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Accumbens functional connectivity during reward mediates sensation-seeking and alcohol use in high-risk youth*

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Abstract

BACKGROUND—Differences in fronto-striatal connectivity in problem substance users have suggested reduced influence of cognitive regions on reward-salience regions. Youth with a family history of alcoholism (FH+) have disrupted ventral striatal processing compared with controls with no familial risk (FH−). As sensation-seeking represents an additional vulnerability factor, we hypothesized that functional connectivity during reward anticipation would differ by family history, and would mediate the relationship between sensation-seeking and drinking in high-risk subjects.

METHODS—Seventy 18–22 year olds (49 FH+/21 FH−) performed a monetary incentive delay task during functional magnetic resonance imaging. Group connectivity differences for incentive (reward/loss) vs. neutral conditions were evaluated with psychophysiological interaction (PPI) analysis, seeded in nucleus accumbens (NAcc). Indirect effects of sensation-seeking on drinking volume through accumbens connectivity were tested.

RESULTS—NAcc connectivity with paracentral lobule/precuneus and sensorimotor areas was decreased for FH− versus increased for FH+ during incentive anticipation. In FH+, task-related functional coupling between left NAcc and supplementary sensorimotor area (SSMA) and right precuneus correlated positively with sensation-seeking and drinking volume and mediated their

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Contributors

MMH, JKZ and RAZ designed the study and wrote the protocol. WYY collected and processed the data. BJW managed the literature searches and summaries of previous related work. BJW, RCW and MMH undertook the statistical analysis, and BJW wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

The author(s) declare that, except for income received from our primary employer, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest, with the exceptions below: Dr. Zubieta, Consultant, Eli Lilly Co, Merck, Forest Pharmaceuticals

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relationship. In FH–, left NAcc-SSMA connectivity correlated negatively with sensation-seeking but was not related to drinking.

CONCLUSIONS—These results suggest preexisting differences in accumbens reward-related functional connectivity in high-risk subjects. NAcc coupling with SSMA, involved in attention and motor networks, and precuneus, a default mode structure, appear to mediate sensation-seeking's effect on drinking in those most at-risk. Differences in accumbens connectivity with attention/motor/default networks, rather than control systems, may influence the reward system's role in vulnerability for substance abuse.

Keywords

Adolescent; alcoholism; functional connectivity; nucleus accumbens; reward; substance use

1. Introduction

Research on the neurobiology of substance abuse has provided evidence for the role of the mesocorticolimbic dopamine system in positive reinforcement of drugs of abuse (Koob and Le Moal, 2001; Le Moal and Simon, 1991; Robbins and Everitt, 1999). Reward processing is associated with dopaminergic projections from the midbrain to the ventral striatum (Schultz, 1998) suggested to encode salience (Horvitz, 2000; Zink et al., 2003), modulate motivation for reward procurement, and consolidate memory traces connected with use of substances (Volkow et al., 2009). The ventral striatum also receives inputs from cortical areas and limbic regions (Groenewegen et al., 1999) involved in cognitive control (Camara et al., 2009b). Functional connectivity studies of reward circuitry, using the nucleus accumbens (NAcc) as a seed region, show an extensive functionally associated network that includes the insular and orbitofrontal cortices, amygdala, hippocampus and midbrain regions in healthy young adults (Camara et al., 2009a).

Reward processing in problem substance users has been studied using a monetary incentive delay (MID) task during functional magnetic resonance imaging (fMRI) finding increased ventral striatal and mesial frontal cortex activation (Bjork et al., 2008b) yet reduced activation in the cerebellum and orbital frontal cortex compared to control subjects (Goldstein et al., 2007). Lack of orbitofrontal activation has been associated with decision-making and regulation deficits in substance-dependent subjects (Paulus et al., 2002). Comparing heroin users to control subjects, stronger resting state connectivity was found between the NAcc reward center and both the medial orbital frontal cortex and the ventral/rostral anterior cingulate, a region associated with craving and emotion regulation (Ma et al., 2010). In heavy drinkers, cue-elicited craving produced strong correlations between the striatum, ventral tegmental/substantia nigra and medial prefrontal cortex, involved in complex cognition (Filbey et al., 2008; Koehlin and Hyafil, 2007). Together, these studies of problem users suggest increased saliency responses, likely associated with craving, perhaps due to compromised regulatory/inhibitory control. However, it is unclear from these studies whether abnormalities are a consequence of substance use, learned addiction-related behaviors, or are related to pre-existing risk.

Parental alcoholism is a significant risk factor for substance use disorders (National Institute on Alcohol Abuse and Alcoholism, 2000), with genetic influences accounting for 40–60% of the variance in substance abuse risk (reviewed in (Nestler, 2000; Tyndale, 2003). fMRI studies evaluating adolescents with a family history of alcoholism (FH+) revealed abnormal suppression of ventral striatal activation during passive viewing of emotional stimuli in adolescents identified as vulnerable based on early drug and alcohol involvement (Heitzeg et al., 2008). Yet during response inhibition, FH+ youth showed increased ventral striatal response (Heitzeg et al., 2010), suggesting a contextually-driven disrupted modulation.

However, ambiguity exists even within a given context. Using a MID task, NAcc reward response differences were seen between non-abusing FH+ adults versus controls (Andrews et al., 2011) while no FH differences were found in young adolescents (Bjork et al., 2008a). The latter study, however, found a relationship between NAcc activation and sensation-seeking scores across all subjects. Sensation-seeking is related to high risk taking and impulsive decision making (Zuckerman, 2007) and been linked with heavy alcohol use, early onset of substance use and polysubstance abuse (Malmberg et al., 2010; Zuckerman, 1972). Animal models of sensation seeking, using novel stimuli as probes, find increased NAcc dopamine response similar to drug reinforcers (Olsen and Winder, 2009; Rebec et al., 1997) which suggest that this trait may share neural circuitry with reward processing. We hypothesized that perhaps familial liability may involve functional connectivity differences between reward and control networks, rather than activation differences in specific structures, as seen in substance users.

The present study, therefore, investigates the role of functional connectivity of reward-related circuitry in vulnerability to substance abuse in young adults. Participants were recruited from the Michigan Longitudinal Study (MLS), an ongoing, prospective community study of FH+ families and contrast nonalcoholic families (FH-) recruited from the same neighborhoods (Zucker et al., 1996, 2000). We used psychophysiological interaction (PPI) analysis to investigate how physiological connectivity is affected by psychological valence (reward processing versus a neutral condition) using a MID task. We hypothesized that connectivity during incentive anticipation between the NAcc and cognitive control regions associated with reward processing would differ by family history. We further hypothesized that individual differences in connectivity during incentive anticipation would mediate the relationship between sensation-seeking and levels of substance use in high-risk youth.

2. METHODS

2.1. Participants

Participants were 70 right-handed young adults (46 males, 24 females), aged 18.0–22.3 years (mean 20.1 ± 1.3), recruited from the MLS, an ongoing study of families with parental alcoholism (2/3 of sample) and contrast nonalcoholic families (1/3 of sample; Zucker et al., 2000). Parental alcoholism was based on DSM-IV criteria; detailed description regarding MLS recruitment and assessments can be found elsewhere (Zucker et al., 1996, 2000). Families in which the mother reported drinking during pregnancy or in which the target child exhibited signs of fetal alcohol syndrome were excluded (e.g., Loukas et al., 2001; Sokol and Clarren, 1989). Subjects' substance use, behaviors and personality are assessed annually beginning at age 11, through age 26. Forty-nine participants in this study had one or both parents with a lifetime history of alcoholism (FH+) and 21 participants had no parental history of alcoholism (FH-), consistent with the entire MLS. All participants were Caucasian.

Exclusionary criteria were: any neurological, acute, uncorrected or chronic medical illness; any current or recent (within six months) treatment with centrally active medications, including sedative hypnotics; and history of psychosis or schizophrenia in first-degree relatives. The presence of most Axis I psychiatric or developmental disorders was exclusionary. However, externalizing disorders were not exclusionary as these may lie on a developmental spectrum with alcoholism risk (Krueger, 1999) namely conduct disorders, attention deficit/hyperactivity disorder (ADHD), or prior substance use disorder (SUD) using DSM-IV criteria. The current sample represents the first 70 neuroimaging participants; data collection is ongoing. Subject characteristics are summarized in Table 1. Written informed consent, approved by the University of Michigan Medical School Institutional Review Board, was obtained.

2.2. Measures

2.2.1. fMRI paradigm—Brain response during anticipation of incentive stimuli was probed using a modified MID task (Knutson et al., 2000; Figure 1). Each 6-second trial consisted of four events: incentive cues (five conditions: \$0.20 win, \$5 win, \$0.20 loss, \$5 loss, \$0 no change); anticipation delay; variable duration target requiring a button press response to gain, or avoid loss, of money; feedback. Subjects were instructed to respond to neutral targets despite no incentive value. Trials were presented in pseudorandom order in two 5-minute runs of twenty trials/condition. Response target duration was calculated based on individual subject's reaction time during a practice session prior to scanning and calibrated for overall success rate of approximately 60%. Participants were paid fixed participation rates plus additional money won during task.

2.2.2. Drinking and drug use—An alcohol consumption variable was created from the Drinking and Drug History (DDHx) Questionnaire (Zucker, 1991; Zucker and Fitzgerald, 1994; Zucker et al., 1990). Participants were asked: how many days/month they drank over the past 6 months; and on a day when they drink, how many drinks they usually have in 24 hours over the same interval. A *drinking volume* (DV) variable (days/month x usual number of drinks) was created using square root transformation ($\sqrt{1+x}$) (Osborne, 2002) and found normally distributed with a one-sample Kolmogorov-Smirnov (KS) test across and within groups ($p's > 0.06$).

2.2.3. Sensation-seeking—The *Multiple Affect Adjective Checklist (MAACL)* (Zuckerman and Lubin, 1965) assessed Sensation-seeking, Positive Affect, Anxiety, Depression, and Hostility. Sensation-seeking scores were normally distributed across and within each group (KS test, $p's > 0.20$).

2.2.4. fMRI data acquisition—Whole-brain blood oxygen level-dependent (BOLD) functional images were acquired on a 3.0 Tesla GE Signa scanner (Milwaukee, WI) using T2*-weighted single-shot combined spiral in/out sequences (Glover and Law, 2001), parameters: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°; field-of-view = 200 mm; matrix size = 64×64; slice thickness = 4 mm, 29 slices. High-resolution anatomical T1 scans were obtained for spatial normalization. Motion was minimized with foam pads and emphasis on importance of keeping still.

2.3. Data analysis

2.3.1. Demographic, psychometric and task measures—Independent t - or χ^2 -tests were used to examine group differences; Fisher's exact test was used for contingency tables with cell sizes less than 5. Response time (RT) and success rate for each incentive condition were normally distributed (KS test, $p's > .17$). Repeated-measures analyses of variance (ANOVAs) were conducted for RT and success rate, separately, assessing performance differences between groups: valence (win/loss) x amount (\$0.20/\$5). Post-hoc t -tests were used to determine sources of significant differences. Pearson correlation was used to evaluate the relationship between sensation-seeking and drinking volume.

2.3.2. Functional data preprocessing—Functional images were reconstructed using an iterative algorithm (Fessler et al., 2005; Sutton et al., 2003) and motion corrected using FSL4.0 (Analysis Group, FMRIB, Oxford, UK). Runs exceeding 2 mm translation or 2° rotation were excluded; 2 subjects each from FH- and FH+ had one run excluded. Image processing was completed using statistical parametric mapping (SPM2, Wellcome Institute of Cognitive Neurology, Oxford, UK). Functional images were spatially normalized to

standard stereotactic space as defined by the Montreal Neurological Institute and spatially smoothed with a 6mm isotropic kernel.

2.3.3. Individual subject statistical maps—A general linear model using SPM's canonical hemodynamic response function (HRF), modeled incentive anticipation, defined as the period between cue and target (Knutson et al., 2001) with regressors for each condition (\$0.20 win, \$5 win, \$0.20 loss, \$5 loss, \$0) and six motion parameters. Contrasts for anticipation of reward (\$0.2 and \$5.0 combined) minus neutral and anticipation of loss (combined) minus neutral were calculated.

2.3.4. NAcc Regions of Interest (ROIs)—Based on *a priori* interest in reward, anatomical 5mm-diameter spherical masks for NAcc were created as specified in Bjork et al (2008a) using MarsBaR (Brett et al., 2002). Figure 1 illustrates mask location: the ventromesial intersection of caudate and putamen (Bjork et al., 2008b). Visual inspection of each dataset confirmed masks were accurately placed on NAcc, repositioning up to 1mm ensured accurate placement. NAcc activations were extracted from each individual's contrast images using MarsBaR. A post-hoc ANOVA (hemisphere x FH x valence x amount) was used to evaluate effects on activation.

2.3.5. Individual and group functional connectivity analysis—

Psychophysiological interaction (PPI) analysis determines regions whose time series of activation exhibit significant covariance with the seed differently in two conditions, i.e. incentive versus neutral condition. Regressing out the contribution of the seed ROI time series and that of the experimental context, the interaction is the contribution-dependent change in regional responses to the experimental factor (Friston et al., 1997), here response to incentive anticipation. PPI analysis was seeded in the NAcc ROIs described above and implemented separately for reward and loss conditions for left and right NAcc, 4 analyses per subject. For each NAcc, time-series data from the primary model was extracted and deconvolved with the HRF to create a neuronal times-series (Gitelman et al., 2003). The interaction term was the product of the neuronal time-series and a contrast vector coding for main effect of task (1 for reward or loss; -1 for neutral), an A - B regressor of interest. This term was convolved with the HRF (Friston et al., 1997). Contrast vectors were also created for the A + B regressor (1 for reward or loss; 1 for neutral), as well as the condition trial not under study, a C regressor (ie., 1 for loss, 0 for reward, 0 for neutral when evaluating for reward connectivity change), to account for all task associated variance. The PPI model regressors consisted of the interaction term, the A-B contrast vector, the extracted time-series, the A+B regressor, the C regressor, and motion regressors from the original design (O'Reilly et al., 2012). Single subject contrasts for the first regressor (interaction term) were calculated which identified regions whose task-driven connectivity with the NAcc seed changes as a function of incentive anticipation, hereafter referred to as connectivity.

Single subject contrasts were used for whole brain 2x2 ANOVAs in SPM with valence (reward/loss) and group (FH-/FH+) as factors for each NAcc. To identify brain regions showing significant group differences in functional coupling, two contrasts were created: FH + minus FH-, and FH- minus FH+. Statistical significance was established at $p < 0.05$, corrected for multiple comparisons at the cluster level. For identified ROIs, connectivity was extracted from individual PPI maps.

Post-hoc analyses included: 1) ANOVAs with FH as the between-subjects factor and valence as the within-subjects factor to confirm main effects of FH, and to investigate main effects or interactions with valence; 2) correlations between connectivity and sensation-seeking and DV, controlling for RT (correction for multiple comparisons: $.05/2 = p = 0.025$). Fisher's Z-transformations were used to determine differences between group correlation coefficients.

Whole brain one-sample t -tests in SPM were also performed on single subject PPI contrasts from each incentive condition to evaluate connectivity with right and left NAcc separately for each FH group. Contrasts identified brain regions with positive and negative connectivity with NAcc.

2.3.6. Model of Connectivity as Mediator of Substance Use—For all ROIs identified in the group level PPI analyses, an indirect effect of connectivity was tested with a bias-corrected bootstrapped mediation analysis using an SPSS macro (Preacher and Hayes, 2004). The dependent variable was DV, the independent variable was sensation-seeking score, and the mediator was connectivity with NAcc. As post-hoc analysis revealed no main effect of valence on connectivity (with the exception of right NAcc-right lingual gyrus; see Results), connectivity for reward and loss trials was linearly combined for this analysis. A point estimate of the indirect effect was derived from the mean of $n=5000$ estimates and 95% confidence intervals computed using the 2.5% highest and lowest scores of the empirical distribution. Indirect effects were considered significant when the bias-corrected and accelerated confidence interval did not include zero (Preacher and Hayes, 2004).

3. Results

3.1. Demographic and psychometric measures

Table 1 shows sample characteristics by FH revealing no group differences in personality measures or diagnoses. The FH+ group exhibited higher counts for abuse/dependence which may suggest future trends. Sensation-seeking showed a trend for a positive correlation with DV for the entire sample ($r=0.22$, $p=0.079$) which was stronger for FH+ ($r=0.29$, $p=0.059$) than FH- ($r=0.08$, $p=0.728$).

3.2. Task performance and activation

Success rate for each condition did not differ between groups ($p's>0.24$). The ANOVA revealed an effect of valence on success rate (win>avoid loss; $F_{1,68}=5.0$, $p=0.028$) and amount ($\$5>\0.20 ; $F_{1,68}=25.0$, $p<0.001$), but there were no interactions between valence, amount and/or FH ($p's>0.13$). Task difficulty, assessed by target duration, did not differ between groups ($p=0.47$).

An effect of valence was found on RT (avoid loss>win; $F_{1,68}=9.5$, $p=0.003$) and amount ($\$0.20>\5 ; $F_{1,68}=4.6$, $p=0.036$), but interaction between valence and amount did not meet significance ($p=0.068$). There were no main effects of group or interactions between group and valence or amount ($p's>0.17$). There was a group x valence x amount interaction ($F_{1,68}=6.7$, $p=0.012$) which was driven by faster RTs for \$5 versus \$0.20 win for FH- subjects that was not seen in FH+ subjects ($p=0.009$). Further group analyses controlled for RT. Table 2 presents a summary of task performance.

The ANOVA revealed significant effects on extracted task NAcc activation of valence (win>avoid loss; $F_{1,68}=70.2$, $p<0.001$) and amount ($\$5>\0.20 ; $F_{1,68}=60.6$, $p<0.001$), and an interaction between hemisphere and valence (right loss>left loss; $F_{1,68}=4.7$, $p<0.034$) but no other interactions ($p's>0.13$). See Figure 1 and Table 2 for task results. An additional post-hoc analysis, excluding all subjects with any diagnosis (FH-, $n=2$; FH+, $n=6$), confirmed the effect of valence and amount on NAcc activation (both $p<0.001$) with no significant interactions ($p's>0.14$), confirming that subjects with diagnosis were not driving activation results.

3.3. PPI connectivity analysis

The whole-brain ANOVA revealed no differences in connectivity by valence but found group differences in NAcc incentive connectivity with midline regions and parietal cortices (FH+>FH-), with a peak cluster centered in the paracentral lobule extending into the precuneus and supplemental motor area, mapping onto the supplementary sensorimotor area (SSMA) (Lim et al., 1994; Penfield and Jasper, 1954). Group differences were also identified in occipital regions (FH->FH+); see Table 3.

The post-hoc ANOVA confirmed a main effect of FH ($p's < 0.023$) on connectivity change for all ROIs. There was a valence x FH interaction ($F_{67,2}=10.9$, $p=0.003$) for incentive connectivity change between right NAcc and right lingual gyrus; post-hoc t -tests revealed that only in FH-, NAcc-lingual connectivity had more significant change with reward rather than loss vs. neutral conditions ($t=3.22$, $p=0.004$). There were no main effects of valence ($p's > 0.07$) or interactions with FH ($p's > 0.19$) on connectivity with other ROIs. Additional post-hoc analyses, excluding subjects with any diagnosis (FH-, $n=2$; FH+, $n=6$), confirmed the main effect of FH on connectivity change for all ROIs was not driven by diagnoses ($p's < 0.048$).

Extracted PPI data revealed midline and parietal areas had positive incentive connectivity changes with NAcc in FH+ as opposed to negative changes for FH-. In contrast, occipital regions had increased incentive connectivity with NAcc in FH- and decreased in FH+ (Figure 3).

The within group whole brain t -tests revealed increased connectivity from neutral to incentive conditions between NAcc and occipital and temporal lobes in FH- and no significant increases in connectivity in FH+. Decreased connectivity was found in FH- between bilateral NAcc and inferior parietal, paracentral and precuneus regions and in FH+ between left NAcc and superior temporal and occipital regions (Figure 2). Extended results, at more lenient voxel-level thresholds of $p < 0.05$ false-discovery-rate-corrected, voxel extent 20, are available in Supplemental Tables 1 and 2¹.

3.4. PPI ROI correlations with psychometric measures

Left NAcc-SSMA, incentive connectivity and sensation seeking correlated positively in FH+ and negatively in FH-, (test between correlation coefficients, $z=-3.82$, $p=0.0001$). Left NAcc-SSMA incentive connectivity was positively correlated with DV in FH+ (Figure 4 and Table 4). Left NAcc-right precuneus and right NAcc-SSMA connectivity also correlated positively with both sensation-seeking and DV in FH+. Correlations for other ROIs can be found in Table 4.

3.5. Test of mediation

The mediation model showed a significant indirect effect of left NAcc-SSMA on the relationship between sensation-seeking and DV for FH+ subjects with the bootstrapped bias-corrected estimate (95% confidence intervals, CI, did not include zero, Figure 5). Left NAcc-right precuneus connectivity also showed a significant indirect (CI: 0.0001 – 0.5055) and right NAcc-SSMA neared significance (CI: -0.0092 – 0.3167). No significant effects were found for other ROIs for either group.

4. DISCUSSION

We used a MID task to probe the reward network of young adults hypothesizing that reward system connectivity would differ based on familial risk for substance abuse and these differences would mediate the relationship between sensation-seeking personality and

drinking behavior. This is the first study to demonstrate differences in anticipatory reward-related functional connectivity based on family history using psychophysiological interaction (PPI) analyses seeded from the NAcc. We found that left NAcc connectivity with SSMA and right precuneus mediated the relationship between sensation-seeking and alcohol consumption in high-risk youth (FH+). Accumbens functional connectivity with the SSMA and precuneus, as well as other frontal and parietal regions including the paracentral lobule and sensorimotor areas, was not only significantly different by group, but these couplings changed in opposite directions in response to the reward task. FH- subjects demonstrated reductions in coupling between these structures during incentive anticipation, while FH+ increased coupling, potentially representing a neurobiological difference related to vulnerability.

Sensation-seeking has been associated with substance use risk (Malmberg et al., 2010), and high alcohol use (Schall et al., 1992; Sher et al., 2000). Here we report no differences by familial risk in sensation-seeking levels, drinking volume, reward task performance and anticipatory striatal activation in young adults. However, we observed group differences in reward-related functional connectivity with the NAcc that influenced the relationship between personality and drinking outcome in the high-risk population.

The NAcc is considered a key node in reward circuitry involved in assigning salience (Knutson and Cooper, 2005; McClure et al., 2004) and is hypothesized to be involved in vulnerability for addiction (Bjork et al., 2008b; Blum et al., 2000). Resting state studies of healthy subjects has shown positive functional connectivity between NAcc and cortical regions including the orbitofrontal, lateral temporal lobe and precuneus (Di Martino et al., 2008). Within-group PPI analysis in our control group revealed decreased task-related connectivity (Figure 2) with some of those same regions consistent with the responses of the brain's default mode network (DMN) which decreases activity during attention-demanding tasks (Greicius and Menon, 2004; Mazoyer et al., 2001; Raichle et al., 2001). Areas positively correlated in resting state may have competing functions when task focus is necessary (Fox et al., 2005). Therefore task-related reductions in connectivity with DMN regions during reward processing may represent expected decoupling as focus shifts to process and react to incentive stimuli.

Of further interest, the between-group PPI identified differences in connectivity with regions that map onto multiple functional networks. Neuroimaging has mapped large-scale networks as distinct functional systems including the DMN, attention/control, visual, auditory/phonology, motor and self-referential networks (Cordes et al., 2002; Damoiseaux et al., 2006; De Luca et al., 2006; Deco and Corbetta, 2011; Dosenbach et al., 2007; Fox et al., 2006; Hampson et al., 2006), which closely represent underlying anatomical connectivity (Deco and Corbetta, 2011). The FH+ subjects in our study had increased striatal couplings with attention and motor structures, specifically the medial SSMA, precuneus and pre-and postcentral gyri, while the FH- subjects decoupled these regions during incentive anticipation, representing distinctly different network utilization.

The precuneus has been identified as a key node within the DMN in functional connectivity analysis (Fransson and Marrelec, 2008). The precuneus has among the brain's highest glucose metabolism consistent with a role requiring high levels of information processing relative to both orientation within and monitoring of external environment (Gusnard and Raichle, 2001). In a resting state study of chronic heroin users, left NAcc had reduced connectivity with left precuneus compared with controls (Ma et al., 2010). Our PPI results reveal dysfunction between these same structures. As expected, the FH- subjects in our sample had reduced connectivity during task, while FH+ increased coupling during active

incentive processing, suggesting pre-existing dysfunctional connectivity between reward and DMN networks in our non-addicted, yet high-risk sample.

Our results are consistent with a recent PPI analysis of eating behaviors (Passamonti et al., 2009) which found connectivity changes between NAcc and premotor areas when viewing appetizing vs. bland foods in subjects with higher food sensitivity. The authors propose the premotor cortex mediates transformation of desire generated by the striatum into preparation for action suggesting inefficient coupling between reward and feeding network as a vulnerability marker for abnormal behaviors such as overeating (Passamonti et al., 2009). As similarities have been suggested between eating behaviors in obesity and drug use in addicts (Volkow and Wise, 2005), the sensorimotor cortex may have a similar preparatory role in addictive substance use. In FH+ subjects, the striatal-SSMA connectivity was positive as opposed to negative for FH– during reward anticipation, potentially representing significant inefficiencies between salience assignment and action.

Furthermore, we found NAcc-SSMA connectivity correlated with sensation-seeking in opposite directions as a function of FH, with higher sensation-seeking associated with increasingly positive connectivity in FH+ subjects. Incentive-related connectivity mediated the relationship between this personality trait and drinking volume in these at-risk subjects, suggesting that individual variations in neural connectivity, and not only discrete brain regions, influence the relationship between personality and outcome. The SSMA, encompassing the mesial portion of the superior frontal gyrus, paracentral lobule, cingulate gyrus and precuneus (Lim et al., 1994), incorporates structures within both the attention and motor networks (Deco and Corbetta, 2011). As such, it is involved in initiation and integration of motor function with visual sensory and emotional guidance, or an “urge to move” (Fox et al., 1985; Lim et al., 1994; Tanji and Evarts, 1976). The accumbens coupling differences in high-risk subjects may represent inefficient communication between salient and internal mentation processes. Therefore, NAcc-SSMA connectivity may mediate the transformation of desire generated by the ventral striatum, represented at an individual-level as a sensation-seeking trait, into preparation to act.

As PPI infers interregional correlations and does not yield information regarding causal or directional relationships between functional coupled regions, or even whether other, unmeasured regions are driving the relationship, interpretation of our results are limited in that regard. The lack of connectivity results from the right NAcc seed may be in part explained by previous work showing left lateralized dopaminergic transmission in basal ganglia structures in response to monetary reward (Zald et al., 2004); this merits further investigation. In addition, as the orbitofrontal cortex and anterior cingulate are areas frequently implicated in processes associated with addiction (Goldstein and Volkow, 2002), it was interesting that we did not find task-related connectivity changes with these executive/cognitive areas as initially hypothesized. Additional study is needed to understand how network interactions might differ by gender, or be impacted by maturation and substance use.

Further, we acknowledge the difficulty in dissociating risk from resilience. In this study, risk was defined as having a parent with a history of alcoholism, yet we did not find that current drinking differed by FH, likely because our subjects are in the transition years of highest substance use in the general population. With continued longitudinal study, we hypothesize divergence within the FH+ group into those with and without alcohol and drug use problems, which may help dissociate risk from resilience. In addition, the present design did not allow for the characterization of response to incentive outcome feedback due to collinearity with anticipation. Given the evidence that striatal responding to outcome

feedback has been associated with risk-related behaviors (Bjork et al., 2010), this will be an important relationship to investigate in the future.

This study found that functional connectivity with reward/salience regions, specifically the NAcc, appears to represent a preexisting neurobiological characteristic of FH+ youth. Despite similar performance and NAcc activation, reward processing in the high-risk group involved positive striatal functional connectivity with attention, motor and DMN structures versus decoupling seen in FH– subjects, suggestive of inefficient inter-network communication. Importantly, NAcc-SSMA and NAcc-precuneus connectivity mediated the relationship between the personality trait of sensation-seeking and drinking in FH+ subjects, representing a potential model of vulnerability. Differences in accumbens connectivity with multiple functional networks, rather than strictly with control regions, may influence the reward system's role in vulnerability for substance abuse.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

A) Schematic illustration of the monetary incentive delay task performed by subjects in the fMRI scanner. B) Location of 5-mm diameter spherical nucleus accumbens mask at the ventromesial intersection of caudate and putamen ($y=13$ MNI). C) Activation in bilateral nucleus accumbens during reward and loss anticipation by family history groups. Error bars: ± 1 Standard Error.

Figure 2.

Regions with negative functional connectivity with NAcc during incentive including areas. FH- controls have reduced task connectivity in regions which map onto default mode network resting state regions representing areas significantly decoupled during incentive processing. A) Functional connectivity for FH- controls with left NAcc; B) functional connectivity for FH- controls with right NAcc; C) Functional connectivity for FH+ with left NAcc; D) functional connectivity for FH+ with right NAcc. Data are displayed on the lateral and medial surfaces of the left hemisphere (Left), the dorsal surface (Center), and the lateral and medial surfaces of the right hemisphere (Right) for each NAcc. Connectivity maps are displayed at cluster-level $p < 0.05$ corrected with the exception of D) which is displayed at cluster-level $p < 0.08$ due to lack of significant clusters at the more stringent threshold.

Figure 3.

Extracted task-related functional connectivity change with NAcc during Incentive>Neutral anticipatory processing by family history group. L, left; R, right; NAcc, nucleus accumbens; SSMA, supplementary sensoriomotor area; PoG, postcentral gyrus; SMA, supplementary motor area; OCC, occipital.

Figure 4.

A) Statistical parametric maps identifying large cluster designated supplementary sensorimotor area (SSMA). B) Correlations between left NAcc–SSMA incentive connectivity change and sensation-seeking by family history group. C) Correlations between left NAcc–SSMA incentive connectivity change and transformed drinking volume for the past six months by family history group.

Figure 5. Meditation model of vulnerability with unstandardized coefficients testing indirect effect of connectivity on relationship of sensation-seeking on drinking volume.

Table 1

Subject Characteristics.

	FH–	FH+	χ^2 or <i>t</i>	p
N	21	49		
Males: Females	8:14	16:32	0.19	0.66
Age - Scanning (years)	20.1 (1.3)	20.1 (1.3)	0.13	0.90
Age - Most Recent Assessment (years)	19.6 (1.6)	19.5 (1.5)	0.31	0.76
IQ (WISC-III) ^a	112 (9)	110 (12)	0.83	0.41
Alcohol Abuse or Dependence	1	5	0.74	0.39
Marijuana Abuse or Dependence	2	4	< 0.01	0.95
Nicotine Dependence	0	1	< 0.01	1.00
Other Drug Abuse or Dependence	1	1	0.30	0.59
Any Substance Use Disorder Dx ^b	2	6	1.37	0.71
Depression Dx	2	0	4.34	0.037 *
Conduct Disorder Dx	0	1	0.48	0.49
Attention Deficit Disorder Dx	1	0	2.13	0.14
Any Dx ^c	2	5	0.08	0.78
Drinking Measure				
<i>Drink Volume (drinks/month)</i>	29.2 (40.4)	31.2 (42.2)	0.18	0.86
<i>Transformed Drinking Volume</i>	4.4 (3.4)	4.5 (3.5)	0.10	0.92
Multiple Affect Adjective Checklist				
Anxiety Youth	1.25 (1.45)	1.43 (2.18)	0.11	0.92
Depression	1.20 (2.28)	1.09 (2.05)	0.49	0.62
Hostility	1.05 (1.50)	1.48 (2.00)	1.22	0.23
Positive Affect	10.95 (4.90)	10.13 (5.18)	0.81	0.42
Sensation Seeking	5.25 (2.47)	5.37 (2.25)	0.68	0.50
Mother/Father/Both Alcohol Abuse	NA	4/6/1	NA	
Mother/Father/Both Alcohol Abuse or Dependence	NA	3/22/24	NA	
Mother Abused other Drugs ^{d,e}	1	5	0.56	0.46
Father Abused other Drugs ^{d,e}	2	15	5.57	0.018 *
Both Abused other Drugs	0	7	3.33	0.07

FH–, family history negative; FH+, family history positive; Dx, diagnosis.

* Significant difference, discussed fully in text.

^a Wechsler Intelligence Scale for Children – 3rd edition. These data were collected when participants were between the ages of 12 and 14 years as part of the ongoing Michigan Longitudinal Study.

^b Includes alcohol abuse or dependence, marijuana abuse or dependence and/or other drug abuse or dependence

^c Includes conduct disorder, attention deficit disorder and/or any substance use disorder, excluding nicotine.

^d Includes endorsing at least one of the following: amphetamines, cocaine, sedatives/hypnotics, opiates, or marijuana.

^e For FH– group: Mother: 1 marijuana only; Father: 1 marijuana only, 1 marijuana and amphetamines.

Data presented as Mean (Standard Deviation) where applicable.

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Table 2**Task Performance and NAcc Activations by Family History**

	FH–	FH+
MID task performance		
Hit Rates (%)		
Lose Small	58 (17)	57 (17)
Lose Big	62 (22)	65 (18)
Neutral	48 (21)	48 (17)
Win Small	62 (15)	57 (18)
Win Big	68 (19)	67 (19)
Hit Response Time (msecs)		
Lose Small *	172 (35)	190 (37)
Lose Big	175 (40)	187 (37)
Neutral	172 (33)	183 (41)
Win Small	176 (33)	182 (42)
Win Big Hit *	159 (40)	182 (41)
MID task activation (effect size)		
Left NAcc		
Lose Small - Neutral	–0.004 (0.586)	0.030 (0.800)
Lose Big - Neutral	0.608 (1.005)	1.000 (0.966)
Win Small - Neutral	0.889 (0.889)	0.780 (1.058)
Win Big Hit - Neutral	1.657 (1.324)	1.807 (1.502)
Right NAcc		
Lose Small - Neutral	0.238 (0.612)	0.032 (0.741)
Lose Big - Neutral	0.797 (1.713)	0.935 (0.917)
Win Small - Neutral	0.897 (0.804)	0.752 (1.011)
Win Big Hit - Neutral	1.756 (1.282)	1.756 (1.296)

FH–, family history negative; FH+, family history positive.

* Significant differences between groups (described fully in text).

Table 3

Brain Regions with Group Differences in Functional Connectivity with Nucleus Accumbens during Incentive Anticipation.

Brain Region	Brodmann's Areas	MNI space			Cluster Size (voxels)	Peak t	Cluster Level p (corrected)
		x	y	z			
Left NAcc							
FH+ > FH-							
R/L SSMA	4/6	6	-36	68	776	5.6	<0.001
R Precuneus	7	16	-64	44	201	5.1	0.009
R Postcentral gyrus	2	46	-28	42	516	4.6	<0.001
L Postcentral gyrus	2/40	-44	-34	44	536	4.4	<0.001
R/L SMA	6	-6	-4	50	262	4.1	0.002
FH- > FH+							
L Calcarine Fissure	18	-16	-70	6	247	4.7	0.003
Right NAcc							
FH+ > FH-							
R Superior parietal gyrus	5	18	-46	58	371	4.6	<0.001
R/L SSMA	6	4	0	50	945	4.5	<0.001
FH- > FH+							
R Middle occipital gyrus	18/19	32	-84	14	209	5.7	0.009
R Lingual gyrus	18	26	-86	-10	517	4.9	<0.001
L Lingual gyrus	18	-12	-74	-12	381	4.3	<0.001

L, left; R, right; NA, not applicable; NAcc, nucleus accumbens; SSMA supplementary sensorimotor area; SMA, supplementary motor area.

Table 4
Statistics for Correlations of Functional Connectivity during Incentive Anticipation with Left NAcc Controlling for Response Time.

Brain Region	FH-			FH+			FH- vs. FH+		
	Sensation- seeking	Trsfld. Drink Vol.		Sensation- seeking	Trsfld. Drink Vol.		Sensation- seeking	Trsfld. Drink Vol.	
	r	p	r	p	r	p	r	p	r
L NAcc									
FH+ vs. FH-									
R/L SSMA	-.589**	.106	.367**		.371**		-3.82 ⁺⁺		-1.02
	.006	.658	.012		.012		0.0001		0.154
R Precuneus	-.078	.094	.317*		.358**		-1.46		-1.01
	.734	.694	.032		.016		0.072		0.313
R Postcentral	-.228	.167	.078		.023		-1.12		0.52
	.335	.481	.604		.881		0.130		0.302
L Postcentral	-.132	.328	.117		-.100		-0.90		1.59
	.578	.158	.438		.514		0.184		0.056
R/L SMA	-.103	.160	.047		.047		-0.54		0.41
	.664	.501	.757		.758		0.295		0.682
FH- vs. FH+									
R Calcarine Fissure	-.207	-.023	-.143		.085		-0.22		-0.39
	.382	.924	.344		.581		0.413		0.348
R NAcc									
FH+ vs. FH-									
R Superior parietal	-.252	.089	.239		.462**		-1.80 ⁺		-1.48
	.284	.709	.109		.001		0.036		0.070
R/L SSMA	-.088	.120	.327*		.488**		-1.54		-1.48
	.711	.615	.034		.001		0.062		0.069
FH- vs. FH+									
R Middle occipital	-.141	-.119	.283		.280		-1.56		-1.46
	.554	.619	.057		.062		0.059		0.072

Brain Region	FH-				FH+				FH- vs. FH+			
	Sensation- seeking		Trsfd. Drink Vol.		Sensation- seeking		Trsfd. Drink Vol.		Sensation- seeking		Trsfd. Drink Vol.	
	r	p	r	p	r	p	r	p	z	p	z	p
R Lingual	.092		-.122		.051		.205		0.15		-1.19	
	.701		.607		.739		.177		0.440		0.117	
L Lingual	-.001		.104		.085		.199		-0.31		-0.35	
	.997		.662		.575		.189		0.378		0.363	

* significant 0.05,

** significant 0.025 corrected for multiple comparisons,

+ results of Fisher's Z-transformation testing differences between correlation coefficients 0.05,

++ significant difference between group correlation coefficients 0.025.

FH-, negative for family history of alcoholism; FH+, positive for family history of alcoholism; Trsfd. Drink Vol., square root transformed drinking volume past 6 months; NAcc, nucleus accumbens; L, left; R, right; SSMA, supplementary sensorimotor area; SMA, supplementary motor area.