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Functional brain changes in early Parkinson's disease during motor response and motor inhibition

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Abstract

Motor impairment represents the main clinical feature of Parkinson's disease (PD). Cognitive deficits are also frequently observed in patients with PD, with a prominent involvement of executive functions and visuo-spatial abilities. We used event-related functional MRI (fMRI) and a paradigm based on visual attention and motor inhibition (Go/NoGO-task) to investigate brain activations in 13 patients with early PD in comparison with 11 healthy controls. The two groups did not report behavioural differences in task performance. During motor inhibition (NoGO-effect), PD patients compared to controls showed an increased activation in the prefrontal cortex and in the basal ganglia. They also showed a reduced and less coherent hemodynamic response in the occipital cortex. These results indicate that specific cortico-subcortical functional changes, involving not only the fronto-striatal network but also the temporal-occipital cortex, are already present in patients with early PD and no clinical evidence of cognitive impairment. We discuss our findings in terms of compensatory mechanisms (fronto-striatal changes) and preclinical signs of visuo-perceptual deficits and visual hallucinations.

Keywords: Parkinson disease; Go/NoGo; fMRI; Motor inhibition

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder whose main clinical feature is motor impairment with resting tremor, rigidity and bradikinesia (Gelb et al., 1999). Degeneration of dopaminergic cells in the substantia nigra and ventral tegmental area represents the neuropathological hallmark of PD. This process is typically associated with the presence of characteristic inclusions in the degenerating neurons, the so-called "Lewy bodies". Additional clinical features, such as cognitive impairment and dementia, are also frequently observed in patients with PD (Aarsland et al., 2001; Adler, 2005). Previous behavioural (Farina et al., 2000; Pillon et al., 2003; Zgaljardic et al., 2003) and functional imaging (Cools et al., 2002; Owen et al., 1998; Owen, 2004) studies in PD have predominantly focussed on the investigation of executive functions. Motor inhibition is also an interesting cognitive function to be explored in PD, as it is supported by neuronal circuits which are typically involved by PD pathology. On the basis of functional imaging results obtained in normal subjects using disjunctive tasks, Rubia et al. (2006) suggested that the basal ganglia play a critical role in the processing of response selection and motor inhibition (Rubia et al., 2006). The idea is that the inhibitory motor response is mediated by the fronto-striato-thalamic loop, which includes the inferior prefrontal cortex, the basal ganglia, the thalamus and the cerebellum for inhibitory control, and the anterior and posterior cingulate gyrus for attentional and error-related processes. Previous behavioural studies in patients with early PD and no cognitive impairment reported the presence of deficits to inhibit ongoing reactions (Dujardin et al., 1999; Franz and Miller, 2002; Gauggel et al., 2004). Further investigations, using event-related evoked potentials (ERP) and

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a Go/NoGo paradim, also suggested a selective impairment of inhibitory functions in patients with PD (Bokura et al., 2001, 2005). Despite evidences of behavioural and electrophysiological abnormalities of motor inhibition in PD, the neural substrates of such a dysfunction still remains largely unknown. Functional magnetic resonance imaging (fMRI) is a powerful tool which allows regional brain activation to be measured in subjects when performing tasks which engage specific brain functions. In presence of brain pathology, fMRI has the potential to detect abnormal patterns of brain activation, which indirectly reflect the presence and the distribution of tissue abnormalities These fMRI abnormalities are often detectable before the appearance of clinical manifestations, thus providing information on specific brain dysfunctions at a preclinical stage. In this study we used event related fMRI and a Go/NoGo paradigm to investigate motor response and motor inhibition in patients with early PD. Our principal aim was to assess whether functional abnormalities of the fronto-striato-thalamic neuronal network are already detectable in patients with early PD as preclinical features of impairment of higher level functions.

2. Methods

2.1. Subjects

Fifteen consecutive patients [F/M = 4/11; mean (S.D.) age: 66.5 (6.4) years] attending a specialist neurological clinic and meeting the diagnostic criteria for probable PD (Gelb et al., 1999) were recruited for the present study. All patients were at a mild to moderate stage of the disease, scoring between stages 1 and 2 of the Hoehn and Yahr (H&Y) Scale (Fahn and Elton, 1987). Patients scoring between stages 1 and 1.5 of the H&Y Scale ($n = 8$) had all a right lateralization of symptoms. The remaining patients ($n = 7$) were at stage 2 of the H&Y Scale. Clinical characteristics of each recruited patient are summarized in Table 1. None of them had any report of cognitive problems or any evidence of cognitive deficits in their daily living activities. An extensive neuropsychological battery (see below) was used to exclude any patient who reported any score outside the normal range. Eleven healthy subjects [F/M = 7/4; mean (S.D.) age = 66.9 (5.7) years] matched for age and education with the patients' group were also studied and served as controls. All subjects (patients and controls) were right handed as assessed by the Edinburgh inventory (Oldfield, 1971). Major systemic, psychiatric, and other neurologic illnesses were carefully investigated and excluded in all the studied subjects. Particular attention was used to exclude those patients who experienced visual hallucinations, those who had episodes of severe depression or autonomic failure, those who manifested resistance to dopaminergic drugs. All the included patients were responsive to treatment with antiparkinsonian drugs: L-DOPA ($n = 2$), Dopamine Agonists ($n = 7$), an association of L-DOPA and Dopamine Agonists ($n = 4$). None of them had his/her medication changed over at least 1 month before enrolment. Pharmacological treatment was not modified from previous regime before or during the fMRI investigation for ethical reasons. The mean (S.D.) levodopa equivalent daily dose (LEDD) (Herzog et al., 2003) in the studied population was:178 mg (ranging from 30 to 420). None of them had his/her medication changed over at least 1 month before enrolment. None of the patients was assuming any additional psychotropic drug. Patients' mean (S.D.) motor subset score (OFF medication) at the Unfield Parkinson's Disease Rating Scale (UPDRS) evaluated immediately before scanning was 21.5 (7.24), ranging from 15 to 40. Local ethics committee approval and written informed consent from each subject were obtained before study initiation.

2.2. Neuropsychological assessment

An extensive neuropsychological battery was administered to all subjects by two trained neuropsychologists

Table 1
Clinical characteristics of the cohort of patients with PD enrolled in the study.

Subject no.	Age years	Sex	Diagnosis	Lateralization	H&Y score	Treatment	LEDD
1	72	F	Probable PD	Bilat.	2	L-DOPA	400
2	65	M	Probable PD	Right	1	DA	54
3	69	F	Probable PD	Right	1	DA	50
4	60	M	Probable PD	Bilat.	2	L-DOPA + DA	450
5	72	M	Probable PD	Bilat.	2	L-DOPA + DA	354
6	69	M	Probable PD	Right	1.5	L-DOPA + DA	54
7	66	M	Probable PD	Bilat.	2	DA	30
8	67	M	Probable PD	Bilat.	2	L-DOPA	400
9	71	M	Probable PD	Right	1.5	DA	100
10	67	M	Probable PD	Right	1	DA	50
11	67	M	Probable PD	Right	1.5	DA	300
12	71	M	Probable PD	Right	1	DA	54
13	67	M	Probable PD	Bilat.	2	L-DOPA + DA	420
14	59	F	Probable PD	Right	1	DA	30
15	78	F	Probable PD	Bilat.	2	L-DOPA	400

DA = Dopamine Agonists; M = male; F = female; H&Y = Hoehn and Yahr Scale; LEDD = Levodopa equivalent daily dose. Diagnosis has been defined according to Gelb's criteria (Gelb et al., 1999).