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

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ABSTRACT

It is hypothesized that the development of substance abuse (SA) may be due to imbalance in functions of the motivation-reward and behavioral inhibition systems in the brain. This speaks to the search for biological risk factors for SA in drug-naïve children who also exhibit motivational and inhibitory control deficits; however, this type of research is currently lacking. The objective of this study was to establish a neurobiological basis for addiction vulnerability using functional magnetic resonance imaging (fMRI) in drug-naïve youth with attention deficit/hyperactivity disorder (ADHD). We hypothesized that children with ADHD alone would show higher activity in regions of the motivation-reward and behavioral inhibition systems than children with ADHD and a parental history of SA. Toward this goal we scanned 20 drug-naïve children with ADHD ages 8–13 while performing an event-related reward task. High ($N=10$) and low ($N=10$) risk subjects were identified, based on parental history of SA. The effects of anticipation, conflict, and reward were assessed with appropriate linear contrasts, and between-group differences were assessed using statistical parametric mapping. The two groups did not differ on behavioral measures of the task. The fMRI results show heightened activation in the brain motivational-reward system and reduced activation of the inhibitory control system in high-risk compared to low-risk children. These results suggest that a functional mismatch between these two systems may represent one possible biological underpinning of SA risk, which is conferred by a parental history of addiction.

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 lifetime 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 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

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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 with control subjects who lack such a 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 functional magnetic resonance imaging (fMRI) studies, both in individuals with (Scheres et al., 2007; Ströhle 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); to 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, 2006), 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, 2011). 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., 2011), 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. Toward this purpose, we designed a task that includes both reward and executive control components. This task was used in conjunction with 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 SA 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, S.D. = ± 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 Lifetime 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 determiner i) whether 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