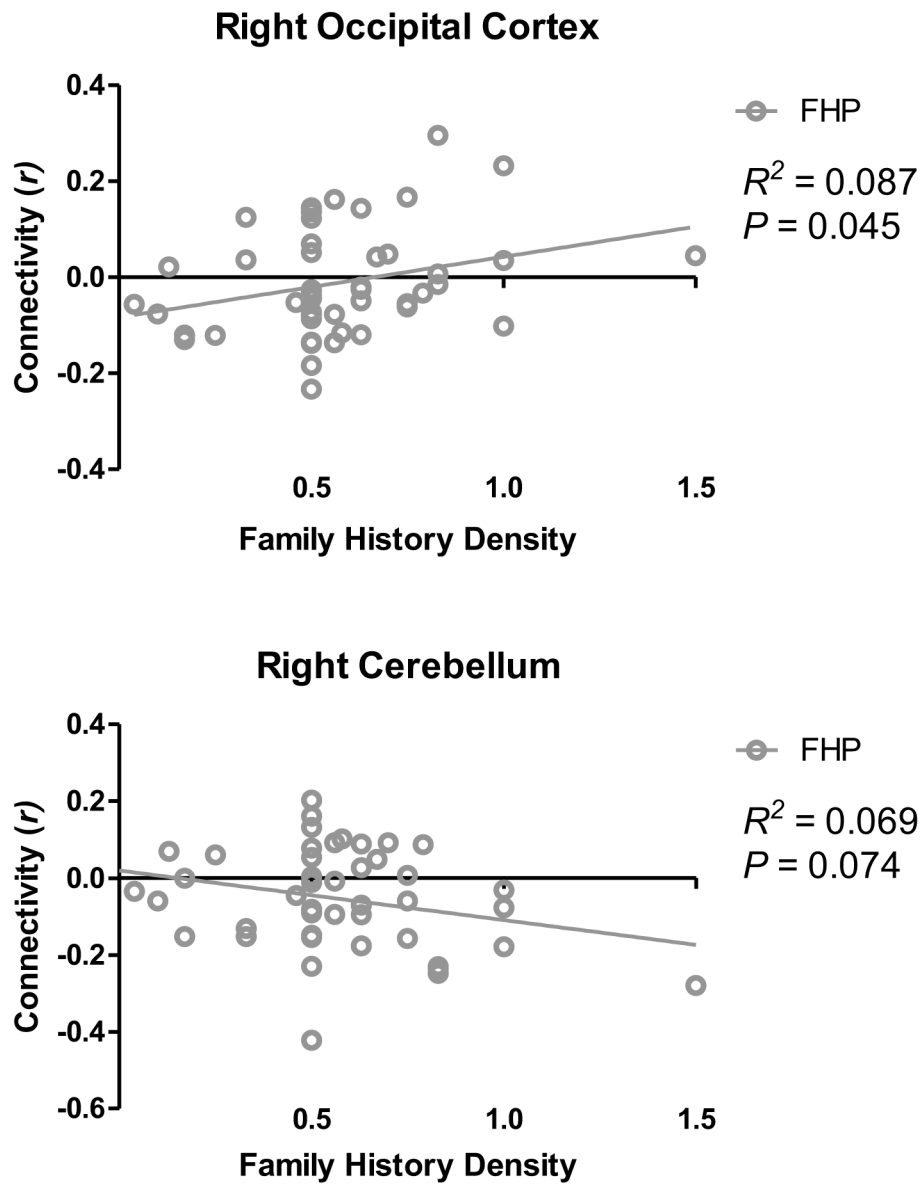Group Differences in Right Nucleus Accumbens Resting State Functional Connectivity

Figure 4.
Family History Density and Functional Connectivity Relationships.

Table 1

Participant Demographics. Means and standard deviations unless otherwise noted.

	FHP[1]	FHN[2]	Statistic	P value
N	47	50	-	-
Female/male	22/25	21/29	$X^2 = 0.23$	0.63
Age	14.57 (1.31)	14.34 (1.28)	$t = 0.87$	0.39
Puberty[3]	3.66 (0.98)	3.48 (0.89)	$U = 1005, Z = -1.32$	0.19
IQ[4]	111.19 (9.90)	113.28 (11.32)	$t = -0.97$	0.34
GPA[5,†]	3.41 (0.53)	3.63 (0.39)	$U = 747, Z = -2.11$	0.035
SES[6,†]	34.60 (14.29)	28.56 (12.36)	$U = 843, Z = -2.41$	0.016
Sensation seeking[7†]	47.51 (20.67)	36.26 (17.18)	$t = 2.77$	0.007
Delay discounting log[k][8]	−4.90 (2.11)	−5.60 (2.50)	$t = -1.32$	0.19
Family history density[9]	0.57 (0.26)	0	-	-
Alcohol use[10]	N = 2	N = 3	-	-
Marijuana use[11]	N = 6	N = 2	-	-
Cigarette use[12]	N = 2	N = 1	-	-

[1] Family history positive for alcoholism.

[2] Family history negative for alcoholism.

[3] Pubertal Development Scale (Petersen et al., 1988); scores translated to Crockett stages, range 1 to 5, with higher scores reflecting greater maturity (Crockett and Petersen, 1987).

[4] Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

[5] Grade Point Average; values range from 0 to 4, with higher scores reflecting higher grades. Missing: FHP: N = 6, FHN: N = 1.

[6] Hollingshead Index of Social Position; higher scores indicate lower socioeconomic status (Hollingshead, 1957).

[7] Zuckerman-Kuhlman Impulsive Sensation Seeking Questionnaire (Zuckerman et al., 1993); scores range from 0 to 90, with higher scores reflecting greater sensation seeking. FHP: N = 47, FHN: N = 42.

[8] Mitchell, 1999. Values closer to 0 indicate greater preference of small immediate reward over larger delayed reward. FHP: N = 46; FHN: N = 31.

[9] Family history density of AUDs (Zucker et al., 1994); total possible values range from 0 to 2 and include AUDs in parents, aunts and uncles, and grandparents. Higher values represent more familial AUDs.

[10] No more than 2 drinks on any single occasion. Maximum alcohol occasions 3 for FHP, and 2 for FHN youth.

[11] Maximum marijuana occasions 5 for FHP, and 3 for FHN youth.

[12] Maximum cigarette use occasions 1 for FHP, and 1 for FHN youth.

[†] Significant difference between groups ($P < 0.05$).

AUD, alcohol use disorder.

Table 2

Significant Group Differences in Resting State Nucleus Accumbens Functional Connectivity

	Group Differences	FHP	FHN	Z score	Number of Voxels	Peak Talairach		
						x	y	z
N		47	50					
L NAcc								
L PG	FHP>FHN	+	−	3.83	103	−26	−43	60
R IFG	FHP>FHN	−	−	3.71	84	44	25	9
L IFG	FHP>FHN	−	−	3.83	80	−47	13	17
R NAcc								
R CER	FHP<FHN	−	+	−3.80	224	44	−62	−36
L STG	FHP>FHN	−	−	3.76	104	−59	−51	10
L OFC	FHP<FHN	−	+	−3.32	70	−3	8	−20
R OCC	FHP>FHN	−	−	2.71	59	15	−62	−7
L PG	FHP>FHN	+	−	3.62	53	−64	−10	19

CER = cerebellum, FHN = family history negative, FHP = family history positive, IFG = inferior frontal gyrus, L = left, NAcc = nucleus accumbens, OCC = occipital cortex, OFC = orbitofrontal cortex, PG = postcentral gyrus, R = right, STG = superior temporal gyrus, + = positive functional connectivity, − = negative functional connectivity, FHP > FHN = more positive functional connectivity or less negative functional connectivity in FHP compared with FHN youth, FHP < FHN = less positive functional connectivity in FHP compared with FHN youth.