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ORIGINAL ARTICLE

Neurofunctional correlates of attention rehabilitation in Parkinson's disease: an explorative study

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Abstract The effectiveness of cognitive rehabilitation (CR) in Parkinson's disease (PD) is in its relative infancy, and nowadays there is insufficient information to support evidence-based clinical protocols. This study is aimed at testing a validated therapeutic strategy characterized by intensive computer-based attention-training program tailored to attention deficits. We further investigated the presence of synaptic plasticity by means of functional magnetic resonance imaging (fMRI). Using a randomized controlled study, we enrolled eight PD patients who underwent a CR program (Experimental group) and seven clinically/demographically-matched PD patients who underwent a placebo intervention (Control group). Brain activity was assessed using an 8-min resting state (RS) fMRI acquisition. Independent component analysis and statistical parametric mapping were used to assess the effect of CR on brain function. Significant effects were detected both at a phenotypic and at an intermediate phenotypic level. After CR, the Experimental group, in comparison with the Control group, showed a specific enhanced performance in cognitive performance as assessed by the SDMT and digit span forward. RS fMRI analysis for all networks revealed two significant groups (Experimental vs Control) × time (T0 vs T1) interaction effects on the analysis of the attention (superior parietal cortex) and central executive neural networks (dorsolateral prefrontal cortex). We demonstrated that intensive CR tailored for the impaired abilities impacts neural plasticity and improves some aspects of cognitive deficits of PD patients. The reported neurophysiological and behavioural effects corroborate the benefits of our therapeutic approach, which might have a reliable application in clinical management of cognitive deficits.

Keywords Parkinson's disease · Cognitive rehabilitation · Attention deficits · Resting-state fMRI · Parieto-prefrontal cortex

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Introduction

Although Parkinson's disease (PD) is considered a motor control disorder, global cognitive function deteriorations represent a common complication, occurring approximately in 40 % of cases [1]. Cognitive impairment in PD patients is mainly characterized by executive deficits, which is characterized by loss of concentration, difficulties in logic reasoning, long-term and procedural memory disturbances, visuospatial deficits and executive dysfunction encompassing difficulty in planning, organizing and regulating goal-directed behaviour [2].

It is well known that cognitive decline has a deleterious impact on quality of life of patients with PD, even beyond that from physical disability alone. Given this effect, the

alleviation of such deficit should become an imperative for PD research and practice. In fact, the amelioration of cognitive deficits may improve everyday functioning in PD, thus greatly reducing the impact of the disease on the lives of people with PD and the overall cost of the disease to society at large. To date, there are no definitive pharmacological treatments for cognitive dysfunctions in PD. In the last few years, cognitive rehabilitation (CR) has shown the potential to reduce disability and improve quality of life in individuals with neurological disorders (stroke, head trauma or multiple sclerosis) and their caregivers [3, 4].

Despite the need for CR services as a standard of care, there is a paucity of research studies designed to investigate treatment approaches for patients with PD. Indeed, research on the effectiveness of CR in PD is in its relative infancy, and nowadays there is insufficient information to support evidence-based clinical protocols. However, in the last few years, some studies have evaluated symptomatic treatments for cognitive dysfunction in PD, and preliminary results have been promising [5–7]. The few existing CR programmes within PD have been aimed at improving overall frontal functions (attention, working memory, calculation, memory, visuospatial abilities). Although these studies had shown a common beneficial effect in treated PD patients, they were characterized by heterogeneous rehabilitative approaches and some methodological limitations. Indeed, only one study was a double-blind randomized, controlled trial [7].

For this reason, this study is aimed at determining the impact of a tailored intervention to improve or restore impaired attention functions in PD patients with predominant attention deficits using a robust statistical design. The idea of a neurorehabilitation program tailored to a specific cognitive deficit has proven very promising in treating other neurodegenerative disorders [5, 8]. Although this approach restricts sample selection, it eliminates potential confounders linked to the presence of additional cognitive impairments and thus helps with the interpretation of the results. Moreover, to better delineate the effectiveness of our proposed method, we investigated the underlying functional activity of associative brain areas by using resting state (RS) functional magnetic resonance imaging (fMRI), which represents a very sensible tool to explore subtle active processes of neuroplasticity that might be driven by CR [8].

Methods

Subjects

One hundred and thirty-seven case patients with clinical diagnoses of PD according to the United Kingdom PD Society Brain Bank criteria [9] were consecutively selected among the outpatients of the Institute of Neurology of the University "Magna Graecia" of Catanzaro, Italy. From this initial cohort we enrolled only PD patients who fulfilled the following criteria: (1) no presence of dementia, according to the DSM-IV criteria; (2) predominant deficits in either attention and/or information processing speed, working memory and/or executive functioning [i.e., failure of at least one of the following tests: symbol digit modality test (SDMT), Trial Making Test (TMT A–B), Paced Auditory Serial Addition Test (PASAT), digit span forward and backward and Stroop word-colour task (ST), see below]; (3) no additional impairment in other cognitive domains (i.e. language, verbal and spatial long-term memory); (4) no evidence of motor complications (i.e., levodopa-induced dyskinesias); (5) no history of psychiatric problems, according to the structured clinical interview of the DSM-IV; (6) no evidence of vascular brain lesions, brain tumour and/or marked brain atrophy on MRI scan and (7) no movement artefacts during MRI exam. The clinical assessment included Hoehn–Yahr (HY) staging and unified Parkinson's disease rating scale (UPDRS) scores. Written informed consent (approved by the Ethical Committee of the University 'Magna Graecia' of Catanzaro) were collected from all subjects enrolled in the study.

From the initial group, 117 PD patients were excluded. Specifically, 30 patients were characterized by dementia; 27 patients were not demented but were, however, characterized by additional cognitive deficits (i.e. language dysfunctions); 30 patients had other additional motor complications incompatible with MRI examination (i.e. dyskinesias); 15 patients had additional psychiatric complications (i.e. major depression or gambling); eight patients were characterized by additional vascular lesions and seven MRI exams were removed due to exaggerated movement artefacts. For this reason, 20 PD patients satisfied inclusion criteria and were enrolled in the study. All PD patients were treated with levodopa. Additional treatments were ropinirole (one patient in Experimental group and two patients in the controls group) and pramipexole (two patients in Experimental group and two patients in the controls group).

Neuropsychological assessment

All patients completed an extensive battery of neuropsychological tests [10] assessing:

(a) Spatial memory: the Rey–Osterrieth Complex Figure Test (ROCFT), which assesses immediate and delayed recall (IR and DR).
(b) Verbal memory: the Selective Reminding Test (SRT), which assesses verbal learning and DR. It also

includes a list of 12 words and uses six consecutive learning trials and a delayed trial (SRT-long-term storage and SRT-consistent long-term retrieval (CLTR).

(c) Visuospatial processing: Judgment Line Orientation Test (JLO).
(d) Verbal fluency: Controlled Oral Word Association Test (COWAT).
(e) Sustained attention and information processing speed: SDMT and PASAT.
(f) To test additional attention abilities and executive functions (such as executive control and task switching) not explored by the BRB, we also included the digit span forward/backward, ST and TMT form A–B.

Cognitive performances were recorded at baseline and after 6 weeks (using form A and B to avoid learning effects). Finally, we further investigated the mood status using the beck depression inventory, the state-trait anxiety inventory (STAI) and aspects of well-being using the Parkinson's Disease Questionnaire (PDQ-39) [11].

Design and procedures

The proposed CR approach has recently been validated [3]. Our study was a blind, randomized, controlled trial divided into four principal stages. The first stage was based on the recruitment of the patients for the study. The patients were not informed about their group assignment or the rationale behind their training performed in our clinic (Experimental group) or at home (Control group). In the second stage, the eligible PD patients underwent MRI examination (T0). Neuropsychological and MRI examinations were performed in the ON phase of medication. In the third stage, subjects were randomly assigned to two groups. The Experimental group met twice a week for 1-h sessions for six consecutive weeks. Sessions consisted of computer-assisted training of several attention ability and information processing tasks. Attention training was performed using the package RehaCom (http://www.Schuhfried.at) (for more information see [3]). The Control group underwent a similar exposure to computerized tests, consisting of 12 individual 1-h sessions over a six-week period. In particular, the Control group performed a simple visuomotor coordination tapping task by using an in-house software. Finally, at the end of the 6-week training, subjects from both groups were given a blind evaluation, using the same protocol employed at a baseline (T1). Two PD patients from the Experimental group and three from the Control group decided not to continue with the protocol. Thus, eight PD patients from the Experimental group and seven PD patients from the Control group completed the protocol (Fig. 1).

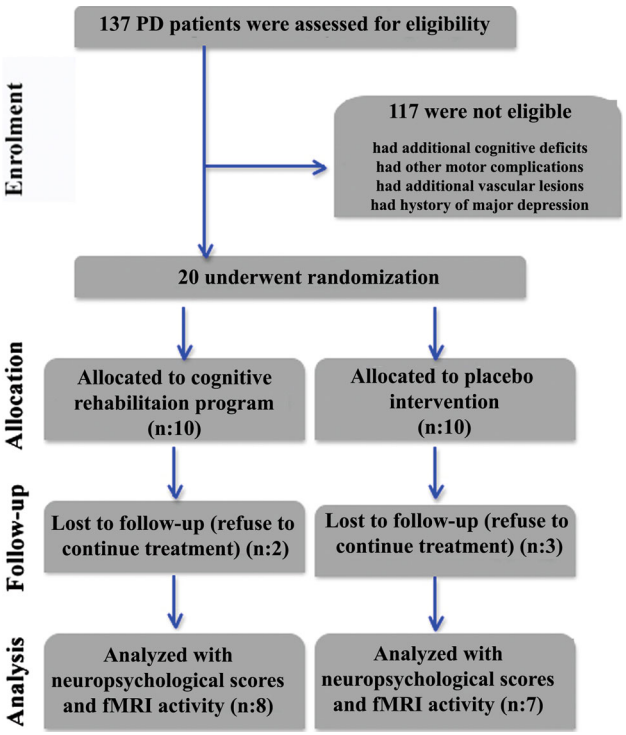

Fig. 1 Flow diagram of subject recruitment and participation in the study. The experimental group participated in an individualized CR program for attention deficits (Rehacom software); the control group received motor therapy re-education (placebo intervention)

Resting state fMRI acquisition and analysis

Scanning was performed on a 3-T scanner (MR750 General Electric, USA). A gradient-echo planar (EPI) T2*-weighted pulse sequence (TR = 2,000 ms, TE = 25 ms, number of axial slices = 39, thickness/gap = 3/0.8 mm, matrix size = 96 × 96) was employed. A total of 200 volumes were acquired for a total imaging time of 7 min. During the functional scan, subjects were asked to simply stay motionless, awake and relaxed with their eyes closed.

Image preprocessing

Group spatial independent component analysis (ICA) was performed using FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and Group ICA for fMRI (http://mialab.mrn.org/software/). Group ICA was constituted by three main stages: data reduction, ICA, and back reconstruction. Individual subjects' data were first reduced by principal components analysis (PCA), next concatenated, and finally reduced again by another PCA step. ICA was then applied to this latter reduced data set. The resulting components reflected group components across all subjects.

Within-group and between-group comparisons for each resting state network (RSN) with potential functional

relevance was assessed using SPM8. ANOVA model was used for performing a group (Experimental vs Control) × time (T0 vs T1) interaction analysis, in order to detect which within-group changes of RS functional activity over time were significant between groups. The head motion parameters were also included as nuisance covariates. Based on previous findings, we decided to use the dorso-lateral prefrontal cortex, ventro-lateral prefrontal cortex, anterior cingulate cortex, superior and inferior parietal lobule, caudate and the whole-cerebellum as a priori regions of interest (ROIs) given their critical engagement on attention abilities and executive functions [12]. All ROIs were created with the "aal.02" atlas included in the Wake Forest University Pickatlas software version 1.04 (http://www.fmri.wfubmc.edu/download.htm). Statistical analyses within ROIs were thresholded by using correction for multiple comparisons [family-wise error (FWE) $p < 0.05$].

Statistical analysis

Statistical analyses were performed with Statistica Version 6.0 (http://www.statsoft.com). Assumptions for normality were tested (using Kolmogorov–Smirnov test) for all continuous variables. All variables were normally distributed, except for educational level, HY and equivalent dose of levodopa. Unpaired t test, Mann–Whitney U test and χ^2 were applied appropriately. Behavioural changes associated with CR therapy were calculated as differential T1–T0 (delta) scores. All statistical analyses had two-tailed alpha levels of <0.05 for defining significance.

Results

Clinical and neuropsychological findings

At the time of inclusion, the two groups were perfectly matched for all demographical and clinical variables (see Table 1). At baseline, there were no significant differences between the Experimental group and the Control group in any of the neuropsychological tests (all p's > 0.05) (Table 2). During the re-test phase any clinical or radiological change was detected in the patients. At a phenotypic level, the differential T1–T0 (delta) scores for each neuropsychological test were compared between the Experimental and Control groups (Table 3). Overall, considering all cognitive and psychological domains, after CR the Experimental group showed significant cognitive improvements in the SDMT (T-value = 4.1, p-level = 0.04) and the digit span forward (T-value = 9.3, p-level = 0.01).

Table 1 Participant's characteristics

Variables	Experimental group	Control group	p values
Age (years)	61.1 ± 12.4	58.3 ± 9.6	*0.24*וו
Education (years)	8 (3–13)	8 (3–10)	*0.88*§
Age at onset (years)	58.1 ± 12.3	54.9 ± 15.3	*0.11*וו
Disease duration (years)	3.5 ± 0.8	3.2 ± 1	*0.38*וו
UPDRS	16.8 ± 8	17.2 ± 2.9	*0.79*וו
HY	2 (1–3)	2 (1–3)	*0.91*§
Levodopa (mg/die)	375 (250–600)	420 (200–600)	*0.34*§

Data וו are given as mean values (SD) or median values (range) when appropriate

וו Unpaired t test

§ Mann–Whitney test

HY Hoehn–Yahr

UPDRS unified Parkinson's disease rating scale

Table 2 Neuropsychological performances in the Experimental and Control groups at baseline

Tests	Baseline (T0)				
	Experimental group		Control group		Statistics
	Mean	SD	Mean	SD	p-values
SRT-LTS	33.3	*5.6*	38.2	*9.1*	0.27
SRT-CLTR	25.5	*11.5*	33.1	*8.8*	0.22
SRT-D	5.7	*2.2*	5.7	*1.6*	0.14
ROCFT IR	17.5	*6.2*	15.4	*8.7*	0.63
ROCFT DR	18	*6.4*	15.1	*7.1*	0.47
COWAT	31.6	*8.2*	36	*9.3*	0.73
PASAT 3″	33.3	*4.1*	38.5	*11.6*	0.28
SDMT	34.54	*11.5*	36.2	*7.4*	0.78
TMT A	51.43	*8*	43.8	*15.3*	0.28
TMT B	125.43	*69.4*	123.8	*64.8*	0.97
TMT B-A	74.6	*57.1*	101	*42*	0.54
ST	18.3	*7.2*	25.1	*6.5*	0.13
Digit span FW	4.14	*1*	6.1	*0.2*	0.08
Digit span BW	3.9	*1.2*	3.6	*0.9*	0.69
JLO	23.6	*3.5*	23.2	*3.5*	0.41
Beck II	5.86	*4.1*	8.9	*4.7*	0.28
Stai-Y1	40.1	*12.1*	46.4	*10*	0.36
Stai-Y2	41.4	*11.3*	40.6	*9.7*	0.91
PQD-39	40.5	*20.7*	40.3	*25.1*	0.99
MMSE	28.7	*1.5*	29.4	*0.5*	0.37

Italic means SD values

RS fMRI

The analysis of RS fMRI detected ten spatial maps of potentially relevant RSNs, including those related to

Table 3 Neurocognitive performances and measures of functional scales in the Experimental and Control groups at baseline and retest

Tests	Baseline (T0)				Re-test (T1)				Delta (T1–T0)		Statistics
	Experimental group		Control group		Experimental group		Control group		Experimental group	Control group	*p*-values
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Verbal memory											
SRT-LTS	33.3	*5.6*	38.2	*9.1*	35	*6.9*	39.37	*10.1*	1.7	1.12	0.92
SRT-CLTR	25.1	*11.5*	33.1	*8.8*	28.9	*5.8*	32.9	*12.5*	3.86	−0.24	0.56
SRT-D	5.7	*2.2*	5.7	*1.6*	6.96	*2.3*	7.8	*1.2*	1.3	0.24	0.39
Spatial memory											
ROCFT IR	17.5	*6.2*	15.4	*8.7*	21.7	*8.1*	19.3	*10.4*	4.16	3.92	0.95
ROCFT DR	18	*6.4*	15.1	*7.1*	22.64	*6.5*	19.1	*9.5*	4.64	4.06	0.85
Verbal fluency											
COWAT	31.6	*8.2*	36	*9.3*	34.83	*8.4*	36.8	*6.5*	3.23	0.8	0.59
Information processing speed/attention/executive functions											
PASAT 3″	33.3	*4.1*	38.5	*11.6*	37.7	*5*	43.9	*10.6*	4.43	5.4	0.79
SDMT	**34.54**	***11.5***	**36.2**	***7.4***	**43.1**	***17.6***	**35**	***10.2***	**8.51**	**−1.12**	**0.04**
TMT A	51.43	*8*	43.8	*15.3*	48.14	*9.4*	42	*15.2*	−3.29	−1.8	0.76
TMT B	125.43	*69.4*	123.8	*64.8*	114.71	*43.5*	97.8	*25.4*	−10.7	−26	0.44
TMT B-A	74.6	*57.1*	101	*42*	70.43	*41.5*	74.8	*22.9*	−4.1	−26.2	0.36
ST	18.3	*7.2*	25.1	*6.5*	20.1	*11.6*	23.02	*3.7*	1.86	−2.1	0.16
Digit span FW	**4.14**	***1***	**6.1**	***0.2***	**5.9**	***0.9***	**5.7**	***0.4***	**1.81**	**−0.5**	**0.01**
Digit span BW	3.9	*1.2*	3.6	*0.9*	4.6	*1.5*	4	*1*	0.7	0.4	0.68
Visuospatial processing											
JLO	23.6	*3.5*	23.2	*3.5*	24.6	*2.6*	24.6	*2.6*	1	−1	0.29
Mood											
Beck II	5.86	*4.1*	8.9	*4.7*	5.7	*6.4*	8.7	*4.7*	−0.1	−1.4	0.61
STAI-Y1	40.1	*12.1*	46.4	*10*	43.1	*13.4*	42.2	*8.3*	3	−4.2	0.24
STAI-Y2	41.4	*11.3*	40.6	*9.7*	37.7	*11.9*	40.8	*12.7*	−3.7	0.2	0.46
Quality of life											
PDQ-39	40.5	*20.7*	40.3	*25.1*	38.1	*15.3*	44.8	*21.5*	−2.38	2.73	0.61
General cognition											
MMSE	28.7	*1.5*	29.4	*0.5*	29.16	*1.1*	29.6	*0.5*	0.43	0.2	0.57

Italic means SD values

Bold values represent significant statistical differences ($p < 0.05$)

SRT-LTS Selective Reminding Test-long term storage, *SRT-CLTR* Selective Reminding Test-consistent long term retrieval, *SRT-D* Selective Reminding Test-delayed, *ROCFT* Rey–Osterrieth Complex Figure Test [immediate and delayed recall (IR/DR)], *COWAT* Controlled Oral Word Association Test, *SDMT* Symbol Digit Modalities Test, *PASAT-3* Paced Auditory Serial Addition Test-3s, *ST* Stroop Test, *TMT* Trial Making Test A–B, *JLO* Judgment Line Orientation Test, *STAI* state-trait anxiety inventory *Y*1 and *Y*2, *PDQ-39* Parkinson's Disease Questionnaire, *MMSE* Mini Mental State Examination

sensorimotor areas, primary and secondary visual cortical areas, primary and secondary auditory areas, default mode network, salience processing network, attention function network and central executive networks (left and right sides) (Fig. 2) [13]. All these components were stable across multiple runs of IC decomposition.

Group × time interaction effects

Considering the interaction effects between groups (Experimental vs Control group) × time (T0 vs T1), after CR the Experimental group demonstrated significantly increased intrinsic functional activity in the left dorsolateral prefrontal cortex within the left central executive RSN when compared to Control group (MNI local maxima: $x = -46$, $y = 50$, $z = 4$, $F = 10.5$, $P_{FWE} = 0.04$). Again, an additional significant functional change was detected in the left superior parietal lobule within the attention RSN (MNI local maxima: $x = -18$, $y = -70$, $z = 52$, $F = 12.2$, $P_{FWE} = 0.03$) (Fig. 3). No significant group × time interaction was found for other RSNs examined.

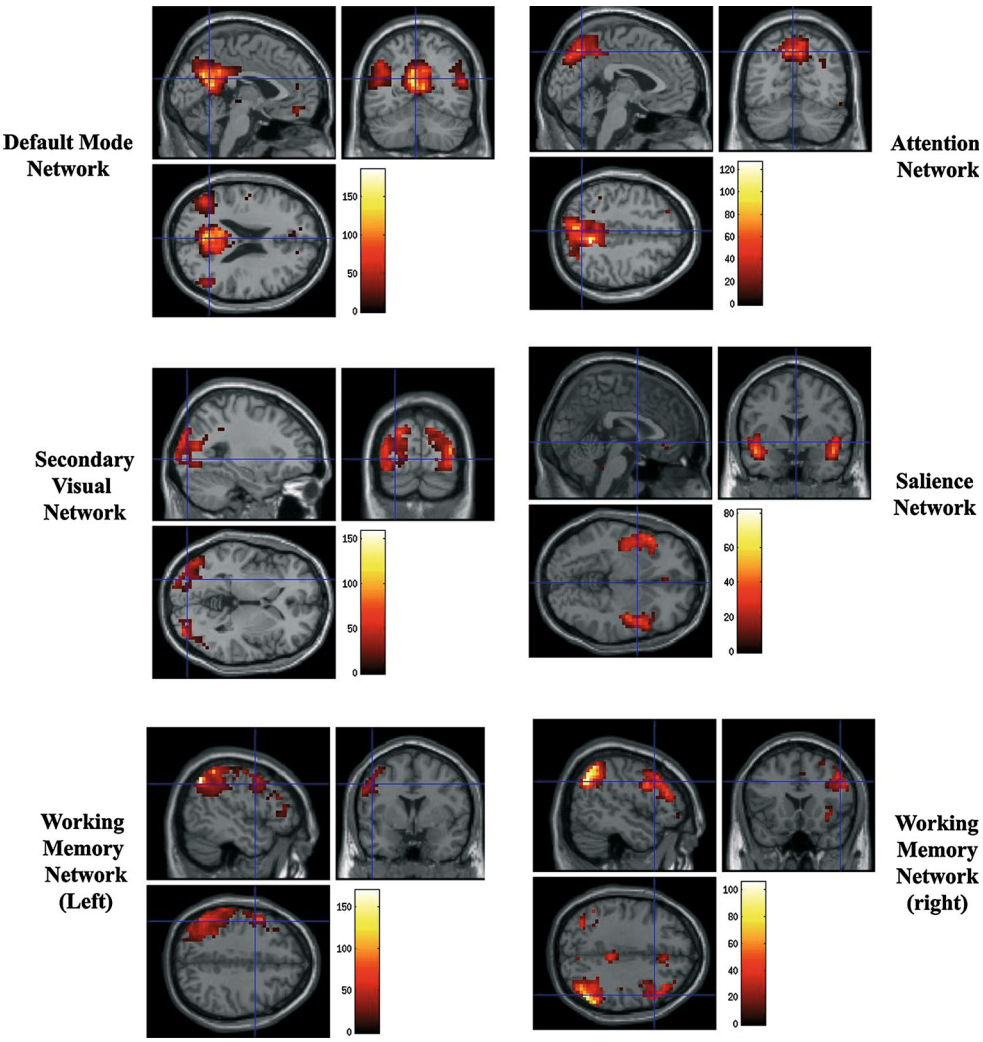

Fig. 2 Spatial maps of *cognitively* functional relevant RSNs from the cohort of PD patients (one sample *t*-contrast thresholded for positive values; $p < 0.05$ FWE corrected for multiple comparisons)

Discussion

The results of the current study are perfectly in line with the reported beneficial effects of CR in other neurological diseases or acquired brain injuries [3, 4, 14]. The proposed therapeutic approach is part of a recent trend to tailor neurorehabilitation programs to a specific cognitive deficit. In fact, recent studies demonstrated that when CR is focused on a specific cognitive domain, significantly positive results are achieved in neurological patients [3, 14]. Apart from the improvement in specific cognitive functions, a strength of this study is the employment of functional neuroimaging, which allows us to confirm that an intensive computer-based training of attention abilities yields adaptive neural plasticity of associated neural networks.

In particular, RS fMRI analysis revealed the presence of a functional reorganization in specific brain regions: the dorso-lateral prefrontal cortex and superior parietal lobule. A large amount of evidence demonstrated that the dorso-lateral prefrontal cortex and posterior parietal cortex are essential for executive functions, particularly in working memory (i.e. keeping spatial information in memory over a short time period). Maintenance and storage are the principal processes required to sustain working memory ability. While storage and buffering have been associated with parietal cortex activities, the dorso-lateral prefrontal cortex has been proposed as a crucial node supporting maintenance processes [12]. Thus, the detected over-activity of the parieto-prefrontal pathway would seem to suggest that our proposed therapeutic strategy acts in recovering specific mechanisms of plasticity (read cognitive strategies) in PD patients, which might help to decrease the emergence of cognitive impairment. Although the exact nature of the processes leading to a cortical over-activation is still unknown, these increased responses have been interpreted as 'compensatory mechanisms' that would have required an increased 'cognitive effort' to achieve a normal level of behavioural performance. Of note, the detected cognitive improvements in the SDMT and digit span forward,

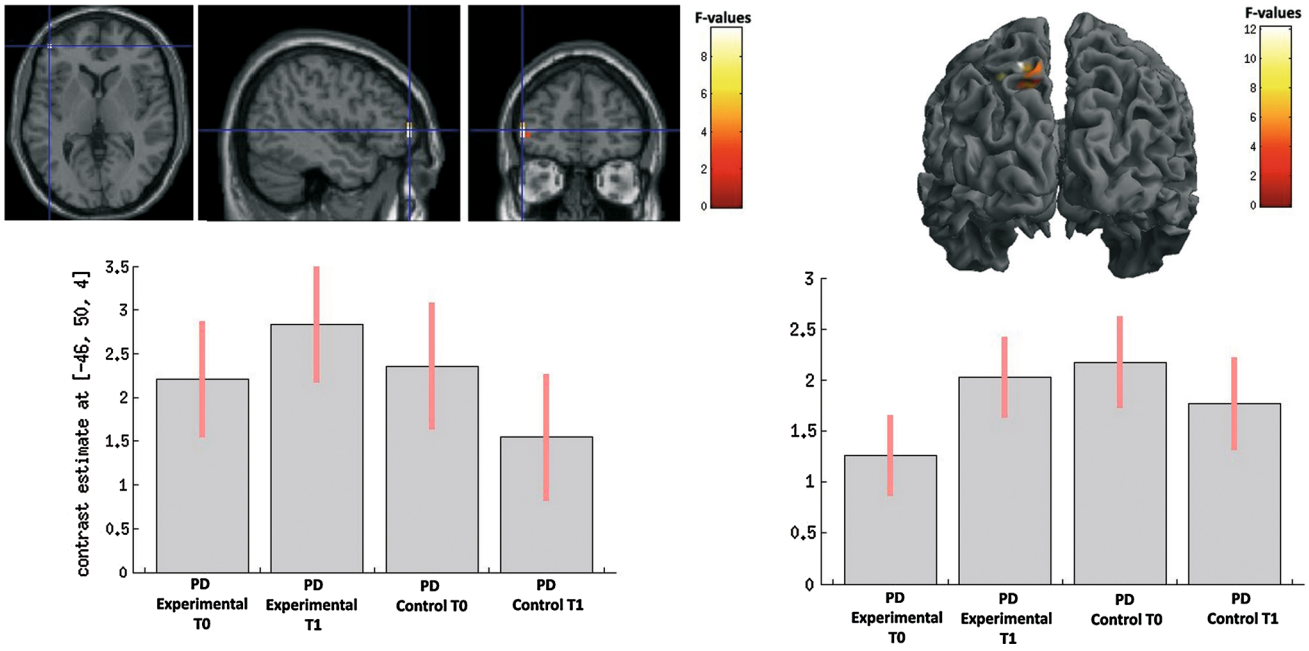

Fig. 3 3D/2D surface renders showing group × time interaction effects on resting state functional activity for all potential brain networks with functional relevance. On the *left side*, the increased activity of the left dorsolateral prefrontal cortex within the left central executive RSN is shown; whereas, on the *right side*, a similar effect driven by the experimental group in the left superior parietal lobule within the attention RSN is shown

perfectly agree with the reported neural changes. In fact, either the SDMT or digit span forward are simple and relatively short tasks that emphasize the speed of information processing and short-term working memory abilities. Moreover, both tasks have been demonstrated to be strongly dependent upon the recruitment of the frontoparietal neural activity [15, 16].

One main study limitation was its relatively small sample size owing to the difficulty in enrolling PD patients with either a predominant attention deficit or a clinical condition compatible with neuroimaging examination. The fact that we have enrolled only 20 PD patients with predominant attention deficits from our large initial group confirms the difficulty in investigating the neural correlates of CR in PD patients and highlights that our findings could not be generalized to all PD populations. Therefore, to sustain the usefulness of our CR therapy for minimizing the emergence of cognitive impairments in PD patients, further studies are warranted employing a larger sample that consider patients with additional cognitive deficits. Despite this methodological limitation, several major strengths distinguish this study. First, our blind, randomized, controlled trial design ensured internal validity of the results. Second, the reported functional changes survived conservative statistical thresholds. Third, based on previous investigations, we conducted a validated intensive training program to improve behavioral outcomes in neurological patients [3, 14].

In conclusion, our study confirms the beneficial effect of the proposed CR strategy focused on attention disorders because attention represents a controlling and integrating function with implications for nearly all other cognitive systems. These findings might represent an important improvement in this research field, since almost all previous works generally employed non-specific interventions where a plethora of cognitive functions were rehabilitated [5–7]. In fact, when CR is tailored on one specific cognitive domain, significant and more effective results may be found in the PD population.

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