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A 4-year dopamine transporter (DAT) imaging study in neuroleptic-naive first episode schizophrenia patients

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ABSTRACT

Alterations in the dopaminergic system have long been implicated in schizophrenia. A key component in dopaminergic neurotransmission is the striatal dopamine transporter (DAT). To date, there have been no longitudinal studies evaluating the course of DAT in schizophrenia. A 4-year follow-up study was therefore conducted in which single photon emission computed tomography was used to measure DAT binding in 14 patients and 7 controls. We compared the difference over time in [^{123}I] FP-CIT striatal/occipital uptake ratios (SOUR) between patients and controls and the relationship between this difference and both symptomatology and functional outcome at follow-up. We also calculated the relationship between baseline SOUR, symptoms and functional outcome at follow-up. There were no statistically significant differences between patients' SOUR changes over time and those of controls. A significant negative correlation was observed between patients' SOUR changes over time and negative symptomatology at follow-up. A significant negative correlation was also found between baseline SOUR in patients and negative symptomatology, and there was a significant association between lower SOUR at baseline and poor outcome. Although the study found no overall differences in DAT binding during follow-up between schizophrenia patients and controls, it demonstrated that differences in DAT binding relate to patients' characteristics at follow-up.

1. Introduction

Dopamine has long been implicated in the pathogenesis of schizophrenia. It has been proposed that hyperactivity of dopamine transmission is responsible for psychotic symptomatology. This idea was initially based on the correlation between therapeutic doses of antipsychotic drugs and their potency to block D2 receptors (Seeman and Lee, 1975) as well as the psychotogenic effects of dopamine-enhancing drugs, such as amphetamine (Lieberman et al., 1987). More recently, brain-imaging studies have observed that amphetamine-induced dopamine release is elevated in schizophrenia patients (Laruelle et al., 1996; Abi-Dargham et al., 1998) and positron emission tomography (PET) studies with [^{18}F]DOPA and [^{11}C]DOPA have observed increased dopamine presynaptic activity in schizophrenia (Reith et al., 1994; Hietala et al., 1995; Lindstrom et al., 1999).

The foregoing studies indicate a disruption in dopaminergic activity in schizophrenia that largely depends on striatal presynaptic activity, as other authors have recently suggested (Howes and Kapur, 2009; Lyon et al., 2011). However, this disruption seems to explain mostly positive symptomatology.

In the early 1990s, a modified dopamine hypothesis emerged. It postulated regionally specific dopamine dysregulation, with subcortical hyperdopaminergia responsible for positive symptomatology and cortical hypodopaminergia responsible for negative and cognitive symptoms (Davis et al., 1991). However, many aspects of the illness were still not adequately explained. These included the etiological origins of the dopaminergic abnormality, the different courses of the

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illness and, in particular, the deteriorating course observed in some patients.

A neurochemical model that tried to explain several symptomatological domains and progressive aspects of schizophrenia was later proposed. The neurochemical sensitization model of the dopaminergic system (Lieberman et al., 1997) postulates that schizophrenia is the consequence of a series of events. It supposes that, initially, there is an abnormal development of cerebral circuits. This abnormal development then causes the dopaminergic system to become unable to adapt to stressful events, and leads to sensitization. During this period, it is suggested that there is a subcortical hyperdopaminergic state responsible for onset of the disease, and that this persistent hyperdopaminergia causes neurotoxicity and loss of dopamine neurons, resulting in a residual state. To date, there has been little evidence supporting this model, and it is important to point out that the critical component of this model is the striatal presynapse.

One of the key components of the striatal presynapse is the dopamine transporter (DAT). Dopamine reuptake via DAT provides the primary mechanism through which dopamine is released from the striatal synapse. It has been suggested that in vivo DAT binding may be a marker of the integrity of dopamine terminals (Hantraye et al., 1992).

Several studies have attempted to examine striatal DAT binding in schizophrenia with conflicting results. Some studies found decreased DAT binding in schizophrenia patients (Laakso et al., 2001; Mateos et al., 2005), whereas others found no differences (Laakso et al., 2000; Laruelle et al., 2000; Schmitt et al., 2005) or an increase (Sjöholm et al., 2004). The inconsistencies between studies could be due to methodological differences, such as different imaging techniques or, more importantly, different characteristics of patients (chronic patients, first episode patients, and good/bad outcome patients). As mentioned, it has been proposed by some authors that there is a loss of dopamine neurons over the course of the illness. Thus, if DAT binding is a marker of the integrity of dopamine terminals, it should vary depending on the patient's illness duration. So far, only two studies (Laakso et al., 2000; Laruelle et al., 2000) have taken duration of the illness into consideration. In the first study, no association was found between duration of illness and DAT binding, whereas in the second, a negative association was found between DAT binding in the putamen nucleus and duration of illness. Nevertheless, a longitudinal approach would be one of the best ways to study DAT binding variations over the course of the illness.

The main aim of the present study was to test the hypothesis that schizophrenia is associated with an accelerated loss of striatal DAT binding over the course of the illness and to examine the relationship between this loss and symptomatology, as well as functional outcome. The second aim of the study was to test whether different baseline striatal DAT binding is associated with different symptomatology and functional outcome at follow-up.

2. Methods

2.1. Subjects

A 4-year DAT single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) follow-up study was carried out, including patients with first-episode schizophrenia and healthy comparison subjects; the MRI methods and results are described in an earlier report (Mané et al., 2009). We recruited antipsychotic-naïve patients hospitalized in the Psychiatric Unit of the Hospital Clinic de Barcelona for their first episode of psychotic illness. Exclusion criteria were the following: Pregnancy, IQ below 80, presence of a major medical or neurological illness, and presence of a substance abuse disorder, except cannabis and nicotine. The study was approved by the Human Ethics Committee of the Hospital Clinic de Barcelona, and all participants gave informed consent. Patients were assessed both at baseline and at follow-up by a trained psychiatrist with the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1999).

Clinical characteristics were assessed at both time points with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1990). Functional outcome was assessed at follow-up with the Global Assessment of Functioning scale (GAF). Controls were screened to rule out current or past history of psychiatric, neurological, or medical illness by using the Structured Clinical Interview for DSM-IV, medical history, and physical examination.

At baseline, 20 first-episode antipsychotic-naïve patients with a DSM-IV diagnosis of a schizophreniform disorder or schizophrenia and 10 controls underwent MRI and DAT SPECT. A total of 14 patients and 7 controls completed the longitudinal study and were reevaluated after 4 years. At baseline, 15 patients met DSM-IV criteria for schizophreniform disorder and 5 patients met criteria for schizophrenia. At follow-up, all patients met criteria for schizophrenia except for two patients who were diagnosed with schizoaffective disorder.

A proportion of the subjects who participated in the cross-sectional study could not be included at follow-up. Reasons for the failure of subjects to participate at follow-up were as follows: refusal to participate (4 patients/1 control), lost contact (1 patient/1 control), and living abroad (1 patient/1 control).

At baseline, there were no statistical differences in demographic and clinical characteristics between subjects included in the follow-up assessment and those subjects who failed to complete the follow-up. Among those who completed the study, scan interval was not significantly different between groups: patients: 48.93 months (11.49) vs. controls: 51.53 months (11.09).

There were no statistically significant differences in handedness between groups (patients: 2 left-handed/12 right-handed; controls: 2 left-handed/5 right-handed). During follow-up, all patients were treated with atypical antipsychotics (12 risperidone and 2 olanzapine), but one of them was treated for 6 months with zuclopenthixol. No patients were tagged as outliers after an individual assessment of scale scores. Table 1 summarizes the demographic and clinical characteristics of subjects who completed the study.

2.2. DAT SPECT and processing

SPECT acquisition was performed at both time points (baseline (T_0) and at 4-year follow-up (T_4)) with the same protocol. One hour

Table 1
Demographic and clinical characteristics of subjects who completed the study.

	Patients who completed the study	Controls who completed the study	*p*
Gender (male/female)	9/5	4/3	n.s
Age-years (m; sd)	26.5 (6.15)	30.01 (4.59)	n.s
Handedness (right/left)	12/2	5/2	n.s
Smoking cigarretes day (m; sd)	14.63 (9.63);	9 (11.74)	n.s
Smokers percentage	10/14	4/7	n.s.
Follow-up duration (months)	48.93 (11.49)	51.53 (11.09)	n.s
PANSS-P Baseline (m; sd)	26.14 (6.09)	–	
PANSS-N Baseline (m; sd)	24.71 (8.52)	–	
PANSS-T Baseline (m; sd)	88.93 (15.6)	–	
PANSS-P Follow-up (m; sd)	13.64 (5.5)	–	
PANSS-N Follow-up (m; sd)	12.5 (3.60)	–	
PANSS-T Follow-up (m; sd)	55.93 (15.62)	–	
GAF Follow-up (m; sd)	66.43 (16.19)	–	

m: mean; sd: standard deviation; PANSS-P: PANSS positive subscale; PANSS-N: PANSS negative subscale; PANSS-G: PANSS general subscale; PANSS-T: total PANSS.