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# Imaging movement-related activity in medicated *Parkin*-associated and sporadic Parkinson's disease☆

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ABSTRACT

Treatment-related motor complications such as dyskinesias are a major problem in the long-term management of Parkinson's disease (PD). In sporadic PD, a relatively early onset of the disease is known to be associated with an early development of dyskinesias. Although linked with early onset, patients with *Parkin*-associated PD often show a stable long-term response to dopaminergic therapy without developing treatment-induced motor complications. Therefore, we reasoned that this difference in vulnerability to develop dyskinesias under long-term dopaminergic therapy may be associated with differences in movement-related activation patterns in *Parkin*-associated compared to sporadic PD. To test this hypothesis, medicated non-dyskinetic patients with either *Parkin*-associated or sporadic PD underwent functional magnetic resonance imaging (fMRI) while performing externally specified or internally selected movements. Patients with *Parkin*-associated and sporadic PD showed no difference in movement-related activation patterns. Moreover, the covariates 'age' and 'disease duration' similarly influenced brain activation in both patient groups. The present finding suggests that a stable long-term motor response in some patients with *Parkin*-associated PD may not be related to differences in cortical recruitment. In conclusion, our findings corroborate a substantial pathophysiologic overlap between *Parkin*-associated and sporadic PD and lend further support to the notion that *Parkin*-associated PD is a suitable genetic model for sporadic PD.



## 1. Introduction

The vast majority of cases of sporadic Parkinson's disease (PD) are considered to be caused by an interaction of multiple genetic and environmental (possibly neurotoxic) factors. In recent years, several genes have been identified that are associated with familial PD [1]. Mutations of the *Parkin* gene are one of the most common monogenic causes of early-onset PD. Homozygous and compound heterozygous carriers of *Parkin* mutations inevitably develop PD. While there are no distinct clinical features which allow differentiating PD patients with and without a mutation in the *Parkin* gene [2,3], some 'red flags' point towards a possible monogenic cause. For example, a relatively early onset of symptoms and a stable, long-term response to levodopa treatment-induced motor complications have both been attributed to *Parkin*-associated PD [4]. In sporadic PD, however, a relatively early onset of disease is associated with an increased frequency of treatment-induced motor complications, such as dyskinesias [5]. This discrepancy suggests a pathophysiological difference between *Parkin*-associated and sporadic PD that may lead to differences in movement-related brain activity in the medicated state.

We used functional magnetic resonance imaging (fMRI) to study whether chronic dopaminergic medication in non-dyskinetic patients with early-onset sporadic PD and *Parkin*-associated PD results in differential regional movement-related cortical recruitment. Studying patients before they might eventually show signs of dyskinesia enabled us to test for differences in cortical recruitment due to a distinct vulnerability to develop dyskinesias in one group. Moreover, this approach prevents the confound of differences in

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motor performance due to emerging dyskinesias. To this end, patients performed sequential finger movements during fMRI while they continued to take their regular dopaminergic medication. Since age, disease duration and dose of dopaminergic seem to influence the occurrence of dyskinesias [5], we further investigated the influence of those covariates on regional movement-related cortical activity.

We tested two alternative hypotheses. Given a substantial clinical and pathophysiologic overlap between *Parkin*-associated and sporadic PD, one might expect no or only minor differences in task-related neuronal activity and covariation with age and disease duration between the patient groups. This outcome would support the role of *Parkin*-associated PD as a model for sporadic PD. On the other hand, if long-term response to dopaminergic drugs results in regional differences in motor-related cortical activity, this would indicate pathophysiological differences and, thus, challenge the usefulness of *Parkin*-associated PD as a human genetic model for sporadic PD.

## 2. Materials and methods

### 2.1. Participants

Twenty PD patients participated in the study. Nine patients were identified as symptomatic carriers of a *Parkin* mutation (mean age: 48.6 ± 10.2 years; mean disease duration: 11.1 ± 9.7 years; 3 women). Eleven individuals were patients with sporadic PD without *Parkin* mutation (mean age: 51.4 ± 4.0 years; mean disease duration: 12.6 ± 3.4 years; 6 women). Only patients without history of dyskinesias were included in the study. Both patient groups continued their regular dopaminergic medication on the day of the experiment. Clinical status of parkinsonism was assessed by two independent investigators who were blinded with respect to mutational status and medication. The investigators also looked for signs of dyskinesia. None were found, although dyskinesia was not formally rated. We also studied ten age-matched healthy controls (mean age: 50.0 ± 8.7 years; 5 women) without *Parkin* mutation. All participants gave their written informed consent to participate. The study was approved by the local Ethics committee.

Clinical and genetic details of each patient are listed in Table 1. Age, disease duration, daily levodopa-equivalent dose (LED), and total motor scores of the United Parkinson's Disease Rating Scale 'off' dopaminergic medication (UPDRS off) did not differ significantly between *Parkin* mutation carriers and non-carriers (*Parkin*-associated PD: 20.9 ± 13.8; sporadic PD: 22.8 ± 12.8).

**Table 1**
Clinical and genetic data of the patients with Parkinson's disease (PD). In patients with a *Parkin* mutation the amount and loci of the mutated alleles are stated.

| Code | Mutated alleles | Locus | Gender | Age | Age of onset | UPDRS off | LED |
|---|---|---|---|---|---|---|---|
| *PD patients with* PARKIN *mutation* | | | | | | | |
| P01 | 2 | delEx7/delEx7 | female | 41 | 35 | 5 | 250 |
| P02 | 1 | del1072 | female | 39 | 38 | 4 | 0** |
| P03 | 1 | 211C > *T* | female | 41 | 33 | 45 | 600 |
| P04 | 2 | del1072/del1072 | male | 54 | 46 | 33 | 75 |
| P05 | 2 | delEx7/del1072 | male | 74 | 64 | 31 | 1150 |
| P06 | 1 | delEx2 | male | 44 | 37 | 13 | 250 |
| P07 | 1 | delEx2-5 | male | 48 | 38 | 31 | 863 |
| P08* | 2 | delEx4/924C > *T* | male | 52 | 15 | 18 | 360 |
| P09* | 3 | delEx3-4/duplEx7-12 | male | 44 | 31 | 8 | 275 |
| *PD patients without* PARKIN *mutation* | | | | | | | |
| S01 | 0 | NA | female | 61 | 57 | 6 | 0** |
| S02* | 0 | NA | female | 57 | 47 | 4 | 0** |
| S03 | 0 | NA | female | 50 | 36 | 49 | 661 |
| S04 | 0 | NA | female | 54 | 41 | 30 | 529 |
| S05* | 0 | NA | female | 47 | 31 | 25 | 0** |
| S06 | 0 | NA | female | 52 | 35 | 16 | 315 |
| S07* | 0 | NA | male | 52 | 41 | 9 | 0** |
| S08 | 0 | NA | male | 49 | 35 | 27 | 925 |
| S09 | 0 | NA | male | 49 | 35 | 33 | 1278 |
| S10 | 0 | NA | male | 49 | 38 | 22 | 870 |
| S11 | 0 | NA | male | 49 | 34 | 30 | 947 |

NA, not applicable; UPDRS, Unified Parkinson's Disease Rating Scale, Part III; LED, levodopa-equivalent dose. * Unusually slow progression. P08, S02 and S07: mild asymmetric rigid-akinetic PD; P09 and S05: mild symmetric rigid-akinetic PD. ** No LED conversion available (e.g. amantadine).

### 2.2. Finger-to-thumb opposition task

The task under study has been described in detail in a previous study on non-manifesting carriers of a single heterozygous *Parkin* mutation [6]. During fMRI, a schematic right hand was presented in the centre of the visual field. Participants were asked to perform thumb-to-finger movements with their right hand when a red dot appeared at the tip of one or four fingers of the schematic hand. In the externally guided task (referred to as EXT task), only a single fingertip was labeled with a red dot, thereby determining the movement. In the internally guided task (referred to as INT task), all four fingers were labeled with a red dot and participants had to select one of those fingers for the thumb-to-finger movement. We used an epoch-related fMRI design to ensure a constant cognitive set. Each epoch lasted 24 s 10 epochs of rest alternated with 10 epochs of sequential finger movements (pseudo-randomized order of 5 epochs per task).

### 2.3. Behavioral data acquisition and analysis

Task performance was monitored on-line during fMRI as previously described [6]. Response times were defined as the time between cue presentation and the fingertip touching the thumb. Mean response times were entered into repeated-measures analysis of variance (ANOVA) with the between-groups factor: 'group' (three levels; *Parkin*-associated PD, sporadic PD and healthy controls) and the within-subject factor 'task' (two levels; INT task, EXT task). *P*-values of $<0.05$ were considered significant.

### 2.4. MRI data acquisition and analyses

The scanning procedures and technical features of MRI data acquisition were identical to those previously used [6]. Images were preprocessed and analyzed using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm). The images were spatially realigned, normalized and smoothed with a Gaussian kernel of 12 mm at full-width half-maximum. Within-subject analysis of task-related blood-oxygen-level dependent (BOLD) signal changes used a general linear model with separate regressors for the INT and EXT task [6].

In a first set of analyses, we focused on regional BOLD signal changes that were influenced by the mode of movement selection and group affiliation. To this end, within-subject contrast images were entered into a repeated-measures ANOVA with the factor 'group' (three levels; *Parkin*-associated PD, sporadic PD and healthy controls) and the factor 'task' (two levels; INT task, EXT task). If the ANOVA demonstrated a significant main effect, we performed follow-up *t*-tests to explore the pattern of between-groups differences. To identify movement-related brain activation patterns that were consistently present in all three groups, we applied a step-wise inclusive masking procedure [7]. To avoid any bias towards a positive finding, we report the results for the masking order that gave the lowest *T*-score.

We were particularly interested in factors, that potentially distinguish *Parkin*-associated and sporadic PD. Therefore, we additionally computed three separate multiple regression models using the individual contrast images for either the INT task, the EXT task or the contrast images comparing both tasks (INT vs. EXT task) of all patients as dependent variable. The multiple regression model consisted of four regressors: 'group' [1 = *Parkin*-associated, −1 = sporadic], 'age' (Table 1), 'duration' (Table 1: age − age of onset), 'LED' (Table 1). Contrast images were computed for each covariate, using the appropriate linear contrasts reflecting a positive or negative linear relationship. In addition, we tested for between-group differences in regression (i.e., group-by-covariate interaction).

A statistical threshold of $p < 0.05$ was applied for these analyses. *P*-values were corrected for multiple non-independent comparisons across the entire brain volume using the false discovery rate method as implemented in SPM2. We report the *T*-value and the location of the regional maxima in Montreal Neurological Institute (MNI) stereotactic space.

## 3. Results

### 3.1. Behavior

Patients showed an excellent long-term response to dopaminergic medication with total motor UPDRS scores ranging from 3 to 8 before the fMRI session. All participants reported that they performed both thumb-to-finger opposition tasks without any problems. Mean response time was 64 ms shorter when movements were internally selected compared to externally cued movements ($F[(5,47)] = 5.82$; $p = 0.0003$). Response times were similar among groups irrespective of the type of task. This was confirmed by the ANOVA which showed no differences in mean response time among groups and no task-by-group interaction ($p > 0.1$).