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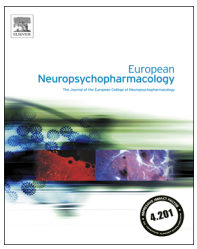

Dopaminergic activity in Tourette syndrome and obsessive-compulsive disorder

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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