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Finger dexterity deficits in Parkinson's disease and somatosensory cortical dysfunction

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ABSTRACT

Introduction: The patho-physiological basis for finger dexterity deficits in Parkinson's disease (PD) is controversial. Previously, bradykinesia was regarded as the major mechanism. However, recent research suggested limb-kinetic apraxia as an important component of impaired fine motor skills in PD. In contrast to bradykinesia, limb-kinetic apraxia only marginally responds to dopaminergic treatment. Here we investigate the novel hypothesis that the dexterity deficits are related to an intrinsic dysfunction of primary somatosensory cortex (S1), which is not reversible by dopaminergic medication.

Methods: Applying a standard and approved dexterity task (coin rotation), brain activation networks were investigated using functional magnetic resonance imaging in PD patients both ON and OFF medication and matched healthy controls.

Results: PD patients both ON and OFF medication showed impaired S1 activation relative to controls ($p < 0.05$; region of interest based analysis). The impaired S1 activation remained unchanged by dopaminergic medication. Despite the considerable clinical deficit, no other brain area showed impaired activation. In contrast, structures of the basal ganglia – motor cortex loop responded to dopaminergic medication. Behaviorally, dexterity performance both ON and OFF was significantly ($p < 0.05$) reduced relative to controls.

Conclusions: Our results provide first evidence that dexterity deficits in PD are related to an S1 dysfunction which is insensitive to dopaminergic treatment.

1. Introduction

Impaired dexterity represents a core symptom of Parkinson's disease (PD). Traditionally, it has been attributed to bradykinesia. Bradykinesia per se responds to dopaminergic therapy. Due to poor dexterity improvements despite dopaminergic therapy, a second source of dexterity deficits was previously suggested: limb-kinetic apraxia (LkA) [1,2]. In general, apraxia is regarded as situated at the interface between cognitive and motor processes [3,4]. Specifically, LkA is defined as a "loss of deftness with a decrease in the ability to correctly perform independent but coordinated finger movements" [5]. The underlying basis for this kind of dexterity deficit, however, is poorly understood and subject to different hypotheses [1].

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Recent literature regarding somatosensory processing deficits in PD (for review see Ref. [6]) indicates that the primary somatosensory cortex (S1) might be critically implicated in dexterity deficits via disturbed sensorimotor integration. The general importance of S1 for dexterity tasks has also been demonstrated by functional imaging studies showing more S1 activation with movements requiring more dexterity (healthy subjects: [7,8]). Concerning PD, Lee et al. [9] found a correlation of discriminative cutaneous sensory dysfunction with impaired coin rotation (CR) performance (but not with bradykinesia). A postcentral dysfunction is also well-documented in patients with LkA as a symptom of a corticobasal syndrome [10]. Furthermore, clumsiness of finger movements was associated with cerebrovascular lesions of S1 and cooling of S1 in monkeys [11,12]. Related to this literature, a recent functional MRI (fMRI) study of PD patients without (OFF) medication showed decreased S1 activation during a coin rotation task. The authors postulated intrinsic S1 dysfunction as the dominant pathophysiology of dexterity deficits in PD [13].

However, considering the strong interplay between S1 and motor areas, it was recently suggested that somatosensory deficits in PD may be associated with an altered basal ganglia – supplementary motor area (SMA) interplay, leading to deficient S1 input from the pre-SMA [6]. This model suggests a primary dysfunction of neuronal networks with the consequence of compromised S1 function. Some behavioral studies support this network model by reporting improved somatosensory performance after improvement of basal ganglia-SMA function due to dopaminergic therapy. Therefore, an unresolved key issue for understanding PD dexterity deficits is whether restoring the basal ganglia – cortex loops by dopaminergic medication also improves S1 activation [14]. If so, S1 deficits could just be an epiphenomenon resulting from altered sensorimotor network performance. In this case, persisting dexterity deficits despite improved S1 activation would argue against S1 dysfunction as the dominant pathophysiology for limb-kinetic apraxia. In contrast, if S1 dysfunction is intrinsic, it should not respond to dopaminergic therapy and persist despite improvement of the basal ganglia – cortex loops. To provide an answer for this critical issue concerning LkA, we performed an fMRI study on dexterity specific S1 modulation and the effects of dopaminergic medication, since it is known to improve functional activity of motor networks and bradykinesia [15]. As yet, the literature on somatosensory cortex response to dopaminergic therapy only consists of studies examining somatosensory-evoked potentials in PD, providing conflicting results [6].

2. Material and methods

2.1. Participants

14 right-handed PD patients (UK-Brain-Bank-criteria for PD) and 14 right-handed healthy controls participated (see Table 1 for inclusion/exclusion criteria and Table 2 for demographic data). Patients with tremor-predominant PD were not included in the current study. Clinical examination showed that all participants were devoid of somatosensory impairment (unremarkable thermesthesia and nociception, as well as kinesthesia, pallesthesia, graphesthesia and two-point discrimination, compare [16]). Those somatosensory tests usually provide pathological results in patients suffering from circumscribed lesions of the somatosensory cortex. Pentagon drawings of Mini-Mental-State-Examination tests were unremarkable for all participants. The latter two findings excluded a bias due to impaired somatosensory and visuospatial function. The motor impairment, daily levodopa dose equivalent of our PD cohort and the lack of a correlation of coin rotation with disease duration were comparable to the previous studies [1,2,16] (see Table 2). The study protocol received prior approval by the local ethics committee (Medical University of Vienna). All subjects provided written informed consent. The work has been carried out in accordance with the Declaration of Helsinki.

2.2. Task

The experimental evidence of 2 independent categories of motor dysfunction in PD (i.e. a dexterity deficit and a bradykinetic deficit) is based on previous work comparing coin rotation and finger tapping tasks [1,2,13]. We used this well-established setup to extract dexterity specific fMRI signals, thereby focusing on the brain areas responding to increased dexterity demands. The setup allowed the minimization of signal contributions related to elemental motor functions (which are sensitive to bradykinesia).

Table 1
Inclusion and exclusion criteria.

	14 mild to moderate PD Patients	14 Healthy controls
Inclusion criteria	Right-handed, right-dominant parkinsonism subjective impairment of dexterity H &Y I-III (OFF/ON) Age 18–85 years No motor fluctuations	Normal neurological and psychiatric status
Exclusion criteria	Relevant pathologies (MRI) History of 2nd neurological illness significant head tremor Disabling rest/action tremor (UPDRS III action tremor > 2) History of psychosis MMSE ON <26	History of CNS disease 1st grade relative with primary movement disorder

MMSE: Mini-Mental-State-Examination; UPDRS: Unified Parkinson's Disease Rating Scale; CNS: Central Nervous System; MRI: Magnetic Resonance Imaging; PD: Parkinson's Disease; H&Y: Hoehn and Yahr stage.

Each patient was investigated two times, OFF and ON medication. Both intra-individual scans were performed within 14 days (minimum distance 3 days). 7 patients underwent the first experiment ON medication, the other 7 patients started with the first experiment OFF medication. The assignment to these two groups (performing OFF or ON first) was performed by the investigators by random (no specific computer software). Experiments in the OFF condition were performed at least 12 h (48 h with extended-release preparations) after the last PD medication. ON state was accomplished by application of the usual individual doses of anti-parkinson medication in our PD patients devoid of motor fluctuations. UPDRS (Unified-Parkinson's-Disease-Rating-Scale) motor score was assessed immediately before each fMRI scan. All experiments in patients were performed in the morning.

The clock-wise flipping of an MR-compatible wooden ring (diameter 25 mm) along the horizontal axis with the first three fingers of the *right* hand served as the target task (CR). Performance on a coin rotation task has been demonstrated as a useful marker for dexterity deficits in PD populations [1,2]. The number of coin turns (180° flips) per task period was counted. One of the authors was standing right next to the MR scanner bed throughout the experiment. This person counted the number of coin turns. To generate a maximum challenge of dexterity specific brain activation and control for variable individual performance limits, the instruction was to "flip the coin as fast as possible". CR performance was hence balanced according to maximum effort with the rationale to challenge brain areas implicated in CR performance and maximize fMRI signal changes specific for dexterity. Another rationale was the fact that different levels of effort cause different levels and different locations of brain activation [17]. Participants could not see the hand performing the action. CR was referenced against a highly standardized elemental motor task, which consisted of simple right index finger tapping (FT) at 1 Hz (self-paced, instruction: "tap index once per second"). This low FT frequency is well accomplishable even for patients OFF medication, and it avoids fatigueing as a confounding variable during faster FT [18]. Beginning and end of CR and FT were indicated by visual cues (a right

Table 2
Demographic and behavioral data.

	Patients OFF	Patients ON	Controls	Difference
Age	60.6 ± 11.8		57.4 ± 9.8	*p = 0.44
Age at PD onset	54.1 ± 11.9			
Disease duration (years)	6.6 ± 4.7			
Female/male	6/8		5/9	
Levodopa equivalent (mg/d)	850 ± 400			
No. Patients H&Y 2/2.5/3	6/7/1	9/5/0		
UPDRS III	28.9 ± 12.8	21.6 ± 8.1		p < 0.05
Coin flips per 20 s	12.8 ± 5.9	14.2 ± 6.7	–	p < 0.05
	12.8 ± 5.9	–	26.4 ± 1.9	p < 0.001
	–	14.2 ± 6.7	26.4 ± 1.9	p < 0.001
Finger taps per 20 s	21.5 ± 3.4	20.4 ± 2.3	19.8 ± 2.1	p = 0.237

Data as mean ± standard deviation. See Section Results for particular statistical tests. UPDRS: Unified Parkinson's Disease Rating Scale; H&Y: Hoehn and Yahr stage; *unpaired t-test.

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