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Reward modulation of cognitive function in adult attention-deficit/hyperactivity disorder: a pilot study on the role of striatal dopamine

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Attention-deficit/hyperactivity disorder (ADHD) is accompanied by impairments in cognitive control, such as task-switching deficits. We investigated whether such problems, and their remediation by medication, reflect abnormal reward motivation and associated striatal dopamine transmission in ADHD. We used functional genetic neuroimaging to assess the effects of dopaminergic medication and reward motivation on task-switching and striatal BOLD signal in 23 adults with ADHD, ON and OFF methylphenidate, and 26 healthy controls. Critically, we took into account interindividual variability in striatal dopamine by exploiting a common genetic polymorphism (3′-UTR VNTR) in the DAT1 gene coding for the dopamine transporter. The results showed a highly significant group by genotype interaction in the striatum. This was because a subgroup of patients with ADHD showed markedly exaggerated effects of reward on the striatal BOLD signal during task-switching when they were OFF their dopaminergic medication. Specifically, patients carrying the 9R allele showed a greater striatal signal than healthy controls carrying this allele, whereas no effect of diagnosis was observed in 10R homozygotes. Aberrant striatal responses were normalized when 9R-carrying patients with ADHD were ON medication. These pilot data indicate an important role for aberrant reward motivation, striatal dopamine and interindividual genetic differences in cognitive processes in adult ADHD. 

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Keywords: attention-deficit/hyperactivity disorder, cognition, DAT1 genotype, dopamine, functional magnetic resonance imaging, human, methylphenidate, reward, striatum, task-switching

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\textbf{Introduction}

Attention-deficit/hyperactivity disorder (ADHD) is characterized by symptoms of inattention, impulsivity and/or hyperactivity (American Psychiatric Association, 1994, 2013). Although originally considered a childhood disorder, ADHD persists into adulthood in many cases, and affects between 2.5 and 4.9% of the adult population (Kooij et al., 2005; Kessler et al., 2006; Polanczyk et al., 2007; Simon et al., 2009). A first-line treatment option for ADHD is prescription of psychostimulant medication, primarily the dopamine and noradrenaline transporter blocker methylphenidate.

ADHD is associated with a wide range of cognitive control deficits that span the domains of attention, response inhibition, working memory and task-switching (Barkley, 1997; Bush et al., 1999). Such cognitive control deficits have been attributed most commonly (albeit not exclusively; see Cortese et al., 2012) to (dorsal) prefrontal cortex dysfunction (Dickstein et al., 2006; Cubillo et al., 2010; Dibbets et al., 2010; McCarthy et al., 2014). Accordingly, effects of methylphenidate on cognitive control deficits in ADHD are considered to reflect action (i.e. increasing synaptic levels of dopamine and noradrenaline) in the prefrontal cortex (Aron et al., 2003; Berridge et al., 2006; Schmeichel et al., 2013; for a review, see Arnsten and Li, 2005). In addition to cognitive control deficits, ADHD is accompanied by processing deficits in the domains of reward and motivation (Sergeant et al., 2003; Sonuga-Barke, 2003; Scheres et al., 2007; Furukawa et al., 2014). Unlike the cognitive control deficits, these reward-related deficits are often attributed to changes in the ventral striatum (Ströhle et al., 2008; Plichta et al., 2009; Hoogman et al., 2011, 2013; Carmona et al., 2012; Volkow et al., 2012; Plichta and Scheres, 2014), as is the modulation of reward-related processing by methylphenidate (Dodds et al., 2008). Indeed, besides acting on noradrenaline transporters, methylphenidate...
acts by blocking dopamine transporters (DAT), which are more abundant in the striatum than in the prefrontal cortex (Volkow et al., 1995; Ciliax et al., 1999).

The observation that both cognitive control deficits and reward-related deficits contribute towards ADHD concurs with the dual pathway model of ADHD, according to which two subtypes of ADHD exist with different developmental pathways, underpinned by different neural circuits and modulated by different branches of the dopamine system (Sonuga-Barke, 2002, 2003, 2005; for more recent models, see Durston et al., 2011; de Zeeuw et al., 2012). More specifically, disturbances in the executive mesocortical dopamine circuit, encompassing the dorsal striatum, dorsomedial thalamus and dorsolateral prefrontal cortex, underlie cognitive deficits in ADHD, whereas motivational deficits are grounded in disturbances in the mesolimbic reward circuit, including the ventral striatum and the orbitofrontal cortex. Here, we approach the issue from a different angle by asking whether cognitive task-related processing deficits and their remediation by methylphenidate reflect indirect modulation of motivation and reward-related processing in the striatum rather than direct modulation of prefrontal processing. This question is grounded in current neuroanatomical and neurochemical models that emphasize a hierarchical arrangement of spiralizing striatongrisestral loops, allowing directional interaction between motivational and cognitive circuits (Haber et al., 2000; Haber, 2003; Ikeda et al., 2013). Furthermore, it concurs generally with a large body of work showing that striatal dopamine is important not just for motor control but also for cognitive functioning (e.g. Cools et al., 1984). It also follows directly from work showing that methylphenidate-induced changes in striatal dopamine release can contribute towards cognitive (attentional) symptoms in ADHD (Glowl and Glow, 1979; Volkow et al., 2012). The hypothesis also concurs with observations that cognitive deficits in children with ADHD can be remediated by increases in motivation (Konrad et al., 2000; Slusarek et al., 2001; Uebel et al., 2010), although inconsistent findings have also been reported (Oosterlaan and Sergeant, 1998; Desman et al., 2008; Shanahan et al., 2008; Karulunas and Huang-Pollock, 2011). None of these studies, however, speak to the neural mechanisms of such motivational effects and their modulation by methylphenidate.

Here, we aimed to assess whether cognitive task-related processing deficits in adult ADHD can be a function of reward-related striatal functioning using functional MRI (fMRI). To index reward effects on cognitive task-related processing, we used a rewarded task-switching paradigm that we established previously to be particularly sensitive to changes in striatal dopamine transmission (Aarts et al., 2010, 2011, 2012, 2014a, 2014b).

One major challenge for studies aiming to isolate dopaminergic drug effects is that such dopaminergic drug effects vary considerably across different individuals as a function of (genetically determined) baseline levels of dopamine (Verheij and Cools, 2008; Cools and D’Esposito, 2011; van Holstein et al., 2011). Previous work suggests the possibility that the effects of methylphenidate emerge only when taking into account such interindividual differences (Clatworthy et al., 2009), for example by exploiting known common polymorphisms in dopamine genes. Here, we stratified our sample by interindividual variation in the 40-bp variable number of tandem repeats (VNTR) polymorphism in the 3’ untranslated region (3’-UTR) of the DAT gene (DAT1, SLC6A3). This is based on several lines of evidence, suggesting an important role for the DAT in the pathophysiology of ADHD. The DAT is the main mechanism responsible for clearing extracellular dopamine in the striatum. Thus, genetic variation of the DAT1 gene might lead to interindividual variation in the availability of DATs and subsequently in dopamine levels. Although it has remained inconclusive in the literature as to which allele leads to decreased DAT availability (Costa et al., 2011; Faraone et al., 2014), genetic fMRI studies have consistently shown the 9-repeat (9R) allele to be associated with increased striatal reward responses (Dreher et al., 2009; Forbes et al., 2009; Aarts et al., 2010). Furthermore, methylphenidate exerts its action in the striatum by blocking the DAT (Volkow et al., 1998, 2002); mice that lack the DAT (i.e. DAT1 knockout mice) show ADHD-like behaviour (Giros et al., 1996; Gainetdinov et al., 1999), and several dopaminergic genes, including the DAT1 genotype, have been implicated in ADHD (Faraone et al., 2005; Brookes et al., 2008; Franke et al., 2008; for a review, see Durston et al., 2009; Gizer et al., 2009; Franke et al., 2010).

In summary, in this pilot study, we tested the hypothesis that the effects of reward motivation on task-switching and striatal BOLD signal vary as a function of the DAT1 genotype in adult patients with ADHD, when they were OFF relative to ON their methylphenidate regimen, compared with healthy controls.

Methods

Participants

We present data from 23 patients with ADHD (mean±SE age 35.74±2.36; 14 men) and 26 healthy control participants (mean±SE age 38.08±2.00; 11 men). Patients visited our centre on two occasions: once after intake of methylphenidate and once after withdrawal from methylphenidate. Healthy controls were also tested on two occasions, without any methylphenidate (see the Procedure section).

Initially, we recruited 57 participants (29 patients with ADHD and 28 healthy controls) from an ongoing study on ADHD and genetics, IMpACT-NL (Hoogman et al., 2011, 2013; Onnink et al., 2014; http://www.impactADHDgenomics.com), in which they were tested extensively, genotyped...
and diagnosed (Table 1). Patients were included if they fulfilled the DSM-IV-TR criteria for ADHD in childhood as well as adulthood. All participants were assessed using the Diagnostic Interview for Adult ADHD (Kooij and Francken, 2007). The Structured Clinical Interviews for DSM-IV (SCID-I and SCID-II) were administered. Assessments were carried out by trained professionals (psychiatrists or psychologists). In addition, a quantitative neuropsychological assessment section). Hence, three patients using methylphenidate were prescribed an equivalent sustained dose (mg) before arriving at the centre. All patients had a current prescription of methylphenidate [either immediate-release (Ritalin; N = 5; mean ± SD 44 ± 22.74 mg/day), or sustained release (Concerta; N = 18; mean ± SD 48.5 ± 21.19 mg/day), and three of them occasionally took Ritalin in addition to Concerta]. All participants were native speakers of Dutch. Participants were compensated for participation and provided written informed consent in a manner approved by the local ethics committee on research involving human participants (CMO Arnhem-Nijmegen 2009/058, NL27180.091.09).

### Procedure
All patients were asked to abstain from alcohol on the day of testing and from nicotine and caffeine at least 1 h before arriving at the centre. The patients were tested once OFF (i.e. withdrawn from Ritalin for 24 h and from Concerta for 48 h before testing) and once ON methylphenidate (i.e. after intake of (mean ± SD) 13.15 ± 5.55 mg of Ritalin, the equivalent of (mean ± SD) 0.16 ± 0.05 mg/kg body weight of Ritalin, half an hour before arriving at the centre). Patients using sustained-release methylphenidate were prescribed an equivalent dose [instant dose (mg) = sustained dose (mg) × 0.278] of immediate-release methylphenidate by the psychiatrist (J.B.) for 1 day (three doses a day). Three patients using additional medication (one antihistamine and two SSRI's) were asked to take the same dose on both sessions. The order of the ON and OFF session was approximately counterbalanced across participants (Table 2). The healthy control group did not take methylphenidate, but was nevertheless tested twice to rule out order effects. Control data were averaged across the two sessions.

### Table 1 Demographics, impulsivity and diagnostic interview for diagnosis × DAT1 group

<table>
<thead>
<tr>
<th>Demographics</th>
<th>ADHD (N = 23)</th>
<th>HC (N = 26)</th>
<th>Univariate GLM/χ²/Fisher’s exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>9R carriers</td>
<td>10R/10R</td>
<td>9R carriers</td>
<td>10R/10R</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Age [mean (SE)]</td>
<td>36.25 (3.78)</td>
<td>35.18 (2.91)</td>
<td>41.1 (2.79)</td>
</tr>
<tr>
<td>IQ (WAIS III) [mean (SE)]</td>
<td>11.58 (0.66)</td>
<td>12.72 (0.54)</td>
<td>12 (0.91)</td>
</tr>
<tr>
<td>Sex: males (N/N%)</td>
<td>7/58</td>
<td>7/64</td>
<td>4/40</td>
</tr>
<tr>
<td>Education level [mean (SE)]</td>
<td>4.75 (0.22)</td>
<td>5.00 (0.30)</td>
<td>5.10 (0.23)</td>
</tr>
<tr>
<td>Handicapped: right handed (N/N%)</td>
<td>12/100</td>
<td>9/82</td>
<td>8/80</td>
</tr>
<tr>
<td>Smokers (N/N%)</td>
<td>6/50</td>
<td>6/55</td>
<td>3/30</td>
</tr>
<tr>
<td>BIS-11 impulsivity scoreb</td>
<td>74.79 (2.74)</td>
<td>71.09 (4.58)</td>
<td>58.9 (3.00)</td>
</tr>
<tr>
<td>SCID-Axis I current comorbiditiesa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive</td>
<td>0/10</td>
<td>1/11</td>
<td>0/9</td>
</tr>
<tr>
<td>Dysthmic</td>
<td>0/10</td>
<td>1/11</td>
<td>0/9</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1/10</td>
<td>1/11</td>
<td>0/9</td>
</tr>
<tr>
<td>Borderline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisocial</td>
<td>1/10</td>
<td>0/10</td>
<td>0/9</td>
</tr>
<tr>
<td>Obsessive–compulsive</td>
<td>2/10</td>
<td>0/10</td>
<td>0/9</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder; GLM, general linear model; HC, healthy controls.

aAdministered during the IMPACT-NL study; values indicate the number of participants fulfilling the criterion/total number of participants in which the SCID-I or SCID-II was administered; 10R/10R = 10R homozygotes.

bUnivariate GLM.

cFisher’s exact test.

dχ²-test.
Sessions were separated by at least 1 week and both sessions took place at approximately the same time of day. With the exception of medication state, the procedure was identical for both groups and both sessions.

**Cognitive task with reward manipulation**

Participants were scanned while performing an established precued task-switching paradigm (Fig. 1) with a reward manipulation (Aarts et al., 2010, 2012, 2014a; van Holstein et al., 2011). The paradigm started ∼60 min after arrival (mean ± SD 91.8 ± 16.1 min after drug intake). The task was programmed and presented using the Presentation (R) software (Version 13, www.neurobs.com).

Participants had to respond to incongruent arrow–word combinations, either by responding to the direction of the arrow or the direction indicated by the word (‘left’ or ‘right’). A task-cue appeared 400 ms before the target indicating the task (arrow or word) that the participant had to perform on the current trial. Relative to the previous trial, the task either changed unpredictably (from arrow to word or vice versa; switch trial) or remained the same (repeat trial). The critical measure of interest, the switch cost, was calculated by subtracting performance on repeat trials from that on switch trials. In addition, we manipulated reward motivation, to assess the effect of reward on task-switching, by presenting high and low reward cues before the task cue. The reward-cue informed the participants whether 1 cent (low reward) or 15 cents (high reward) could be earned with a correct and sufficiently quick response. Immediately after the response, feedback was provided (e.g. ‘correct! 15 cents’). There was a variable interval of 2–6 s between the reward-cue and the task-cues. Participants used their right index and middle fingers to respond on a button box.

On both sessions, the task was practiced twice outside the scanner and once inside the scanner. The first practice block contained 24 trials with the task cue, target and feedback (correct/incorrect). As soon as participants succeeded in completing this block with less than five errors, the second practice block of 24 trials was performed, in which the reward cues were included. The third and final practice block was performed during the acquisition of the anatomical scan. The mean response times (RT) of the correct trials per trial-type (arrow-repeat, arrow-switch, word-repeat, word-switch trials) in this third practice block were used as the response deadline in the main experiment. This ensured equal difficulty across participants and sessions.

The main experiment consisted of 160 trials and lasted ∼35 min with a 30 s break after every 32 trials. In the break, the amount of money that the participant had earned thus far was displayed on the screen and participants were told in advance that the total amount would be added to their financial compensation as a bonus.

**Neuropsychological assessment**

During the first session, participants completed the Barratt Impulsiveness Scale (BIS-11a; Patton et al., 1995), a self-report trait measure of impulsivity. At the beginning of both sessions, participants completed the Bond and Lader (1974) visual analogue scale for a comparison of mood between sessions (16 moods rated on a scale of 0–100, resulting in three mood categories) and an ADHD symptom rating scale (Kooij et al., 2005) to assess self-reported ADHD symptoms. Motor speed was measured using the box completion task (Salthouse, 1996), sustained attention with the digit vigilance or the number cancellation task (Lewis and Kupke, 1977) and verbal fluency with the begin letters D, A and T (Spreen and Benton, 1977).

**Genotyping**

DNA was isolated from EDTA blood samples. Genotyping of the 40-bp VNTR in the 3′-UTR of SLC6A3/DAT1 was carried out as described previously (Hoogman et al., 2013) at the department of Human Genetics of the Radboud University Medical Centre. In line with previous studies reporting the effect of this variant, we established a group of carriers of the 9R allele (i.e. the risk factor for adult ADHD) and a group homozygous for the 10R allele (Colzato et al., 2010; Rokem et al., 2012) (Table 1). We preselected our participants from a previous sample (Hoogman et al., 2013) to homogenize sample numbers per group (diagnosis × genotype) as much as possible. Therefore, Hardy–Weinberg equilibrium was not considered.

In the ADHD group, 12 individuals were carriers of the 9R allele and 11 individuals were homozygous for the 10R allele (Table 1). In the healthy control group, 10 individuals were carriers of the 9R allele and 16 individuals were homozygous for the 10R allele. We performed a power calculation in G*Power (http://www.gpower.hhu.de) on the basis of the effect sizes obtained in an independent dataset using a similar rewarded task-switching paradigm and the same VNTR in the DAT1 gene in
healthy volunteers (Aarts et al., 2010). The power calculation showed that we would need at least eight participants per group (four groups: genotype × diagnosis) to obtain significant effects of genotype on striatal BOLD responses during the rewarded task-switching [effect size = 0.78; α = 0.05; power (1 − β) = 0.8]. Currently, our smallest group includes 10 participants.

Functional magnetic resonance imaging data acquisition
Participants were scanned in a 3T MR scanner (Magnetom TrioTim; Siemens Medical Systems, Erlangen, Germany) using an eight-channel head coil. T2*-weighted images were acquired with a gradient echo planar imaging (EPI) sequence (30 axial slices, repetition time = 2020 ms, echo time = 30 ms, voxel size = 3.5 × 3.5 × 3 mm, field of view = 224 mm, flip angle = 80°). All functional images were acquired in a single run. Stimuli were presented on a computer display projected onto a mirror attached to the head coil. The first four volumes were discarded to allow for T1 equilibrium. Before the acquisition of the functional images, a high-resolution T1-weighted MP-RAGE anatomical scan was obtained (192 sagittal slices, repetition time = 2300 ms, echo time = 3.03 ms, voxel size = 1 × 1 × 1 mm, field of view = 256 mm).

Functional magnetic resonance imaging statistical analyses
Data were preprocessed and analysed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK). First, functional EPI images were spatially realigned and corrected for differences in slice acquisition timing. Structural and functional data were co-registered and normalized to a standard anatomical space (Montreal Neurological Institute) using a unified segmentation procedure (Ashburner and Friston, 2005). The normalized images were smoothed with an isotropic 8-mm full-width-at-half-maximum Gaussian kernel. The preprocessed fMRI time series were analysed at the first level using an event-related approach in the context of the general linear model (GLM). Our statistical model on the first (participant-specific) level considered the factors reward (high, low), task (arrow, word), task-switching (repeat, switch) and feedback (correct-1 cent, correct-15 cents, error-0 cents, too late-0 cents). This resulted in 21 regressors of interest: two regressors for reward-cues, eight regressors for targets (reward × task × task-switching) and four regressors for feedback. All regressors of interest were modelled as a stick function (duration = 0) convolved with a canonical haemodynamic response function. In addition, breaks (duration of 30 s), six motion parameters and their derivatives were modelled as regressors of noninterest. Finally, we included three regressors of noninterest to account for movement-induced intensity changes using the mean time series from the segmented white matter, cerebral spinal fluid and out-of-brain signals (Majdandžić et al., 2007; Verhagen et al., 2008). High-pass filtering (128 s) was applied to the time series of the functional images to remove low-frequency drifts.
At the second level, the reward × task-switching contrast images from the first level were used in three GLMs to assess the effects of reward during task-switching: two models to assess the interaction with the DAT1 genotype and diagnosis (HC vs. ADHD OFF and ADHD ON vs. HC) and one model to test the interaction with the DAT1 genotype and medication (ADHD ON vs. ADHD OFF). Statistical inference \( P < 0.05 \) was performed at the cluster level, correcting for multiple comparisons over the search volume (the whole brain). The intensity threshold necessary to determine the cluster-level threshold was set at \( P < 0.001 \), uncorrected. For each effect, we report the \( t \)-values at the voxel level, the whole-brain corrected \( P \)-values for the cluster \( (P_{\text{cluster}}) \) and the size of the cluster \( (k) \). In addition, supplementary exploratory analyses were carried out, for which the uncorrected threshold was set at \( P < 0.001 \), uncorrected. For each effect, we report the \( t \)-values and \( P \)-values \( (P_{\text{uncorr}}) \) at the voxel level.

**Behavioural statistical analyses**

We excluded the first trial of each block (five trials in total) because these cannot be considered as either repeat or switch trials. All trials to which participants responded (i.e. all trials except response omissions) were included in the analysis, even if the response was too late for a reward to be obtained. For the analysis of the mean RTs, we excluded responses faster than 200 ms. For each participant, we calculated the mean RTs for all the correct responses and the proportion of errors for each of the four conditions, that is reward (high–low) × switching (switch–repeat). To maximize homogeneity of variances between groups and to ensure normal distribution of the data, a natural logarithm (LN) transformation was applied to the mean RTs. The mean proportions of incorrect responses were transformed using the following formula: \( 2 \times \arcsin \sqrt{x} \) (Sheskin 2004). Levene’s tests of homogeneity of variances and Shapiro–Wilk tests of normality showed that this transformation was successful in improving variance between groups and the distribution of the data.

Proportions or errors and mean RTs were analysed using a repeated-measures GLM with the within-participant factors reward (high, low), switching (repeat, switch), the between-participant factor DAT1 genotype (9R carriers, 10R homozygotes) and either the between-participant factor diagnosis (ADHD or healthy control) or the within-participant factor medication (ON, OFF). Effects were considered significant when \( P \)-values were less than 0.05.

**Statistical analysis of mood measures and neuropsychological tests**

Mood values were calculated for each session and reduced to three factors: contentedness, alertness and calmness, according to Bond and Lader (1974). Neuropsychological and demographic differences between groups or medication states and their interaction with the DAT1 genotype were tested using SPSS (IBM Corp. IBM SPSS Statistics for Windows, Version 21.0. Armonk, New York, USA) with univariate or repeated measures GLMs or their nonparametric counterparts (Wilcoxon signed rank or Mann–Whitney \( U \)-tests, respectively; Table 3). Nonparametric DAT1 genotype × medication interactions were assessed using a Mann–Whitney \( U \)-test of the difference between the score OFF and ON medication. Nonparametric DAT1 genotype × diagnosis effects were assessed using the Kruskal–Wallis test (Table 3). An effect was considered significant when \( P \) less than 0.05.

**Results**

**Functional magnetic resonance imaging effects**

**Main task effects**

Across groups and sessions, the cue indicating a high reward, compared with the cue indicating a low reward, elicited a robust response in regions in the striatum, the frontal cortex and the occipital cortex (Table 4). There was also a strong main effect of task-switching during the targets, as evidenced by a greater response in the frontal and parietal regions on switch compared with repeat trials (Table 4).

**ADHD OFF versus healthy controls**

The BOLD signal in the dorsal striatum varied highly significantly as a function of ADHD diagnosis (patients with ADHD OFF their medication versus healthy controls), DAT1 genotype (9R carriers vs. 10R homozygotes) and task (reward × task-switching) \( (x, y, z = -20, 4, 16; t = 4.92; P_{\text{cluster}} < 0.001; k = 324; \text{Fig. 2a-I}) \). This finding concurs with our hypothesis that the effect of reward on task-switching in the striatum would vary as a function of the DAT1 genotype and diagnosis (healthy controls compared with patients with ADHD). The striatal effect was observed because of a greater task-related signal in patients with ADHD carrying the 9R allele compared with 9R carriers in the healthy control group (reward × task-switching × diagnosis in 9R carriers: \( x, y, z = -18, 2, 16; t = 4.90; P_{\text{cluster}} = 0.001; k = 333 \)) and greater task-related signal in the 9R-carrying patients with ADHD compared with the 10R homozygous patients with ADHD (reward × task-switching × DAT1 in patients with ADHD OFF medication: \( x, y, z = -12, -4, 6; t = 4.96; P_{\text{cluster}} = 0.002; k = 295 \)). To illustrate this effect, we extracted the beta values from the cluster in the left dorsal striatum shown in Fig. 2a-I and plotted the results in Fig. 2b. The only other significant neural difference between the ADHD group OFF medication and the healthy control group was observed in the posterior cingulate cortex (reward × task-switching × diagnosis × DAT1: \( x, y, z = -6, -12, 46; t = 5.56; P_{\text{cluster}} < 0.001; k = 338 \)).

**ADHD ON versus healthy controls and ADHD OFF versus ADHD ON**

There was no longer an effect of diagnosis when comparing patients with ADHD ON medication with healthy controls, suggesting that the aberrant striatal response...
Table 3  Mood and neuropsychological assessment

<table>
<thead>
<tr>
<th></th>
<th>9R carriers</th>
<th>10R/10R</th>
<th>9R carriers</th>
<th>10R/10R</th>
<th>9R carriers</th>
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<th>10R/10R</th>
<th>9R carriers</th>
<th>10R/10R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bond and Lader mood scales</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contendedness</td>
<td>67.42 (4.58)</td>
<td>66.91 (7.15)</td>
<td>76.86 (4.83)</td>
<td>76.82 (4.63)</td>
<td>84.69 (3.50)</td>
<td>77.05 (2.82)</td>
<td>F(1,44) = 8.78; P = 0.005</td>
<td>F = 22.74; P = 0.001</td>
<td>F = 1.42; P = 0.05</td>
<td>F = 22.73; P = 0.001</td>
</tr>
<tr>
<td>Alertness</td>
<td>49.36 (4.19)</td>
<td>57.15 (5.90)</td>
<td>71.79 (3.99)</td>
<td>69.38 (4.66)</td>
<td>78.52 (5.15)</td>
<td>69.74 (2.62)</td>
<td>F = 1.42; P = 0.05</td>
<td>F = 22.73; P = 0.001</td>
<td>F = 22.73; P = 0.001</td>
<td>F = 22.73; P = 0.001</td>
</tr>
<tr>
<td>Calmness</td>
<td>59.73 (4.44)</td>
<td>49.46 (7.75)</td>
<td>58.91 (6.07)</td>
<td>62.00 (6.91)</td>
<td>83.40 (4.56)</td>
<td>74.72 (3.52)</td>
<td>F = 1.42; P = 0.05</td>
<td>F = 22.73; P = 0.001</td>
<td>F = 22.73; P = 0.001</td>
<td>F = 22.73; P = 0.001</td>
</tr>
</tbody>
</table>

Neuropsychological assessment

| Motor speed (RT, s: mean (SE)) | 54.09 (2.60) | 54.27 (3.44) | 55.18 (3.32) | 53.36 (2.34) | 69.67 (8.51) | 64.31 (6.05) | MWU = 356; F = 1 M ≤ 0.05 | MWU = 122; F = 0.05 | MWU = 356; F = 0.05 | MWU = 356; F = 0.05 |
| Vigilance (RT, s: mean (SE))   | 219.64 (13.65) | 204.46 (10.39) | 222.00 (10.36) | 199.73 (9.79) | 204.67 (8.41) | 210.09 (9.23) | F = 1.42; P = 0.05 | F = 22.73; P = 0.001 | F = 22.73; P = 0.001 | F = 22.73; P = 0.001 |
| Vigilance (misses)             | 5.09 (1.42) | 5.00 (1.05) | 2.46 (0.64) | 3.82 (1.12) | 2.72 (1.12) | 2.78 (0.61) | F = 1.42; P = 0.05 | F = 22.73; P = 0.001 | F = 22.73; P = 0.001 | F = 22.73; P = 0.001 |
| Verbal fluency (number of words) | 37.55 (3.82) | 42.27 (3.21) | 38.18 (3.48) | 43.36 (3.48) | 46.89 (3.66) | 42.16 (2.11) | F = 1.42; P = 0.05 | F = 22.73; P = 0.001 | F = 22.73; P = 0.001 | F = 22.73; P = 0.001 |

ADHD, attention-deficit/hyperactivity disorder; GLM, general linear model; HC, healthy controls; KW, Kruskal–Wallis test; MPH, methylphenidate; MWU, Mann–Whitney U test; 10R/10R, 10R homozygotes; Wc, Wilcoxon paired signed rank test.

### Attention-deficit/hyperactivity disorder OFF versus healthy controls

There were significant differences in RT between the ADHD group OFF medication and healthy controls. Switch costs in error rates were significantly greater in the healthy control group compared to the ADHD group OFF medication. Task-switching × diagnosis: F(1,45) = 4.44; P < 0.02. The critical effect of reward on switching was present in the ADHD group OFF medication and healthy controls, but not in the ADHD group ON medication. This effect depended on the reward type (i.e., low-routed reward trials relative to high-routed reward trials). The effect of task-switching × reward type × diagnosis: F(1,45) = 5.56; P < 0.05 [1]. In addition, participants made more errors on switch than repeat trials. This effect of task-switching × reward type × diagnosis: F(1,45) = 24.91; P < 0.001. All tasks (main effect of task-switching) were performed significantly better in the ADHD group OFF medication and healthy controls.

### Attention-deficit/hyperactivity disorder ON versus healthy controls

There were no significant differences in RT between the ADHD group ON medication and healthy controls. The critical effect of reward on task-switching × diagnosis: F(1,45) = 4.44; P < 0.02. The effect of task-switching × reward type × diagnosis: F(1,45) = 5.56; P < 0.05 [1]. In addition, participants made more errors on switch than repeat trials. This effect of task-switching × reward type × diagnosis: F(1,45) = 24.91; P < 0.001. All tasks (main effect of task-switching) were performed significantly better in the ADHD group OFF medication and healthy controls.

### Behavioural effects

Participants responded more quickly after a high than a low reward (i.e., low-routed reward trials relative to high-routed reward trials). This effect depended on the reward type (i.e., low-routed reward trials relative to high-routed reward trials). The effect of task-switching × reward type × diagnosis: F(1,45) = 5.56; P < 0.05 [1]. In addition, participants made more errors on switch than repeat trials. This effect of task-switching × reward type × diagnosis: F(1,45) = 24.91; P < 0.001. All tasks (main effect of task-switching) were performed significantly better in the ADHD group OFF medication and healthy controls.

### Table 5

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>DAT1</th>
<th>MPH × DAT1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD OFF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD ON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy controls</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4 BOLD maxima across all participants

<table>
<thead>
<tr>
<th>Label</th>
<th>Brodmann</th>
<th>Side (L/R)</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Cluster size (number of voxels)</th>
<th>Significance (cluster level)</th>
<th>t-value (peak)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main effect reward: high &gt; low reward</strong></td>
<td>Superior parietal lobe (B7)*</td>
<td>7</td>
<td>L</td>
<td>−16</td>
<td>−68</td>
<td>56</td>
<td>3126</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Insular cortex (B13)* extending into the striatum, pallidum and thalamus</td>
<td>13</td>
<td>L + R</td>
<td>30</td>
<td>26</td>
<td>0</td>
<td>3468</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Cingulate gyrus (B32)*</td>
<td>32</td>
<td>L + R</td>
<td>−4</td>
<td>12</td>
<td>40</td>
<td>3171</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Occipital lobe (B16)*</td>
<td>16</td>
<td>L</td>
<td>−26</td>
<td>−94</td>
<td>12</td>
<td>352</td>
<td>P &lt; 0.002</td>
</tr>
<tr>
<td></td>
<td>Cingulate gyrus (B23)*</td>
<td>23</td>
<td>L + R</td>
<td>−4</td>
<td>−30</td>
<td>28</td>
<td>283</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td><strong>Main effect reward: low &gt; high reward</strong></td>
<td>Inferior frontal gyrus</td>
<td>10</td>
<td>R</td>
<td>48</td>
<td>46</td>
<td>8</td>
<td>368</td>
<td>P &lt; 0.002</td>
</tr>
<tr>
<td></td>
<td>Posterior cingulate Precuneus</td>
<td>31</td>
<td>L + R</td>
<td>−6</td>
<td>−56</td>
<td>20</td>
<td>460</td>
<td>P &lt; 0.001</td>
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<tr>
<td></td>
<td>Superior temporal gyrus</td>
<td>39</td>
<td>R</td>
<td>50</td>
<td>−60</td>
<td>26</td>
<td>248</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Superior frontal gyrus</td>
<td>9</td>
<td>L</td>
<td>12</td>
<td>56</td>
<td>26</td>
<td>228</td>
<td>P &lt; 0.02</td>
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<tr>
<td><strong>Main effect switch: switch &gt; repeat</strong></td>
<td>Precuneus (B7)*</td>
<td>7</td>
<td>L</td>
<td>−24</td>
<td>−66</td>
<td>34</td>
<td>3289</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Inferior frontal gyrus (B9)*</td>
<td>9</td>
<td>L</td>
<td>−48</td>
<td>12</td>
<td>28</td>
<td>1675</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Middle frontal gyrus (B11)*</td>
<td>11</td>
<td>L</td>
<td>−24</td>
<td>48</td>
<td>−10</td>
<td>221</td>
<td>P &lt; 0.018</td>
</tr>
<tr>
<td><strong>Main effect switch: repeat &gt; switch</strong></td>
<td>Superior Temporal gyrus</td>
<td>41</td>
<td>R</td>
<td>56</td>
<td>−28</td>
<td>12</td>
<td>694</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Occipital lobe (cuneus)</td>
<td>19</td>
<td>R</td>
<td>14</td>
<td>−88</td>
<td>34</td>
<td>180</td>
<td>P &lt; 0.004</td>
</tr>
<tr>
<td></td>
<td>Superior temporal gyrus</td>
<td>41</td>
<td>L</td>
<td>−44</td>
<td>−32</td>
<td>14</td>
<td>617</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Main effect of reward anticipation during cues and main effect of task-switching during targets at a whole-brain cluster-level corrected threshold of P < 0.05.

*Also significant after FWE correction at the voxel level (P_FWE < 0.05).

healthy control group as a function of DAT1 genotype [the critical interaction between reward × task-switching × diagnosis × DAT1: error rates F(1,45) = 1.37; P > 0.1; RTs F(1,45) < 1].

**ADHD OFF versus ADHD ON**

There was no significant difference between the two medication sessions in RTs or error rates. The critical DAT1 by medication by reward task-switching interaction only trended towards significance for RTs [reward × task-switching × medication × DAT1: F(1,21) = 3.23; P = 0.087; Fig. 2c], and was absent for error rates [reward × task-switching × medication × DAT1: F(1,21) < 1].

In summary, unlike the brain data, the behavioural data did not show any significant effects of diagnosis or medication status and/or genotype on how anticipated reward influences task-switching performance (i.e. reward × task-switching effects). To assess whether the increased BOLD signal in the striatum of 9R-carrying patients with ADHD was accompanied, if anything, by behavioural impairment or improvement, we examined the numerical (marginal trend) pattern in RTs (Fig. 2c). Disentangling this marginally significant effect [reward × task-switching × medication × DAT1: F(1,21) = 3.23; P = 0.087] showed that 9R-carrying patients OFF medication tended to show a greater switch cost on high than low reward trials compared with these patients ON their medication [reward × task-switching × medication in 9R carriers: F(1,11) = 4.40; P = 0.06; Fig. 2c]. These data suggest that the increased dorsal striatal responses in patients with ADHD carrying the 9R allele are accompanied, if anything, by a detrimental effect of reward on task-switching that can be remediated by methylphenidate (Fig. 2b and c).

**Demographic and neuropsychological data**

Table 1 summarizes the demographic and neuropsychological data of the patients with ADHD and healthy controls for the two DAT1 genotype groups. There was no difference between patients and healthy controls, or between the 9R-carrying and 10R homozygous group, in terms of age, IQ, sex, handedness, smoking status and level of education (Table 1), nor an interaction between diagnosis and the DAT1 genotype. As expected, the patients with ADHD scored higher on the Barratt Impulsiveness Scale (mean±SE: 73.00±2.58); that is, they were more impulsive than the healthy controls [mean±SE: 59.27±1.54; t(47) = 4.70; P < 0.001]. There were no differences in current SCID Axis I disorders or SCID Axis II personality traits as a function of diagnosis, DAT1 genotype or diagnosis × DAT1 genotype.

Counterbalancing of the ON and OFF sessions within the two DAT1 genotype patient groups was successful: there was no difference between the two DAT1 groups in the number of patients being ON medication during the first session. Furthermore, there were no significant differences in the dose of Ritalin or Concerta between the DAT1 genotype groups, nor in the number of patients usually taking either form of methylphenidate, or in their ADHD subtype (i.e. combined, inattentive or hyperactive/impulsive) (Table 2).

Table 3 summarizes the mood and neuropsychological test scores. Most importantly, there were no interactions between the DAT1 genotype and either medication state
Rewarded task-switching as a function of the DAT1 genotype in patients with attention-deficit/hyperactivity disorder (ADHD) ON and OFF their methylphenidate medication, relative to healthy controls (HC). (a-I) Increased dorsal striatal responses during rewarded task-switching for patients with ADHD OFF methylphenidate relative to healthy controls, as a function of the DAT1 genotype; (a-II) Increased dorsal striatal responses during rewarded task-switching for patients with ADHD OFF methylphenidate relative to when ON methylphenidate, as a function of the DAT1 genotype; (b) The β values from the whole-brain cluster-corrected cluster in the left striatum depicted in (a-I), showing the direction of the effect; (c) The response times during rewarded task-switching. Positive values reflect an increased switch cost (i.e., slower on switch than on repeat trials) for high reward relative to low reward trials, that is a detrimental effect of reward on the switch cost. Error bars represent the SE of the difference between high reward (switch-repeat) minus low reward (switch-repeat).
(ON or OFF) or diagnosis on mood measures or on the neuropsychological test scores. However, patients OFF medication were reportedly less content and less alert than healthy controls, and compared with when they were ON medication (Table 3; contentedness: ADHD ON median 83, range 41.6–95.2; ADHD OFF median 67.16, range 23.2–97.6). In addition, healthy controls reported more calmness than the patients, both ON and OFF medication (Table 3). There were no differences in motor speed (box completion task) on the time to complete the vigilance test (number cancellation RT) or in verbal fluency. We did observe a difference between the ADHD group OFF medication and the healthy control group for missed items on the vigilance test, that is the ADHD group OFF medication and the healthy control group (median 2, range 0–13). This difference was no longer present when comparing the ADHD group ON medication with the healthy control group (Table 3).

As expected, methylphenidate ameliorated symptom severity (Table 6) both on attentive and on hyperactive symptoms. We did not observe effects of the DAT1 genotype, nor an interaction between the DAT1 genotype and medication status on symptom severity (Table 6).

**Discussion**

We investigated the effects of reward motivation on task-switching in adult patients with ADHD, ON and OFF methylphenidate, relative to a matching healthy control group. Task-related BOLD responses were assessed as a function of interindividual variability in the DAT1 gene. When OFF medication, adults with ADHD showed greater effects of reward on dorsal striatal BOLD responses during task-switching than healthy controls. Critically, this effect was only observed when taking the DAT1 genotype into account, resulting in a strong genotype-by-diagnosis interaction. Specifically, patients carrying the 9R allele showed exaggerated striatal responses relative to healthy controls carrying the same allele as well as relative to patients homozygous for the 10R allele. These aberrant striatal responses were normalized when patients with ADHD were ON medication, such that they no longer differed from those of controls. In short, the present pilot study shows a dysfunctional influence of reward motivation on task-switching in the dorsal striatum of adult patients with ADHD, but only in those carrying the 9R risk allele. These findings, albeit preliminary because of the small sample size, suggest that abnormal cognitive task-related processing in adult ADHD depends critically on interindividual trait differences in striatal dopamine transmission as well as on the motivational state of the individual patient.

The present results indicate the importance of taking into account interindividual variability, as for example indexed by the DAT1 genotype, when assessing task-related BOLD effects in ADHD. This generally concurs with previous fMRI studies in youth with ADHD, which have found that striatal responses during reward anticipation (Paloyelis et al., 2012), as well as striatal responses during more cognitive tasks, that is Go/No-Go paradigms.

**Table 6** Self-reported symptom severity

<table>
<thead>
<tr>
<th></th>
<th>ADHD ON 9R carriers</th>
<th>ADHD OFF 9R carriers</th>
<th>ADHD ON 10R/10R</th>
<th>ADHD OFF 10R/10R</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom severity</td>
<td>Attentive [mean (SE)]</td>
<td>Hyperactive [mean (SE)]</td>
<td>Drug effect</td>
<td>DAT1 effect</td>
<td>Drug × DAT1</td>
</tr>
<tr>
<td></td>
<td>2.67 (0.66)</td>
<td>3.18 (1.11)</td>
<td>7.25 (0.46)</td>
<td>5.64 (0.83)</td>
<td>F(22) = 5.92; P &lt; 0.001 NS</td>
</tr>
<tr>
<td></td>
<td>2.67 (0.66)</td>
<td>2.36 (0.76)</td>
<td>5.33 (0.68)</td>
<td>5.09 (0.72)</td>
<td>F(22) = 5.15; P &lt; 0.001 NS</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder; 10R/10R, 10R homozygotes.
(Durston et al., 2008; Bédard et al., 2010), depend on variations in the DAT1 genotype. A recent study in adults with ADHD failed to extend the effect of the DAT1 genotype on striatal reward responses during reward anticipation, observed in youth (Paloyelis et al., 2012), to adult ADHD (Hoogman et al., 2013). In the current sample with ADHD adults, DAT1 effects on reward-related striatal responses did emerge, but only as a function of cognitive task-related processing. This suggests that, in adults with ADHD, the translation of reward information into (effortful) cognitive processing might be more strongly dependent on variability in the DAT1 gene than reward anticipation itself.

Our study shows that patients with ADHD OFF medication show abnormal BOLD responses in the caudate nucleus during rewarded task-switching, an effect that relied on striatal dopamine signalling as indexed by the DAT1 genotype. In accordance, the caudate nucleus – known to be involved in cognitive flexibility (Cools, 1980; Aarts et al., 2011) – is well positioned to incorporate motivational influences from more ventral regions in the striatum through feed-forward dopaminergic projections (Haber et al., 2000; Grahm et al., 2008; Ikeda et al., 2013). The finding is also remarkably consistent with our previous work using genetic fMRI and PET imaging in healthy volunteers, showing that the effects of reward motivation on cognitive control are altered by dopaminergic transmission in the left caudate nucleus (Aarts et al., 2010, 2014b). In ADHD, Volkow et al. (2009) have shown that dopaminergic transmission in reward-related brain regions is associated with symptoms of inattention, and that connectivity between neural reward and attention networks is impaired (Tomasi and Volkow, 2012). Here, we show that cognitive task-related processing deficits in the striatum (i.e. during task-switching) are modulated by motivation as well as the DAT1 genotype in ADHD. Unlike earlier suggestions (Sonuga-Barke, 2002, 2003; de Zeeuw et al., 2012), ADHD might not be accompanied by isolated deficits in either motivational or cognitive/executive processing pathways, but rather by deficits in the integration between these pathways.

The present finding extends to ADHD our previous work in young healthy volunteers showing that the effects of reward motivation on task-switching and associated striatal signal depend on the DAT1 genotype (Aarts et al., 2010; see also van Holstein et al., 2011). Unlike that previous study, however, the present study did not show any DAT1 genotype effects on rewarded task-switching in healthy controls, in neural or behavioural terms. We are surprised at this lack of effect, but believe that it might reflect a difference in the demographics between the current control group, which was matched to the ADHD group, and the groups in our previous studies that primarily included university students. The most obvious difference is in terms of age, with the current control group being older (mean 38.12 years, SD 10.20) than the healthy volunteers in our previous studies (mean 21.58 years, SD 2.06; and mean 22 years, SD 2.32, for Aarts et al., 2010; van Holstein et al., 2011, respectively). Indeed, studies have consistently observed a reduction in dopamine signalling starting in young adulthood (e.g. Volkow et al., 1996; Reeves et al., 2002). Importantly, the increases in striatal BOLD in the 9R-carrying patients OFF medication were, if anything, accompanied by impaired performance (i.e. increased RT switch cost for high vs. low reward trials, relative to when ON medication). These results contrast with our findings in younger 9R-carrying healthy volunteers who showed increased striatal responses as well as better task-switching performance following high versus low reward cues relative to 10R-homozygotes (Aarts et al., 2010). This suggests that the hyperactivation in the dorsal striatum during rewarded task-switching in the 9R-carrying patients OFF medication is maladaptive for behaviour. The notion of maladaptive striatal hyperactivation in 9R-carrying patients with ADHD is in line with the finding that the 9R allele is the risk allele in adult ADHD (Franke et al., 2010). However, the absence of significant behavioural differences relative to healthy controls precludes statements of normality in terms of performance.

The aberrant striatal responses during rewarded task-switching in patients with ADHD (specifically 9R carriers) relative to controls were absent when patients were ON medication. This suggests that methylphenidate normalized striatal responses, although we only obtained trend effects (i.e. at P<0.001 uncorrected for multiple comparisons) when directly comparing patients ON versus OFF methylphenidate. Our findings suggest that the effects of methylphenidate on cognitive task-related processing are accompanied by modulation of the striatum. This generally concurs with previous work showing that methylphenidate can normalize striatal responses during cognitive processes such as response inhibition (Vaidya et al., 1998; Shafritz et al., 2004; Epstein et al., 2007; Rubia et al., 2009, 2011). Here, we show that such normalization of task-related dorsal striatal responses and performance by methylphenidate depends both on the DAT1 genotype and on reward motivation. This suggests that reward motivational factors interact with the effects of the DAT1 genotype to bias the cognitive response to methylphenidate. Future work should address the obvious next question, that is, whether the discrepancy in the extant literature on the effects of the DAT1 genotype on the clinical response to medication (Kambetz et al., 2014) also reflects variability in the patient’s reward motivational state. Cognitive neuroimaging measures of task-related (motivational) processing might be particularly sensitive to detecting DAT1-dependent effects of methylphenidate in ADHD.

It might be noted that the effects in the OFF state could reflect rebound effects because of short-term medication withdrawal. Future studies, with a longitudinal design or
comparing medication-naive patients with medicated patients, will need to determine whether the current findings reflect rebound or withdrawal effects rather than an unmedicated ADHD state.

Our findings were obtained with a sample of 23 patients with ADHD and 26 healthy controls. This limited sample size calls for caution when generalizing to the population (Munafo and Gage, 2013) and precludes definitive conclusions. The findings should therefore be considered preliminary and in need of replication, as was recently also explicitly highlighted (Button et al., 2013). Nevertheless, we believe that our findings are robust, given extensive convergent evidence. Indeed, we have previously observed effects of the DAT1 genotype on the BOLD signal during rewarded task-switching in the same striatal region (i.e. left caudate nucleus) as we report here (Aarts et al., 2010). Moreover, we have observed previously that striatal dopamine synthesis capacity in the (left) caudate nucleus predicted the effects of reward on cognitive performance during a focused attention task (Aarts et al., 2014b). It is unlikely that our whole-brain corrected results represent a false-positive effect as our power calculation based on an independent dataset (Aarts et al., 2010; Button et al., 2013) confirmed that our sample should be large enough to obtain significantly meaningful effects (see the Methods section). Replication of the effect in independent larger samples in future studies will further increase confidence in the reliability of the effect.

Previously, we have obtained similar results in a PET study in healthy volunteers, showing that dopaminergic transmission in the left caudate nucleus altered the effects of reward motivation on cognitive control (Aarts et al., 2014b). In that study, we used a Stroop interference paradigm instead of a task-switching paradigm, suggesting that our present results can be extended to other domains of cognitive control. However, future work should confirm whether our findings in ADHD can be generalized to domains other than task-switching. Moreover, future studies should also examine variation in other dopaminergic genes, such as COMT (Bilder et al., 2004), to investigate whether the current findings are limited to striatal dopamine processing.

**Conclusion**

Our data suggest a dysfunctional influence of reward motivation on cognitive processing (i.e. task-switching) in the dorsal striatum of adult patients with ADHD, who carry the 9R ADHD risk allele. This deficit is remediated when patients are tested ON methylphenidate. These findings indicate an important role for both reward motivation and interindividual trait differences in striatal dopamine transmission in cognitive processing deficits in adult ADHD.

**Acknowledgements**

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**Conflicts of interest**

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**References**


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