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# Amphetamine-Induced Dopamine Release and Neurocognitive Function in Treatment-Naive Adults with ADHD

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Converging evidence from clinical, preclinical, neuroimaging, and genetic research implicates dopamine neurotransmission in the pathophysiology of attention deficit hyperactivity disorder (ADHD). The *in vivo* neuroreceptor imaging evidence also suggests alterations in the dopamine system in ADHD; however, the nature and behavioral significance of those have not yet been established. Here, we investigated striatal dopaminergic function in ADHD using [$^{11}$C]raclopride PET with a *d*-amphetamine challenge. We also examined the relationship of striatal dopamine responses to ADHD symptoms and neurocognitive function. A total of 15 treatment-free, noncomorbid adult males with ADHD (age: 29.87 ± 8.65) and 18 healthy male controls (age: 25.44 ± 6.77) underwent two PET scans: one following a lactose placebo and the other following *d*-amphetamine (0.3 mg/kg, p.o.), administered double blind and in random order counterbalanced across groups. In a separate session without a drug, participants performed a battery of neurocognitive tests. Relative to the healthy controls, the ADHD patients, as a group, showed greater *d*-amphetamine-induced decreases in striatal [$^{11}$C]raclopride binding and performed more poorly on measures of response inhibition. Across groups, a greater magnitude of *d*-amphetamine-induced change in [$^{11}$C]raclopride binding potential was associated with poorer performance on measures of response inhibition and ADHD symptoms. Our findings suggest an augmented striatal dopaminergic response in treatment-naive ADHD. Though in contrast to results of a previous study, this finding appears consistent with a model proposing exaggerated phasic dopamine release in ADHD. A susceptibility to increased phasic dopamine responsivity may contribute to such characteristics of ADHD as poor inhibition and impulsivity.
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**Keywords:** ADHD; dopamine; PET; [$^{11}$C]raclopride; *d*-amphetamine; executive functions

## INTRODUCTION

Converging indirect evidence from clinical, preclinical, neuroimaging, and genetic research implicates catecholamine, particularly dopamine (DA), neurotransmission in the pathophysiology of attention deficit hyperactivity disorder (ADHD) (Faraone and Mick, 2010; Sontag *et al*, 2010; Spencer *et al*, 1996). The nature of this putative DA dysfunction remains to be elucidated. It could involve one or more presynaptic (eg, synthesis, release, reuptake) or postsynaptic (eg, receptor density, receptor affinity, metabolism) system alterations. Based on the clinical efficacy of stimulants that augment extracellular catecholamine levels, some have hypothesized that ADHD symptoms result from insufficient extracellular DA levels, that is, a hypoactive DA system (Volkow *et al*, 2005). Another model proposes that ADHD symptoms reflect low tonic striatal DA activity coupled with elevated stimulus-evoked phasic DA release (Grace, 2001). According to this model, stimulants confer their therapeutic effects by elevating DA tone that helps attenuate phasic DA release.

More direct measures of DA transmission in ADHD using molecular neuroimaging have produced inconsistent findings. For example, both increases and decreases have been reported for $D_2/D_3$ receptor availability and for dopamine transporter (DAT) binding in ADHD patients *vs* controls (Lou *et al*, 2004; Spencer *et al*, 2005; Spencer *et al*, 2013; Volkow *et al*, 2007a; Volkow *et al*, 2009). Only one study has examined DA release in untreated ADHD (Volkow *et al*, 2007b). Using a methylphenidate challenge, this study found lower DA release in the caudate of adult patients than controls. Together, the findings suggest widespread DA system dysfunctions in ADHD, but the direction of these effects remains unclear.

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These data were presented in part at the 47th and 49th (2010) Annual Meetings of the American College of Neuropsychopharmacology at Scottsdale AZ (December 2008) and Miami FL (December 2010), respectively.
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Neurocognitive concomitants of putative striatal DA alterations in ADHD would presumably include executive dysfunction—a key aspect of the cognitive and behavioral profile of ADHD. Executive functions rely on frontal–striatal circuitry (Alexander *et al*, 1990), and functional imaging studies have linked reduced activation in frontal–striatal circuitry in ADHD to performance deficits on executive function tasks (Dickstein *et al*, 2006). However, few studies to date have linked molecular imaging measures of striatal DA function to neurocognitive performance in ADHD (Lou *et al*, 2004; Rosa-Neto *et al*, 2005).

In this study, we measured striatal DA responses in treatment-naive men with ADHD and healthy controls to a challenge dose of *d*-amphetamine (*d*-amph) using PET with [$^{11}$C]raclopride. This well-established technique yields an index of tracer binding potential ($BP_{ND}$) that is proportional to the number of available $D_2/D_3$ receptors (Laruelle, 2000). The signal is attenuated by drug-induced increases in extracellular DA concentrations, providing an index of DA release. We predicted that *d*-amph-evoked DA release and baseline receptor availability in the striatum would differ significantly between ADHD subjects and healthy controls. As molecular imaging findings in ADHD have been inconsistent, and preclinical models of hyperactivity, impulsivity, and poorly regulated executive function have been linked to both increases and decreases in DA (Sontag *et al*, 2010), group differences and behavior associations in either direction were considered of interest.

## PATIENTS AND METHODS

### Participants

A total of 15 adult men with ADHD (5 combined subtype; 10 predominantly inattentive subtype) and 18 adult male healthy controls completed the study and were included in the analyses. Four participants completed the study but could not be included: three for poor PET data quality (two ADHD), and one (a control) because of a structural anomaly in striatum on MR. Two additional participants began but did not complete the study because of equipment failure.

The diagnosis of ADHD (DSM-IV-TR) required the presence of at least 6/9 inattention symptoms (with or without 6/9 hyperactivity/impulsivity symptoms) since childhood; diagnosis was ascertained by one of the research psychiatrists (CB, LH, and RJ). Symptoms of ADHD (Table 1) were measured as continuous variables in both groups using the Conners' Adult ADHD Rating Scale (CAARS) (Conners *et al*, 1999).

Participants underwent a Structured Clinical Interview for DSM-IV Axis I disorders (SCID I (First *et al*, 1996)) and were excluded for any current or past history of Axis I disorder, other than ADHD. However, 2/15 ADHD participants reported a single mild depressive episode occurring for $\geqslant$2 years in the past. Other exclusion criteria were: a first-degree relative with a history of substance dependence; current use of psychotropic medications; a Beck Depression Inventory (BDI) (Beck and Steer, 1987) score $>13$, an estimated IQ $<80$; a neurological history; a reported history of a head injury with loss of consciousness for $>5$ min; a history of any physical disorder (eg, cardiovascular) contradictory to participation as per comprehensive physical exam; and a positive toxicology screen (cocaine, opiates, phencyclidine, barbiturates, benzodiazepines, $\Delta^9$-tetrahydrocannabinol, amphetamines) as per the Triage Drugs of Abuse urine test (Biosite, San Diego, CA). Controls were excluded for a reported ADHD diagnosis in a first-degree relative.

All ADHD participants were stimulant treatment naive except one who, 2 years before his participation, underwent a 6-month methylphenidate trial. Excluding his data did not change the results. Lifetime stimulant exposure did not exceed two uses for any other participants.

The study was carried out in accordance with the Declaration of Helsinki and was approved by the Research Ethics Board of the Montreal Neurological Institute. All participants gave written informed consent.

### Procedure

Participants underwent two [$^{11}$C]raclopride PET scans, one following a lactose placebo and the other following 0.3 mg/kg p.o. of *d*-amph; capsule administration occurred 60 min before tracer injection and was double blind, randomized, and counterbalanced. PET scans occurred at least 3 days apart. Before each scan, participants were asked to abstain from food, caffeine, and smoking for 4 h and from alcohol for 24 h. A structural magnetic resonance image (MRI) was obtained on a separate day. Participants completed the neurocognitive battery a minimum of 24 h from the time of either PET scan to avoid any drug carryover effects. Toxicology screening occurred on the initial screening interview and before both PET scans and neurocognitive testing.

### Neuroimaging

Participants were scanned on a Siemens ECAT HR+ PET scanner (CTI/Siemens, Knoxville, TN) with lead septa removed (63-slice coverage), with a maximum resolution 4.2-mm, full width at half maximum (FWHM) in the center of the field of view. Attenuation correction was performed using a 12-min $^{68}$Ga transmission scan immediately before tracer injection. The emission scan started simultaneously with the injection of [$^{11}$C]raclopride, as an i.v. bolus, and data were acquired for 60 min in 26 time frames of progressively longer duration. Tracer doses did not differ significantly between scans for either group (controls: placebo $= 7.25 \pm 1.74$, *d*-amph $= 7.41 \pm 1.55$, $p = 0.46$; ADHD: placebo $= 6.44 \pm 0.74$, *d*-amph $= 6.59 \pm .29$, $p = 0.37$), but were marginally higher across scans for controls (controls $= 7.33 \pm 1.63$; ADHD $= 6.51 \pm 0.56$, $p = 0.06$). The [$^{11}$C]raclopride-specific activity, sampled for 10/66 scans, ranged from 335 to 925 Ci/mmol, with the injected dose ranging from 2.34 to 6.46 μg ($3.77 \pm 1.55$). Vital signs were monitored and blood samples for plasma amphetamine collected just before capsule administration, at the time of tracer administration, mid-scan, and at the end of scan. Ratings of subjective drug (or placebo) effects were also obtained (Supplementary Table S4).

High-resolution (1 mm) T1-weighted MRIs were obtained on a 1.5-Tesla Siemens scanner, using gradient echo pulse sequence (TR = 22 ms, TE = 9.2 ms, flip angle = 30°,

**Table 1** Sample Characteristics

| | Controls ($n=18$) | ADHD ($n=15$) | Test statistic (d.f.) | $p$ |
|---|---|---|---|---|
| Age (SD) | 25.44 (6.77) | 29.87 (8.65) | $U_{(33)}=99.50$ | 0.20 |
| *Estimated full scale IQ (SD)* | 116.83 (16.07) | 107.13 (12.78) | $U_{(27)}=51.00$ | 0.06 |
| Abbreviated WAIS-III[a] | 124.25 (14.70) | 109.44 (15.16) | $U_{(17)}=17.00$ | 0.07 |
| Abbreviated WAIS-R[b] | 102.00 (1.63) | 103.67 (8.12) | $U_{(10)}=11.50$ | 0.91 |
| Years of education (SD) | 17.11 (3.32) | 16.20 (3.63) | $t_{(31)}=0.75$ | 0.46 |
| *CAARS t-scores (SD)* | | | | |
| Inattention/memory problems | 43.77 (7.41) | 74.00 (10.49) | $t_{(26)}=8.67$ | <0.0005* |
| Hyperactivity/restlessness | 43.76 (6.08) | 62.27 (12.93) | $t_{(21.79)}=4.82$ | <0.0005* |
| Impulsivity/emotional lability | 42.92 (9.42) | 58.53 (11.28) | $t_{(26)}=3.94$ | 0.001* |
| Problems with self-concept | 43.08 (5.89) | 63.07 (7.64) | $t_{(26)}=7.66$ | <0.0005* |
| DSM-IV inattention | 48.73 (12.49) | 84.4 (8.73) | $t_{(26)}=8.85$ | <0.0005* |
| DSM-IV hyperactivity | 44.69 (8.54) | 68.13 (14.48) | $t_{(26)}=5.11$ | <0.0005* |
| DSM-IV total | 46.69 (11.64) | 81.47 (10.30) | $t_{(26)}=8.39$ | <0.0005* |
| ADHD index | 42.00 (8.45) | 66.86 (8.74) | $t_{(26)}=7.63$ | <0.0005* |
| BDI at intake (SD) | 1.53 (2.00) | 6.04 (3.86) | $U_{(31)}=23.50$ | <0.0005* |
| *Recreational drug use history* | | | | |
| Stimulants: no. of lifetime uses (SD) | 0.06 (0.24) | 0.36 (0.74) | $U_{(32)}=105.00$ | 0.17 |
| Marijuana: no. of lifetime uses (SD) | 18.00 (33.08) | 49.27 (90.07) | $U_{(32)}=119.50$ | 0.22 |
| Nicotine: no. of lifetime uses (SD) | 1359.06 (3677.02) | 1614.13 (5171.99) | $U_{(33)}=128.00$ | 0.81 |
| No. of smokers | 1 | 1 | | |

Group differences: *$p \leqslant 0.05$.
[a]Wechsler Adult Intelligence Scale–Revised (WAIS-R) ($n=9$) (Reynolds *et al*, 1983).
[b]Wechsler Adult Intelligence Scale–III (WAIS-III) ($n=9$) (Pilgrim *et al*, 1999).

FOV = 256 mm, and matrix 256 × 256) for co-registration to the PET images.

## Neurocognitive Battery

A subset of participants (14 ADHD and 12 controls) completed a battery of neurocognitive tests, tapping functions associated with medium to large effect sizes for ADHD in meta-analyses (Nigg, 2005), and suggested to be in part mediated by catecholamine systems (Allman *et al*, 2010; Aron *et al*, 2003; Leyton *et al*, 2007). The battery included two response inhibition tasks: the Stop Signal Paradigm (Logan *et al*, 1984) and the antisaccade task (Hallett, 1978). The Stop Signal Paradigm assesses inhibition by measuring the time required to stop a planned response, that is, stop signal reaction time (SSRT). An auditory stop signal instructs participants to withhold responses on 25% of trials in a choice reaction time task. SSRT measures how early the stop signal must occur relative to a participant's mean response time in order for responses to be successfully withheld.

The antisaccade task measures inhibitory oculomotor control (Hallett, 1978). It requires withholding a reflexive saccade to a suddenly appearing peripheral target and, instead, generating a saccade to its mirror location (ie, an antisaccade). Two measures of inhibitory function were derived from this task: % reflexive saccades toward the target (error rate) and % anticipatory saccades (latency $\leqslant$80 ms) that reflect impulsive responding when waiting for the peripheral target to appear.

The battery also included tasks of working memory, planning, motor speed and cognitive flexibility, and responsivity to reward and punishment. We will subsequently focus only on those tasks that revealed significant differences between the groups; a detailed description of the battery and the results appears in Supplementary Materials and Methods and Supplementary Table S1.

## Analyses

MR volumes were corrected for image intensity nonuniformity (Sled *et al*, 1998) and transformed into the Montreal Neurological Institute (MNI) space using automated feature matching to the MNI305 template (Collins *et al*, 1994).

The PET images were reconstructed using a 6-mm FWHM Hanning filter and corrected for motion (Costes *et al*, 2009). Parametric images were generated by calculating [$^{11}$C]raclopride binding potential values ($BP_{ND}$) (Innis *et al*, 2007) at each voxel using a simplified reference tissue compartmental model (SRTM) with cerebellum as the reference tissue with a very low density of $D_2/D_3$ receptors (Gunn *et al*, 1997; Lammertsma and Hume, 1996). $BP_{ND}$ is a function of the estimated concentration of available $D_2/D_3$ receptors ($B_{Avail}$),

the dissociation constant of the radiotracer from $D_2/D_3$ receptors ($K_D$), and the free fraction of the nonspecifically bound tracer in the brain ($F_{ND}$): $BP_{ND} = F_{ND} \times (B_{Avail}/K_D)$.

As previously described (Boileau *et al*, 2006), mean $BP_{ND}$ values from each individual parametric image were extracted from regions of interest (ROIs) delineated on each individual MRI. The ROIs were based on the functional organization of the striatum (Martinez *et al*, 2003): limbic (LST, includes ventral striatum), associative (AST, includes precommissural dorsal caudate, precommissural dorsal putamen, postcommissural caudate), and sensorimotor (SMST, includes postcommissural putamen). Mean $BP_{ND}$ values were corrected for partial volume effects (Aston *et al*, 2002). $\Delta BP_{ND}$ values were calculated as $(BP_{ND\ placebo} - BP_{ND\ d\text{-amph}})/BP_{ND\ placebo} \times 100$ and used for intergroup statistical analysis in SPSS 17.

To examine specific loci of *d*-amph-induced change in BP in each group, a voxel-wise statistical mapping method was utilized to determine the *t*-statistic associated with the change in $BP_{ND}$ between the *d*-amph and the placebo conditions (Aston *et al*, 2000). Voxels of statistically significant change had *t*-values of $\geqslant 3.8$ that corresponded to $p < 0.05$ based on the random field theory, considering the search volume of the striatum, the reconstructed image resolution of 8 mm at FWHM, and correction for multiple comparisons (Aston *et al*, 2000; Worsley *et al*, 1996).

Plasma amphetamine concentrations were analyzed using combined gas chromatography–mass spectrometry (GC–MS) (Asghar *et al*, 2002). Area under the curve (AUC) was calculated for each participant to reflect plasma amphetamine concentrations over all measurement points.

Behavioral data were analyzed statistically using SPSS 17. Extreme values outside 3 SDs of the mean for a given variable were Winsorized (replaced by the value of their nearest neighbor) (Dixon and Yuen, 1974). Appropriate transformations were used to normalize the distribution for some measures, and analyses were carried out on the transformed data.

## RESULTS

### Participants

ADHD participants did not differ significantly from controls on demographic variables. Estimated IQ was marginally higher in controls ($p = 0.06$; Table 1). Although no participant was clinically depressed, the mean BDI score at intake was significantly higher in the ADHD group than controls ($p < 0.0005$).

### *d*-Amph-Induced Change in $D_2/D_3$ Binding

In the ROI analysis, $\Delta BP_{ND}$ values across three ROIs were significantly correlated with intake BDI scores in the ADHD group ($r_s = -0.68$; $p = 0.007$), but not in controls ($rs = 0.23$; $p = 0.37$). Intake BDI was therefore entered as a covariate in the two-way group × ROI mixed ANCOVA on the $\Delta BP_{ND}$s. One ADHD and one control participant were missing intake BDI scores; their missing values were replaced by the mean of their respective groups. Excluding those participants produced the same results. The ANCOVA revealed a significant group × ROI interaction ($F_{(1.32, 39.70)} = 4.07$; $p = 0.04$). Bonferroni adjusted pairwise comparisons showed greater magnitude $\Delta BP_{ND}$ in the ADHD group than controls in AST (controls: −0.57%; ADHD: 6.08%; $F_{(1, 30)} = 4.24$, $p = 0.05$) and SMST (controls: 3.25%; ADHD: 9.68%; $F_{(1, 30)} = 4.73$, $p = 0.04$), but not in LST (controls: 12.34%; ADHD: 8.62%; $F_{(1, 30)} = 0.02$, $p = 0.82$) (Figure 1b). There were no other main effects or interactions.

To explore the relationship between $\Delta BP_{ND}$ and ADHD symptoms, we performed semipartial correlations between $\Delta BP_{ND}$s and scores on two subscales of the CAARS, the DSM-IV Symptoms of Inattention and the DSM-IV Symptoms of Hyperactivity–Impulsivity subscales. Analyses were conducted across groups and co-varied intake BDI scores. Significance threshold was 0.008 (Bonferroni-corrected to keep 'family-wise' error rate at 0.05). More pronounced $\Delta BP_{ND}$ decreases in AST and SMST were associated with higher inattention scores (AST: $r_{(33)} = 0.47$, $p < 0.0005$; SMST: $r_{(33)} = 0.43$; $p = 0.001$) (Figure 2a). Although regression diagnostics suggested a possible 'lever' (leverage values: $\geqslant 0.47$; standardized DF $\beta$s: $\geqslant 0.40$), nonparametric correlations between inattention scores and residualized $\Delta BP_{ND}$s with intake BDI 'removed' yielded the same results (AST: Rho = 0.43, $p = 0.02$; SMST: Rho = 0.40, $p = 0.03$). $\Delta BP_{ND}$s were not related to hyperactivity scores (all $rs_{(33)} < 0.27$; $ps > 0.17$). LST $\Delta BP_{ND}$s were not significantly correlated with ADHD symptoms ($rs_{(33)} < 0.16$; $ps > 0.29$).

We also examined $BP_{ND}$ on the placebo day. A group × ROI mixed ANOVA revealed a significant group × ROI interaction ($F_{(1.70, 52.80)} = 4.67$, $p = 0.02$), indicating a different pattern of $D_2/D_3$ binding across ROIs as a function of group (Table 2).

The loci of significant DA release for each group are presented using voxel-wise t-maps in Figure 1 and Supplementary Table S2.

### Neurocognitive Performance

In the Stop Signal Paradigm, a two-way mixed ANOVA revealed a significant group × reaction time (RT) type (Go RT *vs* Stop Signal RT) interaction ($F_{(1, 24)} = 5.83$, $p = 0.02$), reflecting longer SSRTs in the ADHD participants than controls ($t_{(24)} = 3.0$; $p = 0.008$), but no group difference on Go RTs (Figure 3).

Independent sample *t*-tests revealed that relative to controls, ADHD participants made significantly more antisaccade (AS) errors ($t_{(19)} = 2.36$; $p = 0.03$). ADHD participants also made significantly more anticipatory responses during the fixation period on both prosaccade (the control condition, where the participant follows the target) and antisaccade trial blocks ($t_{(19)} = 2.67$; $p = 0.02$) (Figure 3). For saccade latency, a two-way group × saccade (antisaccade *vs* prosaccade) ANOVA revealed a trend for a group × saccade interaction ($F_{(1, 17)} = 4.34$; $p = 0.053$), indicating a larger difference between prosaccade and antisaccade latencies in ADHD participants (70 ms) than controls (48 ms).

### *d*-Amph-Induced $\Delta BP_{ND}$ and Response Inhibition

We evaluated associations between $\Delta BP_{ND}$ and response inhibition measures that distinguished between the groups

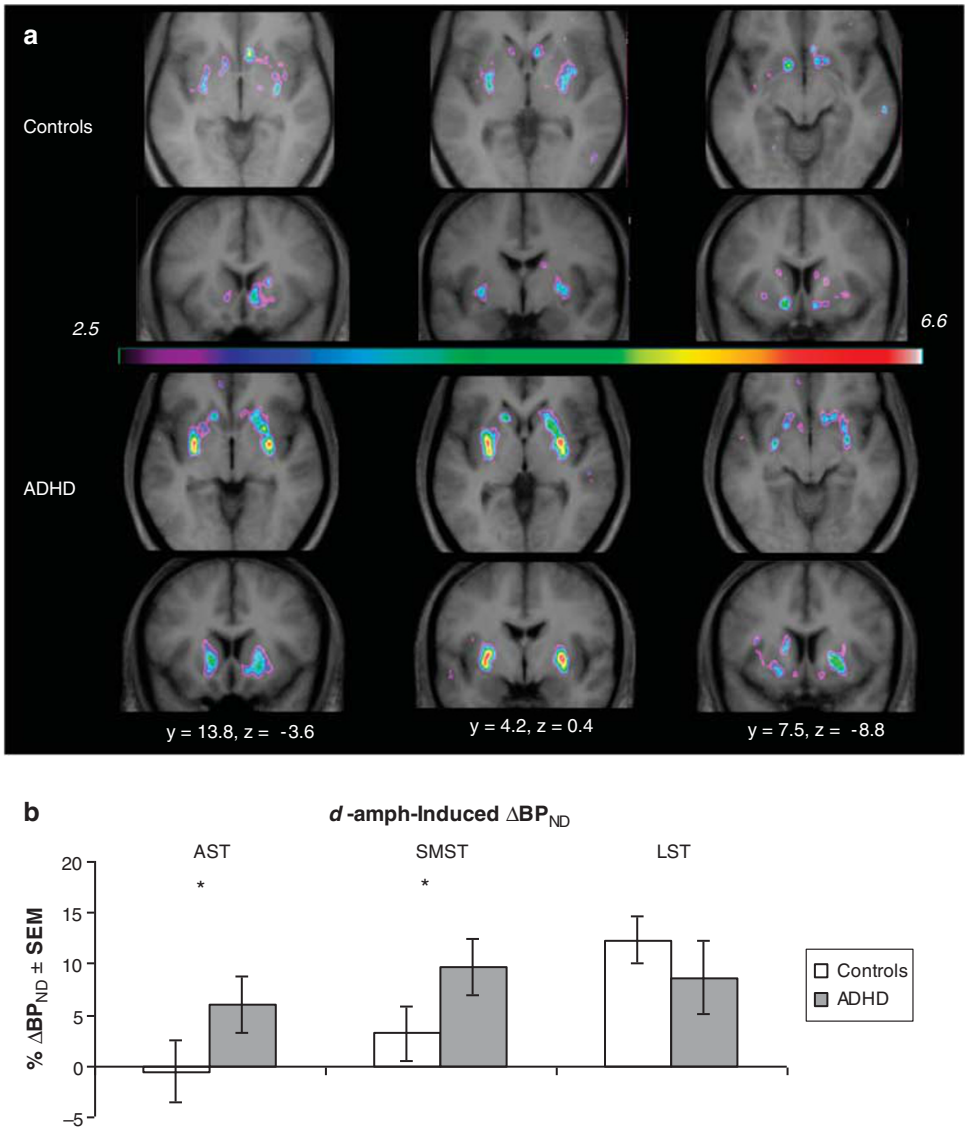


**Figure 1** The *d*-amph-induced change in [$^{11}$C]raclopride binding. (a) Parametric *t*-maps showing *d*-amph-induced decreases in [$^{11}$C]raclopride $BP_{ND}$ for the control (top) and ADHD (bottom) groups. $t > 3.8$ equivalent to $p \leqslant 0.05$ based on random field theory. (b) Mean *d*-amph-induced decreases in [$^{11}$C]raclopride $BP_{ND}$ extracted from three predetermined ROIs: associative (AST), sensorimotor (SMST), and limbic (LST). The *p*-values indicate the significance of the between-group differences in % change in $BP_{ND}$ in each region: $^{*}p \leqslant 0.05$. More positive values indicate larger *d*-amph-induced $BP_{ND}$ decreases (greater DA release).

using semipartial correlations that controlled for the effect of intake BDI on $\Delta BP_{ND}$. Significance threshold was set at 0.0055 to keep family-wise error rate at 0.05 (3 regions, 3 inhibition measures). Larger $\Delta BP_{ND}$s in AST and SMST were associated with higher proportions of antisaccade errors (AST: $r_{(18)} = 0.62$; $p = 0.003$; SMST: $r_{(18)} = 0.63$; $p = 0.002$) and anticipatory saccades (AST: $r_{(18)} = 0.66$; $p_{(18)} = 0.001$; SMST: $r_{(18)} = 0.65$; $p = 0.001$). Correlations for $\Delta BP_{ND}$ in LST were at trend level (AS errors: $r_{(18)} = 0.44$; $p = 0.05$; anticipatory saccades: $r_{(18)} = 0.39$; $p = 0.08$). Longer SSRTs showed trend-level associations with larger $\Delta BP_{ND}$s in AST and SMST (AST: $r_{(23)} = 0.44$; $p = 0.02$; SMST: $r_{(23)} = 0.43$; $p = 0.03$) (Figure 2b). Because regression diagnostics suggested a possible 'lever' (leverage values: $\geqslant 0.47$; Standardized DF $\beta$s: $\geqslant 0.36$), confirmatory nonparametric correlations were conducted using residualized $\Delta BP_{ND}$ values with intake BDI 'removed'. Significant associations remained between both antisaccade variables and $\Delta BP_{ND}$ in AST (AS errors: $Rho_{(19)} = 0.60$; $p = 0.004$; anticipatory saccades: $Rho_{(19)} = 0.58$; $p = 0.005$) and SMST (AS errors: $Rho_{(19)} = 0.59$; $p = 0.005$; anticipatory saccades: $Rho_{(19)} = 0.58$; $p = 0.006$). The trend associations between SSRT and $\Delta BP_{ND}$ in these regions also persisted ($AST_{(24)}$: $Rho = -0.45$; $p = 0.02$; SMST: $Rho_{(24)} = 0.39$; $p = 0.05$). For LST, the trends were not significant with nonparametric analyses (AS errors: $Rho_{(19)} = 0.32$; $p = 0.16$; anticipatory saccades: $Rho_{(19)} = 0.31$; $p = 0.18$).

## Plasma Amphetamine

The peak plasma concentrations following *d*-amph administration were $14.66 \pm 12.35$ ng/ml for controls and $15.16 \pm$

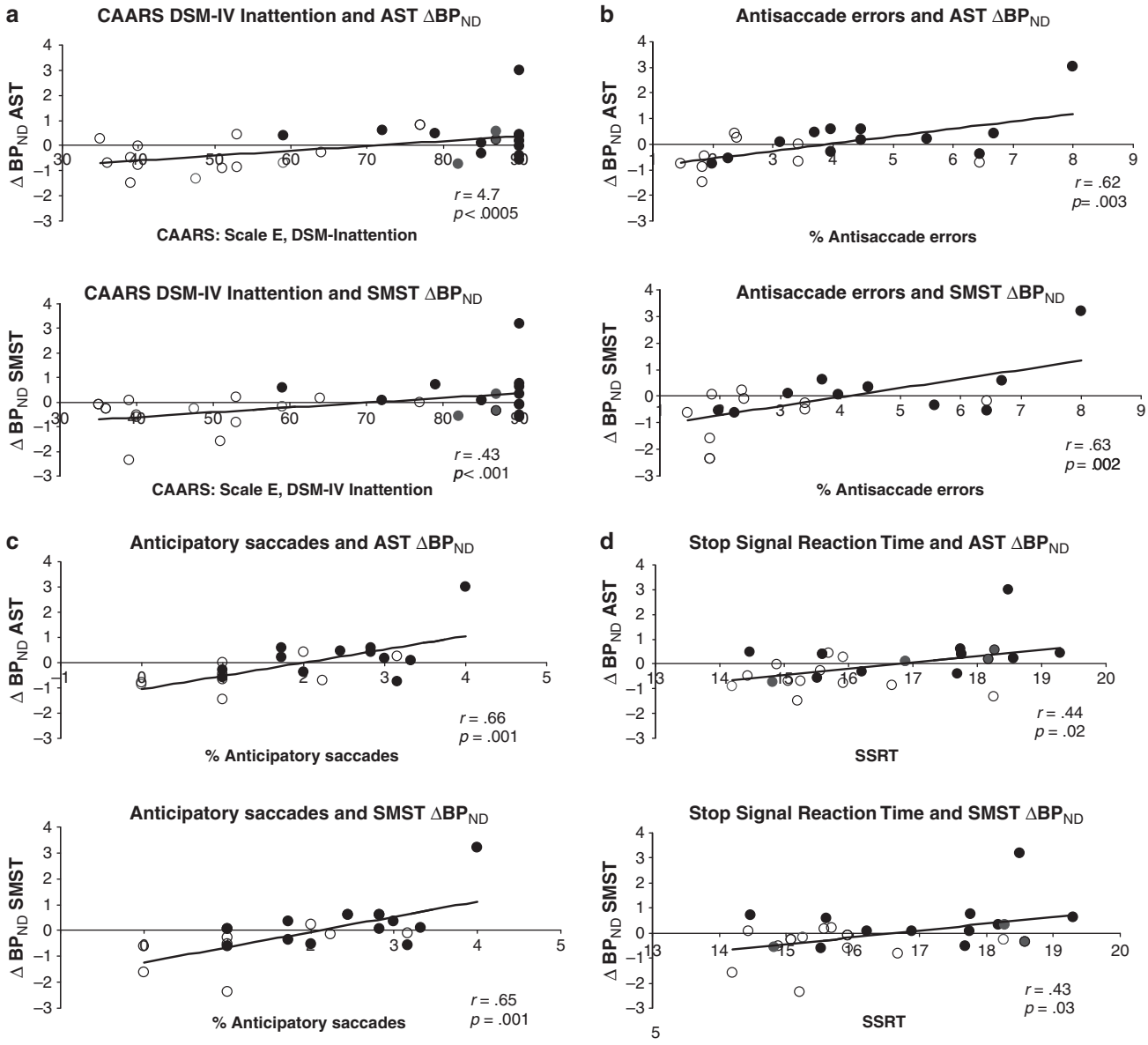


**Figure 2** Associations of $\Delta BP_{ND}$ with ADHD symptoms on the CAARS and response inhibition. Associations between $\Delta BP_{ND}$ and (a) CAARS DSM-IV Inattention symptoms; (b) % antisaccade errors; (c) % anticipatory saccades; and (d) stop signal reaction times. Open symbols represent controls and filled symbols represent ADHD participants. CAARS DSM-IV Inattention t-scores and square root transformed values for neurocognitive performance appear on the x axis; residualized $\Delta BP_{ND}$ values, removing the effect of intake BDI, appear on the y axis. More positive values represent greater *d*-amph-induced $BP_{ND}$ decreases (greater DA release). Note that the correlations are not driven by the ADHD participant in the upper right of the graphs and remain significant with nonparametric analyses.

13.72 ng/ml for ADHD participants. AUC values did not differ between groups (ADHD: $27.50 \pm 30.4$; controls: $23.02 \pm 25.30$) ($t_{(27)} = 0.44$, $p = 0.66$) or correlate with $\Delta BP_{ND}$ in any ROI ($ps > 0.36$). No amphetamine was detected in plasma on the placebo day or before drug administration on the *d*-amph day.

## DISCUSSION

This study provides evidence of an augmented DA response to an amphetamine challenge in the associative (controls: −0.57%; ADHD: 6.08%) and sensorimotor (controls: 3.25%; ADHD: 9.68%) striatal regions in treatment-naive adults with ADHD. Across groups, more pronounced *d*-amph-induced DA responses in these regions were associated with higher self-reported levels of inattention and poorer performance on tests of response inhibition. The two groups did not differ on plasma *d*-amph levels or baseline DA receptor availability.

Although the physiological relevance of an increased *d*-amph-induced $\Delta BP_{ND}$ in ADHD participants is uncertain, it could signal an augmented phasic DA release. In nonanesthetized, nonrestrained, behaving animals, phasic DA release contributes most to the overall increases in extracellular DA in response to amphetamine (Daberkow

**Table 2** $D_2/D_3$ Binding Potential ($BP_{ND}$) in Striatal ROIs

| | Controls | | | ADHD | | |
|---|---|---|---|---|---|---|
| | **Placebo** | ***d*-Amph** | **Placebo *vs* *d*-amph** | **Placebo** | ***d*-Amph** | **Placebo *vs* *d*-amph** |
| AST (SD) | 3.00 (0.41) | 3.00 (0.49) | $t_{(17)} = -0.04$; $p = 0.97$ | 3.25 (0.35) | 3.04 (0.43) | $t_{(14)} = 2.15$; $p < 0.05$ |
| SMST (SD) | 3.53 (0.47) | 3.41 (0.54) | $t_{(17)} = 1.37$; $p = 0.19$ | 3.76 (0.49) | 3.37 (0.48) | $t_{(14)} = 3.24$; $p < 0.006$ |
| LST (SD) | 3.26 (0.39) | 2.86 (0.47) | $t_{(17)} = 5.32$; $p < 0.0005$ | 3.16 (0.53) | 2.85 (0.43) | $t_{(14)} = 2.36$; $p < 0.03$ |
| AST *vs* LST[a] | $t_{(17)} = 3.52$; $p = 0.003$ | $t_{(17)} = 1.34$; $p = 0.12$ | | $t_{(14)} = 0.81$; $p = 0.43$ | $t_{(14)} = 2.31$; $p = 0.04$ | |
| SMST *vs* LST[a] | $t_{(17)} = 2.86$; $p = 0.01$ | $t_{(17)} = 5.87$; $p < 0.005$ | | $t_{(14)} = 5.21$; $p = 0.005$ | $t_{(14)} = 5.16$; $p < 0.005$ | |
| AST *vs* SMST | $t_{(17)} = 9.11$; $p < 0.0005$ | $t_{(17)} = 6.14$; $p < 0.005$ | | $t_{(14)} = 5.95$; $p < 0.0005$ | $t_{(14)} = 4.87$; $p < 0.005$ | |

Abbreviations: AST, associative ROI; LST, limbic ROI; SMST, sensorimotor ROI.
$BP_{ND}$ values for control and ADHD groups on placebo and *d*-amph. Regional pattern of $D_2/D_3$ binding on placebo differed as a function of Group, as described by statistics provided in the last three rows.
[a]The group × ROI interaction was driven by group differences in binding discrepancies between AST *vs* LST ($F_{(1,31)} = 7.20$; $p = 0.01$) and between SMST *vs* LST ($F_{(1,31)} = 4.86$; $p = 0.04$); pairwise comparisons among regions are Bonferroni corrected. Regional $BP_{ND}$ on *d*-amph did not differ significantly as a function of group ($ps > 0.45$).

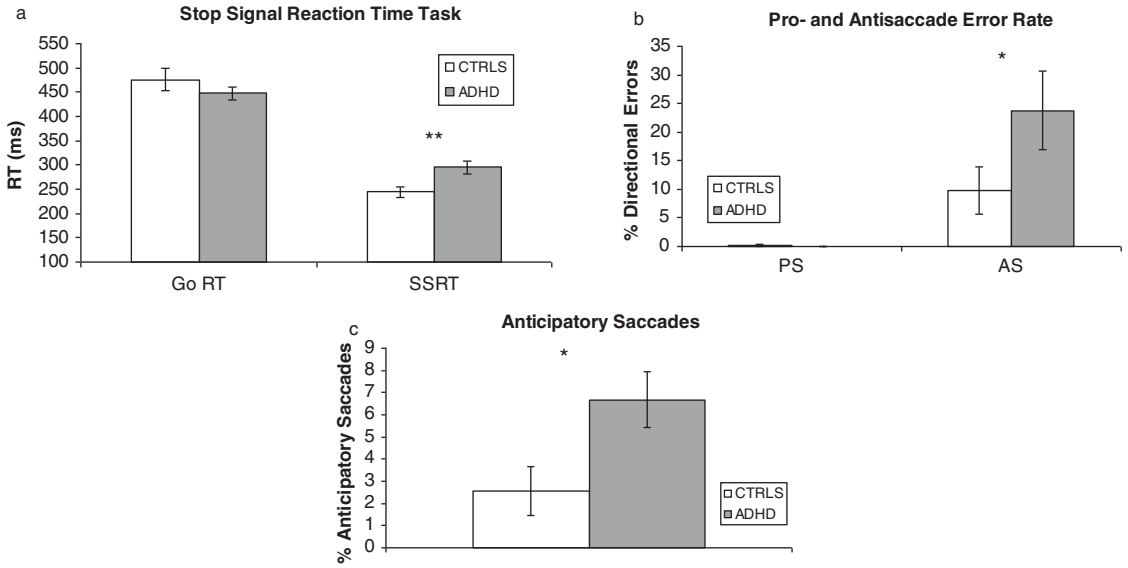


**Figure 3** Neurocognitive performance. (a) Stop Signal Paradigm performance. Go RT, Go Reaction Time; SSRT, Stop Signal Reaction Time. (b) Antisaccade and prosaccade error rate. PS, prosaccade; AS, antisaccade. (c) Anticipatory saccades across the pro- and antisaccade blocks. *$p < 0.05$; **$p < 0.01$.

*et al*, 2013). Our findings would then appear to be in line with one model of DA function in ADHD that postulates augmented phasic DA release ensuing from abnormally low striatal DA tone (Grace, 2001). Exocytotic DA release is not the sole mechanism contributing to $\Delta BP_{ND}$; DA efflux through reverse transport might also affect $BP_{ND}$. To the extent that it does, augmented $\Delta BP_{ND}$ in the ADHD group could signal altered DAT function, higher DAT density, higher number of DA neurons, or greater presynaptic DA stores. The associations between the magnitude of the DA response and levels of inattention across groups suggest that levels of synaptic DA may modulate attentional function in healthy and ADHD individuals. Notably, the augmented $\Delta BP_{ND}$ in ADHD participants is unlikely to have resulted from stimulant sensitization (Boileau *et al*, 2006): the ADHD participants were stimulant treatment naive (except one subject) and the majority had no prior stimulant exposure.

We observed significant differences in DA response between ADHD participants and controls in associative and sensorimotor ROIs but not in limbic striatum. These ROIs are based on the topography of functionally distinct cortico–striatal–thalamo–cortical circuits in non-human primates (Haber, 2010). According to a recent delineation of striatal subregions based on corticostriatal connectivity in humans (Tziortzi *et al*, 2013), our peak voxels of DA release in the AST map onto loci connected with prefrontal executive cortical areas; peak voxels in SMST map onto loci connected with executive and premoter regions. Thus, it is plausible that the group differences in DA release in these striatal regions are linked with executive and motor control, but not with motivation and reward.

Across both groups, greater *d*-amph-induced DA release in associative and sensorimotor ROIs was associated with poorer performance on tasks of response inhibition; the ADHD group had impaired performance of these tasks. This

finding is consistent with previous research in animals and humans that has implicated striatal DA neurotransmission in response inhibition and impulsivity (Buckholtz *et al*, 2010; Dalley *et al*, 2007; Rosa-Neto *et al*, 2005). Some of these findings have suggested that overstimulation of striatal DA receptors by DA is associated with disinhibition: trait impulsivity has been positively associated with amph-induced striatal DA release in healthy controls (Buckholtz *et al*, 2010); in adolescents with ADHD, poorer performance off drug on a behavioral measure of impulsivity and inattention has been associated with greater methylphenidate-induced DA responses (Rosa-Neto *et al*, 2005). The association of an amplified DA release to response inhibition could be mediated by activation of striatal D1 receptors in the *direct pathway* of the basal ganglia circuits that could decrease discharge of the globus pallidus internal and substantia nigra pars reticulata, in turn disinhibiting thalamic nuclei and the superior colliculus (Alexander *et al*, 1990; Hikosaka *et al*, 2000), thus causing weaker inhibition of skeletomotor and oculomotor circuits. Alternatively, the association could be mediated via striatal D2 receptors in the indirect pathway, as D2 stimulation is believed to prevent inhibitory learning (Dagher, 2012).

Our results are at variance with one previous report of a blunted methylphenidate-induced DA response and lower placebo $BP_{ND}$ levels in the caudate of adults with ADHD relative to healthy controls (Volkow *et al*, 2007b). Although placebo $BP_{ND}$ values in the two studies were very similar for controls, they were $\approx$11% lower for the ADHD participants in the study of Volkow *et al* (2007b) than here. Differences in methodology could have contributed to the discrepancy in findings. All of our participants were male; the previous study included females with a trend for a higher proportion of females in the ADHD than control group. Sex differences in striatal DA receptor binding, DA release, and ADHD-relevant personality traits have been reported (Munro *et al*, 2006; Pohjalainen *et al*, 1998; Riccardi *et al*, 2006). Another possible difference is previous substance use. Although the study of Volkow *et al* (2007b) excluded individuals who met criteria for substance abuse or dependence, the paper did not report on the amount of subclinical recreational substance use. Even 'casual' drug use is associated with a blunted DA response to amph (Casey *et al*, 2013); group differences on this variable could affect $\Delta BP_{ND}$. Finally, probes for the dopamine system differed between studies: methylphenidate and *d*-amph augment extracellular DA levels through different mechanisms, and the route of administration (oral *vs* intravenous) and the dose also differed.

Interpretation of the present data should be considered in light of the following. (1) We interpret the association between disinhibition and striatal $\Delta BP_{ND}$ as reflecting a meaningful relationship of stable traits. However, these variables were estimated at different times and only once in each participant. Nonetheless, high test–retest reliability of our inhibition measures (Ettinger *et al*, 2003; Logan *et al*, 1984) as well as of $\Delta BP_{ND}$ to *d*-amph (Kegeles *et al*, 1999) supports the interpretation that dopaminergic dysfunction is related to response inhibition deficits in ADHD. (2) Our sample size had power to detect only associations of a medium to large effect size, given the Bonferroni correction for multiple comparisons. Larger studies may find associations of $\Delta BP_{ND}$ with other aspects of neurocognition that were not significant here. In addition, there is some inherent instability in correlations found in smaller samples. (3) The magnitude of *d*-amph-induced decreases in [$^{11}$C]raclopride binding in the control group is at the lower end of the range of $\approx$10–20% observed in previous studies using a similar dose of oral *d*-amph. However, the difference between groups in $\Delta BP_{ND}$ that we observed here cannot be attributed to group differences in dose or to a lack of responsiveness to the drug on the part of the controls. Plasma amphetamine levels were nearly identical between the groups, and the subjective and cardiovascular responses of controls were significant and similar in magnitude to those observed in ADHD participants (Supplementary Tables S3 and S4). (4) Because the sample here was exclusively male, findings cannot be generalized to females.

In conclusion, this study provides evidence of an augmented striatal DA response to an amphetamine challenge in treatment-naive men with ADHD. Whether an enhanced striatal DA responsivity underlies response inhibition deficits and impulsivity in ADHD remains a matter of conjecture, but the indirect evidence presented here supports this possibility.

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## REFERENCES

Alexander GE, Crutcher MD, DeLong MR (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. *Prog Brain Res* **85**: 119–146.

Allman A-A, Benkelfat C, Durand F, Sibon I, Dagher A, Leyton M *et al* (2010). Effect of d-amphetamine on inhibition and motor planning as a function of baseline performance. *Psychopharmacology* **211**: 423–433.

Aron AR, Dowson JH, Sahakian BJ, Robbins TW (2003). Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry* **54**: 1465–1468.

Asghar SJ, Baker GB, Rauw GA, Silverstone PH (2002). A rapid method of determining amphetamine in plasma samples using pentafluorobenzenesulfonyl chloride and electron-capture gas chromatography. *J Pharmacol Toxicol Methods* **46**: 111–115.

Aston J, Gunn R, Worsley K, Ma Y, Evans AC, Dagher A (2000). A statistical method for the analysis of positron emission tomopgraphy neuroreceptor ligand data. *Neuroimage* **12**: 245–256.

Aston JA, Cunningham VJ, Asselin MC, Hammers A, Evans AC, Gunn RN (2002). Positron emission tomography partial volume correction: estimation and algorithms. *J Cereb Blood Flow Metab* **22**: 1019–1034.

Beck AT, Steer RA (1993). Manual for the Revised Beck Depression Inventory. Psychological Corporation: San Antonio, TX.

Boileau I, Dagher A, Leyton M, Gunn RN, Baker GB, Diksic M *et al* (2006). Modeling sensitization to stimulants in humans: an [11C]raclopride/positron emission tomography study in healthy men. *Arch Gen Psychiatry* **63**: 1386–1395.

Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS *et al* (2010). Dopaminergic network differences in human impulsivity. *Science* **329**: 532.

Casey KF, Benkelfat C, Cherkasova MV, Baker GB, Dagher A, Leyton M (2013). Reduced dopamine response to amphetamine in subjects at ultra-high risk for addiction. *Biol Psychiatry* e-pub ahead of print 16 October 2013 (doi:10.1016/j.biopsych.2013.08.033).

Collins DL, Neelin P, Peters TM, Evans AC (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr* **18**: 192–205.

Conners CK, Erhart D, Sparrow E (1999). *Conners' Adult ADHD Rating Scales. Technical Manual*. Multi-Health Systems: New York.

Costes N, Dagher A, Larcher K, Evans AC, Collins DL, Reilhac A (2009). Motion correction of multi-frame PET data in neuroreceptor mapping: Simulation based validation. *Neuroimage* **47**: 1496–1505.

Daberkow DP, Brown HD, Bunner KD, Kraniotis SA, Doellman MA, Ragozzino ME *et al* (2013). Amphetamine paradoxically augments exocytotic dopamine release and phasic dopamine signals. *J Neurosci* **33**: 452–463.

Dagher A (2012). Addiction as aberrant learning-evidence from Parkinson's disease. *Addiction* **107**: 248–250.

Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Laane K *et al* (2007). Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science* **315**: 1267–1270.

Dickstein SG, Bannon K, Castellanos FX, Milham MP (2006). The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. *J Child Psychol Psychiatry* **47**: 1051–1062.

Dixon W, Yuen K (1974). Trimming and winsorization: a review. *Stat Papers* **15**: 157–170.

Ettinger U, Kumari V, Crawford TJ, Davis RE, Sharma T, Corr PJ (2003). Reliability of smooth pursuit, fixation, and saccadic eye movements. *Psychophysiology* **40**: 1–9.

Faraone SV, Mick E (2010). Molecular genetics of attention deficit hyperactivity disorder. *Psychiatr Clin North Am* **33**: 159–180.

First MB, Spitzer RL, Gibbon M, Williams JBW (1996). *Structured Clinical Interview for DSM-IV Axis I Disorders*. Biometrics Research Department, New York State Psychiatric Institute New York.

Grace AA (2001). Psychostimulant actions on dopamine and limbic system function: relevance to the pathophysiology and treatment of ADHD. In: Solanto MArnsten AFCastellanos FX (eds) *Stimulant Drugs and ADHD: Basic and Clinical Neuroscience*. Oxford University Press: New York, pp 134–157.

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ (1997). Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage* **6**: 279–287.

Haber SN (2010). Convergence of limbic, cognitive, and motor cortico-striatal circuits with dopamine pathways in the primate brain. In: Iversen LIversen SDDunnett SBBjorklund A (eds) *Dopamine Handbook*. Oxford University Press: Oxford, pp 38–48.

Hallett PE (1978). Primary and secondary saccades to goals defined by instructions. *Vision Res* **18**: 1279–1296.

Hikosaka O, Takikawa Y, Kawagoe R (2000). Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiol Rev* **80**: 953–978.

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN *et al* (2007). Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *J Cereb Blood Flow Metab* **27**: 1533–1539.

Kegeles LS, Zea-Ponce Y, Abi-Dargham A, Rodenhiser J, Wang T, Weiss R *et al* (1999). Stability of [123I]IBZM SPECT measurement of amphetamine-induced striatal dopamine release in humans. *Synapse* **31**: 302–308.

Lammertsma AA, Hume SP (1996). Simplified reference tissue model for PET receptor studies. *Neuroimage* **4**(3 Pt 1): 153–158.

Laruelle M (2000). Imaging synaptic neurotransmission with in vivo binding competition techniques: a critical review. *J Cereb Blood Flow Metab* **20**: 423–451.

Leyton M, aan het Rot M, Booij L, Baker GB, Young SN, Benkelfat C (2007). Mood-elevating effects of d-amphetamine and incentive salience: the effect of acute dopamine precursor depletion. *J Psychiatry Neurosci* **32**: 129–136.

Logan GD, Cowan WB, Davis KA (1984). On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform* **10**: 276–291.

Lou HC, Rosa P, Pryds O, Karrebaek H, Lunding J, Cumming P *et al* (2004). ADHD: increased dopamine receptor availability linked to attention deficit and low neonatal cerebral blood flow. *Dev Med Child Neurol* **46**: 179–183.

Martinez D, Slifstein M, Broft A, Mawlawi O, Hwang DR, Huang Y *et al* (2003). Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. *J Cereb Blood Flow Metab* **23**: 285–300.

Munro CA, McCaul ME, Wong DF, Oswald LM, Zhou Y, Brasic J *et al* (2006). Sex differences in striatal dopamine release in healthy adults. *Biol Psychiatry* **59**: 966–974.

Nigg JT (2005). Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: the sate of the field and salient challenges for the coming decade. *Biol Psychiatry* **57**: 1424.

Pilgrim BM, Meyers JE, Bayless J, Whetstone MM (1999). Validity of the Ward seven-subtest WAIS-III short form in a neuropsychological population. *Appl Neuropsychol* **6**: 243–246.

Pohjalainen T, Rinne JO, Någren K, Syvälahti E, Hietala J (1998). Sex differences in the striatal dopamine D2 receptor binding characteristics in vivo. *Am J Psychiatry* **155**: 768–773.

Reynolds CR, Willson VL, Clark PL (1983). A four-test short-form of the WAIS-R for clinical screening. *Clin Neuropsychol* **5**: 111–116.

Riccardi P, Zald D, Li R, Park S, Ansari MS, Dawant B *et al* (2006). Sex differences in amphetamine-induced displacement of [18F]fallypride in striatal and extrastriatal regions: a PET study. *Am J Psychiatry* **163**: 1639–1641.

Rosa-Neto P, Lou HC, Cumming P, Pryds O, Karrebaek H, Lunding J *et al* (2005). Methylphenidate-evoked changes in striatal dopamine correlate with inattention and impulsivity in adolescents with attention deficit hyperactivity disorder. *Neuroimage* **25**: 868.

Sled JG, Zijdenbos AP, Evans AC (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging* **17**: 87–97.

Sontag TA, Tucha O, Walitza S, Lange KW (2010). Animal models of attention deficit/hyperactivity disorder (ADHD): a critical review. *Atten Defic Hyperact Disord* **2**: 1–20.

Spencer T, Biederman J, Madras B, Faraone S, Dougherty D, Bonab A *et al* (2005). In vivo neuroreceptor imaging in attention-deficit/hyperactivity disorder: a focus on the dopamine transporter. *Biol Psychiatry* **57**: 1293–1300.

Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S (1996). Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *J Am Acad Child Adoles Psychiatry* **35**: 409–432.

Spencer TJ, Biederman J, Faraone SV, Madras BK, Bonab AA, Dougherty DD *et al* (2013). Functional genomics of attention-deficit/hyperactivity disorder (ADHD) risk alleles on dopamine transporter binding in ADHD and healthy control subjects. *Biol Psychiatry* **74**: 84–89.

Tziortzi AC, Haber SN, Searle GE, Tsoumpas C, Long CJ, Shotbolt P *et al* (2013). Connectivity-based functional analysis of dopamine release in the striatum using diffusion-weighted MRI and positron emission tomography. *Cereb Cortex* e-pub ahead of print, 2 January 2013 (doi:10.1093/cercor/bhs397).

Volkow ND, Wang G-J, Newcorn J, Fowler JS, Telang F, Solanto MV *et al* (2007a). Brain dopamine transporter levels in treatment and drug naïve adults with ADHD. *Neuroimage* **34**: 1182.

Volkow ND, Wang G-J, Newcorn J, Telang F, Solanto MV, Fowler JS *et al* (2007b). Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* **64**: 932–940.

Volkow ND, Wang GJ, Fowler JS, Ding YS (2005). Imaging the effects of methylphenidate on brain dopamine: new model on its therapeutic actions for attention-deficit/hyperactivity disorder. *Biol Psychiatry* **57**: 1410–1415.

Volkow ND, Wang GJ, Kollins SH, Wigal TL, Newcorn JH, Telang F *et al* (2009). Evaluating dopamine reward pathway in ADHD: clinical implications. *JAMA* **302**: 1084–1091.

Worsley KJ, Marrett S, Neelin P, Vandal AC, Friston KJ, Evans AC (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Hum Brain Mapp* **4**: 58–73.

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