The neural correlates of specific executive dysfunctions in Parkinson's disease

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Several functional neuroimaging studies in patients with Parkinson's disease (PD) have suggested that changes in the fronto-parietal-striatal networks are associated with deficits in executive functioning. However, executive functions (EF) are multifaceted and include three dissociable components: working memory, response inhibition, and task-switching. This study investigated which component of executive functioning is most strongly associated with fronto-parietal-striatal efficiency in PD. PD patients (with and without executive dysfunction), and age-matched healthy subjects, completed a battery of cognitive tests previously shown to discriminate among the three EF components. Principal component analysis conducted on the selected cognitive test variables yielded three expected EF components. The component scores were used in regression analysis to assess the relationship between the EF efficiency and blood oxygenation level-dependent (BOLD) signal related to performing the n-back, an experimental task that draws upon multiple components of executive functioning: working memory, response inhibition, and task-switching. We found distinct neural correlates of specific executive dysfunctions in patients with PD. However, all of them seem to be associated with fronto-parietal-striatal efficiency.

Key words: Parkinson's disease, executive function, working memory, inhibition, task-switching, principal components analysis, functional magnetic resonance imaging (fMRI)

INTRODUCTION

Parkinson's disease (PD) is an aging-related neurodegenerative disorder characterized by motor symptoms such as bradykinesia, rigidity, and resting tremor (Strafella et al. 2007, 2008). However, patients with PD have also demonstrated diverse cognitive problems (Dubois and Pillon 1997, Amick 2006, Gawrys et al. 2008), even at relatively early stages of the disease. Cognitive impairments involve predominantly executive functions (EF) and are related specifically to deficits in working memory, control of attention, set shifting, and planning (for reviews see Taylor and Saint-Cyr 1995, Owen and Doyon 1999).

It is generally assumed that executive dysfunctions in PD are caused by degeneration of the basal ganglia and/or the frontal cortex. Several functional neuroimaging studies in PD patients have confirmed the involvement of the fronto-striatal networks in executive dysfunctions, the nigrostriatal and mesocortical

pathways in particular (Owen et al. 1998, Dagher et al. 2001, Cools et al. 2002, Mattay et al. 2002, Monchi et al. 2004, 2007, Nagano-Saito et al. 2008). The majority of functional MRI (Monchi et al. 2004, 2007, Nagano-Saito et al. 2008) and $H_2^{15}O$ PET (Owen et al. 1998) studies demonstrated reductions in fronto-striatal activation in PD patients, as compared to normal controls, during tasks involving executive processes.

Only few studies used the functional neuroimaging techniques to tie changes in brain activation with the level of executive functioning in PD (e.g., Lewis et al. 2003, Christopher et al. 2014, Nagano-Saito et al. 2014). Those studies have consistently shown that PD patients with cognitive impairment, as compared to cognitively normal PD patients and healthy controls, displayed a reduced activation in fronto-striatal circuitry when performing a working memory task (Lewis et al. 2003) or set-shifting task (Nagano-Saito et al. 2014). Such findings have suggested that changes in the fronto-striatal activation in PD are associated with deficits in executive functioning. However, EF is a broad term encompassing a wide array of capacities. It is not clear yet which specific executive deficits are particularly associated with the level of activation in frontal and striatal regions. Prior work has searched for any evidence of association between the level of brain activity and some aspects of EF, but none has explored the relationship of the activation and executive functions in the context of a previously validated structure of EF components. These include: working memory, defined as system is responsible for a short-term storage and manipulation of multiple pieces of transitory information; inhibition, being a capacity to supersede an already-initiated response, or a response that is pre-potent in a given situation; and task-switching, as an ability to change stimulus-response associations (Miyake et al. 2000, Van Snellenberg and Wager 2009). Theoretical considerations and neuroimaging studies of healthy subjects suggest that these three EF components are likely to be supported by overlapping, yet somewhat distinct, fronto-parietal-striatal networks (Konishi et al. 1998, Garavan et al. 1999, Sohn et al. 2000, Sylvester et al. 2003, McNab and Klingberg 2008). Frontal and parietal cortical areas are reciprocally interconnected with each other and project to basal ganglia and thalamus, in concert mediating executive functions (for a review see: Rubia 2011). However, working memory processes are thought to rely mainly on lateral areas of the prefrontal cortex

extending from BA 10 through mid-dorsolateral prefrontal cortex (Duncan and Owen 2000, Petrides 2000, McNab and Klingberg 2008). Task-switching engages more posterior regions of dorsolateral prefrontal cortex (e.g., inferior frontal junction) as well as parietal regions (e.g., intraparietal sulcus) (Konishi et al. 1998, Sohn et al. 2000, Derrfuss et al. 2005). The inhibition of an already-initiated response seems to rely upon a right-lateralized fronto-parietal circuit (Garavan et al. 1999, Sebastian et al. 2013). All the three of EF components can be affected by PD (Chong et al. 2000, Frank et al. 2007, Yogev-Seligmann et al. 2008), but it is not known whether each of them is specifically related to the changes in BOLD signal in fronto-striatal networks. In order to determine which component of executive functioning is most strongly associated with changes in frontal and striatal activity, we asked patients with Parkinson's disease (with and without executive dysfunction) and age-matched healthy adults to complete a battery of cognitive tests chosen to be primarily indicative of particular EF components.

Principal component analysis of the selected measures from cognitive tests was used to approximate the EF efficiency in the domains of working memory, response inhibition, and task switching. So as to address the effect of individual cognitive capacity for executive processes on the neural activation, we used scores on each EF components to predict individual blood oxygenation level-dependent (BOLD) signal in subjects performing the n-back task (Cohen et al. 1993, 1997). This experimental task draws upon multiple components of executive functioning (Barbey et al. 2011). Although only few studies have examined the processes involved in the n-back performance (e.g. Hockey and Geffen 2004, Kane et al. 2007, Jaeggi et al. 2010), it was shown that the n-back task and traditional measures of working memory capacity (digit span forward and digit span backward) share a common variance with values between $r=0.17$ and $r=0.30$ (Jaeggi et al. 2010). Also inhibitory control and task switching seem to share a considerable amount of variance with n-back performance. For instance, a study of children (Ciesielski et al. 2006) showed that 2-back performance is substantially correlated with Stroop performance ($r=0.55$) and Wisconsin Card Sorting ($r=0.56$). These data suggest that n-back task provides a measure of working memory, inhibitory control and task-switching. Thus, we predicted that the altered brain activation in cognitively impaired PD patients

would correlate in a regionally specific manner with different EF components that emphasize processing in different neural networks.

METHODS

Subjects

All the participants provided a written informed consent. The protocol was approved by the Warsaw Medical University ethics committee. Forty patients with idiopathic PD and 22 healthy adult controls participated in the study. However, from an original cohort of 62 subjects, individuals were excluded from further analysis if their head movements in the scanner were found to exceed 2 mm in any direction, leaving a total of 48 subjects. As a result, the groups taking part in the study included 30 patients with PD (13 males) and 18 healthy controls (8 males). All the participants were right-handed, without an early left-to-right handwriting switch that could change the cortical representations of motor and cognitive functions (Grabowska et al. 2012). Parkinson's disease was diagnosed by a clinical neurologist, on the basis of akinesia associated with tremor and/or rigidity, and responsiveness to levodopa therapy. No patient had a history of neurological or psychiatric disease [including depression, as measured with the Beck Depression Inventory (Beck et al. 1961)] other than Parkinson's disease. Patients with advanced, unmanageable on-off effects were excluded from the study. Those included in the study received different treatment adjusted to the stage of a disease and their tolerance of the particular drugs' side-effects. Timing, dose and frequency of the medications were scheduled in order to avoid wearing-off symptoms. Almost half of the participants (14 of 30) had taken controlled-release levodopa, and one of these patients additionally used tolcapone. One patient did not take any anti-parkinsonian medication. Another two did not take lewodopa (one of them had taken ropinirol, the other one selegiline). In total, 12 patients were treated with long-acting direct dopamine agonist. The examination was performed in the middle of a period between medications doses. Since this period ranged from 3 to 8 hours, we did not standardize the time of testing across the patients group. Patients who scored <26 on the Mini Mental State Examination (MMSE) were excluded in order to avoid the inclusion of patients with possible dementia (Folstein et al. 1975). Such a rigorous cut-off point was employed because of the fact that relatively young, highly educated participants were included in the study. It has been repeatedly recommended to use cut-off higher than 24 points in younger and higher educated patients (Crum et al. 1993, O'Bryant et al. 2008). Moreover, it was shown that the best cut-off to distinguish between demented and non-demented PD patients was 26 MMSE points (Dubois et al. 2007). Control subjects were closely matched with the Parkinson's disease patients for their age, years of education, and gender. None of control subjects had a history of a head injury, stroke or any neurological or psychiatric diseases. An expert radiologist examined all MRIs so as to exclude the potential brain abnormalities and subjects with microvascular lesions, if apparent on T_2-weighted images. All the subjects (patients and controls) displayed normal, conventional imaging results. The demographic and clinical characteristics of the two groups are reported in Table I.

Participants accomplished standard clinical measures of executive functions, and then underwent fMRI investigation during the performance of n-back task.

Neuropsychological assessment

We used two tests examining working memory [taken from the Wechsler Adult Intelligence Scale, the third edition (Wechsler 1997)]. The Digit Span Forward Test assessed WM storage, as required for the maintenance of information in WM, whereas the Digit Span Backward Test assessed WM executive involved the manipulation of the contents of WM. During the former test, the experimenter pronounces a sequence of digits aloud at a pace of one digit per second, and then the participant is asked to repeat the digits back in a given order. In the latter, a participant is also presented with a series of digits and must immediately repeat them back, but in a reverse order. In both tests, the length of the sequence begins at 2 and increases by 1 each time the participant completes a sequence correctly. Whenever a participant makes an error, a different sequence of the same length is presented. If that sequence is also completed incorrectly, the test is over. A participant's digit span is defined as the length of the last sequence completed correctly.

Table I

Characteristics of Parkinson's and control participants				
	Group mean (SD)		**Difference**	
	Control	**PD**	**t (df) or χ2**	**P**
Sociodemographics				
Number of subjects	18	30		
Age	57.11 (6.62)	56.03 (7.51)	0.52 (39.56)	0.61
Sex (M/F)	8/10	13/17	0.01	0.94
Education	14.69 (3)	13.51 (2.92)	1.26 (35.16)	0.22
Duration of disease (years)		6,75(5,25)		
Hoehn & Yahr stage		2 (1)		
l-dopa dose (mg)		851,58 (596,25)		
dopamine agonist use		12/30		
MAO Inhibitors use		2/30		
COMT inhibitors use		1/30		
Amantadine use		6/30		
Neuropsychological tests				
WCST (cat. completed)	5.67 (0.69)	3.53 (2.11)	5.1 (38.01)	**<0.001**
WCST (perseverations)	12 (9.32)	31.07 (21.74)	–4.2 (42.67)	**<0.001**
WCST (other errors)	10.44 (7.53)	18.03 (9.33)	–3.09 (41.89)	**0.004**
TMT (A time)^2	34 (14.58)	46.17 (14.26)	–2.83 (35.44)	**0.008**
TMT (B time)^2	61.61 (21.26)	104.77 (41.056)	–4.79 (45.28)	**<0.001**
TMT (B – A time)^2	27.61 (12.35)	58.6 (34.17)	–4.5 (39.79)	**<0.001**
Stroop (part 1 time)^2	14 (3.2)	14.2 (2.55)	–0.23 (29.9)	0.82
Stroop (part 2 time)^2	19.61 (5.07)	21.57 (5.42)	–1.26 (37.88)	0.22
Stroop (part 3 time)^2	24.22 (6.61)	29.77 (6.64)	–2.81 (36.07)	**0.008**
Stroop (part 3 – 1 time)^2	10.22 (6.55)	15.57 (5.7)	–2.87 (32.07)	**0.007**
Stroop (part 3 – 2 time)^2	4.61 (4.66)	8.2 (4.59)	–2.6 (35.45)	**0.014**
Digit span forward^1	7.06 (1.77)	5.9 (1.37)	2.38 (29.33)	**0.024**
Digit span backward^1	6.78 (1.56)	5.6 (1.38)	2.65 (32.59)	**0.012**
MMSE	29.28 (1.02)	28.93 (1.13)	1.09 (39.12)	0.28
Experimental task				
2-back (hits)	16.22 (1.4)	15 (1.95)	2.52 (44.4)	**0.015**
2-back (false alarms)	0.5 (1.15)	1.93 (2.01)	–2.38 (45.74)	**0.004**

(TMT) Trial Making Test; (WCST) Wisconsin Card Sorting Test; (MMSE) Mini-mental State Examination. Raw score means (standard deviations) and ranges are reported for all variables. Cognitive assessments were conducted when PD participants were taking their medication therapy. [1]Values are number correct; [2]Values are time in seconds. Bold type indicates group differences (P<0.05).

An assessment tool used to measure the inhibition of an already-initiated response was the Trail Making Test (TMT) (Reitan and Wolfson 1993). The test requires a subject to connect 25 consecutive targets on a sheet of paper. There are two parts of the test. In part A, all the targets are numbers (1...25.) and a tested person needs to connect them in sequential order. In part B, the subject alternates between numbers and letters (1, A, 2, B, ...L, 13). The inhibition of an already-initiated response occurs in part B, wherein the subject alternates between two response sets. The score is the time needed to complete part B minus the time needed to complete part A.

The Stroop Test (Stroop 1935) requires an inhibition of a prepotent (but erroneous) response. This response is likely to be initiated, which means that the need to inhibit an already-initiated response also occurs in this test. We used a Victoria version of the Stroop Test (Spreen and Strauss 1998) including three subtests. In the first subtest, subjects were presented with a list of 24 dots that differed in the ink color. The subjects' task was to name the ink color of each dot. In the second subtest, subjects were presented with the list of 24 words that differed in ink colors, and subjects named the color of ink for each word. In the third subtest, subjects were presented with a list of 24 words that were also color-names themselves. In this presentation, however, the ink color of words was discordant with the color indicated by their meaning. Again, subjects were asked to tell the color of the ink and ignore the word's semantic meaning. The score of the Stroop Color-Word task was computed by subtracting the time needed for subtest 1 from that of subtest 3.

The Wisconsin Card Sorting Test (WCST) (Heaton et al. 1993) is a common measure of task-switching in humans. In this test, participants match test cards to one of four reference cards according to one of three classification rules. However, the rule is not given explicitly and the participants have to discover it themselves, using feedback following each match. After a fixed number of correct matches (ten, in our study), the rule is changed without notice, and participants have to switch to a new mode of classification using the skill of task-switching. In order to perform the task successfully, participants had to change stimulus-response associations (e.g., they had to shift from responding based on the color of stimulus to responding based on its shape).

Cognitive task during fMRI

During an fMRI investigation, participants performed an experimental task of working memory and executive functions, namely the n-back task (Cohen et al. 1993, 1997). The task requires WM storage and WM executive (WM executive involves continuous updating of the information held in WM, as in an n-back task), inhibition of an already-initiated response, and task switching (that is required in conditions in which the stimulus set was changed, as in an n-back task).

Specifically, the participants performed a letter variant of the 2-back task, and a simple vigilance task (0-back) as a control. The stimuli were sequences of white uppercase letters on a black background, presented centrally in pseudorandom order. The letters (Arial Bold font; size, 32 points) were selected from a set containing 17 consonants (B, C, D, F, G, H, J, K, L, M, N, P, R, S, T, W, Z). The V and Q consonants were not used, since they are very rarely used in the subjects' native script of Polish. Stimuli were back-projected from a multimedia projector (DLP Data Projector NEC LT 265 G) on a screen located about 3 m away from the magnet. Stimulus presentation time was 500 ms with an inter-stimulus interval of 2500 ms. During the inter-stimulus interval, a blank black screen was presented. In the 0-back task, subjects had to identify the target letter "X", with all other letter stimuli treated as non-targets. In order to perform the 2-back task, subjects had to identify a target, namely any letter identical to the one that was presented two stimuli before, with all other letters counted as non-targets. Subjects were instructed to respond to each target (approximately 33% of the stimuli for both the 0-back and 2-back tasks) with their right index finger, using a one-button response pad. Before scanning, the subjects were trained on a version of the task designed to use it outside the scanner.

fMRI data acquisition

MRI data was acquired with GE Signa Excite 1,5T scanner. Functional run consisted of 120 volumes and the following parameters were used: 28 slices, TR=3000 ms, TE=50 ms, FA=90 degrees, slice thickness=4 mm (0.5 mm gap), matrix size=128×128, FoV=240 mm, in-plane resolution 1.88×1.88 mm. High-resolution T1-weighted images were acquired to improve the quality of registration.

Statistical analyses

Behavioral data

Table I presents sociodemographic and cognitive characteristics of patients with Parkinson's disease and controls. Statistical analyses of the relationship between sociodemographic and neuropsychological variables were carried out using Welch's *t*-tests, which assumes, contrary to the classical Student's *t*-test, heterogeneous variance between the studied groups by adjusting degrees of freedom (Welch 1947).

The raw scores of neuropsychological tests could not be used in a regression analysis to predict BOLD signal in the brain, because of a relatively high colinearity between scores. Therefore, the principal component analysis (PCA) was performed on the selected results of neuropsychological test. The following scores were included: forward digit span as a measures of WM storage; backward digit span as a measures of WM executive; the Stroop Test (difference between the third and first subtest) as a measure of inhibition of the prepotent response; Trail Making Test (part B minus A), as a measure of the inhibition of an already initiated response; WCST (number of completed categories and number of perseverative errors) as a measure of task-switching efficiency. Principal components with eigenvalues >1 were extracted. Orthogonal Varimax rotation was used in order to alleviate colinearity between components.

The n-back task performance was interpreted in the context of the Signal Detection Theory (SDT) (Banks 1970). In the framework of SDT, each item of the n-back task is classified as either signal (a letter repeated after n other letters) or noise (all other letters). If a participant presses a button when the signal is presented, the reaction is classified as a 'hit'. Not responding when a target is present is called a 'miss'. When a person reacts to a noise, the response is classified as a 'false alarm', and finally no reaction to noise is classified as a 'correct rejection'. The number of responses in each of the above classes is calculated for each subject. The data for all subjects is analyzed with a hierarchical Bayesian SDT model (Lee and Wagenmakers
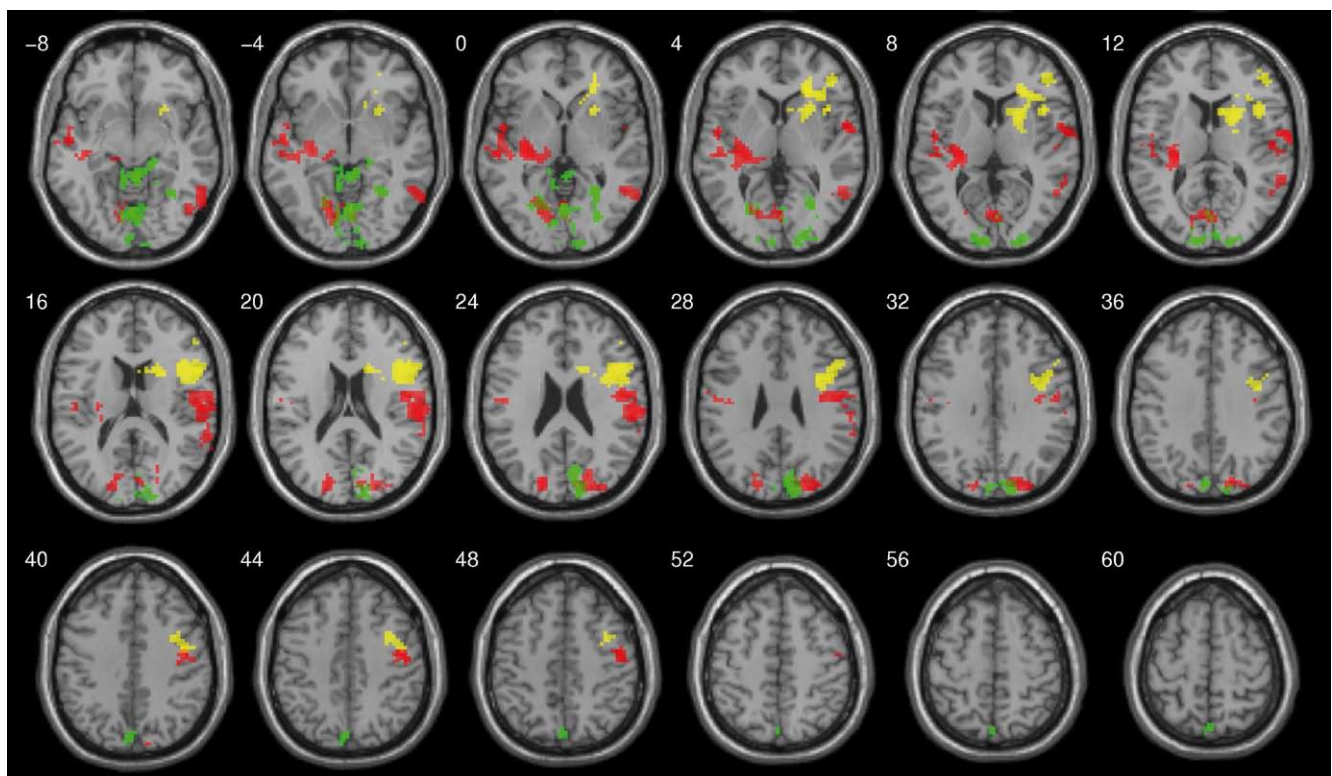

Fig. 1. Brain areas showing significant relationship with principal components representing executive functions. Brain areas related to different components are color-coded: green – working memory (negative correlation), red – inhibition (positive correlation), yellow – task switching (positive correlation).

Table II

Varimax-rotated principal components and neuropsychological test loadings

Neuropsychological test	Principal component		
	Task switching	**Working memory**	**Response inhibition**
WCST 1	**−0.936**	0.032	−0.181
WCST 2	**0.905**	−0.24	0.134
Stroop (3 - 1)	0.37	−0.196	**0.757**
TMT (B - A)	0.04	−0.099	**0.903**
Digit span forward	0.019	**0.884**	−0.263
Digit span backward	−0.299	**0.857**	−0.024
Eigenvalue	1.924	1.623	1.508
% variance explained	32.061	27.045	25.136

2013) which estimates two values for each subject: discriminability (d') and bias. d' refers to the ability of the subject to discriminate between signals and noise, and the larger the value, the better the performance. Bias is a measure of strategy used by the subjects. A high value of bias represents a tendency to reject responses, which results in higher correct rejection rates at the expanse of increase in miss rate, and therefore represents a more 'conservative' strategy. It has been shown that d' captures these aspects of executive functions that might be missed by digit span task (Haatveit et al. 2010). However, we decided to test both d' and bias measures to describe the n-back task performance.

In order to confirm that executive functions measured as principal components of neuropsychological tests are related to the n-back task performance, simple linear regressions was performed with extracted principal components as predictors, and d' and bias as dependent variables.

fMRI data

The functional data were preprocessed with different software packages in order to overcome several issues related to the quality of our dataset acquired on a mid–range (1.5T) system. First, spurious signal variations were removed from the functional volumes with AFNI 3dDespike utility followed by a simultaneous realignment and slice timing correction with NiPy (Roche 2011). Subsequently, a median functional volume was affine registered to the anatomical T1 image with the use of FSL, and the outliers (with a related signal change greater than 3 standard deviations) were identified with nipype. A GLM analysis was performed in FSL with a design matrix extended on following nuisance regressors: (1) outlier volumes, (2) motion parameters (and their 1st and 2nd derivatives). The remaining analyses were performed on residuals. The functional data was smoothed with an 8-mm-istotropic Gaussian kernel (FSL), normalized to the MNI space, and resampled to 3 mm isotropic voxel resolution (ANTS). A standard GLM was used with double-gamma HRF as a basis function (FSL). Contrast parameter estimates (2-back *versus* 0-back), along with their variance, were entered into 2nd level modeling. The second level design matrix included values for 3 principal components derived from neuropsychological testing. Age, sex, years of formal education and disease status (control/PD) were entered as covariates of no interest. Mixed effects modeling was used to estimate group-level correlations with behavioral measures. The results were thresholded at $Z = 2.3$ and corrected for multiple comparisons at cluster significance level of $P < 0.01$.

Table III

Brain areas showing significant linear relationship with cognitive functioning level

Predictor	Cluster index	Peak label	BA	Size (vox)	MNI coordinates	Z-score	P value
Working memory (negative)	1	R Lingual Gyrus	18	1125	3, −76, −12	4.18	<0.0001
Inhibition/ selection (positive)	1	R Central Opercular Cortex	40	655	54, −15, 14	4.54	0.0004
	2	L Putamen	N/A	451	−29, −21, 2	4.41	0.0049
	3	L Intracalcarine Cortex	17	424	−2, −72, 11	4.27	0.0069
Task switching (positive)	1	R Inferior Frontal Gyrus, pars opercularis	44	669	54, 11, 17	4.18	0.0005
		R Caudate	N/A		21, 11, 14	3.73	
		R Putamen	N/A		24, 11, 8	3.23	

(R) right; (L) left; (BA) Brodmann area; (vox) voxels

RESULTS

The PCA yielded 3 principal components explaining 84.24% of the variance of input variables (Table II). The first component, accounting for 32.06% of the variance, was loaded mainly by the scores obtained in WCST. This could be considered to be a task-switching factor. The second component accounted for 27.04% of the variance, and was loaded mainly by scores from the working memory tasks: Digit Span Forward and Digit Span Backward. The third component added further 25.14% to the variance, and comprised scores from response inhibition tasks: the TMT and the Stroop test.

Linear regression has shown that all principal components representing executive functions are significantly related to d' estimates based on the n-back task. A model including an intercept and all PCs was significantly better than a model including only the intercept ($F_{3,44}$=5.56, P=0.002) and explained 22.9% of variance. Task-switching PC had the strongest effect size (t_{44}=2.55, P=0.014, partial η^2=0.13), inhibition being the second strongest (t_{44}=2.33, P=0.025, partial η^2=0.11) and memory being the weakest (t_{44}=2.08, P=0.043, partial η^2=0.09). These results confirm that

n-back task performance depends on the measured executive functions.

Table III lists brain regions in which the activations showed significant correlations with the measures of working memory, response inhibition, and task-switching. Linear regression analysis indicated negative relationship between working memory scores and activity in the right lingual gyrus; positive relationship between response inhibition scores and the activity in the right central opercular cortex, left putamen and left intracalcarine cortex; and a positive relationship between task-switching scores and the activity in the frontal and striatal regions: the right inferior frontal gyrus (pars opercularis), putamen and caudate. Figure 1 presents brain areas showing significant relationship with principal components representing executive functions.

DISCUSSION

The present study showed that distinct components of executive functioning correlated with activation in different brain regions that are thought to support specific cognitive processes. We found that WM storage and WM executive efficiency (as measured with for-

ward and backward span) negatively correlated with activation in the right occipital lobe at the lingual gyrus. In other words, poorer working memory was associated with higher BOLD signal in this area. Although the lingual gyrus is not typically recruited for working memory tasks or seen in group differences in fMRI tasks with PD patients versus controls, this region was shown to be deactivated in healthy subjects during n-back tasks (Migo et al. 2014). It is thus possible that the lingual gyrus belongs to the default mode network, which involves a number of regions deactivated during cognitive tasks (Raichle et al. 2001). Therefore, our result may reflect a subtle disruption of normal coordination of network interactions in PD patients with WM deficits. This explanation is consistent with a study of patients with mild cognitive impairment and healthy control subjects, wherein participants completed the 3-back task (Migo et al. 2014). fMRI data showed group differences driven by a task-related deactivation of lingual gyrus being present in controls, but not in patients. The authors suggest that the absence of such deactivations in the n-back task could be early indicators of pathology in patients with mild cognitive impairment.

Interestingly, a recent MRI study has shown that the thickness of lingual gyrus can be used as a criterion for dementia prognosis in patients with PD (Trufanov et al. 2013). Our study, in which a worsening of working memory performance correlated with an enhanced activation in the lingual gyrus on the 2-back task, have suggested that a failure of deactivations in this brain area may be the neural correlate of working memory dysfunction. In addition, it seems that changes in frontal and striatal activations in PD are not associated with deficits in the working memory maintenance and updating. Instead, it appears plausible that a disrupted coordination between fronto-striatal and default brain networks is responsible for the WM deficits. This disruption, however, could be caused by fronto-striatal degeneration in PD. This result seems to stay in contrast with previous findings of decreased fronto-striatal activity during working memory task in PD without dementia (Lewis et al. 2003). However, Lewis and colleagues (2003) used a working memory task that was much more demanding and required not only a storage and updating of information in working memory, but also inhibition of information from previous trials and changes of stimulus-response associations from trial to trial. Nevertheless, we cannot exclude that

the PD patients participating in the study by Lewis and others (2003) were more cognitively impaired than those in our study, and that the neural circuit processing of EFs changes with the onset of dementia in PD.

There is considerable evidence suggesting that response inhibition relies upon a right-lateralized fronto-parietal-basal-ganglia circuit (e.g., Garavan et al. 1999, Sebastian et al. 2013). Accordingly, we found that poorer inhibitory performance positively correlated with lower BOLD signal in a peak located in the right parietal lobe (central opercular cortex). However, in our study, response inhibition positively correlated also with the activation in motor (left putamen) and visual (left occipital intracalcarine cortex) pathways. Some explanation of this result is provided by an fMRI study comparing healthy younger and older adults on the Stroop task and reporting, with regard to the older subjects, that the regions in the putamen and the occipital lobe were additionally activated (Zysset et al. 2007). These activations were more pronounced in the left hemisphere. The authors suggest that with increasing age, compensatory visuo-motor strategies become involved. This corresponds to the compensatory-recruitment hypothesis which claims that the additional brain regions might be brought to enable optimal performance (Reuter-Lorenz 2002). Our results suggest that these additional regions and processes are not engaged in cognitively impaired PD patients and do not allow for an equal inhibitory performance as for the healthy subjects.

The additional recruitment of regions responsible for visual processing and the execution of a motor response may be difficult in PD because of extensive atrophy in those structures. Volumetric analyses have consistently shown that the putamen volume was significantly decreased in patients with PD as compared with controls (e.g., Nemmi et al. 2014), and that the putamen atrophy was correlated with the severity of both motor and cognitive impairments (Geng et al. 2006). Moreover, PD patients with dementia exhibited extensive atrophy in the occipital lobe at the intracalcarine gyrus (Melzer et al. 2012) and in the right parietal lobe (Ellfolk et al. 2013). Grey matter loss in those areas correlated with a global cognitive score, but not with a motor impairment in PD. Further study documented a higher rate of cortical thinning in the occipital and parietal areas in patients with Parkinson's disease with mild cognitive impairment, as compared to both cognitively stable patients, and healthy controls

(Hanganu et al. 2014). These results indicate that the early presence of mild cognitive impairment in patients with PD is associated with a faster rate of grey matter thinning in posterior cortical regions. The authors suggested that this specific pattern of brain degradation associated with an early presence of mild cognitive impairment might serve as a marker of developing dementia. Similarly, it has been suggested that a posterior brain dysfunction, rather than a frontal dysfunction, is predictive of later PD dementia (Firbank et al. 2003, Williams-Gray et al. 2007, 2009, Miller et al. 2013). For example, in a single-photon emission tomography (PET) study, nondemented PD patients, and PD patients with dementia to a much greater extent, exhibited decreased perfusion in parietal regions, leading the researchers to propose that this sign may be an early marker of PD dementia (Firbank et al. 2003). Our results are consistent with these data. We found a relationship between a cognitive dysfunction in PD and a decreased activation in posterior (parietal-occipital) brain areas. However, our results have suggested that only one specific executive deficit (poorer response inhibition) is associated with the level of activation in parietal and occipital areas. It is thus possible that a decreased activation in those areas during tasks assessing response inhibition may be considered as a potential marker of later dementia in PD.

Finally, our results showed that poorer task-switching performance positively correlated with lower BOLD signal in frontal and striatal regions: the right inferior frontal gyrus (pars opercularis), putamen and caudate. Thus, fronto-striatal circuitry seems to be involved just in task-switching, in which participants had to change stimulus-response associations in order to perform the task successfully. This could include changes in the dimension of a stimulus to which responses are to be made (as in the WCST), or conditions in which the stimulus set was changed (as in the n-back task). The current findings are compatible with functional imaging studies of non-demented PD patients that reported reduced frontal and striatal activation in PD individuals with executive impairment relatively to a cognitively unimpaired PD subjects that had to change the stimulus-response associations from trial to trial (Lewis et al. 2003, Nagano-Saito et al. 2014). Other functional MRI studies support the notion that the caudate nucleus has a key role in task-switching (Rogers et al. 2000, Monchi et al. 2001, Cools et al. 2004). For example, event-related fMRI studies using the WCST in young

healthy adults (Monchi et al. 2001) confirmed a significant activation of the caudate nucleus, specifically when subjects received a negative feedback (that is, when a task-switching was required). Similarly, the putamen exhibited greater activity during matching response after negative feedback by the participants, but not when matching after positive feedback, which implies a greater involvement during novel than during routine actions (for a review see Petrides 2000). All this data is in line with our findings showing that deficient deactivation in frontal and striatal areas may be the neural correlate of task-switching dysfunction in PD.

A limitation of the present study is that we do not assess whether, and to what extent, l-dopa medication in PD influence the activation of the brain areas that we identified for the working memory, inhibition and task-switching processes, respectively. We cannot distinguish the effects of the medication from "pure" effects of the disease. On the other hand, dopaminergic medication has previously shown to alleviate executive dysfunctions in the early phase of PD, especially cognitive inflexibility, which is associated with dorsal striatum (for a review see: Cools 2006). L-dopa treatment was shown to ameliorate the working memory deficits and had no effect on the attentional set-shifting impairment (Lewis et al. 2005). Another study revealed that levodopa improved performance in a working memory task in unmedicated PD patients (Mollion et al. 2003). In the light of these data it is rather unlikely that a decreased performance in working memory, task-switching, and response inhibition observed in our study were produced by lewodopa medication. We suppose that poorer task-switching, as positively correlated with lower BOLD signal in fronto-striatal circuitry, reflects dopamine depletion, which was not fully-ameliorated by L-dopa treatment. We propose similar interpretation of the poorer inhibitory control, and its correlation with lower BOLD in left putamen. Nevertheless, further investigations with PD patients in the "ON" and "OFF" states should consider the effect of dopaminergic medication on the neural correlates of the three EF components.

CONCLUSION

We found distinct neural correlates of specific executive dysfunctions in patients with Parkinson's disease. However, all of these seem to be associated with fronto-parietal-striatal efficiency. The neural

correlates of poorer task-switching (lower activations in the right inferior frontal gyrus, putamen and caudate) showed that the fronto-parietal-striatal dysfunction is associated with task-switching deficits. The neural correlate of working memory dysfunction (deficient deactivation in occipital lingual gyrus) may reflect disrupted coordination between fronto-parietal-striatal and default brain networks. The neural correlates of deficits in response inhibition (failure of activations in the right posterior parietal cortex, left putamen, and left occipital intracalcarine cortex) additionally suggests that not only fronto-patietal-striatal dysfunction, but also a deficient recruitment of regions involved in visual processing, may be responsible for inhibitory deficits in PD.

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