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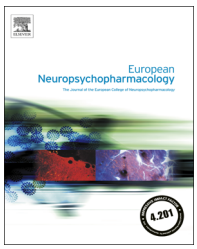

Dopaminergic activity in Tourette syndrome and obsessive-compulsive disorder

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Abstract
Tourette syndrome (TS) and obsessive-compulsive disorder (OCD) both are neuropsychiatric disorders associated with abnormalities in dopamine neurotransmission. Aims of this study were to quantify striatal $D_{2/3}$ receptor availability in TS and OCD, and to examine dopamine release and symptom severity changes in both disorders following amphetamine challenge.
Changes in [^{11}C]raclopride binding potential (BP_{ND}) were assessed using positron emission tomography before and after administration of D-amphetamine (0.3 mg kg^{-1}) in 12 TS patients without comorbid OCD, 12 OCD patients without comorbid tics, and 12 healthy controls. Main outcome measures were baseline striatal $D_{2/3}$ receptor BP_{ND} and change in BP_{ND} following amphetamine as a measure of dopamine release.
Voxel-based analysis revealed significantly decreased baseline [^{11}C]raclopride BP_{ND} in bilateral putamen of both patient groups vs. healthy controls, differences being more pronounced in the TS than in the OCD group. Changes in BP_{ND} following amphetamine were not significantly different between groups. Following amphetamine administration, tic severity increased in the TS group, which correlated with BP_{ND} changes in right ventral striatum. Symptom severity in the

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OCD group did not change significantly following amphetamine challenge and was not associated with changes in BP_{ND}.
This study provides evidence for decreased striatal $D_{2/3}$ receptor availability in TS and OCD, presumably reflecting higher endogenous dopamine levels in both disorders. In addition, it provides the first direct evidence that ventral striatal dopamine release is related to the pathophysiology of tics.

1. Introduction

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by the presence of vocal and motor tics (Robertson, 2000). Obsessive-compulsive disorder (OCD) is an anxiety disorder characterized by obsessions that cause anxiety, and compulsions aimed at reducing that anxiety (Leckman et al., 2010). There is considerable overlap between the two disorders in terms of clinical phenomenology, epidemiology, genetics, immunology, and treatment (Ferrao et al., 2009). Despite these commonalities, it is still not clear to which extent pathogenetic mechanisms in TS and OCD are similar, although it has been assumed that abnormalities in dopaminergic (DA) neurotransmission within fronto-striatal circuitry are of key importance in both disorders (Gerard and Peterson, 2003; Denys et al., 2004).

The dopamine hypothesis of TS and OCD is based predominantly on clinical evidence and molecular imaging studies. For example, dopamine receptor antagonists are effective as monotherapy in reducing tics in TS (Robertson, 2000) and as an adjunct to SSRIs in reducing symptoms in OCD (Denys, 2006; Vulink et al., 2009). Moreover, dopamine agonists may provoke tics (Lowe et al., 1982; Borcherding et al., 1990) and induce obsessive-compulsive behavior (Borcherding et al., 1990; Lemus et al., 1991). Molecular imaging studies using radiotracers binding to DA receptors have yielded conflicting results in TS (Gerard and Peterson, 2003). Some studies have supported the hypothesis that DA receptors are involved (Albin et al., 2003; Gilbert et al., 2006; Singer et al., 2002; Wong et al., 1997, 2008), other studies failed to show differences (Albin et al., 2009; George et al., 1994; Meyer et al., 1999; Turjanski et al., 1994). There are only a few reports on DA receptor binding in OCD, but these consistently have shown evidence for decreased D_2 receptor availability (Denys et al., 2004; Olver et al., 2009; Perani et al., 2008).

The inconsistencies in previous molecular imaging studies in TS may be explained by a number of methodological factors, including limited power of positron emission tomography (PET) and single photon emission computerized tomography (SPECT) studies, heterogeneity within subject populations, especially with regard to symptom severity and co-morbidity, and changes in DA receptor expression and/or function due to the clinical use of DA antagonists.

In the present study, we aimed to elucidate the role of DA neurotransmission in TS and OCD using the extensively validated PET tracer [^{11}C]raclopride (Gunn et al., 1997; Lammertsma et al., 1996). [^{11}C]raclopride binds to $D_{2/3}$ receptors and may be used to evaluate in vivo receptor binding at rest, as well as capture more dynamic aspects of DA transmission. Indeed, the change in [^{11}C]raclopride binding following amphetamine challenge, which increases endogenous DA levels, is considered an indirect measure of DA release (Laruelle, 2000; Spitzer et al., 1992). Furthermore, amphetamine administration has been associated with induction of tics and compulsive behaviors, especially when high doses are used (Borcherding et al., 1990; Castellanos et al., 1997). Consequently, measuring changes in [^{11}C]raclopride following amphetamine administration in TS and OCD patients may serve as a measure of symptom related DA release.

Two previous studies using this paradigm reported increased [^{11}C]raclopride displacement in the putamen in a sample of 5 TS patients (Laruelle, 2000; Singer et al., 2002) and, in an extended sample of 14 TS patients and 10 control subjects in the right ventral striatum (Laruelle, 2000; Wong et al., 2008). The majority of patients in the second study, however, had a co-morbid diagnosis of OCD, which in itself may be associated with abnormalities in DA neurotransmission.

The purpose of the present study was to directly compare baseline availability of striatal $D_{2/3}$ receptors and amphetamine-induced DA release between TS patients without OCD, OCD patients without tics or TS, and healthy controls.

2. Experimental procedures

2.1. Subjects

Patients were recruited through referrals from the academic outpatient clinic for anxiety disorders of the Academic Medical Center (AMC) Amsterdam and GGZinGeest, Amsterdam. Healthy control subjects were recruited through advertisements.

All subjects were interviewed by trained psychiatrists and diagnoses were confirmed using the Structural Clinical Interview for DSM-IV axis I disorders (SCID-I) (Spitzer et al., 1992). Tic history and severity were assessed using the Yale Tic Symptom Check List and the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989) and obsessive-compulsive symptoms using the Yale Brown Obsessive Compulsive Scale (YBOCS) (Goodman et al., 1989). Affective symptoms were assessed using the Hamilton Depression (HAM-D) and Anxiety (HAM-A) rating scales. Control subjects were included when there was no current or past psychiatric diagnosis. All subjects were free of psychotropic medication for at least 6 months. Nine TS subjects never had taken medication for their tics. One subject had used antipsychotic medication until 1 year before the study and two subjects had used an alpha$_2$ agonist several years before inclusion. Seven OCD subjects had never used medication for their obsessive-compulsive symptoms, whereas five had used SSRIs until 6 months before the study. Two TS subjects and three OCD subjects had a history of co-morbid depressive episodes, and one OCD subject had a co-morbid panic disorder.

Subjects were excluded when they had a history of regular use of psychoactive drugs or a positive urine drug screen, a history of neurological disease, or more than one risk factor for cardiovascular

disease. All subjects were in good physical health, based on medical history, physical examination, electrocardiogram, MRI of the brain and routine blood screening. Written informed consent from all subjects was obtained after a complete description of the study. Medical ethics committees of all participating centers approved the study protocol.

2.2. Radiochemistry

[^{11}C]raclopride was prepared as previously described (Bossong et al., 2009), in accordance with the EU guideline "Eudralix volume 4: good manufacturing practices". The precursor O-desmethyl raclopride hydrobromide was provided by ABX, Radeberg, Germany.

2.3. PET procedure

PET scans were performed using an ECAT EXACT HR+ (Siemens/CTI, Knoxville, TN, USA), which acquires 63 transaxial planes with an axial field of view of 15.5 cm, covering the entire brain. [^{11}C]raclopride was delivered intravenously using a computerized infusion pump (MedRad, Beek, the Netherlands). A priming bolus of 28 mL, administered over 3.1 min, was followed by a constant infusion over 88 min at a rate of 0.15 mL min^{-1}, resulting in a bolus to infusion ratio (K_{bol}) of 112 min (Carson et al., 1997). Mean injected dose was similar for controls, TS patients and OCD patients (708±125, 757±43 and 756±101 MBq, respectively; $p>0.1$). Forty minutes after start of [^{11}C]raclopride administration, subjects were placed in the PET camera for a 40 min scanning period, consisting of 8 consecutive frames of 5 min. After emission scanning a 10 min transmission scan was performed to correct for photon attenuation. Correction for emission contamination was performed using the dwell profile method (van der Weerdt et al., 2004). During scanning, subjects were immobilized with a custom made head holder. Subject motion was monitored continuously using laser beams, and corrected immediately when necessary. After the first PET scan, subjects could rest outside the camera for approximately 2 h to allow for decay of carbon-11. Before the second scanning session, amphetamine (0.3 mg kg^{-1}) was given intravenously over 2 min, directly followed by [^{11}C]raclopride administration. The protocol for the second scanning session was identical to that of the first. Subjects were under constant cardiovascular monitoring during both scans. Measurements of symptom severity were performed before and after administration of amphetamine, while subjects were still outside the scanner. Both YBOCS and YGTSS were administered immediately before injection, 20 min after injection of [^{11}C]raclopride, and after completion of the scan (120 min after injection). Forty minutes after amphetamine administration, a venous sample was collected to assess amphetamine plasma levels using a procedure based on liquid chromatography-mass spectrometry (LC-MS). Amphetamine plasma levels were similar across groups (controls 48.3±10.2 μg/L, TS 51.4±12.6 μg/L, OCD 50.5±7.1 μg/L, $p=0.77$). All [^{11}C]raclopride scans were reconstructed using FORE+2D FBP with a 0.5 Hanning filter, resulting in a transaxial spatial resolution of ~7 mm full width at half maximum (FHWM) in the center of the field of view.

2.4. Magnetic resonance imaging procedure

Structural T1 weighted MRI scans were acquired for all subjects on an Intera (Philips, Best, the Netherlands) 3T scanner (echo time, 4.6 ms; repetition time, 30 ms; flip angle, 30°; resolution, $0.89 \times 0.89 \times 1$ mm^3).

2.5. Data analysis

Non-displaceable binding potential (BP_{ND}) of [^{11}C]raclopride (Innis et al., 2007) was used as measure of D_2/D_3 receptor availability. Primary outcome parameters were baseline BP_{ND} and the reduction in BP_{ND} (ΔBP_{ND}) induced by amphetamine. BP_{ND} was defined as the distribution volume ratio (DVR) minus one (Lammertsma et al., 1996). As scans were performed during steady state, DVR corresponds with the ratio between activity concentrations in target (C_T) and reference (C_{CBL}) tissues. Cerebellum, which is devoid of D_2/D_3 receptors, was used as reference tissue. Each PET frame was individually co-registered to the structural T1 scan to correct for motion between frames. For both baseline and amphetamine scans, parametric BP_{ND} maps were generated from the summed PET images using $BP_{ND}=(C_T-C_{CBL})/C_{CBL}$. To assess whether steady state conditions were achieved, [^{11}C]raclopride concentrations were calculated for all eight frames of each scan. Changes in concentration between frames were

Table 1 Baseline characteristics of all subjects.

	Tourette's syndrome			Obsessive-compulsive disorder			Healthy controls			*F*	*p*
	Mean	Range	SD	Mean	Range	SD	Mean	Range	SD		
Age	31	20-45	8.1	35.8	21-56	11.5	32	21-56	12	0.8	0.46
Sex (male/female)	8/4			4/8			4/8			6.6[a]	0.04
Number of current tics (0-37)	10.7	4-23	6.2	0	0	0	0	0	0	-	-
YGTSS (0-50)	17.0	7-28	7.8	0	0	0	0	0	0	-	-
YBOCS (0-40)	5.1	0-15	5.5	23.6	12-32	5.5	0	0	0	13.7	<0.001 OCD vs. HC $p<0.001$ OCD vs. TS $p<0.001$ TS vs. HC ns
Hamilton Depression Rating Scale (0-68)	2.1	0-8	2.6	10.7	4-26	7.1	1.3	0-3	1	57.6	<0.001 OCD vs. HC $p<0.001$ OCD vs. TS $p<0.001$ TS vs. HC ns
Hamilton Anxiety Rating Scale (0-56)	2.9	0-16	4.7	13.9	2-34	9.4	0.75	0-3	1	16.1	<0.001 OCD vs. HC $p<0.001$ OCD vs. TS $p=0.02$ TS vs. HC ns

YGTSS=Yale Global Tic Severity Scale.
YBOCS=Yale Brown Obsessive Compulsive Scale.
[a]Chi-square.

minimal (slopes varied between −0.01 and −0.02) and these changes were similar across groups and between conditions.

A voxel-based analysis of these parametric images was performed using SPM2 (Wellcome Trust Center for Neuroimaging, London, UK). The structural MRI of each subject was normalized to the SPM T1-MRI template and subsequently this transformation was applied to the co-registered parametric BP_{ND} images. Normalized PET scans were smoothed using a 5 mm Gaussian filter resulting in an overall resolution of 8.5 mm FWHM. To limit the search volume, a functional mask of the striatum was created from the main effect of displacement in all subjects (baseline BP_{ND} > post-amphetamine BP_{ND}). In a balanced design, such a mask is orthogonal with respect to comparisons of interest (i.e., group differences), and is likely to be more specific than anatomical ROIs (Friston et al., 2006). This mask was used in all of the following analyses. Voxel-wise one-way ANOVA was used to assess the location of peak differences between groups at baseline, which are reported at a threshold of $p<0.05$ with Family Wise Error (FWE) correction for the search volume. Results at $p<0.005$ uncorrected are reported as trends. Displacement was assessed using a voxel-wise one-way ANOVA with ΔBP_{ND} images, created by subtracting amphetamine images from baseline images for each subject. Mean baseline BP_{ND} values were added as covariate to the model, to correct for baseline differences.

Regression analyses were performed for mean symptom severity scores (YGTSS for TS, YBOCS for OCD) measured during the baseline scan with baseline BP_{ND} as independent variable and severity scores as dependent variables. Similarly, changes in symptom severity (difference between YBOCS and YGTSS scores measured immediately before and 20 min after injection of amphetamine) were correlated to ΔBP_{ND} images.

Table 2 Areas with significant differences in baseline BP_{ND} between groups.

Region	MNI-coordinates	Cluster size	Z-score
Controls > OCD > TS			
Left putamen	−22 2 −2	28	3.52**
Right putamen	34 2 6	68	3.43**
Controls > TS			
Left putamen	−22 0 -2	38	3.60**
Right putamen	34 2 4	93	3.49**
Controls > OCD			
Left putamen	−14 6 −8	2	2.60*

*$p<0.005$ uncorrected.
**$p<0.05$ FWE corrected.

3. Results

3.1. Demographic data

Twelve patients with TS (4 women), 12 patients with OCD (8 women) and 12 healthy control subjects (8 women) participated in the study. Subject characteristics are provided in Table 1. Groups were matched for age. For the TS group, the

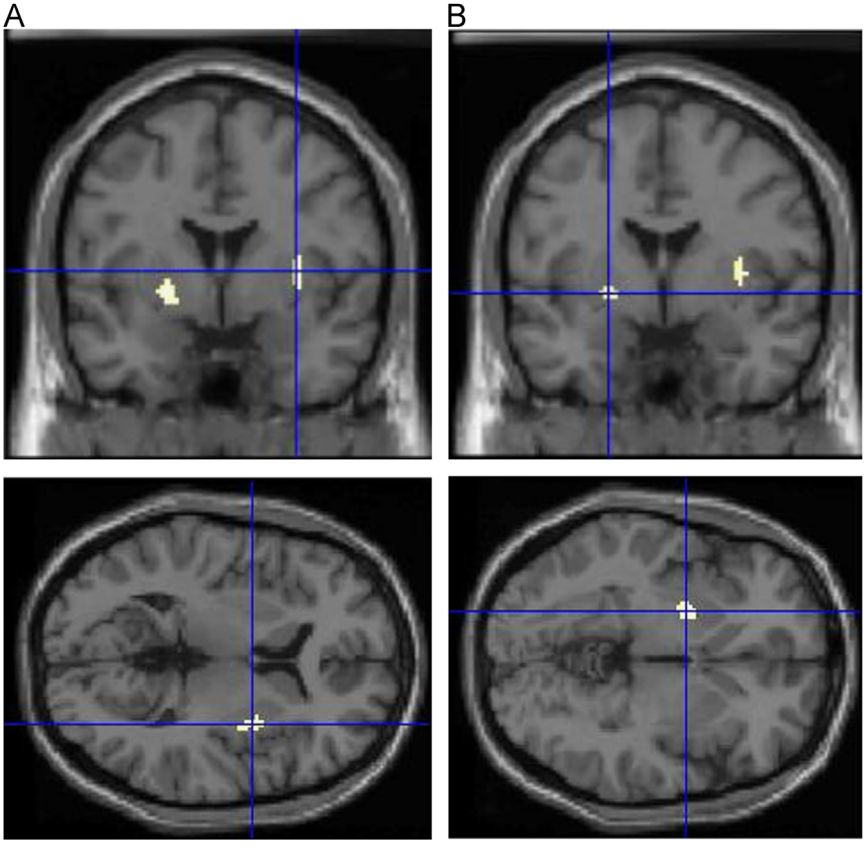
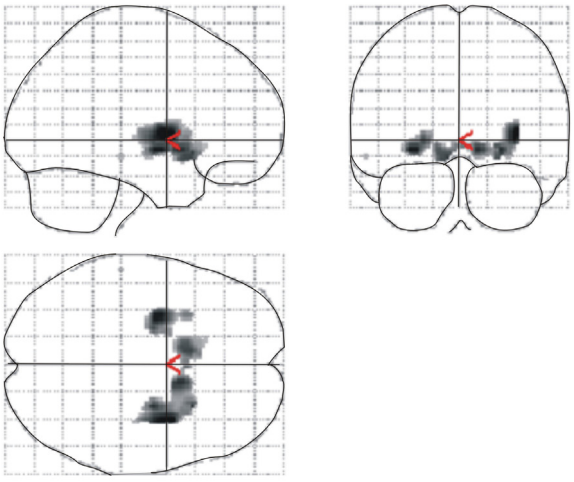
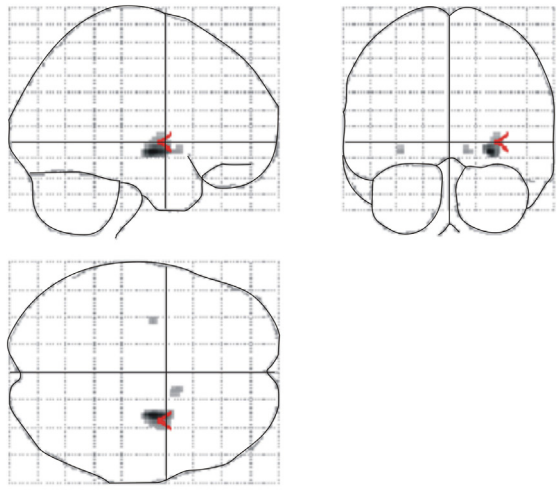


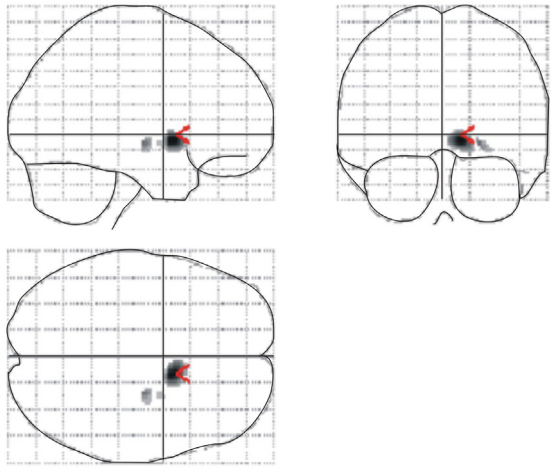
Fig. 1 Decreased baseline BP_{ND} in TS and OCD (contrast HC > OCD > TS) in bilateral putamen. (A) right putamen (B) left putamen.



Right caudate (12 8 -6) Z=4.18, right putamen (26 -8 -8 and 34 2 2) Z=4.18 and Z=4.53, left caudate (-8 14 -10) Z=4.05, left putamen (-28 -6 -6) Z=4.38.



OCD: Right caudate (12 6 -6) Z=3.34, right putamen (26 -8 -6) Z=4.50, left putamen (-30 -8 -6)



TS: Right caudate (12 6 -4) Z=5.03

Fig. 2 Displacement (BP_{ND} baseline vs. BP_{ND} post-amphetamine) in healthy controls (upper panel), OCD (middle panel) and TS (lower panel).

mean number of current tics at baseline ranged from 4 to 23 (overall mean 11±6) with a mean YGTSS score of 19±8, and the mean number of current obsessions or compulsions was 9±8, with a mean YBOCS severity score of 5±6. For the OCD group, the mean YBOCS score was 24±6. OCD symptoms were of the following subtypes: washing (Gerard and Peterson, 2003), aggressive thoughts (Ferrao et al., 2009), forbidden thoughts (Robertson, 2000), symmetry/ordering (Leckman et al., 2010) and perfectionism/doubt (Leckman et al., 2010).

3.1.1. Baseline BP_{ND}

Differences in baseline BP_{ND} between healthy controls, TS and OCD are listed in Table 2. Omnibus testing revealed significant between-group differences in bilateral putamen extending into bilateral caudate nucleus, with the highest baseline BP_{ND} values in healthy controls, lowest values in TS patients and intermediate values in OCD patients (see Fig. 1). Post hoc testing confirmed that baseline BP_{ND} was significantly decreased in TS patients vs. healthy controls in bilateral putamen. Baseline BP_{ND} was decreased in OCD patients vs. healthy controls in left ventral putamen at trend level. Baseline BP_{ND} differences between OCD and TS patients were not statistically significant.

3.1.2. Amphetamine induced BP_{ND} changes

Main effects of amphetamine administration on BP_{ND} for all groups are shown in Fig. 2. Displacement was present in bilateral striatum (putamen and caudate nucleus), being most pronounced in healthy controls. A group by displacement effect at trend level in the left ventral caudate (MNI coordinates: −14 26 −2, 8 voxels, $Z=2.75$, $p<0.005$) suggested decreased BP_{ND} displacement in TS, but these differences disappeared after correcting for baseline binding.

3.1.3. Post-amphetamine BP_{ND}

An omnibus test showed no significant between-group differences in BP_{ND} after administration of amphetamine.

3.1.4. Behavioral response correlates

Following amphetamine administration, tic severity increased significantly in the TS group ($p=0.003$), with a mean of 3.5±4.6 points on the YGTSS. This increase in tic severity correlated positively ($\rho=0.85$) with displacement in right ventral caudate at a borderline significance level (Fig. 3 and Table 3). A negative correlation at trend level ($p=0.005$, uncorrected) between baseline tic levels and baseline BP was found in left ventral putamen and right ventral caudate (Table 3). Finally, a negative correlation ($\rho=-0.75$), between post-amphetamine YGTSS and post-amphetamine BP_{ND} was found in the right ventral striatum.

In OCD patients, correlations between OCD severity and baseline BP_{ND}, and between changes in YBOCS and displacement were not statistically significant.

4. Discussion

The current [^{11}C]raclopride PET study aimed to directly compare dopaminergic neurotransmission in TS patients without OCD symptoms, OCD patients without tics and healthy controls. Both TS and OCD patients showed lower striatal $D_{2/3}$ receptor binding at baseline than healthy controls, although in the OCD group only at trend level.

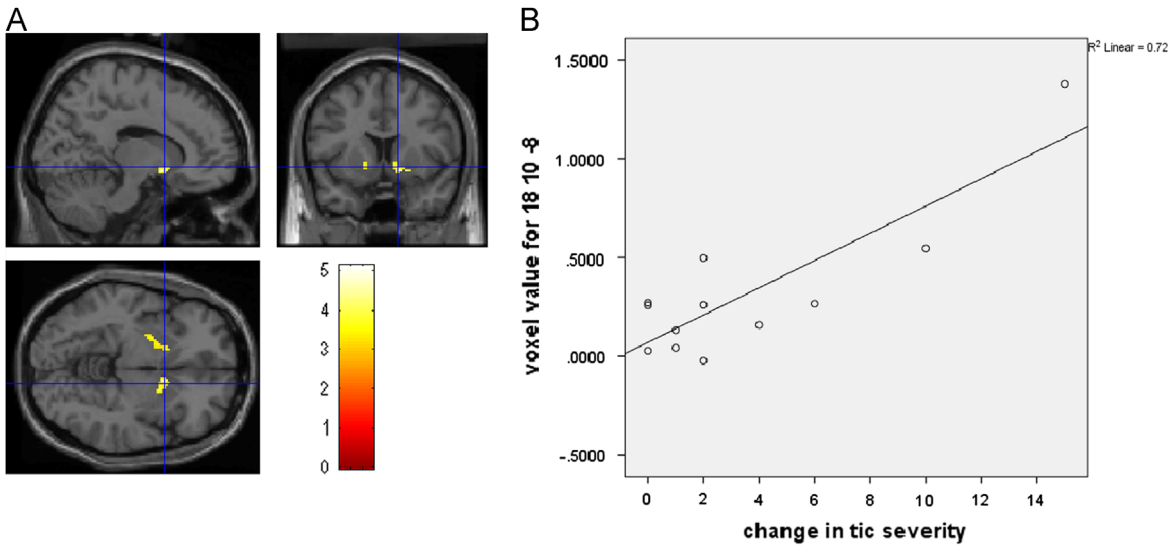


Fig. 3 (A) Regions showing a significant correlation between changes in tic severity and DA release in the TS group. (B) Scatter plot illustrating correlation between DA release and change in tic severity at MNI coordinate 18 10 −8 (right ventral caudate).

Table 3 Correlations between YGTSS scores and BP_{ND} for the baseline scan.

Region	MNI coordinates	Cluster size	Z-score
Positive correlation displacement and YGTSS increase			
Right ventral caudate	18 10 -8	17	3.51**
Negative correlation BP_{ND} at baseline and YGTSS at baseline			
Left ventral putamen	−14 14 −2	3	2.55*
Negative correlation BP_{ND} post-amphetamine and YGTSS post-amphetamine			
Right ventral caudate	6 12 0	19	3.60***

YGTSS = Yale Global Tic Severity Scale.
*$p < 0.005$ uncorrected.
**$p < 0.001$ uncorrected ($p = 0.06$ FWE corrected).
***$p < 0.05$ FWE corrected.

There were no significant differences between amphetamine-induced changes in BP_{ND} between the three groups. Tic severity in TS patients increased after the amphetamine challenge, which was correlated with the displacement in right ventral striatum, whereas no changes in symptom severity in OCD patients were observed.

4.1. Baseline [^{11}C]raclopride binding

The finding of decreased baseline [^{11}C]raclopride BP_{ND} in TS is in contrast with other PET studies, in which no differences in binding between TS and controls were found (Singer et al., 2002; Turjanski et al., 1994; Wong et al., 2008). Differences in PET scan acquisition, data analysis methodology, and patient characteristics may have accounted for these discrepant findings. Interestingly, a trend for a negative correlation between baseline BP_{ND} and tic severity was found, suggesting that decreased baseline BP_{ND} is indeed a pathological feature of TS.

The observation of low baseline striatal [^{11}C]raclopride binding in OCD at trend level is in line with other SPECT and PET studies, substantiating the hypothesis of dopaminergic dysfunction in OCD. Using [^{123}I]iodobenzamide ([^{123}I]IBZM) SPECT, Denys et al. (2004) showed significantly decreased $D_{2/3}$ receptor availability in left caudate nucleus within a group of 10 OCD patients compared with 10 age matched healthy controls. Schneier et al. (2008) found comparable striatal $D_{2/3}$ decrease in 8 predominantly drug-naïve OCD patients compared with 7 control subjects. Perani et al. (2008) demonstrated significantly decreased striatal [^{11}C] raclopride binding in dorsal caudate, dorsal putamen and ventral striatum of 9 drug-naïve OCD patients compared with 9 controls. $D_{2/3}$ alterations were more prominent in ventral striatum.

Decreased baseline [^{11}C]raclopride binding to striatal $D_{2/3}$ receptors, observed in both TS and OCD, may be due to

several mechanisms. It may result from (1) decreased $D_{2/3}$ receptor density and/or affinity, for instance due to receptor internalization, (2) increased levels of endogenous dopamine competing with the radiotracer, or (3) a combination of these phenomena. To assess whether increased levels of endogenous dopamine are the most plausible explanation for the lower baseline BP_{ND} observed in both patient groups, a dopamine depletion study should be conducted, as has been done in patients with schizophrenia (Abi-Dargham et al., 2009). If confirmed, the tonic/phasic model of DA release (Grace and Bunney, 1983) could explain these abnormalities in dopamine neurotransmission in TS. The single-spike "tonic" firing pattern supplies a constant low extrasynaptic concentration of DA, whereas burst firing of the neurons leads to massive DA release into the synapse which is named the "phasic" response. Amphetamine induced DA release is believed to mimic this phasic response (Grace and Bunney, 1983). Synaptic DA concentrations measured during the baseline scan are thus likely to reflect a combination of both tonic and phasic DA responses during rest. As such, increased endogenous DA levels at baseline in both patient groups may be a result of increased phasic firing at rest, supporting a hyperdopaminergic state that has been hypothesized to underlie TS and OCD (Denys et al., 2004; Wong et al., 2008).

4.2. Changes in BP_{ND} following amphetamine challenge

Contrary to previous studies, TS patients did not show increased amphetamine induced DA release compared to controls. Differences in patient characteristics and methodology may have accounted for these discrepant findings. Wong et al. (2008) studied a sample in which the majority of the TS patients (10 out of 14) were also diagnosed with OCD. These authors showed that only the subset of TS+OCD patients display significantly increased DA release in the ventral striatum as compared to controls. This raises the question if increased DA release might be related to either TS or OCD, or both. Our sample consisted of OCD patients without tics and TS patients without OCD to differentiate between the contributions of either disorder to striatal dopamine dysregulation. Since our results show no increased DA release in OCD, it is unlikely that OCD was responsible for increased DA release in the previous study. However, we did not find increased DA release in the TS group either, which may have been due to the fact that our sample was less severely affected, as a result of excluding patients with co-morbidity. Moreover, TS with co-morbid OCD is associated with changes in limbic brain areas both structurally as well as functionally, whereas TS without OCD is associated with abnormalities in motor areas (Worbe et al., 2010, 2011). Thus, the finding of increased ventral striatal DA release in the study by Wong et al. (2008) may be specific for TS patients with associated OCD, which were excluded from our study.

A second difference between the current study and previous studies is related to PET scan acquisition protocols. In these previous studies, amphetamine was administered 5 min before bolus injection of [^{11}C]raclopride and the start of the emission scan. In the present study a bolus plus continuous infusion protocol was used and emission scanning was performed under steady state conditions. It has been argued that scanning under steady state conditions is less susceptible to artifacts due to changes in cerebral blood flow and washout rate of the tracer (Carson et al., 1997; Laruelle, 2000), which is preferable when administering amphetamine as this may affect blood flow. Another advantage of the bolus plus constant infusion protocol is that after administration of amphetamine subjects stayed outside the scanner during infusion, which enabled us to record changes in symptom severity. Amphetamine-induced DA release in the ventral striatum was related to increased tic severity, which provides evidence that ventral striatal DA release is related to the pathophysiology of tics. This finding is substantiated by the correlation between tic severity and dopaminergic tone (at baseline as well as post-amphetamine), but seems to be difficult to reconcile with the low to normal amphetamine induced DA release in the TS group as compared to controls. However, it may be argued that only a small increase in DA may suffice to cause progressive symptoms, when DA concentrations are already increased at rest in the TS group.

Tics tend to follow a waxing and waning course, are partially under voluntary control and tic severity often decreases after adolescence (1), which led to the hypothesis that tics decrease with increasing prefrontal control over (abnormal) striatal function (Peterson et al., 2001). Indeed, cognitive techniques have been successful in controlling tics. Grace et al. (2007) noted that both increased tonic and phasic DA release can shift the balance from medial prefrontal cortical (mPFC) control towards limbic control of goal directed behavior. Increased tonic DA, acting on D_2 receptors, attenuates mPFC activity, whereas increased phasic DA, acting on D_1 receptors enhances limbic control. In this model, D_2 receptor antagonists, the main pharmacological treatment for TS, increase mPFC control and may thus restore dopaminergic balance. On the other hand, increased ventral DA release might result in reinforcement of corticostriatal circuits, facilitating the progressive formation of tics (Groenewegen et al., 2003; Maia and Frank, 2011; Saka and Graybiel, 2003).

4.3. Limitations

Several limitations of our study warrant further discussion. The control and TS group were not well matched for gender, with relatively more females in the control group. Gender differences in both baseline D_2 receptor binding as well as DA release have been observed, and males reportedly to have relatively higher dopamine release than females (Munro et al., 2006) and increased baseline D_2 binding (Pohjalainen et al., 1998). However, as the TS group contained more males than the control group, bias due to gender would have resulted in increased DA release in the TS group and increased baseline binding. Moreover, secondary analyses including gender as a covariate yielded similar results (data not shown). Menstrual phase of the female subjects in our study was not evaluated and might also have influenced D_2 receptor measurements, as was shown in female monkeys (Czoty et al., 2009), but not in humans (Nordstrom et al., 1998). Although our sample was not

entirely treatment naïve, only one patient had used a D_2 receptor antagonist in the past, therefore confounding effects of previous neuroleptic use are unlikely.

In our study we compared OCD and TS patients, but excluded TS patients with OCD to investigate the contribution of either disorder; an additional comparison between a group of TS patients with and without OCD, controlling for symptom severity, may further increase our understanding of the similarities and differences between the two disorders.

Unfortunately, individual differences in impulsivity were not assessed. Impulsivity may be one of the explanations for lack of control over tics and compulsive behaviors in TS and OCD. In addition, impulsivity has been associated with baseline binding of [^{11}C]raclopride and its displacement after amphetamine (e.g. Oswald et al., 2007). Nevertheless, both YGTSS and YBOCS contain items for control over tics and compulsions, respectively, and no correlation between scores on these items and [^{11}C]raclopride binding or amphetamine induced displacement was observed (data not shown). Finally, although comparable with earlier studies, the sample with 12 subjects in each subject group was modest, so any hypotheses regarding etiology should be made with caution.

4.4. Conclusion

Baseline striatal $D_{2/3}$ receptor binding in TS and OCD was decreased in TS and OCD patients, supporting the hypothesis of chronically increased dopaminergic activity in both disorders. Dopaminergic dysfunction may be a common pathophysiologic mechanism in TS and OCD, explaining considerable overlap between the two disorders in terms of clinical phenomenology.

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Contributors

All authors had full access to all study data. Dr. Denys takes responsibility for both integrity of the data and accuracy of data analysis. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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