Supplementary Methods

Participants

Participants were recruited from the New York University Child Study Center Clinical Services. Ads were placed on the Child Study Center website and in University newsletters. Information leaflets were provided to parents of prospective participants through Child Study Center clinicians, YMCA's, local independent schools, recreation centers, summer camps and other community settings. Additionally, notices were placed on local bulletin boards.

A total of twenty-nine adolescents in the age range of 12-17 were enrolled (16 with ADHD (14 boys, 2 girls) and 13 controls (10 boys, 3 girls). Three boys with ADHD were excluded from data analyses because they took medication on the day of scanning. One boy with ADHD was excluded due to comorbid psychotic symptoms. One boy with ADHD was excluded due to excessive motion during all runs of the experiment. One boy in the control group was excluded because ADHD-related scores on the parent questionnaires were elevated, even though the diagnostic interview did not confirm a diagnosis of ADHD. One boy in the control group was excluded because of IQ below 75. Therefore, the sample that was used for statistical analyses consisted of twenty-two participants (11 with ADHD (9 boys, 2 girls) and 11 controls (8 boys, 3 girls).

Inclusion criteria and screening procedure

All subjects had to have an IQ above 75. In order to be assigned to the ADHD group, participants had to have at least one T-score above 65 on an ADHD-related scale on the Conners' Parent Rating Scale-Revised-Long version (CPRS-R-L) (Conners et al 1998a), and had to meet DSM-IV criteria for either of the three ADHD subtypes based on

the semi-structured parent interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al 1997). In order to be assigned to the normal control (NC) group, participants had to have T-scores below 65 on all ADHD-related scales of the CPRS-R-L.

For those participants who had already been evaluated by a clinician in the NYU Child Study Center and been diagnosed with ADHD, we still administered the K-SADS-PL. However, if parent rating scales had been administered by the clinician, we asked parents' permission to use the scores as obtained by the clinician.

A stepwise selection procedure was used for the ADHD as well as for the normal control group. In the first stage, parents received an informed consent form and assent form and the following questionnaires: the Child Behavior Checklist (CBCL) (Achenbach, 1991), the Teacher Report Form (TRF)[3], the CPRS-R-L, the Conners' Teacher Rating Scale-Revised-Long version (CTRS-R-L) (Conner et al 1998b),and a demographics questionnaire. Parents returned the completed questionnaires. The CPRS-R-L was used as a selection instrument in the first stage of the study. Adolescents were preliminarily assigned to the ADHD group if they had a T-score above 65 on at least one of the following CPRS-R-L scales: Inattention-Cognitive problems, Hyperactive-Impulsive, ADHD Index, DSM-IV Inattentive, DSM-IV Hyperactive, or Global Index Restless-Impulsive. Adolescents with T-scores below 65 on all the ADHD-related scales of the CPRS-R-L were included in the NC group. Because of difficulties obtaining teacher questionnaires from most participants, and the conceptual difficulty of integrating multiple teacher reports in most cases, we did not use teacher ratings as a selection

criterion or include them as a variable for analyses. In the second stage, participants and their parent(s) were invited for the first meeting.

If the participant was in the provisional ADHD group, we interviewed the parent(s) using the K-SADS-PL, and the participant was administered the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999) and the Wide Range Achievement Test (WIAT) (Wechsler 2001). The WASI consists of the Vocabulary, Block Design, Matrix Reasoning, and Similarities subtests. The WIAT consists of the Word Reading, Spelling, and Numerical Operations subtests. The WASI was used as a selection instrument, whereas the WIAT was used descriptively. Participants who did not meet DSM-IV criteria for any of the ADHD subtypes based on the interview, and/or participants with an estimated full scale IQ below 75, were excluded from the study. This occurred for two participants. If the participant met DSM-IV criteria for ADHD, (s)he was invited for the scan session. Participants who used psychostimulant drugs were asked to discontinue medication the morning prior to testing. Participants were questioned about marijuana use. One boy with ADHD, who was excluded due to medication use on the day of scanning, reported to have used marijuana on several occasions in the past. All others reported that they did not use marijuana.

Participants in the NC group completed the WASI and the WIAT during a first visit. If the participant's estimated full scale IQ was below 75, the participant was excluded from the study. This happened for one participant. If the participant's IQ was 75 or higher, (s)he was invited for the scan session.

Group Characteristics

Table 1 shows the demographic and behavioral characteristics of the groups. The ADHD group consisted of 9 boys and 2 girls, and the NC group consisted of 8 boys and 3 girls, ranging in age from 12-17. Groups did not differ in terms of age, estimated full scale IQ, or level of achievement.

Six subjects in the ADHD group met criteria for ADHD-combined type (ADHD-C), and five for ADHD-inattentive type (ADHD-I). Three of the participants with a current diagnosis of ADHD-I also demonstrated currently impairing symptoms of hyperactivity/impulsivity, but failed to meet full DSM-IV criteria for ADHD-C. Two of these participants had met criteria for ADHD-C in the past. Four participants with ADHD (two with ADHD-C and two with ADHD-I) met DSM-IV criteria for comorbid oppositional defiant disorder. One boy with ADHD-C met DSM-IV criteria for conduct disorder. As shown in Table 1, scores on all the ADHD-related scales of the parent questionnaires were statistically significantly elevated for the ADHD group compared to the NC group. Five of the participants in the ADHD group were treated with psychostimulants and discontinued medication the morning prior to scanning (allowing a washout of about 24 hours). All of these participants used Concerta® which results in negligible blood levels within less than 24 hours (Swanson et al 2003)

Task

Using the Monetary Incentive Delay Task (Knutson et al., 2001), participants were instructed to press a button as quickly as possible with their dominant index finger when the target (a white square) was presented in the centre of the screen. The target was preceded by one of 9 cues (250 ms in duration). Circle-shaped cues signaled the possibility of winning money by responding fast (during target presentation), square-

shaped cues signaled the possibility of losing money by not responding fast (after target presentation), and triangle-shaped cues instructed participants not to respond when they saw the target (rest trials). Circle- and square shaped cues had lines in them that indicated how much money was at stake: 3 lines corresponded to $5, 2 lines to $1, 1 line to $0.20, and 0 lines to $0. We use the term "gain trials" to refer to trials on which $0.20, $1, or $5 could be won, "loss avoidance trials" to refer to trials on which $0.20, $1, or $5 could be lost, and "control trials" to refer to trials that had a circle with no line as a cue ($0 could be won) or a square with no line as a cue ($0 could be lost). The delay between the cue and the target was variable (2000-2500 ms), as was the duration of the target (160-435 ms). Based on reaction times collected during 180 practice trials before scanning, target durations were set such that participants should win on ~66% of gain trials and avoid losing on ~66% of loss avoidance trials. Following the target, outcome (1650 ms in duration) informed participants whether they had won or not (gain trials), lost or not (loss avoidance trials), and the total cumulative amount at that point was presented. The outcome display was preceded by an interval. The length of this interval was variable such that the total trial duration of each trial was 6 seconds. A cross-hair was presented in the centre of the screen during the pre-target delay and during the pre-outcome delay. Participants were presented with a total of 180 trials (6 seconds in duration): 54 gain trials (18 of each incentive value), 54 loss avoidance trials (18 of each incentive value), 36 control trials, and 36 rest trials. Trials were presented in three 60-trial blocks. Trial types were equally divided across blocks, and within blocks, trials were presented in a pseudo-random order. Rest trials were designed to allow comparison of preparation for motor and non-motor responses and were not included in the contrasts performed.

Procedure

Before task practice, participants were informed that they would play a game in which they were going to win real money, but that the practice session did not involve real money. Before task practice, the experimenter read standard instructions to the participants. Participants were instructed to press the button as quickly as possible when the target appeared. They were told that responding during target presentation would lead to gain or loss avoidance, depending on the cue. Before performing the task in the scanner, participants had to be able to demonstrate understanding of the task by explaining it to the experimenter. After task completion in the scanner, participants were paid the total amount of money that they had won. Families also received $25 as a compensation for the visit.

MRI acquisition

A magnetization prepared rapid gradient echo pulse (MPRAGE) sequence was used to acquire anatomical T1-weighted images in 176 slices using a Siemens Allegra 3T head-only MRI scanner with the following parameters: repetition time (TR) = 2500 ms, echo time (TE) = 4.35 ms, matrix size = 256 x 256, field of view (FOV) = 256 mm, slice thickness = 1 mm. The duration of the anatomic scan was approximately 11 minutes. Participants were shown cartoons during the anatomic scans.

During the Monetary Incentive Delay task, echo planar imaging (EPI) blood oxygenation level dependent (BOLD) images were acquired transversally in 35 slices, with the following parameters: TR = 2000 ms, TE = 30 ms, matrix size = 64 x 64, FOV = 192 mm, slice thickness = 4 mm, 3 x 3 mm in-plane resolution. Images were acquired in 3 runs of 180 2-second volumes each (6 minutes per run). fMRI volume acquisitions

were time-locked to the offset of each cue and thus were acquired during anticipatory delay periods (see Fig. 1). Stimuli were presented on an LCD video projector (NEC, MultiSync 830+) placed at the rear of the bore with a projection screen positioned behind the participant's head. A mirror through which participants saw the projection screen was secured to the head coil (Siemens). Head motion was limited by using a vacuum pillow (Bionix, Toledo, Ohio) and foam pads. A response button box was placed in the participant's dominant hand, while a squish ball (to signal the experimenter to terminate the scan if necessary) was placed within reach of the non-dominant hand. Scanning sessions lasted less than one hour.

Behavioral Analysis

ANOVAs with valence (two levels: positive and negative) and incentive magnitude (four levels: $0, $0.2, $1, and $5) as a within-subject factor and group (two levels: ADHD and NC) as a between-subject factor were performed in order to study the effect of group, valence, and incentive magnitude on hit rates, reaction times for hits, variability in responding for hits, and proportion of premature responses. If interactions were significant, additional ANOVAs were run for gain trials and loss avoidance trials separately (with group as a between-subject factor and incentive magnitude as within subject factor), in order to interpret the significant interactions.

fMRI analysis

Brain Voyager version QX (Brain Innovation B.V., Maastricht, The Netherlands) was used for preprocessing and analyzing the data. The following preprocessing steps were applied to the echoplanar image volumes: (1) slice scan time correction (using sinc interpolation), (2) linear trend removal, (3) temporal high-pass filtering to remove low-

frequency non-linear drifts of 3 or fewer cycles per time course, (3) 3D motion-correction to correct for small head movements by spatially aligning all volumes to the first volume of the first functional run, (4) spatial smoothing, imposing a 4 mm full-width half-maximum (FWHM) Gaussian smoothing kernel in the space domain.

Functional runs (task blocks) with less than 3 mm motion were included for analyses. Two runs of one subject in the normal control group were excluded from analyses due to excessive motion, and for two subjects in the ADHD group, one run each was excluded because of excessive motion. We tested whether groups differed in terms of amount of motion by comparing groups for the three translation parameters and the three rotation parameters of rigid body transformation. ANOVAs showed that groups did not differ significantly on any of the translation or rotation parameters (all F's < 2.2). Functional and structural measurements were then coregistered, and normalized using the standard 9-parameter landmark method of Talairach and Tournoux (1988).

The analyses focused on reward anticipation. Therefore, general linear models (one for the ADHD group, one for the control group) were defined that included the regressors which modeled the BOLD response to the 2-second epoch following the cue: anticipation of winning $0.20, $1, $5, or $0, anticipation of avoiding the loss of $0.20, $1, $5, or $0, anticipation of not responding. In order to control for activation related to the last 2-second epoch of each trial (outcome), regressors which modeled the BOLD response to outcome were also included in the models. Each regressor was convolved with a standard gamma model of the hemodynamic impulse-response function (Boynton et al 1996). The resulting general linear models were corrected for temporal autocorrelations using a first-order autoregressive model. Random effect analyses were

run for each group separately by time-course contrasts between gain trials and control trials. Statistical maps were thresholded for significance at $p<0.0001$. Then, for striatal regions that were active in either group (minimum cluster size 2 functional voxels of 3x3x4 mm each), region-based ANOVAs were run for gain trials and loss avoidance trials separately, with group as a between-subject factor, and increase in BOLD signal (parameter estimate) across $ amounts as dependent variable. The increase in parameter estimates across $ amounts for each valence was calculated as follows: for each individual, a regression function with $ amount as predictor and parameter estimate as dependent variable was generated. The regression coefficients were used as dependent variable, and reflect the increase in parameter estimate as a function of increasing $ amount. ANOVA with valence as within-subject factor and group as between-subject factor was conducted as well, which allowed examination of the specificity of striatal activity to anticipation of reward. To determine specificity of striatal activation in association with reward anticipation, we also conducted this ANOVA for outcome, controlling for anticipation. Finally, we also report full brain analyses for each group contrasting BOLD signal immediately following cue presentation for gain trials versus control trials thresholded for significance at $p<.0001$ and $p<.001$ (Supplementary Results). Full brain analyses for each group contrasting BOLD signal immediately following cue presentation for gain trials versus control trials are reported in the Supplementary Results.

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