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Neurology 2006;66;1629

DOI 10.1212/01.wnl.0000218194.12054.60

This information is current as of December 20, 2011

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Effects of antidepressant treatment with rTMS and fluoxetine on brain perfusion in PD

F. Fregni, MD, PhD*; C.R. Ono, MD, PhD*; C.M. Santos, MD; F. Berman, MD, PhD;
C. Buchpiguel, MD, PhD; E.R. Barbosa, MD, PhD; M.A. Marcolin, MD, PhD; A. Pascual-Leone, MD, PhD;
and K.D. Valente, MD, PhD

Abstract—Background: Although depression is highly prevalent in Parkinson disease (PD), little is known about the neural correlates associated with depression and antidepressant treatment in PD. **Objective:** To examine the effects of fluoxetine and repetitive transcranial magnetic stimulation (rTMS) on regional cerebral blood flow (rCBF) using SPECT in patients with PD and depression. **Methods:** Twenty-six patients were enrolled into two groups: One received active rTMS and placebo medication and the other sham rTMS and fluoxetine 20 mg/day. Brain SPECT was performed at baseline and after 2 and 8 weeks. Changes in rCBF were compared across timepoints and correlated with clinical scores. In addition, baseline rCBF of these patients was compared with that of 29 healthy, age-matched subjects. **Results:** At baseline, patients with PD and depression showed significantly lower rCBF in the left prefrontal cortex, posterior cingulate gyrus, left insula, and right parietal cortex when compared with healthy controls. Both treatments induced significant clinical improvement and increases in rCBF in the posterior cingulate gyrus and decreases in rCBF in the right medial frontal gyrus. These changes were significantly correlated to the clinical outcome. Furthermore, the comparison between these two treatments revealed that whereas rTMS treatment was associated with an increased perfusion in the right and left prefrontal cortex, fluoxetine treatment was associated with a relative rCBF increase in the occipital lobe. **Conclusion:** Depression in patients with Parkinson disease is correlated with a dysfunction of the frontal–limbic network that can be modulated by two different antidepressant therapies.

NEUROLOGY 2006;66:1629–1637

Depression is an important factor for the quality of life of patients with Parkinson disease (PD),¹ impacting daily functional activities,^{2,3} but it remains frequently untreated.^{2,4} Treatment options for depression in PD include antidepressants, electroconvulsive therapy (ECT), and repetitive transcranial magnetic stimulation (rTMS).⁵ There is still controversy about the best treatment for depression

in PD because of concerns regarding the relative efficacy and tolerability of available antidepressants,⁶ the adverse effects of ECT,⁷ and the efficacy of rTMS. In addition, the lack of knowledge about the mechanisms of action of these therapies in PD patients contributes to the difficulties in the clinical management of these patients.

To date, there are no studies that investigated the effects of antidepressant treatments, such as antidepressants and rTMS, on brain activity in PD patients with depression. In major depression, neuroimaging studies have shown an increase in brain activity in prefrontal and limbic areas after rTMS treatment,⁸⁻¹⁰

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*These authors contributed equally to the article.

From the Harvard Center for Noninvasive Brain Stimulation (F.F., F.B., A.P.-L.), Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA; Departments of Nuclear Medicine (C.R.O., C.B.), Psychiatry and Neurology (C.M.S., E.R.B., M.A.M., K.D.V.), University of Sao Paulo, Brazil; and Department of Psychiatry and Psychotherapy (F.B.), Charité Campus Mitte, University Medicine Berlin, Germany.

Supported by a grant within the Harvard Medical School Scholars in Clinical Science Program (NIH K30 HL04095-03) to F.F. and by K24 RR018875 to A.P.-L.

Disclosure: The authors report no conflicts of interest.

Received August 17, 2005. Accepted in final form February 23, 2006.

Address correspondence and reprint requests to Dr. F. Fregni, Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, 330 Brookline Ave., KS 452, Boston, MA 02215; e-mail: ffregni@bidmc.harvard.edu

cognitive behavioral therapy,¹¹ and oral antidepressants.¹²⁻¹⁵ Because the pathophysiology of depression in PD might be different from that in major depression, antidepressant treatments might have a different effect on regional cerebral blood flow (rCBF) in these two types of depression. In this study, we sought to evaluate the effects of rTMS and fluoxetine on rCBF at weeks 2 and 8 of treatment in PD patients with depression and to evaluate rCBF differences between PD patients with depression (baseline evaluation) and age-matched control subjects.

Methods. Study population. We studied 26 patients (66.3 ± 7.9 years, 10 women) with idiopathic PD who fulfilled the UK Parkinson's Disease Brain Bank criteria and had major or minor depression according to the Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV) criteria, based on the Structured Clinical Interview for DSM-IV. Although there is controversy about the best instrument to diagnose depression in PD, DSM-III and -IV have been used in several studies of PD and comorbid depression.^{2,3,16-18} The item of psychomotor retardation of the DSM-IV was not taken into account in the diagnosis of depression, as this can be present with equal frequency in PD patients with and without depression.¹⁶ In addition, we studied 29 healthy subjects (mean age of 65.2 ± 7.2 years; 9 women) with no current or past history of any psychiatric or neurologic disorder.

Patients were excluded if they had been using antidepressants within 2 months of the study, ferromagnetic metallic implants, history of seizures, major head trauma, dementia, or depression with psychotic symptoms. All patients remained stable on their regular antiparkinsonian medications as prescribed by their treating physician. They all gave written informed consent to participate in the study, which was approved by the local institutional review board.

Experimental design. Patients were randomly assigned to one of two groups according to a computer-generated randomization list: Group 1, active rTMS and placebo medication (13 patients); Group 2, sham rTMS and fluoxetine 20 mg (13 patients). The demographic and baseline clinical features were not significantly different between the groups (table).

The rCBF was examined using SPECT. All patients underwent SPECT sessions at baseline, at the end of week 2, and at week 8 of the study. To avoid conducting a SPECT session immediately after the last rTMS session, the investigation at week 2 was done 24 hours after the end of the 2-week course of rTMS (real or sham). The interval of 24 hours seems to be enough to avoid the immediate, acute effects of rTMS on brain activity. For instance, it has been shown that 10 minutes of 1-Hz rTMS to the motor cortex decreases cortical excitability that lasts only 10 minutes.¹⁹ In addition, a SPECT study in depressed patients showed that rCBF during the first session of rTMS was not changed when compared with baseline, but when performed after 10 days of rTMS, there was a significant change of rCBF in the site of stimulation; therefore, rCBF changes induced by rTMS depend also on the number of sessions of rTMS. We chose to perform an evaluation at week 8 (6 weeks after the end of rTMS treatment) to assess whether the changes in brain perfusion after 2 weeks of rTMS treatment were long lasting; it has been shown that the behavioral effects induced by a 2-week course of rTMS can last up to 3 months after this treatment.^{5,20,21}

For each of the SPECT sessions, patients were instructed not to take their morning medications (therefore, antiparkinsonian medications were withheld for at least 12 hours prior to the examination). All SPECT sessions were performed at the same time of the day (between 8:00 AM and 10:00 AM). In addition, healthy controls and patients underwent SPECT at the same scanner and during the same period of time.

The neurologic and psychiatric assessments were performed by blinded raters at baseline, week 2, and week 8. Both raters underwent specific training to ensure adequate intrareliability. These evaluations included the following scales: 1) Hoehn and Yahr Scale; 2) Unified Parkinson's Disease Rating Scale (UPDRS; Motor part III); 3) patients' activities of daily living (ADL) assessed using the Schwab and England Activities of Daily Living Scale; 4)

Table Demographic and baseline clinical characteristics

	rTMS group		Fluoxetine group		p Value*
	Mean/n	SD	Mean/n	SD	
No. of patients	13		13		
Demographic data					
Age, y	67.54	6.83	65.04	8.93	0.80
Men	8		8		0.999
Women	5		5		
Parkinson features					
Duration of disease, y	7.08	3.66	7.85	4.94	0.65
ADL	76.92	15.48	71.54	23.04	0.84
Hoehn-Yahr	1.85	0.90	1.92	1.26	0.41
UPDRS	32.15	12.21	37.23	17.87	0.91
Psychiatric features					
BDI	25.92	9.98	26.85	8.12	0.80
HRSD	25.54	6.57	27.46	6.60	0.57
MMSE	25.77	3.65	24.69	4.17	0.53

* Using Student *t* test for continuous variables and Fisher exact test for categorical values. Note that the low score of baseline MMSE indicates the low level of education of these patients (patients with dementia were excluded from this study).

rTMS group = active repetitive transcranial magnetic stimulation (rTMS)/ placebo pill; fluoxetine group = sham rTMS/ fluoxetine; ADL = activities of daily living; UPDRS = Unified Parkinson's Disease Rating Scale; BDI = Beck Depression Inventory; HRSD = Hamilton Rating Scale for Depression; MMSE = Mini-Mental State Examination.

21-item Hamilton Rating Scale for Depression (HRSD); 5) Beck Depression Inventory (BDI); and 6) Mini-Mental State Examination (MMSE).

Magnetic stimulation. Patients were comfortably seated in a dental chair for the intervention. A pair of surface electrodes was placed over the right abductor pollicis brevis muscle. These electrodes were connected to a Dantec Electromyography (Medtronic, Minneapolis, MN). Electromyography was used to measure the motor threshold (MT). MT was defined as the lowest TMS intensity required to elicit motor evoked potentials (MEPs) of ≥0.05 mV peak-to-peak amplitude in the contralateral resting abductor pollicis brevis muscle in at least 5 of 10 trials with the coil over the optimal scalp position. During the rTMS treatment, we targeted the left prefrontal area by placing the coil over a point 5 cm anterior and in the same parasagittal plane from the optimal position for induction of MEPs in the right abductor pollicis brevis muscle. The coil was held tangentially to the skull with the handle pointing occipitally and aligned parallel to the midline of the subject's head.

Focal rTMS of the left dorsolateral prefrontal cortex was performed using a commercially available figure-of-eight coil (outside diameter of each wing 7 cm) and a Dantec stimulator (1.5 T version; Medtronic). Stimulation parameters were frequency of 15 Hz and stimulation intensity of 10% above each patient's resting MT. The treatment protocol consisted of 10 sessions over the course of 2 weeks, typically administered Monday through Friday. At each session, a train of 75 stimuli was delivered over 5 seconds followed by a 10-second intertrain interval. A total of 40 trains were delivered in each session, resulting in a total number of 3,000 pulses per day. For the sham treatment group, stimulation parameters were the same; however, a sham coil (Dantec; Medtronic) was used. After the 2-week period of stimulation (sham or active), patients in both groups were instructed to keep taking the medication (fluoxetine or placebo) until the follow-up evaluation at week 8.

One can argue that the duration of rTMS treatment (2 weeks) might not have been long enough as recent investigations have shown that the antidepressant effect of rTMS is associated linearly with the number of the sessions.^{22,23} In other words, more sessions of rTMS are associated with a larger antidepressant ef-

fect. However, our initial results (patients that did not undergo SPECT) and a previous study²⁴ showed that 2 weeks of rTMS treatment were sufficient to induce a significant antidepressant effect in patients with PD. In addition, at the time of this investigation, no safety data regarding the use of rTMS for more than 2 weeks in PD were available.

Medication. Patients in Group 2 were placed on fluoxetine 20 mg/day, whereas patients in Group 1 were given a daily pill of glucose (placebo). All pills (fluoxetine or glucose) and the containers that were given to the patients had the same appearance and were made in the same laboratory. The containers were labeled only with the patient's study number.

Brain SPECT. Image acquisition. Initially, an IV injection of 740 MBq (20 mCi) of ^{99m}Tc-ethyl cysteinate dimer was administered. The patients remained in the supine position in a quiet, dimly lit room and were instructed to keep their eyes closed. Thirty minutes after injection, the SPECT scan was recorded using a dual-head gamma camera with dedicated collimator for brain studies (fan beam; E.CAM; Siemens, Hoffman Estate, IL). The rotation time was determined through counts per frame (at least 100,000 counts), and 128 projections were acquired. SPECT images were processed on a workstation E-soft (Siemens) with Butterworth filter (with 0.75 cutoff and order 5). The reconstruction yielded 4.8-mm voxels with a 128 × 128 matrix and 128 slices. In-plane spatial resolution was 10.6/6.7 mm full width at half-maximum (FWHM) in the center of view.

Image analysis. We analyzed the SPECT images using statistical parametric mapping for Windows software SPM2 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK), implemented using MATLAB software, version 6.0 (Mathworks, Sherbon, MA). First, we transformed the images that were in DICOM format to ANALYZE format and then converted them for neurologic convention using MRICRO software, version 1.39 (www.mricro.com). SPECT images were normalized using the template of SPECT models in SPM, with bilinear interpolation after smoothing using a Gaussian filter with 12 mm FWHM. The pixel values were normalized by scaling the activity in each pixel proportional to the global activity (proportional scaling) to stabilize the variance related to the substantially different global activity. Planned comparisons between the conditions were performed using *t* statistics for each voxel. These analyses generated statistical parametric maps of the *t* statistic, which were subsequently converted to unit normal distribution (*Z* scores).

We performed within- and between-group comparisons—increases and decreases in rCBF (paired *t* test)—using SPECT data obtained at baseline, week 2, and week 8. In addition, we compared the baseline data across study groups against age- and gender-matched controls (two-sample *t* test). For the comparisons with healthy controls, we performed both contrasts (increase and decrease); however, we only reported the contrast of healthy controls > PD patients as the contrast of PD patients > healthy controls did not reveal significant findings.

For the statistical threshold, we decided to report the results using the threshold to false discovery rate (FDR) with a corrected *p* value of less than 0.05. However, for exploratory purposes, we also decided to report the findings using the statistical threshold at *Z* > 3.09 (corresponding to *p* < 0.001, uncorrected) for each voxel and also using a threshold of *Z* > 2.33 (uncorrected, corresponding to *p* < 0.01 at each voxel) as a trend toward a differential rCBF; this low threshold was employed for areas that made sense to us post hoc. We decided to use uncorrected *p* value to avoid false negatives as the corrected *p* value can be a rather conservative method, but we acknowledge that the results using the uncorrected *p* value threshold should be interpreted as preliminary and therefore should be further confirmed. Finally, the results of our study are in accordance with our hypothesis a priori: Antidepressant treatment would result in rCBF changes in the prefrontal and cingulate cortex. Thus, our discussion emphasizes the perfusion changes in the frontal–limbic network rather than other areas that are not associated with mood modulation and hence being more likely false-positive results.

In addition, we performed, for each group, a correlation analysis between changes in relative rCBF and changes in the clinical scores (as indexed by HRSD) for selected areas (those that showed a significant change in rCBF after treatment and were also clinically relevant). The results of this analysis were corrected for

multiple comparisons; therefore, we reported only results at *p* = 0.01 (i.e., 0.05/5, Bonferroni correction).

Analysis of behavioral data (neurologic and psychiatric evaluation). The neurologic and psychiatric evaluations are not the focus of this study, as these data have been reported elsewhere.⁵ Here we will address these results only to provide a characterization of the study population as needed for the interpretation of SPECT results. For both groups, HRSD, BDI, UPDRS, ADL, and MMSE scores were calculated at weeks 0, 2, and 8. We analyzed changes in these outcome variables with treatment using repeated measures analysis of variance with two factors: time (baseline, week 2, and week 8) and group (active rTMS/placebo medication and sham rTMS/fluoxetine). The threshold for significance was set at *p* < 0.05.

Results. Clinical changes induced by rTMS treatment and fluoxetine. There were no significant differences in the demographic, psychiatric, and neurologic characteristics of the two groups of patients (see the table). The findings of the clinical effects of fluoxetine and rTMS have been published elsewhere.⁵ Although the sample of patients in this study (26 patients) does not represent the complete sample of patients (42 patients) of our previous study, the clinical results of this reduced sample of patients is similar to that of full sample: An overall analysis of variance showed neither significant group effect nor interaction term for all of the clinical outcomes (BDI, HRSD, MMSE, and UPDRS); however, time effect was significant for the mood-related outcomes (BDI and HRSD; *p* < 0.001 for both endpoints), suggesting a significant improvement of the depression in both groups. Furthermore, although there were more responders in the rTMS group (five responders, 38.4%) compared with the fluoxetine group (four responders, 30.1%), this difference did not reach significance ($\chi^2[1 df] = 0.17, p = 0.5$).

Between-group rCBF analysis: Baseline analysis. The comparison of rCBF between PD patients with depression and healthy control subjects showed five main clusters of decreased perfusion in PD patients with comorbid depression (*p* < 0.001 uncorrected and *p* < 0.05 FDR corrected). These areas include the left prefrontal cortex (left middle frontal gyrus [Brodmann area (BA) 9] and inferior frontal gyrus [BA 9], therefore involving the dorsolateral prefrontal cortex), right posterior cingulate gyrus (BA 23 and 31), left insula (BA 13), right parietal lobe (BA 5 and 40), and right cerebellum (see table E-1 on the *Neurology* Web site; go to www.neurology.org). To determine whether the groups were similar at baseline, we performed the following contrasts: rTMS > fluoxetine and fluoxetine > rTMS. This analysis disclosed a difference in rCBF (*p* < 0.001 uncorrected) only for the comparison rTMS > fluoxetine (left temporal gyrus, BA 21), but not for the contrast fluoxetine > rTMS.

Within-group rCBF analysis: rTMS group. For the group that received rTMS treatment, the main finding for the rCBF comparison (using the threshold of *p* < 0.001 uncorrected) between post 2 weeks of treatment vs baseline was an increased blood flow in the anterior and posterior cingulate gyrus (BA 23, 24, and 30). In addition, other cortical areas such as the right orbitofrontal area (BA 47), left insula (BA 13), and right superior (BA 22) and middle (BA 39) temporal gyrus showed significant increases in rCBF. There were also increases in rCBF in the left cerebellum and left substantia nigra after 2 weeks of rTMS. On the other hand, there were rCBF decreases in frontal areas such as the left and right medial frontal gyrus (BA

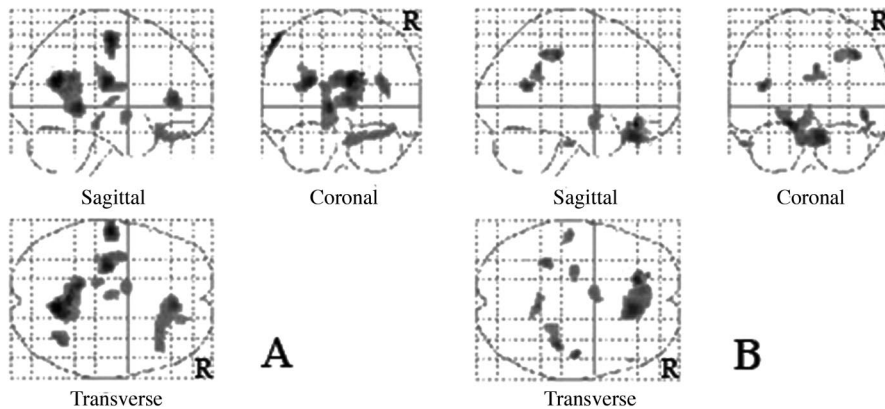


Figure 1. Three orthogonal projections of repetitive transcranial magnetic stimulation-induced brain activity in patients with Parkinson disease after 2 (A) and 8 (B) weeks of treatment. In both figures, the statistical threshold was set at $p < 0.001$ at each voxel level. Although there is less perfusion after 8 weeks (follow-up) compared with immediately after 2 weeks of treatment, similar areas continued to be activated. See table E-2 for the anatomic locations and Z score of each area.

10), the left middle temporal gyrus (BA 21), the right fusiform gyrus (BA 19), and the right cerebellum after 2 weeks of rTMS (figure 1; also see table E-2). With use of the threshold of $p < 0.05$ corrected, there were significant rCBF increases in the anterior and posterior cingulate gyrus (BA 23, 24, and 30) and significant rCBF decreases in the right and left medial frontal gyrus (BA 10) after 2 weeks of treatment.

After 8 weeks, although the clusters were smaller compared with immediately after treatment, the blood flow in the left and right posterior cingulate gyrus (BA 23) was still enhanced ($Z = 2.99$, $p < 0.002$ uncorrected). In addition, rCBF in the left and right orbitofrontal area (BA 11) and the left superior temporal gyrus was increased after 6 weeks of the end of the treatment compared with baseline ($p < 0.05$ FDR corrected). On the other hand, after 8 weeks of rTMS treatment, there was a decrease in blood flow ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected) predominantly in the right hemisphere. The following right-sided areas showed decreased blood flow after 8 weeks of treatment: medial frontal gyrus (BA 10), temporal superior gyrus (BA 22), and cerebellum. Few left-sided areas (putamen and fusiform gyrus [BA 37]) showed decreased blood flow after 8 weeks of treatment compared with baseline (see table E-2).

Within-group rCBF analysis: Fluoxetine group. For the fluoxetine group, the comparison of rCBF after 2 weeks vs baseline also showed an increased blood flow in the posterior cingulate gyrus (BA 31; $p < 0.001$ uncorrected and $p = 0.08$ FDR corrected). This was similar to the findings in the rTMS group. However, despite the fact that both groups had similar clinical depression improvement, there were significant differences in their SPECT results

after treatment. For the fluoxetine group, the increases in rCBF were more pronounced in posterior areas such as the left and right occipital lobe (BA 18 and 19) and right parietal lobe (BA 40) ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected). Furthermore, other areas of the limbic system such as the left parahippocampal gyrus showed an increase in blood flow after 2 weeks of fluoxetine ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected). Similar to the findings after rTMS treatment, 2 weeks of fluoxetine was associated with decreases in rCBF in the right prefrontal lobe (medial and inferior frontal gyrus [BA 11 and 47]), right occipital lobe [BA 31], and left insula [BA 13] ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected) (figure 2; see also table E-3).

After 8 weeks of treatment, some of the areas that showed increased blood flow after 2 weeks of treatment still showed increases in rCBF compared with baseline, such as right occipital lobe (BA 19), right superior temporal gyrus (BA 22), and right cerebellum ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected). In addition, there were increases in rCBF in some motor areas such as the left precentral (BA 4) and postcentral gyrus (BA 1) and left midbrain (substantia nigra); however, these areas reached only the threshold of $p < 0.001$ uncorrected. Interestingly, after 8 weeks of treatment, there was a decrease in rCBF (not detected after 2 weeks of treatment) in the contralateral right precentral gyrus (BA 44) ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected) (see table E-3).

Between-group rCBF analysis: rTMS > fluoxetine. To compare the difference in treatment effects on rCBF between the two groups, we compared the contrasts T2 > T0, T8 > T0, and T8 > T2 between groups (i.e., we analyzed: rTMS [ΔT] > fluoxetine [ΔT]). For the contrast T2 > T0,

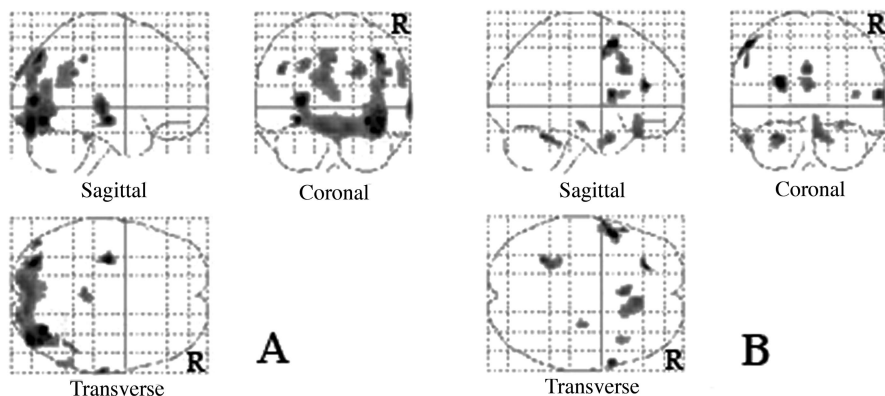


Figure 2. Three orthogonal projections of fluoxetine-induced brain activity in patients with Parkinson disease after 2 (A) and 8 (B) weeks of treatment. In both figures, the statistical threshold was set at $p < 0.001$ at each voxel level. See table E-3 for the anatomic locations and Z score of each area.

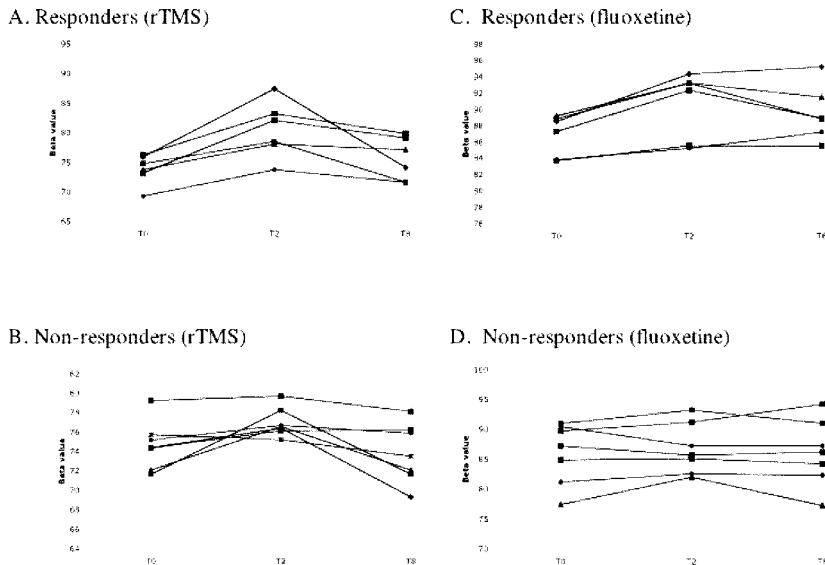


Figure 3. The β value (an index of rCBF) for each subject for posterior cingulate is shown at baseline, week 2, and week 8. The results are presented in two separate figures in which we divided patients into two groups according to the rate of depression improvement (responders: improvement of more or equal to 30% in the Hamilton Rating Scale for Depression [HRSD] [we used the value of 30% to have groups with balanced number of subjects] and nonresponders: improvement of less than 30% in the HRSD). (A) Responders in the repetitive transcranial magnetic stimulation (rTMS) group; (B) nonresponders in the rTMS group; (C) responders in the fluoxetine group; (D) nonresponders in the fluoxetine group.

the analysis rTMS (ΔT) > fluoxetine (ΔT) showed rCBF increases ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected) in the prefrontal cortex (left superior frontal gyrus [BA 8 and 11], right superior frontal gyrus [BA 11], right medial frontal gyrus [BA 11], and left and right inferior frontal gyrus [BA 11]) and a trend toward a significant rCBF increase in the cingulate cortex (posterior and anterior cingulate gyrus [BA 23, 24, and 32]) ($p < 0.001$ uncorrected and $p < 0.1$ FDR corrected). For the contrast T8 > T2, the results were similar; however, this difference was less pronounced (perhaps due to a slight decrease of the effects of rTMS after 6 weeks). The following areas showed relative rCBF increases: prefrontal cortex (left middle frontal gyrus [BA 10] and right orbitofrontal gyrus [BA 13]) and anterior cingulate cortex (BA 25) ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected). Interestingly, the increase in the rCBF was slightly larger in the left prefrontal cortex—the site of stimulation (compared with the right prefrontal cortex). Finally, the analysis of the contrast T8 > T2 showed few differential effects between the two groups (possibly because the effects of rTMS were long-lasting). This analysis disclosed two small clusters of differential perfusion in the right rectal gyrus (BA 11) and left middle frontal gyrus (BA 8) ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected) (see table E-4).

Between-group rCBF analysis: Fluoxetine > rTMS. For the contrast fluoxetine > rTMS, analogous analyses were carried out. The contrast T2 > T0 revealed rCBF increases in the temporo-occipital area: right fusiform gyrus and cuneus (BA 19), right superior temporal gyrus (BA 22), and right supramarginal gyrus (BA 40) for the fluoxetine compared with the rTMS group ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected). For the contrast T8 > T0, the results were similar: a relative rCBF increase in the temporo-occipital cortex (right precuneus [BA 7] and middle temporal gyrus [BA 21]) ($p < 0.001$ uncorrected and $p < 0.05$ FDR corrected). Finally, for the contrast T8 > T2, there were only two small clusters of increased rCBF in the right superior temporal gyrus (BA 22) and in the left precentral gyrus (BA 6) that only reached the threshold of $p < 0.001$ uncorrected (see table E-5).

Correlation of clinical response to change in rCBF. We analyzed the relationship between clinical response and change in rCBF for the posterior cingulate gyrus (increase in rCBF) and for the right medial frontal gyrus (decrease in rCBF) after 2 weeks of treatment in both groups. This analysis disclosed that an improvement in depression was correlated with an increase in the activity in the posterior cingulate gyrus ($r = 0.69$, $p = 0.008$ for the fluoxetine group and $r = 0.74$, $p = 0.004$ for the rTMS group) (see figure E-1) and with a decrease in rCBF in the right medial frontal gyrus ($r = -0.68$, $p = 0.01$ for the fluoxetine group and a trend toward a significant correlation for the rTMS group; $r = -0.53$, $p = 0.058$). We also plotted rCBF in these two areas (posterior cingulate gyrus and right medial frontal gyrus) at baseline, week 2, and week 8 and showed the results in two separate figures in which we divided patients into two groups according to the rate of depression improvement (we set a threshold of 30% improvement in the HRSD). These figures showed that patients with larger mood improvement had a significant rCBF increase in the posterior cingulate gyrus (figure 3) and rCBF decrease in the right medial frontal gyrus (figure 4) after 2 weeks of treatment. This effect was slightly less pronounced in the evaluation of week 8. Finally, there was no correlation between the decrease in rCBF in the precentral gyrus and the scores in the UPDRS for the fluoxetine group after 8 weeks of treatment ($r = -0.05$, $p = 0.85$).

Discussion. In our SPECT study, patients with PD and comorbid depression showed significantly lower blood flow in the left prefrontal cortex, including the dorsolateral prefrontal cortex, posterior cingulate gyrus, left insula, and the right parietal cortex, when compared with healthy control subjects. Effective antidepressant treatment with either rTMS or fluoxetine was associated with rCBF increases in the posterior cingulate gyrus and rCBF decreases in the right medial frontal gyrus after 2 weeks of treatment. These changes in the rCBF after 2 weeks of either treatment were significantly associated with

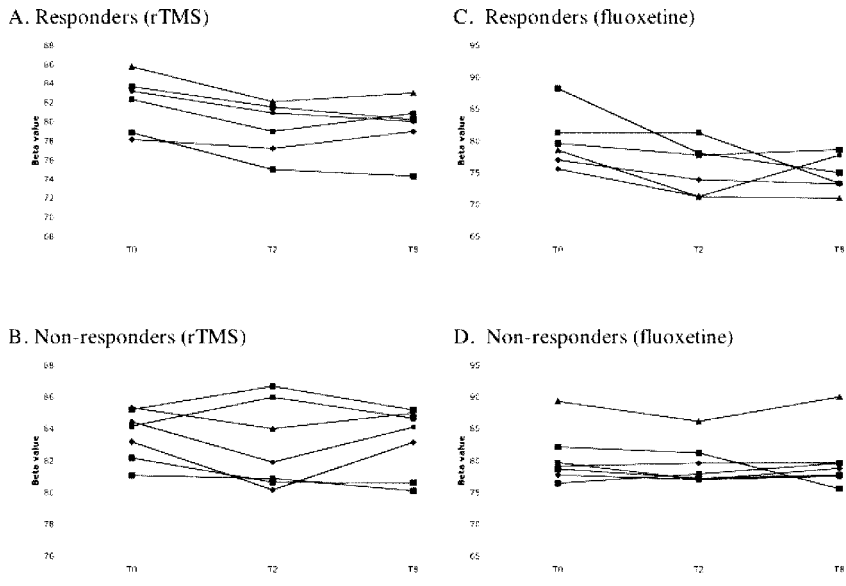


Figure 4. The β value (an index of rCBF) for each subject for right medial frontal gyrus is shown at baseline, week 2, and week 8. The results are presented in two separate figures in which we divided patients into two groups according to the rate of depression improvement (responders: improvement of more or equal to 30% in the Hamilton Rating Scale for Depression [HRSD] [we used the value of 30% to have groups with balanced number of subjects] and nonresponders: improvement of less than 30% in the HRSD). (A) Responders in the repetitive transcranial magnetic stimulation (rTMS) group; (B) nonresponders in the rTMS group; (C) responders in the fluoxetine group; (D) nonresponders in the fluoxetine group.

the clinical outcome as indexed by HRSD. However, some differences in rCBF changes were observed between these two treatments. Treatment with rTMS resulted in a differential increase in rCBF in the left and right prefrontal cortex (more pronounced in the left hemisphere) and posterior and anterior cingulate gyrus when compared with fluoxetine, and the inverse comparison (fluoxetine compared with rTMS) resulted in a differential rCBF in the temporo-occipital area including fusiform, cuneus, and temporal gyrus.

The results of this study suggest that patients with PD and depression have a hypoactivity in areas such as the left prefrontal cortex and the cingulate gyrus when compared with healthy control subjects. Previously, several studies have shown that major depressive disorder is associated with decreased brain activity of the left prefrontal cortex and the cingulate gyrus^{8,10,13,25-27} and that these alterations might be reverted after a successful antidepressant treatment.^{11,12,14,15,28,29} The results of the current study therefore indicate that comorbid depression in PD might affect a neural network similar to major depressive disorder that involves bilateral frontal, limbic, and paralimbic areas.

The results of our study are partially in accordance with a previous study (with five patients with PD and depression) that showed decreased metabolic activity in the prefrontal cortex in PD patients with depression compared with healthy control subjects,³⁰ but this hypoactivation was located in the infero-orbital area only, whereas we showed a decreased perfusion of other areas of the left prefrontal cortex, such as the middle frontal gyrus. Furthermore, this study showed no differential metabolic activity in the posterior cingulate gyrus in PD patients with comorbid depression compared with control subjects and PD patients without depression. This difference might be explained by the severity of the depression at baseline (10.4 in the previous study vs 26.6 in our

study as indexed by the HRSD). Greater severity of depression may affect additional areas of the frontal–limbic network, perhaps indicating that the entire mood-related neuronal network is impaired. Our findings were in accordance with a similar further study in which the comparison of brain metabolism between PD patients with depression and healthy control subjects yielded significant differences in the medial prefrontal cortex (BA 9) and cingulate cortex (BA 32) metabolism.³¹ Finally, one can argue that the differential brain perfusion between PD patients with comorbid depression and control subjects in our study might be because of the differential brain perfusion between PD patients and control subjects rather than PD patients with depression and control subjects. Although this is a possible explanation, a previous study that compared brain activity between PD patients (without depression) and healthy control subjects showed brain hypoactivation in the following areas: right cuneus, left precuneus, left superior parietal lobe, and right superior frontal gyrus.³² The only area of decreased brain activity reported in our study that coincides with the results of this previous study is the right parietal area. Furthermore, a previous cross-sectional study showed that the rCBF comparison between PD with depression vs PD without depression and PD with depression vs healthy control subjects yielded the same results: decreased rCBF in the medial prefrontal cortex (BA 9) and cingulate cortex (BA 32).³¹ Furthermore, this study revealed that the comparison between PD without depression and healthy controls showed no significant difference in the rCBF in the prefrontal and cingulate gyrus.

Interestingly, patients with PD (without depression) show decreased brain perfusion in the right frontal cortex compared with control subjects.³² In contrast, we showed that PD patients with comorbid depression have a decreased brain activity in the contralateral area: the left prefrontal cortex. This

finding might suggest that comorbid depression in PD might shift the imbalance of the brain activity in the prefrontal cortex. Whereas PD patients have a decreased activity in the right prefrontal cortex, PD patients with depression have it in the left prefrontal cortex. Such imbalance between the right and left hemispheric brain activity has earlier been reported in major depression.^{33,34}

After 2 weeks of treatment, both groups showed a decrease in rCBF in the right medial inferior frontal gyrus. Although we did not observe an increase in the rCBF in the left prefrontal cortex after either treatment, the decrease in rCBF in the right prefrontal cortex might suggest that the imbalance in left/right hemisphere observed in patients with major depression¹⁵ can be reverted with these two treatments. These findings are in line with previous rTMS⁸ and antidepressant²⁹ studies.

Depression scores after treatment with rTMS were significantly associated with perfusion changes in some areas of the frontal–limbic network, such as an increase in rCBF in the anterior and posterior cingulate cortex and orbital frontal gyrus and a decrease in rCBF in the right prefrontal cortex, specifically the right medial frontal gyrus. Furthermore, the treatment with rTMS resulted in a differential rCBF increase in the left prefrontal and cingulate cortex compared with fluoxetine. These findings are in accordance with studies that investigated the use of rTMS for the treatment of major depression and showed that rTMS treatment is associated with changes in brain activity in a similar neural network.^{8–10} Indeed, several studies have shown an abnormally reduced blood flow and metabolism in the dorsal anterior cingulate in depressed subjects^{11,35} that is reverted after successful antidepressant treatment.^{15,28} In addition, previous research has shown that the comparison of brain activity between responder and nonresponder PD patients to antidepressant treatment reveals an increased activity in the rostral cingulate gyrus (BA 24).³⁶ Furthermore, we showed clinically and through neuroimaging that the effects of 2 weeks of rTMS were still significant after 6 weeks of follow-up. Although there was a small decrease in the magnitude of the clinical depression improvement and rCBF changes after 6 weeks of the end of rTMS treatment, the clinical and brain activity effects were still significant when compared with baseline. Moreover, we showed a significant increase in rCBF in the left midbrain (substantia nigra) that might indicate that the stimulation of the prefrontal cortex activates the midbrain–frontal pathway and results in an increase in the dopamine release. This finding, although speculative, corroborates previous studies that showed a release of dopamine after prefrontal stimulation in humans³⁷ and animals.³⁸ Although we showed no significant motor improvement after rTMS treatment, a recent meta-analysis suggests that rTMS treatment is associated with a significant motor improvement in PD.³⁹

The group of patients that received fluoxetine had an increased blood flow after the treatment in some areas that were similar to those of patients that received rTMS, such as posterior cingulate gyrus. However, this group of patients also had an increased blood flow in other areas of the limbic system such as parahippocampal gyrus and other cortical areas such as occipital and parietal cortex. Furthermore, similar to the findings of the rTMS group, these areas of increased perfusion tended to maintain an increased level of activity (compared with baseline) after 8 weeks of treatment. These results should be compared with those of a similar study in which brain metabolism as indexed by PET during the treatment with fluoxetine was assessed at baseline, week 1, and week 6 in patients with major depression.⁴⁰ Although the population and time points of the evaluations in this study were different from ours, there are some concordant findings of both studies such as sustained brain activity increase in the brainstem, premotor, and inferior parietal cortex and some partially concordant findings such as changes in the posterior cingulate gyrus activity; however, whereas the former study (with patients with major depression) showed an increase in the activity in the left and right prefrontal cortex, we showed a decrease in the right prefrontal cortex rCBF. Interestingly, the comparison between changes induced by rTMS vs changes induced by fluoxetine in our study showed that the rTMS group had a relative prefrontal cortex perfusion increase. Although one can speculate that less activity in the prefrontal cortex could be associated with less depression amelioration, both groups of patients (rTMS and fluoxetine) had a similar mood improvement.

Our findings converge to the evidence that prefrontal and posterior cingulate cortex are involved in the neural network of mood modulation in PD patients with depression. Because the prevalence of depression is abnormally high in PD patients, it has been long hypothesized that dopamine plays an important role in mood regulation and might indeed modulate the frontolimbic network. A recent study compared brain activity between PD patients with clinically significant levodopa-related mood fluctuations and similar patients with motor, but not mood, fluctuations.⁴¹ The results of this study showed that the rCBF response to levodopa in medial frontal and posterior cingulate gyrus was significantly different between these two groups of patients. The authors of this study suggest that dopaminergic structures such as caudate nucleus, anterior cingulate gyrus, and orbital frontal cortex might decrease (owing to dopamine deficiency) the modulation to posterior cingulate and other prefrontal areas that might result in depression.

Finally, our results might suggest that whereas the prefrontal rTMS might affect a specific network previously correlated to mood regulation (frontal–limbic network), fluoxetine seems to affect a similar network, but, in addition, other cortical areas such

as motor and occipital cortex. Although one can say that changes in brain perfusion in motor areas after fluoxetine treatment might explain the adverse motor effects of this therapy as suggested by some authors, we did not find a significant correlation between the UPDRS scores and rCBF changes in the precentral gyrus. We showed an increased perfusion in the occipital cortex after the antidepressant treatment with fluoxetine. Although we cannot exclude an artifact completely, this is unlikely as both groups of patients were exposed to the same conditions and stayed with the eyes closed during the SPECT exam. In addition, two previous studies showed increased occipital activity after antidepressant treatment with selective serotonin reuptake inhibitor. For instance, treatment with fluxovamine¹² and sertraline¹⁴ increases blood flow in the occipital cortex in patients with major depression. It has been proposed that small serotonergic centers in the brain can affect widespread cortical areas.^{12,14} In addition, an increase in the global cerebral blood flow could explain this unexpected finding in the occipital lobe. However, the use of antidepressants does not result in an increase in the global CBF¹⁵ in contrast to high-frequency rTMS that can cause such global perfusion increase in patients with major depression.⁹

This study has some limitations. Although compared with other studies with similar design, our study has a relatively adequate sample size, we cannot exclude completely that our analysis was underpowered to detect differences in rCBF between the rTMS and fluoxetine group. Furthermore, because there was a 12-hour levodopa withdrawal before SPECT study, some patients might have been in the "off" state. Because the "off" state is associated with mood dysphoria, patients might have been studied in a dysphoric state. Although this might have biased our results, patients were controls of themselves, and in addition, the proportion of patients with motor fluctuation was small (less than 20%).

Due to ethical reasons, we did not include a placebo group,⁵ and thus the results of this study might have been due to nonspecific effects such as a spontaneous recovery of depression rather than a specific effect of rTMS or fluoxetine. Although we cannot rule out this alternative explanation completely, some reasons may give support to the specific effects of both treatments. We showed a specific effect of these treatments when comparing the differences in rCBF between the two treatment groups, such as that the treatment with rTMS resulted in a relative increase in rCBF in the prefrontal and cingulate cortex and fluoxetine in rCBF increase in the temporo-occipital cortex. Nonspecific effects might have affected both groups similarly. Second, we showed a significant correlation between rCBF changes and depression improvement (as indexed by HRSD). In addition to the lack of a placebo group, one can also argue that our results might be similar if PD patients without depression were studied. However, the correlation between the SPECT and clinical data and the results

showing an increased perfusion in areas extensively correlated with mood render this alternative explanation less likely.

Some technical limitations regarding the SPECT exam should be entertained. First, one important consideration is that SPECT measures the CBF that does not generally reflect exactly brain metabolism, which is a better surrogate for brain activity (compared with cerebral perfusion). In addition, a previous study showed that fluoxetine interferes with Ca²⁺ signaling mechanisms in the vascular smooth muscle⁴² and therefore can increase CBF. This mechanism might have been responsible for some of the effects observed in this study that could not be measured directly. Second, the results from the comparison between healthy subjects vs PD patients with depression at baseline might be partially explained by regional volume loss; that is, the loss of gray matter can result in a relative decrease in signal intensity. Although there is a controversy about the areas that are more likely to be affected by this partial volume effect (PVE) as the results of the correlation between age and brain perfusion between pre- and post-PVE correction vary across different studies,^{43,44} PVE correction might decrease the negative effects of brain atrophy on brain perfusion. As we did not use the PVE correction, some of the differences in rCBF between PD patients with depression at baseline and healthy subjects could be explained by the relative effect of brain atrophy on rCBF. However, our results showed important clusters of rCBF change with large *Z* scores that were in line with previous literature.

Acknowledgment

The authors thank Barbara Bonetti for administrative support.

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**Effects of antidepressant treatment with rTMS and fluoxetine on brain perfusion
in PD**

F. Fregni, C. R. Ono, C. M. Santos, et al.
Neurology 2006;66;1629
DOI 10.1212/01.wnl.0000218194.12054.60

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