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The Relationship between Parkinson's Disease Symptom Side-of-Onset, Performance on the Unified Parkinson's Disease Rating Scale Part IV: Motor Complications, and Environmental Exposures

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The Relationship between Parkinson's Disease Symptom Side-of-Onset, Performance on the Unified Parkinson's Disease Rating Scale Part IV: Motor Complications, and Environmental Exposures

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Abstract:

Parkinson's disease (PD) is a neurodegenerative condition associated with aging and is 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. Unfortunately, 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. Little is known about the differences in left and right onset PD in relationship to response to levodopa treatment; however previous studies have found that side of onset was associated with differential motor and cognitive PD-related symptoms. For example, those with right side onset have faster disease progression than those with left side onset.

Purpose: The objective for this study was to examine differences in MRMF and environmental exposures between left and right onset PD in 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 (1^{st}, 3^{rd} quartile)= 2.0 (2.0, 3.0)).

Methods: We conducted two-tailed independent sample t-tests to examine the differences on the Movement Disorders Society Unified Parkinson disease rating scale (MDS-UPDRS) scores between PD patients with left versus right onset. We then looked at the biserial point correlation and odds of several environmental exposures between right and left onset patients. Finally, we created a logistic regression model to try to examine the ability of environmental exposures to predict side of onset.

Results: Right onset PD was significantly associated with more OFF time (p=0.04), greater impact of motor fluctuations (p=0.02) and more complex MRMF (p=0.01), implying people with right onset PD may have more complications with levodopa treatment. Additionally, we found occupational pesticide exposure to be significantly associated with right onset PD (OR=0.267, CI= 0.072, 0.995) and that pesticide exposures through occupational and proxy (well water, living on a military base) sources were significantly associated with more severe motor symptoms of PD.

Conclusions: Pesticide exposure may be associated with more severe motor symptoms of PD. Alternative and/or adjuvant treatments to alleviate motor symptoms of PD may be particularly beneficial for controlling PD symptoms for those with right onset PD.

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Introduction:

Approximately 1% of adults over 65 years old, which is more than 1 million people, in the United States have Parkinson's disease (PD). PD is a neurodegenerative disease that results in tremors, rigidity, shuffling gait, impaired kinesthesia, and frequently reduced cognition (Litvan et al., 2012). Although not fatal, PD reduces mobility and quality of life (QOL) for those diagnosed (Opara, Brola, Leonardi, & Błaszczyk, 2012). The neuromechanisms for PD involve degradation of the basal ganglia, particularly the substantia nigra pars compacta (SNpc), which results in decreased synthesis and release of the neurotransmitter, dopamine (DA) and excess cholinergic activity (Le et al., 2015).

Surgical treatments for PD are available. Deep brain stimulation (DBS) has been applied to three neuronal targets: the ventral intermediate nucleus of the thalamus (Vim), the globus pallidus internas (GPi) and the subthalamic nucleus (STN) in the treatment of PD (Pollak et al., 2002). Vim DBS appears to reduce contralateral tremors, while STN and GPi stimulation appear to reduce OFF-time and dyskinesia (Pollak et al., 2002). Cell transplant therapies to replace the damaged neural tissue have had promising but varying results in animal models, but such therapies are not yet available to PD patients in a clinical setting (Wolff et al., 2015). In addition to surgical interventions, several pharmaceutical treatments are also used to alleviate symptoms and slow the progression of PD. Table 1 provides a summary of the most common pharmaceutical treatments (Le et al., 2015). Although many drugs are available, PD is treated almost ubiquitously with DA replacement therapy medication called levodopa (3,4- dihydroxy-L-phenylalanine; also known as L-DOPA) (Lewitt, 2008). Levodopa can cross the blood-brain barrier. Once in the brain, levodopa is converted into DA by dopa decarboxylase and alleviates many of the symptoms associated with PD. Dopamine often has negative side effects, including nausea and vomiting. As such, levodopa is often paired with other drugs such as carbidopa that

inhibit levodopa from being converted into DA until after if crosses the blood-brain barrier and reaches the intended neuronal DA receptors (Lewitt, 2008).

Although levodopa/carbidopa is considered the "Gold Standard" for PD treatment, levodopa has decreasing efficacy over time (Tsugawa et al., 2015). Motor fluctuations or "OFF-time" refers to periods when the DA replacement therapy does not effectively work to improve PD symptoms. In other words, OFF-time is when the levodopa is "wearing off," but it is not yet time for another dose. OFF-time is a medication related motor fluctuation (MRMF), and is unpleasant and undesirable for PD patients, yet OFF-time is common. In fact, OFF-time is experienced by nearly 75% of all PD patients (Tsugawa et al., 2015). Furthermore, OFF times develop in about 40% of Parkinson's patients within 4-6 years of initiating levodopa treatment (Ahlskog & Muenter, 2001). Approximately 10% of all PD patients develop OFF-time per year on levodopa treatment. These statistics suggest nearly all PD patients eventually develop OFF-time (Denny & Behari, 1999). 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 (Denny & Behari, 1999). OFF-time, dyskinesia, and dystonia are undesirable phenomena occurring in PD patients related to levodopa. Therefore, 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).

Unlike some other neurodegenerative disorders, PD symptoms begin on one side. Therefore, unilateral symptom onset is a criterion for definite PD diagnosis (Hughes et al., 1992). 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 (Baumann, Held, Valko, Wienecke,

& Waldvogel, 2014). 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 (Frazzitta et al., 2015). Left side of onset was found to be associated with extended period of survival after diagnosis, and delayed ambulatory impairments (e.g., delayed impaired internal guidance of movement) compared to right onset (Munhoz et al., 2013). Experience of apathy in right side onset was significantly higher than patients with left onset symptoms (Harris, McNamara, & Durso, 2013). Patients with right onset PD also showed significantly higher levels of novelty seeking than the left onset patients (Harris, McNamara, & Durso, 2015). The causes for these subtle yet significant differences in disease experience by side of onset are not understood but seem to suggest differences in neurobiological factors associated with PD and in disease progression based on side of onset. These differences in PD progression could be important for developing long-term individualized therapeutic treatment plans for PD patients.

PD is thought to be caused by a combination of genetic and environmental factors (Di Monte, Lavasani, & Manning-Bog, 2002); however, the exact causes of Parkinson's disease remain unknown. Certain genetic factors are known to increase the risk for developing PD, and the heritability of PD is thought to be approximately 27% (Do et al., 2011). However, only 5%-10% of total PD cases can be explained by genetics (Klein & Westenberger, 2012). Although it is possible that genetic factors related to PD have not yet been identified, the discrepancy in heritability and prevalence of PD strongly support the hypothesis that environmental factors have a role in facilitating the onset of PD. Researchers are still conducting studies to discover and understand which environmental factors might be related to PD.

Several studies have provided evidence to support an environmental link in the development of PD. The possible link between environmental exposures and PD was first

established by the discovery that the synthetic opiate byproduct 1-methyl-4-phenyl tetrahydropyridine can cause parkinsonism through its neurotoxic metabolite, 1-methyl-4-phenylpyridinium (Langston, Ballard, Tetrud, & Irwin, 1983). Since then, risk factors for developing PD have been explored. Pesticide exposure, drinking well water, rural living and agricultural employment, and brain injury with loss of consciousness have all shown some association to the development of PD (Dick et al., 2007). Zhang et al. (2014) found an inverse relationship between alcohol consumption and risk for PD (Zhang, Jiang, & Xie, 2014). Research involving dietary factors related to PD has been inconclusive (Kamel et al., 2014). For reasons that are not yet clear, smoking has been shown to be a protective factor against developing PD (Chen et al., 2010). As of yet, no single environmental factor of combination of factors has been shown to completely explain the development of PD, supporting the hypothesis that PD is caused by a complex combination of both genetic and environmental risk factors.

Little is known about the relationship between the side-of-symptom onset and experience of OFF-time in patients with PD, and even less is known about environmental factors which may predict on which side PD symptoms begin. Exploring the relationship between environmental factors known to be associated with PD and side of onset may offer clues for right vs. left onset PD etiology, while 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 were furthermore interested in exploring which if any environmental exposure factors might be related to PD side of onset. We also explored the relationship between OFF time and type of environmental risk factors to examine possible mediation effects between environmental exposures and response to DA replacement therapy. It is our hope that

our findings might contribute to the ability of physicians to tailor treatment for PD to best serve individual patients given which side their PD symptoms manifested.

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. Veterans with and without 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.

Participants:

All participants were aged 40 and older, could walk 3 meters or more with or without assistance and had a clinical diagnosis of PD based upon established criteria determined by a board-certified neurologist with specialty training in movement disorders (Hughes, Daniel, Kilford, & Lees, 1992). 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). PD participants must have shown clear symptomatic benefit (e.g., alleviated rigidity, bradykinesia, and tremor) from antiparkinsonian medications, e.g., levodopa (Kempster et al., 2007). Participants were in Hoehn and Yahr stages I-IV. Hoehn and Yahr (HY) scale is a clinical rating scale, which defines broad categories of motor function in PD (Table 2)

(Hoehn & Yahr, 1967). Participants were tested at least 12 hours after their last anti-parkinsonian medication dose to reduce medication-related performance fluctuations. No genetic assessments for PD were performed on this sample, and therefore individual genetic factors related to PD are unknown for sample individuals.

Hemispheric dominance affects neuronal structure, and handedness can indicate hemispheric dominance where right-handedness suggests left-hemispheric dominance (Raemaekers, Schellekens, Petridou, & Ramsey, 2018). Data were analyzed from right-handed individuals only to control for the possibility that hemispheric dominance might be a confounding factor in patient response to DA-replacement therapy. Due to the limited number of left handed participants in the study (n=7) we did not perform statistical analyses on left handed individuals. Patients who were not currently taking any DA-replacement therapy were also excluded from this analysis, as the UPDRS IV measure would not be appropriate for these patients. The resulting sub-sample of 64 individuals includes 32 individuals who experienced right-side onset of PD and 32 individuals who experienced left-side onset.

Measures:

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. Participants were evaluated for disease severity with the Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008) parts I-IV by a qualified and experienced rater blinded to study purposes.

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 (Goetz et al., 2008)

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.

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 fluctuation, 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 MDS-UPDRS-IV is the primary outcome measure of this study. Higher MDS-UPDRS IV sum scores indicate greater experiences of OFF time.

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 (Oldfield, 1971). 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.

Environmental Exposures Questionnaire was delivered through an online survey or in interview format depending on participant preference. The environmental exposures questionnaire was developed to broadly assess presence and duration of exposure factors known to be related to PD. Development of the survey included a literature review using PubMed Database with search terms "Environmental exposures and Parkinson's Disease," "Causes of Parkinson's Disease," and "Environment and Parkinson's Disease." Based on this literature review, environmental factors that were found to be either significant or inconclusively related to Parkinson's Disease were converted into questions on the Environmental Exposures Questionnaire. The questions (Appendix A) in our environmental exposures survey are therefore consistent with current knowledge about environmental factors associated with the development of PD (Brown et al., 2017; Chen et al., 2010; Di Monte et al., 2002; Dick et al., 2007).

Analysis:

Data were analyzed using Statistical Analysis Software (SAS). A two-sample t-test was performed to test the null hypothesis that there was no relationship between side-of-onset and UPDRS sum scores, as well as individual components of UPDRS Part IV. A logistic regression analysis was used to examine the relationship between environmental exposure factors and side of onset. Two years elapsed between the initial data collection and the environmental exposures questionnaire survey. Emails containing encrypted survey links were sent to all participants from the full sample, including left handed individuals and those not taking DA

replacement medication, for those who had provided an email address. The participants who did not respond to the initial email were sent a follow-up email and called on the phone. Two additional voice messages were left for individuals who were not reached by phone call.

Of the right-handed individuals on DA replacement therapy included in the initial analysis who were reached, only one person declined participation. Five people were confirmed deceased, and nine additional participants' phone numbers were no longer valid. One participant was not well enough to participate in the survey, and two participants had not provided reliable contact information for the initial study. The remaining participants had active voice messaging services but did not return the calls. The resulting analysis of the environmental exposures questionnaire data contains responses from 44 individuals, 23 with right-onset PD and 21 with left-onset PD. Our environmental exposures questionnaire data is missing responses from 20 individuals, right onset n=9.

Data from participants who provided answers to the environmental exposures survey were included. For individual questions missing a participant's response and for items where the participant answered "I don't know (my exposure status)", the sample average response for that specific variable was imputed. Of the 484 individual data points used in this analysis from the exposures questionnaire, 12 points were imputed using this method. A biserial correlation analysis was performed to examine relationships between environmental exposures and MDS-UPDRS Parts I-IV sum scores and part IV individual items related to MRMF. Higher UPDRS scores indicate more serious PD symptoms, and exposure was coded as 1, 2 (no/not exposed, yes/exposed).

Results:

Our dataset contains information from 68 individuals with PD (right side of onset: 50%). Table 2 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. Table 3 shows the results of the independent samples 2-tailed t-test (alpha=0.05) which tests the null hypothesis that there is no difference in average MDS-UPDRS component sum score between individuals with right vs. left PD onset. There is a not a significant difference in UPDRS IV sum score (representing the amount of MRMF) between the group of participants with right onset and the group of participants with left onset (t=-1.89, p= 0.06). In fact, we found that UPDRS sum scores for individual sections are not significantly associated with PD side of onset in our sample. However, itemized analysis of MDS-UPDRS Part IV is a more meaningful comparison of MRMF differences between groups because each question measures slightly different types of MRMF. The specific breakdown of differences between the group of participants with right vs left onset and related to MDS-UPDRS Part IV, including OFF state, are shown in Table 4. Individuals with right-onset PD had significantly more OFF time, including time spent in OFF state, functional impact of MRMF, and complexity (unpredictability) of MRMF, than people 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.

Our next series of analyses focused on MDS-UPDRS and Environmental Exposures comparisons. Table 5 shows the environmental exposures profile of the sample (n=44) by side of PD symptom onset. We found that the odds of occupational pesticide exposure among those with right onset were 0.267 times (CI: 0.072, 0.995) the odds of occupational pesticide exposure among left onset patients. There were no other significant differences in the odds of being

exposed for any other environmental factor. Table 6 shows the biserial point correlations for MDS-UPDRS sum scores and environmental exposures, while table 7 summarizes the correlations between environmental exposure factors and MDS-UPDRS Part IV: Motor Complications items. Using the point-biserial Pearson's correlation coefficient, occupational pesticide exposure, drinking well water at home, and working with metals were all significantly negatively correlated with UPDRS Part II (motor impact of PD on daily living). Ever having lived on a military base was significantly negatively correlated with UPDRS Part III (motor signs of PD) Sum Score. These results suggest that, for our sample, pesticide exposure is related to an increase of motor symptoms of PD. Having a relative with PD was significantly correlated with the UPDRS Part IV item 2, functional impact of dyskinesias, which might suggest genetic effect modification of this MRMF.

For our final analysis, we were interested in seeing if any of the environmental exposure factors might be able to predict side of onset. Table 8 summarizes the logistic model where the dependent variable is side of onset and the dependent variables are exposures. This logistic regression is an exploratory analysis only. We counted right onset as an event given that our hypothesis was that patients with right onset PD were more likely to have harmful exposures. The full model could predict right onset PD with over 90% accuracy based on different exposures. The second model (stepwise selection criteria, alpha=0.20) was about 79% successful at predicting right side onset. The third model (stepwise selection, alpha=0.10) was only about 41% successful at prediction. Based on these results, we have evidence that a combination of exposure factors is likely related to PD side of onset.

Discussion:

In summary, we found that right side of PD onset is significantly associated with MRMF, including time spent in the OFF state, functional impact of fluctuations, and complexity of motor

fluctuations. We cannot present evidence to support that being exposed or not exposed to any of the exposure factors included in the environmental exposures questionnaire differed significantly by side of onset in this small sample of people with mild-moderate PD.

Our data seem to suggest a possible effect modification for motor symptoms with pesticide exposure, since we observed some significant negative correlations between occupational pesticide exposure, drinking well water at home, and working with metals, which were all significantly negatively correlated with UPDRS Part II (motor impact of PD on daily living) Sum Scores, and ever having lived on a military base with UPDRS Part III (motor signs of PD) Sum Scores. This negative correlation suggests that people with PD who had these exposures have more serious motor symptoms. Interestingly, drinking well water at home and living on a military base are both proxy indicators for pesticide exposure (Brown, Gessesse, Butler, & MacIntosh, 2017; Ross et al., 2015). Therefore, our data seems to suggest a relationship between pesticide exposure and a greater impact on the motor symptoms of PD. Other studies have found that pesticide exposure might be a contributing factor in the development of PD (Dick et al., 2007), and therefore we are not surprised that pesticide exposure may also impact the individual symptoms of PD. We were surprised that our data suggests that being exposed occupationally to pesticides has reduced odds of right PD onset, but those with right onset who were exposed to pesticides had more motor symptoms of PD. Since our study was not looking at causes of PD, but rather interested in understanding factors that influence symptoms of PD by side of onset, more research is needed to elucidate the relationship between occupational pesticide exposure and PD symptoms.

One possible explanation for our findings that individuals with right-onset PD had significantly more OFF time, greater functional impact of MRMF, and more complex medication-related motor fluctuations than people with left-onset PD could be attributed to 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 (Haaxma et al., 2010). Indeed, another study conducted on right-handed PD patients found a 55% greater difference in right and left-hand dexterity among right onset patients than in left onset patients (Haaxma et al., 2010). This same study concluded that in right handed PD patients, the non-dominant right hemisphere may be more susceptible to DA denervation than the dominant left hemisphere (Haaxma et al., 2010). Our findings are consistent with this Haaxma et al. (2010) study.

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.

Strengths:

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. We hope that this research, together with other studies related to MRMF, can continue to inform and refine treatment of PD and help with improving the lives of individuals with PD through more effective symptom management.

Additionally, we believe that the component of our study related to environmental exposure factors' associations with PD side of onset is a novel line of research. Many studies on environmental exposures and PD are focused on discovering causal factors related to PD. The next logical step in these studies is to examine how environmental exposures impact the

individual with PD. Understanding the relationships between symptoms of PD and environmental exposures could help us to understand how these exposures moderate damage the substantia nigra for PD patients, as well as their direct and indirect impacts (if any) on the rate of DA neuronal damage that occurs in PD. Our study provides evidence that supports a relationship between environmental exposures and PD symptoms which could provide justification for future research to elucidate these relationships further.

Limitations:

The analysis of the MDS-UPDRS Part IV and side of onset relationship is limited by having few left-handed participants and therefore only including right-handed individuals. This lack of left-handed participants is likely since only about 10% of the USA population is left-handed rather than measurement or systematic bias. However, the resultant associations found to be present in these 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. Another limitation of our study is that we were not able to contact many of the participants from the initial study to complete the environmental exposures survey. Because many participants were elderly, we suspect that some of the participants whom we could not reach are deceased, and/or that age- and disease-related conditions may have prevented people from being able to respond. Additionally, the exposures questionnaire provides only general environmental exposure data in an attempt to capture a broad number of possible exposures. Research should continue to explore relationships between individual exposure factors and PD side of onset.

Generalizability of our findings is additionally limited by our small sample size. Our sample size was too small to support a robust logistic regression analysis to model exposure factors that might predict symptom side of onset, and we lack responses from 24 of 68 participants. The small sample size increases the likelihood that the exposures questionnaire data was confounded by unmeasured exposures, as well as biased from the healthy worker effect. That is, the people who were deceased or most advanced in their illness were not able to participate in the questionnaire, and their responses might have been systematically different from individuals who answered the exposures questionnaire. However, the logistic regression model for this study was completed as a part of exploratory data analysis. Both our correlation analysis between side of onset and exposures and our logistic regression model show that, for our sample, factors outside of the exposures in our questionnaire are influencing side of onset. It is possible that genetic factors and other unmeasured exposures are better predictors of side of onset. It is also probable that the nature of our described relationships between the exposure and outcome variables would change with an increased sample size.

Finally, having a blood relative with PD was significantly correlated with the UPDRS Part IV item 2, functional impact of dyskinesias. This finding could suggest that genetic factors play a role in not only the development of PD, but also in the experience of certain motor symptoms. However, only 14 participants reported having a blood relative with PD, and five participants did not know if they had a blood relative with PD. We do not, therefore, have sufficient evidence to explain the heritability of symptoms of PD measured in the MDS-UPDRS.

Many factors related to causation, progression, etiology, and treatment of PD are not well explained. The 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 or in relationship to environmental exposure factors. Our study gives evidence of such relationships and can act as

justification for similar lines of research. By continuing to explore and elucidate relationships between PD side of onset and other factors, we hope to increase understanding of Parkinson's disease. It is our hope that such an increased understanding will eventually result in prevention of the illness as well as more effective treatments and higher quality of life for individuals living with PD.

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Appendix A: Environmental Exposures Questionnaire

- Do you currently or have you ever smoked tobacco?
- Do you currently or have you ever used other recreational drugs?
- Do you currently or have you ever consumed caffeinated beverages?
- Prior to developing symptoms of PD, did you have a blood relative with Parkinson's disease?
- Prior to developing symptoms of PD, did you have head trauma?
- Prior to developing symptoms of PD, did you have exposure to pesticides as part of your job (e.g., farming)?
- Prior to developing symptoms of PD, did you have exposure to using pesticides at home (e.g., Roundup)?
- Were you ever living in a home with well water as the primary source for drinking water?
- Have you ever worked with metals? (Ex. construction, mechanical, welding, etc.)
- Have you ever lived on a military base?

Table 1: Pharmaceutical Treatments for PD (Le et al., 2015)

Mechanism of Drug	Name of Drug(s)	Description
Increase L-DOPA availability in the Central Nervous System (CNS)	Levodopa (L-DOPA)/ carbidopa	Carbidopa prevents pre-CNS conversion of levodopa to DA, levodopa increases DA availability
Increase L-DOPA availability in Central Nervous System (CNS)	Entacapone, tolcapone	Prevents peripheral L-DOPA degradation
Increase DA availability	Amantadine	Increases DA release and decreases DA reuptake in the synapse
Prevent DA breakdown	Selegiline	Blocks conversion of DA into 3-MT
Prevent DA breakdown	Tolcapone	Blocks conversion of DA to DOPAC
Dopamine Agonist	Bromocriptine	Derived from ergot
Dopamine Agonist	Pramipexole, ropinirole	Non-ergot
Reduce excess cholinergic activity	Benztripine	Antimuscarinic, improves tremor and rigidity
Reduce excess cholinergic activity	Atropine	Antimuscarinic, improves tremor and rigidity

Table 2: 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 (1^{st}, 3^{rd} 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

Table 3: MDS-UPDRS sum scores by Side of Onset

MDS-UPDRS Component	Right Onset	Left Onset	t-statistic	p-value
Part I Score (Mean, SD)	13.12, 7.13	12.94, 7.42	-0.1	0.92
Part II Score (Mean, SD)	16.09, 8.58	13.91, 9.05	-0.84	0.4
Part III Score (Mean, SD)	33.54, 12.36	36.66, 11.02	-0.58	0.56
Part IV Score (Mean, SD)	4.68, 3.80	2.38, 3.00	-1.89	0.06
Total Score (Mean, SD)	67.43, 24.09	66.02, 24.50	-0.88	0.38

No relationship was significant at the alpha=0.05 level

Table 4: MDS-UPDRS Part IV Items by Side of Onset

MDS-UPDRS Part IV Component	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

Table 5: Side of Onset and Environmental Exposure Factors

Exposure Variable	Right Onset (n)		Left Onset (n)		χ_2	P-Value	OR	95% CI
	Yes	No	Yes	No	------	------	--------	----------
Occupational Pesticide Exposure	5	17	11	10	4.984	0.083	0.267*	(0.072, 0.995)
Caffeinated Beverages	23	0	19	1	2.295	0.318	Undefined	Undefined
Alcoholic Beverages	18	5	18	3	0.410	0.52	0.60	(0.124, 2.89)
At-Home Pesticide Use	15	6	16	5	2.037	0.361	0.781	(0.197, 3.105)
Working with Metals	3	20	5	16	0.855	0.355	0.48	(0.099, 2.319)
Living on a Military Base	7	16	7	14	0.043	0.837	1.225	(0.317, 4.741)
Blood Relative with PD	9	11	5	13	1.221	0.543	2.127	(0.548, 8.258)
Smoking	11	12	11	10	0.091	0.763	0.833	(0.255, 2.724)
Head Trauma	11	12	7	14	0.954	0.329	1.833	(0.540, 6.22)
Well Water at Home	8	15	5	15	1.605	0.448	1.60	(0.425, 6.03)
Recreational Drug Use	8	15	4	16	2.2794	0.3199	2.133	(0.531, 8.579)

***** Significantly different odds between right and left onset patients

Table 6: Biserial Correlations, MDS-UPDRS Sum Scores and Environmental Exposures

	UPDRS I		UPDRS II		UPDRS III		UPDRS IV		UPDRS Total	
Variable	**r**	**P-Val.**	**r**	**P-Val.**	**r**	**P-Val.**	**r**	**P-Val.**	**r**	**P-Val.**
Smoking	0.077	0.621	-0.129	0.406	0.107	0.491	-0.013	0.934	0.026	0.865
Alcohol	0.063	0.687	0.089	0.566	0.227	0.139	0.186	0.227	0.182	0.237
Recreational Drugs	0.072	0.644	0.227	0.138	0.123	0.426	0.163	0.291	0.181	0.241
Caffeine	0.212	0.166	0.125	0.419	-0.077	0.624	0.136	0.378	0.090	0.562
Relative w. PD	0.072	0.642	0.072	0.643	0.086	0.580	-0.046	0.769	0.079	0.608
Head Trauma	0.057	0.715	-0.149	0.335	0.097	0.530	-0.007	0.963	0.010	0.949
Occ. Pest.	-0.267	0.079	-0.327	0.031*	-0.157	0.309	-0.005	0.974	-0.265	0.082
At-Home Pest.	-0.114	0.463	-0.152	0.324	-0.200	0.193	-0.221	0.149	-0.212	0.168
Well Water	-0.19	0.217	-0.414	0.005*	-0.199	0.196	-0.269	0.077	-0.331	0.028*
Metals	-0.020	0.896	-0.301	0.047*	-0.175	0.256	-0.049	0.753	-0.199	0.196
Military Base	-0.244	0.111	-0.176	0.252	-0.321	0.033*	-0.168	0.276	-0.307	0.042*

*Significant at the alpha=0.05 level

Table 7: Correlations between UPDRS: IV Items and Environmental Exposures

	UPDRS IV: 1		UPDRS IV: 2		UPDRS IV: 3		UPDRS IV: 4		UPDRS IV: 5		UPDRS IV: 6	
Var.	r	P-Val.	r	P-Val.	R	P-Val.	r	P-Val.	r	P-Val.	r	P-Val.
Smoking	0.184	0.232	0.218	0.155	0.023	0.884	-0.101	0.515	-0.094	0.542	0.065	0.675
Alcohol	0.141	0.361	0.103	0.506	0.235	0.125	0.119	0.442	0.111	0.472	0.046	0.767
Drugs	-0.036	0.816	0.109	0.482	0.208	0.175	0.099	0.521	0.203	0.186	-0.066	0.668
Caffeine	0.086	0.578	0.034	0.826	0.110	0.479	0.091	0.556	0.116	0.455	0.071	0.647
Relative	-0.032	0.835	-0.307	0.042*	-0.168	0.277	-0.019	0.903	0.013	0.934	0.130	0.402
Trauma	-0.196	0.203	-0.040	0.795	0.023	0.882	0.035	0.819	-0.044	0.778	0.114	0.461
Occ. Pest.	0.009	0.954	0.085	0.584	0.138	0.372	-0.029	0.850	-0.107	0.488	0.014	0.927
Home Pest.	-0.230	0.134	-0.133	0.389	-0.123	0.426	-0.226	0.141	-0.193	0.210	0.029	0.853
Well Water	-0.139	0.368	-0.095	0.540	-0.216	0.159	-0.232	0.129	-0.270	0.076	0.017	0.915
Metals	0.260	0.088	0.103	0.506	-0.235	0.125	0.067	0.668	-0.093	0.549	-0.038	0.805
Military	0.081	0.602	-0.085	0.583	-0.073	0.638	-0.077	0.621	-0.261	0.087	-0.108	0.486

*Significant at the alpha=0.05 level

Table 8: Logistic Regression Model for Predicting Right Side of Onset by Environmental Exposure Status

	Stepwise Model Selection alpha=0.20					Stepwise Model Selection alpha=0.10				
Variable	**B**	**SE**	**Wald χ^2**	**p-value**	**OR**	**B**	**SE**	**Wald χ^2**	**p-value**	**OR**
Smoking	---	---	---	---	---	---	---	---	---	---
Alcohol	-1.426	1.062	1.803	0.179	0.24	---	---	---	---	---
Drugs	1.685	0.945	3.178	0.075	5.39	---	---	---	---	---
Caffeine	---	---	---	---	---	---	---	---	---	---
Relative	---	---	---	---	---	---	---	---	---	---
Trauma	-1.719	0.924	3.459	0.063	0.179	---	---	---	---	---
Occ. Pest.	2.766	1.073	6.649	0.01*	15.895	1.316	0.668	3.877	0.049*	3.727
Home Pest.	---	---	---	---	---	---	---	---	---	---
Well-water	-1.832	1.105	2.748	0.097	0.16	---	---	---	---	---
Metals	2.025	1.139	3.160	0.076	7.574	---	---	---	---	---
Military	---	---	---	---	---	---	---	---	---	---
Intercept	-1.509	2.359	0.409	0.522	---	-2.053	1.140	3.241	0.072	---
AIC	59.199					60.792				
Conc. %	79.30%					41.00%				
Somer's D	0.631					0.286				

*Significant at alpha-0.05