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# [$^{18}$F]FDG PET Study in Obsessive–Compulsive Disorder
## A Clinical/Metabolic Correlation Study after Treatment

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**Background.** We used [$^{18}$F]FDG and PET in patients with obsessive–compulsive disorder (OCD) to evaluate cerebral metabolic involvement before and after treatment with serotonin-specific reuptake inhibitors.
**Method.** In 11 untreated, drug-free adults, regional cerebral metabolic rate for glucose (rCMRglu) was compared with that of 15 age-matched normal controls.
**Results.** rCMRglu values were significantly increased in the cingulate cortex, thalamus and pallidum/putamen complex. After treatment a significant improvement in obsessive–compulsive symptoms on the Y-BOC scale ($t = 3.59$, $P < 0.01$) was associated with a significant bilateral decrease of metabolism in the whole cingulate cortex ($P < 0.001$). Clinical and metabolic data were significantly intercorrelated (Kendall's $\tau = 0.65$; $P < 0.01$).
**Conclusions.** These findings indicate that OCD is associated with functional hyperactivity of a selected neuronal network and that treatment to reduce symptoms may have a selective neuromodulatory effect on cingulate cortex.

Obsessive–compulsive disorder (OCD), usually beginning in childhood or early adulthood, is characterised by persistent thoughts (obsessions) and repetitive behaviours (compulsions) sufficiently severe to be experienced by the patient as intrusive and senseless and to interfere with the activities of daily life. Extreme slowness in the execution of routine activities, such as eating and washing, dominates the clinical picture in some patients. Some of these cases, on examination, reveal neurological signs, such as cogwheel rigidity, upper-limb asynkinesia and adventitious movements (Hymas *et al*, 1991). The condition may have a biological basis in that an association with head trauma (McKeon *et al*, 1984), epilepsy (Kettl & Marks, 1986) or other neurological diseases involving basal ganglia (Modell *et al*, 1989) has been reported. In particular, the similarity of some motor behaviours in OCD with those of movement disorders with defined basal ganglia pathology, such as in Sydenham's chorea and post-encephalitic Parkinsonism, has led to the hypothesis of a basal ganglia dysfunction (Schilder, 1938). Compulsions and obsessions, as well as motor changes such as involuntary movements and hypertonia, have been described in von Economo post-encephalitic disease (Kaufman, 1985) and basal ganglia lesions in Gilles de La Tourette syndrome, a neurological disease characterised by ritualistic behaviour and compulsions (Robertson, 1989).

Brain imaging techniques including TC and MRI studies show morphological changes of basal ganglia structures in OCD patients (Garber *et al*, 1989; Luxenberg *et al*, 1989; Scarone *et al*, 1992). The results of several PET studies show a hypermetabolism in the basal ganglia and a variable involvement (i.e. reduction or increase) of frontal regions and cingulate cortex (Baxter *et al*, 1987; Swedo *et al*, 1989). However, most of these studies involve heterogeneous groups of patients and the possible role of associated depression has not been considered (Baxter *et al*, 1987). Little and conflicting information is available on the effect of treatment on regional cerebral metabolism (Swedo *et al*, 1989; Benkelfat *et al*, 1990; Baxter *et al*, 1992; Swedo *et al*, 1992).

The pharmacological therapy of OCD is based mainly on the use of serotonergic re-uptake inhibitors (Insel & Zohar, 1987) and clinical studies have confirmed the efficacy of these agents in reducing obsessive–compulsive symptoms (Goodman *et al*, 1990).

Indeed, a 'serotonin hypothesis' of OCD has been raised on the basis of biochemical and pharmacological studies which seem to indicate an increase of serotonergic function is responsible for the condition (Flament *et al*, 1987; Insel & Zohar, 1987). The question of whether therapeutic effects are mediated only via the serotonergic system, deserves further study; other mechanisms such as actions on opiate system, blockade of $Ca^{2+}$ channels and uncoupling on oxidative phosphorylation have been suggested (Insel & Zohar, 1987).



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## Method

This study measured regional cerebral metabolism, using [$^{18}$F]FDG and PET, in a group of patients with OCD before and after treatment with serotonin-specific re-uptake inhibitors (SSRIs) in order to evaluate (a) the cerebral metabolic involvement in drug-free OCD patients; (b) the effect of therapy on the cerebral metabolic pattern; and (c) the clinical/metabolic correlations. Treatment was with fluvoxamine, mean dosage 300 mg/day (four cases), fluoxetine, mean dosage 30 mg/day (two cases), or clomipramine, mean dosage 200 mg/day (three cases).

### Subjects and protocol

Eleven patients (mean age 26.1, s.d. 6.12) who fulfilled the DSM-III-R diagnostic criteria for obsessive-compulsive disorder (OCD) (American Psychiatric Association, 1987) entered the study (Table 1). There were seven checkers and four washers and all patients were diagnosed by trained clinicians using the diagnostic interview schedule for DSM-III-R (DIS) (Robins *et al*, 1989). None of the patients scored for diagnosis of axis-I, thus excluding affective and anxious disorders. In addition, nine of this patient group underwent a follow-up PET study after three months of treatment.

Additional selection criteria included a negative history for: (1) birth complications or perinatal trauma; (2) parasomnias in childhood and/or adolescence and any other sleep disorders in adulthood; (3) epilepsy; (4) drugs and/or alcohol abuse; (5) head trauma; (6) metabolic and endocrine disease. Physical and neurological evaluations were within normal limits in all cases. The subjects were untreated and free from benzodiazepines and other psychotropic drugs for at least two weeks prior to entering the study.

The fifteen age-matched healthy controls (11 males and 4 females; mean age 28.23 ± 7.13) were free from past and present neurologic and psychiatric disease and from chronic and acute intake of CNS-acting drugs.

Both OCD and control groups had attained a medium-high education level and scored in the normal range on the Wechsler Adult Intelligence Scale.

[$^{18}$F]FDG PET studies were performed in both patients and normal subjects in resting conditions (eyes open and ears unplugged). All patients were evaluated for severity of symptoms at the time of the PET scans, before and after treatment, using the Yale-Brown obsessive compulsive scale (Y-BOCS) (Goodman *et al*, 1989*a*,*b*).

Informed consent was obtained from both patients and controls and the experimental protocol was approved by the Ethics Committee of the Scientific Institute H San Raffaele.

### PET method

[$^{18}$F]FDG PET studies were performed using a four-ring whole-body positron emission tomograph (Siemens/CPS, 931-04/12). The scanner allows the simultaneous acquisition of data from seven axial planes (four direct and three cross planes), slice thickness 6.75 mm, covering an axial field of view of 5.4 cm. The image spatial resolution for a line source in air, positioned in the centre of the field of view, was 6.1 full width at half maximum (FWHM). A transmission scan was taken, using

Table 1
Demographic and clinical characteristics of OCD patients

| Cases | Age (years) | Sex | Disease duration (years) | Y-BOCS O 1st | Y-BOCS C 1st | Y-BOCS O 2nd | Y-BOCS C 2nd |
|---|---|---|---|---|---|---|---|
| 1 | 33 | F | 3 | 18 | 8 | 7 | 6 |
| 2 | 32 | F | 10 | 7 | 0 | 7 | 5 |
| 3 | 23 | M | 15 | 15 | 16 | 10 | 12 |
| 4 | 21 | F | 1 | 16 | 13 | 5 | 5 |
| 5 | 30 | F | 3 | 12 | 13 | 0 | 0 |
| 6 | 18 | M | 4 | 18 | 17 | 20 | 19 |
| 7 | 36 | F | 11 | 19 | 16 | 7 | 7 |
| 8 | 28 | F | 4 | 10 | 13 | - | - |
| 9 | 24 | F | 13 | 12 | 16 | - | - |
| 10 | 18 | M | 2 | 17 | 14 | 14 | 9 |
| 11 | 24 | F | 17 | 12 | 9 | 9 | 5 |

Y-BOCS-O: Yale-Brown obsessive compulsive scale - Obsession subscores.
Y-BOCS-C: Yale-Brown obsessive compulsive scale - Compulsion subscores.
1st: at first PET evaluation. 2nd: at second PET evaluation.

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ring sources of $^{68}$Ge, to measure attenuation in the scanned cross sections for later attenuation correction. Patients and controls were positioned with the head symmetrically aligned along the orbitomeatal line (Bettinardi *et al*, 1991). 250–300 MBq of [$^{18}$F]FDG were injected as a bolus, followed by a rapid arterial blood sampling to obtain the arterial input function. Arterial blood samples were collected every 2–3 seconds in the first minute, then at 1.5, 3.0, 5.0, 7.5, 10, 15, 25, 35, 45 and 65 minutes from the injection time. At a point 45 minutes from the tracer injection (steady state), two spatially consecutive emission scans (10 minutes each) were taken, thus obtaining 14 axial slices, parallel to the orbitomeatal line, of the whole brain. Values of local cerebral metabolic rate of glucose (rCMRglu) were calculated according to a clinical model proposed by Reivich and co-workers (1985).

### PET data analysis

Image analysis was performed using 'Analyze' software (BRU/Mayo Clinic) implemented on SUN SPARC workstations. Numerical data were obtained using circular regions of interest with a diameter corresponding to 1.5 FWHM (9.6 mm), manually drawn on all cortical and subcortical grey structures. Average values of rCMRglu were calculated from the multiple regions of interest (ROIs) included within the major anatomical subdivisions, which were identified with reference to a neuroanatomical atlas (Damasio & Damasio, 1989). Coronal sections were also obtained to better identify cerebral mesial regions such as cingulate cortex and hippocampus. These average values, corresponding to the 17 anatomical regions for each hemisphere listed in Tables 2 and 3, were used for statistical analysis.

### Statistical analysis

The rCMRglu values of the OCD patients were compared with those of the controls. In order to remove the confounding effect of inter- and intra-subject variation of global hemispheric activity on rCMRglu, we used a repeated measures analysis of covariance (ANCOVA) with global hemispheric activity as covariate and one between-subject factor: group (OCD v. normal controls), and two within-subject factors: cerebral region (the 17 regions listed

Table 2
Absolute and covariate-adjusted values of rCMRglu (mg 100g$^{-1}$ min$^{-1}$) in OCD patients and controls

| | Absolute values[1] | | Covariate-adjusted values[2] | | |
|---|---|---|---|---|---|
| | OCD patients ($n=11$) | Controls ($n=15$) | OCD patients ($n=11$) | Controls ($n=15$) | $P$ value[3] |
| Frontal | | | | | |
| basal | 6.22±0.83 | 6.64±0.84 | 6.43 (6.25–6.60) | 6.49 (6.35–6.63) | NS |
| lateral | 6.90±0.91 | 7.34±1.00 | 6.98 (6.84–7.16) | 7.17 (7.02–7.31) | NS |
| rolandic | 7.10±0.87 | 7.62±1.11 | 7.35 (7.18–7.53) | 7.44 (7.29–7.59) | NS |
| Parietal | 6.79±0.83 | 7.22±0.92 | 6.86 (6.84–7.17) | 7.06 (6.93–7.20) | NS |
| Temporal | | | | | |
| polar | 5.05±0.58 | 5.04±0.76 | 5.19 (4.92–5.48) | 4.93 (4.70–5.17) | NS |
| superior | 6.29±0.69 | 6.72±0.70 | 6.45 (6.19–6.70) | 6.61 (6.40–6.82) | NS |
| middle/inferior | 6.07±0.78 | 6.32±1.00 | 6.29 (6.14–6.46) | 6.15 (6.02–6.28) | NS |
| mesial | 4.88±0.63 | 4.70±0.69 | 5.00 (4.65–5.35) | 4.93 (4.70–5.16) | NS |
| Cingulate cortex | | | | | |
| anterior | 6.78±0.60 | 6.06±0.57 | 6.87 (6.54–7.20) | 5.91 (5.64–6.18) | <0.0001 |
| medium | 6.58±0.65 | 5.92±0.59 | 6.66 (6.29–7.03) | 5.85 (5.56–6.16) | <0.001 |
| posterior | 7.09±0.73 | 6.04±0.59 | 7.19 (6.74–7.63) | 6.33 (5.96–6.70) | <0.001 |
| Occipital | | | | | |
| lateral | 6.78±1.03 | 7.25±0.87 | 6.98 (6.63–7.34) | 7.10 (6.80–7.39) | NS |
| calcarine | 8.52±1.30 | 8.92±1.22 | 8.80 (8.34–9.26) | 8.71 (8.33–9.09) | NS |
| Basal ganglia | | | | | |
| putamen/pallidum | 7.99±1.21 | 7.54±0.91 | 8.19 (7.73±8.66) | 7.38 (7.05–7.70) | <0.001 |
| caudate | 7.25±1.03 | 7.27±0.81 | 7.44 (7.07±7.83) | 7.13 (6.82±7.44) | NS (<0.5) |
| Thalamus | 7.77±1.22 | 7.05±1.20 | 7.89 (7.53±8.53) | 6.84 (6.44±7.25) | <0.001 |
| Cerebellum | 5.87±0.68 | 6.11±0.70 | 6.01 (5.69±6.34) | 6.04 (5.74–6.28) | NS |

1. Mean absolute rCMRglu values±s.d.
2. Mean rCMRglu values adjusted for global hemispheric metabolism with the 95% CI (in parentheses).
3. Significant values at $P<0.002$ according to Bonferroni's correction.
NS: not significant.

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Table 3
Covariate-adjusted rCMRglu (mg 100 $g^{-1}$ $min^{-1}$) values[1] with 95% confidence intervals of means in OCD cases studied at follow-up

| | 1st study ($n=9$) | 2nd study ($n=9$) | $P$ value[2] |
|---|---|---|---|
| Frontal | | | |
| basal | 6.28 (5.88–6.68) | 6.53 (6.13–6.93) | NS |
| lateral | 6.96 (6.57–7.34) | 7.01 (6.62–7.39) | NS |
| rolandic | 7.18 (6.83–7.52) | 7.43 (7.08–7.77) | NS |
| Parietal | 6.86 (6.49–7.23) | 6.91 (6.54–7.27) | NS |
| Temporal | | | |
| polar | 5.06 (4.92–5.48) | 5.24 (4.93–5.54) | NS |
| superior | 6.29 (5.99–6.58) | 6.54 (6.24–6.84) | NS |
| middle/ inferior | 6.11 (5.82–6.40) | 6.46 (6.17–6.75) | NS |
| mesial | 4.88 (4.56–5.19) | 4.58 (4.26–4.89) | NS |
| Cingulate cortex | | | |
| anterior | 6.89 (6.69–7.08) | 6.11 (5.91–6.30) | <0.0001 |
| medium | 6.61 (6.34–6.87) | 6.03 (5.76–6.29) | <0.001 |
| posterior | 7.20 (6.86–7.53) | 6.44 (6.10–6.77) | <0.001 |
| Occipital | | | |
| lateral | 6.91 (6.64–7.17) | 6.98 (6.71–7.24) | NS |
| calcarine | 8.64 (8.37–8.90) | 8.57 (8.30–8.83) | NS |
| Basal ganglia | | | |
| putamen/ pallidum | 7.98 (7.52–8.43) | 8.09 (7.63–8.54) | NS |
| caudate | 7.22 (6.77–7.66) | 7.27 (6.82–7.71) | NS |
| Thalamus | 7.85 (7.27–8.42) | 7.98 (7.40–8.55) | NS |
| Cerebellum | 5.89 (5.55–6.22) | 6.18 (5.84–6.55) | NS |

1. Values are adjusted for global hemispheric metabolism.
2. Significant values set at $P<0.002$ according to Bonferroni's correction.

in Table 2) and hemispheric (left and right). The interaction effects, when significant, were tested using the appropriate univariate ANCOVA, further analysed with Bonferroni's correction for multiple comparisons, set at $P<0.002$. The adequacy of the covariate model was tested *a priori*, evaluating the homogeneity of slopes assumption, i.e. the parallelism of covariates between the groups (Winer, 1971).

A repeated measures ANCOVA was also applied to rCMRglu values, obtained in the first and second PET study, in the nine OCD patients evaluated longitudinally after treatment.

A paired, two-tailed Student's $t$-test or, when appropriate, a non-parametric Wilcoxon signed rank test, were used to evaluate differences in Y-BOCS scores (obsessive, compulsive and total) between the initial and follow-up clinical evaluation.

A conservative, non-parametric Kendall's $\tau$ rank correlation, with correction for tied values, was used to study the relationship between changes observed in Y-BOCS scores and changes in rCMRglu at the initial and follow-up examination.

## Results

Table 2 shows the mean absolute and adjusted rCMRglu values for the different cerebral regions in OCD patients and normal controls. In the first PET evaluation, a repeated measures ANCOVA demonstrated a significant region effect ($F=6.50$; $P<0.001$), but no significant group effect on global cerebral metabolism ($F=1.90$; NS) and hemispheric effect ($F=0.74$; NS). The group $x$ region interaction was also significant ($F=10.56$; $P<0.0001$), indicating a different pattern of regional metabolic activity between OCD patients and normal controls.

The subsequent analysis of regional differences showed a significant bilateral increase of rCMRglu in anterior ($P<0.0001$), middle ($P<0.001$) and posterior ($P<0.001$) cingulate cortex, pallidum/putamen complex ($P<0.001$) and thalamus ($P<0.001$) (Table 2).

In the follow-up study, a significant reduction in obsessive–compulsive symptoms on Y-BOCS was observed between the first and second evaluation for mean total scores (25.6 v. 13.5; $t=3.59$; $P<0.01$), mean compulsive (11.1 v. 6.1; $t=2.65$; $P<0.05$) and mean obsessive scores (14.5 v. 7.38; $t=4.13$; $P<0.01$).

The repeated measures ANCOVA showed, for the nine longitudinally evaluated OCD cases, a significant region effect ($F=6.67$; $P=0.001$) and a significant time $x$ regions interaction ($F=7.59$; $P=0.001$). No significant effect of time on global cerebral metabolic activity ($F=0.33$; NS) and hemisphere ($F=0.14$; NS) was demonstrated.

The subsequent analysis of regional differences between the first and second PET study revealed a significant bilateral decrease of rCMRglu in the anterior ($P<0.0001$), middle ($P<0.001$) and posterior ($P<0.001$) cingulate cortex (Table 3).

Changes of metabolic activity in the whole cingulate cortex were significantly correlated with changes for Y-BOCS total scores ($\tau=0.65$; $P<0.01$), and for compulsive ($\tau=0.75$; $P<0.01$) and obsessive ($\tau=0.55$; $P=0.02$) scores.

## Discussion

This study found a specific pattern of metabolic involvement in cortical and subcortical structures, namely cingulate cortex, pallidum/putamen and thalamus, in OCD patients. This was characterised by an increase of glucose consumption in comparison with normal controls. These results are partly consistent with those of Swedo and co-workers (1989, 1992) who found hypermetabolism in left and right anterior cingulate cortex and in the right thalamus,

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and also demonstrated an increase in orbital and prefrontal metabolic activity. Hypermetabolism within the frontal lobe and caudate nuclei has also been described by Baxter *et al* (1987, 1992). A trend towards hypermetabolism was also present in our series, bilaterally, at the level of caudate nucleus.

Differences in scanner resolution, scanning techniques and methods of analysis and, in particular, heterogeneity of clinical aspects and pharmacological treatments of OCD patients, could explain the discrepancies among the results. Because of the high axial and transaxial resolution of our scintigraphic equipment, we were able to accurately identify deep and subcortical structures.

The lack of frontal involvement could be related to the absence of other major psychiatric disorders, including affective and anxiety disorders, in the present OCD series. In addition, the first PET evaluation was performed in drug-free patients, thus reducing the possibility of pharmacological interference.

These results suggest that OCD symptoms are associated with a dysfunction of the cingulate-striatum-pallidum-thalamic circuit. This circuit has been linked to self-generation, selection and control of willed actions and constitutes one of several parallel neural loops dedicated to behavioural motor output (De Long & Georgopulos, 1981). The input nuclei of this circuit (caudate and putamen) receive substantial projections from several regions of the cerebral cortex, including motor, sensory, prefrontal and limbic cortical areas. The output nucleus (globus pallidum) sends its axons to the thalamus and by this route projects back upon the cortex (De Long & Georgopulos, 1981). A major aspect of this circuitry is that it is functionally linked to multiple levels of complex motor and behavioural processing and that these loops participate in the selection and modulation of willed actions (Alexander *et al*, 1990; Passingham, 1993).

The role played by the cingulate cortex in the control of complex behaviour has also been observed in a number of PET studies involving the internal generation of willed responses (Pardo *et al*, 1990; Frith *et al*, 1991; Paus *et al*, 1993). The role of cingulate cortex in the control and activation of motor routines is also in agreement with the results of neurophysiological stimulation of human anterior cingulate cortex inducing involuntary movements (Talairach *et al*, 1973). Furthermore, extensive anterior cingulate infarcts may produce akinetic mutism, characterised by a suppression of voluntary speech and movement (Laplane *et al*, 1981; Nemeth *et al*, 1988).

These data suggest that impairment of this circuit may affect selection, generation and control of self-generated actions and thus may explain OCD symptoms such as uncontrolled repeated activity (compulsions) and persisting thoughts (obsessions).

After treatment with SSRIs, significant metabolic changes were found only in the cingulate cortex, bilaterally. Hoen-Saric and co-workers (1991) found a decreased regional cerebral blood flow in mesial frontal cortex after treatment with fluoxetine. Other authors have shown decreased metabolic activity in caudate and orbitofrontal cortex after treatment with clomipramine (Benkelfat *et al*, 1990) and in caudate, thalamus and cingulate cortex after treatment with fluoxetine (Baxter *et al*, 1992). Swedo and co-workers (1992) using both clomipramine and fluoxetine reported a normalisation of glucose consumption in the orbitofrontal cortex.

Conversely, we did not find significant modifications of metabolic activity in pallidum/putamen complex and thalamus after treatment. As suggested by Swedo *et al* (1992), a longer follow-up study after treatment may be necessary to reveal changes of cerebral metabolic activity in these areas.

The neural and pharmacological mechanism of SSRIs in producing significant clinical modifications in OCD remains unexplained. The therapeutic effects require weeks of drug administration, thus the mechanism of action may relate to long-term adaptive changes, and not to an acute release of serotonin. In fact, the acute administration of a specific serotonergic agonist to patients with OCD has been found to provoke an exacerbation of symptoms (Zohar *et al*, 1987). The mechanism of action of SSRIs has been suggested to be due to either a down-regulation of serotonin receptors or a desensitisation of presynaptic serotonin receptors (Peroutka & Snyder, 1980; Goodman *et al*, 1990).

A reduction of metabolism in the cingulate cortex after treatment may be either a direct or indirect effect of therapy. First, the serotonergic system, modulated by the treatment, may act principally on the serotonin receptors present in this area (Tork, 1990). PET studies using specific receptors tracers will help to highlight this issue. Second, the metabolic reduction in the cingulate cortex may represent an epiphenomenon resulting from the reduction of obsessive–compulsive symptoms. This hypothesis is supported by the significant correlation between improvement of symptoms and changes of metabolic activity in cingulate cortex shown in the series of patients studied at follow-up. Alternatively, a general reduction of anxiety induced by this treatment, may have had a functional effect on cingulate cortex, an area recognised as having a relationship with the emotional processes (Kupfermann, 1991).

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## Conclusions

Our findings indicate that OCD is associated with a functional overactivity of neuronal circuits interconnecting selected cerebral structures. These are part of neural loops related to the control of behavioural and motor output. The regional neuromodulatory effect of treatment on cingulate cortex, associated with a reduction of symptoms, may therefore be the functional equivalent of therapeutic effect of surgical isolation of cingulate cortex from surrounding structures (Sachdev *et al*, 1992).

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