

## Previous Injury and Chronic Pain are Associated with Side of Onset in Parkinson's Disease

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### Abstract

#### Background

Parkinson's disease (PD) motor symptoms are frequently asymmetric and the factors that influence the side of onset are unclear.

#### Objective

To explore whether peripheral injury and associated chronic limb pain may influence the side of onset.

#### Methods

We administered a questionnaire to 128 PD patients in a tertiary movement disorder clinic. Handedness, date and type of limb injury(s) and duration of associated pain, and date and side of onset were ascertained.

#### Results

Sixty-two subjects reported limb injuries prior to the onset of PD symptoms, 30 with and 32 without chronic pain (i.e.,  $\geq 2$  months). There was no association between injury and PD onset side overall ( $p=0.334$ ). In subjects with chronic pain associated with limb injuries, however, side of injuries was associated with the side of PD symptom onset ( $p=0.030$ ).

#### Conclusions

Limb injury with chronic pain may be related to the side of PD symptom onset. Future studies may shed light on the nature of this observation.

**Keywords:** Parkinson's disease; Peripheral limb injury; Side of onset; Handedness

### Introduction

Parkinson's disease (PD) is marked by neuronal loss in the substantia nigra that results in decreased dopaminergic input into the basal ganglia (BG) [1]. PD motor symptoms like bradykinesia, rigidity, resting tremor, and gait difficulties often present asymmetrically [2]. The factors that are associated with or influence side of PD onset are, however, unclear.

Handedness has been investigated as a probable cause for asymmetric onset of PD motor symptoms, and there appears an overall link between dominant hand and PD side of onset [3]. The association, however, only accounts for PD side of onset in 60% of subjects. This suggests that other factors may contribute to the determination of PD onset side.

Peripheral nerve injury is related to several movement disorders such as dystonia, and sometimes associated with laterality [4,5]. It has been proposed that sensory input from peripheral nerve injuries may modulate BG-related brain circuitry, particularly if the injuries were intense and persistent [5]. The current study was designed to explore whether limb injury and associated pain may be related with the side of onset in PD.

### Methods

We conducted a retrospective study on 116 controls and 128 subjects with PD who presented consecutively to a movement disorder clinic between May 1, 2012 and December 31, 2012. Detailed demographic data for the subjects are provided in Table 1. Controls were companions of the subjects. PD diagnosis was confirmed [6] by a movement disorders specialist (XH) who also ascertained the side of symptom-onset via congruent history and physical exam. Initial date of disease onset was obtained through personal subject history, along with age, gender, and handedness. The study was approved by the Penn State Hershey Institutional Review Board and was conducted in accordance with the principles of the Declaration of Helsinki.

Past injury history was obtained via a short questionnaire (Supplementary Table). The questionnaire consisted of six questions regarding previous limb injury serious enough to require medical attention. The interview was conducted by an investigator (IT) blinded to side of PD onset. Arbitrarily, past injuries and pain that persisted  $\geq 2$  months were defined as chronic. Because some subjects may have endured

	Total PD	PD w/o Injury	PD w/ Injury	
			<2 mo	>2 mo
<b>Duration of associated chronic pain</b>				
<b>n</b>	128	64	32	32
<b>Age (mean ± SD, y)</b>	71.0 ± 9.1	70.2 ± 9.3	70.8 ± 10.3	68.1 ± 8.4
<b>Gender (M/F)</b>	80/48	36/28	20/12	24/8
<b>Handedness (R/L/A)</b>	116/11/1	57/6/1	31/1	28/4
<b>Side of onset (R/L/Sym/NA)</b>	76/43/5/4	39/18/4/3	22/10	15/15/1/1

**Table 1:** Description of Parkinson's subjects\*

\*These numbers do not reflect subjects that have been excluded from the analyses. Abbreviations: Mo = month; PD = Parkinson's disease; R/L/A = Right/Left/Ambidextrous; R/L/Sym/NA = Right/Left/Symmetrical/Not applicable.

multiple limb injuries in their lifetime, we developed a system to assess the dominant side of past limb injuries. First, we generated a scoring system to gauge the intensity and duration of pain associated with each injury (Supplementary Table 2). Then, we obtained a composite score of each injury by multiplying the intensity score with the duration score. The dominant injury side was defined as the side with the highest combined score.

We compared demographic and clinical characteristics for the groups by t-test, chi-square test, and Fisher's exact test, as appropriate. The effects of injury and handedness on side of PD onset were evaluated by Fisher's exact tests. The Cochran-Mantel-Haenszel test was used to assess the association between injury and side of PD onset. A two-sided p value of <0.05 was considered statistically significant.

## Results

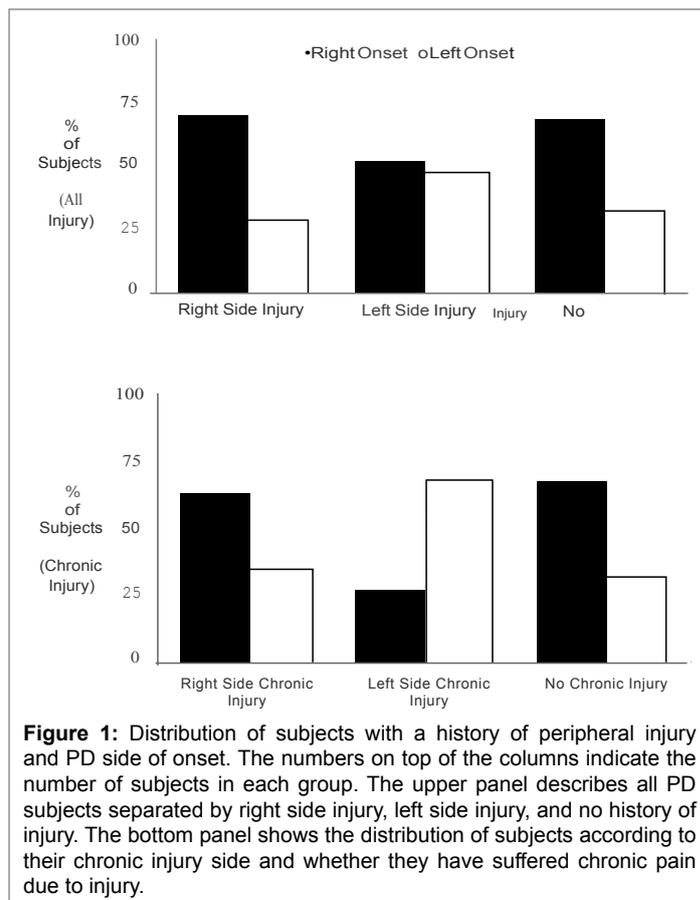
Of the 128 PD subjects, 126 PD subjects were able to answer the limb injury questionnaire. Among them, 62 (49%) subjects experienced injury(s) versus 55 of 116 controls (47%;  $p=0.780$ ). Among the 128 PD subjects, 114 PD subjects had known history of injuries and clear asymmetrical side of onset, and were included in the analysis for the effect of injury on PD onset side.

The side of injury had no significant influence on the side of onset in subjects with both acute and chronic injuries ( $p=0.334$ , Figure 1, top). There was, however, a significant influence of side of injury with chronic pain on PD side of onset, with concordant rates of 64% and 73% for right and left side injury and onset, respectively, ( $p=0.030$ , Figure 1, bottom). After adjusting for handedness, the trend persisted ( $p=0.067$ ).

## Discussion

The factors underlying the asymmetric presentation of PD have puzzled the field. This study explored for the first time the potential relationship between limb injury and PD side of onset. The results do not support the notion that limb injury is associated with PD side of onset; however, chronic pain associated with injury may be linked to the side of PD onset. The latter observation is both novel and intriguing, although the exact nature of the association is unknown.

In the past, animal experiments have shown that peripheral limb injury can modulate brain function [4,7]. Animals subjected to thermal injury have been shown to have reduced movement of the affected limb, and decreased enkephalin content of the globus pallidus, especially after prolonged duration [4]. In addition, peripheral injury also has been implicated in dystonia [4,5,8]. Thus, it is possible that peripheral limb



**Figure 1:** Distribution of subjects with a history of peripheral injury and PD side of onset. The numbers on top of the columns indicate the number of subjects in each group. The upper panel describes all PD subjects separated by right side injury, left side injury, and no history of injury. The bottom panel shows the distribution of subjects according to their chronic injury side and whether they have suffered chronic pain due to injury.

injury may modulate the BG and influence the side of symptom onset of PD. On the other hand, it is well known that PD can affect many non-motor systems. Chronic pain has been known to be part of PD, as many PD patients have reported differential pain [9], and levodopa has been shown to be associated with increased pain threshold in PD [10]. Thus, it is conceivable that higher chronic pain from limb injuries may represent the lower pain threshold in the pre-PD state.

This study is limited by being relatively small scale, retrospective, and the arbitrary categorization of injuries. In addition, we did not account for other conditions associated with chronic limb pain. Nevertheless, this is the first exploration of whether there is a link between chronic pain associated with past limb injury and side of PD onset. The results warrant future studies, and may have important clinical and basic scientific implications.

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## Disclosure of Conflicts of Interest

None of the authors have any to disclose.

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