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Reward circuit connectivity relates to delay discounting in children with attention-deficit/hyperactivity disorder

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Abstract
Attention-deficit/hyperactivity disorder (ADHD) is a prevalent psychiatric disorder that has poor long-term outcomes and remains a major public health concern. Recent theories have proposed that ADHD arises from alterations in multiple neural pathways. Alterations in reward circuits are hypothesized as one core dysfunction, leading to altered processing of anticipated rewards. The nucleus accumbens (NAcc) is particularly important for reward processes; task-based fMRI studies have found atypical activation of this region while the participants performed a reward task. Understanding how reward circuits are involved with ADHD may be further enhanced by considering how the NAcc interacts with other brain regions. Here we used the technique of resting-state functional connectivity MRI (rs-fcMRI) to examine the alterations in the NAcc interactions and how they relate to impulsive decision making in ADHD. Using rs-fcMRI, this study: examined differences in functional connectivity of the NAcc between children with ADHD and control children; correlated the functional connectivity of NAcc with impulsivity, as measured by a delay discounting task; and combined these two initial segments to identify the atypical NAcc connections that were associated with impulsive decision making in ADHD. We found that functional connectivity of NAcc was atypical in children with ADHD and the

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ADHD-related increased connectivity between NAcc and the prefrontal cortex was associated with greater impulsivity (steeper delayed-reward discounting). These findings are consistent with the hypothesis that atypical signaling of the NAcc to the prefrontal cortex in ADHD may lead to excessive approach and failure in estimating future consequences; thus, leading to impulsive behavior.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent and persistent psychiatric disorder, which emerges early in childhood (American Psychiatric Association, 2000). The disorder is estimated to affect about 5% of the population world-wide (Polanczyk et al., 2007), is associated with several comorbid disorders, has poor long-term outcomes, and remains a major public health concern (Rommelse et al., 2009). A primary concern is to better characterize neural mechanisms related to ADHD so as to guide our understanding of pathophysiology.

1.1. ADHD heterogeneity

Until recently, causal and mechanistic models of ADHD have centered on identifying a single core dysfunction; in other words, many studies are designed with the premise of the existence of an individual major dysfunction. Thus, investigators typically compare a group of children with ADHD defined by core symptoms (e.g. via DSM criteria) to a group of control children without the disorder. Statistical group differences based on psychometrics, functional brain imaging, or genetics are then used to inform causal models of ADHD.

One necessary assumption of this approach is that ADHD (or even its clinical subtypes) represents a homogenous patient population. However, there is now considerable justification suggesting that multiple developmental and pathophysiological pathways inform ADHD symptomatology (Fair et al., 2012; Nigg et al., 2004; Sonuga-Barke et al., 2003). The implications of this premise are considerable. Including multiple etiologically distinct subgroups as a unitary sample in any study is likely to produce muted effects and could be why only modest effect sizes are often seen for large genetic and behavioral studies, and why neuroimaging studies yield difficult to replicate effects (Hyman, 2007). Of course, overcoming the limitations of conventional research in mental disorders is not straightforward and may require new approaches to understanding complex disease (Hyman, 2007). Nevertheless, understanding the neurobiology underlying the disease phenotypes is essential for improving treatment and consequently for the wellbeing of individuals with ADHD.

A two-step approach could be considered, that might include, first, a traditional group comparison of a group of children with ADHD to a group of control children to find brain connections that are atypical in the disorder. This approach may identify connections that are on average atypical in ADHD, even if the effects are not detectible or expected in all ADHD subjects (Nigg et al., 2005; Sonuga-Barke et al., 2003). However, this approach would not clarify to what component of the disorder an atypical connection is related. Therefore, this conventional approach could then be followed, as a second step, by a dimensional method that would identify how those brain connections relate to specific endophenotypes even if they are not atypical in all subjects with the disease. In this sense, one might be able to identify neural circuits related to the etiology of relatively homogeneous *component behaviors*. In this report we apply this multi-level approach to elucidate the mechanisms of atypical reward processing in ADHD. The described approach does not rely on DSM-IV defined subgroups; instead, it focuses on a narrower behavioral domain central to ADHD—reward valuation (Sagvolden et al., 2005).

1.2. The role of impaired reward processing

Recent theories have proposed that ADHD arises from alterations in multiple neural pathways (Nigg and Casey, 2005; Sonuga-Barke, 2005). Nigg and Casey (2005) theorized that impairment in cognitive control circuits would contribute to executive dysfunctions, while impairment in affective and reward systems would lead to altered signaling of rewards and consequently to atypical approach and avoidance behaviors. They hypothesized that individuals with ADHD fail to estimate future consequences (future reward or non-reward), and thus exhibit behavior characterized by excessive approach (Nigg and Casey, 2005). Their idea is broadly similar to that of Sonuga-Barke (2005), who hypothesized that two pathways are involved in ADHD: (1) changes within the executive circuit, resulting in executive/inhibitory deficits, and (2) alterations in the reward circuit, resulting in delay aversion (Sonuga-Barke, 2005).

One region that seems to be particularly important for motivational/reward processes is the nucleus accumbens (NAcc), which has been relatively under-researched in ADHD, despite strong theoretical interest in the involvement of motivational/reward processes in the disorder. Functional MRI studies have concluded that the main brain regions recruited while subjects experienced appropriate rewarding stimuli (e.g., money or positive feedback) include the ventral striatum—or NAcc (McClure et al., 2004b). In addition, functional MRI studies in ADHD have found decreased NAcc activation during reward anticipation (Plichta et al., 2009; Scheres et al., 2007).

To examine the interactions between NAcc and other regions of the brain and how these interactions relate to reward processing, we used resting-state functional connectivity MRI (rs-fcMRI). Rs-fcMRI assesses spontaneous intrinsic correlated blood oxygen level dependent (BOLD) activity while subjects are not performing a specific task