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Increased pre-SMA activation in early PD patients during simple self-initiated hand movements

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Abstract The slowness of movement, termed bradykinesia, is one of the main symptoms of Parkinson's disease (PD). This symptom may be due to the inability of PD patients to maximise the speed of internally driven movements. The mesial premotor areas and in particular the pre-supplementary motor area (pre-SMA) seem to play a crucial role in the temporal initiation of movements in humans and animals. However, this activation seems to be debatable in imaging studies of PD patients. We performed a motor paradigm with temporally self-initiated movements in nine de novo PD patients before and after initiation of dopaminergic medication. The main finding was an increased activation of the pre-SMA in de novo PD patients compared with healthy age-matched control subjects. This result indicates the contribution of the pre-SMA in the temporal initiation of self-generated movements and in the disease pathology of PD. Increased bilateral activation of the superior cerebellum, mainly on the ipsilateral side, and a decreased activation of the ipsilateral inferior cerebellum in PD patients were also present. These findings provide new insights into the activation pattern of the cerebellum in PD patients.

Key words fMRI · Parkinson's disease · de novo · self-initiated movement

Introduction

Functional magnetic resonance imaging (fMRI) is utilized in an attempt to understand the underlying brain mechanisms producing voluntary movements. Parkinson's disease (PD) functions as a well defined model of a movement disorder with the leading symptom of bradykinesia and the underlying main disease pathology being confined to neurodegeneration of the nigrostriatal dopaminergic neurons in the substantia nigra. Furthermore, the symptoms of PD improve after administration of dopaminergic medication.

Bradykinesia, the slowness of movement, appears to result from the inability of PD patients to maximise their movement speed when required to drive internally their motor output [25]. Various aspects appear to contribute to the self-initiation of movements: 1) the selection of movement speed, 2) the selection of the direction of movement, 3) the selection of the kind of movement, and 4) the movement timing. In particular, PD patients have trouble with movement timing. The difficulty of initiating movements without external cueing and the improvement of movement performance using external cues are well-known clinical characteristics in PD patients [11]. PD patients are performing motor tasks faster with the help of external timing cues compared with temporally self-initiated movements [14, 18, 25, 35]. By contrast, healthy control subjects perform self-initiated movements faster than externally cued movements [25].

The mesial premotor areas seem to play a crucial role

with regard to self-initiated movements. As early as 1936, Forster reported, that lesions of the SMA in humans are associated with hypokinesia similar to that seen in PD [13]. Investigations of temporally self-initiated movements in healthy subjects revealed increased activation of the pre-SMA compared with movements triggered by external timing cues [8, 10, 23].

Activation of the mesial premotor areas in PD patients has shown ambiguous findings in functional imaging studies. Although the majority of studies report a decreased activation of the SMA proper in PD using fMRI [3, 19] and PET [6, 21, 22, 27, 28, 33], there are also reports of increased activation of the pre-SMA in PD using paradigms with complex sequential finger movements [5] as well as temporally self-initiated complex sequential finger movements [31]. It is important to note that the majority of studies showing decreased activation of the SMA in PD patients employed in movement paradigms with timing cues [6, 22, 27, 33].

The goal of the present study was to investigate the effect of temporal self-initiation of simple hand movements on the mesial premotor areas in early PD patients using fMRI. A motor paradigm consisting of repetitive opening and closing of the fist at a rate of about 1 Hz was used to generate temporally self-initiated movements and to minimise the effect of movement complexity on the activation of mesial premotor areas [5].

Methods

Subjects

We investigated nine right-handed drug-naive patients with a clinical diagnosis of predominantly bradykinetic idiopathic Parkinson's disease and nine healthy age-matched control subjects (four male, five female, mean age 60.6 ± 8.3 years). Patients had no warning symptoms of atypical parkinsonian syndromes or clinical signs of depression. All patients showed a lateralised expression of PD-related symptoms with a significant response in the acute levodopa challenge test and to mono-therapy with levodopa for a period of about 4 weeks (for clinical details see Table 1). The healthy control subjects had a normal neurological examination and no history of a neurological disease. Handedness was determined by simple inquiry. Subjects were first scanned in the OFF condition, before any medication for the treatment of PD had ever been administered. Imaging in the ON condition was performed approximately 4 weeks later, after patients showed a significant response to mono-therapy with levodopa. Prior to each scanning, patients were assessed with the part III of the Unified Parkinson's Disease Rating Scale [12] and the Hoehn and Yahr disability scale [20]. The study was approved by the Ethics Committee of the University of Magdeburg. Every subject provided written informed consent prior to examination.

Paradigm

The activation paradigm consisted of fist opening and closing of the right hand with a frequency of approximately 1 Hz. All subjects were instructed to practice the motor task in advance before the scan, until they were able to perform the task at the desired movement rate and amplitude, as described elsewhere [30]. Subjects were instructed not to move any other part of the body, not to think about the fist clenching during rest, and to ignore the scanning noise. The training was terminated when the patients over-learned the task. One of the investigators acted as an observer who visually inspected the execution of the exact movement, frequency and amplitude during scanning. During each session, subjects were presented with visual cues indicating either movement or rest periods. Within the movement periods, the subjects performed the over-learned hand movement at their own timing pace. Visual online monitoring by one of the investigators ensured exact task performance and did not reveal mirror movements during execution of the unilaterally performed task during all sessions.

Data acquisition

After training and instruction, the motor task involved four alternating epochs of 30 seconds rest and 30 seconds motor activation over a period of 4 minutes during whole head scanning with a neuro-opti-

Table 1 Demographical and clinical data of patients

Patient	UPDRS		H&Y stage OFF	levodopa ON	days of treatment	side affected	handed-ness	age (years)	disease duration (years)	sex
	OFF	ON								
1	25	13	2	500	35	left	right	67	3	m
2	16	8	1	300	28	left	right	68	2	m
3	20	10	1	300	28	left	right	56	1	f
4	20.5	14.5	1	300	29	left	right	73	1	m
5	19.5	8	1	300	28	left	right	62	1	m
6	23.5	12.5	2	300	26	left	right	55	3	f
7	22	11	2	300	28	right	right	62	1	m
8	20	9.5	1	300	28	right	right	54	1.5	f
9	18.5	10	1	200	24	right	right	73	1.5	f
MEAN	20.6+	10.7	1.3	311.1	28.2			63.3	1.7	
SD	2.7	2.2	0.4	42.0	2.9			6.1	0.7	

+ significantly different from ON condition ($p < 0.001$, paired t-test)

mised 1.5-T GE Signa Horizon LX scanner with the standard quadrature head coil (General Electric Company, Milwaukee, WI, USA). After a set of high-resolution structural T1 weighted images, functional images were acquired using single shot gradient echo planar imaging (FOV 20 cm, TR 2 s, TE 40 ms). Each run consisted of 129 volumes. Whole head volumes were recorded (23 slices oriented to the plane connecting anterior and posterior commissure, 5 mm thickness, 1 mm gap between slices, in plane resolution 3.125 mm).

Data analysis

Image processing and statistical analysis were carried out using the SPM99 analysis package (Wellcome Department of Cognitive Neurology, London, UK) and MATLAB (Mathworks, Natick, MA) software on a Pentium 1000 PC running Windows 2000. The first 4 scans were excluded from analysis in order to allow T1 stabilisation. Pre-processing of the data took several steps: In the first step, for each functional run, images were realigned to the first image of the session. The resulting mean image of coregistered functional scans of each run was used to determine the individual normalisation parameters for each functional session. Those images were then normalised into the MNI space using the template provided by SPM99 (resulting in isotropic 4 mm voxels). Finally, images were smoothed using a 12-mm-full-width-at-half-maximum Gaussian kernel to increase signal to noise ratio and to minimise the effects of individual variations in gyral anatomy [15]. These adjusted measures were subject to statistical analysis. Voxels associated with the motor task were identified by using the General Linear Model approach for the time series data [16]. We defined a design matrix comprising contrasts modelling the alternating periods of each motor task using a boxcar reference vector convolved with a hemodynamic response function. Significant group motor task versus rest, between- and within-group differences were determined for all tasks using a fixed-effects model [17]. Voxels were considered significant above the statistical threshold of $p < 0.05$ ($T = 4.55$), corrected for multiple comparisons. Only voxels with a cluster-volume larger than 30 are reported results.

Results

Clinical and demographical data

UPDRS scores significantly improved in all patients subsequent to levodopa treatment (for detailed information see Table 1). There was no significant age difference between the PD (mean age 63.3 ± 6.1 years) and control (mean age 60.6 ± 8.3 years) groups ($p = 0.5$, two sample t-test).

Motor activation in control subjects

Significant activation maxima for the comparison between movement and rest periods were seen in the contralateral primary sensorimotor cortex (SM1), in the lateral premotor cortex, the SMA, and in the ipsilateral cerebellum (see Table 2 and Fig. 1A).

Table 2 Group comparison for right hand movements versus rest in controls, PD patients ON and OFF medication

Cortical region	BA	x	y	z	Z-score
Controls					
L primary sensorimotor	3/4	−40	−25	60	9.69
SMA proper	6	−4	−20	56	8.69
R lateral premotor	6	32	−24	68	7.80
L lateral premotor	6	−60	−20	40	6.28
	6	−60	4	20	5.63
	6	−56	−4	44	5.56
R cerebellum		20	−52	−44	8.32
PD OFF					
L primary sensorimotor	3/4	−26	−28	60	9.75
SMA proper	6	−4	−12	60	9.02
L lateral premotor	6	−60	8	6	8.47
R lateral premotor	6	36	−12	60	8.48
	6	56	16	−8	7.44
R inferior parietal	40	64	−24	20	8.17
	40	48	−36	48	8.16
R superior cerebellum		16	−56	−28	8.86
		4	−68	−20	8.68
L superior cerebellum		−28	−64	−32	8.23
PD ON					
L primary sensorimotor	3/4	−40	−28	60	9.68
SMA proper	6	0	−8	64	9.09
L lateral premotor	6	−60	4	6	8.28
R lateral premotor	6	32	−12	64	8.06
R inferior parietal	40	64	−28	24	7.64
	40	48	−40	52	7.36
R superior cerebellum		20	−56	−28	8.41
		4	−68	−20	8.20
L superior cerebellum		−24	−68	−32	7.61

MNI x, y and z coordinates and Z-scores are shown; $p < 0.05$, corrected; extent threshold 30 voxels; *R* right, *L* left, *SMA* supplementary motor area, *BA* Brodman area

Motor activation in PD patients in OFF and ON condition

Significant activation maxima for comparison between movement versus rest were seen in the contralateral SM1, in the lateral premotor cortex, in the right inferior parietal cortex, the SMA, and in the ipsilateral and contralateral superior cerebellum in patients before (OFF) and after initiation of dopaminergic medication (ON) (see Table 2 and Figs. 1B and C).

Within group comparison: PD patients OFF vs ON condition

Applying a fixed model analysis and a corrected threshold of $p < 0.05$, significant relatively increased activation for comparison between PD patients in the OFF condition versus the ON condition was noted in the left supe-

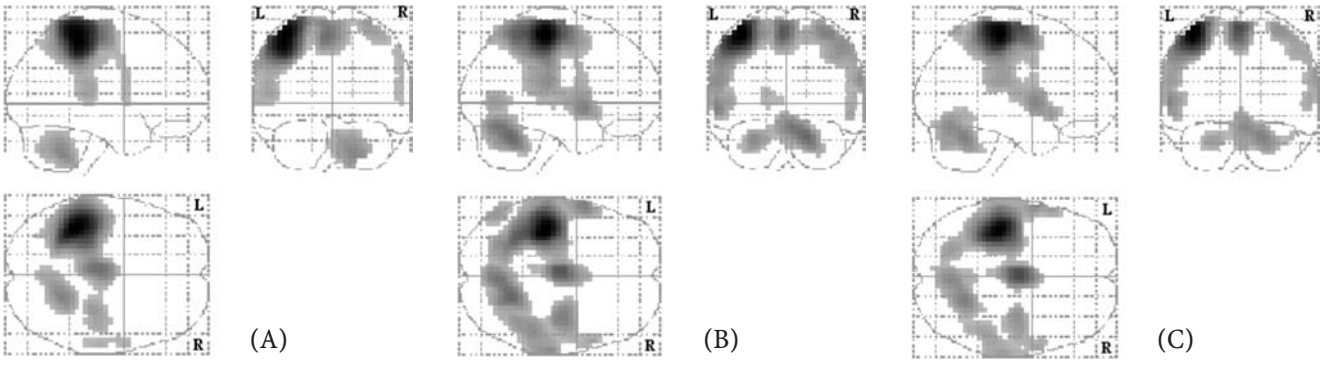

Fig. 1 Group analysis of motor activation induced by simple self-initiated right hand movements in healthy controls (**A**), patients with PD in the OFF (**B**), and in the ON condition (**C**) (*p < 0.05* corrected, extent threshold 30 voxels). BOLD signal increases are displayed within the 'glass brain' for sagittal (*upper left*), coronal (*upper right*) axial (*lower left*) perspective. *R* right; *L* left

rior parietal cortex and in the right dorsolateral prefrontal cortex. No significant activation increases were observed when comparing PD subject scores from both ON and OFF conditions (see Table 3 and Fig. 2).

Between group comparison: controls vs PD patient in OFF and controls vs PD patient in ON condition

Significant activation increases in PD patients relative to controls ($p < 0.05$, corrected) were observed in the contralateral SM1 and adjoining lateral premotor and parietal cortex, and in the pre-SMA, as well as in the ipsilateral and contralateral superior cerebellum in the PD patients before and after initiation of dopaminergic medication (see Table 4 for details). In addition, activation of the contralateral lateral premotor cortex in PD patients in the OFF condition was noted (Fig. 3A). We also found significantly decreased activation of the bilateral superior parietal areas, as well as in the ipsilateral inferior cerebellum in both conditions in the PD cohort (Fig. 3B).

Table 3 Inter-group comparison for right hand movements between PD patients ON and OFF medication

Cortical region	BA	x	y	z	Z-score
PD OFF > PD ON					
R DLPFC	9	24	0	64	5.87
	9	32	4	56	5.71
	9	40	0	40	4.82
L superior parietal	7	−32	−52	60	7.01

MNI x, y and z coordinates and Z-scores are shown; $p < 0.05$, corrected; extent threshold 30 voxels; *R* right; *L* left; *SMA* supplementary motor area; *BA* Brodman area; *DLPFC* dorsolateral prefrontal cortex

Discussion

To our knowledge, this is the first fMRI study to investigate temporally self-initiated simple hand movements in de novo patients with idiopathic Parkinson's disease. The main finding is a relatively increased BOLD response of the pre-SMA in patients with early, drug-naive PD before and after initiation of dopaminergic medication compared with healthy age-matched controls while performing simple temporally self-initiated hand movements. This finding indicates a contribution of the pre-SMA in the pathology and in the overall clinical presentation of PD.

Supplementary motor area

The deficit of self-initiated timing of movements in PD patients and its improvement by the means of timing cues is well recognised (see above). Investigations involving humans and animals indicate a major role of the SMA regarding the internal generation of movements. While the pre-SMA has reportedly shown relatively increased activation during the performance of temporally self-initiated [10, 23] and complex movements [2], the SMA proper is believed to have a motor executive function in healthy humans [2, 36]. Moreover, studies in monkeys revealed that lesions in the SMA elicit a more decreased performance of temporally self-initiated sequential movements than of externally cued movements [7, 37].

While we revealed a relatively increased activation of the pre-SMA in early PD during the performance of temporally self-initiated simple hand movements, other studies have described a decreased activation of the SMA proper employing timing cues [3, 6, 19, 22, 27, 33]. It is important to note that most of these studies applied self-initiated movements in respect to freely chosen directions.

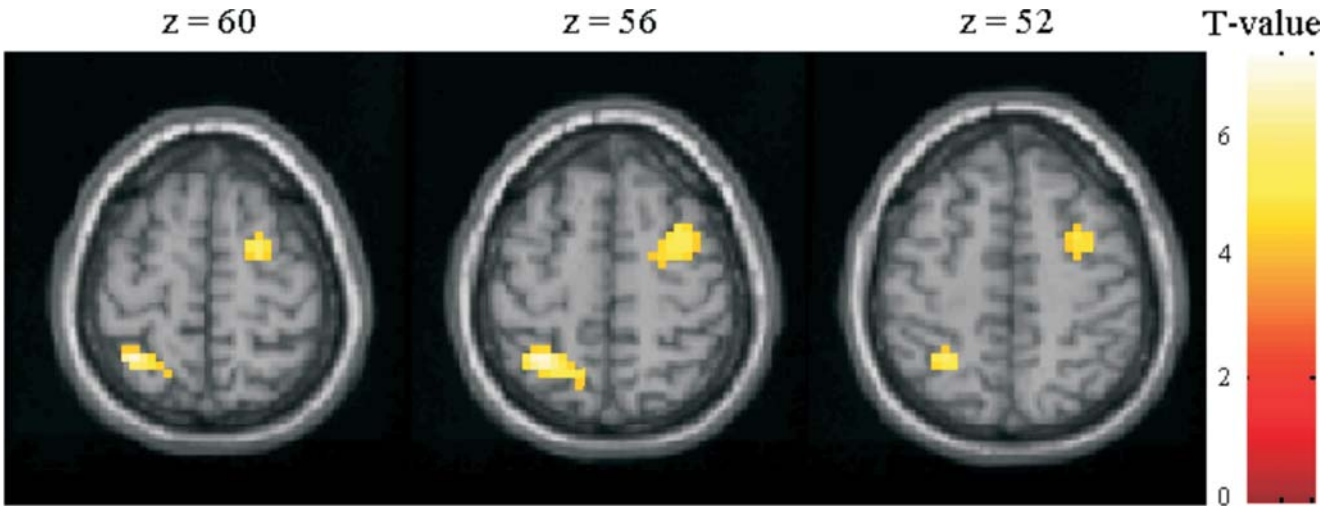

Fig. 2 Within-group analysis for the comparison between PD patients in the OFF and in the ON condition showing areas with significantly increased activation ($p < 0.05$ corrected, extent threshold 30 voxels). Color coded T-values are displayed onto three axial slices of the normalised T1-weighed template image provided by SPM (neurological orientation)

Therefore, the application of self-initiation in respect to movement selection and movement timing appears to elicit different effects within the mesial premotor areas.

Our finding of increased pre-SMA activation is in agreement with the results of Sabatini and colleagues (2000) who investigated self-initiated complex sequential finger movements in PD patients [31]. They interpreted this finding in association with the high complexity of their motor task. However, our motor paradigm consisted of very simple hand movements only. Therefore the relatively increased pre-SMA activation in PD patients compared with controls is more likely to be an effect of the temporal self-initiation of movements.

According to the motor loop of the basal ganglia model, the dopaminergic deficit in PD leads to an increase of the indirect pathway [1]. The resulting disinhibition of the subthalamic nucleus induces an increased inhibition of the basal ganglia output structures (internal segment of the globus pallidus and the substantia nigra pars reticularis) to the thalamus. Consequently, there is a diminished activation of thalamo-cortical connections that in turn cause a reduced motor function. Our finding of increased pre-SMA activation might represent a compensational activation of ancillary cortical pathways to ensure adequate motor function despite the existing deficit. The presence of timing cues, however, might not require the increased activation of the pre-SMA [3, 6, 19, 22, 27, 33].

Increased activation of the pre-SMA has also been shown as part of the PD-related changes of motor learning using PET [4, 26]. However, an effect of learning in our study design is unlikely, as all subjects over-learned the motor task before scanning.

Not in agreement with our findings are earlier PET studies using temporally self-initiated movements, which did not show an increased activation of the SMA in PD patients compared with control subjects [21, 28].

This might partially be attributed to the longer disease durations and to the progressed disease stages of the patients investigated in these studies [21, 28]. In patients with early PD, the pre-SMA might still be able to compensate for dopaminergic deficiency by activating additional surrounding areas. This ability might be lost in later disease stages. Furthermore, the region of interest-based (ROI) data analysis approach employed formerly could have contributed to their findings. ROIs incorporating SMA proper and pre-SMA [28] could have resulted in an extinction effect of increased and decreased activity in these areas. The application of a voxel-based analysis using statistical parametric mapping (SPM), as used in our study, allows for the differentiation of different parts of the mesial frontal cortex.

The finding of altered mesial premotor function in early PD patients during temporally self-initiated movements supports the potential functional contribution of these areas in the disease pathology of PD. In accordance with the clinical finding of improvement of motor performance to timing cues, this finding underscores the importance of further investigations regarding the effect of temporal external and internal cuing in PD patients.

Cerebellum

To our knowledge, this is the first fMRI study to investigate cerebellar activation in PD patients. Previous stud-

Table 4 Between-group comparison for right hand movements between controls and PD patients ON and OFF medication

Cortical region	BA	x	y	z	Z-score
Controls < PD OFF					
L primary sensorimotor	3/4	−40	−20	56	8.02
	3/4	−52	−24	36	6.05
Pre-SMA	6	0	4	60	7.23
R lateral premotor	6	36	−8	60	7.51
L inferior parietal	40	−60	−20	20	5.51
R superior parietal	7	16	−72	56	6.81
L superior cerebellum		−28	−64	−28	7.13
R superior cerebellum		4	−68	−20	7.77
		12	−60	−24	7.24
Controls > PD OFF					
L superior parietal	40	−40	−40	48	7.90
	40	−40	−44	60	7.67
	7	−36	−44	68	7.67
	7	−48	−64	44	7.27
	7	−40	−76	32	4.56
R superior parietal	2	28	−32	64	7.04
	2	12	−24	60	5.62
	7	28	−44	72	6.18
R inferior cerebellum		16	−48	−48	7.46
Controls < PD ON					
L primary sensorimotor	3/4	−32	−16	64	7.43
Pre-SMA	6	0	4	64	7.97
R superior cerebellum		4	−68	−16	7.17
		16	−68	−24	5.84
L superior cerebellum		−20	−72	−28	6.73
Controls > PD ON					
L superior parietal	7	−36	−48	64	8.29
	7	−40	−40	44	8.12
R superior parietal	2	28	−28	68	7.50
R inferior cerebellum		16	−48	−48	7.79

MNI x, y and z coordinates and Z-scores are shown; $p < 0.05$, corrected; extent threshold 30 voxels; *R* right; *L* left; *SMA* supplementary motor area; *BA* Brodman area

ies were limited to partial volume scans and therefore focused on the SM1 and prefrontal cortical areas only. ROI-based analysis of perfusion PET revealed relatively increased activation of the ipsilateral cerebellar hemisphere during hand movements in akinetic parkinsonian patients [29]. Our results extend this previous report of cerebellar motor activation in PD patients showing an increased bilateral superior cerebellar and an ipsilateral decreased inferior cerebellar activation in comparison to controls. Such changes in cerebellar motor activation in PD patients may signify an attempt to compensate for the malfunctioning motor loop [1] by utilising alternative motor pathways as the cerebellum.

Activation in other cortical areas

Our study showed relatively increased activation of the contralateral SM1 in PD patients before and after the administration of levodopa. These results confirm previous reports of relatively increased activation of the contralateral SM1 using fMRI in PD patients [19, 31]. As discussed in these publications, this increase might account for an attempt to compensate for the impaired function due to malfunction of the basal ganglia. The failure to show relatively increased ipsilateral activation in the SM1 in PD as shown in other fMRI studies [19, 31] and to reveal changes in the prefrontal cortex might be explained by the simplicity of our motor task. While ipsilateral activation of the sensorimotor area in healthy subjects has been shown to occur with more complex paradigms [24, 34], the prefrontal cortex is thought to be involved in the cognitive planning of movements [38].

Relatively increased bilateral lateral premotor as well as relatively increased and decreased parietal cortex activation were noted in concordance with other fMRI [19, 31] and PET studies [5, 33]. These activation changes are thought to signify a compensatory mechanism for the malfunction of the striatofrontal projections using the lateral premotor and parietal areas.

Limitations

We employed a fixed-effect analysis to analyze differences between conditions and groups. This kind of analysis is reportedly useful in studies using smaller sample sizes as in the current investigation [17]. Fixed-effect analysis reduces the effects of freedom and shows therefore a higher sensitivity than random-effects model. However, a fixed-effect analysis assumption can only be made about "typical" changes of the particular population from which the sample was collected.

We are aware that visual observation does not measure the exact physiological parameters of power, amplitude and frequency. However, as subjects were trained to perform the task in a similar pattern, and visual inspection ensured an accurate task performance, possible differences should only be minor. Although studies have shown correlations of force [9] as well as movement frequency [32] on the fMRI signal in sensorimotor areas, significant differences can only be observed for substantial changes in power and frequency. Therefore, possible minor changes in our study should not account for the significant differences between the groups nor between the OFF and ON condition.

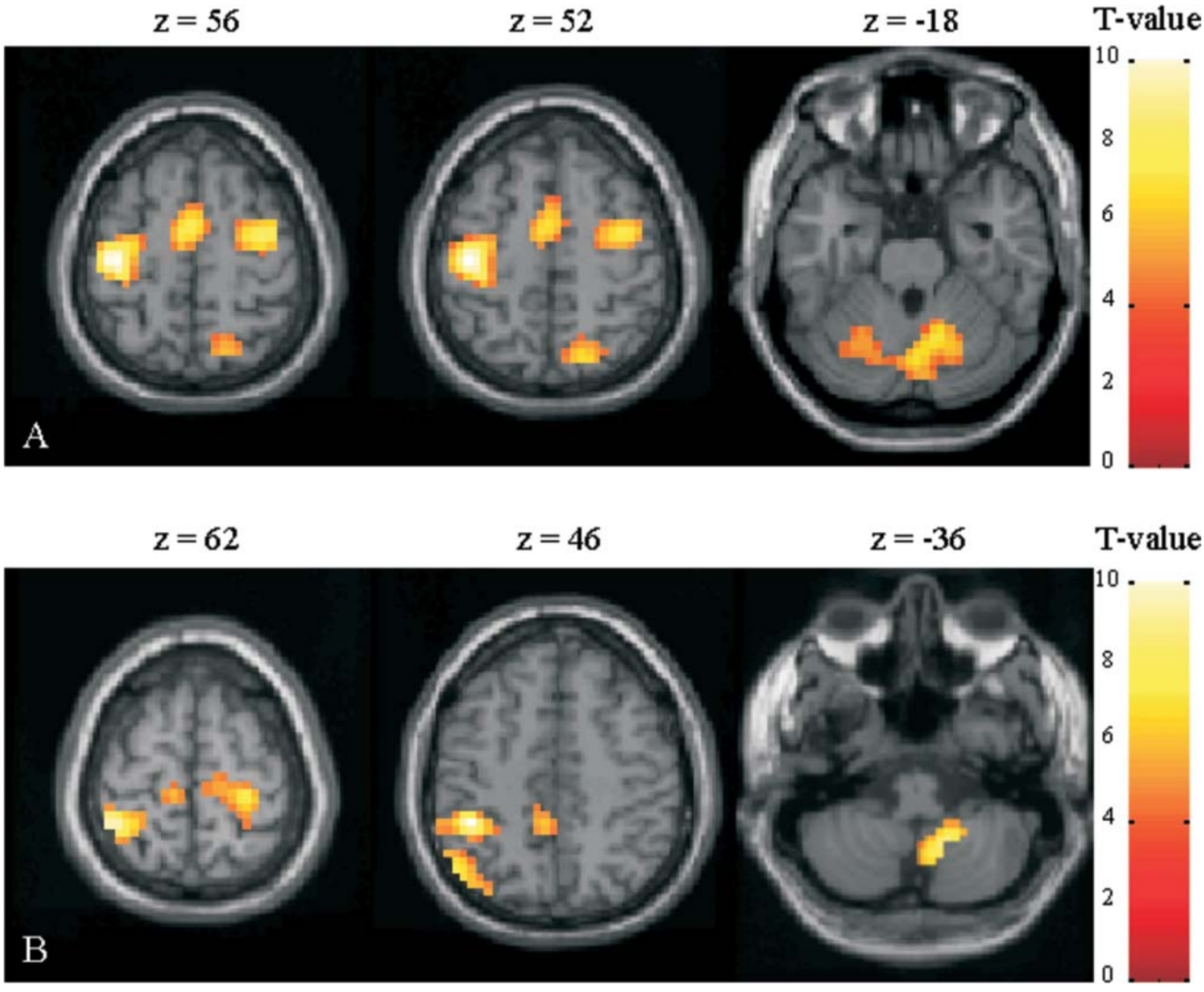

Fig. 3 Between-group analysis for the comparison between PD patients in the OFF condition and healthy age-matched control subjects showing areas with significant increased (**A**) and decreased activation (**B**) ($p < 0.05$ corrected, extent threshold 30 voxels). Colour coded T-values are displayed onto three axial slices of the normalised T1-weighed template image provided by SPM (neurological orientation)

Summary

In summary our data revealed relatively increased activation of the pre-SMA in early de novo PD patients compared with control subjects while performing simple temporally self-initiated hand movements. These findings indicate the importance of the pre-SMA in the generation of temporally self-initiated movements and its contribution to the clinical presentation of PD. In addition, this is the first fMRI study to describe motor activation of the cerebellum in PD patients. Relative increased activation of the ipsilateral cerebellum was noted, and to a lesser degree in the contralateral cerebellum, as well as decreased activation of the ipsilateral inferior cerebellum relative to control subjects.

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