



## The association between Parkinson's disease symptom side-of-onset and performance on the MDS-UPDRS scale part IV: Motor complications



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### ABSTRACT

**Introduction:** Parkinson's disease (PD) is a neurodegenerative condition associated with aging characterized by loss of dopamine-producing neurons in the substantia nigra pars compacta and a reduction in dopamine levels in the striatum. PD is commonly treated using dopamine-replacement medication called levodopa. Levodopa has decreasing efficacy over time. Periods when levodopa is not effective at controlling symptoms of PD are called “OFF-time” or “medication-related motor fluctuations,” (MRMF). One characteristic of PD is unilateral side of symptom onset. Previous studies have found that side of onset was associated with differential motor and cognitive PD-related symptoms. The main study objective was to examine differences in left and right onset PD patients and OFF-time as measured by the Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) Part IV Sum Score and Part IV item scores.

**Methods:** 64 individuals with mild-moderate PD (age: M(SD) = 68.72 (8.88)), years with PD: M(SD) = 6.61 (5.05); Hoehn and Yahr stage Med (1st, 3rd quartile) = 2.0 (2.0, 3.0) were assessed with the MDS-UPDRS parts I-IV. We conducted two-tailed independent sample *t*-tests to examine the differences between PD patients with left versus right onset.

**Results:** Right onset PD was significantly associated with more overall MRMF ( $p = 0.01$ ), more OFF-time ( $p = 0.04$ ), greater impact of motor fluctuations on daily life ( $p = 0.02$ ) and more complex (unpredictable) MRMF ( $p = 0.01$ ).

**Conclusion:** People with right onset PD have more complications with levodopa treatment. Alternative and/or adjuvant treatments to levodopa may be particularly beneficial for those with right onset PD.

### 1. Introduction

Approximately 1% of adults over 65 years old in the United States, more than 1 million people, have Parkinson's disease (PD). PD is a neurodegenerative disease resulting in tremors, bradykinesia, rigidity and shuffling gait [1]. The neuromechanisms for PD involve degradation of the basal ganglia, particularly the substantia nigra pars compacta (SNpc), resulting in decreased synthesis and release of the neurotransmitter dopamine (DA) and excess cholinergic activity [2]. Although not fatal, PD reduces mobility and quality of life (QOL) for those diagnosed [3].

Disease progression and experience of different motor symptoms

vary greatly between PD patients [4]. For example, approximately 50% of people with PD experience right onset and 50% experience left onset, with some variability [5]. In fact, unilateral symptom onset is a criterion for clinical PD diagnosis [4]. Research suggests that PD patients have different PD experiences depending on which side the symptoms begin. Patients with right side onset have significantly more rapid disease progression of motor symptoms compared to left side onset PD patients [6]. Patients with right side onset of symptoms also showed significantly decreased muscle strength on both sides of the body compared to healthy controls, while left side onset patients showed no differences from controls [7]. Left side onset was found to be associated with extended period of survival after diagnosis, and delayed

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ambulatory impairments (e.g., delayed impaired internal guidance of movement) compared to right onset [8]. Experience of apathy in right side onset was significantly higher than in patients with left onset symptoms [9]. Patients with right onset PD also showed significantly higher levels of novelty seeking than the left onset patients [10]. The causes for these subtle yet significant differences in disease experience by side of onset are not well understood. These differences in PD progression could be important for developing long-term individualized therapeutic treatment plans for PD patients.

Although levodopa is considered the “Gold Standard” for PD treatment, levodopa has decreasing efficacy over time [11]. Medication related motor fluctuations (MRMF) or “OFF-time” refer to periods when the DA replacement therapy does not effectively work to improve PD symptoms. OFF-time is a common yet unpleasant and undesirable symptom for PD patients. In fact, OFF-time is experienced by nearly 75% of all PD patients [11]. Furthermore, OFF-time develops in about 40% of Parkinson's patients within 4–6 years of initiating levodopa treatment [12]. Every year, approximately 10% of all PD patients who previously had no OFF-time and are treated with levodopa will develop OFF-time [12]. These statistics suggest nearly all PD patients eventually develop OFF-time [13]. Other MRMF include dyskinesia and dystonia. Dyskinesia refers to involuntary movements that develop over time in 24–89% of all PD patients who are taking levodopa, while dystonia refers to sustained posturing (such as a prolonged muscle contraction) and can be painful [13]. Understanding factors related to MRMF is important for adequately controlling the symptoms of PD and helping PD patients to have better quality of life (QOL).

Understanding the relationship between PD side of onset and differing response to DA replacement therapy may have implications for treating the symptoms of PD. Given that those with right side onset seem to experience more difficulty overall, we were interested in whether they would also experience more MRMF than those who had left side onset. We conducted a cross-sectional data analysis to explore differences in MRMF and OFF-time between right side and left side onset PD patients. Recognizing differences in progression according to the side of onset and differing responses to DA replacement therapy might allow physicians to tailor treatment for the individual PD patient based on which side their PD symptoms manifested first.

## 2. Methods

The Institutional Review Board at Emory University School of Medicine and the Research and Development Committee of the Atlanta VA approved this work. Participants provided written informed consent before participating. This study included both veteran and non-veteran participants. Veterans with PD were recruited through the VA Informatics and Computing Infrastructure (VINCI) database. Veterans with a code associated with PD diagnosis on the VINCI system were sent a letter from the study team telling them about the study. Other routes of recruitment for non-veteran participants included PD support groups, educational meetings, newsletters and foundation events, physician referrals, word of mouth and outreach events. Interested individuals provided contact information and were contacted later to make an initial appointment for assessment. All paper and electronic data files were coded and de-identified to maintain participant confidentiality.

### 2.1. Participants

All participants were aged 40 and older and had a clinical diagnosis of PD based upon established criteria determined by a board-certified neurologist with specialty training in movement disorders [4]. At the time of diagnosis, individuals must have presented with asymmetric symptoms that included at least 3 of 4 cardinal signs of PD (rigidity, bradykinesia, tremor, postural instability). Only right handed participants were included because some studies have linked handedness to side of PD onset [14]. PD participants must have shown clear

symptomatic benefit (e.g., alleviated rigidity, bradykinesia, and tremor) from antiparkinsonian medications, e.g., levodopa [15]. Participants were in Hoehn and Yahr stages I-IV. Hoehn and Yahr scale is a clinical rating scale, which defines broad categories of motor function in PD (Table 2) [16]. The resulting sample included 64 individuals including 32 individuals who experienced right-side onset of PD and 32 individuals who experienced left-side onset. No genetic assessments for PD were performed, and therefore genetic factors related to PD are unknown for this sample of individuals.

### 2.2. Measures

Participants were evaluated for disease severity with the Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) [17] through a combination of assessments by a qualified and experienced rater blinded to study purposes, and self-reports based on the previous week of symptoms. MDS-UPDRS has four parts. I: Non-motor Experiences of Daily Living (interview and self-report questionnaire); II: Motor Experiences of Daily Living (questionnaire); III: Motor Examination (rated); IV: Motor Complications (interview). Twenty questions are completed by the patient or caregiver. Item-specific instructions are provided. The MDS-UPDRS contains 65 items. Items in each section are summed to obtain the individual's sum score [17]. Higher MDS-UPDRS sum scores indicate greater disease severity.

Part I assesses the non-motor impact of PD on patients' experiences of daily living. There are 13 questions. Part 1A is administered by the rater (six questions) and focuses on complex behaviors. Part 1B is a component of the self-administered Patient Questionnaire and covers seven items on non-motor experiences of daily living.

Part II assesses the motor impact of PD on the patient's experience of daily living. There are 13 questions, and this section is also completed by the patient or caregiver.

Part III assesses the motor signs of PD. This section is administered by a trained examiner wherein the examiner observes the participant performing several motor tasks (i.e. rising from a chair, toe tapping, etc.). The examiner also observes tremor, muscle rigidity, posture, and gait. Participants were tested on all measures while “off” medications (a 12-hour defined “off” period) at a standardized time of day for each of the three evaluations. Participants were observed while “off” medications to avoid dyskinesia, and medication fluctuations that impact functional activity. Trained raters administered measures according to standard procedures. Assessments were videotaped for blinded ratings.

Part IV is delivered in interview format. It is a self-reported indication of MRMF such as dyskinesias, time spent in the off state, functional impact and complexity of fluctuations, and off-state dystonia. Complexity refers to predictability of OFF-time and MRMF, with less predictable OFF state periods considered to be more complex MRMF. For each of six questions, scores from 0 (none) to 4 (severe) are assigned to describe the participants' experiences.

The Edinburgh Handedness Inventory was delivered in interview format. This is a ten-item questionnaire designed to assess handedness by self-report of the preferred hand for carrying out common activities such as writing and drawing, throwing, and using utensils such as a toothbrush, knife, and spoon [18]. Based on the participants' responses, a “laterality quotient” is calculated that indicates which hand is dominant and to what extent the participant prefers to use that hand for common tasks.

#### 2.2.1. Analysis

Independent two-sample *t*-tests were performed to determine differences between right and left side of onset groups on the MDS-UPDRS parts I-IV sum scores and PART IV item scores. Data were analyzed

**Table 1**  
Participant characteristics.

Participant characteristic	Right onset (n = 32)	Left onset (n = 32)	Total (n = 68)
Male (n, %)	21, 32.81%	20, 31.25%	41, 64.1%
Female (n, %)	11, 17.19%	12, 18.75%	23, 35.9%
Age (Mean, SD)	67.06, 8.47	70.38, 9.11	68.72 (8.88)
Years Education (Mean, SD)	16.0, 2.78	16.65, 2.26	16.32 (2.55)
Years with PD (Mean, SD)	6.81, 5.51	6.41, 4.62	6.61 (5.05)
Hoehn & Yahr Score* Med (1st, 3rd qrtile)	2.0, (2.0, 2.5)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
Black/African-American (n, %)	4, 6.25%	6, 9.38%	10, 15.6%
Hispanic or Latino (n, %)	1, 1.56%	0, 0.0%	1, 1.6%
White/Caucasian (n, %)	24, 37.5%	25, 39.06%	49, 76.6%
Multiracial (n, %)	2, 3.12%	1, 1.56%	3, 4.7%
Other Race/Ethnicity (n, %)	1, 1.56%	0, 0.0%	1, 1.6%

\*Hoehn and Yahr Scale:

- 1 = Only unilateral involvement, usually with minimal or no functional disability.
- 2 = Bilateral or midline involvement without impairment of balance.
- 3 = Bilateral disease, mild to moderate disability with impaired postural reflexes; physically independent.
- 4 = Severely disabling disease; still able to walk or stand unassisted.
- 5 = Confinement to bed or wheelchair unless aided.

using Statistical Analysis Software [19]. Alpha was set at 0.05.

### 3. Results

Our dataset contains information from 64 individuals with PD (right side of onset: 50%). Table 1 shows frequencies for side of symptom onset and other characteristics of the sample. There were 23 women and 41 men in our sample. Right onset participants were, on average, 67.26 years old, had 15.88 years of education, had been living with PD for 7.09 years, and were at Hoehn and Yahr stage 2.19. Left onset participants were, on average, 70.15 years old, had 16.48 years of education, had been living with PD for 6.62 years, and were at HY stage 2.

There is a significant difference in MDS-UPDRS IV sum score between the groups of participants with right onset versus left onset ( $t = 2.93$ ,  $p = 0.01$ ). This result indicates that individuals with right onset PD have greater experiences of MRMF, as compared to individuals with left onset PD. However, we did not find evidence that the non-motor impact of PD on patients' experiences of daily living (MDS-UPDRS Part I), the motor impact of PD on the patient's experience of daily living (MDS-UPDRS Part II), or motor signs of PD (MDS-UPDRS Part III) were significantly different for right vs. left PD onset participants (Table 2).

MDS-UPDRS Part IV itemized differences (dyskinesias, time spent in the OFF state, functional impact and complexity of fluctuations, and off-state dystonia) between participants with right vs left onset are shown in Table 3. Individuals with right onset PD had significantly more OFF-time, including time spent in OFF state (item 3), functional impact of MRMF (item 4), and complexity (unpredictability, item 5) of MRMF, than people with left onset PD. In other words, MRMF were less

**Table 2**  
MDS-UPDRS sum scores by Side of Onset.

MDS-UPDRS parts I-IV	Right onset	Left onset	t-statistic	p-value
Part I Score (Mean, SD)	13.12, 7.13	12.94, 7.42	-0.03	0.97
Part II Score (Mean, SD)	16.09, 8.58	13.91, 9.05	0.63	0.53
Part III Score (Mean, SD)	33.54, 12.36	36.66, 11.02	-1.36	0.18
Part IV Score (Mean, SD)	4.68, 3.80	2.38, 3.00	2.93	0.01*
Total Score (Mean, SD)	67.43, 24.09	66.02, 24.50	-0.04	0.97

\* Significant at the alpha = 0.05 level.

predictable, occurred more often, and had a greater impact on the quality of life of participants who had right onset PD than those with left onset PD. Based on these results, we have evidence to support our hypothesis that Parkinson's patients with right onset are, on average, more impacted by MRMF than left onset PD patients. We found no differences in dyskinesia or dystonia experiences between right and left PD onset patients.

### 4. Discussion

Our findings support the body of research that suggests PD symptom side of onset influences disease progression and experience. Although many existing studies compare PD side of onset with other motor and cognitive variables, this study is, to our best knowledge, the first to look at the associations between MRMF and side of onset. This line of research, together with other studies related to MRMF, should be able to inform and refine treatment of PD and help with improving the lives of individuals with PD through more effective symptom management.

One possible explanation for individuals with right onset PD having significantly more OFF-time, greater functional impact of MRMF, and more complex medication-related motor fluctuations than people with left-onset PD could be unequal distribution of DA receptors in the central nervous system for right and left onset patients. Studies have shown that in the healthy brain there is asymmetrical distribution of DA receptors across brain hemispheres, and that there are higher levels of dopamine in the left than right striatum [20].

The relationship between MRMF and PD symptom side of onset has important clinical and pharmaceutical implications for treating patients with PD. Because there may be less long-term symptom relief from levodopa/carbidopa treatment among individuals with right-onset PD, right-onset PD patients may be better candidates for surgical interventions including DBS earlier on in the disease.

The analysis of the MDS-UPDRS Part IV and side of onset relationship is limited by excluding left-handed participants. The resultant associations found to be present in right-handed individuals may not persist across left-handed individuals due to possible neurological differences in right and left-handed individuals. A study with similar aims of the current study utilizing purposive recruitment to include a balance of right-handed and left-handed participants is needed to explore whether the relationships between OFF-time and side-of-onset persist across the left-handed population.

A strength of this study is that side of onset has not previously been examined as a possible indicator for patient response to DA replacement medication. Our study gives evidence of such relationships and can act as justification for similar lines of research. Additionally, asking the patient which side their PD symptoms began on is straightforward and requires little time. If side of onset can be used as a predictor for patient response to levodopa, then clinicians can easily use this information to help individual patients select the most effective PD therapies.

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**Table 3**  
MDS-UPDRS Part IV items by side of onset.

MDS-UPDRS Part IV Items	Right onset	Left onset	t-statistic	p-value
ITEM 1. Time Spent with Dyskinesia (Mean, SD)	0.31, 0.54	0.22, 0.42	0.78	0.44
ITEM 2. Functional Impact of Dyskinesias (Mean, SD)	0.09, 0.30	0.0, 0.0	1.79	0.08
ITEM 3. Time Spent in OFF State (Mean, SD)	1.06, 0.69	0.56, 0.27	2.15	0.04*
ITEM 4. Functional Impact of Fluctuations (Mean, SD)	1.22, 1.43	0.47, 1.02	2.42	0.02*
ITEM 5. Complexity of Motor Fluctuations (Mean, SD)	1.59, 1.58	0.66, 0.27	2.78	0.01*
ITEM 6. Painful OFF-State Dystonia (Mean, SD)	0.44, 0.84	0.34, 0.65	0.5	0.62

\* Significant at the alpha = 0.05 level.

### Declarations of interest

None.

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