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Neural reward processing in paediatric Tourette syndrome and/or attention-deficit/hyperactivity disorder

Sophie E.A. Akkermans[a,b,*], Daan van Rooij[a,b], Jilly Naaijen[a,b], Natalie J. Forde[b,c], Regina Boecker-Schlier[d], Thaira J.C. Openneer[c], Andrea Dietrich[c], Pieter J. Hoekstra[c], Jan K. Buitelaar[a,b,e]

[a] Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Department of Cognitive Neuroscience, Nijmegen, the Netherlands
[b] Radboud University, Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging, Nijmegen, the Netherlands
[c] University of Groningen, University Medical Center Groningen, Department of Child and Adolescent Psychiatry, Groningen, the Netherlands
[d] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim/Heidelberg University, Mannheim, Germany
[e] Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, the Netherlands

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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is the most common comorbidity in individuals with Tourette syndrome (TS). Yet, it is unclear to what extent TS and ADHD show overlapping or distinct neural abnormalities. ADHD has been associated with altered reward processing, but there are very few studies on reward processing in TS. This study assessed neural activation of basal ganglia and thalamus during reward anticipation and receipt in children with TS and/or ADHD. We analysed mean activations of *a priori* specified regions of interest during an fMRI monetary incentive delay task. Data was used from 124 children aged 8–12 years (TS $n = 47$, of which 29 had comorbid ADHD; ADHD $n = 29$; healthy controls $n = 48$). ADHD severity across ADHD and TS groups and healthy controls was marginally related to hypoactivation of the right nucleus accumbens during reward anticipation; this effect was not moderated by TS diagnosis. We detected no associations of neural activation with TS. The association between ADHD severity and hypoactivation of the right nucleus accumbens during reward anticipation, independent of the presence or absence of TS, is in line with the view of nucleus accumbens hypoactivation as a dimensional, neurofunctional marker of ADHD severity, transcending the boundaries of primary diagnosis.

1. Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder defined by the presence of motor and vocal tics (American Psychiatric Association, 2013). Up to 86% of individuals with TS also present with psychiatric comorbidities at some point during their lifetime (Hirschtritt et al., 2015). Attention-deficit/hyperactivity disorder (ADHD) is the most common comorbidity (El Malhany et al., 2015), with a prevalence of approximately 50% in referred TS samples (Freeman et al., 2000). Both disorders have been associated with abnormalities in the basal ganglia (globus pallidus, GP; caudate nucleus, Cau; putamen, Put; nucleus accumbens, NAcc) and thalamus (Thal) (Cubillo et al., 2012; Ganos et al., 2013; Langen et al., 2011). However, due to a lack of direct comparisons, it remains unclear to what extent these disorders have common and distinct neural underpinnings. The present functional magnetic resonance imaging (fMRI) study aimed to increase this understanding by investigating neural reward processing in children with TS and/or ADHD and healthy controls. Of this sample, basal ganglia structure, glutamate levels, and anterior cingulate cortex cytoarchitecture have been reported previously (Forde et al., 2018, 2017; Naaijen et al., 2017).

The core symptoms of inattention and hyperactivity-impulsivity in ADHD, as well as related problems with motivation, delay aversion and risk-taking, have been hypothesized to be caused in part by altered reinforcement sensitivity, implicating basal ganglia regions (Dichter et al., 2012; Fareri et al., 2008; Ma et al., 2016). For example, some studies found that participants with ADHD had stronger activation in the dorsal and ventral striatum (Furukawa et al., 2014; Paloyelis et al., 2012) or dorsal striatum only (Strohle et al., 2008) in response to monetary gains. However, this was not observed in other similar studies

* Corresponding author.
E-mail address: s.akkermans@donders.ru.nl (S.E.A. Akkermans).

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Table 1
Group characteristics

	Control	ADHD	TS + ADHD	TS − ADHD	Difference test[a]
N (males/females)	48 (32/16)	29 (12/17)	33 (29/4)	14 (12/2)	–
Age in years, *M* (*SD*)	11.0 (1.0)	10.8 (1.4)	10.8 (1.5)	10.6 (1.2)	$\chi^2 = 1.82$; $p = .610$
[b]IQ, *M* (*SD*)	111 (11)	103 (10)	107 (13)	102 (12)	$F = 4.20$; $p = .007$ Control > ADHD Control > TS − ADHD
Handedness left/right, *n*	5/43	2/27	3/30	0/14	–
[c]Head motion, *M (SD)*	0.11 (0.08)	0.20 (0.12)	0.23 (0.18)	0.25 (0.23)	$\chi^2 = 17.44$; $p < .001$ ADHD > Control TS + ADHD > Control TS − ADHD > Control
[d]ADHD diagnosis/sub-threshold, *n*	0/0	28/1	29/4	0/0	–
[e]ADHD severity, *M* (*SD*)	4.3 (4.8)	27.9 (9.0)	27.6 (8.8)	9.6 (5.9)	ADHD vs. TS + ADHD: $t = 0.14$; $p = .888$
[f]Tic severity, *M* (*SD*)	–	–	Total = 22.1 (9.1) Motor = 14.4 (5.1) Vocal = 7.7 (5.9)	Total = 18.5 (7.2) Motor = 12.9 (3.9) Vocal = 5.6 (4.7)	Total: $t = 1.31$; $p = .198$
[f]Age tic onset in years, *M* (*SD*)	–	–	Motor = 5.9 (1.7) Vocal = 6.6 (1.7)	Motor = 5.5 (2.1) Vocal = 6.7 (1.9)	Motor: $t = 0.60$; $p = .549$ Vocal: $t = 0.22$; $p = .828$
[f]Duration since tic onset in years, *M* (*SD*)	–	–	Motor = 4.9 (1.7) Vocal = 4.2 (1.7)	Motor = 5.1 (1.7) Vocal = 3.9 (1.8)	Motor: $t = 0.27$; $p = .785$ Vocal: $t = 0.47$; $p = .639$
[g]Compulsive behaviour, *M* (*SD*)	0.10 (0.37)	0.76 (1.27)	2.55 (3.02)	2.71 (4.41)	$\chi^2 = 42.13$; $p < .001$ TS + ADHD > ADHD > Control TS − ADHD > ADHD > Control
[h]OCD, *n*	–	0	8	2	–
[d]ODD	–	2	0	1	–
[d]GAD, *n*	–	2	2	0	–
[i]Medication use, *n*					
Stimulant current/past	–	20/1	8/7	0/0	–
Atomoxetine current/past	–	0/2	0/1	0/0	–
Antipsychotic current/past	–	1/0	5/2	2/1	–
Clonidine current/past	–	0/0	2/4	0/1	–

[a] Group differences between two groups were tested with independent-samples *t*-tests. Group differences between more than two groups were examined by means of an analysis of variance (ANOVA) or, if parametric assumptions were not met, the non-parametric Kruskal-Wallis test. Dunn's Test of Multiple Comparisons Using Rank Sums (uncorrected) was used for post hoc comparisons of the Kruskal-Wallis test. Significant differences at $p \leq .05$ between groups are noted with the direction (> or <) of the effects.

[b] Estimated from 4 Wechsler Intelligence Scale for Children-III (Wechsler, 2002) subtests.

[c] Head motion is defined as the mean root mean square of the frame-wise displacement across functional scans (Jenkinson et al. 2002).

[d] Established through the Kiddie Schedule for Affective Disorders and Schizophrenia semi-structured interview (Kaufman et al., 1997).

[e] Raw scores of the DSM-IV combined subscale (range 0–54) of the Conners' Parent Rating Scale – Revised Long (Conners et al., 1998).

[f] Determined with the Yale Global Tic Severity Scale (Leckman et al., 1989). Total (range 0–50), motor, and vocal tic severity ratings exclude impairment score.

[g] Compulsive behaviour subscale score (range 0–18) from the Repetitive Behavior Scale – Revised (Lam and Aman, 2007).

[h] Total score ≥ 16 on the Children's Yale-Brown Obsessive Compulsive Scale (Scahill et al., 1997).

[i] As determined from parental report.

Abbreviations: ADHD – attention-deficit/hyperactivity disorder, GAD – generalized anxiety disorder, OCD – obsessive-compulsive disorder, ODD – oppositional defiant disorder, TS + ADHD – Tourette syndrome with comorbid ADHD, TS − ADHD – Tourette syndrome without comorbid ADHD.

(Boecker et al., 2014; Scheres et al., 2007; Stoy et al., 2011; von Rhein et al., 2015). A more robust finding on altered reward processing in ADHD is that adolescents and adults with ADHD display hypoactivation of the NAcc during the anticipation of monetary rewards (Boecker et al., 2014; Plichta and Scheres, 2014), although see Paloyelis et al. (2012) and von Rhein et al. (2015) for discordant results. Only two studies have focused on children (aged 8–12 years) with ADHD, of which one could not confirm NAcc hypoactivation (Kappel et al., 2015). In the other study, NAcc hypoactivation was seen in children with ADHD symptoms irrespective of whether the primary diagnosis was ADHD or autism spectrum disorder (ASD; van Hulst et al., 2017). Indeed, ADHD characteristics are commonly present in other disorders and even in healthy controls, and it has been proposed that a dimensional view of ADHD may be more appropriate than the view of ADHD as a distinct category (Chabernaud et al., 2012). The above suggests that NAcc hypoactivation could be related to the ADHD symptom dimension within TS.

So far, reward processing has scarcely been investigated in TS. As TS is characterized by the presence of motor and vocal tics, most research has been devoted to delineating the contribution of the basal ganglia circuits to the generation and suppression of tics, and motor control in general. However, basal ganglia regions are also involved in reward processing (Fareri et al., 2008) and both tics and reward processing are thought to strongly depend on the dopamine system (Buse et al., 2013; Schultz, 2015). Accordingly, it has been proposed that tic formation may result from inappropriate reinforcement and chunking of motor responses, possibly implicating altered phasic dopamine transmission in the dorsal striatum (Cau and Put) (Delorme et al., 2016; Ganos et al., 2013). Support for this theory comes in part from reinforcement learning paradigms. Using these paradigms, enhanced behavioural sensitivity to reward was shown in non-medicated adults with TS without comorbid ADHD, which was alleviated or even reversed by dopamine antagonists (Delorme et al., 2016; Palminteri et al., 2009, 2011), although a contradicting finding was described by Marsh et al. (2004). Just one fMRI study has reported on reinforcement learning in TS (Worbe et al., 2011). Here, impaired reinforcement learning and lower neural response to reward receipt in NAcc and cortical reward areas were associated with more severe comorbid obsessive-compulsive symptoms and the use of dopamine antagonists, but not related to TS per se. The study was, however, conducted in adults, who may represent a subgroup of TS with a neurobiological signature distinct from that of children. Moreover, several important areas for TS and reward processing (left Put, Cau, GP, Thal) were not investigated. Therefore, further exploration of the theory of altered reinforcement

sensitivity in TS is warranted.

Here, we examined neural reward processing in 8-to-12-year-old children with TS and/or ADHD, thereby focusing on a scarcely investigated age group where tics are most prevalent. Our first aim was to assess monetary reward anticipation in relation to ADHD comorbidity in TS, by using a monetary incentive delay paradigm (MID; Knutson et al., 2001). We expected to replicate the key finding of hypoactivation of the NAcc during reward anticipation in an ADHD group compared with healthy controls. As our main hypothesis, we hypothesized that this would also be seen in TS with comorbid ADHD, but not in TS without comorbid ADHD. Next to traditional tests for group differences, which presume underlying categorical mechanisms (Sonuga-Barke, 1998), we employed a dimensional analysis of ADHD severity across all groups. This is more in keeping with the dimensional view of ADHD as described above (Chabernaud et al., 2012).

The current MID paradigm also has a reward receipt phase which can probe activation of the dorsal striatum (e.g. Boecker et al., 2014), likely reflecting action reinforcement (Fareri et al., 2008). Accordingly, our second aim was to test the aforementioned theory of altered reinforcement sensitivity involving the dorsal striatum in TS. We additionally explored other key TS regions (GP, Thal) found to be involved in reward processing (Haber and Knutson, 2010). Based on the behavioural evidence of heightened reward sensitivity discussed above, we hypothesized hyperactivation of Cau or Put during reward receipt to be a characteristic of the TS groups. Following from the reviewed evidence on reward receipt processing in ADHD, it is a possibility that dorsal striatal hyperactivation is also associated with ADHD. Again, the tests for group differences were complemented with tests modelling ADHD severity as a dimension across groups.

2. Methods

2.1. Participants

Our sample with usable data for analysis included participants with a diagnosis of TS with comorbid ADHD (TS + ADHD; $n = 33$), participants with TS without comorbid ADHD (TS − ADHD; $n = 14$), participants with ADHD without tics (ADHD; $n = 29$) and healthy controls (control; $n = 48$). See Table 1 for group characteristics. Inclusion criteria for all participants were age 8–12 years, Caucasian descent, IQ > 70, no major physical illness, no present or past neurological disorders or head injuries, and no contraindications for MRI. Participants with TS had a diagnosis of Tourette's disorder or Persistent Motor or Vocal Tic Disorder (motor type) according to the DSM-5 (American Psychiatric Association, 2013) and were allowed psychiatric comorbidities such as obsessive-compulsive disorder (OCD). The ADHD and TS + ADHD groups included participants who met DSM-5 criteria for ADHD diagnosis or presented with sub-threshold ADHD (defined as 4 or 5 symptoms in the inattention and/or hyperactivity-impulsivity domain). Exclusion criteria for the ADHD group were past or present tics, ASD, or OCD. Other common comorbidities (e.g. oppositional defiant disorder [ODD] or conduct disorder [CD]) were allowed. Healthy controls had to be free of psychiatric disorders and have scores within the normal range on the Child Behavior Checklist and Teacher Report Form (Achenbach and Rescorla, 2001). Furthermore, they were not included if a first-degree family member was diagnosed with a psychiatric disorder. Procedures were approved by the regional ethics committee (CMO Regio Arnhem-Nijmegen). Written informed consent was obtained from parents/guardians and additionally written assent from the child when aged 12. Participants were asked to stop stimulant medication from 48 h before the testing day (4 could not fully comply, but they did not take their medication on the testing day; this makes it unlikely that results are influenced by acute stimulant effects). Of the overall 152 participants that underwent fMRI assessment, 28 were excluded based on fMRI quality ($n = 17$; see supplement for details on quality assessment), incidental findings ($n = 1$), and not following task instructions ($n = 13$).

2.2. Diagnostic and phenotypic information

To assess ADHD diagnosis and screen for the presence of other psychiatric disorders (ODD, CD, OCD, TS, and affective disorders), the Kiddie Schedule for Affective Disorders and Schizophrenia semi-structured interview (Kaufman et al., 1997) was administered to parents of all participants. In the event of an elevated score on one of the screening items, the full module for that disorder was applied. To confirm TS diagnosis and assess symptom severity in participants with TS, parent(s) and child were interviewed using the Yale Global Tic Severity Scale (Leckman et al., 1989). Additionally, the Children's Yale-Brown Obsessive Compulsive Scale (Scahill et al., 1997) was administered to all participants with TS to examine the presence and severity of comorbid OCD symptoms (and to other participants in case an OCD screening item was answered positively). All interviews were carried out by trained and experienced researchers who were monitored by a child- and adolescent psychiatrist (JKB). Our outcome measure of ADHD severity was based on the Conners' Parent Rating Scale - Revised Long (CPRS-RL; Conners et al., 1998), as completed by the parents. Parents further reported on past and present medication use (for more information see Table 1) and filled in the Repetitive Behavior Scale - Revised (RBS-R; Lam and Aman, 2007), to rate compulsive behaviours. Children performed four subtests (block design, vocabulary, similarities, and picture completion) of the Wechsler Intelligence Scale for Children-III (Wechsler, 2002), allowing an estimation of full-scale IQ. These latter measures were checked for their confounding influence on the results.

2.3. Experimental paradigm

We used a modified version of the MID task with fMRI assessment to measure neural responses to reward anticipation and receipt (see Fig. 1). The MID task (original version by Knutson et al., 2001) is known to activate the ventral striatum/nucleus accumbens during reward anticipation. The current design has also been shown to probe the dorsal striatum during reward receipt (e.g. Boecker et al., 2014). Reward anticipation was established by presentation of a monetary reward cue, a happy smiley, indicating the possibility of receiving a monetary reward (0.50 euro). Verbal cues consisted of a scrambled smiley and indicated that solely a verbal reward ("Fast reaction!") could be obtained. To win the trial, participants were required to press a button with their right index finger as fast as possible in response to a flash (duration = 100 ms) that immediately followed the cue. The response window for a win (the same for monetary and verbal conditions) was adapted (made 5% shorter or longer) based on the participant's performance, to account for inter-individual differences and to facilitate similar amounts won across participants (~60% hits on monetary trials). The response window was maximally 1 s long. After the response to the flash and an additional time lag of 200 ms, verbal or monetary feedback was shown on the screen (duration = 1.5 s). This included the current account balance. Finally, a blank screen was shown for 3 s minus RT, to equalize trial durations. To boost the child's motivation level, a monetary reward of 2 instead of 0.50 euro was given approximately every eighth monetary win. The task was ~10 min (shortened compared to Boecker et al., 2014) in duration and consisted of in total 36 monetary and 34 verbal trials in pseudo-randomized order. Jitter was introduced in cue duration (3–5 s, mean 4 s) to cover the entire hemodynamic response function (HRF). Outside of the scanner, participants were instructed in the meaning of the cues and were told that the total amount of money won during the task would be transferred to their parent's bank account. Furthermore, they performed 10 practice trials on a laptop.

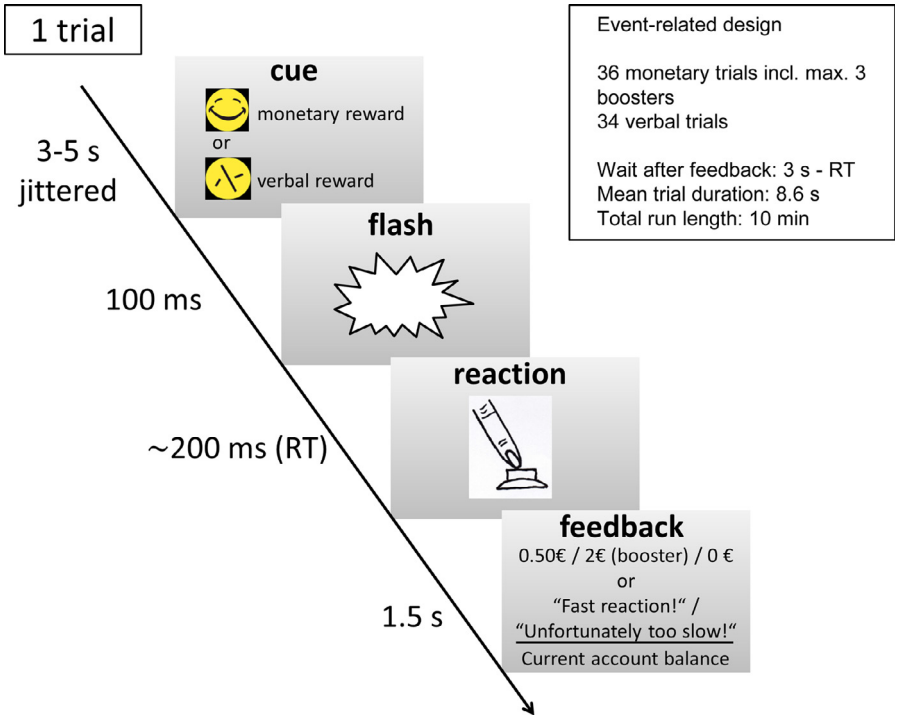

Fig. 1. Monetary incentive delay task. Monetary or verbal reward is cued by a laughing or scrambled smiley, respectively. To obtain the reward, participants have to respond with a fast button press to a flash. The response is followed by either monetary or verbal feedback.
Adapted with permission from Boecker et al. (2014).

2.4. Behavioural analysis

Behavioural outcome measures for monetary and verbal reward conditions included mean reaction time (MRT), coefficient of variation (intra-individual standard deviation divided by the individual mean), and percentage of hits. To establish whether anticipation of monetary reward resulted in faster responses than anticipation of verbal reward (response time speeding; MRT verbal minus MRT monetary), we performed a paired *t*-test on differences between verbal and monetary conditions in MRT across all groups (i.e. controls, ADHD, TS + ADHD, TS − ADHD). Within-group outliers > 3 *SD* on response time speeding were excluded. Descriptive statistics of the performance measures are presented for the groups separately, along with the corresponding tests for group differences in means (see Table 2 for more information).

Additionally, we tested in a regression (dimensional) model whether ADHD severity or presence of TS was associated with the degree of response time speeding. The raw scores of the CPRS-RL DSM-IV combined subscale were used as a continuous measure of ADHD severity, with scores present for all participants. For TS, a dichotomous factor seemed more appropriate due to the absence of tics in the ADHD and control groups. We further included a linear interaction term TS × ADHD severity, to test whether the effect of ADHD was moderated by the presence of TS or vice versa. In case the interaction term was non-significant, it was dropped from the model. For all statistical tests, the significance threshold was set at $p \leq .05$ and for conciseness we only report full statistics for significant or trend level results. This also applies to the ROI models described below.

Table 2
Task performance per group

	Control *M* (*SD*)	ADHD *M* (*SD*)	TS + ADHD *M* (*SD*)	TS − ADHD *M* (*SD*)	Difference test[a]
[b]MRT verbal reward in ms	309.3 (45.95)	352.2 (67.45)	346.6 (77.3)	347.5 (83.5)	$\chi^2 = 11.38$; $p = .010$
[c]MRT monetary reward in ms	264.4 (34.1)	300.8 (49.2)	303.0 (73.6)	287.4 (37.3)	$\chi^2 = 12.17$; $p = .007$
[d]Response time speeding in ms	44.9 (39.0)	51.3 (59.7)	43.6 (65.3)	60.1 (79.2)	$\chi^2 = 0.55$; $p = .909$
CV verbal reward	0.51 (0.16)	0.49 (0.17)	0.57 (0.15)	0.55 (0.19)	$\chi^2 = 5.66$; $p = .129$
CV monetary reward	0.44 (0.21)	0.49 (0.22)	0.54 (0.18)	0.54 (0.22)	$\chi^2 = 5.09$; $p = .166$
[e]Hits verbal reward in %	42.3 (6.9)	38.6 (7.1)	41.3 (9.2)	41.2 (8.5)	$\chi^2 = 4.26$; $p = .235$
[e]Hits monetary reward in %	58.7 (9.2)	60.5 (6.6)	59.5 (8.8)	58.7 (9.2)	$F = 0.20$; $p = .894$

[a] Group differences were examined by means of an analysis of variance (ANOVA) or, if parametric assumptions were not met, the non-parametric Kruskal-Wallis test. Dunn's Test of Multiple Comparisons Using Rank Sums (uncorrected) was used for post hoc comparisons of the Kruskal-Wallis test.

[b] Significant post hoc: ADHD > C [z = 2.99; $p = .001$]; TS + ADHD > C [z = 2.35; $p = .009$]; TS − ADHD > C; [z = 1.98; $p = .024$]. Non-significant post hoc: ADHD > TS + ADHD [z = 0.67; $p = .251$]; ADHD > TS − ADHD [z = 0.31; $p = .378$]; TS − ADHD > TS + ADHD; [z = 0.22; $p = .414$].

[c] Significant post hoc: ADHD > C [z = 3.13; $p < .001$]; TS + ADHD > C [z = 2.54; $p = .006$]; TS − ADHD > C; [z = 1.74; $p = .041$]. Non-significant post hoc: ADHD > TS + ADHD [z = 0.64; $p = .262$]; ADHD > TS − ADHD [z = 0.63; $p = .263$]; TS − ADHD > TS + ADHD; [z = 0.14; $p = .445$].

[d] MRT of the verbal reward condition minus MRT of the monetary reward condition.

[e] Hits are responses to the flash within the reaction time window.

Abbreviations: ADHD – attention-deficit/hyperactivity disorder, C – Control, CV – coefficient of variation, MRT – mean reaction time, TS + ADHD – Tourette syndrome with comorbid ADHD, TS − ADHD – Tourette syndrome without comorbid ADHD.

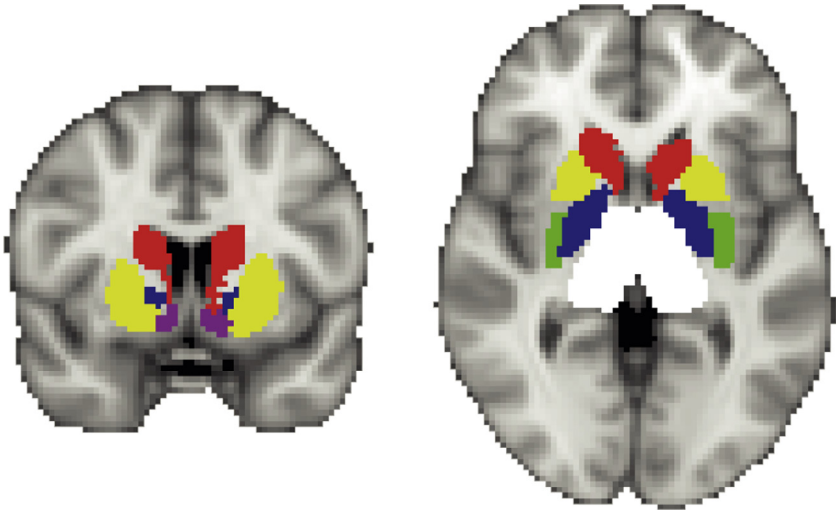

Fig. 2. Regions of interest. The regions of interest displayed here are an example from one participant overlaid on an MNI152 template brain. Legend: white – thalamus, blue – globus pallidus, red – caudate nucleus, pink – nucleus accumbens, yellow – anterior putamen, green – posterior putamen.

2.5. Regions of interest

For the following *a priori* specified regions of interests (ROIs) we created subject-specific anatomical masks using the FSL-FIRST toolbox for automatic subcortical segmentation (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST; Patenaude et al., 2011): NAcc, Cau, anterior putamen (AntPut), posterior putamen (PostPut), GP, and Thal. Left and right volumes were analysed separately. We took into account that the anterior and posterior regions of the putamen are functionally distinct (e.g. von Rhein et al., 2016) and used a line through the anterior commissure as a reference point to label the anterior and posterior parts of the Put. We left a gap of 4 mm between these parts to minimize signal overlap. Since there is less consensus on the separation of other regions of the basal ganglia in smaller functional subregions, we chose to use the standard anatomical boundaries. For outliers (> 3 *SD*) on the volumes of the ROIs, we visually inspected FSL-FIRST output for evident segmentation errors. This resulted in the exclusion of one participant for the left NAcc analysis. Examples of ROIs are displayed in Fig. 2.

2.6. FMRI participant-level analysis

Functional scans were pre-processed using a pipeline integrating FSL tools (https://fsl.fmrib.ox.ac.uk/fsl/; see online supplement for details on image acquisition, pre-processing, and quality checks). A first-level analysis for each participant was conducted in Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/; see supplement). Here, contrast images for reward anticipation (monetary reward cue minus verbal cue) and receipt (both win feedback conditions minus both no-win feedback conditions) were created for each participant. The contrast of the monetary minus verbal cue conditions is thought to be suitable to capture the reward system (including the nucleus accumbens), because the reward system is more strongly activated during the anticipation of monetary compared to verbal reward, while other systems (related to general cue, response and feedback processes) are similarly activated (Kirsch et al., 2003). The contrast for reward receipt was chosen in line with Boecker et al. (2014) to reveal activation in the dorsal striatum. By collapsing both win minus both no-win conditions, we obtained more power compared to examining monetary and verbal feedback conditions separately (but see supplement for a comparison of these conditions). Mean values of contrast estimates for anticipation or receipt were extracted from the ROIs using the SPM_summarise function and imported into R statistics (R Core Team, 2014) for subsequent group-level analyses.

2.7. FMRI group-level analysis

To check whether general whole-brain task effects were in accordance with reward processing literature, activation maps were created by performing one-sample *t*-tests across the whole sample on the reward anticipation and receipt contrast images. Also, we checked whether there were significant (at $p < .05$ corrected for the familywise error rate, FWE) effects outside of the ROIs by conducting whole-brain tests for group differences and regression analyses for the main effects of TS and ADHD severity, on the above contrast images. ROI analyses consisted of two parts: (1) Examine the hypothesis that ADHD is associated with hypoactivation in the NAcc during reward anticipation in both ADHD and TS + ADHD (2) Test whether TS is associated with hyperactivation of Cau, AntPut, PostPut, GP or Thal during reward receipt. For both aims, we used a categorical approach and a dimensional approach. For each ROI outcome measure (mean contrast estimate of reward anticipation or receipt) we excluded within group outliers > 3 *SD*. Group differences were examined by means of an analysis of variance (ANOVA) or, if parametric assumptions were not met, the non-parametric Kruskal-Wallis test. Dunn's Test of Multiple Comparisons Using Rank Sums (uncorrected) were used for post hoc comparisons of the Kruskal-Wallis test. Regression (dimensional) models were specified with ADHD severity, TS and their interaction as predictors across the whole sample. See the description of the behavioural analysis above for the definition of these variables. In case the interaction term was non-significant, it was dropped from the model. We used bootstrapping (2000 replicates) to confirm 95% confidence intervals of regression estimates (more robust against violations of assumptions) which are visualized in the figures where applicable. Reward anticipation and reward receipt analyses were corrected for multiple comparisons (number of ROIs) using the M_{eff} (effective number) of independent tests according to the method described by Li and Ji (2005). This method accounts for the dependency between measurements of different ROIs.

2.8. Check for potential confounders

For significant ROI models, we checked whether the significant predictors had explanatory value over and above that of potential confounders by means of a 2-step hierarchical regression procedure (described further in the online supplement). The following potential confounders were included in the first step: sex, age, IQ, handedness, head motion (RMS-FD), ODD diagnosis (yes/no), generalized anxiety disorder diagnosis (yes/no), RBS-R compulsive behaviour subscale

score, stimulant use (never/past/current), and antipsychotic use (never/past/current). In the second step, the predictor of interest was added, and significance of model fit improvement was assessed with analysis of variance.

3. Results

3.1. Behavioural results

See Table 2 for descriptive statistics of task performance measures per group (i.e. controls, ADHD, TS + ADHD, TS − ADHD) and the accompanying tests for group differences. There were no differences in the percentage of hits for monetary rewards (average payoff ~ €15). All three patient groups responded on average slower than control participants. Across all groups, participants responded on average 46 ms faster in the monetary compared to the verbal condition; $t(123) = 9.8$, $p < .001$. There were no outliers > 3 *SD* on response time speeding and response time speeding was not associated with TS, ADHD severity or their interaction (all model *p*-values ≥ .161).

3.2. fMRI results

3.2.1. Whole-brain task activation

Across all participants, reward anticipation (monetary cue minus verbal cue conditions) elicited increased activity in several brain areas typically associated with reward processing (Boecker et al., 2014; Plichta et al., 2013) including the bilateral NAcc extending into the Thal, Cau, AntPut, and GP (see Fig. 3A). During reward receipt (win feedback minus no-win feedback), higher activity was observed in the bilateral dorsal striatum (amongst other regions; see Fig. 3B). Whole-brain analyses returned no significant group differences or main effects of TS or ADHD severity for either of the conditions.

3.2.2. ROIs reward anticipation

Two participants were excluded as outliers for the right NAcc analysis, and one for the left NAcc analysis. Kruskal-Wallis tests did not yield significant differences between ADHD, TS + ADHD, TS − ADHD, and control groups for the right ($\chi^2 = 3.49$, $p = .322$) or the left ($\chi^2 = 1.05$, $p = .788$) NAcc. No dimensional model significantly predicted anticipatory activity of the left NAcc (model without interaction term, $p = .821$). For the right NAcc anticipatory activity, a model without interaction term bordered on the significance threshold of $\alpha = .05$; $F(2,119) = 3.0$, $p = .052$, $R^2 = .048$; $p_{adjusted} = .066$ when adjusted for the effective number of tests ($M_{eff} = 1.27$). Within this model, ADHD severity was negatively associated with activity of the right NAcc ($\beta = -0.22$, $p = .023$), and no main effect was found for TS diagnosis ($p = .949$). To summarize, we detected a marginally significant relationship between ADHD severity and hypoactivation of the right NAcc during reward anticipation; an effect which was independent of the presence or absence of TS. This relationship is depicted in Fig. 4.

3.2.3. ROIs reward receipt

There were no significant differences between ADHD, TS + ADHD, TS − ADHD and control groups in activation of ROIs during reward receipt (all models $p > .05$, range $p = .059$–$.781$). However, the left GP ANOVA bordered on significance ($F_{3,120} = 2.55$, $p = .059$. $R^2 = .060$), and pairwise comparisons showed a trend for higher activation of left GP in all groups compared to controls (ADHD, $p = .047$; TS + ADHD, $p = .073$; TS − ADHD, $p = .026$). In the dimensional models, ADHD severity, TS diagnosis, or their interaction did not predict the mean response to reward receipt of any of the ROIs (all models $p > .05$, range $p = .188$–$.933$ for models without interaction term), except for the left GP; $F(2,121) = 3.1$, $p = .047$, $R^2 = .049$. In this model, higher ADHD severity was marginally related to higher activity of the left GP during reward receipt ($\beta = 0.17$, $p = .067$), and no main effect was found for TS diagnosis ($p = .326$). However, the model did not survive corrections for multiple comparisons ($p_{adjusted} = .261$ based on $M_{eff} = 5.55$). In short, the results of the reward receipt condition showed no differential activation of ROIs in dorsal striatum, Thal, and right GP in participants with TS compared to participants without TS. Although not passing the adjusted significance threshold, there was trend visible that all patient groups displayed stronger activation of the left GP compared to controls, which seemed to be partly related to their ADHD symptoms. These left GP effects are displayed in Fig. 5.

3.2.4. Check for potential confounders

In the online supplement, analyses are described that assess whether significant predictors from the above analyses explain any variance in the activation of the ROIs over and above the variance explained by potential confounders. For completeness, TS diagnosis was also included. Results of these analyses suggest that ADHD severity explained variance in the activation of the right NAcc during reward anticipation over and above the variance explained by potential confounders and TS diagnosis ($\Delta R^2 = .041$; $F_{1,\ 107} = 4.86$; $p = .030$). Within the full model, ADHD severity was the only predictor with a significant unique

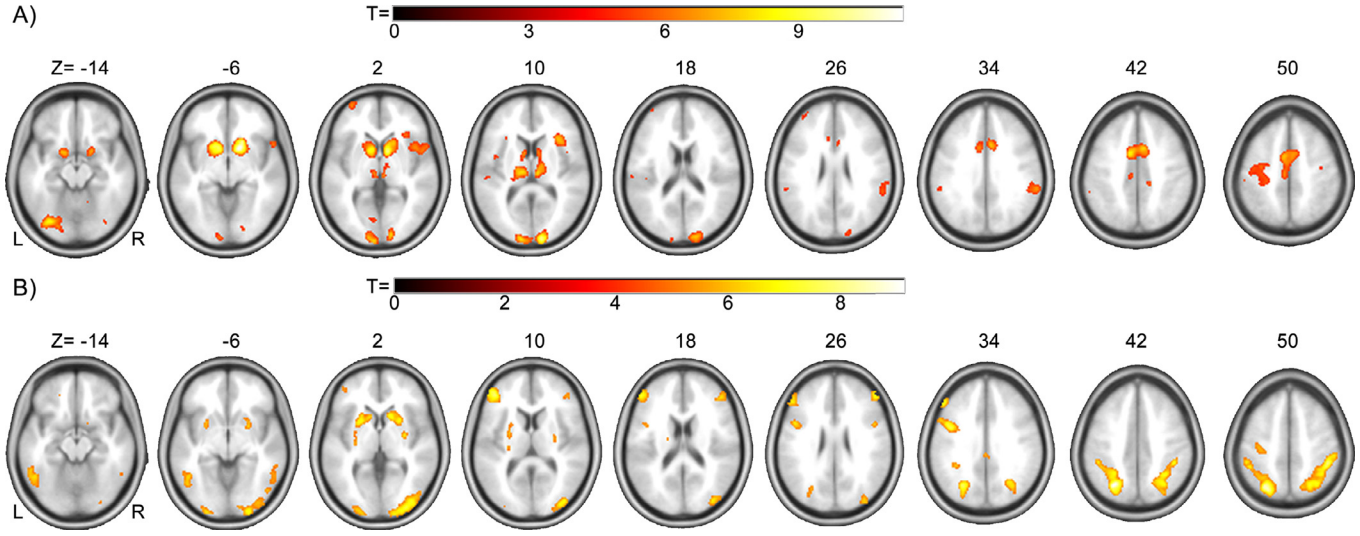

Fig. 3. Monetary incentive delay task activation results for A) reward anticipation (monetary cue > verbal cue), and B) reward receipt (win feedback > no-win feedback). Results come from one-sample *t*-tests across the total sample thresholded at $p < .05$ corrected for the familywise error rate (FWE).

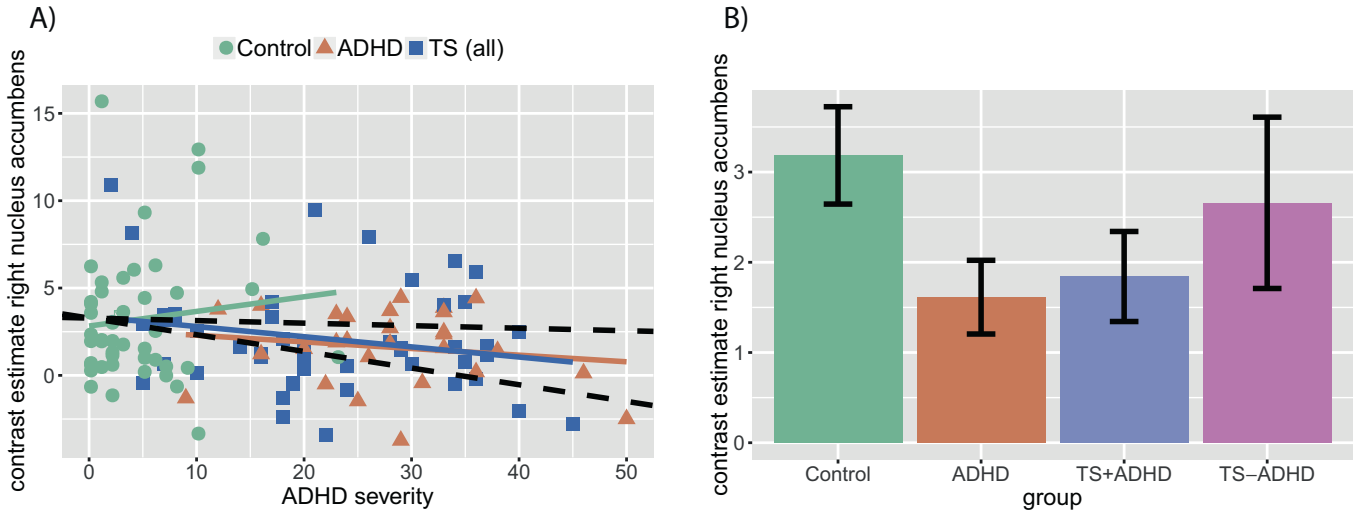

Fig. 4. A) Association between ADHD severity and right nucleus accumbens reward anticipation estimates. ADHD severity reflects raw scores of the DSM-IV combined subscale of the Conners' Parent Rating Scale – Revised Long (Conners et al., 1998). Dashed regression lines represent the bootstrapped 95% confidence interval of the regression estimate from the model estimated for the total sample. Coloured regression lines are plotted for the groups separately for illustrative purposes. B) Average right nucleus accumbens reward anticipation estimates per group. Error bars denote *SE*. Abbreviations: ADHD – attention-deficit/hyperactivity disorder, TS – Tourette syndrome, TS + ADHD – Tourette syndrome with comorbid ADHD, TS − ADHD – Tourette syndrome without comorbid ADHD.

contribution ($\beta = -0.30$, $p = .030$).

For the activation of the left GP during reward receipt, adding ADHD severity did not add significantly to the variance explained by potential confounders and TS diagnosis ($\Delta R^2 = .019$; $F_{1,109} = 2.63$; $p = .108$). The models revealed a significant effect of head motion on neural activation, although this effect was in the opposite direction to that of ADHD severity and TS diagnosis. See online supplement for detailed statistics on the models and individual predictors.

4. Discussion

The current study addressed neural reward processing in children with TS (with/without comorbid ADHD), ADHD, and healthy controls. In line with our first hypothesis, we detected a marginally significant relationship between ADHD severity and hypoactivation of the right NAcc during reward anticipation; an effect which was independent of the presence or absence of TS. We found no support for our second hypothesis of a relationship between TS and hyperactivation of the Cau, Put, GP, or Thal during reward receipt. Yet, although not surviving correction for multiple comparisons, there was some indication that the (left) GP constitutes a promising target for future investigations of TS/ADHD comorbidity and reward receipt. Due to the tentative nature of this result, we chose not to interpret it further. Behaviourally, all patient groups responded generally slower than controls.

The observed association between NAcc hypoactivation and ADHD severity was marginally significant and as such warrants replication. Nevertheless, it is consistent with a substantial body of work in adolescent and adult ADHD samples (Boecker et al., 2014; Plichta and Scheres, 2014), although see Paloyelis et al. (2012) and von Rhein et al. (2015). Association of ADHD with specifically right as opposed to bilateral NAcc reward processing also constitutes a familiar phenomenon (Nymberg et al., 2013; van Hulst et al., 2017) and may be due to

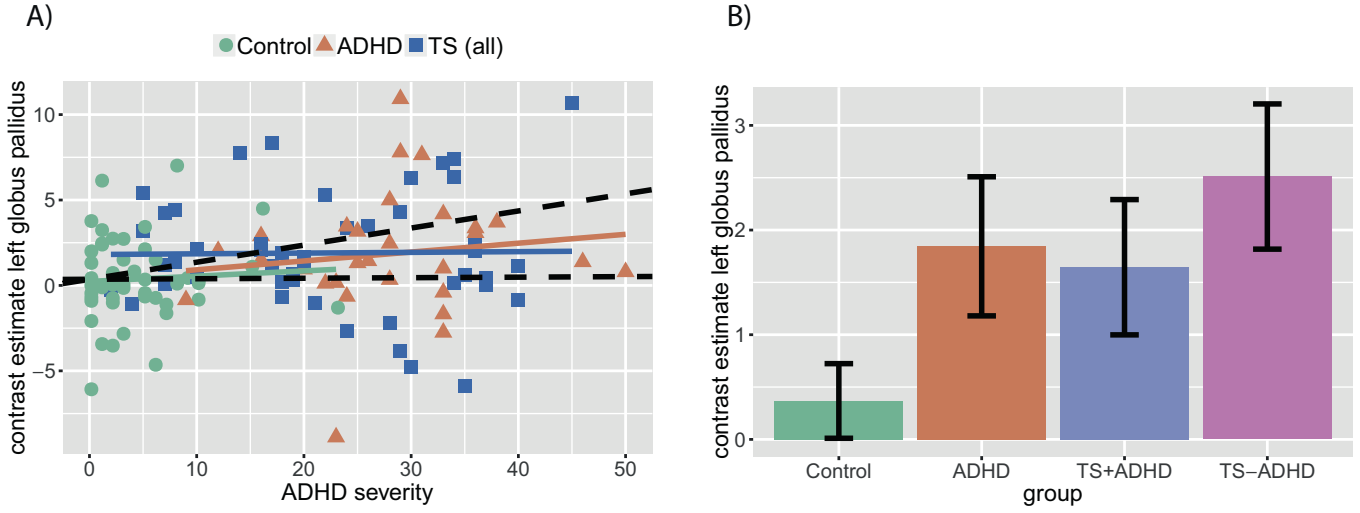

Fig. 5. A) Association between ADHD severity and left globus pallidus reward receipt estimates. ADHD severity reflects raw scores of the DSM-IV combined subscale of the Conners' Parent Rating Scale – Revised Long (Conners et al., 1998). Dashed regression lines represent the bootstrapped 95% confidence interval of the regression estimate from the model estimated for the total sample. Coloured regression lines are plotted for the groups separately for illustrative purposes. B) Average left globus pallidus estimates per group. Error bars denote *SE*. Abbreviations: ADHD – attention-deficit/hyperactivity disorder, TS – Tourette syndrome, TS + ADHD – Tourette syndrome with comorbid ADHD, TS − ADHD – Tourette syndrome without comorbid ADHD.

general asymmetries in the human striatal dopamine system (Martin-Soelch et al., 2011). We extend upon earlier work by corroborating NAcc hypoactivation in children aged 8–12 years, a scarcely studied age group yielding inconsistent previous reports (Kappel et al., 2015; van Hulst et al., 2017). The findings in children imply that alterations in reward pathways are a central characteristic of ADHD and do not just represent a marker of an ADHD subtype persisting into adulthood (van Hulst et al., 2017). For example, distinct patterns of neural reward processing have been shown between participants with remitting ADHD relative to those with persistent ADHD, possibly reflecting differences in risk factors and/or compensatory mechanisms (Wetterling et al., 2015). The fact that the relation between ADHD severity and NAcc hypoactivation was independent of main categorical diagnosis (TS or ADHD) supplements a similar observation of NAcc hypoactivation in both ADHD and ASD with comorbid ADHD (van Hulst et al., 2017). Lastly, in the current study, a dimensional analysis appeared to be more sensitive in detecting a NAcc effect than a categorical analysis of group differences. Together, the above supports the notion of ADHD severity as a dimensional construct with NAcc hypoactivation during reward anticipation as a neurofunctional marker, irrespective of main diagnosis.

The findings showed no relationship between NAcc activation during reward anticipation and TS. However, the classical and still dominant view of TS is that it involves excessive dopamine signalling in the striatum (Buse et al., 2013; Maia and Conceição, 2017). Moreover, the BOLD signal in the NAcc is thought to reflect dopamine release (Knutson and Gibbs, 2007) (although no one-to-one relationship was found by Lohrenz et al., 2016). Therefore, one might argue that altered reward-related NAcc activation was also to be expected in TS. Yet, the NAcc/ventral striatum has been implicated in TS to a lesser extent than the dorsal striatum including the Cau and Put (Langen et al., 2011; Yael et al., 2015). It has been suggested that comorbid conditions in TS may result from a more widespread pathophysiology, extending from the dorsal (motor) striatum to the ventral (limbic) striatum (Yael et al., 2015). This spatial explanation would be in line with our finding of an association between right NAcc activation and ADHD severity. On the neurotransmitter level, however, the comorbidity of TS with ADHD, supposedly involving reduced as opposed to increased striatal dopamine release, is not straightforward to explain (Buse et al., 2013). An intriguing explanation would be that TS with comorbid ADHD constitutes a different neurobiological subtype of TS, sharing important underlying mechanisms with ADHD. The fact that the dopamine reuptake inhibitor methylphenidate has been found to be an effective treatment for ADHD within TS, generally without exacerbating tics (Groenman et al., 2017), provides some support for this view. Based on the present study we cannot make suggestions about whether TS with comorbid ADHD is more similar to TS or ADHD in terms of dopaminergic functioning. We recommend future studies to replicate the NAcc result, and further focus on the contribution of dopamine dynamics to NAcc functioning in TS and/or ADHD.

We found no support for our hypothesis of hyperactivation of the Cau, Put, GP, or Thal during reward receipt in TS. This is consistent with the only other study of neural reactivation during reward receipt in TS, although in that study the left Put, Cau, GP, and Thal were not investigated (Worbe et al., 2011). Together, these functional neuroimaging results do not point to a role for altered neural processing of reward outcome in TS. However, some recent behavioural studies did report increased appetitive reinforcement learning and habit formation in adults with TS without ADHD (Delorme et al., 2016; Palminteri et al., 2009, 2011), which has been proposed to result from abnormal reinforcement signals in the dorsal striatum Yet, decreased instead of increased habit learning was seen in children with TS (Marsh et al., 2004). Discrepancies within and between neuroimaging and behavioural findings could be due to variation in age. The shape of the neurodevelopmental trajectory may be different in patients compared to controls, and persistent cases may present with stronger abnormalities (Debes et al., 2015). Notably, structural abnormalities in basal ganglia are more apparent in older TS samples (Forde et al., 2017). Discrepancies could also be due to variations in paradigms used. For example, the current MID paradigm did probe activation of the dorsal striatum during reward receipt but differs from the above-mentioned studies in that stimulus-response associations are instructed as opposed to learned. Hence, it was not designed to uncover behavioural abnormalities in reinforcement learning. More work is needed to elucidate where the behavioural evidence of atypical reinforcement learning in TS converges and what could be the underlying neural mechanisms.

The present study should be regarded in light of its strengths and limitations. First, our sample contained few participants with TS without comorbid ADHD. Therefore, the power to detect a specific TS effect may have been limited. As a second limitation, our sample contained imbalances: an overrepresentation of males and obsessive-compulsive comorbidity in the TS group, more head motion and lower IQ in both patient groups, and different medications used. These imbalances, however, match known characteristics of these groups. In contrast to the known male preponderance among individuals with ADHD, our ADHD group included more girls than boys. Controlling for the potential confounding effects of sex, age, head motion, compulsive behaviour, IQ, medication status, and comorbid ODD or generalized anxiety disorder did not change the results. However, the high number of participants on stimulant medication (although not on the day of scanning) could have weakened our ADHD effects due to possible normalization of striatal activation (Mizuno et al., 2013). A further limitation is the fact that we did not assess the potential influence of pubertal status. Our participants' age of 8–12 years could coincide with the onset of puberty, which is associated with changes in the brain's reward system (Somerville and Casey, 2010). Yet, the groups we studied all had similar age distributions and we observed no relationship between age and NAcc activation. The age range of 8–12 years was also a main strength of this study, because it covers a period when tics are most prevalent. Additionally, the combined sample of individuals with TS and/or ADHD, makes this study an important step into newly-chartered territory focusing on neural reward processing in TS and its overlap with ADHD.

To conclude, we found that ADHD severity was marginally related to hypoactivation of the right NAcc during reward anticipation, independent of the presence or absence of TS. This is in line with the view of NAcc hypoactivation as a dimensional, neurofunctional marker of ADHD symptoms, irrespective of primary diagnosis. No associations between TS and neural reward processing were detected.

CRediT authorship contribution statement

Sophie E.A. Akkermans: Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft, Writing - review & editing. **Daan van Rooij:** Software, Data curation, Methodology, Supervision, Writing - review & editing. **Jilly Naaijen:** Data curation, Investigation, Project administration, Writing - review & editing. **Natalie J. Forde:** Data curation, Investigation, Project administration, Writing - review & editing. **Regina Boecker-Schlier:** Methodology, Visualization, Writing - review & editing. **Thaira J.C. Openneer:** Investigation, Writing - review & editing. **Andrea Dietrich:** Conceptualization, Funding acquisition, Resources, Methodology, Writing - review & editing. **Pieter J. Hoekstra:** Conceptualization, Funding acquisition, Resources, Methodology, Writing - review & editing. **Jan K. Buitelaar:** Conceptualization, Funding acquisition, Resources, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

JKB has been a consultant to / member of advisory board of / and/

or speaker for Lundbeck, Shire, Roche, Medice, Novartis, and Servier. He has received research support from Roche and Vifor. He is not an employee of any of these companies, nor a stock shareholder of any of these companies. The other authors have no conflicts of interest to report.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.08.004.

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