Increased Neural Responses to Reward in Adolescents and Young Adults With Attention-Deficit/Hyperactivity Disorder and Their Unaffected Siblings

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Objective: Attention-deficit/hyperactivity disorder (ADHD) is a heritable neuropsychiatric disorder associated with abnormal reward processing. Limited and inconsistent data exist about the neural mechanisms underlying this abnormality. Furthermore, it is not known whether reward processing is abnormal in unaffected siblings of participants with ADHD.

Method: We used event-related functional magnetic resonance imaging (fMRI) to investigate brain responses during reward anticipation and receipt with an adapted monetary incentive delay task in a large sample of adolescents and young adults with ADHD (n = 150), their unaffected siblings (n = 92), and control participants (n = 108), all of the same age.

Results: Participants with ADHD showed, relative to control participants, increased responses in the anterior cingulate, anterior frontal cortex, and cerebellum during reward anticipation, and in the orbitofrontal, occipital cortex and ventral striatum. Responses of unaffected siblings were increased in these regions as well, except for the cerebellum during anticipation and ventral striatum during receipt.

Conclusion: ADHD in adolescents and young adults is associated with enhanced neural responses in frontostriatal circuitry to anticipation and receipt of reward. The findings support models emphasizing aberrant reward processing in ADHD, and suggest that processing of reward is subject to familial influences. Future studies using standard monetary incentive delay task parameters are needed to replicate our findings.

Key Words: ADHD, reward processing, cognitive control, familiality, nucleus accumbens

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Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder affecting about 5% of children worldwide,[1] and is characterized by a pattern of impairing and persistent inattention and/or hyperactivity and impulsivity.[2] Research on cognitive aspects of ADHD has long focused on executive functions, such as working memory and response inhibition.[3] However, more recent cognitive models of ADHD have indicated deficits in reward processing.[4] Children with ADHD appear to be more sensitive to the positive effects of rewards on performance,[5,6] make more risky decisions to obtain rewards,[7] have stronger preference for immediate compared to delayed rewards,[8,9] and show steeper temporal discounting compared to control participants.[10,11] However, reports on behavioral measures of reward processing are inconsistent, and findings often remain unreplicated (see, for example[7,12,13]). Little is known about the neural underpinnings of reward processing in particular in adolescents with ADHD. Our study aimed to investigate the neural mechanisms underlying reward processing in adolescents and young adults with ADHD, their unaffected siblings, and control participants.

Frontostriatal brain networks, including the orbitofrontal cortex, medial prefrontal cortex, and the ventral striatum (VS), play a crucial role in reward processing (reviewed by Haber and Knutson[14]). Accordingly, studies investigating reward processing using a monetary incentive delay (MID) task have found alterations in VS signaling in both healthy populations and participants with ADHD (reviewed by Plichta and Scheres[15]).

However, the manner in which VS signaling is altered is dependent on the studied population. Control participants with impulsive traits showed an increase of the striatal response to reward, whereas participants with ADHD mostly had decreased striatal responses to reward. VS responses during reward anticipation for adolescents with ADHD were observed to be lower than for control participants, but no differences were observed during reward receipt.[16] However, an increased response in the same VS area during reward receipt but not during reward anticipation has been reported as well.[17] This inconsistency may be related to the small-to-moderate sample sizes and

Supplemental material cited in this article is available online.

differences in task and study design. We aimed to resolve this discrepancy by assessing reward anticipation and reward receipt using an adaptation of the MID task in a large population of adolescents and young adults with ADHD and control participants. The MID task has been repeatedly shown to elicit a neural response in the VS to both reward anticipation and receipt (reviewed elsewhere[15,18]).

ADHD has a strong genetic loading, with an estimated heritability of about 80%.[19] Siblings of participants with ADHD, who share on average 50% of their genetic information, have a 2- to 8-fold elevated risk of ADHD relative to control participants.[20] Despite the high heritability of ADHD, identification of genes that contribute to the etiology of the clinical phenotype has proven to be challenging. The identification of endophenotypes may be helpful in unraveling the genetic component of ADHD. Endophenotypes are objective measures that represent heritable vulnerability traits associated with the disorder in the population and are thought to be intermediates on the pathway from genotype to phenotype.[21] Importantly, because of their assumed heritability, it has been proposed that valid endophenotypes can be found at a higher rate in unaffected family members than in the general population.[21,22] So far, 2 studies have investigated the familiality of behavioral measures of reward processing in the context of ADHD. These studies have reported oversensitivity to reward and abnormal preference for immediate reward in unaffected siblings.[6,9] Moreover, genetic effects on reward processing in control participants have been described.[23] Therefore, we investigated whether neural measures of reward processing in unaffected siblings are intermediate between those of participants with ADHD and control participants, thus supporting their role as an endophenotype of ADHD.

METHOD

Study Participants

This study was approved by the local ethics committee of participating centers. Written informed consent was obtained from all participants or their legal guardians (for participants <12 years of age). We considered data from 571 participants of the NeuroIMAGE cohort, a large-scale cohort of families with 1 or more children with ADHD and control families recruited for the International Multicenter ADHD Genetics (IMAGE) study.[24,25] Detailed recruitment and testing procedures for NeuroIMAGE have been described elsewhere.[26]

At the time of follow-up, clinical status was reassessed by a trained professional administering the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS)[27] to parents and children and complemented by ADHD questionnaires (Conners' Parent and Teacher Rating Scales[28,29]; detailed diagnostic procedures available in von Rhein *et al.*[26]). Diagnosis was based on *DSM-5* criteria.[2] Both unaffected siblings and control participants were free of ADHD.

The descriptive characteristics of the sample are summarized in Table 1. After applying exclusion criteria (see Supplement 1, available online), we were able to analyze 350 individuals: 150 participants with ADHD (68 predominantly inattentive, 21 predominantly hyperactive-impulsive, and 61 combined-type), 92 unaffected siblings, and 108 control participants. Age was not significantly different between groups (Table 1), whereas gender was unequally distributed, with a higher percentage of men with ADHD compared to the other groups ($\chi^2[2] = 23.3$; $p < .01$).

As expected in a clinical sample of participants with ADHD, the majority had a history of treatment with ADHD medication (n = 114 of 150). ADHD medication consisted of treatment with methylphenidate with immediate release (MPH-IR; n = 103), methylphenidate with extended release (MPH-ER; n = 84), atomoxetine (n = 14), and/or dextroamphetamine (n = 8). All participants had discontinued use of medication for 48 hours before testing.

Reward Anticipation Paradigm

We used a modified version of the MID task[30-32]; participants were asked to respond as quickly as possible to a target by pressing a button. Before this target, a cue indicated the possibility of gaining a reward after a button press within a given time window. Every trial ended with a feedback screen informing about the outcome of the current trial. Depending on the participants' performance, the response window for a correct response was adapted in the next trial, resulting in an expected hit rate of 33%. The experiment lasted 12 minutes, and a total of € 5 could be gained. At the end of the experiment, the awarded money was paid to the participant (see Supplement 1, available online, and Figure S1 for a detailed description of the task).

Compared with the original task, our version differed on 2 main aspects: hit rate (33% versus 66%) and reward magnitude (€0.20 versus $5). The rationale behind these adaptations was firstly to increase the demands of the task with stronger task engagement as a result. Secondly, our adaptations aimed at meeting the practical constraints of our study. Considering that we limited ourselves to rewarded and neutral conditions, rewarding participants according to the original task parameters would have led to disproportionate monetary rewards (approximately €80), which was a concern for us and our ethical review board.

Behavioral Measures

Behavioral outcome measures were reaction time and coefficient of variation (CV) in the rewarded and neutral conditions. Based on trials with correct responses (i.e., no premature responses [reaction time, RT <100 ms], too many [>1] or too early [i.e., before target onset] button presses or no response at all), we calculated mean reaction times. The CV was defined as the standard deviation divided by the mean. Values were log10 transformed to improve normal distribution of the data.

Image Analysis

After image acquisition, preprocessing, and initial nuisance regression (see Supplement 1, available online), statistical parametric maps were estimated for each participant with a general linear model (generalized linear model [GLM]; FSL FEAT). First-level regressors included 6 regressors of interest (onset times of rewarded and neutral cues, hits, and misses, each with a duration of 0 seconds) and 6 regressors of no interest. The latter regressors comprised the following: onsets of rewarded and neutral targets; cue, target, and outcome onsets of error events; and a motion regressor. Error events comprised events of trials with incorrect responses. The motion regressor was inserted to control for possible movement artifacts.[33] Head movements from 1 image to the next exceeding 0.5 mm in the x, y, or z direction were considered movement artifacts. Onset of this error event was set to 8 seconds before the movement, and all events within this 8-second interval were discarded. To ensure that we had a sufficient amount of events to model our regressors of interest, we included only those participants with at least 5 events per event type (see Table S1,