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# Fluvoxamine Treatment and D$_2$ Receptors: a Pet Study on OCD Drug-Naïve Patients

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Changes in D$_2$ receptors during antidepressant therapy have been reported in patients with major depressive disorder using PET/SPET. The aim of this study was to evaluate modifications in D$_2$ receptors that might occur in patients affected by obsessive-compulsive disorder (OCD) during serotonin reuptake sites inhibitors (SSRIs). To this purpose, we measured the *in vivo* binding of [$^{11}$C]raclopride ([$^{11}$C]Rac)in the brain of a group of OCD naïve patients before and after the repeated administration of the inhibitor SSRI fluvoxamine. Eight patients with a Diagnostic and Statistical Manual of Mental Disorders IVth edition diagnosis of OCD completed the study undergoing a PET scan and a complete clinical evaluation before and during treatment with fluvoxamine. Patients have been compared also with a group of nine age-matched normal volunteers. Fluvoxamine treatment significantly improved clinical symptoms and increased [$^{11}$C]Rac binding potential (BP) in the basal ganglia of OCD patients ($7.5 \pm 5.2$, $6.9 \pm 6.9$, and $9.9 \pm 9.3\%$ in dorsal caudate, dorsal putamen, and ventral basal ganglia, respectively; $p < 0.01$) to values closer to those observed in the group of normal subjects. Chronic treatment with fluvoxamine induces a slight but significant increase in striatal [$^{11}$C]Rac BP of previously drug-naïve OCD patients. The modifications in D$_2$ receptor availability might be secondary to fluvoxamine effects on serotoninergic activity.
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## INTRODUCTION

Obsessive-compulsive disorder (OCD) is a heterogeneous mental disorder, often disabling, with different clinical presentations, including primary obsessions and secondary (obsession-dependent) compulsions. Several theories indicate that OCD has biological as well as psychological causes. Although the molecular causes of OCD remain unsolved, a dysfunction in a neuronal loop running from the orbital frontal cortex to the cingulate gyrus, striatum (caudate nucleus and putamen), globus pallidus, thalamus, and back to the frontal cortex has been suggested. This hypothesis is supported by neurological (Laplane *et al*, 1989), neurosurgical (Mindus *et al*, 1994; Oliver *et al*, 2003; Rauch, 2003), and imaging findings (Baxter *et al*, 1992; Breiter *et al*, 1996; Saxena *et al*, 1998; Trivedi, 1996). The exact nature of the molecular events that evoke OCD symptoms is not known

and several hypotheses have been put forward. The activity of 'OCD loop' is regulated by different neurotransmitters including: glutamate, serotonin dopamine, and GABA (McDougle *et al*, 1993). In particular, cortical glutamatergic neurons present within the circuit co-express dopamine D$_1$ and serotonin 5HT$_2$ receptors, whereas dopamine D$_2$ receptors are expressed by cortical presynaptic inhibitory interneurons and postsynaptic striatal neurons. The clinical efficacy of serotonin reuptake sites inhibitor (SSRI) has focused the role of serotonin and serotonin receptors in OCD (Baumgarten and Grozdanovic, 1998). However, other findings suggest a possible role also for dopamine and dopamine receptors. In particular, (a) dopamine regulates cortico-striatal-thalamo-cortical circuits through its activity on indirect and direct pathway (Alexander and Crutcher, 1990); (b) structural damages to the basal ganglia, a region particularly rich in dopamine receptors, promote OCD symptoms (Carmin *et al*, 2002); (c) a supersensitivity to cataleptic induction by the D$_2$ receptor antagonist sulpiride was observed in the D1CT mice, an animal model that shows symptoms of human compulsive disorders associated with cortical-limbic hyperactivity (Campbell *et al*, 1999); (d) differences in D$_2$ dopamine receptor binding in the head of the caudate nucleus predict phenotypic severity in

monozygotic twins discordant for Tourette syndrome severity (Wolf et al, 1996); and (e) a reduced availability of D$_2$ receptors subtypes has been recently described in the left caudate nucleus of patients with OCD (Denys et al, 2004). In addition, preclinical studies on rodents indicated that the repeated administration of antidepressants affect dopamine D$_2$ receptors (Ainsworth et al, 1998a; Ainsworth et al, 1998b; Spyraki and Fibiger, 1981). A modulation of dopaminergic system after SSRIs administration has also been demonstrated in vivo using imaging techniques. In particular, serotoninergic neurons have been found to tonically inhibit the nigrostriatal dopamine system, an effect that is probably modulated via 5HT2A receptors (Dewey et al, 1995). A modification in D$_2$ receptors availability has been observed in patients suffering from major depression treated with SSRI. An increased D$_2$ receptor availability has been demonstrated in the striatum and anterior cingulate gyrus of unipolar depressed patients responders to SSRI treatment but not in nonresponder patients (Klimke et al, 1999; Larisch et al, 1997).

Up to now, no one has attempted to investigate in vivo in OCD patients the effect of SSRI treatment on dopamine D$_2$ receptors. The aim of this study was to assess the effect of repeated administration of the selective SSRIs fluvoxamine on the in vivo binding of [$^{11}$C]raclopride ([$^{11}$C]Rac), a selective D$_2$ dopamine receptor antagonist, in the basal ganglia of patients with OCD. To avoid the effect of any antidepressant therapy performed before the PET study, the in vivo binding of [$^{11}$C]Rac was examined in a group of drug-naïve patients before and after clinical response to fluvoxamine therapy.

## PATIENTS AND METHODS

### Patients

Nine subjects, six males and three females, with a clinical diagnosis of primary OCD according to the Diagnostic and Statistical Manual of Mental Disorders IVth edition (DSM-IV) criteria, were included in the study. Each subject signed a written informed consent according to the study protocol that was approved by the Ethical Committee of the Scientific Institute H San Raffaele. Patients were recruited in the Psychiatric Department of the Scientific Institute S Raffaele Hospital, Milan. All patients were evaluated by psychiatrists and diagnosed as having OCD, according to the criteria of the DSM-IV (American Psychiatric Association, 1994). Patients were drug naïve for antidepressants, mood stabilizers, such has lithium, anticonvulsants, and neuroleptics. The previous use of benzodiazepines, unless chronic, was not considered an exclusion criterion. Their use was permitted at the time of the study if the clinical conditions of the patients made it necessary, but patients were required to suspend, if possible, the use of benzodiazepines for a period of at least five half-lives of the drug, before PET study. Patients assuming benzodiazepines at the time of first PET examination maintained the drug assumption at the same dosage at the time of second PET study. A complete physical examination was performed at the time of recruitment to exclude any systemic or neurologic disease. A history of birth and head trauma and any other diagnosis of Axis I according to the DSM-IV

were considered exclusion criteria. All patients were evaluated by means of structured psychiatric interview (DIS (Robins, 1989)) based on DSM-IV for Axis I diagnoses. Each patient was examined with the Yale–Brown Obsessive Compulsive Scale (Y-BOCS), administered the same day of each PET scan. Patients were considered as fluvoxamine responders when their initial Y-BOCS scores were reduced by at least 35% (Goodman and Price, 1992; Mundo et al, 1997). D$_2$ receptors availability of OCD patients measured before or during fluvoxamine administration were compared with that of a group of nine healthy individuals (one female and eight males) ranging from 22 to 48 years (mean: $26.55 \pm 8.32$ years).

### Pharmacological Treatment and Study Design

The effect of fluvoxamine was evaluated by means of a within-subject trial. Each patient underwent a PET study before (PET-I) and after (PET-II) a minimum of 12 weeks' fluvoxamine full-dose treatment. Each patient started fluvoxamine treatment the night after the PET-I study. Starting dose was 50 mg once a day increased to 50 mg every 4 days to reach the maximum dose of 300 mg/day (range: 150–300 mg/day).

### PET Studies

PET studies were performed with an 18-ring tomograph (GE Advance; General Electric Medical System, Milwaukee, WI, USA). One 10-min transmission scan was carried out with an external $^{68}$Ge ring source. At the end of the transmission scan, patients received an intravenous injection of 5 ml of saline solution containing approximately $1.07 \pm 05$ nmol of [$^{11}$C]Rac (PET-I—mean dose: $218 \pm 67$ MBq, range: 148–318 MBq, mean specific activity at the time of injection: $50 \pm 20$ MBq/µmol; PET-II: mean dose: $235 \pm 71$ MBq, range: 185–66 MBq, mean specific activity at the time of injection: $56 \pm 41$ MBq/µmol). Immediately after tracer injection, 35 sequential scans (slice thickness 4.25 mm; axial field of view 15.5 cm) were simultaneously acquired in 3D mode, according to the following schedule: four scans of 1 min each followed by three scans of 2 min each and 10 scans of 5 min each (total scanning time = 60 min). Trans-axial images were reconstructed using a Shepp–Logan filter (cutoff 5 mm filter width) in the transaxial plane, and a Shepp–Logan filter (cutoff 8.5 mm) in the axial direction. Images were corrected for decay and attenuation by means of a 10-min transmission scan performed before radioligand injection.

### Data Analysis

Reconstructed images derived from normal subjects and patients were transferred to a SUN-SPARC workstation for image processing. Each plane was realigned over time to correct for patient's movement during acquisition time using SPM99 software. [$^{11}$C]Rac binding to dopamine D$_2$ receptors was calculated using the simplified reference tissue model (Lammertsma et al, 1996). This model allows the calculation of the binding potential (BP) of the radioligand for the receptor of interest (in our case [$^{11}$C]Rac and dopamine D$_2$) and the relative influx of

radioactivity (RI) using a brain area devoid of the receptor of interest (in our case the cerebellum), as a reference region. Radioactivity distribution images were transformed pixel by pixel into BP images and relative influx images (RI) using the RPM (reversible reference tissue model) software developed by R Gunn et al (Gunn et al, 1997). Parametric images were then normalized to the Montreal Neurological Institute (MNI) stereotactic space (Evans et al, 1993) using SPM99 software (Wellcome Department of Imaging Neuroscience). Fluvoxamine effect was evaluated using both an automatic localization of significant changes in [$^{11}$C]Rac binding at a voxel level (SPM99) and a region of interest (ROI) analysis. Both analyses were performed on BP images normalized to an MNI-raclopride template described previously (Meyer et al, 1999). ROIs were defined on the standard Montreal Neurological Institute (MNI)-space T1-weighted MRI, corresponding to the MNI-raclopride and positioned according to the method described by Mawlawi et al (2001). The following regions were sampled: ventral striatum, bilaterally (VST), dorsal caudate, bilaterally (DCA), and dorsal putamen, bilaterally (DPU).

Statistical analysis in SPM included analysis of t map (SPM($t$)) to evaluate differences between conditions (naïve vs fluvoxamine treatment), correlations or groups (normal subjects vs patients in naïve condition; normal subjects vs patients during treatment condition). BP images were masked to include only signal from the basal ganglia, based on $p > 0.5$ (Ashburner and Friston, 1997).

Statistical analysis of ROIs was performed using the Wilcoxon sum-rank test for paired data when comparing clinical scores or BP values assessed within each single region (caudate or putamen) before and during fluvoxamine treatment. Absolute and relative ((PET-I-PET-II)/PET-I) differences for clinical scores and BP values were calculated. As no differences were detected between sides, the condition effect was evaluated on mean regional values. Bonferroni's correction was applied for multiple compar-

isons. Spearman correlation coefficients were also calculated between pre–post-treatment absolute and relative differences in test scores and [$^{11}$C]Rac BP.

BP values of OCD patients sampled at PET-I or at PET-II were also compared with those obtained from normal subjects using a Student's $t$-test for unpaired data. Age was not considered as confounding variable as no significant differences between patients and controls were detected (mean age values: $28 \pm 5$ and $26 \pm 8$ years, respectively).

## RESULTS

### Pharmacological Treatment

Clinical and demographic characteristics of OCD patients are shown in Tables 1 and 2. None of the patients included in the study received benzodiazepine treatment before or during PET studies. Drug response was evaluated by reduction in Y-BOCS total score after 12 weeks of full-dose drug treatment. None of the patients had to interrupt the pharmacological treatment because of side effects but one patient refused to undergo the second PET study. Eight patients ($28.7 \pm 4.6$ years; six males) completed the study performing the second PET scan $4.2 \pm 1.5$ months later fluvoxamine treatment significantly improved clinical symptoms as revealed by the mean reduction of Y-BOCS total scores (mean relative difference: $-43.54\%$, $p = 0.003$; mean absolute values at PET-I: $29.5 \pm 4.7$; mean absolute values at PET-II: $17 \pm 8.7$), compulsions total scores (mean relative difference: $-40.92\%$, $p = 0.002$; mean absolute values at PET-I: $15.2 \pm 2.7$; mean absolute values at PET-II: $9 \pm 3.7$), obsessions total scores (mean relative difference: $-38.12\%$, $p = 0.01$; mean absolute values at PET-I: $14 \pm 2.6$; mean absolute values at PET-II: $9.25 \pm 4.6$). In three patients, fluvoxamine was not effective: one patient (no. 4) showed totally lack of modifications both in the clinical scales and in the subjective weighted improvement, whereas

**Table 1** Clinical Data of Patients

| Patient | Other axis I diagnosis | First degree familial psychiatric illnesses | Obsessions | Compulsions | Insight (B–F)[a] |
|---------|------------------------|---------------------------------------------|------------|-------------|------------------|
| 1 | | Panic attack<br>OCD<br>Tic | Contamination<br>Somatic<br>Others | Wash<br>Check | 3–2 |
| 2 | | | Aggressive<br>Magic thought | Check<br>Repetitive rituals | 1–1 |
| 3 | | OCD | Aggressive<br>Sexual<br>Religious | Repetitive rituals<br>Mental rituals | 1–1 |
| 4 | | | Contamination<br>Order<br>Somatic<br>Others | Wash<br>Check<br>Ordering<br>Others | 2–2 |
| 5 | Compulsive buying | OCD<br>Major depression | Aggressive<br>Magic thought<br>Order | Check<br>Mental rituals<br>Magic rituals | 1–1 |
| 6 | | | Order | Ordering | 1–1 |
| 7 | | | Contamination | Wash | 3–3 |
| 8 | | | Contamination | Wash | 2–1 |

[a]B–F = Insight dimension before (B) and during fluvoxamine (F).

**Table 2** Demographic and Clinical Data of Patients

| Patient | Gender | Age (years) | Onset (years) | Y-BOCS | OBS | COMP | CGI | NIMH |
|---|---|---|---|---|---|---|---|---|
| 1 | F | 27 | 5 | 32 | 15 | 17 | 5 | 12 |
| 2 | M | 31 | 20 | 27 | 14 | 13 | 5 | 10 |
| 3 | M | 25 | 12 | 30 | 15 | 15 | 4 | 11 |
| 4 | M | 20 | 4 | 35 | 19 | 16 | 6 | 12 |
| 5 | F | 31 | 8 | 22 | 11 | 11 | 4 | 10 |
| 6 | M | 29 | 23 | 36 | 16 | 20 | 5 | 13 |
| 7 | M | 33 | 14 | 28 | 14 | 14 | 5 | 10 |
| 8 | M | 34 | 20 | 26 | 11 | 15 | 4 | 10 |
| Mean | | 28±5 | 3±7 | 29±5 | 14±3 | 15±3 | 4.7±0.7 | 11±1 |

M, male; F, female; Y-BOCS, Yale–Brown Obsessive-Compulsive Scale total scores; OBS, Y-BOCS Obsessions scores; COMP, Y-BOCS Compulsion scores; CGI, Clinical global impression scores; NIMH, National Institute of Mental Health Obsessive-Compulsive Scale.
Data are representative of the mean±SD and each single values of fluvoxamine dose, treatment duration, and the percentage of variation of clinical scores.

**Table 3** Pharmacological Data of Patients who Completed the Study

| Patient | Fluvo (mg/day) | Treatment (months) | Y-BOCS (% mod.) | OBS (% mod.) | COMP (% mod.) | CGI (% mod.) | NIMH (% mod.) |
|---|---|---|---|---|---|---|---|
| 1 | 200 | 3 | −68.7 | −33.3 | −41.2 | −60 | −50 |
| 2 | 300 | 6 | −25.9 | −28.6 | −23.1 | −40 | −20 |
| 3 | 200 | 5 | −33.3 | −33.3 | −33.3 | −25 | −36.4 |
| 4 | 300 | 3 | 0 | 0 | 0 | 0 | 0 |
| 5 | 200 | 7 | −72.7 | −72.7 | −72.7 | −50 | −40 |
| 6 | 150 | 3 | −55.6 | −50 | −60 | −60 | −46.1 |
| 7 | 250 | 3 | −57.1 | −57.1 | −57.1 | −60 | −40 |
| 8 | 250 | 4 | −35 | −30 | −40 | −25 | −30 |
| Mean | 233±50 | 4.2±1.5 | −43.5±24.5 | −38.1±21.9 | −40.9±22.9 | −40.0±21.9 | −32.8±16.2 |

Y-BOCS, Yale–Brown Obsessive-Compulsive Scale total scores; OBS, Y-BOCS Obsessions scores; COMP, Y-BOCS Compulsion scores.
Data are representative of the mean±SD and each single values of: Fluvoxamine dose, treatment duration, and the percentage of variation of clinical scores.

the other two (nos. 2 and 3) experienced some symptoms improvement but not enough to classify them as clinical responders (Table 3).

## D$_2$ Receptors Binding

Statistical analysis, based on Wilcoxon test, shows that chronic treatment with fluvoxamine increased the *in vivo* binding of [$^{11}$C]Rac in the basal ganglia of previously drug-naïve OCD patients. Mean BP values measured before and after fluvoxamine treatment, and the uncorrected *p*-values are shown in Table 4. After clinical response, fluvoxamine significantly increased [$^{11}$C]Rac BP values in all basal ganglia subregions. In the cerebellum, we failed to find any significant differences in the mean values of integrated radioactivity concentration divided by the injected doses between pre- and post-treatment condition (naïve: $0.0021 \pm 0.0017$; fluvoxamine: $0.0018 \pm 0.0006$; $p = 0.810$) indicating that the increase in [$^{11}$C]Rac BP found after fluvoxamine was not due to changes in radioactivity concentration in the reference region. No significant condition differences were found between tracer-specific

**Table 4** Mean Values of Rac BP (Absolute Values and Percentage Changes) Before and After Treatment with Fluvoxamine

| Region | BP-PET-I | BP-PET-II | % Changes | *p** |
|---|---|---|---|---|
| DCA | 2.04±0.19 | 2.18±0.12 | +7.9 | 0.0078 |
| DPU | 2.41±0.2 | 2.56±0.13 | +6.9 | 0.015 |
| VST | 1.56±0.11 | 1.71±0.07 | +9.7 | 0.0078 |

DCU, dorsal caudate; DPU, dorsal putamen; VTS, ventral striatum.
Values are the mean±SD of [$^{11}$C]Rac BP of the eight patients who underwent two PET scans.
*Wilcoxon *t*-test for paired comparison.

activity and injected dose. Single subjects modifications of [$^{11}$C]BP in VST, DCA, and DPU are shown in Figure 1. After treatment with fluvoxamine, symptoms significantly or partial remittance and increase of [$^{11}$C]Rac BP were consistently found in seven out of the eight subjects examined (VST: range: 2.36–22.16%; DCA: range: 0.45–14.50%; DPU: range: 2.06–17.32%). In the remaining subject
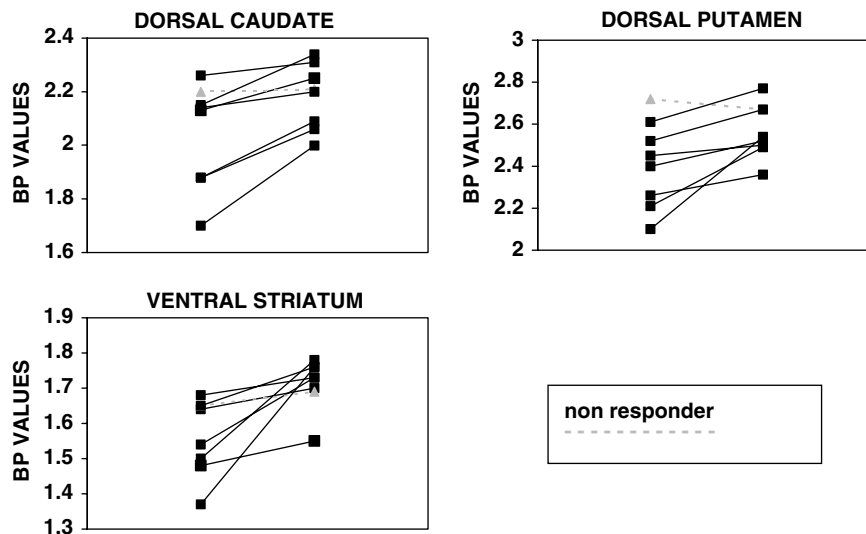
**Figure I** Modifications in individual BP values in the DCA, DPU, and VST of each of the eight patients who completed the study measured before (PRE) and during fluvoxamine therapy. Modifications of BP values of subject 4, the only patient who did not respond at the time of the second PET scan, are indicated as dotted line.
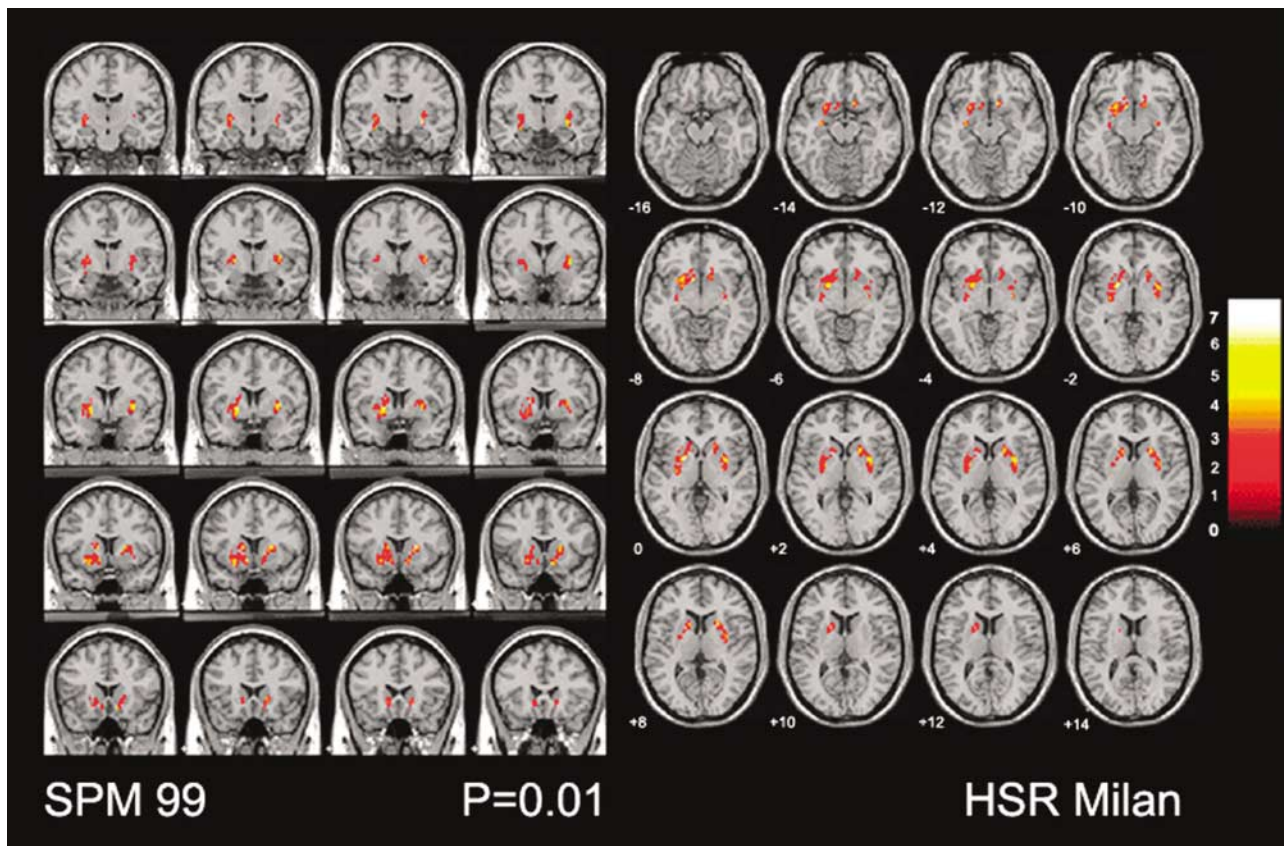


**Figure 2** SPM99 analysis. Axial and coronal view of the clusters of significant differences in [$^{11}$C]Rac BP between naïve and fluvoxamine conditions (paired *t*-test, *p* threshold = 0.01). As indicated by the figure, repeated administration of fluvoxamine induced a mean increase of $D_2$ receptors availability.

(no. 4), the increase in BP was present in VST but not in DCA and DPU where a slight decrease was observed. Interestingly, in the same subject we failed to observe any reduction in the clinical scale scores. However, using Spearman coefficient analysis we did not found any significant correlation between (a) illness duration, age of

onset, clinical score, and BP values measured during naïve condition and (b) modifications in clinical scores and BP values induced by fluvoxamine treatment.

A significant increase in receptors availability was also observed using the voxel-based analysis SPM99. Clusters of significant increase in BP values were observed in the left

($Z = 3.63$) and right ($Z = 3.44$) putamen and in the left ($Z = 3.60$) and right caudate ($Z = 3.59$) (Figure 2).

In naïve conditions, striatal [$^{11}$C]Rac BP were significantly lower than those observed in normal subjects (Perani et al, 2006). However, after fluvoxamine treatment, the mean values of BP were closer to those observed in normal subjects and particularly in the DCA where no significant differences between groups were observed (Table 5). Similar results were obtained using SPM. As showed in Figure 3, after fluvoxamine treatment, regional differences between patients and normal subjects were confined to the left aspects of VST ($p$ threshold $= 0.01$).

**Table 5** Mean Values of Rac BP in the Group of Normal Subjects and Relative Differences with the Group of OCD Patient Evaluated at PET-I or at PET-II

| Region | BP-normal | % PET-I | % PET-II |
|--------|-----------|---------|----------|
| DCA | | −10.1* | −4.1 |
| DPU | | | −4.3* |
| VST | | −15.7** | −7.6* |

Values are the mean ± SD of [$^{11}$C]Rac BP of the nine normal subjects. Mean values of the mean relative differences between OCD patients evaluated at PET-I or PET-II and normal subjects are also reported.
*$p < 0.05$; **$p < 0.001$. Student's $t$-test between normal subjects and OCD patients evaluated at PET-I and normal subjects and OCD patients evaluated at PET-II.

## DISCUSSION

The aim of our study was to evaluate whether SSRI treatment was able to modify dopaminergic system and in particular dopamine D₂ receptors availability in OCD patients. To start the evaluation of this issue and in order to avoid confounding results deriving from previous pharmacological treatments, the study was conducted on a small group of subject never treated with SSRI or other medications used in OCD patients. However, despite the small number of subjects our sample has the clear advantage to present regional values of D₂ receptors availability completely independent from the residual effects of previous pharmacological therapies.

Repeated administration of fluvoxamine significantly modifies striatal D₂ receptors availability. In particular, an increase in [$^{11}$C]Rac BP was consistently found in all
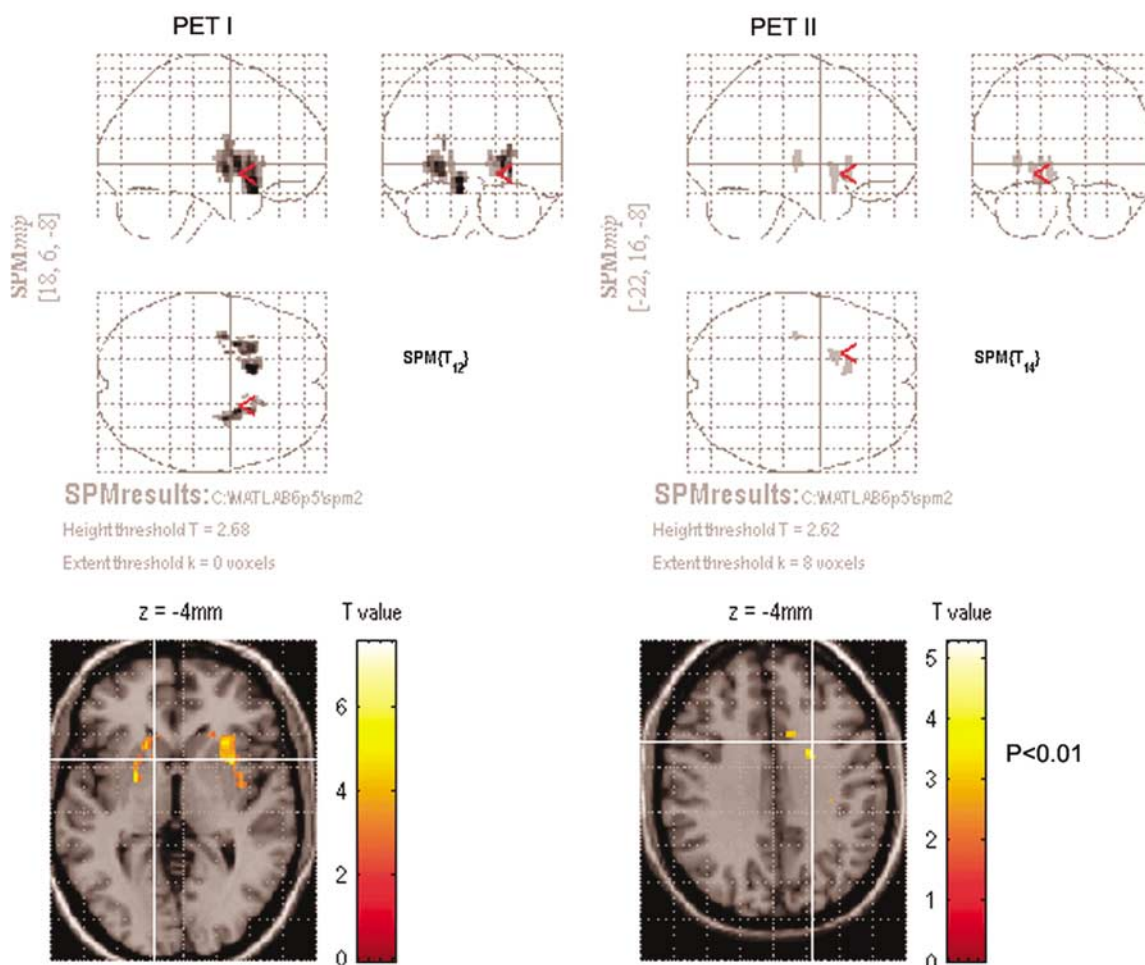


**Figure 3** SPM99 analysis. 2D maps and one representative axial view of the clusters of significant reduction of [$^{11}$C]Rac BP in the basal ganglia of OCD patients evaluated during naïve conditions (PET-I) and during fluvoxamine treatment (PET-II) in comparison with normal controls (unpaired $t$-test, $p$ threshold $= 0.01$).

subjects examined in the VST and in seven out of eight patients in the DCA and DPU with a mean increment higher than that previously observed in reproducibility studies. In fact, using a similar data analysis in normal subjects, a reproducibility ranging from −7 to 8% has been reported (Volkow et al, 1996).

Imaging studies on SSRI effect in normal subjects reported: (a) increase (Dewey et al, 1995; Penttilä et al, 2004), (b) no changes (Fowler et al, 1999), or (c) decrease (Tiihonen et al, 1996) in D$_2$ receptors availability. In agreement with the results of our study, an increase in D$_2$ receptors availability was observed in patients with major depression responder to SSRIs therapy but not in non-responder patients (Klimke et al, 1999; Larisch et al, 1997). In the present study on OCD patients, we failed to find any correlations between the degree of clinical response and the increase in tracer BP. However, the group of OCD patients evaluated in our study is probably to small to find any correlation between BP and clinical modifications or to separate responder from nonresponder patients. In parti-cular, of the eight patients recruited only one was fully nonresponder at the time of the second PET study. Interestingly, in that patient, the increase in receptors availability was confined to the ventral striatum and not to the dorsal aspect of the basal ganglia.

The mean increase observed in our study is in line with rodent studies indicating an increase in central DA D$_2$-like receptor function induced by repeated administration of SSRIs (Ainsworth et al, 1998a). The same authors also reported an increase in D$_2$ receptor mRNA and protein expression that was particularly evident in the shell region of rat nucleus accumbens (Ainsworth et al, 1998b). [$^{11}$C]Rac binding has been proven to be sensitive to modification in extracellular concentration of exogenous or endogenous dopamine (Seeman et al, 1989; Laruelle, 2000a). Thus, changes in the in vivo binding of [$^{11}$C]Rac could be related either to modifications in receptors expression or extra-cellular levels of dopamine. This property of [$^{11}$C]Rac binding, has been used, as an innovative strategy, to measure in living human subjects the modification in extracellular/synaptic dopamine concentration induced by pharmacological or behavioral stimulations (Laruelle, 2000b; Koepp et al, 1998). A complex interaction between serotonin and dopamine system has been extensively described also using emission tomography techniques. In particular, serotonin neurons have been found to modulate striatal dopamine release (Dewey et al, 1995). The basal firing of dopamine neuron rising from ventral tegmental area is negatively modulated by SSRIs (Di Mascio et al, 1998). Microdialysis studies in rats and monkeys indicate that SSRI reduce striatal dopamine levels (Dewey et al, 1995; Di Rocco et al, 1998; Smith et al, 2000) and some of SSRIs side effects have been associated with the reduction of striatal dopamine levels induced by their administration (Damsa et al, 2004; Shioda et al, 2004). Thus in the light of these results, the increase in receptors availability observed in this study, may be consequent to the reduction of dopamine concentration induced by fluvoxamine. This speculation is also in line with other preclinical and imaging findings indicating an increased dopaminergic tone in OCD striatum. In particular, (a) the administration in rodents of dopamine mimetic such as amphetamine,

cocaine induces some stereotypic behaviors that resemble obsessive behaviors observed in OCD patients (Goodman et al, 1990; Grace, 2000; Pitman, 1989); (b) the increase in dopamine transporter (DAT) density reported in two out of three different SPET studies on OCD patients (Cheon et al, 2004; Kim et al, 2003; Pogarell et al, 2004).

Finally, fluvoxamine treatment increases D$_2$ receptors availability in OCD patients reporting striatal BP to values closer to those observed in normal volunteers. This observation is in line with the reduced D$_2$ receptors availability recently reported in drug-free OCD patients (Denys et al, 2004) and suggests that the increase in BP induced by fluvoxamine represents more a normalization than an increase of D$_2$ receptors availability.

The major finding of the study is that fluvoxamine treatment increases D$_2$ receptors availability in the dorsal and ventral striatum of OCD patients responder or partial responder to SSRI therapy. The group evaluated in our study is too small to make any conclusion on the role played by dopaminergic system or by dopamine receptors in the efficacy of SSRIs treatment in OCD patients. However of particular interest are the observations that (a) after fluvoxamine treatment, OCD patients have mean BP values closer to those of normal volunteers; (b) in the fully nonresponder subjects, we failed to find any increase in BP values in the dorsal part of the basal ganglia. These findings suggest that in OCD patients, fluvoxamine treatment normalized D$_2$ receptors availability and also with the limit of a single subject observation, this normalization is not present in the dorsal striatum of the full nonrespon-der patient. To conclude, our results indicate that dopamine system is modified by the SSRI fluvoxamine and represent interesting informations to be used as starting point for further researches on the role played by dopamine in OCD.

## REFERENCES

Ainsworth K, Smith SE, Sharp T (1998a). Repeated administration of fluoxetine, desimipramine and tranylcypromine increases dopamine D2-like but not D1-like receptor function in the rat. J Psychopharmacol 12: 252–257.

Ainsworth K, Smith SE, Zetterstrom TS, Pei Q, Franklin M, Sharp T (1998b). Effect of antidepressant drugs on dopamine D1 and D2 receptor expression and dopamine release in the nucleus accumbens of the rat. Psychopharmacology (Berlin) 140: 470–477.

Alexander GE, Crutcher MD (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 13: 266–271.

Ashburner J, Friston K (1997). Multimodal image coregistration and partitioning—a unified framework. Neuroimage 6: 209–217.

Baumgarten HG, Grozdanovic Z (1998). Role of serotonin in obsessive-compulsive disorder. Br J Psychiatry Suppl 35: 13–20.

Baxter Jr LR, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC et al (1992). Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry 49: 681–689.

Breiter HC, Rauch SL, Kwong KK, Baker JR, Weisskoff RM, Kennedy DN et al (1996). Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. Arch Gen Psychiatry 53: 595–606.

Campbell KM, McGrath MJ, Burton FH (1999). Differential response of cortical-limbic neuropotentiated compulsive mice

to dopamine D1 and D2 receptor antagonists. *Eur J Pharmacol* **371**: 103–111.

Carmin CN, Wiegartz PS, Yunus U, Gillock KL (2002). Treatment of late-onset OCD following basal ganglia infarct. *Depress Anxiety* **15**: 87–90.

Cheon KA, Ryu YH, Namkoong K, Kim CH, Kim JJ, Lee JD (2004). Dopamine transporter density of the basal ganglia assessed with [$^{123}$I]IPT SPECT in drug-naive children with Tourette's disorder. *Psychiatry Res* **130**: 85–95.

Damsa C, Bumb A, Bianchi-Demicheli F, Vidailhet P, Sterck R, Andreoli A *et al* (2004). 'Dopamine-dependent' side effects of selective serotonin reuptake inhibitors: a clinical review. *J Clin Psychiatry* **65**: 1064–1068.

Denys D, van der Wee N, Janssen J, De Geus F, Westenberg HG (2004). Low level of dopaminergic D2 receptor binding in obsessive-compulsive disorder. *Biol Psychiatry* **55**: 1041–1045.

Dewey SL, Smith GS, Logan J, Alexoff D, Ding YS, King P *et al* (1995). Serotonergic modulation of striatal dopamine measured with positron emission tomography (PET) and *in vivo* microdialysis. *J Neurosci* **15**: 821–829.

Di Mascio M, Di Giovanni G, Di Matteo V, Prisco S, Esposito E (1998). Selective serotonin reuptake inhibitors reduce the spontaneous activity of dopaminergic neurons in the ventral tegmental area. *Brain Res Bull* **46**: 547–554.

Di Rocco A, Brannan T, Prikhojan A, Yahr MD (1998). Sertraline induced Parkinsonism. A case report and an *in-vivo* study of the effect of sertraline on dopamine metabolism. *J Neural Transm* **105**: 247–251.

Evans AC, Collins DL, Mills SR, Brown ED, Kelly RL, Peters TM (1993). 3D statistical neuroanatomical models from 305 MRI volumes. *Proc. IEEE-Nuclear Science Symposium and Medical Imaging Conference* **3**: 1813–1817.

Fowler JS, Wang GJ, Volkow ND, Ieni J, Logan J, Pappas N *et al* (1999). PET studies of the effect of the antidepressant drugs nefazodone or paroxetine on [$^{11}$C]raclopride binding in human brain. *Clin Positron Imaging* **2**: 205–209.

Goodman WK, McDougle CJ, Price LH, Riddle MA, Pauls DL, Leckman JF (1990). Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive compulsive disorder? *J Clin Psychiatry* **51**(Suppl): 36–43.

Goodman WK, Price LH (1992). Assessment of severity and change in obsessive compulsive disorder. *Psychiatr Clin North Am* **15**: 861–869.

Grace AA (2000). The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and psychostimulant craving. *Addiction* **95**(Suppl 2): S119–S128.

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ (1997). Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage* **6**: 279–287.

Kim CH, Koo MS, Cheon KA, Ryu YH, Lee JD, Lee HS (2003). Dopamine transporter density of basal ganglia assessed with [$^{123}$I]IPT SPET in obsessive-compulsive disorder. *Eur J Nucl Med Mol Imaging* **30**: 1637–1643.

Klimke A, Larisch R, Janz A, Vosberg H, Muller-Gartner HW, Gaebel W (1999). Dopamine D2 receptor binding before and after treatment of major depression measured by [$^{123}$I]IBZM SPECT. *Psychiatry Res* **90**: 91–101.

Koepp MJ, Gunn RN, Lawrence AD, Cunningham VJ, Dagher A, Jones T *et al* (1998). Evidence for striatal dopamine release during a video game. *Nature* **393**: 266–268.

Lammertsma AA, Bench CJ, Hume SP, Osman S, Gunn K, Brooks DJ *et al* (1996). Comparison of methods for analysis of clinical [$^{11}$C]raclopride studies. *J Cereb Blood Flow Metab* **16**: 42–52.

Laplane D, Levasseur M, Pillon B, Dubois B, Baulac M, Mazoyer B *et al* (1989). Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions. A neuropsychological, magnetic resonance imaging and positron tomography study. *Brain* **112**(Part 3): 699–725.

Larisch R, Klimke A, Vosberg H, Loffler S, Gaebel W, Muller-Gartner HW (1997). *In vivo* evidence for the involvement of dopamine-D2 receptors in striatum and anterior cingulate gyrus in major depression. *Neuroimage* **5**: 251–260.

Laruelle M (2000a). Imaging synaptic neurotransmission with *in vivo* binding competition techniques: a critical review. *J Cereb Blood Flow Metab* **20**: 423–451.

Laruelle M (2000b). The role of endogenous sensitization in the pathophysiology of schizophrenia: implications from recent brain imaging studies. *Brain Res Brain Res Rev* **31**: 371–384.

Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang DR *et al* (2001). Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D(2) receptor parameter measurements in ventral striatum. *J Cereb Blood Flow Metab* **21**: 1034–1057.

McDougle CJ, Goodman WK, Leckman JF, Price LH (1993). The psychopharmacology of obsessive compulsive disorder. Implications for treatment and pathogenesis. *Psychiatr Clin North Am* **16**: 749–766.

Meyer JH, Gunn RN, Myers R, Grasby PM (1999). Assessment of spatial normalization of PET ligand images using ligand-specific templates. *Neuroimage* **9**: 545–553.

Mindus P, Rasmussen SA, Lindquist C (1994). Neurosurgical treatment for refractory obsessive-compulsive disorder: implications for understanding frontal lobe function. *J Neuropsychiatry Clin Neurosci* **6**: 467–477.

Mundo E, Bareggi SR, Pirola R, Bellodi L, Smeraldi E (1997). Long-term pharmacotherapy of obsessive-compulsive disorder: a double-blind controlled study. *J Clin Psychopharmacol* **17**: 4–10.

Oliver B, Gascon J, Aparicio A, Ayats E, Rodriguez R, Maestro De Leon JL *et al* (2003). Bilateral anterior capsulotomy for refractory obsessive-compulsive disorders. *Stereotact Funct Neurosurg* **81**: 90–95.

Penttilä J, Kajander J, Aalto S, Hirvonen J, Nagren K, Ilonen T *et al* (2004). Effects of fluoxetine on dopamine D2 receptors in the human brain: a positron emission tomography study with [$^{11}$C]raclopride. *Int J Neuropsychopharmacol* **7**: 1–9.

Perani D, Gorini A, Bellodi L, Panzacchi A, Henin M, Pietra L, Matarrese M *et al* (2006). *In vivo* PET study of 5HT$_2$ serotonin and D$_2$ dopamine receptors in obsessive-compulsive disorder (2006). *Neuroimage* **31**(S1): 665.

Pitman RK (1989). Animal models of compulsive behavior. *Biol Psychiatry* **26**: 189–198.

Pogarell O, Tatsch K, Juckel G, Hamann C, Mulert C, Popperl G *et al* (2004). Serotonin and dopamine transporter availabilities correlate with the loudness dependence of auditory evoked potentials in patients with obsessive-compulsive disorder. *Neuropsychopharmacology* **29**: 1910–1917.

Rauch SL (2003). Neuroimaging and neurocircuitry models pertaining to the neurosurgical treatment of psychiatric disorders. *Neurosurg Clin North Am* **14**: 213–223, vii–viii.

Robins LN (1989). Diagnostic grammar and assessment: translating criteria into questions. *Psychol Med* **19**: 57–68.

Saxena S, Brody AL, Schwartz JM, Baxter LR (1998). Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *Br J Psychiatry Suppl* **173**: 26–37.

Seeman P, Guan HC, Niznik HB (1989). Endogenous dopamine lowers the dopamine D2 receptor density as measured by [$^{3}$H]raclopride: implications for positron emission tomography of the human brain. *Synapse* **3**: 96–97.

Shioda K, Nisijima K, Yoshino T, Kato S (2004). Extracellular serotonin, dopamine and glutamate levels are elevated in the hypothalamus in a serotonin syndrome animal model induced by tranylcypromine and fluoxetine. *Prog Neuropsychopharmacol Biol Psychiatry* **28**: 633–640.

Smith TD, Kuczenski R, George-Friedman K, Malley JD, Foote SL (2000). *In vivo* microdialysis assessment of extracellular

serotonin and dopamine levels in awake monkeys during sustained fluoxetine administration. *Synapse* **38**: 460–470.

Spyraki C, Fibiger HC (1981). Behavioural evidence for supersensitivity of postsynaptic dopamine receptors in the mesolimbic system after chronic administration of desipramine. *Eur J Pharmacol* **74**: 195–206.

Tiihonen J, Kuoppamaki M, Nagren K, Bergman J, Eronen E, Syvalahti E *et al* (1996). Serotonergic modulation of striatal D2 dopamine receptor binding in humans measured with positron emission tomography. *Psychopharmacology (Berlin)* **126**: 277–280.

Trivedi MH (1996). Functional neuroanatomy of obsessive-compulsive disorder. *J Clin Psychiatry* **57**(Suppl 8): 26–35 (discussion 36).

Volkow ND, Ding YS, Fowler JS, Wang GJ (1996). Cocaine addiction: hypothesis derived from imaging studies with PET. *J Addict Dis* **15**: 55–71.

Wolf SS, Jones DW, Knable MB, Gorey JG, Lee KS, Hyde TM *et al* (1996). Tourette syndrome: prediction of phenotypic variation in monozygotic twins by caudate nucleus D2 receptor binding. *Science* **273**: 1225–1227.