Parental substance abuse and function of the motivation and behavioral inhibition systems in drug-naïve youth

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Keywords

fMRI; motivation-reward; behavioral inhibition; risk for substance abuse; ADHD

1. Introduction

Substantial evidence indicates that parental history of substance abuse (SA) and childhood attention deficit/hyperactivity disorder (ADHD) are associated with risk for later addiction. For instance, the biological children of alcoholics are at greater risk for alcoholism than the general population (Johnson and Leff, 1999), and parental dependence on any substance confers increased risk to offspring not only for life-time drug dependence but also for disruptive behavior disorders (Marmorstein et al., 2009). In addition, childhood ADHD has been associated with a greater prevalence of SA in adolescence and early adulthood (Chilcoat and Breslau, 1999; Barkley et al., 2003; Mannuzza et al., 2008). These observations suggest that vulnerability to addiction may be conferred by an inherited latent factor (Slutske et al., 1998) that increases the incidence of both SA and externalizing disorders including ADHD and conduct disorder (CD) (Young et al., 2000; Kendler et al., 2003). Although childhood ADHD and parental history of SA may independently contribute to the risk for addiction, the neurobiological components of such predisposition, particularly before exposure to drug abuse, are unknown.

1.1. Reward Processing in SA and ADHD

It has been hypothesized that the clinical presentation of SA may be linked to relative imbalance in functions of the motivation-reward and behavioral inhibition systems in the brain (Goodman, 2008). Dopamine deficiency in the mesolimbic motivation-reward circuitry, a condition known as the "Reward Deficiency Syndrome" (Blum et al., 2000), is

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thought to confer vulnerability for SA, with addicts using drugs of abuse to increase dopamine levels transiently in the mesolimbic motivation-reward networks particularly in the ventral striatum. Recent findings indicate that individuals suffering from Reward Deficiency Syndrome, possessing a paucity of dopaminergic and/or serotonergic receptors and a higher rate of synaptic dopamine catabolism as compared with the general population, are predisposed to self-medicating with any substance or behavior that will activate dopamine release (Blum et al., 2011). Relevant also is a more recent discovery of pre-existing differences in dopamine $D_{2/3}$ receptor expression in the striatum of high-impulsive rats, suggesting a neural endophenotype that may likewise pre-dispose to addiction in humans (Cumming et al., 2010). Beyond this finding in rodents, reduced dopamine transporter and receptor density in the striatum has been documented in adult methamphetamine abusers (Chang et al., 2007) and blunted striatal activity has been reported in detoxified alcoholics (Wrase et al., 2007) and in adults with parental alcoholism compared to control with no such history (Andrews et al., 2011). Further, impulsiveness in human subjects has been linked to $D_{2/3}$ receptor availability in the striatum and midbrain (Lee et al., 2009; Buckholtz et al., 2010). Impulsivity has also been negatively correlated with striatal activation in fMRI studies, both in individuals with (Scheres et al., 2007; Strohle et al., 2008) and without ADHD (Stark et al., 2011). Moreover, both youths with high levels of externalizing behaviors (Bjork et al., 2010) and adults with childhood ADHD (Stoy et al., 2011) have shown altered activation in the ventral striatum, orbito-frontal cortex and the insula. As with substance abuse, dopamine plays a role in executive functions often affected in ADHD, and medications used in the treatment of ADHD augment catecholamine function (Del Campo et al., 2011).

1.2. Behavioral Inhibition in SA and ADHD

Given the fact that an action to engage in drug abuse involves a dialectic between a tendency to respond to potentially rewarding environmental stimuli and cortical inhibitory systems, ADHD-related deficits in behavioral inhibition can predispose an individual to SA (Ivanov et al., 2008). Behavioral inhibition is a complex behavior that has been assessed using paradigms that test the ability to suppress emotions (Beauregard et al., 2001; Levesque et al., 2003; Phan et al., 2005), thoughts and memories (Wyland et al., 2003; Anderson et al., 2004), inhibit motor responses (Garavan et al., 1999; Liddle et al., 2001; Rubia et al., 2003; Blasi et al., 2006; Li et al., 2006; Chevrier et al., 2007) and to evaluate and resolve conflict (Walsh et al., 2010). These paradigms generally elicit activation in the anterior cingulate, ventrolateral prefrontal and insular cortices. Accordingly, reduced responsiveness in these brain regions may reflect a predisposition for the later development of disorders characterized by the inability to inhibit undesired behavioral patterns, including obsessive compulsive disorder, Tourette's syndrome, posttraumatic stress disorder, SA and ADHD (Lerner et al., 2009). More specifically, hypofunction of the anterior cingulate gyrus, which is an integral part of the detecting attentional network (Fan and Posner, 2004) has been observed in patients with ADHD (Bush, 2010). Such deficits may, in turn, compromise an individual's ability to monitor responses and adjust behavior to meet changing environmental demands.

1.3. Preliminary Model for SA Risk

Behavioral inflexibility in combination with high motivational drive may be an important factor in the development of addiction (Hommer et al., 2011), and the strong motivational drive to seek drugs paired with weakened ability to voluntarily control such impulses has been viewed as the mechanism underlying addiction behaviors (Koob and Volkow, 2010; Volkow et al., 2010). Notably both ADHD and SA have been conceptualized as disorders of altered motivation as well as impaired inhibitory control (Volkow et al., 2010). If these putative dysfunctions precede the onset of drug use they may be viewed as constitutional

factors that predispose an individual for the development of SA. The identification of a biological underpinning of risk for SA would be studied best in children who have no prior exposure to drugs (Hommer et al., 2011) but exhibit motivational and inhibitory deficits, such as those observed in patients with ADHD (Volkow et al., 2010), a research direction that is currently unexplored. This study, therefore, examined the contribution of parental history of SA to functional activation in the brain motivation-reward and response monitoring neurocircuits in drug-naïve children with purported deficits in motivation and behavioral control. Towards this purpose, we designed a task that includes both reward and executive control components. This task was used in conjunction with functional magnetic resonance imaging (fMRI) to assess brain activation in 20 children who had no history of SA and met diagnostic criteria for ADHD. Based on the available literature related to deficits in reward processing in ADHD and SA, we hypothesized that the participants who had parental history of SA in addition to ADHD would exhibit less activation in regions of the motivation-reward network, specifically the caudate, orbitofrontal cortex and the insula during the reward components of the task. Further, given the existing evidence suggesting that high impulsivity is associated with elevated risk for later SA, we hypothesized that children with ADHD plus parental history of substance abuse would show reduced activation in the anterior cingulate gyrus during conflict resolution.

2. Methods

2.1. Participants

Twenty drug naïve children aged 8 to 13 years (Mean=10.53, SD= ±1.44) were recruited through fliers posted at the Mount Sinai Child and Adolescent Psychiatry Outpatient Clinic and by word of mouth. Study procedures were approved by the Mount Sinai Institutional Review Board. The legal guardian for each child gave written informed consent and each child provided written assent to an individual unaffiliated with the study. Each family was reimbursed $100 for completion of the study protocol. The initial visit included vital signs measurement and a full medical, developmental and family history as well as assessment of contraindications for MRI. Current and past psychiatric histories were evaluated using the Kiddie-SADS Present and Life Time Version (Kaufman et al., 1997), which was administered to both the parent and the child. All children met DSM IV-TR criteria for ADHD combined or inattentive type. Parents also completed the Conners ADHD Parent Rating Scale (Conners, 2000), which provides measures for ADHD symptom severity, and the Child Behavior Checklist (CBCL), which provides a measure for aggression (Achenbach, 1991). The Matrix Reasoning and Vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Ryan et al., 2003) were administered to estimate Full Scale IQ (FSIQ). Major psychotic, bipolar and mood disorders, mental retardation (FSIQ<75) as well as prior stimulant treatment, any drug use/experimentation and in-utero exposure to drugs were exclusion criteria. Parental history of substance abuse, which mostly (9 out of 10 in each group) was attributed to a parent who did not participate in the evaluation, was assessed using a semi-structured interview administered to the parent/caregiver. The semi-structured interview asked about past and present substance use for each biological parent. It also queried the type of drug used and the length of abuse, when it occurred. When a positive report was elicited additional questions were asked to determine whether i) the drug use represented a persistent pattern of behavior, ii) if it caused functional impairment and iii) if treatment was deemed necessary. In all cases of reported substance abuse, the reporting parent described the abuse as being a "serious drug problem" and indicated that the affected parent needed "treatment".

The children were further subdivided into two risk groups based on parental history of substance abuse: i) Low Risk (LR) group (n=10) included youth who met DSM criteria for ADHD and had no parents with substance abuse, and ii) High Risk (HR) group (n=10)

included youth who met DSM criteria for ADHD and had at least one biological parent with a history of substance abuse. Demographic characteristics for the two risk groups are presented in Table 1.

2.2. Procedures

Participants underwent task training on a desktop computer and performed one block of the Anticipation-Conflict-Reward (ACR) task (see below). The participants were also trained in a mockscanner, which provided an opportunity for children to familiarize themselves with the scanning environment. The actual MR scan was performed on a separate visit. About 45 minutes before the scan, participants practiced the ACR task again on an office desktop. The length of the scan averaged 35–40 min.

2.3. Anticipation-Conflict-Reward (ACR) Paradigm

The ACR task uses an event-related design with three temporally distinct probes of reward anticipation, conflict resolution, and reward outcome respectively. A pilot study using the task in 16 healthy adults showed that reward and target components of the task engaged components of the motivation-reward and behavioral inhibition systems accordingly (Ivanov et al., 2007). The ACR was modified to be more developmentally appropriate for the current study, by creating a narrative about the purpose of the task and including animation images for the cues, targets and outcomes (Figure 1, supplemental materials).

The ACR consists of four 6-minute and 20-sec locks including 32-trial with a 30-sec fixation (rest period) at the beginning and the end of each block. All trials begin with a cue presented at fixation for 500 ms, followed by a 2000 ms fixation period. The target is then displayed at fixation for 750 ms, followed by a 1750 ms response window. After this reward outcome is displayed at fixation for 750 ms. The inter-trial interval is jittered from 0 ms to 5000 ms with a mean of 2500 ms in each block and the total length of each trial averages 7750 ms, including the inter-trial interval. There are two cue events, non-reward and reward cue, which are depicted as moneybags that are either blank or contained a "$", respectively. Targets consist of right- or left-pointing central airplanes that are flanked by double airplanes, which are either congruent or incongruent in direction with the central plane. Children were instructed to respond in the direction of the central airplane as quickly as possible. Reward outcomes were defined in relation to the preceding cues and subject responses as either i) expected reward (reward cues followed by $1 win for correct responses), ii) expected non-reward (nonreward cues followed by $0 for correct responses), iii) unexpected non-reward (reward cue followed by $0 for correct responses) and iv) punishment (either cue followed by $1 loss for errors). Since the ACR task is a performance-dependent task, all errors were linked to punishment outcomes. Trial types were determined by counterbalancing across the two cues (reward vs. non-reward), four targets (left vs. right, congruent vs. incongruent), and three reward outcomes (not including punishment). Participants were told that if they respond correctly to the target that followed a reward cue they can receive a one dollar reward. They were also instructed that if they will not respond or if the response was incorrect or slow a dollar would be taken away. The reward outcome was depicted by an image of a dollar bill; expected and unexpected non-reward outcomes were portrayed by the grayed-out shape of a dollar bill, and punishment was depicted as a hand grabbing a dollar bill. The maximum win for the whole task was $32. The running total was presented at the end of each block of the task. It is noteworthy that the rewards in this task were virtual; children were shown the amount of money they won during the task but did not actually win that much money. However, as children are used to this type of virtual reward in the video games they play, the reward paradigm used here was thought to be developmentally appropriate and likely to be effective.

2.4. Image Acquisition

All participants were scanned on a 3.0 Tesla Siemens Allegra (Siemens Medical Systems) head dedicated MRI scanner using a high-performance head gradient system. Participants were fitted with headphones, and their heads were stabilized with firm foam padding. Stimuli were projected via an SVGA projector system onto a rear-projection screen mounted at the head of the magnet bore. Subjects viewed the stimuli through a mirror on the head coil positioned above their eyes. Scan sessions began with shimming and sagittal localization. A high-resolution T2-weighted anatomical brain scan was acquired with a turbo spin-echo (TSE) pulse sequence with a repetition time (TR) of 4050 ms, echo time (TE) of 99 ms, flip angle of 170°, 210 mm field of view (FOV), and 512 x 336 matrix. Forty axial slices were acquired at a thickness of 4 mm with no gap and an in-plane resolution of 0.47×0.47 mm. This sequence was obtained to register and align the functional images with a reference brain. Functional T2*-weighted images depicting the blood oxygenation level-dependent (BOLD) signal were acquired at the same 40 slice locations using gradient-echo echo-planar images with a TR of 2500 ms, TE of 27 ms, flip angle of 82°, FOV of 240 mm, and an acquisition matrix of 64×64. Each functional image comprised a brain volume of 40 axial slices, each 3 mm thick with 1mm gaps and an in-plane resolution of 3.75×3.75 mm. All images were acquired with slices positioned parallel to the anterior commissure – posterior commissure line. The participants all completed 4 runs of 380 seconds each, yielding data from 152 time points per participant.

2.5. Statistical Analysis

2.5.1. Behavioral Analyses—Three-way Group (HR, LR) x Cue (reward, non-reward) x Flanker (congruent, incongruent) ANCOVAs were performed with RT and accuracy as dependent variables. The alpha level for these analyses was set at $p < 0.05$. Post hoc pairwise t-tests were performed to compare between-groups RT for reward, unexpected non-reward and punishment trials, as well as RT for the trials that followed each of these trial types in order to assess the patterns of RT change following different reward outcomes.

2.5.2. fMRI Analyses—Image processing was conducted using statistical parametric mapping (SPM5; Wellcome Department of Imaging Neuroscience, London, U.K.). Standard SPM pre-processing of the four functional time series was performed individually for each subject. The functional scans were slice scan time-corrected, realigned to the first volume to correct for inter-scan motion, co-registered to the T2 image, normalized to a standard template (Montreal Neurological Institute), and spatially smoothed with an $8 \times 8 \times 8$ mm^3 full-width at half-maximum (FWHM) Gaussian kernel. First level (within-subject) analyses were conducted individually for each participant with a general linear model (GLM) to quantify the relationship between the observed event-related BOLD signals and regressors encoding expected trial-specific responses. Regressors were created by convolving a train of time-locked delta functions, encoding the occurrence of each trial type, with the canonical hemodynamic response (Friston et al., 1998). The six movement estimates created during motion correction were entered as covariates of no interest (Johnstone et al., 2006). The design matrix comprised 10 regressors: 6 for cue (reward vs. non-reward) and flanker type (congruent or incongruent) effects and 4 for outcome-related effects. The first 6 regressors comprised 2 regressors modeling the main effect of reward vs. non-reward cue over all trials (i.e. anticipation), while the effects of reward and congruence (and their interaction) were modeled for correct (and non-punishment) trials in an additional 4 regressors. The four outcome related effects were: reward following reward cue, non-reward following reward cue, non-reward following non-reward cue or punishment for incorrect or missing response. The main effect of reward anticipation was tested with appropriate linear contrasts of the parameter estimates for the reward cue minus non-reward cue. The neural substrate of cognitive inhibition was tested by contrasting incongruent vs. congruent flankers (the main

effect of congruency in correct trials). The outcome-related effects were tested with three contrasts: the effect of reward per se was summarized by subtracting the expected non-reward from the expected reward. The effect of surprising outcomes was assessed by subtracting the expected non-reward outcome from the unexpected non-reward. Finally, we quantified punishment-related responses (i.e. money loss due to incorrect responses minus expected non-reward). Based on the piloting of the task we determined that minimum of 15 event of each contrast will be sufficient in order to complete the analyses.

2.5.3. Hypotheses Testing—To test our hypotheses regarding activation due to reward and behavioral inhibition, we used the usual summary statistic approach for second level (between-subject) inference: First level (subject-specific) contrast images of the above effects, for high-risk and low-risk participants, were entered into separate second-level (random-effects) analyses of covariance (ANCOVA). In addition to group effects (High Risk vs. Low Risk), the omnibus ANCOVA model was supplemented with the following covariates: FSIQ, ADHD severity score, age and gender to remove potential effects of these variables from those of group differences. Group matching for ADHD severity score, age and gender assured that these variables were orthogonal to the Group (High Risk vs. Low Risk) variable. The resulting Statistical parametric t-maps (SPMs) were used to test for activation on the groups separately and group differences. The height (intensity) threshold of each activated voxel was considered significant at a nominal alpha level of $p < 0.01$ and a cluster extent of 85 contiguous resampled voxels ($2 \times 2 \times 2$ mm^3) was established via Monte-Carlo simulations to correct for multiple voxel comparisons at $p < 0.05$.

3. Results

3.1. Behavioral Results

There were no significant differences between the groups on RT and accuracy (Table 2). There were significant main effects of flanker on RT (F=9.09, df=2/18, p=0.007) and on accuracy (F=8.58, df=2/18, p=0.009), but there were no main effects of cue. Post-hoc analyses showed that RT decreased for both groups following reward; conversely, RT increased following a surprising outcome and punishment. RT increase (i.e. slower response) was significant only for the LR group for trials following a surprising non-reward outcome (F=1.83, df=1/9, p=0.04), and was highly significant for both groups following punishment. While subjects from both groups exhibited the same response adjustment following punishment (i.e. slower RT), RT for HR subjects was significantly shorter following a punishment trial (F=6.37, df=1/9, p=0.001; supplemental materials), suggesting a tendency for more impulsive responding and poor response monitoring.

3.2. Neuroimaging Results

3.2.1. Reward Anticipation—Second-level analysis of reward *minus* non-reward cue contrasts showed that both groups activated the right visual cortex and fusiform gyrus (supplemental materials). The HR group showed significantly higher activation than the LR group in the left insula cortex, extending to the head of the left caudate and also in the left inferior prefrontal cortex that extended into the left orbito-frontal cortex (OFC) (Table 3 & Figure 2). In contrast, LR children exhibited significantly higher activation in the premotor/ supplementary motor cortex bilaterally compared to the HR group (results not shown).

3.2.2. Target Response—SPMs of the incongruent minus congruent flanker contrast showed robust activation in a distributed cortico-thalamic network including the right fusiform gyrus, right somatosensory association and temporal cortices, right caudate, right dorso-medial prefrontal cortex as well as supplemental motor area and thalamus bilaterally over both groups (Table 4). Between group comparison showed significantly higher

activation in the dorso-medial prefrontal and anterior cingulated cortex (ACC) in the LR than the HR group (Figure 3), whereas the HR group had higher activation in the somatosensory association and insula cortices bilaterally (results not shown).

3.2.3. Reward Outcome Trials

3.2.3.a. Expected Reward: SPMs of the expected reward (i.e. reward outcome that followed a reward cue and correct flanker response) minus expected non-reward (i.e. neutral outcome that followed a nonreward cue and correct flanker response) contrast showed increased activation in somatosensory and fusiform cortices bilaterally in the whole sample (supplemental materials). The HR group exhibited higher activation than the LR subjects in the anterior insula cortex bilaterally and in the left OFC (Table 3 & Figure 4).

3.2.3.b. Surprising non-reward: The unexpected non-reward (i.e. non-reward outcome that followed a reward cue and correct flanker response) minus expected non-reward elicited deactivation in the right posterior insula cortex for the whole sample (results not shown). The HR group showed higher activation in the right hippocampus and the right middle occipital cortex but not in any motivation-reward system related regions (results not shown).

3.2.3.c. Punishment: Contrasts of punishment (i.e. money loss due to incorrect flanker response minus expected non-reward) for both groups elicited activation in a widely distributed cortical network including the left ACC, supplemental motor area, middle frontal gyrus, temporal, parietal and occipital cortices (supplemental materials). In addition, the punishment contrast also elicited deactivation in the head of the left caudate for all subjects. In contrast, the HR subjects showed higher activation in the right insula cortex (Table 3 & Figure 5).

The additional regressors introduced in the analyses showed that the IQ differences did not influence the activation in regions of interest (supplemental materials) whereas no appreciable effects of gender were detected.

4. Discussion

The findings of this study indicate that reward components of the ACR task (e.g. reward cues and reward outcomes including expected rewards and punishments) elicit more activity related to both reward anticipation and reward notification in brain regions of the motivational-reward system in children at high-risk for substance abuse; conversely, cognitive conflict elicit higher activation in brain regions associated with the behavioral inhibition system in low-risk than in high-risk subjects. These differences are not accounted for by the severity of ADHD symptoms as high- and low-risk subjects did not differ on their ADHD-RS scores. Also there were no significant differences in performance between the groups; therefore performance on the ACR task did not account for the differences in brain activation between the two groups. Lastly, the groups did differ in FSIQ (Table 1) but the patterns of brain activity linked to this variable could not explain the differences seen in reward/motivation nor the behavioral inhibition systems because FSIQ was used as a separate regressor in the second level analyses (supplemental materials).

4.1. Reward Sensitivity in Youth at Risk for SA

Hypo-activity of the striatum and other regions within the motivational-reward system has been hypothesized to represent a constitutional predisposition for later SA. In addition, adolescents with ADHD exhibit lower striatal activation than control subjects during reward cue/outcome trials (Scheres et al., 2007), which suggests that striatal hypoactivity in childhood may be accounted for by the presence of ADHD. Therefore the differences in

brain motivational-reward system response between the two groups may be explained by i) hypoactivity in the brain reward circuitry in the LR subjects linked to ADHD, and ii) hyperactivation of these same brain regions in the HR relative to the LR subjects, which may be linked to the presence of parental history of SA. One study that examined adolescents without SA, with and without alcoholic parents (Bjork et al., 2008) found no differences in brain reward activation between these groups; however, as shown here, they also demonstrated reward-related activation in OFC and insula. It is, therefore, possible that the influence of parental history of addiction on the brain sensitivity to reward may be different in childhood than adolescence. Alternatively, the study by Bjork et al. (2008) focused on the effects of family history of alcoholism in youths with no psychiatric conditions, as illustrated by compatible CBCL scores in the two groups. This suggests that in this sample the adolescents with parental alcoholism may have been resilient to the development of drug related disorders and in that respect no much different than the controls. In our study we examined the contribution of parental SA in children who were all diagnosed with ADHD and had elevated scores on ADHD symptom severity and CBCL aggression scales. Therefore, the reported differences in our sample are attributable to the effects of familial SA in the context of already developed childhood psychopathology.

4.2. Behavioral Inhibition in Youth at Risk for SA

Numerous reports have linked activity in the ACC and dorso-medial prefrontal cortex to the ability to inhibit behavioral impulses and to monitor behavioral errors (Modirrousta and Fellows, 2008). It has also been suggested that functional interactions between dorso-medial prefrontal and motor cortices may produce a top-down control signal that inhibits inappropriate responding (Nandakumar and Laubach, 2006). Conversely, abnormal ACC activation is conceptualized as underlying the deficits in behavioral self-control and response monitoring observed in ADHD; accordingly, altered ACC activation is one of the most consistently replicated finding in ADHD research (Bush et al., 2005). Further, deficient behavioral self-control, a prominent characteristic of addiction related problems, may also facilitate the transition from childhood ADHD to adolescent SA (Ivanov et al., 2008). As all subjects in this study shared a common clinical risk factor of childhood ADHD, the observed between – group differences during the congruent/incongruent targets of the ACR task could be attributed to the risk status of the subjects. Therefore, we suggest that parental SA may further compromise the functions of the behavioral inhibition system and that HR status in this sample will be associated with greater deficits in conflict/response monitoring as evident by lower activation in ACC and dorso-medial prefrontal cortex. Such biological correlates may set the stage for increased risk for SA- a hypothesis supported by reports suggesting that deficits in behavioral control are associated with elevated risk for the development of substance abuse related problems in humans (Kirisci et al., 2005).

4.3. Motivation and Behavioral Inhibition Networks in Drug Naïve Youth at High and Low Risk for SA – Is There a Dissociation of Function?

The observed activation differences in the caudate nucleus, OFC and insula between the HR and LR groups in relation to reward incentives are consistent with findings of preexisting abnormalities in the fronto-striatal motivational circuit in children of alcoholics (Heitzeg et al., 2010). These findings may reflect heightened sensitivity in brain regions involved in reward seeking, reward reinforcement and reward related learning in HR individuals. If true, the presence of constitutional high sensitivity to reward-related stimuli may be linked to a propensity to seek, identify and direct behavior towards potentially rewarding stimuli, which may include the use of drugs of abuse. Such a behavioral propensity may be less pronounced in individuals who are more efficient in suppressing and modulating behavioral impulses (as was the case in the LR group). This notion is further supported by our behavioral results, showing that LR subjects significantly decreased their RT following negative outcomes.

Conversely, individuals with deficits in their ability to modulate behaviors may be more likely to perseverate in seeking reward, following initial drug exposure and, therefore, to further develop impulsive behaviors consistent with drug abuse. The observation that HR subjects decreased their RT following negative outcomes to a lesser degree and tended to respond significantly faster than the LR group further supports the above hypotheses. These results are consistent with the notion that increased sensitivity to expectations for reward may overpower the brain control circuits (Volkow et al., 2010). Our study provides preliminary evidence that a possible disassociation between the responsiveness of the motivational-reward (higher in HR vs. LR subjects) and the behavioral inhibition system (lower in HR vs. LR subjects) may be a constitutional abnormality linked to parental SA. Therefore, vulnerability for later addiction in children who have parents with SA may be associated with a functional mismatch between an overactive motivational-reward network and a deficient inhibitory control system.

4.4. Limitations

This study examined a relatively small sample of drug naive ADHD youth with and without parental history of SA and therefore we consider the reported results preliminary. Having said this, the significant results we obtained (with small groups) suggest that the effect sizes are very large, however, they should be replicated in future studies. One methodological limitation is that we used a narrative interview to assess parental SA instead of any kind of validated or commonly-used instrument. Further, the current structure of the ACR task does not include a condition for "surprising reward following a non-reward cue," and therefore the data presented here do not constitute a fully factorial design. We hope to include this additional task component in future studies. The lack of a typically-developing control group represents a challenge for interpreting the study results, since it is not possible to know whether the directions of the observed differences in activation are either "low" or "high" when compared to children without risk for SA.

4.5. Conclusions

This study examined fMRI activation of the motivational-reward and inhibitory control systems in drug-naïve youth who may be at risk for later SA. The results suggest heightened activation in brain regions of the motivational-reward system and possibly deficiency in activation of the inhibitory control system in children with ADHD and parental history of SA when compared to children with ADHD alone. We posit that a possible functional mismatch between these two systems may present one biological underpinning of SA risk, which is conferred by a parental history of addiction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

Achenbach, T. Manual for the Child Behavior Checklist/4–18 and 1991 profile. University of Vermont, Department of Psychiatry; Burlington: 1991.

Anderson MC, Ochsner KN, Kuhl B, Cooper J, Robertson E, Gabrieli SW, Glover GH, Gabrieli JD. Neural systems underlying the suppression of unwanted memories. Science. 2004; 303(5655):232–5. [PubMed: 14716015]

Andrews MM, Meda SA, Thomas AD, Potenza MN, Krystal JH, Worhunsky P, Stevens MC, O'Malley S, Book GA, Reynolds B, Pearlson GD. Individuals family history positive for alcoholism show functional magnetic resonance imaging differences in reward sensitivity that are related to impulsivity factors. Biological Psychiatry. 2011; 69(7):675–83. [PubMed: 21126735]

Barkley R, Fischer M, Smallish L, Fletcher K. Does the treatment of attention deficit/hyperactivity disorder with stimulants contribute to drug use/abuse? A 13-year prospective study. Pediatrics. 2003; 111(1):97–109. [PubMed: 12509561]

Beauregard M, Levesque J, Bourgouin P. Neural correlates of conscious self-regulation of emotion. Journal of Neuroscience. 2001; 21(18):RC165. [PubMed: 11549754]

Bjork JM, Chen G, Smith AR, Hommer DW. Incentive-elicited mesolimbic activation and externalizing symptomatology in adolescents. Journal of Child Psychology and Psychiatry. 2010; 51(7):827–37. [PubMed: 20025620]

Bjork JM, Knutson BD, Hommer W. Incentive-elicited striatal activation in adolescent children of alcoholics. Addiction. 2008; 103(8):1308–19. [PubMed: 18851716]

Blasi G, Goldberg TE, Weickert T, Das S, Kohn P, Zoltick B, Bertolino A, Callicott JH, Weinberger DR, Mattay VS. Brain regions underlying response inhibition and interference monitoring and suppression. European Journal of Neuroscience. 2006; 23(6):1658–64. [PubMed: 16553630]

Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, Lubar JO, Chen TJ, Comings DE. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. Journal of Psychoactive Drugs. 2000; 32(Suppl):i–iv. 1–112.

Blum K, Liu Y, Shriner R, Gold MS. Reward circuitry dopaminergic activation regulates food and drug craving behavior. Current Pharmaceutical Design. 2011; 17(12):1158–67. [PubMed: 21492092]

Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH. Dopaminergic network differences in human impulsivity. Science. 2010; 30;329(5991):532.

Bush G. Attention-deficit/hyperactivity disorder and attention networks. Neuropsychopharmacology. 2010; 35(1):278–300. [PubMed: 19759528]

Bush G, Valera EM, Seidman LJ. Functional neuroimaging of attention-deficit/hyperactivitydisorder: a review and suggested future directions. Biological Psychiatry. 2005; 57(11):1273–84. [PubMed: 15949999]

Chang L, Alicata D, Ernst T, Volkow N. Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. Addiction. 2007; 102(Suppl1):16–32. [PubMed: 17493050]

Chevrier AD, Noseworthy MD, Schachar R. Dissociation of response inhibition and performance monitoring in the stop signal task using event-related fMRI. Human Brain Mapping. 2007; 28(12):1347–58. [PubMed: 17274022]

Chilcoat H, Breslau N. Pathways from ADHD to early drug use. Journal of the American Academy of Child and Adolescent Psychiatry. 1999; 38(11):1347–1354. [PubMed: 10560220]

Goodman A. Neurobiology of addiction: an integrative review. Biochemical Pharmacology. 2008; 75(1):266–322. [PubMed: 17764663]

Conners, K. Conners' Rating Scales-Revised Technical Manual. North Tonawanda, New York: Multi Health Systems; 2000.

Cumming P, Caprioli D, Dalley JW. What have positron emission tomography and 'Zippy' told us about the neuropharmacology of drug addiction? British Journal of Pharmacology. 2010; 163(8):1586–604. [PubMed: 20846139]

Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The Roles of Dopamine and Noradrenaline in the Pathophysiology and Treatment of Attention-Deficit/Hyperactivity Disorder. Biological Psychiatry. 2011; 15;69(12):145–57.

Fan J, Posner M. Human attentional networks. Psychiatrische Praxis Suppl. 2006; 2:S210–4.

Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. Event-related fMRI: characterizing differential responses. Neuroimage. 1998; 7(1):30–40. [PubMed: 9500830]

Garavan H, Ross TJ, Stein EA. Right hemispheric dominance of inhibitory control: an eventrelated functional MRI study. Proceedings of the National Academy of Science. 1999; 96(14):8301–6.

Goodman A. Neurobiology of addiction: an integrative review. Biochemical Pharmacology. 2008; 75(1):266–322. [PubMed: 17764663]

Heitzeg M, Nigg JW, Yau WY, Zucker RA, Zubieta JK. Striatal dysfunction marks preexisting risk and medial prefrontal dysfunction is related to problem drinking in children of alcoholics. Biological Psychiatry. 2010; 1;68(3):287–95.

Hommer DW, Bjork JM, Gilman JM. Imaging brain response to reward in addicitive disorders. Annals of the New York Academy of Science. 2011; 1216:50–61.

Ivanov, I.; Clerkin, S.; Schulz, K.; Fan, J.; Halperin, JM.; Newcorn, JH. Dopamine effects on ventral striatal and orbitofrontal activation during a reward – Conflict Task in Adult Volunteers. Poster session at the annual meeting of the College on the Problems of Drug Dependence; 2007.

Ivanov I, Schulz K, London E, Newcorn J. Inhibitory Control Deficits in Childhood and Risk for Substance Use Disorders. The American Journal of Drug and Alcohol Abuse. 2008; 34(3):239–58. [PubMed: 18428067]

Johnstone T, Ores-Walsh KS, Greischar LL, Alexander AL, Fox AS, Davidson RJ, Oakes TR. Motion correction and the use of motion covariates in multiple-subject fMRI Analysis. Hum Brain Mapping. 2006; 27(10):779–88.

Johnson JL, Leff M. Children of substance abusers: overview of research findings. Pediatrics. 1999; 103(5 Pt 2):1085–99. [PubMed: 10224196]

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry. 1997; 36(7):980–8. [PubMed: 9204677]

Kendler K, Prescott C, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Archives of General Psychiatry. 2003; 60(9):929–37. [PubMed: 12963675]

Kirisci L, Vanyukov M, Tarter R. Detection of youth at high risk for substance use disorders: longitudinal study. Psychology of Addictive Behaviors. 2005; 19(3):243–52. [PubMed: 16187802]

Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35(1):217–38. [PubMed: 19710631]

Levesque J, Eugene F, Joanette Y, Paquette V, Mensour B, Beaudoin G, Leroux JM, Bourgouin P, Beauregard M. Neural circuitry underlying voluntary suppression of sadness. Biological Psychiatry. 2003; 53(6):502–10. [PubMed: 12644355]

Lee B, London ED, Poldrack RA, Farahi J, Nacca A, Monterosso J, Mumford J, Bokarius AV, Dahlbom M, Mukherjee MJ, Bilder RM, Brody AL, Mandelkern MA. Striatal dopamine D2/D3 receptor availability is reduced in methamphetamine dependence and linked to impulsivity. Journal of Neuroscience. 2009; 29(47):14734–740. [PubMed: 19940168]

Lerner A, Bagic A, Hanakawa T, Boudreau EA, Pagan F, Mari Z, Bara-Jimenez W, Aksu M, Sato S, Murphy DL, Hallett M. Involvement of insula and cingulate cortices in control and suppression of natural urges. Cerebral Cortex. 2009; 19(1):218–23. [PubMed: 18469316]

Li CS, Huang C, Constable RT, Sinha R. Imaging response inhibition in a stop-signal task:neural correlates independent of signal monitoring and post-response processing. Journal of Neuroscience. 2006; 26(1):186–92. [PubMed: 16399686]

Liddle PF, Kiehl KA, Smith AM. Event-related fMRI study of response inhibition. Human Brain Mapping. 2001; 12(2):100–9. [PubMed: 11169874]

Mannuzza S, Klein RG, Truong NL, Moulton JL 3rd, Roizen ER, Howell KH, Castellanos FX. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. American Journal of Psychiatry. 2008; 165(5):604–9. [PubMed: 18381904]

Marmorstein N, Iacono W, McGue M. Alcohol and illicit drug dependence among parents:associations with offspring externalizing disorders. Psychological Medicine. 2009; 39(1):149–55. [PubMed: 18410699]

Modirrousta M, Fellows L. Dorsal medial prefrontal cortex plays a necessary role in rapid error prediction in humans. The Journal of Neuroscience. 2008; 28(51):14000–14005. [PubMed: 19091989]

Nandakumar NS, Laubach M. Top-down control of motor cortex ensembles by dorsomedial prefrontal cortex. Neuron. 2006; 52(5):921–931. [PubMed: 17145511]

Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: a functional magnetic resonance imaging study. Biological Psychiatry. 2005; 57(3):210–9. [PubMed: 15691521]

Rubia K, Smith AB, Brammer MJ, Taylor E. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. Neuroimage. 2003; 20(1):351–8. [PubMed: 14527595]

Ryan JJ, Carruthers CA, Miller LJ, Souheaver GT, Gontkovsky ST, Zehr MD. Exploratory factor analysis of the Wechsler Abbreviated Scale of Intelligence (WASI) in adult standardization and clinical samples. Applied Neuropsychology. 2003; 10(4):252–256. [PubMed: 14690807]

Scheres A, Milham MP, Knutson B, Castellanos FX. Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. Biological Psychiatry. 2007; 61(5): 720–24. [PubMed: 16950228]

Slutske WS, Heath AC, Dinwiddie SH, Madden PA, Bucholz KK, Dunne MP, Statham DJ, Martin NG. Common genetic risk factors for conduct disorder and alcohol dependence. Journal of Abnormal Psychology. 1998; 107(3):363–74. [PubMed: 9715572]

Stark R, Bauer E, Merz CJ, Zimmermann M, Reuter M, Plichta MM, Kirsch P, Lesch KP, Fallgatter AJ, Vaitl D, Herrmann MJ. ADHD related behaviors are associated with brain activation in the reward system. Neuropsychologia. 2011; 49(3):426–34. [PubMed: 21163276]

Ströhle A, Stoy M, Wrase J, Schwarzer S, Schlagenhauf F, Huss M, Hein J, Nedderhut A, Neumann B, Gregor A, Juckel G, Knutson B, Lehmkuhl U, Bauer M, Heinz A. Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. Neuroimage. 2008; 39(3): 966–72. [PubMed: 17996464]

Stoy M, Schlagenhauf F, Schlochtermeier L, Wrase J, Knutson B, Lehmkuhl U, Huss M, Heinz A, Ströhle A. Reward processing in male adults with childhood ADHD-a comparison between drug-naïve and methylphenidate-treated subjects. Psychopharmacology (Berl). 2011; 215(3):467–81. [PubMed: 21298512]

Volkow ND, Wang GJ, Fowler JS, Tomasi JS, Telang F, Baler R. Addiction: decreasedreward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. Bioessays. 2010; 32(9):748–55. [PubMed: 20730946]

Volkow ND, Wang GJ, Newcorn JH, Kollins SH, Wigal TL, Telang F, Fowler Js, Goldstein RZ, Klein N, Logan J, Wong C, Swanson JM. Motivation deficit in ADHD isassociated with dysfunction of the dopamine reward pathway. Molecular Psychiatry. 2010

Walsh BJ, Buonocore MH, Carter CS, Mangun GR. Integrating conflict detection and attentional control mechanisms. Journal of Cognitive Neuroscience. 2010; 23(9):2211–21. [PubMed: 21126158]

Wrase J, Schlagenhauf F, Kienast T, Wustenberg T, Bermpohi F, Kahnt T, Beck A, Strohle A, Juckel G, Knutson B, Neinz A. Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. Neuroimage. 2007; 35(2):787–94. [PubMed: 17291784]

Wyland CL, Kelley WM, Macrae CN, Gordon HL, Heatherton TF. Neural correlates of thought suppression. Neuropsychologia. 2003; 41(14):1863–7. [PubMed: 14572519]

Young SE, Stallings MC, Corley RP, Krauter KS, Hewitt JK. Genetic and environmental influences on behavioral disinhibition. American Journal of Medical Genetics. 2000; 96(5):684–95. [PubMed: 11054778]
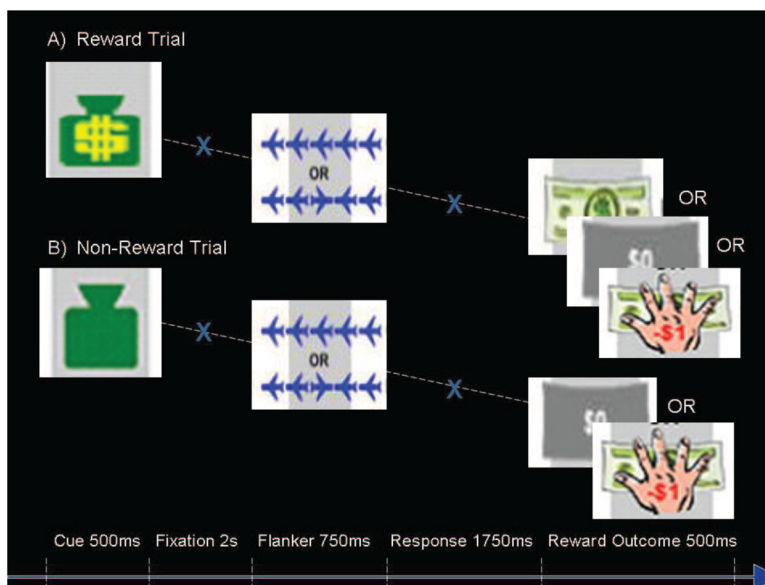
Figure 1. The Anticipation, Conflict, Reward (ACR) Task
Presented is the temporal relationship between the cue, flanker and outcome components of the ACR task. There is equal number of reward (n=64) and non-reward cues (n=64) as well as congruent (n=64) and incongruent (n=64) flankers that are randomly presented during the 4 sessions of the task. The outcome is performance-dependent: subjects must respond as quickly as possible by pushing a button (left or right) that corresponds to the direction of the central airplane. If the response is correct there is 50% chance of reward in the amount of $1; slow and/or incorrect responses result in $1 loss.
A) Reward trial starts with a presentation of a Reward Cue followed by a Flanker and Reward Outcome that could be a $1 win OR $0 no-win OR -$1 loss;
B) Non-Reward trial starts with a presentation of a Non-Reward Cue followed by a Flanker and Reward Outcome that could be a $0 no-win OR -$1 loss;
The time duration of the components of the ACR task is presented at the bottom of the figure.
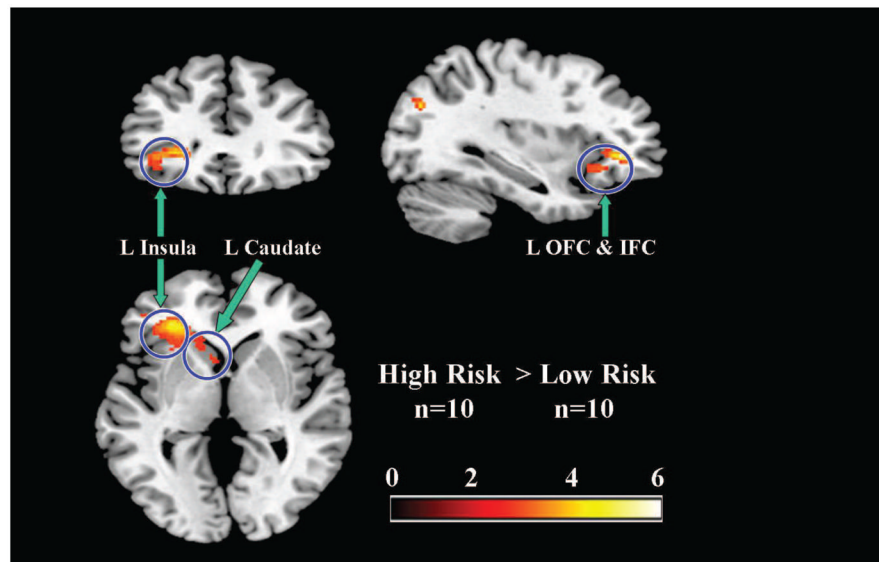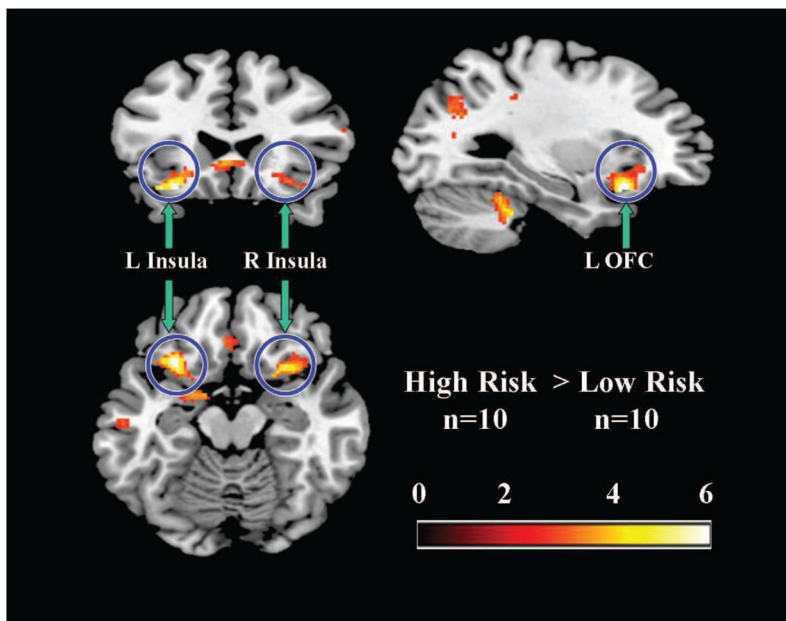
Figure 2. Activation during Anticipation (Reward Cue – Non-Reward Cue)
Presented in sagittal, coronal, and axial views are blood oxygenation level-dependent (BOLD) signal differences between the groups. BOLD signal in the left caudate, insula, orbito-frontal (OFC) and inferior frontal (IFC) cortices was higher in the high-risk than in the low-risk group. The figures were thresholded at $p < .01$ (one-tailed); the color bar indicates values of T.
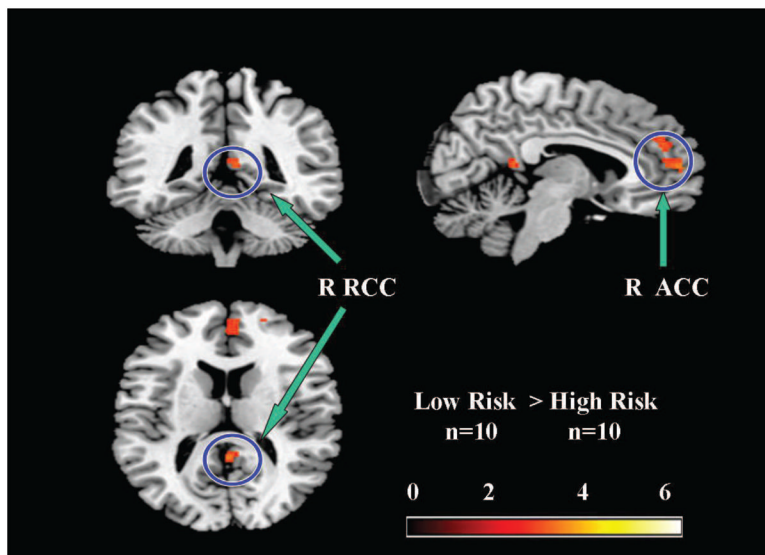
Figure 3. Activation during Conflict (Incongruent – Congruent Flanker)
Presented in sagittal, coronal, and axial views are blood oxygenation level-dependent
(BOLD) signal differences between the groups. BOLD signal in the right anterior cingulated
cortex (ACC) and retrosplenial cingulate cortex (RCC) was higher in the low- risk than in
the high-risk group. The figures were thresholded at $p < .01$ (one-tailed); the color bar
indicates values of T.

Figure 4. Activation during Reward (Expected Reward – Expected Non-Reward)
Presented in sagittal, coronal, and axial views are blood oxygenation level-dependent
(BOLD) signal differences between the groups. BOLD signal in the bilateral insula and the
left orbitofrontal cortex (OFC) was higher in the high risk than the low risk group. The
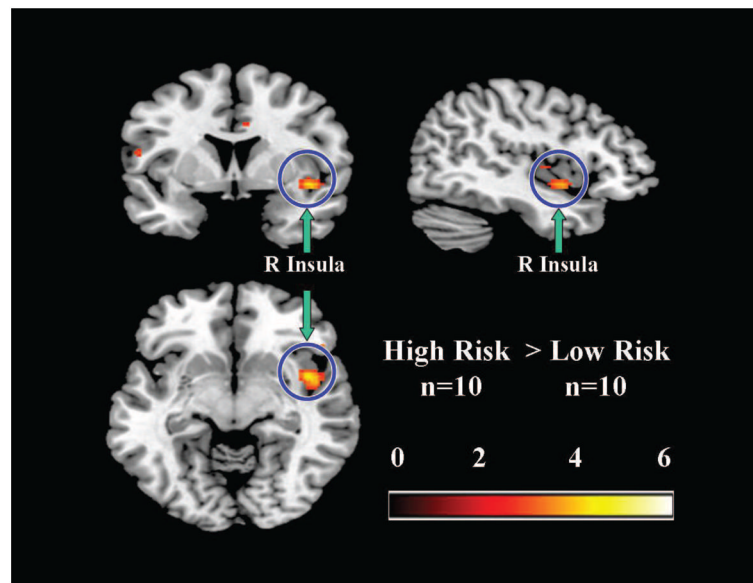figures were thresholded at $p < .01$ (one-tailed); the color bar indicates values of T.

Figure 5. Activation during Punishment (Punishment – Expected Non-Reward)
Presented in sagittal, coronal, and axial views are blood oxygenation level-dependent
(BOLD) signal differences between the groups. BOLD signal in the right insula cortex was
higher in the high risk (HR) vs. low risk (LR) group. The figures were thresholded at $p < .01$
(one-tailed); the color bar indicates values of T.

Table 1

Demographic and Psychometric Characteristics of the Sample

	Low Risk (n=10)	High Risk (n=10)	p-values
Age	10.75±1.5	10.33+1.4	0.58
FSIQ	101.81±13	89.62±11.1	0.04*
ADHDRS	37.60±10.2	38.01±10.3	0.93
CBCL Aggression	63.63±7.26	61.14±8.65	0.56
Gender (boys/girls)	9/1	9/1	0.93

Table 2

Behavioral Performance on the ACR Task for the Two Groups

Behavioral variables	Low Risk (n=10)	High Risk (n=10)	p values
Reaction Time Non-Reward X Congruent	542±55ms	517±73ms	0.41
Reaction Time Non-Reward X Incongruent	569±99ms	545±97ms	0.58
Reaction Time Reward X Congruent	528±64ms	493±55ms	0.20
Reaction Time Reward X Incongruent	573±116ms	554±46ms	0.64
Accuracy Non-Reward X Congruent	87±15%	87±13%	0.96
Accuracy Non-Reward X Incongruent	68±26%	63±25%	0.69
Accuracy Reward X Congruent	87±13%	88±13%	0.97
Accuracy Reward X Incongruent	67±26%	66±27%	0.92

Table 3

Brain Regions Activated during Anticipation, Reward and Punishment Components of the ACR Task:

Region	Side	Talairach coordinates			T-values	No. of voxels
Anticipation HR>LR						
Inferior frontal gyrus[1]	Left	−32	42	−4	6.07	368
Anterior insular cortex[2]	Left	−32	22	10	3.39	368
Reward HR>LR						
Orbito-frontal cortex	Left	−28	26	−8	4.31	348
Anterior insula cortex	Left	−28	20	−18	6.07	368
Punishment HR>LR						
Anterior insula cortex	Right	42	4	−8	4.53	88

[1] blood oxygenation level-dependent signal activation extended from the left inferior frontal gyrus to the left OFC;

[2] blood oxygenation level-dependent signal activation extended from the left insula cortex to the head of the left caudate;

Table 4

Brain Regions Activated during Flanker Components of the ACR Task:

Region	Side	Talairach coordinates			T- values	No. of voxels
Flanker (HR+LR)						
Superior Occipital cortex	Right	24	−60	40	6.83	989
Precuneus	Right	16	−66	48	6.83	989
Middle Occipital cortex	Right	30	−66	30	4.03	989
Fusiform gyrus	Right	46	−64	−16	5.94	358
Inferior Temporal cortex	Right	50	−56	−14	5.81	358
Inferior Occipital cortex	Right	36	−78	0	3.25	358
Thalamus	Right	12	−10	14	5.31	212
Thalamus	Left	−2	−14	18	3.53	212
Caudate	Right	14	−2	16	2.95	212
Supplemental motor area	Right	6	20	46	3.56	207
Supplemental motor area	Left	0	10	50	2.76	207
Dorso-medial prefrontal cortex	Left	0	24	40	4.84	207
Flanker LR>HR						
Anterior cingulate cortex	Right	6	54	10	3.40	334
Dorso-medial prefrontal cortex [1]	Left	−2	48	22	3.39	334

[1] blood oxygenation level-dependent signal activation extended from the left dorsomedial prefrontal cortex to the left ACC;