



# Cognitive rehabilitation in Parkinson's disease: evidence from neuroimaging

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Cognitive impairment in Parkinson's disease (PD) has received little attention to date and as such, there are currently very few treatment options available. The aim of the present study was to determine whether cognitive training might alleviate these cognitive symptoms and if so, whether such changes might be correlated with altered brain patterns. The performance of 10 PD patients and 10 paired healthy controls was assessed in a modified version of the Stroop task performed in association with functional magnetic resonance imaging, and half of the PD patients were given 6 months of cognitive daily training based on Sudoku exercises. Results showed that the training program improved the cognitive performance in the Stroop test of the trained Parkinson's patients during MRI, specifically in terms of reaction time, and of correct and missing answers. Moreover, training provoked reduced cortical activation patterns with respect to untrained patients that were comparable to the patterns of activation observed in controls. Based on these findings, we propose that cognitive training can contribute significantly to save brain resources in PD patients, maybe by readdressing the imbalance caused by the alterations to inhibitory circuitry. Furthermore, these data strongly support the development and use of standardized cognitive training programs in PD patients.

**Keywords:** cognitive training, fMRI, Parkinson's disease, Stroop test

## INTRODUCTION

Upon its initial description in 1817, Parkinson's disease (PD) was defined as a "shaking palsy," with no reference made to any cognitive impairment (Parkinson, 1817). Many years later, cortical Lewy bodies were described in Parkinsonian patients and cognitive symptoms were added to list of symptoms (Dubois and Pillon, 1997). Nowadays, it is widely accepted that the dopaminergic denervation characteristic of PD is accompanied by alterations to other neurotransmitter systems, resulting in a wide range of cognitive (Vera-Cuesta et al., 2006) and emotional symptoms (Schiffer et al., 1988).

Classically, cognitive parkinsonian symptoms affect executive functions and more specifically, attention (Zgaljardic et al., 2003; Sammer et al., 2006). The inability to implement appropriate cognitive strategies is thought to underlie the majority of cognitive deficits observed in PD patients, leading to impaired performance in neuropsychological tests such as the Tower of London (Owen, 2004), the utilization of semantic cues (Tweedy et al., 1982), problem solving (Morris et al., 1988), conscious decision-making (Brand et al., 2004), attentional set shifting (Williams-Gray et al., 2008), and temporal ordering (Vriezen and Moscovitch, 1990).

Several specific cognitive stimulation programs have been designed to improve the cognitive capacity of PD patients. Some studies have reported improvements in patient performance using

generic cognitive stimulation programs lasting 10–12 weeks (Wade et al., 2003) or 10 sessions (30 min each), which offer training in a variety of activities (Sammer et al., 2006). The use of generic neuropsychological training batteries has also been shown to improve verbal fluency, logic memory, and performance in the Raven's matrix test (Sinforiani et al., 2004), as well as information processing speed, visuospatial and visuoconstructive abilities, and executive functions, although no effects on quality of life have been described (Prats et al., 2011). Nevertheless, an improvement in some symptoms of depression has been reported in PD patients participating in cognitive programs (Dobkin et al., 2007; Charidimou et al., 2011).

In the present study, we used functional magnetic resonance imaging (fMRI) techniques to evaluate the effects of cognitive training on functional brain activation. Few studies have combined neuroimaging and attention tasks (e.g., Stroop test: Stroop, 1935) in PD patients to evaluate cognitive improvement after training, although the Stroop test has been used previously in conjunction with neuroimaging as a comparative tool to compare controls and patients (Rektorová et al., 2005; Vanderhasselt et al., 2006). When healthy volunteers perform the Stroop test there activation of specific areas of the brain has been detected, including the anterior cingulate/paracingulate cortex (ACC), pre-supplementary motor areas (preSMA), parietal cortex, and dorsolateral prefrontal cortex

(DLPFC; Bench et al., 1993; Hadland et al., 2001). In ON Parkinsonian patients a specific bilateral response in the DLPFC has been reported (Fera et al., 2007). However, the relative contribution of these specific regions in the Stroop task remains unclear (MacDonald et al., 2000; Rushworth et al., 2002; Klein et al., 2005). By contrast, the subject of a continuing source of debate (MacDonald et al., 2000; Rushworth et al., 2002; Klein et al., 2005).

Here, we hypothesized that the cognitive deterioration in PD patients would be reflected by some impairment in performing the Stroop test when compared with controls. Accordingly, the patterns of brain activation associated with the test would involve a wider range of areas in PD patients than in controls. Finally, we set out to determine whether cognitive training of PD patients would improve their performance in the Stroop test and restrict the extent of brain activation.

## MATERIALS AND METHODS

Ten ON state Parkinsonian patients participated in the study, which was carried out 90–120 min after the oral administration

of their medication (six females and four males, mean age  $\pm$  SD:  $60.5 \pm 3.45$ ,  $H$  and  $Y$  score =  $2.5 \pm 0.5$ ). The control group was comprised of 10 age-matched volunteers (see **Table 1** for demographic data and  $p$  values). All participants were informed about the aims of the study and the conditions of confidentiality at a meeting, and they all gave their informed consent in accordance with the provisions of the Ethics Committee of the Reina Sofia University Hospital of Murcia (Spain) where the fMRI tests were performed.

All experimental subjects were evaluated at the beginning of the study (“first evaluation” measures) using a neuropsychological battery that covered: their clinical history; the Unified Parkinson’s Disease Rating Scale (UPDRS; Fahn and Elton, 1987); the mini mental state examination (MMSE; Folstein et al., 1975); and the Montgomery Asberg Depression Rating Scale (MADRS; Asberg et al., 1978; Montgomery and Asberg, 1979). All patients received daily levodopa drugs [mean dose (mg/day)  $\pm$  SD  $455 \pm 45.7$ ], either alone or in combination with: a DA agonist/anticholinergic agent in two patients; Pergolide in two patients; Pramipexole, one patient.

**Table 1 | Overview of the participants indicating the experimental group, subject number, demographics, and test scores.**

| Group                 | Subjects | Gender    | Age             | Years of education | MMSE            | UPDRSI         | UPDRSII        | UPDRS III       | MADRS           | Age onset       | Duration       |
|-----------------------|----------|-----------|-----------------|--------------------|-----------------|----------------|----------------|-----------------|-----------------|-----------------|----------------|
| Control               | 1        | M         | 64              | 8                  | 30              | 0              | 0              | 0               | 4               | –               | –              |
|                       | 2        | F         | 58              | 11                 | 30              | 0              | 0              | 0               | 7               | –               | –              |
|                       | 3        | F         | 61              | 8                  | 29              | 0              | 0              | 0               | 2               | –               | –              |
|                       | 4        | F         | 49              | 8                  | 30              | 0              | 0              | 0               | 4               | –               | –              |
|                       | 5        | M         | 64              | 9                  | 30              | 0              | 0              | 0               | 5               | –               | –              |
|                       | 6        | M         | 62              | 8                  | 29              | 0              | 0              | 0               | 11              | –               | –              |
|                       | 7        | F         | 59              | 9                  | 30              | 0              | 0              | 0               | 5               | –               | –              |
|                       | 8        | F         | 63              | 8                  | 30              | 0              | 0              | 0               | 4               | –               | –              |
|                       | 9        | M         | 59              | 10                 | 30              | 0              | 0              | 0               | 4               | –               | –              |
|                       | 10       | F         | 57              | 9                  | 30              | 0              | 0              | 0               | 2               | –               | –              |
| Average               |          |           | 59.6 $\pm$ 4.47 | 8.8 $\pm$ 1.03     | 29.8 $\pm$ 0.42 | 0 $\pm$ 0      | 0 $\pm$ 0      | 0 $\pm$ 0       | 4.87 $\pm$ 2.64 | –               | –              |
| PD trained            | 1        | M         | 62              | 8                  | 25              | 7              | 16             | 34              | 3               | 65              | 12             |
|                       | 2        | M         | 63              | 7                  | 27              | 1              | 6              | 19              | 17              | 63              | 9              |
|                       | 3        | F         | 57              | 6                  | 26              | 3              | 3              | 15              | 14              | 58              | 6              |
|                       | 4        | F         | 60              | 10                 | 26              | 1              | 6              | 19              | 22              | 58              | 9              |
|                       | 5        | M         | 56              | 8                  | 26              | 6              | 17             | 31              | 12              | 61              | 7              |
| Average               |          |           | 60.1 $\pm$ 3.04 | 7.8 $\pm$ 1.48     | 26 $\pm$ 0.7    | 3.6 $\pm$ 2.79 | 9.6 $\pm$ 6.42 | 23.6 $\pm$ 8.35 | 14.6 $\pm$ 5.27 | 61.5 $\pm$ 3.08 | 8.6 $\pm$ 2.30 |
| PD-untrained          | 6        | F         | 55              | 6                  | 26              | 3              | 3              | 15              | 16              | 55              | 5              |
|                       | 7        | F         | 59              | 8                  | 26              | 6              | 17             | 31              | 12              | 66              | 8              |
|                       | 8        | M         | 64              | 9                  | 25              | 5              | 14             | 28              | 4               | 60              | 7              |
|                       | 9        | M         | 63              | 7                  | 26              | 3              | 8              | 14              | 14              | 61              | 10             |
|                       | 10       | F         | 65              | 7                  | 26              | 4              | 7              | 16              | 18              | 58              | 8              |
| Average               |          |           | 61.2 $\pm$ 4.14 | 7.4 $\pm$ 1.14     | 25.8 $\pm$ 0.44 | 4.2 $\pm$ 1.31 | 9.8 $\pm$ 5.63 | 20.8 $\pm$ 8.04 | 12.8 $\pm$ 5.40 | 60 $\pm$ 4.06   | 7.6 $\pm$ 1.8  |
| Controls vs. PD       |          | $p$ Value | 0.69            | 0.06               | 0.00            | 0.00           | 0.00           | 0.00            | 0.00            | –               | –              |
| Trained vs. untrained |          | $p$ Value | 0.63            | 0.72               | 0.6             | 0.72           | 0.97           | 0.69            | 0.6             | 0.71            | 0.55           |

*Subj*, subjects; *YoEduc*, years of education; *Age Onset*, age at onset; *Duration*, duration of the disease; *Controls vs. PD*, comparison between controls and PD patients (trained and untrained, during the first evaluation); *Trained vs. Untrain*, comparison between trained and untrained PD patients during the first evaluation.

The inclusion criteria were as follows: aged 50–80; diagnosed with PD (Foltynie et al., 2002) with onset after 40 years of age; a clinical history of symptom progression; and right-handed. Due to the methods used (fMRI techniques), subjects with metallic spectacle frames (or any piece of metal in their body) were excluded. Patients with tremor, dyskinesia, or substantial motor impairment were not considered for the study, nor were those incapable of properly using the index finger for tapping-like tasks. These specific limitations made selection of the Parkinsonian group very difficult.

In the first evaluation, all subjects were assessed with a neuropsychological battery and they completed an “easy” Sudoku  $4 \times 4$  to check their competence in the task. Immediately before the scan, each subject received specific information related to the experimental task and they were allowed to become confident with the use of the three experimental buttons on the keyboard that they had to press, the keys matching the ink color (from left to right: red, blue, and green). All participants were scanned using a modified version of the Stroop paradigm. Later on, half of the PD subjects (trained-PD,  $n = 5$ ) voluntarily participated in the cognitive rehabilitation program while the remaining PD patients (untrained PD = 5) and the controls received no cognitive training. The cognitive training program involved performing one easy level Sudoku table at home every day for 6 months (4-by-4 grid with 2-by-2 blocks). Sudoku focuses on working memory using numerical items, while requiring no mathematical calculation. Sudoku is a conflictual task in which the user receives mutually incompatible information via rows and columns (Elser et al., 2007), and both working memory and attention are probably essential to complete this task. At weekly meetings a trained psychologist checked the Sudoku block, corrected it and explained the errors to each patient. After 6 months, all patients and controls were re-evaluated while undergoing fMRI (“second evaluation”) using a parallel version of the former Stroop test that followed exactly the same procedure as in the first evaluation. No changes to the medication were made during the course of the study.

The experimental cognitive paradigm used was a modified version of the Stroop test (MacLeod, 1991; Schroeder et al., 2002; Scholes et al., 2007), which was previously tested for its suitability in a pilot phase ( $n = 16$ ). This task consisted of “congruent” items [animal names always printed in the same color: *Alce* (Moose in English) written in blue ink; *Rana* (Frog in English) written in red ink; *Visón* (Mink in English) written in green ink], and “incongruent” items [color names written in incongruently colored ink: *Rojo* (red in English) written in green or blue ink; *Verde* (green in English) written in blue or red ink; *Azul* (Blue in English) written in red or green ink]. According to Schroeder et al. (2002) the animal name used should have the same number of letters as the color that begins with the same letter (i.e., both *Rana* and *Rojo* have four letters and begin with the letter “R,” as do *Visón* and *Verde*, and *Alce* and *Azul*). The use of animal names as congruent items rather than patches of color was based on previous research suggesting that the latter were more likely to produce a Stroop facilitation effect in healthy participants (Barch et al., 1999, 2004; Barch and Carter, 2005). While based on different exercises, both the training task

(Sudoku) and the evaluation task (Stroop test) required attention-related skills. This allowed us to verify that any improvements observed reflected an enhancement of functional ability and that they were not simply the result of training in a specific skill.

A Siemens Symphony (1.5 T) MRI system equipped for echo-planar imaging (EPI) was used for data acquisition and the EPI images were acquired using the following parameters: repetition time = 3000 ms; echo time (ET) = 50 ms; flip angle =  $90^\circ$ ; FoV =  $230 \times 230$ ,  $128 \times 128$  matrix; and 28 contiguous slices covering the entire brain parallel to the anterior commissure–posterior commissure (AC–PC; thickness = 3.0 mm; gap = 1 mm; in-plane resolution =  $2.5 \text{ mm} \times 1.8 \text{ mm} \times 5 \text{ mm}$ ). A high-resolution 3-D anatomic set of images was collected for each participant, as well as T1-weighted images of the functional acquisition slices. The head coil set of mirrors permitted subjects to view the target, which was projected onto the opposite wall. The subject held the experimental keyboard in the right hand (LUMINA PAD from Cedrus company, model LU430-3B), which was compatible with magnetic resonance devices. Subjects could not see the three button keyboard and thus, they were required to memorize the key positions. To help the subjects relax they were shown neutral images while the anatomical sequence was applied. A BOLD functional sequence (9 min, 6 s long) was then selected and the stimuli were divided into 9 groups of 10 congruent stimuli and 9 groups of 10 incongruent stimuli, each delivered alternately in blocks. Each of the stimuli lasted for 3,000 ms, during which time the subject had to reply by pressing the correct key (Figure 1). No feedback was provided to the subjects.

All time series were converted into statistical parametric maps (SPM) and subsequently analyzed using the SPM5 package (Wellcome Department of Cognitive Neurology, London, UK). Studies were visually inspected for artifacts such as ghosting and a six parameter rigid body transformation was used for image realignment (three rotations and three translations). The realigned databases were normalized with a Talairach frame (Talairach and Tournoux, 1988), applying a 12 parameter affine transformation and a voxel size of  $3 \text{ mm} \times 3 \text{ mm} \times 3 \text{ mm}$ . An 8-mm full-width-half-maximum (FWHM) isotropic Gaussian kernel was used to smooth the data. The data were also screened to ensure high quality, as demonstrated by small motion correction (all patients displayed the following parameters: 2 mm translation displacement,  $1^\circ$  rotation). Predetermined condition effects at each voxel were calculated using  $t$ -statistics, producing a statistical image for “Incongruent” and “Congruent” vs. control/trained-PD/untrained PD contrasts, and for “Incongruent” vs. “Congruent,” in a subject-specific fixed effect model. The statistical images generated for the contrasts were then entered into a one-sample  $t$ -test model (random-effects analysis) to explore the main effect of the tasks for each individual contrast ( $p = 0.005$  corrected, cluster size  $K = 10$  voxels) and for each group (trained-PD, untrained PD, and controls). In the SPM analysis a  $p$  value of 0.05 was taken as the activation threshold for each comparison. First level model analysis was carried out considering the condition “item-type” (with two levels: incongruent items and congruent items) in each group. Second level analysis was performed considering two conditions: (i) Item-type (with two levels: incongruent items and congruent

items), and (ii) Group (Control, trained-PD, and untrained PD patients).

**BEHAVIORAL ANALYSIS**

*t*-Tests were carried out for both the “first evaluation” and “second evaluation,” considering the variable “groups” and with three levels (control vs. Trained-PD and Untrained PD). All test scores (MMSE, MADRS, UPDRS, Sudoku latency, and Stroop responses) were analyzed in all three groups with the level of significance set at  $p < 0.05$ . Following this, Bonferroni’s correction was applied to significance values. Sudoku scores corresponded to the valuation made just before the scan session, while the Stroop scores correspond to the data obtained during the scan session. The scores of neuropsychological tests were corrected for age, gender, and education.

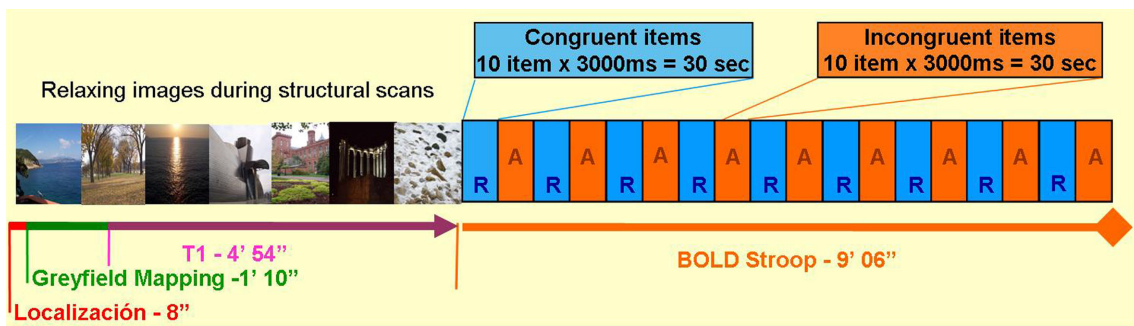
**RESULTS**

**QUESTIONNAIRE SCORES**

Both the results of the first and second evaluations are presented considering the three different groups studied (controls, trained, and untrained patients), although during the first evaluation there

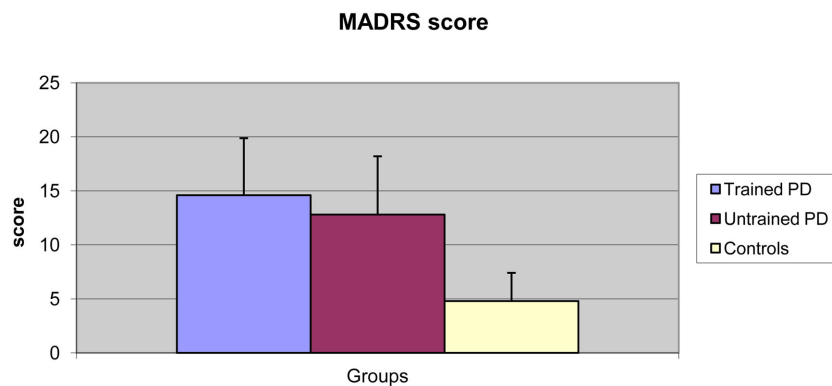
was just one group of patients. Scores have been analyzed by splitting the group in two (trained and untrained patients) to enable the groups in the first evaluation to be compared with those in the second evaluation.

There were significant differences in the MADRS scores between patients and controls in the first evaluation ( $\bar{X}_{\text{control}} = 4.87 \pm 2.64$  vs.  $\bar{X}_{\text{PD}} = 13.71 \pm 5.64$ ;  $p \leq 0.05$ ; **Figure 2**). Moreover, the scores in MMSE were significantly lower in both the PD patient groups than in the healthy subjects ( $\bar{X}_{\text{control}} = 29.78 \pm 0.22$  vs.  $\bar{X}_{\text{trained-PD}} = 26 \pm 0.41$  vs.  $\bar{X}_{\text{untrained PD}} = 25.75 \pm 0.25$ ;  $p \leq 0.001$ ), although there was no significant difference between the trained and untrained PD patients ( $p > 0.005$ , **Table 1**). With respect to the Sudoku puzzles, PD patients needed significantly more time to solve an “easy” Sudoku (measured in seconds) than the controls (mean  $\pm$  SD;  $\bar{X}_{\text{control}} = 3.5 \text{ sec} \pm 0.52$  vs.  $\bar{X}_{\text{trained-PD}} = 26.2 \text{ sec} \pm 6.43$  vs.  $\bar{X}_{\text{untrained PD}} = 27.7 \text{ sec} \pm 10.18$ ;  $p \leq 0.001$  corrected; **Table 2**). However, when the two PD patient groups were compared there were no significant differences in the UPDRS subscale I, although the scores for both types of PD patient were significantly higher than those of the control subjects in the UPDRS subscale I ( $\bar{X}_{\text{control}} = 0.0 \pm 0$  vs.  $\bar{X}_{\text{trained PD}} = 3 \pm 2.82$  vs.  $\bar{X}_{\text{untrained PD}} = 4 \pm 1.14$ ;



**FIGURE 1 | Scheme of the scan sequences.** During the first three sequences (anatomical sequences) relaxing images were projected. After that, the functional sequence was presented alternatively in

blocks of items as follows: Congruent items (R blocks) and incongruent items (A blocks). Blocks consisted of 10 items, each 3 s long (30 s long blocks).



**FIGURE 2 | Montgomery Asberg Depression Rating Scale scores from control subjects and patients (trained and untrained) at the first evaluation demonstrating the significant differences between both groups ( $p > 0.001$ ).**

$p > 0.001$ ), subscale II ( $\bar{X}_{\text{control}} = 0.0 \pm 0$  vs.  $\bar{X}_{\text{trained PD}} = 9.27 \pm 5.67$  vs.  $\bar{X}_{\text{untrained PD}} = 10.75 \pm 6.38$ ;  $p > 0.001$ ) and subscale III ( $\bar{X}_{\text{control}} = 0.0 \pm 0$  vs.  $\bar{X}_{\text{trained PD}} = 21.75 \pm 8.38$  vs.  $\bar{X}_{\text{untrained PD}} = 23.25 \pm 6.63$ ;  $p > 0.001$ ; **Table 1; Figure 3**).

During the second evaluation untrained PD patients needed significantly more time to solve an “easy” Sudoku (measured in seconds) than trained-PD patients or controls (mean  $\pm$  SD;  $\bar{X}_{\text{control}} = 3.22 \text{ sec} \pm 0.33$  vs.  $\bar{X}_{\text{trained PD}} = 18 \text{ sec} \pm 4.9$  vs.  $\bar{X}_{\text{untrained PD}} = 27.1 \text{ sec} \pm 9.12$ ;  $p \leq 0.001$  corrected: **Table 2**).

**STROOP TEST SCORES**

The reaction times (RT, ms) in the first evaluation differed significantly between the control and PD patient groups ( $\bar{X}_{\text{control}} =$

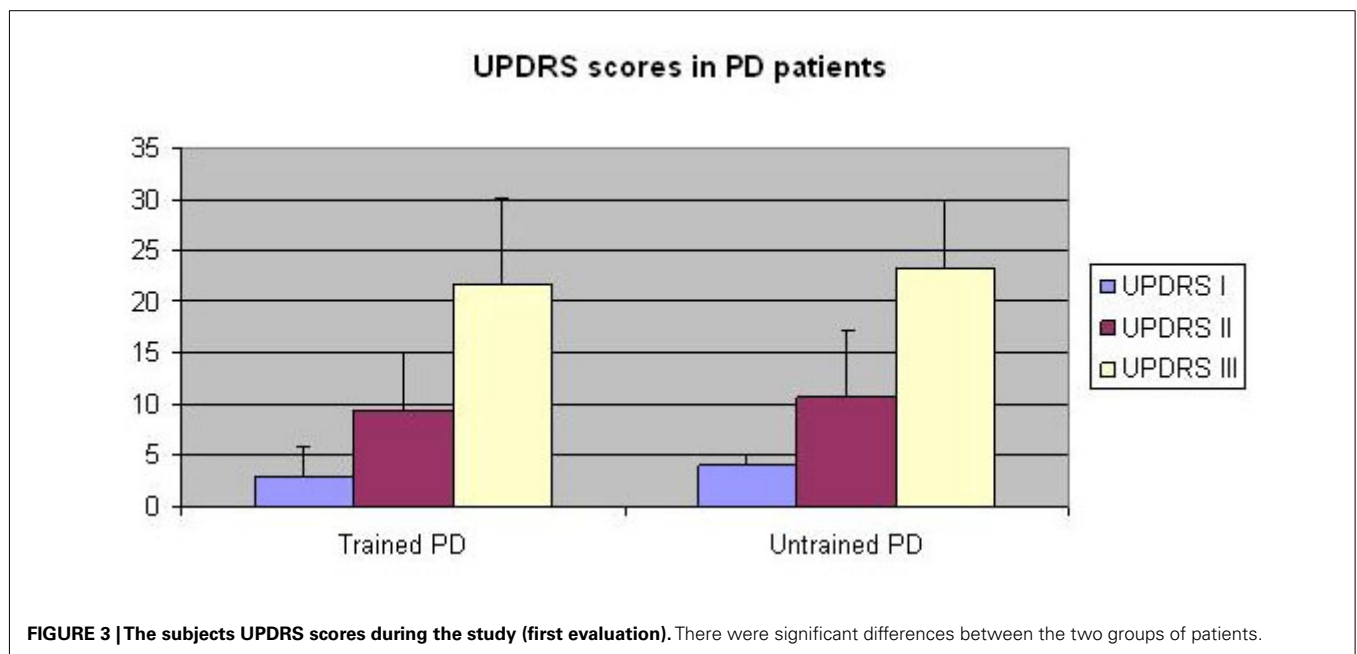
$897.6 \pm 192$  vs.  $\bar{X}_{\text{trained PD}} = 1130.42 \pm 283$  vs.  $\bar{X}_{\text{untrained PD}} = 1232.33 \pm 345$ ;  $p \leq 0.001$ ; **Figure 2**), whereas no differences were observed between the groups in terms of the number of correct responses ( $\bar{X}_{\text{control}} = 59.67 \pm 0.27$  vs.  $\bar{X}_{\text{trained PD}} = 52.42 \pm 1.83$  vs.  $\bar{X}_{\text{untrained PD}} = 45.33 \pm 14.45$ ;  $p \geq 0.05$ ), the number of incorrect responses ( $\bar{X}_{\text{control}} = 0.41 \pm 2.66$  vs.  $\bar{X}_{\text{trained PD}} = 2.75 \pm 1.83$  vs.  $\bar{X}_{\text{untrained PD}} = 5.73 \pm 2.75$ ;  $p \geq 0.05$ ) or the number of missing responses ( $\bar{X}_{\text{control}} = 0.08 \pm 0.91$  vs.  $\bar{X}_{\text{trained PD}} = 1.6 \pm 1.83$  vs.  $\bar{X}_{\text{untrained PD}} = 8.33 \pm 4.45$ ;  $p \geq 0.05$ ; **Table 2**).

In the second evaluation, there were significant differences in the Stroop task reaction times between the two groups of PD patients ( $\bar{X}_{\text{trained PD}} = 955 \pm 173$  vs.  $\bar{X}_{\text{untrained PD}} = 1154 \pm 252$ ;  $p \leq 0.01$ ), as well as between both PD patient groups and the

**Table 2 | Mean Stroop scores (correct, incorrect, missing answers, and reaction time) in PD and controls from the first and second evaluation.**

|                           | Correct           | Incorrect       | Missing         | RT                | SUDOKU           |
|---------------------------|-------------------|-----------------|-----------------|-------------------|------------------|
| <b>1ST EVALUATION</b>     |                   |                 |                 |                   |                  |
| Control                   | 43.33 $\pm$ 0.27  | 0.41 $\pm$ 2.66 | 0.08 $\pm$ 0.91 | 397.6 $\pm$ 192   | 3.5 $\pm$ 0.52   |
| Train-PD                  | 59.67 $\pm$ 1.83  | 2.75 $\pm$ 1.83 | 1.6 $\pm$ 1.83  | 1130.42 $\pm$ 283 | 26.2 $\pm$ 6.43  |
| Untrain-PD                | 52.42 $\pm$ 14.45 | 5.73 $\pm$ 2.75 | 8.33 $\pm$ 4.45 | 1232.33 $\pm$ 345 | 27.7 $\pm$ 10.18 |
| Control-PD (p value)      | 0.07              | 0.06            | 0.11            | 0.001             | 0.001            |
| Train-untrained (p value) | 0.23              | 0.17            | 0.09            | 0.25              | 0.82             |
| <b>2ND EVALUATION</b>     |                   |                 |                 |                   |                  |
| Control                   | 59.53 $\pm$ 0.31  | 1.5 $\pm$ 1.89  | 0 $\pm$ 0       | 891 $\pm$ 199     | 3.22 $\pm$ 0.33  |
| Train-PD                  | 58.42 $\pm$ 1.83  | 1.41 $\pm$ 1.5  | 0.16 $\pm$ 0.33 | 955 $\pm$ 173     | 18 $\pm$ 4.9     |
| Untrain-PD                | 53.33 $\pm$ 14.45 | 2.25 $\pm$ 3.61 | 4.75 $\pm$ 4    | 1154 $\pm$ 252    | 27.1 $\pm$ 9.12  |
| Control-PD (p value)      | 0.08              | 0.38            | 0.44            | 0.001             | 0.001            |
| Train-untrained (p value) | 0.04              | 0.21            | 0.00            | 0.01              | 0.05             |

On both occasions, significant differences were observed between controls and PD patients in Stroop RT ( $p \leq 0.001$ ) and Sudoku speed ( $p \leq 0.001$ ). Additional differences were observed in the second evaluation only between trained and untrained PD patients regarding the numbers of correct and missing answers ( $p \leq 0.05$ ,  $p \leq 0.001$ , respectively), and the RT ( $p \leq 0.01$ ) in the Stroop test, and in the Sudoku solving time  $p \leq 0.05$ .



**FIGURE 3 | The subjects UPDRS scores during the study (first evaluation).** There were significant differences between the two groups of patients.



control subjects ( $\bar{X}_{\text{control}} = 891 \pm 199, p \leq 0.001$ ). The number of correct ( $\bar{X}_{\text{control}} = 59.58 \pm 0.31$  vs.  $\bar{X}_{\text{trained PD}} = 58.42 \pm 1.83$  vs.  $\bar{X}_{\text{untrained PD}} = 52.33 \pm 14.45; p \geq 0.005$ ), incorrect ( $\bar{X}_{\text{control}} = 1.5 \pm 1.89$  vs.  $\bar{X}_{\text{trained PD}} = 1.41 \pm 1.5$  vs.  $\bar{X}_{\text{untrained PD}} = 2.25 \pm 3.61;$

$p \geq 0.005$ ) and missing responses ( $\bar{X}_{\text{control}} = 0 \pm 0$  vs.  $\bar{X}_{\text{trained PD}} = 0.16 \pm 0.33$  vs.  $\bar{X}_{\text{untrained PD}} = 4.75 \pm 4; p \geq 0.005$ ) did not differ significantly between any group of subject in the second evaluation (**Table 2**). Finally, there was a significant difference in the RT between the first and second evaluation of PD trained patients ( $p \geq 0.05$ ), and in the correct ( $p \geq 0.05$ ) and missing answers ( $p \geq 0.01$ ) during the Stroop task, but not in the incorrect answers ( $p \geq 0.05$ ).

## BRAIN ACTIVATION

During the first evaluation, the control group exhibited a classical activation pattern associated with the Stroop test, specific to incongruent > congruent activations. This pattern involves the bilateral anterior cingulate cortex, right superior parietal cortex, and left superior temporal gyrus, as well as additional areas, such as the left inferior temporal gyrus, right cuneus gyrus, and left precuneus gyrus. During the task, the PD patients (trained and untrained) exhibited extensive activation throughout the cortex, involving the bilateral superior frontal gyri, left inferior parietal gyrus, bilateral parahippocampal gyri, left superior temporal gyrus, right putamen and globus pallidum, and the left tail of the caudate nucleus (see **Table 3** for more detailed information). The differences in the activation pattern between controls and PD patients (control > PD) principally involved the left precentral gyrus, left medial frontal gyrus, right precuneus, and left inferior parietal gyrus. When the brain activation patterns between trained and untrained PD patients during the first evaluation were compared there were no significant differences ( $p = 0.05$ ).

The results of the second evaluation revealed that in untrained PD patients there was significantly stronger activation of areas such as the right putamen, left ventrolateral prefrontal cortex, left frontal superior gyrus, right frontal medial gyrus, left superior temporal gyrus, left precuneus gyrus, bilateral cuneus gyri, left angular gyrus, and left lingual gyrus, when compared with the trained PD patients ( $p = 0.05$ ). By contrast, in trained PD patients there was stronger activation in the right superior and medial temporal gyri than in untrained PD patients ( $p = 0.05$  see comparisons in **Figure 4**). Moreover, there were no significant differences in the brain activation of the control subjects between the first and second evaluation ( $p = 0.05$ ).

When the activation pattern during the second evaluation was compared between controls and trained PD patients (control > trained PD), the latter showed greater activation of right anterior cingulate gyrus, left inferior frontal gyrus, right medial frontal gyrus, left angular gyrus, left precuneus gyrus, right supra-marginal gyrus, left superior parietal gyrus, right medial temporal gyrus, left parahippocampal gyrus, and left insula and thalamus.

## DISCUSSION

In the present study, PD patients that completed a cognitive training program showed significant improvements in reaction time

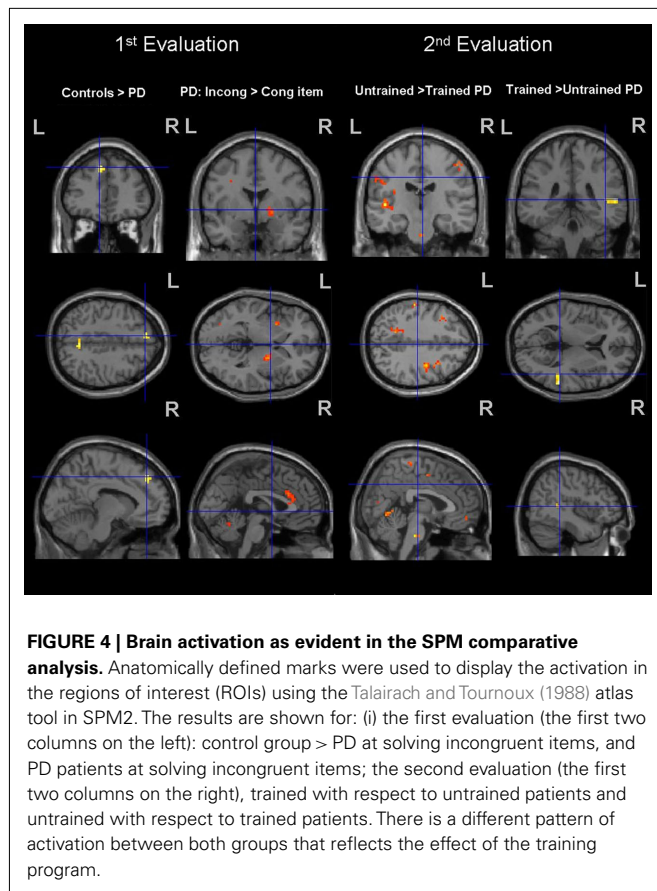
when performing an attention task, which corresponded with attenuated pattern of brain activation. “Interestingly, in Stroop task, the number of correct responses in trained patients did not improve in the second evaluation, while missing responses were significantly reduced and incorrect responses improved. Differences in correct responses between first and second evaluation were not statistically significant. This lack of improvement in correct responses could be due to the no effect of the training on that aspect of the Stroop task.” No differences in the neuropsychological assessment (UPDRS, MMSE, Stroop scores, and reaction time) or brain activation were observed between the two PD groups during the initial evaluation. However, after training those who participated in the program had significantly faster reaction times, approximating to the scores of the control subjects, and with significant alterations in their pattern of brain activation. Indeed, in untrained patients there was an over-activation of the frontal, temporal, and parietal areas when compared with the trained patients. Hence, the changes observed in the trained patients (when comparing first and second evaluation) appear to be linked to the concomitant alterations in brain activity, reflecting the effects of the cognitive training. Previous studies have linked cortical over-activation in PD to the depletion of neurotransmitters, including dopamine, noradrenaline, serotonin, and their metabolites (Scatton et al., 1983). In fact, abnormal neurotransmitter levels are associated with the impairment of inhibitory and excitatory cortical processes. Cortico-cortical connections are thought to depend on the inhibitory capacity of the cortex, which is impaired in Parkinsonian patients (Bares et al., 2003; McNamara et al., 2007). Thus, it is plausible that impairment of cortical inhibition could result in the inappropriate activation of certain brain areas, consistent with the broader pattern of activation in PD patients than in controls. Such impairments may also account for the slowness observed in PD patients during task resolution.

In agreement with previous studies, the key differences in the basic activation pattern observed between PD patients and controls when performing the Stroop test involved the activation of the DLPFC and basal ganglia, two regions strongly affected by dopamine depletion in PD, as well as the fronto-parietal circuitry. In the early stages of PD, the greatest reduction in dopamine is observed in the dorsal striatum, which primarily projects to the DLPFC, while the ventral striatum that projects to the ACC and orbitofrontal cortex is less affected (Cohen et al., 2000). The DLPFC is sensitive to the presence of conflict when a top-down modulation of posterior processing areas is needed to guide response selection toward task relevant information (Liu et al., 2006), as occurs in the Stroop test. Increased activation was also observed in the basal ganglia of PD patients when compared with controls (right putamen and globus pallidum, and left caudate nucleus tail), which was probably related to the effects of medication (Carey et al., 1995). Dopaminergic drugs are associated with an “inverted U” effect, whereby too much or too little dopamine can decrease PD patients’ performance. This effect does not depend on the neuropsychological specificity of the drug, disease duration, or severity but rather, on cognitive demands (Cools et al., 2001). Finally, under healthy conditions the Stroop task requires a group of fronto-parietal circuits

**Table 3 | Activation related to the training condition in controls and trained or untrained PD patients during the Stroop test in both the first and second evaluation ( $p = 0.05$ ).**

| x   | y   | z   | Area I             | Area II  | Lobe   | Hem |
|---|-----|-----|--------------------|----------|--------|-----|
| <b>1ST EVALUATION</b>                               |     |     |                    |          |        |     |
| <b>Experimental group incongruent vs. congruent</b> |     |     |                    |          |        |     |
| 6   | 9   | 51  | Superior           | Gyrus    | F      | R   |
| -6  | 15  | 48  | Superior           | Gyrus    | F      | L   |
| -36   | -6  | 30  | Precentral         | Gyrus    | F      | L   |
| 42  | -51 | 33  | Supramarginal      | Gyrus    | P      | R   |
| 42  | -30 | 39  | Inferior           | Gyrus    | P      | R   |
| 42  | -27 | 48  | Somatosensorial 1  | Gyrus    | P      | R   |
| -54   | -57 | 27  | Superior           | Gyrus    | T      | L   |
| -30   | -75 | -6  | Lingual            | Gyrus    | O      | L   |
| -27   | -24 | -9  | Parahippocampal    | Gyrus    | L      | L   |
| 18  | -6  | 27  | Cingular           | Anterior | L      | R   |
| 3   | 24  | 21  | Anterio cingulate  | Gyrus    | L      | R   |
| 24  | -3  | -3  | Put amen           | Nucleus  | BG     | R   |
| 18  | 3   | -6  | Lateral GP         | Nucleus  | BG     | R   |
| -18   | -27 | 18  | Caudate            | Tail     | BG     | L   |
| -3  | -60 | -21 | Culmen             | Anterior | Cereb  | L   |
| -18   | -54 | -30 | Anterior           | Lobe     | Cereb  | L   |
| -15   | -60 | -36 | Posterior amygdala | Nucleus  | Cereb  | L   |
| -24   | -60 | -24 | Anterior culmen    | Lobe     | Cereb  | L   |
| <b>Control vs. experimental group</b>               |     |     |                    |          |        |     |
| -36   | -12 | 36  | Precentral         | Gyrus    | F      | L   |
| -6  | 39  | 42  | Medial             | Gyrus    | F      | L   |
| 3   | -57 | 45  | Precuneus          | Gyrus    | P      | R   |
| -45   | -24 | 27  | Inferior           | Gyrus    | P      | L   |
| <b>2ND EVALUATION</b>                               |     |     |                    |          |        |     |
| <b>Experimental group: trained vs. untrained</b>    |     |     |                    |          |        |     |
| 51  | -39 | 6   | Superior           | Gyrus    | T      | R   |
| 48  | -42 | 3   | Medial             | Gyrus    | T      | R   |
| <b>Experimental group: untrained vs. trained</b>    |     |     |                    |          |        |     |
| 39  | 6   | 36  | Precentral         | Gyrus    | F      | R   |
| -27   | 36  | 30  | Superior           | Gyrus    | F      | L   |
| 6   | 51  | -9  | Medial             | Gyrus    | F      | R   |
| -42   | 44  | 24  | Medial             | Gyrus    | F      | L   |
| -48   | -21 | 33  | Somatosensorial 1  | Gyrus    | P      | L   |
| -12   | -54 | 36  | Precuneus          | Gyrus    | P      | L   |
| -36   | -69 | 30  | Angular            | Gyrus    | P      | L   |
| -45   | -21 | 3   | Superior           | Gyrus    | T      | L   |
| -63   | -36 | 6   | Superior           | Gyrus    | T      | L   |
| 6   | -78 | 21  | Cuneus             | Gyrus    | O      | R   |
| -9  | -78 | 21  | Cuneus             | Gyrus    | O      | L   |
| -9  | -66 | 0   | Lingual            | Gyrus    | O      | L   |
| -9  | -57 | -36 | Amygdala           | Nucleus  | Cereb  | L   |
| -9  | 21  | -3  | Anterior cingular  | Gyrus    | L      | L   |
| 18  | -60 | 12  | Posterior cingular | Gyrus    | L      | R   |
| -36   | -15 | 18  | Medial             | Lobe     | In     | L   |
| -24   | -15 | 6   | Putamen            | Nucleus  | BG     | R   |
| -15   | -12 | 9   | Ventrolateral      | Area     | Thalam | L   |
| 0   | -60 | 3   | Anterior           | Culmen   | Cereb  | L   |
| -3  | -66 | -30 | Uvula              | Nucleus  | Cereb  | L   |
| 15  | -51 | -3  | Anterior           | Lobe     | Cereb  | R   |

Experimental group: PD patients group (Trained and untrained).



specialized in “conflict detection” and “conflict adaptation” (Egner and Hirsch, 2005). This function relies on the frontal regulation of attention, mediated by the frontal cortex itself. The frontal cortex receives dopamine projections from the mesocortical pathway (Alexander et al., 1986) and it is critically involved in cognitive and emotional tasks. The degeneration of these projections and the consequent hypofunction of the prefrontal cortex have been previously well defined in PD (Stam et al., 1993; Braak et al., 2004).

The pattern of brain activation in each PD group and the control subjects corresponded to those described classically (Cohen et al., 1990; Pardo et al., 1990; Carter et al., 1995, 2000; MacLeod and Dunbar, 1988; Doder et al., 1999; Peterson et al., 1999; Barch et al., 2001; Milham et al., 2001, 2002; Kerns et al., 2004; Lange-necker et al., 2004; Harrison et al., 2005; Brown and Eyler, 2006; Fera et al., 2007; Lewis et al., 2008). The concordance in the brain activation patterns observed while performing the Stroop test and those in previous studies further validates the use of this version of the test for this type of evaluation (Schroeder et al., 2002). Indeed, we observed no significant differences in Stroop scores between PD patients and controls, as seen previously (Brown and Marsden, 1991; Brück et al., 2005). Distinct patterns of brain activation between controls and patients appeared in both the first and second evaluation, and they become more complex after training, involving more brain areas (mostly frontal and parietal). These areas are associated with the classical Stroop pattern that

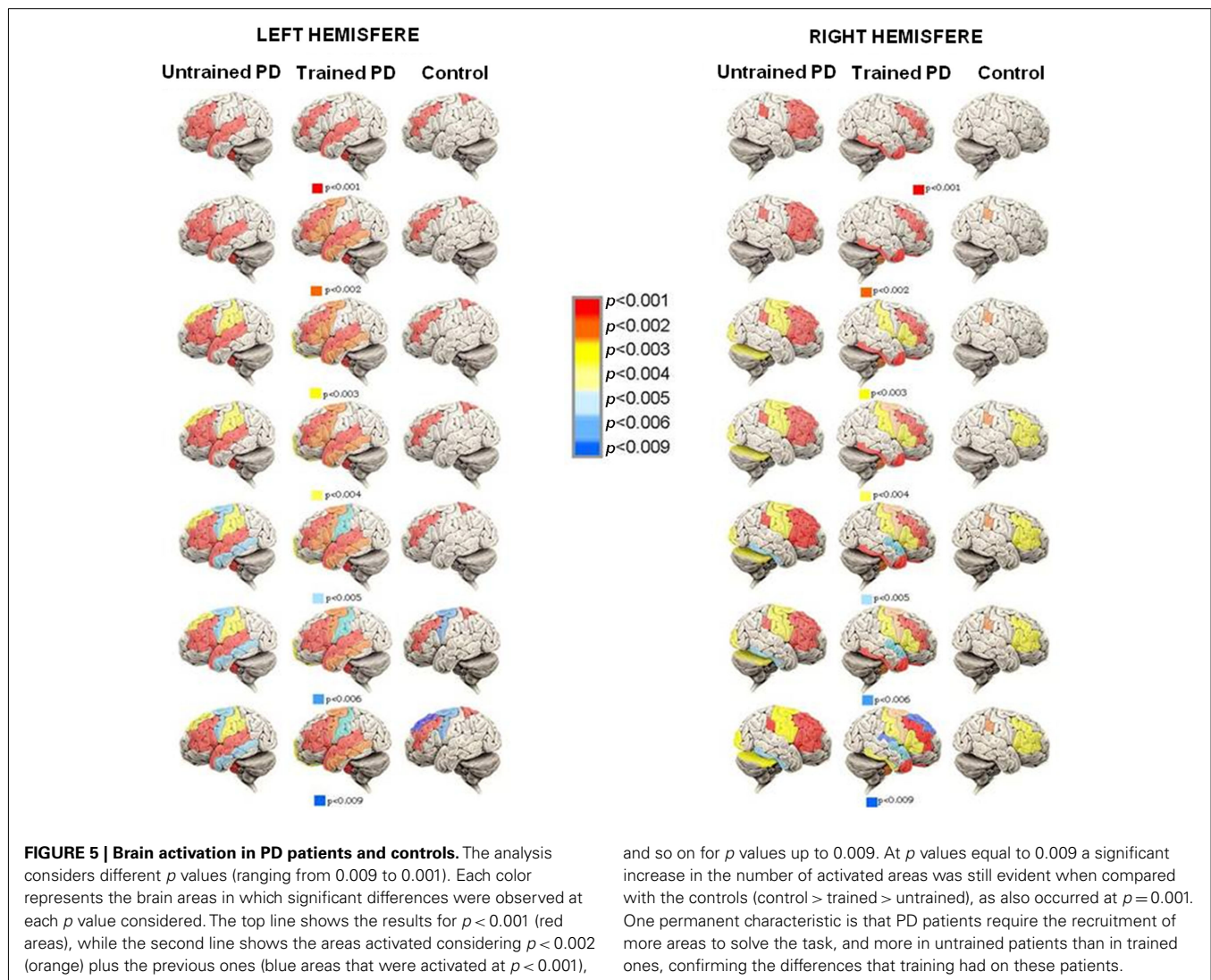
has been described previously (Cohen et al., 1990). In fact, there was an over-activation of the frontal, temporal, and parietal areas in trained PD patients with respect to untrained patients, and the recruiting of these areas is compulsory to perform the Stroop task, as described classically under healthy conditions, albeit to a lesser extent (MacLeod and Dunbar, 1988). This is again another example of the problem of cortical inhibition that, even under training conditions, can partially improve but still persists in PD brains.

It could be argued that the PD patients and healthy controls exhibited similar activation patterns, although the activation in the latter group was less intense, probably reflecting the correct inhibitory cortical activity. This issue was addressed further by considering the results of the second evaluation. In order to verify the differences in activation during the Stroop task across all three groups, a first level analysis in SPM was run considering different  $p$  values (from 0.001 to 0.009, each indicated by a different color) and using FDR correction (Figure 5). When different levels of restriction were considered (being more or less liberal in the selected criteria), activation patterns differed in all three groups after training. One persistent characteristic is that PD patients recruited more areas to solve the task, and even more in untrained patients than in trained ones, these results confirm the significance of the differences in brain activation in PD patients. Impaired cortico-cortical connections have been described in PD (McNamara et al., 2007) and their effects are ameliorated by levodopa/dopaminergic medication, in conjunction with the relief of clinical symptoms (Lefaucheur, 2005). Although both PD groups were ON medication, the effect of the training ameliorated the differences between PD trained patients and controls, as shown by the altered patterns of brain activation.

To date, there is no standardized program to quantify cognitive impairment in PD patients. We would propose that Sudoku training may contribute to improve the cognitive strategies used by PD patients in problem solving, improving their ability to generate internally applicable rules. Such training helps facilitate effective cognitive behavior demands, inductive reasoning, and spontaneous cognitive flexibility, processes that are typically impaired in PD (Goebel et al., 2010) and susceptible to improvement by training. To the best of our knowledge, this is the first study to investigate the potential of Sudoku tasks in cognitive training, which may represent an interesting tool for cognitive conflict research. An adequate cognitive strategy requires the retention of decision-making information in the working memory, which in turn involves the inhibition of irrelevant information. As such, training in the development of internal strategies for conflict resolution should improve the performance of PD patients in these types of tasks.

Given the small sample size involved, which reduced the statistical power of our analyses, our data should be interpreted with caution, even though several previously published neuroimaging studies have included nine or even fewer PD patients (George et al., 1993; Owen et al., 1998; Whalen et al., 1998; Doder et al., 1999; Langenecker et al., 2004; van Veen and Carter, 2005; Marié et al., 2007; Monchi et al., 2007; Lewis et al., 2008). The pathology and typical aging problems [such as visual, motor





(tremor), and dystonic impairments] found in these patients significantly complicates the generation of larger study groups, an issue that should be addressed in future studies. Interestingly, the 6-month cognitive training period (based on Sudoku exercises) undertaken by the PD patients appeared to have a medium term effect, as determined by the Stroop RT and accuracy, as well as a positive effect on brain activity, producing a significant reduction in cortical activation while performing the Stroop task. These improvements appear to reflect a change in functional patterns corresponding to the training. However, it is also important to stress that patients were not randomized to be trained and untrained and that there might be a bias vs. more “cognitively capable” patients choosing to do the Sudoku training.

Although no proved by current data, we speculate that former improvement in cognitive performance and the changes in brain activation could probably have a positive effect on patients’ UPDRS score. Cognitive features are briefly assessed in UPDRS I so that training would improve the score in that subscale. Regarding

the motor subscale, improving cognitive abilities could also have a positive effect on motor features due to both higher motivation of the patient (given their improved ability to deal with different situations) and the reactivation of brain pathways through cognitive training (as some cognition and motor planning takes place in frontal areas).

For all these reasons we suggest that a standardized cognitive program should be considered as routine therapy for Parkinsonian patients, to be applied in combination with motor therapy, as has been effectively demonstrated for other pathologies such as stroke (Rand et al., 2010).

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