rTMS treatment for depression in Parkinson’s disease increases BOLD responses in the left prefrontal cortex

Ellison Fernando Cardoso¹, Felipe Fregni², Fernanda Martins Maia³, Paulo S. Boggio⁴,⁵, Martin Luis Myczkowski⁶, Karen Coracini⁶, Adriana Lopes Vieira⁶, Luciano M. Melo⁶, João R. Sato¹, Marco Antonio Marcolín⁶, Sergio P. Rigonatti⁶, Antonio Cesário Cruz Jr.¹, Egberto Reis Barbosa⁶ and Edson Amaro Jr.¹

¹ NIF, LIM-44, Department of Radiology, University of São Paulo, São Paulo, Brazil
² Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
³ Department of Neurology, University of São Paulo, São Paulo, Brazil
⁴ Department of Psychology, Neuroscience Center, Mackenzie Presbyterian University, São Paulo, Brazil
⁵ Department of Experimental Psychology, University of São Paulo, Brazil
⁶ Department of Psychiatry, University of São Paulo, São Paulo, Brazil

Abstract

The mechanisms underlying the effects of antidepressant treatment in patients with Parkinson’s disease (PD) are unclear. The neural changes after successful therapy investigated by neuroimaging methods can give insights into the mechanisms of action related to a specific treatment choice. To study the mechanisms of neural modulation of repetitive transcranial magnetic stimulation (rTMS) and fluoxetine, 21 PD depressed patients were randomized into only two active treatment groups for 4 wk: active rTMS over left dorsolateral prefrontal cortex (DLPFC) (5 Hz rTMS; 120% motor threshold) with placebo pill and sham rTMS with fluoxetine 20 mg/d. Event-related functional magnetic resonance imaging (fMRI) with emotional stimuli was performed before and after treatment – in two sessions (test and re-test) at each time-point. The two groups of treatment had a significant, similar mood improvement. After rTMS treatment, there were brain activity decreases in left fusiform gyrus, cerebellum and right DLPFC and brain activity increases in left DLPFC and anterior cingulate gyrus compared to baseline. In contrast, after fluoxetine treatment, there were brain activity increases in right premotor and right medial prefrontal cortex. There was a significant interaction effect between groups vs. time in the left medial prefrontal cortex, suggesting that the activity in this area changed differently in the two treatment groups. Our findings show that antidepressant effects of rTMS and fluoxetine in PD are associated with changes in different areas of the depression-related neural network.

Key words: Depression, fluoxetine, fMRI, Parkinson, rTMS.

Introduction

Depression is the most common psychiatric disease in patients with Parkinson’s disease (PD) (Janca, 2002). Although a number of studies have been performed to investigate the pathophysiology of depression in PD, many questions remain unanswered. Since depression in PD is highly prevalent and not related to the progression of motor symptoms (Brown and Jahanshahi, 1995), it has been proposed that depression in PD might be causally related to the degenerative process and not only reactive to disease disabilities. For instance, patients with depression and PD fail to produce a euphoric response after administration of methylphenidate. Because the effect produced by this agent depends on the integrity of dopamine mesolimbic pathways, this implies that degeneration of dopamine neurons is probably involved in the mechanisms leading to depression in
PD (Cantello et al., 1989). However, treatment with l-dopa does not alleviate depression in most of the cases (Tom and Cummings, 1998).

The stimulation of the dorsolateral prefrontal cortex (DLPFC) with repetitive transcranial magnetic stimulation (rTMS) has been shown to be effective to treat depression in PD patients (Dragasevic et al., 2002; Fregni et al., 2004). The main rationale in using rTMS over the DLPFC is that left DLPFC hypoactivity has been characterized as a critical hallmark in previous models of the pathophysiology of depression (Gainotti, 1972; Mottaghy et al., 2002), and the increase of its activity has been associated with symptoms remission (Bench et al., 1995).

Neuroimaging studies have shown that PD patients with depression have reduced brain activity in the prefrontal areas, such as the orbital-inferior and left medial prefrontal cortex and cingulate gyrus (Fregni et al., 2006c; Mayberg and Solomon, 1995; Ring et al., 1994). In addition, a group of PD patients with satisfactory response to antidepressant treatment showed increased activity in the cingulate gyrus when compared to a group of PD patients with no response to treatment (Fregni et al., 2006c; Mayberg and Solomon, 1995).

In order to extend these previous investigations, our group has studied the effects of two different types of antidepressants on brain activity using single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI). The former study has been published elsewhere (Fregni et al., 2006c) and herein we describe the results of the fMRI investigation using different parameters of rTMS treatment.

We aimed to investigate the neural correlates associated with rTMS treatment in PD patients with depression using event-related fMRI in a parametric design. Facial perception is a fundamental task in our daily life and plays a critical role in social interactions. Evidence from neuropsychological, neurophysiological, and functional imaging studies indicated that face perception is mediated by a specialized system in the human brain. This system involves a core system that includes early perceptual information about faces where the inferior occipital gyrus, fusiform face area, superior temporal sulcus play an important role (Ganel et al., 2005; Haxby et al., 2002; Zangenehpour and Chaudhuri, 2005). Emotional recognition and face perception involve the activity of amygdala, insula, orbitofrontal cortex and ventral striatum. The areas linked to emotional regulation include the anterior cingulate and dorsolateral and medial prefrontal cortices (Leppanen, 2006; Phillips et al., 2003a,b). Depressed patients show a diminished ability to discern affective (happy or sad) facial expressions (Persad and Polivy, 1993). In addition, brain activity associated with facial perception changes before and after the treatment of depression (Fu et al., 2004).

We investigated the neural response induced by face presentation with different emotional valences in patients with PD, before and after antidepressant treatment with either rTMS or fluoxetine in a randomized, double-blind study.

Because rTMS and fluoxetine have different mechanisms of action (Fleischmann et al., 1996; George et al., 2003; Moller and Volz, 2006), we hypothesized that rTMS and fluoxetine would modulate brain activity in different areas of the neural network involved with processing of emotional stimuli. Based on previous studies we hypothesized that fluoxetine would mainly decrease the activity in amygdala (Davidson et al., 2003; Fu et al., 2004) and rTMS would increase the activity in the DLPFC (Catafau et al., 2001). We believe that in PD the rTMS results would be similar, according to our previous investigation using SPECT (Fregni et al., 2006c) at rest. Whereas in the SPECT study modifications of self-referenced mood were studied, in the actual study non-self-referenced mood-related information processing was under study. Thus the actual study delivers some information about mood-related ‘perception of the world’, which is important in its own right. It is still unknown if the same areas would be modulated by either fluoxetine or rTMS while the subjects are actively engaged in a task with stimuli of emotional content. Therefore, this study is important in shedding light on the pathophysiology of depression in PD and the mechanisms of action of two different types of antidepressants in PD patients with depression.

**Methods**

**Study population**

We studied 21 patients with idiopathic PD and major depression according to the UK Parkinson’s Disease Brain Bank and DSM-IV criteria, respectively. A score of at least 16 points on the Hamilton Rating Scale for Depression (HAMD) was chosen in order to avoid including patients with mild depression, as placebo effect would be more likely in this population (Wilcox et al., 1992). Patients were excluded if they had been using antidepressants within 1 yr of the beginning of the study or had ferromagnetic metallic implants, a history of seizures, major head trauma, dementia, previous neurological surgeries, or depression with...
psychotic symptoms. All patients were recruited from the Movement Disorders Clinics of Hospital das Clínicas – University of São Paulo (São Paulo – Brazil) and all gave written informed consent. The study was approved by the local ethics committee – University of São Paulo (Project Approval number: 414/03).

Patients were randomly assigned according to a computer-generated random list to one of two groups. Group 1: active rTMS and placebo drug treatment (11 patients); group 2: sham rTMS and 20 mg/d fluoxetine (10 patients). Dopaminergic medication, as well all other medications were kept constant throughout the trial (Fig. 1).

**Psychiatric and neurological evaluation**

Psychiatric and neurological evaluations were carried out before and after 2 and 4 wk of treatment by two raters, blinded to study group assignment and each other’s evaluation results. Psychiatric evaluation included the HAMD, the Beck Depression Inventory (BDI), and the Mini-Mental State Examination (MMSE).

Neurological evaluation included the Hoehn and Yahr (HY) scale, the Unified Parkinson’s Disease Rating Scale (UPDRS, part III), and the Schwab and England activities of daily living index (SE).

**Transcranial magnetic stimulation**

Focal rTMS of the left DLPFC was undertaken using a figure-of-eight coil and a Dantec MagPro2 stimulator (Medtronic, Minneapolis, MN, USA). At each session, the resting motor threshold (MT) of the right abductor of pollicis brevis muscle (the thumb) was determined, as described by Pascual-Leone et al. (1994). Stimulation occurred over the left DLPFC, which was defined as the region 5 cm rostral to the point of optimal stimulation for the right abductor pollicis brevis muscle at a parasagittal plane in the left hemisphere. We used a figure-of-eight-shaped coil, perpendicular to an imaginary line extending from the point of stimulation to the subject’s nose. Each TMS session consisted of 50 trains of 15 s each, using an intensity of 120% MT and 5 Hz frequency. Patients received three rTMS sessions per week (on alternating week days) in a total of 12 sessions for 4 wk. For the sham treatment, the same parameters were applied using a sham coil (Medtronic).

**Drug treatment**

Patients of both groups were instructed to take one pill of either placebo or fluoxetine (20 mg) daily. We chose fluoxetine (a serotonin selective reuptake inhibitor; SSRI) because this drug is the standard treatment for depression in PD (Weintraub and Stern, 2005) and is also the most commonly used in clinical practice (Weintraub et al., 2003).

**Functional MRI**

Eckmann’s faces were morphed to produce neutral, low and high intensities of sadness, as shown in Figure 2. An event-related fMRI paradigm, similar to Fu et al. (2004) was used. Facial stimuli and baseline trials (crosshair fixation) were presented in random order. Each trial and control condition was presented for 2 s, and the inter-trial interval was randomly varied according to a Poisson distribution (2–12 s; mean 5 s). Patients were instructed to choose whether the presented face was of a male or female by button press. Reaction time and number of wrong answers were recorded. The stimulus presentation was synchronized with the scanner via an optic relay triggered by the radio-frequency pulse (Zurc & Zurc, São Paulo, Brazil). All images were acquired in a 1.5 T GE scanner, equipped with a 33 mT/m gradient. The images were oriented according to the AC–PC line, 15 slices with 7 mm slice thickness (0.7 gap), a total of 168 brain volumes were acquired, 64 × 64 pixels, 20 × 20 mm FOV, flip angle 90°, 2.0 s TR, 40 ms TE, gradient echo EPI acquisition. All patients were examined in two sessions before and two sessions after treatment, this test–retest procedure was chosen to account for inter-session variability within a given subject. The faces were randomly permuted between the four sessions to avoid habituation effects. Each stimulus set had 5–20% of the faces unique to each session. All patients were instructed to take their habitual L-dopa dosage 30 min before the scan.

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**Figure 1.** Study design. After inclusion in the study, patients underwent two fMRI sessions, psychiatric and neurological evaluations. Thereafter they were divided by a random computer-generated list in two treatment groups: fluoxetine/sham rTMS or rTMS/placebo. The treatment was applied for 4 wk. Patients were then re-evaluated in the same two fMRI session as well as receiving psychiatric and neurological examinations.
The fMRI statistical analyses were performed using the free software Brain Activation Mapping (XBAM, www.brainmap.co.uk). The statistical analyses in XBAM are GLM based, similar to most used software, except for the use of non-parametric statistical inference tests, where the significance is obtained via permutations after wavelet transformation, which have been shown to control adequately the type I error with minimal distributional assumptions (Breakspear et al., 2004; Bullmore et al., 2003).

At first, the EPI images were pre-processed for movement realignment, slice time correction and spatial smoothing. For each condition, the haemodynamic response function (HRF) in GLM was determined considering the convolution of experimental designs with two Poisson functions (peak at 4 s and 8 s). Volterra interactions were also included in the model.

In order to evaluate the conditions effect size, or activation contrasts between conditions, the residual sum-of-square quotient (SSQ) (percentage of residual variance explained by the null hypothesis model) was calculated for each voxel in the whole volume, resulting in SSQ maps, analogous to F statistics in SPM (www.fil.ion.ucl.ac.uk/spm). Hence, the voxel SSQ is the statistic of interest, which will be used in further analysis. In order to obtain a multi-subject evaluation, the SSQ maps of all individuals were warped to the standard space of Talairach and Tournoux (1998). The generic brain activation map (GBAM) is then calculated considering the median of SSQ maps across subject. Finally, the statistical significance of GBAM is evaluated using non-parametric permutation tests (Brammer et al., 1997). The group pre-/post-treatment comparisons were performed using the ANOVA approach, assuming the individuals’ SSQ as observations, and inference testing using permutation testing.

### Results

Patients tolerated the treatment well. There were mild adverse effects only, such as mild headache that was equally distributed in both treatment groups. Table 1 shows clinical and demographic characteristics divided by treatment group. Both treatment groups had similar values at baseline.

#### Clinical outcomes

There was a significant reduction in depression scores after 4 wk of treatment in both treatment groups – a two-way ANOVA showed a significant time effect ($p < 0.0001$ for both BDI and HAMD), but the interaction term was not significant ($p = 0.07$ for BDI and $p = 0.26$ for HAMD). In addition, there was also a significant effect of time for MMSE scores ($p = 0.0028$). In contrast, for the motor scores, there were no significant changes ($p = 0.96$ for HY and $p = 0.17$ for UPDRS) (see Table 2 for more details).

#### fMRI results

For the fMRI results, we show the results from 18 patients (nine patients in the fluoxetine group and nine in TMS group). Two patients initially randomized to TMS group and one patient to fluoxetine group were not able to perform the post-treatment tests because of technical problems with our scanner. Since

### Image analysis

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the exclusion of these three patients was not related to the treatment, this exclusion did not affect our results. Neither the number of wrong answers, nor reaction times changed when comparing the before and after treatment performances (Table 3). Moreover, we did not find significant changes in reaction time across faces with different sadness valences (Table 4).

Comparison of pre- vs. post-treatment

In order to compare the effects of negative vs. neutral pictures (sadness contrast) at baseline, and after the treatment we used a within-group ANOVA test. The differences in the contrast of 100% sadness faces vs. neutral faces between baseline and after treatment were analysed for each group separately. In addition, we also analysed whether the group × time interaction (ANOVA 2 × 2) and the correlation between behavioural and blood oxygen level-dependent (BOLD) changes using Pearson’s correlation test were significant.

In the rTMS group (Figure 3), after treatment, the contrast of 100% sadness vs. neutral faces showed increases in the anterior cingulate gyrus (ACC) [Brodman’s Area (BA 25)] and left DLPFC activity – including the median portion of middle frontal gyrus extending to the inferior frontal gyrus (BA 9 and BA 46) – and decreases in the right fusiform gyrus (BA 18) and right DLPFC (BA 9 and BA 46) compared to baseline.

Table 2. Clinical data before and after rTMS treatment

<table>
<thead>
<tr>
<th></th>
<th>rTMS</th>
<th>Fluoxetine</th>
<th>Main effect of group</th>
<th>Interaction time vs. group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>HY</td>
<td>2.54</td>
<td>2.64</td>
<td>2.50</td>
<td>2.40</td>
</tr>
<tr>
<td></td>
<td>(0.82)</td>
<td>(0.81)</td>
<td>(0.53)</td>
<td>(0.52)</td>
</tr>
<tr>
<td>SE</td>
<td>75.45</td>
<td>67.27</td>
<td>77.00</td>
<td>74.00</td>
</tr>
<tr>
<td></td>
<td>(15.70)</td>
<td>(17.94)</td>
<td>(13.37)</td>
<td>(14.30)</td>
</tr>
<tr>
<td>UPDRS</td>
<td>38.64</td>
<td>42.36</td>
<td>34.70</td>
<td>36.70</td>
</tr>
<tr>
<td></td>
<td>(12.80)</td>
<td>(16.69)</td>
<td>(11.96)</td>
<td>(13.54)</td>
</tr>
<tr>
<td>BDI</td>
<td>23.36</td>
<td>14.91</td>
<td>26.10</td>
<td>11.00</td>
</tr>
<tr>
<td></td>
<td>(5.89)</td>
<td>(9.51)</td>
<td>(9.12)</td>
<td>(6.31)</td>
</tr>
<tr>
<td>HAMD</td>
<td>22.64</td>
<td>13.45</td>
<td>22.70</td>
<td>9.50</td>
</tr>
<tr>
<td></td>
<td>(5.18)</td>
<td>(8.86)</td>
<td>(6.43)</td>
<td>(4.86)</td>
</tr>
<tr>
<td>MMSE</td>
<td>24.55</td>
<td>27.36</td>
<td>25.10</td>
<td>26.40</td>
</tr>
<tr>
<td></td>
<td>(2.94)</td>
<td>(2.80)</td>
<td>(3.75)</td>
<td>(3.37)</td>
</tr>
</tbody>
</table>

Two-way ANOVA with two factors: group (rTMS and fluoxetine) and time (pre- and post-treatment).

HY, Hoehn and Yahr; SE, Schwab and England activities of daily living index; UPDRS, Unified Parkinson’s Disease Rating Scale (part III); BDI, Beck Depression Inventory; HAMD, Hamilton Rating Scale for Depression; MMSE, Mini Mental State Examination.

Table 3. Reaction time and percentage of right answers in the fMRI experiment

<table>
<thead>
<tr>
<th></th>
<th>Mean reaction time</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rTMS</td>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Valence</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Neutral</td>
<td>1.22</td>
<td>1.19</td>
<td>1.18</td>
</tr>
<tr>
<td>50% Sadness</td>
<td>1.19</td>
<td>1.15</td>
<td>1.13</td>
</tr>
<tr>
<td>100% Sadness</td>
<td>1.20</td>
<td>1.19</td>
<td>1.17</td>
</tr>
<tr>
<td>Right answers</td>
<td>81%</td>
<td>84%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Mean reaction time and percentage of right answers. Participants received a joystick that had only two buttons. They were instructed to push one if the face was male and the other if female. The joystick was connected to the same computer that presented the stimuli. After each stimulus presentation, reaction time and the chosen answer were recorded through a computer program. Neither the number of wrong answers, nor reactions time changed (according to Mann–Whitney statistical test) when comparing the pre- and post-treatment performances. Moreover, no differences were detected across different sadness valences.
In the fluoxetine group (Figure 4), the same contrast (100% sadness vs. neutral faces), after treatment, showed more activation in the right medial prefrontal cortex [including supplementary motor area and frontal eye field (BA 6 and BA 8) and right premotor areas (BA 6)] compared to baseline.

Although fluoxetine and rTMS increase activation in left medial prefrontal cortex [pre-supplementary motor area (SMA)], rTMS seems to provide an additional increase in its activity as the interaction term between time vs. treatment was significant (Figure 5).

**Correlation analysis**

There was no significant correlation between the differences (pre- vs. post-treatment) in HAMD and BDI vs. the differences in SSQ.

**Discussion**

After treatment, rTMS induced decreased activation in the right DLPFC (including middle and inferior frontal gyrus), right fusiform gyrus and cerebellum and increased BOLD responses in the left DLPFC (BA 9 and BA 46) and ACC (BA 25). Fluoxetine, otherwise, induced an increased activation in right medial prefrontal cortex [including supplementary motor area and frontal eye field (BA 6 and BA 8) and right premotor areas (BA 6)].

These results are partially concordant with the previous literature. The only study addressing the neural correlates of depression treatment in PD with rTMS and fluoxetine (Fregni et al., 2006c) was performed with SPECT at rest. 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 ACC. Treatment with fluoxetine resulted in a differential rCBF in the temporal-occipital area including fusiform, cuneus, and temporal gyrus. In this study, rTMS has induced activity increases in the left and decreases in the right prefrontal area. The main reason for the differences between the results from this study and Fregni’s study (Fregni et al., 2006c) might be the technical differences between SPECT and fMRI. For instance, whereas SPECT does not account for task-related activation, fMRI does. Therefore activity changes in the SPECT study might indicate self-referenced mood changes, while the fMRI study might indicate mood-related perception changes. In addition, the rTMS parameters used in the SPECT study were also different.

Although in our previous study (Fregni et al., 2006c), we found a significant improvement in mood using other parameters of stimulation such as...
a frequency of 15 Hz; we decided to use different parameters of stimulation (5 Hz frequency, and intensity of 120% MT) for two reasons: (i) in a previous study from the same laboratory of this study, we observed that 5 Hz rTMS has a large antidepressant effect that seems superior compared to other studies that used stimulation of 10 Hz or 20 Hz (Rumi et al., 2005); (ii) we also decided to perform three sessions per week in order to prolong the treatment for an entire month, since recent studies showed that a prolonged period of treatment increases the antidepressant effects of rTMS (Avery et al., 2006; Fitzgerald et al., 2006).

Our results agree with past rTMS studies on patients with major depression that showed an increased activation in the left DLPFC after stimulation of this area with high-frequency rTMS. In a study with 17 patients Mottaghy et al. (2002) demonstrated that, after 2 wk of treatment, rTMS reversed a significant left/right asymmetry favouring the right hemisphere. The increase in prefrontal, and decrease in limbic area activity were correlated with symptomatic improvement.

The increase in the left DLPFC activity in the rTMS group after treatment suggests that the DLPFC activity imbalance in depression holds for PD patients with depression. The hypoactivity of the left DLPFC has been a critical hallmark in previous models of the pathophysiology of depression. This area has been principally linked to emotional regulation in facial perception (for review see Leppanen, 2006). Previous studies showed that lesions in left prefrontal areas lead to depressive symptoms (Gainotti, 1972; Gasparrini et al., 1978). Furthermore SPECT studies (Bench et al., 1992, 1993; George et al., 1993) have shown a normalization of baseline hypoactivity in the left DLPFC after treatment for depression (Bench et al., 1995). These observations suggest that modulation of activity in the left prefrontal cortex might ameliorate depression. Finally two previous studies showed that
PD patients with depression also have a hypoactivity in the left DLPFC compared to healthy controls (Fregni et al., 2006c) and PD patients without depression (Ring et al., 1994).

New imaging techniques have provided the means to better understand the neural mechanisms underlying depression symptoms (Mayberg et al., 2000; Seminowicz et al., 2004). Current models from SPECT studies are based on maladaptive functional interactions between limbic and cortical regions (and not only DLPFC) that normally are responsible for maintaining homeostatic emotional control in response to cognitive and somatic stress (Mayberg, 2003; Seminowicz et al., 2004). Different antidepressant treatments, such as antidepressants, cognitive behavioural therapy and electroconvulsive therapy (ECT), produce different changes in the connectivity maps with a graded involvement of cortico limbic dysfunction. For instance, more aggressive treatments, such as ECT, modulate subcortical regions – as opposed to predominantly cortical changes that are observed in patients responding to cognitive behavioural therapy. (Seminowicz et al., 2004) In our study, rTMS and fluoxetine induced changes in predominantly cortical areas.

Network effects of rTMS have also been demonstrated using neurophysiological parameters in stroke. In fact, inhibitory 1 Hz rTMS of the unaffected hemisphere decreased local cortical excitability and increased it in the contralateral healthy hemisphere (Fregni et al., 2006b). We have applied rTMS with high frequency (5 Hz), but in a different area and found an opposite effect: a decrease in activation in the contralateral and an increase in the ipsilateral DLPFC which might be related to the same mechanism proposed in the previous study, i.e. a modulation of the transcallosal inhibition between the stimulated and unstimulated hemisphere.

We did not observe changes in amygdala activation with either fluoxetine or rTMS. Previous studies report an increased amygdala activity in depressed patients that subsides after treatment with antidepressants (Davidson et al., 2003; Fu et al., 2004; Sheline et al., 2001). It has been recently reported that SSRIs modulate amygdala activation in healthy volunteers, showing that the amygdala is modulated not only by mood improvement, but also by serotonergic pathways (Harmer et al., 2006). A possible explanation for the lack of amygdala activation in our study is because of its involvement in the degenerative processes that underlie PD (Harding et al., 2002). Also in PD patients, the degeneration of dopaminergic pathways induces an abnormal function of amygdala that is partially restored with L-dopa (Tessitore et al., 2002). The lack of significant changes in amygdala in our study might be related to differences in the genesis of depression in PD and its treatment effects.

We found evidence that rTMS is associated with a decreased BOLD response in the fusiform gyrus.
Davidson et al. (2003) showed that acutely depressed patients had an increased activity in the fusiform gyrus which might be related to its connections to amygdala that is usually hyperactivated in depression. Therefore, the amygdala-related altered activity in the fusiform gyrus might increase the gain for potentially threatening visual stimuli.

In the fluoxetine group we found a greater activation in the premotor cortex and right medial prefrontal cortex extending to the ACC. The ACC represents a fundamental area in the depression-related network. Previous studies have demonstrated that activity in the ACC may predict response to antidepressant treatment with venlafaxine (Davidson et al., 2003). Moreover, the changes in activity in ACC was correlated with symptomatic improvement in patients with major depression treated with fluoxetine (Fu et al., 2004).

Although both treatments induced increased activation in the dorsal medial pre-frontal after treatment, rTMS induced an incremental increase when compared to fluoxetine, as the interaction term was significant. This effect might have been a result of its local effects on the left prefrontal cortex. We did not adopt a factorial design and therefore did not have the groups ‘fluoxetine and rTMS’ and ‘placebo only’ (this one for ethical reasons). Therefore the results of this study have to be interpreted cautiously, since the interaction of the effects of both treatments cannot be estimated. What our results have shown is that rTMS and fluoxetine change facial perception-related activity in different ways, with a common increase in activity of the medial prefrontal cortex that is higher in the rTMS group compared to the fluoxetine group. Taking into account previous explained limitations, we may speculate that the ‘add-on’ effect of rTMS plus fluoxetine observed in clinical practice might be related to the fact that these therapies change the activity in different brain areas. Conca and colleagues were the first to propose a possible add-on effect of rTMS when combined to antidepressants (Conca et al., 1996). Rumi and colleagues in a double-blind, controlled study comparing the effects of real vs. sham rTMS in 44 patients with major depression that were being simultaneously treated with amitriptyline showed that rTMS increases the antidepressant response, decreasing the time to exert its effects (Rumi et al., 2005). In addition, another study with 99 patients receiving different antidepressants (venlafaxine, sertraline, or escitalopram) in combination with a 2-wk period of sham or active 15 Hz rTMS of the DLPFC also showed earlier improvement in the active rTMS group (Fitzgerald et al., 2006). Future studies should explore this question further in order to explore the neural correlates of this interaction seen in clinical practice.

Another limitation of this study is the method of sham rTMS, since this procedure does not induce the same scalp sensation. However, patients were naive to rTMS, therefore decreasing the likelihood that they would realize whether treatment was active or not. Finally in a recent meta-analysis, Fregni et al. (2006a) showed that sham rTMS induces a small non-significant placebo effect (as indexed by UPDRS) with an effect size of 0.1 only.
Acknowledgements

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Statement of Interest

None.

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Antidepressant treatment in Parkinson’s disease