Nature and Laterality of Motor Symptoms in Parkinson's Disease and Relationships to Cognitive Profile

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DEDICATION

To my mother, with love

And in loving memory

of my father and my grandparents

Introduction

Idiopathic Parkinson's disease (PD) is a progressive neurological disorder often characterized by motor and non-motor symptoms. Motor symptoms typically involve bradykinesia, rigidity, tremor, and postural instability. Non-motor symptoms can be diverse, and include autonomic dysfunction, depression, cognitive impairments, sensory and sleep abnormalities (Jankovic, 2008). Worldwide, PD is found in approximately 1% of individuals over the age of 60 (Samii, Nutt & Ransom, 2004). It is often idiopathic in nature and may sporadically occur. However, nearly 33% of individuals with two or more first degree relatives with the disorder will eventually develop PD (Duffy, 2005), suggesting a genetic component. Other possible causes of PD have been identified including environmental factors such as exposure to herbicides and pesticides or damage caused by abnormal oxygen free radicals (Maraganore, 2000; LeWitt, 2000). The progression of PD is unpredictable in many patients as some show symptoms for decades before severe disability develops, while others show a much more rapid progression. Varying responses to medication, age at symptom onset, nature of initial symptoms and other factors likely affect survival times. In a large scale study of the natural progression of PD before the widespread use of levodopa therapies, Hoehn and Yahr (1967) found average survival rates between 10 and 14 years post initial symptom onset. More recently, medications and treatments have reduced mortality rates to levels just slightly higher than age-matched controls without PD (Dewey Jr., 2000).

In brief, the pathophysiology of PD involves a depletion of dopamine-producing cells in the substantia nigra. Lewy bodies, or alpha synuclein deposits, develop in the substantia nigra resulting in decreased activity and cell death. In the normal brain, neurons in the substantia nigra

send projections to the striatum of the basal ganglia and release the neurotransmitter dopamine. Under optimal conditions, projections in the basal ganglia circuitry communicate in two pathways (Direct and Indirect). Both pathways begin in the cortex which projects to the striatum. The Direct pathway then projects to the internal segment of the globus pallidus/substantia nigra pars reticulate (GPi/SNr), the thalamus and then back to the cortex. In contrast, the Indirect pathway projection from the striatum to the external segment of the globus pallidus, the subthalamic nucleus, the GPi/SNr, thalamus, and again back to the cortex. In individuals with PD, decreased activity of the substantia nigra results in a drop in dopamine levels in the striatum. This lack of dopamine is hypothesized to disrupt the striatal component of the Direct and Indirect pathways, which may be responsible for motor symptoms as well as cognitive symptoms (Taylor & Saint-Cyr, 1995).

Cognitive impairment is common in individuals with PD. The prevalence of dementia in PD ranges from 10% (Duffy, 2005) to 24-31% (Aarsland, Zaccai, Brayne, 2005), with an 80% risk of dementia by 15 years of disease (Aarsland et al. 2005). Most germane to the present study is the issue of cognitive impairment in the absence of dementia. Individuals often develop less global cognitive impairments in memory, language, visuospatial abilities and executive function (Muslimovic, Post, Speelman &Schmand, 2005; Taylor & Saint-Cyr, 1995). Interestingly, there is some evidence to suggest that the characteristics of initial motor symptoms may relate to an individual's cognitive profile later in the progression of the disease. As such, the purpose of the current study is to examine how the nature and laterality of initial motor symptoms relate to cognitive profiles in individuals with PD. To this end, a summary will first be provided of studies relating the nature of motor symptoms to cognitive profiles in individuals with PD. Next,

the issue of symptom laterality and its relationship to cognition will be reviewed, followed by the interaction of symptom nature and laterality. Finally, an overview of the cognitive-linguistic deficits associated with PD will be provided.

Nature of motor symptom onset and cognition in individuals with Parkinson's disease

The cardinal motor symptoms of PD are tremor, bradykinesia, rigidity, and postural instability. The type of tremor most common in individuals with PD is a resting tremor, which occurs when the body part is relaxed and decreases upon voluntary movement. Tremor for these individuals often occurs in the fingers (pill-rolling), hands, chin, lip, or legs while at rest ("resting tremor"). The presence of tremor in the head and neck area may cause a tremulous vocal quality in speech tasks such as vowel prolongation (Duffy, 2005).

A second hallmark motor symptom of PD is bradykinesia, or slowness of movement. Berardelli and colleagues (2001) found that individuals with bradykinesia showed slow movement and a longer pause time between movements when compared to controls on a sequential movement task. The authors attributed bradykinesia to slowness in formulating the instructions to move (motor programming) or to slowness in executing the instructions. Akinesia and hypokinesia are also common in PD and are often used synonymously with bradykinesia. Akinesia is the reduced initiation of spontaneous movement and often manifests as reduced facial expression and natural arm movement during walking. Hypokinesia is the production of smaller than intended movements and can result in micrographia and festination. Reduced range of movement may also contribute to prosodic insufficiency (e.g., monopitch, monoloudness, reduced stress) in the speech of some individuals with PD (Duffy, 2005).

The third primary motor symptom of PD is rigidity. Clinically, this stiffness results in resistance when an individual's limb is passively moved. In some individuals, both the agonist and antagonist muscle groups are activated simultaneously resulting in an overall stiffness of the limbs or other affected areas (Hurtig, 2000). Rigidity also may contribute to common patient reports of drooling, dysphagia, and speech difficulties, such as inappropriate silences (Duffy, 2005).

The final cardinal motor symptom, postural instability, commonly occurs following the onset of other motor symptoms and results from a loss of postural reflexes (Jankovic, 2008). Although prominent postural instability early in disease progression is suggestive of alternative diagnoses, the symptom is common late in PD progression (Selikhova, Williams, Kempster, Holton, Revesz & Lees, 2009). Postural instability is a significant contributor to serious health risks such as falls/hip fractures for individuals with PD.

According to the UK Parkinson's disease Society Brain Bank Clinical Diagnostic Criteria, a diagnosis of PD requires the presence of bradykinesia and one or more of the other primary motor symptoms (tremor, rigidity, postural instability), the absence of unusual features such as extreme balance impairment that may signal other movement disorders, and a response to levodopa treatment (Hughes, Kilford & Lees, 1992; see Appendix A). Patients often report tremor, rigidity, or bradykinesia to be predominant at disease onset (Hurtig, 2000). A growing body of research has focused on separating individuals diagnosed with PD into clinical subgroups based on their initial motor symptoms to determine whether relationships exist between clinical motor phenotype and cognitive impairment. Elgh and colleagues (2009) gave a neuropsychological test battery to individuals diagnosed with idiopathic PD (n=88) within 1-2

months of inclusion in the study, and again after 1, 3, and 5 years. Individuals with concomitant dementia or severe cognitive dysfunction defined as a Mini Mental State Exam (MMSE) of <24 were excluded. The authors found that participants who experienced initial bradykinesia or rigidity at onset performed significantly worse than individuals who experienced initial tremor and individuals in an age matched healthy control group (n=30). Similarly, Williams and colleagues (2007) assessed individuals diagnosed with mild to severe idiopathic PD (n=108). They also reported that cognitive impairment (per the Dementia Rating Scale-2 and MMSE) was correlated with bradykinesia and rigidity but not tremor. In their study, motor symptom severity but not disease duration also correlated with cognitive impairment. Furthermore, in a post-mortem study, Selikhova and colleagues (2009) divided a group of donors with pathologically verified PD (n=242) into subgroups including early disease onset, tremor-dominant, non-tremor dominant (bradykinesia/rigidity dominant) and rapid disease progression without dementia. In terms of motor symptom severity and survival time, the authors found that individuals with an initial onset of tremor were similar to individuals with an initial onset of bradykinesia/rigidity. However, individuals with bradykinesia/rigidity onset had significantly higher levels of cognitive impairment and higher levels of Lewy body deposits found in neocortical regions of the brain than individuals with tremor onset. Alternatively, individuals with tremor onset were found to have Lewy body deposits more focally located in their brainstem or limbic areas. Selikhova and colleagues suggested that bradykinesia/rigidity onset has a strong correlation with cognitive impairment and that this relationship likely has a biological basis.

Although the neural pathways responsible for bradykinesia, rigidity and tremor are not fully understood, it has been suggested that input to the basal ganglia from different cortical

areas terminates within specific areas of the basal ganglia which connect to specific areas of the thalamus. These thalamic areas project back to the same areas of the cortex from which the circuit originated (Delong & Wichmann, 2007). Moreoever, it has been suggested that physiological pathways responsible for bradykinesia and rigidity may contribute to PD related cognitive deficits while pathways responsible for tremor may be part of a separate network (Elgh et al., 2009; Katzen et al., 2006). This idea is further supported by a post-mortem study by Jellinger (1999) which suggested that individuals who experienced initial tremor onset had dopamine-producing cell loss in differing areas of the substantia nigra than individuals with initial bradykinesia/rigidity onset. Specifically, individuals with tremor onset had cell loss in the medial substantia nigra, while individuals with bradykinesia/rigidity onset had more significant cell loss in the ventrolateral substantia nigra. Ventrolateral portions of the substantia nigra compacta are part of a dopaminergic pathway to the ventral portions of the striatum, an area that is strongly connected to more cognitive areas of the brain such as the dorsolateral prefrontal cortex (Middleton & Strick, 2000). These findings point to neuropathological differences between individuals with bradykinesia/rigidity and tremor onset that may predict a greater disruption to cognitive pathways in the former.

In summary, factors that contribute to bradykinesia or rigidity at symptom onset may be distinct from factors causing tremor, and those factors may predict the pattern of cognitive decline. Recent research suggests that the nature of the predominant motor symptom at PD onset may correlate with cognitive performance. Specifically, initial onset of tremor predicts better performance on cognitive measures than initial onset of bradykinesia or rigidity. Despite the apparent emerging consensus regarding the relationship of cognitive profile and nature of motor

symptom onset, this association becomes clouded when laterality of symptom presentation is considered.

Laterality of motor symptoms and cognition in individuals with Parkinson's disease

Individuals with PD often do not experience motor symptoms symmetrically, but rather report that symptoms affect one side of their body more severely than the other. In a large scale study, Uitti, Baba, Whaley, Wszolek and Putzke (2005) found that 90% of participants with PD (n=1277) demonstrated asymmetrical motor symptoms at disease onset. While this is true especially at symptom onset, it has been shown that even in later stages of the disease, symptoms can remain more severe on one side of the body (Holtgraves, McNamara, Cappaert & Durso, 2010; Kempster et al. 1989). Motor symptoms that manifest unilaterally are driven by neuronal input from the contralateral cortex and basal ganglia. Thus, when an individual with PD experiences a left-sided motor symptom, the origins are typically the right basal ganglia circuit.

It is common practice to characterize the asymmetry of motor symptoms in individuals with PD. Several methods have been utilized in previous research including the asymmetry index (AI) or similar formula (Foster, Black, Antenor-Dorsey, Perlmutter & Hershey, 2008; Holgraves et al. 2010; Tomer, Levin & Weiner, 1993; Uitti et al. 2005) using scores from standardized scales such as the Columbia Rating Scale (Duvoisin, 1970) or the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn & Elton, 1987; Goetz et al., 2008). For this method, AI is the sum of the total right-sided motor symptom score minus the total left-sided motor symptom score divided by the sum of the total symptom score. AI then ranges from -1 to 1, with scores nearest -1 indicating left-sided asymmetry, scores closest to 0 indicating symmetrical symptoms, and scores closest to 1 indicating predominantly right-sided symptoms. Other methods include using

a ratio for left and right sided symptoms (Spicer et al. 1988; Starkstein et al., 1987) or the difference between left and right motor scores (Cubo et al. 2010; Huber et al. 1992). One recent study did not classify individuals as having either right-sided symptom predominance (R-PD) or left-sided symptom predominance (L-PD) exclusively, but rather calculated a right *and* left motor composite score for each individual in order to find relationships between lateralized motor symptoms and cognitive profile regardless of predominant side of motor symptoms (Cooper, Mikos, Wood, Kirsch-Darrow, Jacobson, Okun, Rodriguez, Bowers & Fernandez, 2009).

Kempster and colleagues (1989) found a relationship between unilateral onset of motor symptoms in individuals with PD and greater degeneration of cells of the substantia nigra on the contralateral side. The authors suggested that loss of dopamine producing cells leads to initial symptom asymmetry even as the disease progresses and individuals experience symptoms on both sides of their body. Animal studies have found that the right basal ganglia of adult rats contains higher dopamine receptor density and affinity (Giardino, 1996), which may signify more projections from the right basal ganglia to the frontal lobes than occur in the left hemisphere. If the same is true in humans this could in part explain why left onset symptoms have a higher correlation with cognitive impairment than right onset symptoms, as will be discussed below (Katzen et al. 2006). Furthermore, Tomer and colleagues (1993) found that side of motor symptom onset rather than the current status of symptom asymmetry was more strongly correlated with performance on a neuropsychological test battery designed to measure executive function, memory, working memory, attention, and visuospatial processing.

Numerous studies have investigated the relationship between laterality of symptoms and specific aspects of cognition. A recent review examined 36 studies related to motor symptom asymmetry in PD and cognitive profile across the domains of visuospatial function, language, attention, executive function, and memory (Verreyt, Nys, Santens & Vongerhoets, 2011). According to the review, there are differences in the cognitive profiles of individuals with right predominant versus left predominant motor symptoms, however these differences have been inconsistent across studies in each of the cognitive domains.

With respect to *executive function*s, Verreyt and colleagues (2011) found no evidence for differences in executive functioning with respect to inhibition, verbal fluency, or set shifting. As discussed in their review, some researchers found that individuals with L-PD demonstrate reduced performance on executive measures including abstract reasoning, attention span, set shifting, problem solving and planning as compared to individuals with R-PD (Katzen et al., 2006; Tomer et al., 1993). These results were supported by an additional study (Cheesman, Barker, Lewis, Owen & Brooks, 2011) that was published after the Verreyt review. Other studies included in the review have reported no significant relationship between symptom asymmetry and performance on tasks of executive functions (Holtgraves et al., 2010; Starkstein & Leiguarda, 1993). In contrast, several researchers have found that individuals with R-PD demonstrated worse performance than individuals with L-PD on measures of executive function (Huber, Miller, Bohaska, Christy & Bornstein 1992; Starkstein & Leiguarda, 1993). Based on these inconsistent results, Verreyt and colleagues (2011) suggested that no compelling evidence exists concerning differences in executive function impairment based on laterality of motor symptoms.

With respect to attention, 11/14 studies reviewed in the Verreyt et al. (2011) review found no difference between L-PD and R-PD groups on measures of basic sustained attention (e.g., WAIS-R Digit span task, counting by 3's, serial digit learning) and measures of complex attention. In contrast, 5/10 studies reviewed found that individuals with L-PD had a right-sided attention bias when compared to individuals with R-PD using measures of spatial attention (e.g., line bisection and cancellation tasks). Direnfeld, Albert, Volicer, Langlais, Marquis & Kaplan (1984) found results that individuals with L-PD performed worse on neuropsychological measures than individuals with R-PD and attributed the differences to the right hemisphere's role in mediating attention. The Verreyt review (2011), however, found evidence to suggest that attention differences based on motor symptom laterality exist mainly in the spatial domain.

Research has found that the basal ganglia- thalamo-frontal pathways have a large effect on memory function (Middleton & Strick, 2000). Dopamine depletion in the basal ganglia disrupts these pathways and may therefore result in worse memory performance in individuals with PD (Pillon, Boller, Levy & Dubois, 2001). Verreyt and colleagues (2011) concluded that in approximately half of the studies they reviewed, no difference was found between R-PD and L-PD groups in terms of either verbal or visual memory (15/28 studies). When differences were found, left dominant motor symptoms correlated with worse performance on visuospatial memory tasks (5/6 studies), while right dominant motor symptoms correlated with worse performance on verbal memory tasks (5/7 studies). Several investigators reviewed found greater memory impairment, both in verbal learning and verbal/visual delayed and immediate memory tasks in L-PD groups (Direnfeld et al. 1984; Tomer et al. 1993). L-PD also has been associated with poorer visuospatial memory (Amick, Grace, Chou, 2006; Foster et al. 2008; Starkstein &

Leiguarda, 1993). Conversely, other researchers have found that individuals with R-PD have greater impairments in verbal memory (Starkstein, Leiguarda, Gershanik & Berthier, 1987). While, the majority of studies have found no differences in memory function based on asymmetry of motor symptoms, when differences were found, results were dependent on whether tasks were visually or verbally mediated.

Individuals with PD have been found to demonstrate difficulty on *visuospatial* tasks such as visual orientation and line orientation tasks. Verreyt and colleagues (2011) reported that individuals with L-PD performed worse than those with R-PD in orientation and mental imagery tasks, while there was no difference between groups in other domains of visuospatial function like drawing, construction, and object recognition. Katzen and colleagues (2006) found that individuals with right-sided tremor onset performed comparably to age-matched controls on these tasks, whereas individuals with left-sided of tremor, bradykinesia or rigidity performed significantly worse on visuospatial tasks. These results suggest that laterality in combination with nature of motor symptoms may affect visuospatial function, which may in part explain inconsistent results in this area. Others found no difference in visuospatial function between individuals with right or left sided motor symptom predominance (Huber et al. 1992; Spicer, Roberts & Lewitt, 1988). According to the Verreyt review, when differences in visuospatial function between groups were found, they suggested worse performance for individuals with L-PD than R-PD. These results are consistent with evidence obtained from studies that examined performance on visual memory tasks.

Finally, researchers have reported somewhat ambiguous results in terms of *language* performance and laterality of symptoms in individuals with PD. In part these results may relate

to the intricate relationship between language and cognition and the fact that many cognitive assessments carry components of both. For example, the semantic verbal fluency portion of the Controlled Oral Word Association Test (COWAT) task taxes language (semantics and lexical retrieval) but also executive functions such as inhibiting other categories of words and sustaining attention on the task. According to Verreyt and colleagues (2011), no L-PD versus R-PD group differences are reported in the literature regarding language comprehension or repetition tasks. The reviewers did find evidence of worse performance on naming and vocabulary tasks by R-PD groups as compared to L-PD groups. In contrast, one study (Holtgraves et al. 2010) that used more comprehensive and functional measurements of language production and use than naming tasks found that L-PD groups performed worse than R-PD groups. Specifically, greater left-sided symptom predominance was associated with the use of fewer verbs, fewer function words, and shorter sentences during a language sample than individuals with right-sided symptom predominance (Holtgraves et al. 2010). This finding is interesting in light of the fact that the majority of individuals are left brain dominant for language. These results may also be explained by research showing that the right hemisphere plays a large role in pragmatics of language (Jung-Beeman, 2005), that may also have affected the discourse performance of participants in this study. Similarly, other researchers found that individuals with right-sided tremor onset performed significantly better on semantic and phonemic verbal fluency measures when compared to individuals with PD with other types of symptom onset (Katzen et al. 2006). In contrast, several researchers have found greater impairments in naming and vocabulary (Spicer et al., 1988; Starkstein et al. 1987) and verbal expression (Huber et al., 1992) in individuals with right sided predominant symptoms.

Thus, there is a lack of consensus in studies examining laterality of symptoms. Part of the variability may stem from the differing approaches used for group categorization, in terms of nature of symptoms and laterality, as well as neuropsychological testing. Another source of variability likely relates to the timing of the symptom profile. That is, Verreyt and colleagues (2011) found that only five studies out of 36 determined laterality based on motor symptoms at time of *onset* (e.g., Amick et al. 2006; Katzen et al. 2006; Tomer et al, 1993, 2007; Wright, Gurfinkel, King & Horak, 2007). The remaining studies determined laterality at the time of neuropsychological testing in order to consider severity and degree of motor asymmetry. Tomer and colleagues (1993) claim that motor symptoms at onset have a relationship with cognitive profile, but this relationship is not evident when current motor symptoms are analyzed. This discrepancy may be due in part to the clinical difficulty of accurately characterizing an individual's predominant side and type of motor symptom as the PD progresses without minimizing other symptoms (Katzen et al, 2006). Furthermore, medications and treatments do not ameliorate motor symptoms equally and may cloud the clinical profile of the patient.

Interaction of nature and laterality of motor symptom onset and cognition in individuals with Parkinson's disease

There is some evidence to suggest that it is the *interaction* of laterality and nature of motor symptoms at disease onset that is related to cognitive profile in individuals with PD. Katzen and colleagues (2006) found that individuals who developed bradykinesia or rigidity as their predominant initial motor symptom performed significantly worse on a neuropsychological test battery regardless of the side of symptoms at onset. Individuals who experienced tremor as their predominant initial motor symptom performed significantly worse on the test battery when

they experienced left-sided onset. However, individuals who presented with predominant right-sided tremor onset performed similarly to age-matched controls. As such, nature and laterality of symptom onset may together predict cognitive function in individuals with PD. Katzen and colleagues (2006) and Williams and colleagues (2009) analyzed the differences in cognitive profile based on both nature and laterality of motor symptoms at disease onset. This area of study deserves continued investigation especially in light of the findings of Williams and colleagues (2009) that both nature and laterality were significant predictors of decreased cognition in individuals with asymmetric PD.

Appendix B provides a summary of investigations that examined the nature and/or laterality of symptoms in PD and how these symptoms relate to cognitive profile. Before describing the proposed methodology of the current study, a brief summary will be provided of the typical cognitive-linguistic deficits of individuals with PD and the common neuropsychological measures used to assess these aspects of cognition.

Cognitive-linguistic functioning in individuals with PD

The nature and severity of cognitive impairment in individuals with PD varies widely, from widespread deficits to relatively intact functioning, even at later stages of the disease (Dewey Jr., 2000; Katzen et al., 2006). Most agree that PD can have a detrimental influence on the domains of executive functions, working memory, memory, visuospatial functioning and perhaps indirectly, language. *Executive functions* signify the ability to plan, initiate and monitor goal-directed behavior, and are often linked to cognitive skills such as problem solving, initiation of actions, inhibition, planning, organizing, and self-awareness. Common, formal assessment tools include the Trails Making Test (Gordon, 1972), the Stroop Color Word Interference test

(Stroop, 1992), the Tower of London Test (Shallice, 1982), the Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993), the WAIS-R Digit Symbol subtest and Letter Number Sequencing subtest (Wechsler, 1997). Additionally, there are measures that require the use of executive functions within language tasks. These measures include the Controlled Oral Word Association Test (COWAT) phonemic and semantic verbal fluency tasks (Benton, Hamsher, Varney & Spreen, 1983).

Executive function impairment in individuals with PD is commonly reported, even in the early stages of PD. Difficulties with initiation, reasoning and planning (Uekermann, et al., 2004), set shifting (Owen, James, Leigh, Summers, & Marsden, 1992), problem solving (Brown, Schneider, & Lidsky, 1997; McKinlay, Grace, Dalrymple-Alford, & Roger, 2010), and organization (Taylor, Saint-Cyr, & Lang, 1990) are typical. Others have found complications in the realms of planning (Weintraub, Moberg, Culbertson, Duda, Katz, & Stern, 2005), verbal fluency (McKinlay et al., 2010), category fluency (Elgh et al., 2009), cognitive flexibility (Price, & Shin, 2009), and inhibitory control (Weintraub et al., 2005; McKinlay et al., 2010) spanning the course of the disease.

Working memory is another set of complex cognitive processes that is often directly or indirectly linked to executive functions. Verbal working memory is typically measured using n-back tests, digit ordering tasks or dual-task paradigms, such as the listening span task originally developed by Danemann and Carpenter (1980). Visuospatial working memory is measured using similar tasks; however, instead of auditory stimuli, visual stimuli are presented. Frequently used measures are mental reconstruction tasks where the participant is required to identify how an object would appear if rotated or folded. Another task is The Corsi Block-Tapping Test

(Corsi, 1972; Milner, 1971), which is similar to the digit ordering task. For this test, the administrator taps a particular sequence on nine same-colored blocks that are scattered on a surface. Immediately after, the participant taps the sequence in a reversed order. Impairments in both visuospatial and verbal working memory in the PD population are well documented (Bublak, Müller, Grön, Reuter, & von Cramon, 2002; Campos-Sousa et al., 2010; Gabrieli, Singh, Stebbins, & Goetz, 1996; Gilbert, Belleville, Bherer, & Chouinard, 2005; Kemps, Szmalec, Vandierendonck, & Crevits, 2005), even in individuals with mild PD (Cooper, Sager, Jordan, Harvey & Sullivan, 1991; Gabrieli et al., 1996; Lewis, Slabosz, Robbins, Barker, & Owen, 2005).

Memory is a set of broad cognitive functions with many contributing components. The Wechsler Memory Scale-III (Wechsler, 1997) is a widely administered, comprehensive battery used to assess all aspects of memory, including verbal and nonverbal memory, as well as working memory. There are myriad standardized tests and tasks that assess discrete aspects of memory. The Hopkins Verbal List Learning Test-Revised (Brandt & Benedict, 2001) is an example of a commonly utilized assessment of verbal short term memory in which a 12-item word list is presented three times to the examinee. Long term memory can be assessed using the delayed recall component of this test which asks the participant to recall the 12-item list after a 25 minute delay. Similarly, the Brief Visual Memory Test-Revised (BVMT-R) (Benedict, 1997) asks the participant to recall six abstract figures after viewing each figure for 10 seconds across three trials; long term visual memory is again assessed following a 25 minutes delay.

Individuals with PD without dementia have been reported to experience memory difficulties that span the various forms and processes of memory. These deficits are often related

to episodic memory (Elgh et al., 2009), prospective memory (Costa, Peppe, Caltagirone, & Carlesimo, 2008; Whittington, Podd, & Stewart-Williams, 2006), recognition memory (Whittington et al., 2006; Whittington, Podd, & Kan, 2000) and verbal short-term memory (Cooper et al, 1991).

Visuospatial function is commonly measured using the Benton Judgment of Line Orientation (JOLO; Benton, Hamsher, Varney & Spreen, 1983), a measure in which an individual is asked to recognize the lines on an answer card that match the position and direction of those from a stimulus card. Other measures of visuospatial function are included in subtests of the Wechsler Adult Intelligence Scale (WAIS), in which the examiner constructs a design using colored blocks or shows a stimulus card, and asks the examinee to construct the same design using a separate set of colored blocks.

Visuospatial dysfunction is considered a common cognitive deficit for individuals with PD. In fact, participants with PD have been shown to perform significantly worse than age matched controls in cognitive testing on visuospatial tasks even when impaired executive functioning has been controlled (McKinlay et al., 2010). Visuospatial deficits have been frequently reported in individuals with a wide range of PD severity (McKinlay et al. 2010; Muslimovic et al., 2005; Woods & Troster, 2003). It is important to consider motor deficits resulting from bradykinesia when interpreting the results of individuals with PD on many tasks that require physical movement.

Language production is commonly measured at the single word level in neuropsychological test batteries by several measures including phonological verbal fluency, semantic verbal fluency, action verbal fluency, and confrontation naming. The COWAT (Benton

et al., 1983) measures both phonologic and semantic verbal fluency. As previously mentioned, verbal fluency measures include aspects of executive function in a linguistic context. A common confrontation naming assessment is the Boston Naming Test (BNT) (Benton et al. 1983) in which the participant is shown a drawing of an item and asked to name that item. Phonemic and semantic cues are given if the examinee incorrectly names an item. Measures of language skills at the discourse level have been developed, including the Linguistic Inquiry and Word Count program (Pennebaker, Booth & Francis, 2007), a program that determines frequency of linguistic variables during naturalistic discourse, including measures of proportion of verbs, proportion of function words, and sentence length.

While language deficits are not often associated with PD, subtle language abnormalities have been identified. As summarized in Spencer, Sanchez, McAllen and Weir (2010), individuals with PD have been shown to differ significantly from controls on measures of language comprehension involving complex syntax (Angwin, Chenery, Copland, Murdoch, & Silburn, 2006), implied information (Murray & Stout, 1999), and metaphors (Monetta & Pell, 2007). Impairments have also been observed in inference generation (Monetta, Grindrod, & Pell, 2008), the provision of specific and sufficient semantic definitions (Lewis, Lapointe, Murdoch, & Chenery, 1998), lexical and morpho-syntactic priming (Angwin, et al., 2007) and confrontation naming (Muslimovic, et al., 2005). Additionally, discourse production impairments have been reported, with a trend toward decreased informational content and syntactic complexity (Murray, 2000). These "language" impairments have mainly been attributed to disruption of high-level cognitive processes, such as executive function, processing speed, and working memory. Traditional domains of language such as phonology, semantics,

and syntax are not thought to be specifically affected. Rather, organized and efficient access to these linguistic domains may be altered as a result of disruption to cognitive circuits mediated by the basal ganglia, thalamus, and prefrontal cortical areas.

In light of the unexplained variability of cognitive-linguistic functioning in individuals with PD, and the potential association with the nature and laterality of motor symptom onset, the current study will examine the relationship between clinical disease parameters and patterns of cognitive dysfunction. Specifically, the neuropsychological performance of clinical subgroups (right tremor predominant onset, left tremor predominant onset, right bradykinesia/rigidity predominant onset, left bradykinesia/rigidity predominant onset) will be investigated, after accounting for influential demographic and clinical variables (age, sex, education, disease duration, disease severity, and depression severity).

METHODS

Participants

Participants were recruited from the Pacific Northwest Udall Center's (PANUC) Parkinson's Disease Registry with approval by the University of Washington Institutional Review Board. Approximately 600 individuals with idiopathic PD were initially considered for eligibility for the proposed study. To be included in the registry, participants needed to fit the UK Brain Bank Clinical Diagnostic Criteria for Parkinson's Disease (Hughes, Kilford & Lees, 1992; see Appendix A for specific inclusion/exclusion criteria). Participants were recruited from both the University of Washington (Seattle area) and Oregon Health Sciences University (Portland area) patient populations. Additional exclusion criteria were used to determine eligibility for the current study. Specifically, participants were excluded for (1) history of stroke, traumatic brain injury, seizure disorder, psychiatric disorder or previous neurosurgical operation, (2) severe active depression as determined by a score $\geq$ 12 on the 15 item Geriatric Depression Scale (GDS; Sheikh & Yesavage, 1986), (3) severe dementia as determined by a score $\leq$ 17 (Dalrymple-Alford et al. 2010; Gill, Freshman, Ravina & Blender, 2008; Hoops, Nazem, Sideroft, Duda, Xie, Stern & Weintraub, 2009) on the Montreal Cognitive Assessment (MoCA; Nasreddine, et al., 2005), (4) left hand dominance, (5) symmetric presentation of motor symptoms, (6) documented presence of genetic mutations (LRRK2 mutations), and (7) age of onset < 45 years. Once inclusion/exclusion criteria were applied, 323 participants remained and are described in Table 1. Subgroups were formed based on the participants' report of nature (predominant bradykinesia/rigidity or tremor) and laterality (right or left) of initial motor symptom at PD onset, resulting in 4 groups: left-sided tremor predominant onset (L-TO), right-

sided tremor predominant onset (R-TO), left-sided bradykinesia/rigidity predominant onset (L-B/RO), and right-sided bradykinesia/rigidity predominant onset (R-B/RO). To identify potential covariates for further statistical models, demographic descriptors and potentially confounding clinical variables were checked for group differences with nonparametric tests of equality for quantitative variables and with chi square tests for sex. Nominal *p* values are reported in Table 1.

Table 1. Demographic and clinical data for participants grouped by predominant initial motor symptoms.

Demographic/ Clinical Data	**Right-sided onset**		**Left-sided onset**		**Significance**
	Bradykinesia/ Rigidity	*Tremor*	*Bradykinesia/ Rigidity*	*Tremor*	
N (total= 323)	41	130	39	113	
Age at testing (yr.)	66.49 (8.02)	70.54 (8.76)	69.85 (8.58)	68.2 (7.72)	0.0379*
Sex (M/F)	28/13	91/39	23/16	80/33	0.562
Race					
White	41	122	38	109	
Asian	0	3	1	1	
Native American	0	2	0	0	
Black	0	1	0	0	
Mixed	0	1	0	3	
Education (yr.)	16.82 (2.89)	15.87 (2.77)	16.08 (2.85)	16.01 (2.65)	0.3622
Age of Onset (yr.)	57.22 (8.38)	61.79(9.08)	61.21 (9.22)	60.27 (8.46)	0.0283*
Disease duration (yr.)	6.73 (3.00)	6.39 (4.85)	6.78 (4.93)	5.993 (4.82)	0.4445
Family History (-/+)	29/12 (29.27%)	93/32 (25.6%)	32/5 (13.51%)	64/42 (39.62%)	
Number of family members with PD	0.37	0.34	0.16	0.5	
UPDRS Total	26.46 (11.87)	28.41 (12.56)	27.03 (12.71)	28.08 (11.75)	0.6866
GDS	5.24 (1.32)	6.11 (1.81)	6.49 (1.96)	5.82 (1.58)	0.0247*
MMSE	28.34 (1.88)	27.57 (1.99)	27.77 (2.12)	27.66 (2.09)	0.1569

Note. Yr. = years, M = male, F = female, PD = Parkinson's disease, UPDRS = Unified Parkinson's Disease Rating Scale (possible range of 0 [no symptoms] to 108 [severe symptoms]), GDS = Geriatric Depression Scale; possible range 0 [best] to 15 [worse], MMSE = Mini Mental Status Exam, *indicates significant differences between groups at $p < 0.05$.

Protocol

The Registry is comprised of an "annual" sample (approximately 150 individuals) and a "clinical" sample (approximately 450 individuals). Participants belonging to the annual sample complete a full neuropsychological test battery and the Unified Parkinson's Disease Rating Scale (MDS- UPDRS; Goetz et al., 2008) every year at the VA Puget Sound Healthcare System. See Appendix C for the descriptive statistics for all assessment measures included in the initial data review. Participants in the clinical sample complete the UPDRS and a shortened version of the neuropsychological test battery at their home every three years; this testing is administered by a physician's assistant. Demographic information for all participants was obtained through an initial participant interview and questionnaire including date of birth, gender, ethnicity, education level, occupation, marital status, and handedness. Family history of PD, previously taken or current PD related medication types, and other health history from a short medical questionnaire were also recorded.

Neuropsychological Testing Battery

The protocol was designed to measure domains known to be affected in individuals with idiopathic PD. See Appendix D for a full list of measures included in the neuropsychological test battery for the annual and clinical samples. Variables chosen for further analysis in the current study were based on (1) item distribution, (2) cross-correlation of the variables, (3) number of participants who completed the measure, and 4) the need for adequate representation in each cognitive-linguistic domain. Variables judged to have a significantly skewed distribution were

log-transformed. Based on these factors, the test variables selected for the main analysis are provided in Table 2.

Table 2. List of test variables selected for the main analysis.

Cognitive Domain	Assessment
Language	Semantic verbal fluency (vegetables, total number in 60 seconds) Phonemic verbal fluency (FAS sum, sum of "F", "A", "S") Shipley II vocabulary subtest (total score)
Visuospatial	Judgment of Line Orientation (JOLO, total correct)
Attention/Memory	Hopkins Verbal Learning Test (HVLT) total recall score
Frontal Executive	Letter Number Sequencing subtest of Wechsler Adult Intelligence Scale III (WAIS III, total score) Digit Symbol (WAIS-R, total score)
Cognitive Screens	Montreal Cognitive Assessment (MoCA, total score)

Note. The division of tests into discrete cognitive domains is rather arbitrary given the parallel contributions of cognitive-linguistic processes for any given test. However, these domains (and the corresponding assessments) are well established in the literature (Benedict, 1997; Benton et al. 1983; Brandt & Benedict, 2001; Gordon, 1972; Hoops et al. 2009; Shallice, 1982).

Characterization of Disease Severity, Symptoms and Laterality

Disease severity was measured by the UPDRS at the time of neuropsychological testing. Laterality and nature of motor symptoms *at disease onset* was determined by participant report. During the initial interview, each participant was specifically asked the date of first PD symptom onset, which symptoms were present at time of onset, laterality of symptoms at time of onset, and date of diagnosis.

Data Analysis

Preliminary descriptive analyses were conducted for the demographic, clinical and test variables. Data were screened for skewness, kurtosis and outliers. Demographic variables included age at testing, sex, race, years of education, and age at disease onset. Clinical variables included disease duration, disease severity (as measured by UPDRS III total score at the time of

neuropsychological testing), Geriatric Depression Scale score, and number of family members with PD. A Kruskal-Wallis equality of populations rank test was used to determine equivalence of the demographic and clinical variables between the four subgroups of interest (see Table 1). Demographic and clinical variables that were associated with subgroup membership were considered potential confounders and included as covariates in the main analyses.

Logistic regression was used to calculate which cognitive-linguistic variables predicted membership in the four subgroups of interest (L-TO, R-TO, L-B/RO, R-B/RO) using STATA ® software (Statacorp, 2011). Three logistic regression models using the same set of input variables were run, a binomial model comparing left versus right side of onset, a binomial model comparing the type of onset symptom, and a multinomial model comparing the right onset group with tremor as the predominant symptom against the three other subgroups defined by laterality and symptom type. In all three regression models, the selected cognitive variables were regressed on the selected subgroups. For each model, statistical significance was set a nominal alpha of 0.05.

Results

Tremor was the predominant initial motor symptom for 75.2% of participants and bradykinesia/rigidity was the predominant initial motor symptoms for 24.8% of participants. Reported in Table 3 are the means and standard deviations of each cognitive-linguistic variable of interest for the four subgroups (L-TO, R-TO, L-B/RO, R-B/RO) based on both initial laterality and nature of motor symptoms.

Table 3. Means (standard deviations) of cognitive variables of interest for four subgroups of participants with idiopathic PD based on nature and laterality of motor symptoms at disease onset.

Cognitive Variables	**Right-sided onset**		**Left-sided onset**	
	Bradykinesia/ Rigidity	*Tremor*	*Bradykinesia/ Rigidity*	*Tremor*
N (total=323)	41	130	39	113
Semantic Verbal Fluency Vegetables	12.51 (4.30)	12.29 (4.83)	12.28 (4.52)	12.80 (4.65)
Phonemic Verbal Fluency FAS sum	37.24 (9.56)	38.67 (13.71)	38.87 (15.05)	38.76 (12.51)
Shipley II Vocabulary	34.56 (2.84)	33.95 (3.74)	34.21 (3.01)	34.30 (2.79)
JOLO	12.46 (2.03)	11.97 (2.49)	11.40 (1.99)	11.91 (2.60)
WAIS-R Digit Symbol	37.13 (14.34)	37.47 (11.62)	35.85 (14.51)	40.63 (12.67)
WAIS-III Letter Number Sequencing	9.16 (2.52)	8.27 (2.64)	8.12 (3.84)	8.82 (2.66)
HVLT total recall	22.11 (5.37)	21.17 (6.05)	21.71 (5.52)	20.98 (5.93)
MoCA	24.49 (2.65)	24.19 (3.04)	24.85 (3.01)	24.84 (2.79)

Note. Shipley II Vocabulary; possible score range 0 [worse] to 40 [best]; JOLO = Judgment of Line Orientation; possible score range 0 [worse] to 15 [best], WAIS-R Digit Symbol = Wechsler Adult Intelligence Scale-Revised Digit Symbol subtest; possible score range 0 [worse] to 93 [best], WAIS-III Letter Number Sequencing; possible score range 0 [worse] to 21 [best], HVLT = Hopkins Verbal Learning Test total recall; possible score range 0 [worse] to 36 [best], MoCA = Montreal Cognitive Assessment; possible score range 0 [worse] to 30 [best].

Chi squared tests revealed that the four subgroups were equivalent with respect to sex, years of education, disease duration and disease severity (see Table 1). Groups were significantly

different with respect to age at initial neuropsychological testing (χ^2 (3,323) = 8.43, p = 0.0379), age at disease onset (χ^2 (3,323) = 9.07, p = 0.0283), and Geriatric Depression Scale total score (χ^2 (3,323) = 9.38, p = 0.0247). Age at initial neuropsychological testing and age at disease onset had a Pearson's correlation of 0.83. Due to this high correlation, age at disease onset was chosen to represent both measures. Therefore, participants' age at disease onset and their Geriatric Depression Scale total score were selected as covariates for the regression analyses. See Appendix E for complete results including regression coefficients, standard errors, *z* values, *p* values, and 95% confidence intervals for all three regression models.

Table 4 reports the first logistic regression model with cognitive variables as predictors of laterality of motor symptoms for the participants for whom complete data were available (n = 269). The values given in Table 4 are regression coefficients (β) with 95% confidence intervals. The β values calculated from this model are measures of the association of the cognitive variables, age of onset, and GDS total score with the laterality of initial motor symptoms. Overall, this regression model did not significantly differentiate the left-onset group from the right-onset group (prob > χ^2 = 0.21).

Table 4. Multivariate predictors of laterality of motor symptoms in individuals with PD (left- versus right-sided predominant symptoms at disease onset).

Laterality	**Coef.**	**95% lower**	**95% upper**	***p***
Vegetable	0.01	-0.06	0.07	0.839
FAS sum	0.00	-0.03	0.02	0.874
Shipley 2	0.03	-0.06	0.12	0.519
JOLO	-0.12	-0.23	0.00	0.045*
WAIS digit symbol	0.02	-0.01	0.04	0.229
Letter number sequencing	-0.01	-0.12	0.10	0.813
HVLT total	-0.05	-0.11	0.01	0.110
MoCA	0.14	0.03	0.25	0.010*
Age at onset	0.00	-0.03	0.03	0.874
GDS total	-0.04	-0.20	0.12	0.612
Cons	-2.29	-6.53	1.95	0.289

Note. JOLO = Judgment of Line Orientation, WAIS-R Digit Symbol = Wechsler Adult Intelligence Scale-Revised Digit Symbol subtest, HVLT = Hopkins Verbal Learning Test total recall, MoCA = Montreal Cognitive Assessment, GDS = Geriatric Depression Scale total score, cons = constant, Coef = β coefficient, 95% lower = lower 95% confidence limit, 95% upper = upper 95% confidence limit *p* values with an asterisk (*) indicate a nominally significant predictive value of the β coefficient.

However, the strongest evidence for association came from the JOLO, a measure of visuospatial function, in which reduced performance was predictive of left sided symptom onset, and the MoCA, a general cognitive screening, in which better scores were predictive of left sided symptom onset. These significant *p* values, however, can only be interpreted in the context of the model as a whole.

Table 5 reports the second logistic regression model with predictors of nature of motor symptoms (n=269). β values calculated from this model are measures of the association of the cognitive variables, age of onset and GDS total score with the nature of motor symptoms. Similar to the regression model for laterality, the model for nature of motor symptoms did not significantly differentiate the tremor group from the bradykinesia/rigidity group (prob > χ^2 =

0.78). Additionally, no coefficients for variables of interest suggested evidence predicting the nature of motor symptoms.

Table 5. Multivariate predictors of nature of motor symptoms (tremor versus bradykinesia/rigidity predominant symptoms).

Nature	Coef.	95% lower	95% upper	*p*
Vegetable	0.02	-0.06	0.10	0.559
FAS sum	0.00	-0.03	0.03	0.845
Shipley 2	0.00	-0.11	0.10	0.988
JOLO	0.02	-0.11	0.15	0.800
WAIS digit symbol	0.02	-0.01	0.05	0.110
Letter number sequencing	-0.02	-0.15	0.11	0.791
HVLT total	-0.04	-0.10	0.03	0.297
MoCA	-0.02	-0.14	0.11	0.802
Age at onset	0.02	-0.02	0.06	0.264
GDS total	0.08	-0.11	0.26	0.409
Cons	-0.67	-5.64	4.29	0.791

Note. JOLO = Judgment of Line Orientation, WAIS-R Digit Symbol = Wechsler Adult Intelligence Scale-Revised Digit Symbol subtest, HVLT = Hopkins Verbal Learning Test total recall, MoCA = Montreal Cognitive Assessment, GDS = Geriatric Depression Scale total score, cons = constant, *Coef* = β coefficient, 95% lower = lower 95% confidence limit, 95% upper = upper 95% confidence limit, *p* = *p* value. No variables of interest were significant predictors of the nature of motor symptoms.

Table 6 reports the multinomial logistic regression model with predictors of subgroups based on *both* laterality and nature of motor symptoms at disease onset. Regression coefficients (β) with 95% confidence intervals are reported. The βs calculated from this model are measures of the association of the cognitive variables, age of onset, and GDS total score with subgroups based on both laterality and nature of motor symptoms. The right-sided tremor predominant subgroup was compared against the other three subgroups based on both laterality and symptom type (Katzen et al., 2006). In contrast to the regression models run for laterality only and symptom nature only, the regression model with subgroups based on both laterality and symptom

type was found to significantly differentiate the L-TO, L-B/RO and R-B/RO subgroups from the R-TO subgroup (prob > χ^2 = 0.04).

Table 6. Multinomial logistic regression with predictors of group membership based on nature and laterality of initial motor symptoms. Subgroups are compared against right-sided tremor predominant onset group (R-TO); *p* values are reported.

Cognitive Variable	R-B/RO	L-B/RO	L-TO
Vegetable	0.760	0.728	0.771
FAS sum	0.143	0.580	0.315
Shipley 2	0.922	0.798	0.488
JOLO	0.277	0.046*	0.301
WAIS digit symbol	0.284	0.575	0.224
Letter number sequencing	0.218	0.596	0.602
HVLT total	0.834	0.777	0.046*
MoCA	0.669	0.038*	0.064
Age at onset	0.011*	0.863	0.199
GDS total	0.010*	0.818	0.069
Cons	0.145	0.230	0.938

Note. JOLO = Judgment of Line Orientation, WAIS-R Digit Symbol = Wechsler Adult Intelligence Scale-Revised Digit Symbol subtest, HVLT = Hopkins Verbal Learning Test total recall, MoCA = Montreal Cognitive Assessment, GDS = Geriatric Depression Scale total score, cons = constant, R-B/RO = right sided bradykinesia/rigidity onset subgroup, L-B/RO = left sided bradykinesia/rigidity onset subgroup, L-TO = left sided tremor onset subgroup, Statistical significance was set to a value of $p < 0.05$ for all tests. Significant *p* values are indicated with an asterisk (*).

When compared against the base group (R-TO), individuals with left bradykinesia/rigidity onset performed significantly worse on measures of visuospatial function (β = -0.18, p = 0.046). Additionally, the left bradykinesia/rigidity onset group performed significantly better on the MoCA than individuals in the right onset tremor group (β = 0.18, p = 0.038).

Individuals in the right bradykinesia/rigidity group significantly differed from the base group (R-TO) with respect to two variables. This group was significantly younger at their disease onset than individuals in the R-TO group (β = -0.07, p = 0.011). Additionally, the R-B/RO group

scored significantly better on the Geriatric Depression Scale than individuals in the base group (β = -0.41, p = 0.010). Individuals in the left sided tremor onset group performed significantly worse on the HVLT, a measure of verbal memory, than the base group (β = -0.07, p = 0.046).

Table 7 summarizes the predictive characteristics of group membership based on the results of the multinomial regression analysis.

Table 7. Predictive characteristics of group membership defined by laterality and nature of initial motor symptoms based on logistic regression.

	Laterality of Initial Motor Symptoms	
Nature of Motor Symptoms	*Left Sided*	*Right sided*
Tremor	1. Worse HVLT total recall scores	Base Group
Bradykinesia/Rigidity	1. Worse JOLO scores 2. Better MoCA scores	1. Younger age of onset 2. Lower GDS levels (less reported depression)

Note. HVLT = Hopkins Verbal Learning Test, JOLO = Judgment of Line Orientation, MoCA = Montreal Cognitive Assessment, GDS = Geriatric Depression Scale.

Discussion

The purpose of this study was to examine the relationship between clinical disease parameters and patterns of cognitive dysfunction in light of the unexplained variability of cognitive-linguistic functioning in individuals with PD. Specifically, the study examined the potential association between the nature and laterality of motor symptom onset and test variables across the cognitive domains of language, visuospatial function, verbal memory, and executive function. The neuropsychological performance of clinical subgroups (right tremor predominant onset (R-TO), left tremor predominant onset (L-TO), right bradykinesia/rigidity predominant onset (R-B/RO), left bradykinesia/rigidity predominant onset (L-B/RO) was investigated, after accounting for influential demographic and clinical variables.

Three separate logistic regression analyses were conducted to examine demographic and cognitive variables that predicted group membership based on nature of initial motor symptoms, laterality of initial motor symptoms, and the interaction of laterality and nature of initial motor symptoms. The results suggest that demographic and cognitive input variables did not significantly differentiate participants into binary subgroups when nature and laterality of initial motor symptoms were considered in isolation. However, the demographic and cognitive variables did significantly differentiate subgroups based on *both* laterality and nature (R-TO, R-B/RO, L-TO, L-B/RO). *This finding suggests that the combination of laterality at disease onset and nature of motor symptoms is significantly associated with the cognitive-behavioral profile of individuals with PD.*

Nature of motor symptom onset

In terms of nature of motor symptoms, it was hypothesized based on previous research that bradykinesia/rigidity group membership was predictive of worse cognitive performance than tremor group membership (Elgh et al. 2009; Selikova et al. 2009). Researchers had theorized that neural pathways responsible for bradykinesia/rigidity are topographically distinct from pathways responsible for tremor, and the association between bradykinesia/rigidity motor symptoms and cognitive impairment was biologically based. Bradykinesia is thought to be related to dysfunction of the "direct" pathway of the basal ganglia, which functions to facilitate movement (Obeso et al., 2008). Tremor has been linked to increased neuronal synchronization of cell firing leading to oscillatory patterns of output from the basal ganglia (Obeso et al., 2008). The results from the current study suggest that despite the different putative origins of motor symptoms in PD, this factor alone does not significantly differentiate subgroups in terms of cognitive outcomes.

Laterality of motor symptom onset

Laterality of motor symptoms was also considered by some to be related to the pattern of cognitive functioning in PD. Obeso and colleagues (2008) suggested that before individuals with PD show outward symptoms of their disease, their body compensates for slowly decreasing dopamine levels through internal adjustments to maintain normal motor activity. Eventually, these adjustments are unable to adequately compensate and cardinal motor symptoms begin to manifest clinically. These motor symptoms are generally predominant on one side of the body versus the other, indicating the body's inability to continue to compensate for dysfunction in the contralateral hemisphere. The results of the present study suggest that laterality alone did not

significantly differentiate the subgroups with PD. However, there was evidence that individuals with left motor symptom onset (i.e., right hemisphere dysfunction) have reduced visuospatial ability and better performance on a general cognitive screening than those with right motor symptom onset.

Interaction of nature and laterality of motor symptoms and cognitive-linguistic profile

In their review of the relationship between laterality of motor symptoms and cognitive profile in individuals with PD, Verreyt and colleagues (2011) found inconsistent results across cognitive domains. With respect to *executive function*, the authors reported that performance in this domain did not appear to be related to laterality of motor symptoms. The results of the current study align with this finding; performance on measures of executive function (WAIS-R digit symbol and WAIS-III letter number sequencing) did not predict group membership based on laterality or nature of motor symptoms at disease onset. Together, these outcomes indicate that when executive function is measured using a broad range of assessments across large sample sizes, there is little relationship between executive function and laterality or nature of motor symptoms. It is likely that executive functions are bilaterally influenced (Smith et al., 2011), therefore negating any between-group laterality differences.

With respect to *memory*, Verreyt et al. (2011) found that right sided symptoms resulted in worse performance on measures of verbal memory in 5 of 7 studies reviewed. The current study included a measure of verbal memory only, the HVLT. No measure of visual memory was included in the main analysis. When looking at laterality only or nature only of motor symptoms, verbal memory was not a significant predictor of group membership. However when considering the interaction of both factors, the L-TO subgroup performed significantly worse than the R-TO

group on this measure of verbal memory. This difference suggests that reduced verbal memory performance was associated with a combination of left sided and tremor predominant motor symptoms. While they did not look at the interaction of both laterality and nature of motor symptoms, Direnfeld and colleagues (1984) and Tomer and colleagues (1993) each found that left sided motor symptoms were associated with reduced memory performance. In contrast, Katzen and colleagues (2006) found that individuals with right sided onset performed better than individuals with left sided onset on the California Verbal Learning Test, a similar assessment to the HVLT. These results are interesting and suggest that even in the verbally mediated tasks, memory is supported by right hemisphere functioning.

With regard to *visuospatial* tasks such as line orientation, as was measured by the JOLO, Verreyt and colleagues (2011) reported that individuals with left sided symptoms performed worse than individuals with right sided symptoms across several studies. Additionally, Katzen and colleagues (2006) found that individuals with L-TO onset performed worse than individuals with R-TO onset on visuospatial tasks. Similarly, the current study found that worse performance on the JOLO predicted left sided group membership, that is, the L-B/RO group performed significantly worse than the R-TO group. These results are consistent with research suggesting that the right hemisphere contributes most to tasks that are visually mediated (Amick et al. 2006; Tomer et al. 1993) and provides supportive evidence of a right hemisphere influence on tasks of visuospatial function.

Within the *language* domain, the review by Verreyt and colleagues (2011) suggested that right sided symptoms were associated with worse performance on naming and vocabulary measures than left sided symptoms. In contrast, Katzen and colleagues (2006) found that R-TO

individuals with PD performed better on semantic and phonemic verbal fluency measures then other subgroups. The current study found no significant differences between subgroups based on laterality and/or nature of motor symptoms on measures of semantic and phonemic verbal fluency, or on the Shipley II vocabulary subtest. This finding may, in part, be explained by the contribution of executive function skills for completing measures of verbal fluency, which are also not predictive of group membership. The null results from the Shipley vocabulary subtest are interesting. Considering most individuals are left hemisphere dominant for language, one would expect that right sided symptom onset would be predictive of language deficits. The present results suggest that verbal fluency and vocabulary measures are influenced little by laterality or nature of motor symptoms. It should be noted that the breadth of measures in the language domain was limited. The Boston Naming Test, an assessment that focuses more directly on language access and naming, was omitted from the main analysis because of a low sample size. Moreover, a discourse level language measure was not included in the neuropsychological test battery. As previously discussed, discourse level language processes are often affected in individuals with PD to a greater extent than word level semantic access or object naming measures. A discourse level language measure might have been more sensitive to the types of language deficits documented in individuals with PD.

Finally, individuals in the R-B/RO group significantly differed from the base group (R-TO) with respect to two variables. First, the R-B/RO group was significantly younger when they were diagnosed with PD and younger at the time of neuropsychological testing than individuals in the R-TO group. Additionally, the R-B/RO group reported significantly less depression on the Geriatric Depression Scale than individuals in the R-TO base group. Van der Hoek and

colleagues (2011) similarly reported a trend towards reduced prevalence of a major depressive disorder in the bradykinesia/rigidity dominant group compared to the tremor dominant group in their study characterizing depressive symptoms in motor subgroups of individuals with PD. It is possible that less depression and younger average age in the R-B/RO subgroup may have buffered their performance across cognitive measures in comparison with the base group. Further research is recommended to examine possible genetic factors contributing to this intriguing finding of younger age and less depressive symptoms within this subgroup.

Overall, the results of the current study reinforce the findings of Katzen et al. (2006) that laterality and nature must be considered in combination to unveil the relationship between cognitive profile and initial motor symptoms. However, while Katzen and colleagues found that the R-TO subgroup performed better than other subgroups and similarly to healthy controls, the current study found that subgroup performance varied by cognitive domain.

Limitations

The complete neuropsychological test battery included a variety of measures from each cognitive domain. To maintain the highest level of power for the logistic regression analysis, only measures that were completed by both the annual and clinical samples were included, thereby significantly reducing the breadth of cognitive variables included in the analysis. The parsing of variables, however, allowed for a significantly larger sample size (323 participants) than previous research with similar objectives.

A second limitation of this study was that predominant motor symptoms were based on patient report, as determined by a health questionnaire completed on the same day as the neuropsychological testing. Although the neurologist or physician's assistant who administered

the neuropsychological test battery reviewed participant motor presentation on the day of testing, chart reviews for the current study were not completed. This information would have further verified that the patient's self- report matched the medical record from their PD diagnostic evaluation.

Clinical implications and future directions

The results from the current study suggest that patterns of cognitive decline are associated with nature and laterality of initial motor symptoms. This information is valuable for patients, families, and clinicians to develop functional treatment goals aimed towards maintenance of cognitive skills in specific cognitive domains, to teach compensatory strategies early in the disease progression in specific cognitive domains, and to assist in decision making concerning long term care. Specifically, for individuals with PD who present with initial left sided symptoms, a clinician may recommend a visuospatial screening measure. Moreover, individuals who present with left sided tremor at diagnosis may be particularly at risk for verbal memory assessment and may benefit from early screenings.

To enhance the current study, a cluster analysis is recommended for future research to examine characteristics of subgroups that naturally form without a priori hypothesis. These subgroups may then be compared to the hypothesis driven subgroups to examine additional factors contributing to patterns in cognitive profile in individuals with idiopathic PD.

This study found evidence to support the significance of motor phenotype associations with patterns of cognitive profile. Other research has focused on the neurophysiological processes that contribute to clinical profile (Delong and Wichmann, 2007; Middleton and Strick, 2000; Obeso et al. 2008; Taylor and Saint-Cyr, 1995). Delong and Wichmann (2007) and Obeso

and colleagues (2008) looked at changes in discharge rate, pattern, and synchronization of neuronal discharge from the basal ganglia in individuals with PD. While some authors suggest that cognitive loops of the basal ganglia that connect to the pre-frontal dorsolateral cortex may be distinct from motor loops that connect to the motor cortex and supplementary motor cortex (Delong & Wichmann, 2007), others suggest that currently accepted theoretical models do not explain cognitive deficits in PD (Obeso et al, 2008). Pathways from the cortex to basal ganglia are poorly understood and continue to be a fascinating subject for continued future research.

Another intriguing finding in the current research concerns the genetic component of PD subtypes. For example, the L-B/RO group had only 13% of members who had at least one other immediate family member with PD, whereas the other three groups had at least one other immediate family member with PD between 25-39% of the time. Further research is recommended to examine possible relationships between genetic influence and clinical PD subgroups.

In sum, the current study has provided evidence to suggest that patterns of cognitive profiles in individuals with idiopathic PD should be determined from information regarding the combination of laterality and nature of motor symptoms at disease onset. The investigation of these motor variables in isolation may obscure the continued elucidation of clinical subgroups.

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Appendix A. UK Brain Bank Criteria

SUBJECT ID

PD CLINICAL DATA SHEET, PART I

Date _____/_____/_____

Reviewer: _____

Step 1, Inclusion criteria

1) Does subject have bradykinesia? Yes ☐ No ☐ Unknown ☐

2) Does subject have at least one of the following symptoms:

Muscular rigidity Yes ☐ No ☐ Unknown ☐

4-6 Hz rest tremor Yes ☐ No ☐ Unknown ☐

Postural instability Yes ☐ No ☐ Unknown ☐

Postural instability must not be caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Step 2, Exclusion criteria

3) Does subject have any of the following: Yes ☐ No ☐ → **if yes, STOP, does not meet criteria**

- ☐ History of repeated strokes with stepwise progression of parkinsonian features
- ☐ History of repeated head injury
- ☐ History of definite encephalitis
- ☐ Oculogyric crises
- ☐ Neuroleptic treatment at onset of symptoms
- ☐ Sustained remission
- ☐ Strictly unilateral features after 3 years
- ☐ Supranuclear gaze palsy (other than restriction of upward gaze)
- ☐ Cerebellar signs
- ☐ Early severe autonomic involvement
- ☐ Early severe dementia with disturbances of memory, language, and praxis
- ☐ Babinski sign
- ☐ Presence of cerebral tumor or communicating hydrocephalus on CT scan
- ☐ Negative response to large doses of levodopa (if malabsorption excluded)
- ☐ MPTP exposure

Step 3, Supportive prospective positive criteria for Parkinson's disease

(Three or more required to be eligible for study)

4) Unilateral Onset Yes ☐ No ☐ Unknown ☐

5) Rest tremor present Yes ☐ No ☐ Unknown ☐

6) Progressive disorder Yes ☐ No ☐ Unknown ☐

7) Persistent asymmetry affecting side of onset most Yes ☐ No ☐ Unknown ☐

8) Excellent response (70-100%) to levodopa (or DA) Yes ☐ No ☐ Inadequate/No Trial ☐

9) Severe levodopa-induced chorea Yes ☐ No ☐ Unknown ☐

10) Levodopa response for 5 years or more Yes ☐ No ☐ Unknown ☐

11) Clinical course of 10 years or more Yes ☐ No ☐ Unknown ☐

Subject meets UKPDSBB Clinical Diagnostic Criteria Yes ☐ No ☐ Unknown ☐

Other

12) Hoehn & Yahr Stage: 1 ☐ 1.5 ☐ 2 ☐ 2.5 ☐ 3 ☐ 4 ☐ 5 ☐

13) Documented orthostatic hypotension Yes ☐ No ☐ Unknown ☐

14) Peripheral neuropathy Yes ☐ No ☐ Unknown ☐

15) History of hyperkinesia Yes ☐ No ☐ Unknown ☐

16) History of dystonia Yes ☐ No ☐ Unknown ☐

17) Dementia Yes ☐ No ☐ Unknown ☐

18) Neurologist: Agarwal ☐ Gerton ☐ Griffith ☐ Hu ☐ Kim ☐ Ro ☐ Roberts ☐ Samii ☐ Other ☐_____

Are there any medical, neurological, or psychiatric conditions, other than PD, that you are aware of that could compromise this subject's cognition.

_____

_____

_____

Appendix B. Studies examining the relationship between nature/side of symptom onset and cognitive-linguistic function in individuals with Parkinson's disease.

Study	N	Mean Age (SD) in yrs	Sex M/F	Mean Education (SD) in yrs	PD Severity	Side of Onset Determination	Initial Motor Symptom Determination	Cognitive measures	Conclusions
Amick, Grace & Chou (2006)	30 PD	**LPD:** 66.8 (7.5) **RPD:** 59.9 (11.9)	20/10	**LPD:** 12.9 (2.7) **RPD:** 15.2 (3.9)	*H&Y range:* **LPD:** 1-4 **RPD**: 1-4 *UPDRS:* **LPD:** *M* = 25.4 (10.9) **RPD:** *M*= 18.2 (16.6)	Retrospective medical chart review (based on patient report and motor examination)	H&Y scale and UPDRS motor section within two months of cognitive testing	• Either Dementia Rating Scale (DRS) or MMSE converted to DRS • Learning Hopkins Verbal Learning Test- Revised (HVLT-R) • Learning Brief Visual Memory Test- Revised (BVMT-R) • Delayed Recall HVLT-R • Delayed Recall BVMT-R	LPD group had poorer visual learning and delayed recall relative to verbal memory skills; RPD group had poorer verbal than visual memory.
Cheesman, Barker, Lewis, Robbins, Owen, Brooks (2005)	16 PD	61.3 (7.0)	8/ 8	Not reported	*H&Y range:* 1.0-2.5 *M*=2.0 (0.4) *UPDRS*: *M*= 34.8 (10.2)	N/A	N/A	• National Adult Reading Test • Phonological Fluency • Semantic Fluency • Subtests of the Cambridge Neuropsychological Test • Tower of London (TOL)	Right caudate dopamine uptake correlated with TOL and left anterior putamen uptake with verbal working memory task performance.
Cooper, Mikos,	117	65.03 (9.81)	Not	Not	*UPDRS*	Minimum of a 2 point difference	UPDRS motor scale	• DRS • MMSE	Right sided motor impairment was

Wood, Kirsch-Darrow, Jacobsen, Okun, Rodriguez, Bowers & Fernandez, 2009	PD		reported	reported	*M= 41.81 (13.02), range= 15-81*	between right and left symptoms on UPDRS motor scale *all symptoms included in analysis for participants- no predominant side determination	determined at time of testing	• Verbal fluency • HVLT-R • WMS subtests • Stroop color word interference • Digit span backwards • TMT • Benton Test of Facial recognition • JOLO	associated with decreased verbal memory, visuoperceptual skills, and verbal fluency. Left sided motor symptoms were not associated with any cognitive domains.
Direnfeld, Albert, Volicer, Langlais, Marquis & Kaplan, 1984	10 PD 10 AD 12 Controls	**PD:** 69.0 (5.9) **AD:** 67.6 (6.7) **Control:** 62.5 (7.4)	32/0	**PD:** 11.0 (3.4) **AD:** 11.0 (4.5) **Control:** 12.0 (3.0)	Overall PD severity rated on a scale from 0-5.	Based on patient report, history and physical examination at time of study	Cardinal features rated on a scale of 0-4 at time of study	• Boston Naming Test (BNT) • Subtests of Boston Diagnostic Aphasia Exam (BDAE) • Subtests of WAIS • Subtests of Weschler Memory Scale (WMS) • Hooper Visual Organization Test (HVOT) • Clock Drawing • Supraspan Test	No significant differences were reported in language and attention tasks between PD groups. LPD and RPD groups had worse visuospatial function scores than controls. LPD group performed worse than RPD group and controls in memory. All tests completed in the "off" state.

Elgh, Domellöf, Linder, Edström, Stenlund & Forsgren (2009)	88 PD 30 Controls	**PD:** 68.1 (9.3) **Control:** 68.2 (6.6)	**PD:** 49/39 **Control:** 16/14	**PD:** 9.9 (4.1) **Control:** 11.5 (3.5)	*UPDRSIII* range= 5-48 *M*=23.8 (9.7)	N/A	UPDRS scores determined at time of study	• Subtests of WMS • Free and Cued Selective Reminding Test • BVMT • Digit Span-WAIS III • Electronic tapping test -Western Psychological Services (WPS) • Trail Making Test (TMT) • Controlled Oral Word Association (COWAT) • BNT • Benton Judgment of Line Orientation Test • Wisconsin card sorting test (WCST)	Cognitive impairment correlated with symptoms of bradykinesia, speech impairment, and rigidity but not tremor in the PD group. All tests completed in the "off" state.
Foster, Black, Hershey, Antenor-Dorsey & Perlmutter, (2008)	35 PD 28 controls	**RPD:** 59.3 (12.0) **LPD:** 57.5 (11.0) **Control:** 54.1 (14.0)	**PD:** 26/ 28 **Control:** 18/25	**RPD:** 15.5 (2.7) **LPD:** 14.8 (2.8) **Control:** 14.8 (2.8)	H&Y stage I or II	Medical chart review and patient report; side of symptoms at time of study obtained by UPDRS score	UPDRS scores determined at time of study	• Subtests of WMS • Short term spatial memory • Spatial delayed response (SDR) • Verbal fluency • Subtest of Wide Range Achievement Test-3R	Participants with LPD had poorer SDR than participants with RPD who performed similarly to controls. Smaller right substantia nigra volumes correlated with poorer SDR scores.

Holtgraves, McNamara, Cappaert, & Durso, (2010)	31 PD	69.8 (SD not reported)	30/1	88% completed high school; 51% completed some college	H&Y stage II-III; *M*= 2.57 (0.63)	Motor symptom asymmetry score determined by UPDRS at time of study	UPDRS scores determined at time of study	• Linguistic Inquiry and Word Count program • Stroop task • Phonological fluency • Semantic fluency • Autobiographical memory task	LPD group produced fewer verbs, function words, and shorter sentences than RPD group in a natural context independent of overall motor severity.
Huber, Miller, Bohaska, Christy & Bornstein, 1992	22 PD	**RPD:** 63.7 (7.3) **LPD:** 66.5 (5.5)	Reported as not significantly different between groups	**RPD:** 13.9 (3.2) **LPD:** 14.4 (1.8)	H&Y stage II Schwab and England functional disability scale: RPD: 78.3 LPD: 73	Motor symptom asymmetry score determined by UPDRS at time of study; only participants with continued predominance on side of initial onset were included.	UPDRS scores determined at time of study	• WAIS-R • Verbal Concept Attainment Test • WCST • WMS-R	RPD group had greater cognitive impairment on verbally mediated tasks compared to the LPD group. RPD group performed similarly to LPD groups in tasks of visuospatial function.
Katzen, Levin, & Weiner (2006)	58 PD 40 control	**RSO-T:** 67.07 (5.3) **RSO-BR:** 59.75 (14.1) **LSO-T:** 65.47 (9.9) **LSO-BR**: 67.92 (8.2) **Controls:** 68.3 (6.1)	**PD:** 33/25 **Control:** 29/21	**RSO-T:** 13.07 (3.1) **RSO-BR:** 14.17 (2.9) **LSO-T:** 14.16 (2.3) **LSO-BR:**	H&Y stages I-IV Northwestern University Disability Scale range: 18.00 (12.82)-21.11 (12.54)	Determined by patient report (interview) and retrospective medical chart review	Determined by patient report (interview) and retrospective medical chart review	• BNT • COWAT • California Verbal Learning Test (CVLT) • Ghent Embedded Figures Test (GEFT) • HVOT • Judgment of Line Orientation Test (JLOT) • WCST	RSO-BR, LSO-BR, and LSO-T had poorer scores in visuospatial, memory, and executive function tasks than RSO-T participants. RSO-T group performed similarly to healthy controls in all cognitive testing.

				14.08 (2.0) **Controls** 13.5 (2.3)					
Selikhova, Williams, Kempster, Holton, Revesz, & Lees (2009)	242 PD (post-mortem)	**EDO:** 47.3 (6.5) **TD:** 66.1 (6.7) **NTD:** 64.8 (6.5) *Note, ages are age at disease onset	163/79	Not reported	H&Y stages 1-IV *Note, H&Y stages were reported at onset, and 5, 8, 10, 15 years post onset	N/A	Determined from clinical records at time of diagnosis using a 0-4 severity scale	• Time of dementia onset was defined by impairment of activities of daily living due to cognitive impairment (determined by retrospective medical chart review) • MMSE	NTD group had more severe cortical Lewy body pathology and were more likely to suffer from dementia than TD, EDO and RDP groups. Authors suggest a link between bradykinetic onset, cognitive decline and high cortical Lewy body occurrence is strong and likely to have a biological basis.
Spicer, Roberts & Lewitt, 1988	15 PD	**LPD:** 56.6 (7.0) **RPD:** 56.6 (9.8)	11/4	**LPD:** 12.9 (2.6) **RPD:** 13.7 (1.7)	Columbia Rating Scale (CRS) LPD: 13.75 (3.78) RPD: 21.14	CRS at least 2:1 ratio completed at time of testing	CRS rating scale determined at time of study	• Visual naming • Facial Recognition • JOLO • COWAT • Form Sequence Learning • Serial Digit Learning • MMSE • Subtest of WAIS-R	RPD groups had poorer serial digit learning, confrontation naming, and verbal fluency scores. No significant difference was found on tasks of line orientation or facial recognition.

					(10.52)				
Starkstein, Leiguarda, Gershanik & Berthier, 1987	18 PD	**LPD:** 58.6 (SD not reported) **RPD:** 56 (SD not reported)	12/6	**LPD:** 12 years **RPD:** 10 years	CRS determined at time of testing LPD: 53 RPD: 48	CRS at least 3:1 ratio completed at time of testing	CRS scores determined at time of study	• WAIS • WCST • Benton Test of Verbal Fluency • Auditory Verbal Learning Test • Benton Visual Retention Test • Line Bisection Task	RPD had poorer scores on verbal memory tasks and errors on the WCST than LPD group. There was no difference between groups on visuospatial tasks or word fluency tasks.
Tomer, Levin, Weiner (1993)	88 PD	**LSO:** 64.5 (7.9) **RSO**: 64.3 (10.4)	55/33	**LSO:** 14.1 (2.4) **RSO**: 14.5 (2.9)	H &Y stages: **LSO**= 2.1 (0.8) **RSO** = 1.9 (1.0) Columbia University motor disability scale (CUMDS) : **LSO**: 18.3(11.6) **RSO**: 15.6(10.5)	Initial neurological examination (chart review) and patient report. Motor symptom asymmetry score determined by CUMDS at time of study	CUMDS scores determined at time of study	• Subtests of WAIS-R • BNT • Verbal fluency • BJLO • Benton Facial recognition test • HVOT • GEFT • Gorham proverbs • recitation of month backwards, counting by 3 • WCST • WMS • CVLT • Benton's Visual Retention test	LSO group had poorer immediate and delayed verbal recall, word retrieval, semantic verbal fluency, visuospatial analysis, abstract reasoning, attention span, and mental tracking than RSO group as determined by side of symptom onset (rather than current symptom asymmetry). Authors suggest an overall modulatory function of cognition by the right dopaminergic system.

Williams, Seignourel, Crucian, Okun, Rodriguez, Skidmore, Foster, Fernandez, (2007)	108 PD	67.12 (10.4)	Not reported	14.69 (3.36)	Total motor UPDRS score: *M* = 38.8 (13.9) MMSE: *M*= 27.3 (3.4)	Motor symptom asymmetry score determined by UPDRS at time of study	UPDRS scores determined at time of study	• MMSE • DRS-2	Right-sided symptoms (for laterality), axial symptoms (for region), and bradykinesia (for type of symptoms) were the most significant predictors of cognitive performance. Cognitive impairment is correlated with motor symptom severity but not disease duration.

Note. PD = Parkinson's disease; LPD = Left sided predominant motor symptoms; RSO = right sided predominant motor symptoms; H&Y = Hoehn and Yahr (1967) staging criteria; UPDRS= Unified Parkinson's Disease rating scale (); AD= Alzheimer's dementia; RSO-T= Right-sided onset-tremor; RSO-BR= right-sided onset- bradykinesia/rigidity; LSO-T= Left-sided onset-tremor; LSO-BR= Left sided onset-bradykinesia/rigidity; EDO= Earlier disease onset; TD= tremor dominant; NTD= non-tremor dominant; LSO= left side onset; RSO= right side onset.

Appendix C. Means (standard deviations) of cognitive variables of interest for four subgroups of participants with idiopathic PD based on nature and laterality of motor symptoms at disease onset

Cognitive Variables	**Right-sided onset**		**Left-sided onset**	
	Bradykinesia/ Rigidity	*Tremor*	*Bradykinesia/ Rigidity*	*Tremor*
N (total=323)	41	130	39	113
Semantic Verbal Fluency				
Animals	18.707 (6.59)	18.06 (6.32)	18.08 (6.09)	19.08 (5.76)
Vegetables	12.512 (4.30)	12.29 (4.83)	12.28 (4.52)	12.80 (4.65)
Phonemic Verbal Fluency				
F words	12.902 (3.69)	13.25 (4.80)	13.64 (5.00)	13.42 (4.41)
A words	11.024 (3.78)	11.59 (4.93)	11.56 (4.96)	11.29 (4.62)
S words	13.317 (3.82)	13.64 (5.72)	13.67 (6.41)	14.05 (5.27)
FAS sum	37.244 (9.56)	38.67 (13.71)	38.87 (15.05)	38.76 (12.51)
Shipley Vocabulary	34.561 (2.84)	33.95 (3.74)	34.21 (3.01)	34.30 (2.79)
JOLO	12.463 (2.03)	11.97 (2.49)	11.40 (1.99)	11.91 (2.60)
WAIS-R Digit Symbol	37.13 (14.34)	37.47 (11.62)	35.85 (14.51)	40.63 (12.67)
Letter Number Sequencing	9.156 (2.52)	8.27 (2.64)	8.12 (3.84)	8.82 (2.66)
G Stroop	168 (35.16)	166.15 (36.28)	153.15 (27.21)	182.89 (28.19)
Stroop Interference correct	29.357 (9.80)	29.53 (9.37)	24.86 (9.54)	32.54 (7.69)
Trails A time	41.425 (18.68)	46.97 (26.89)	44.56 (25.77)	41.15 (28.03)
Trails B time	131.575 (90.51)	148.96 (79.63)	159.26 (91.39)	127.23 (76.45)
Trails B-A time	90.15	101.99	114.69	86.08
HVLT immediate				
Trial 1	5.14 (1.70)	5.28 (1.87)	5.29 (1.95)	5.18 (1.97)
Trial 2	7.8 (2.26)	7.478 (2.29)	7.89 (2.17)	7.45 (2.21)
Trial 3	9.17 (2.16)	8.42 (2.52)	8.54 (2.13)	8.35 (2.38)
Trial 4	7.8 (3.35)	6.61 (3.66)	7.54 (3.23)	6.89 (3.72)
HVLT total recall	22.11 (5.37)	21.17 (6.05)	21.71 (5.52)	20.98 (5.93)
HVLT total retention %	80.95 (29.00)	73.19 (35.41)	82.95 (27.04)	76.07 (35.49)
*Logical Memory immediate	11.14 (3.53)	11.5 (3.85)	13.67 (4.39)	11.35 (3.93)
*Logical Memory Delayed	9.48 (4.19)	9.48 (4.08)	11.22 (4.41)	9.76 (4.28)
DRS-2 Mattis	136.9 (5.33)	135.22 (6.21)	137.85 (4.49)	136.17 (7.04)
MMSE	28.34 (1.88)	27.57 (1.99)	27.77 (2.12)	27.66 (2.09)
MoCA	24.49 (2.65)	24.19 (3.04)	24.85 (3.01)	24.84 (2.79)

Note: Table includes complete battery of assessments administered to participants in the annual sample. Tests with an asterisk were not included in the shortened test battery of the clinical sample. Variables chosen for further analysis were based on (1) item distribution, (2) cross-correlation of the variables, (3) number of participants who completed the measure, and 4) the need for adequate representation in each cognitive-linguistic domain.

Appendix D. Complete Neuropsychological Testing Battery

1. Mattis
2. Hopkins Verbal Learning Test (HVLT) Registration
3. Trails Making Test A & B
4. Digit Symbol, Wechsler Adult Intelligence Scale –Revised (WAIS-R)
5. Judgment of Line Orientation (JOLO)
6. Stroop
7. HVLT Delayed Recall
8. HVLT Delayed Recognition
9. Letter Number Sequencing (WAIS-III)
10. Montreal Cognitive Assessment (MoCA) includes "F"
11. Phonemic Verbal Fluency "A" and "S"
12. Semantic Verbal Fluency "Animals" and "Vegetables"
13. Shipley Vocabulary II
14. Logical Memory 1 Wechsler Memory Scale-Revised (WMS-R)*
15. Benton Visual Retention Test (BVRT) Immediate Recall- Form C*
16. Tower of London*
17. Boston Naming Test*
18. BVRT Delayed Recall (17-22 minutes)*
19. BVRT Copy Task- Form C*
20. Digit Span (WAIS-R)*
21. Logical Memory II (WMS-R)*
22. Logical Memory Delayed Recognition (WMS-R)*
23. Mini Mental Status Exam (MMSE)*

Note: Assessments marked with an asterisk (*) were included only in the full neuropsychological test battery administered to the annual sample.

Appendix E. Logistic regression results

```
. mlogit side_tremor vegetables_nomiss fas_sum_nomiss shipley_2_nomiss jolo_tota
> l_correct_nomiss wais_digit_symbol_score_nomiss let_num_sequencing_total_nomis
> s   hvlt_total_recall_nomiss moca_score ageatonset gds_total

Iteration 0:   log likelihood = -333.60466
Iteration 1:   log likelihood =  -312.3015
Iteration 2:   log likelihood = -311.20619
Iteration 3:   log likelihood = -311.20048
Iteration 4:   log likelihood = -311.20048

Multinomial logistic regression                 Number of obs   =        269
                                                LR chi2(30)     =      44.81
                                                Prob > chi2     =     0.0402
Log likelihood = -311.20048                     Pseudo R2       =     0.0672

------------------------------------------------------------------------------
 side_tremor |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
RO__NT       |
vegetable~ss |  -.0184003   .0602745    -0.31   0.760    -.1365361    .0997355
fas_sum_no~s |  -.0317231   .0216802    -1.46   0.143    -.0742155    .0107694
shipley_2_~s |    .007701   .0788181     0.10   0.922    -.1467795    .1621815
jolo_tota~ss |   .1217195   .1119017     1.09   0.277    -.0976038    .3410427
wais_digi~ss |  -.0221398     .02065    -1.07   0.284    -.0626132    .0183335
let_num_se~s |   .1261272   .1023916     1.23   0.218    -.0745567    .3268111
hvlt_total~s |   .0108582   .0517905     0.21   0.834    -.0906493    .1123656
  moca_score |  -.0404515   .0945921    -0.43   0.669    -.2258486    .1449457
  ageatonset |  -.0711781   .0280623    -2.54   0.011    -.1261791    -.016177
   gds_total |  -.4109572   .1597192    -2.57   0.010    -.7240011   -.0979134
       _cons |   5.454696   3.744133     1.46   0.145    -1.883669    12.79306
-------------+----------------------------------------------------------------
RO_T         |  (base outcome)
-------------+----------------------------------------------------------------
LO__NT       |
vegetable~ss |  -.0194574   .0559754    -0.35   0.728    -.1291673    .0902524
fas_sum_no~s |   .0109372   .0197673     0.55   0.580     -.027806    .0496804
shipley_2_~s |    .019482   .0759808     0.26   0.798    -.1294377    .1684017
jolo_tota~ss |  -.1762936   .0882596    -2.00   0.046    -.3492792   -.0033079
wais_digi~ss |  -.0116404   .0207786    -0.56   0.575    -.0523657     .029085
let_num_se~s |  -.0473208   .0892455    -0.53   0.596    -.2222387    .1275971
hvlt_total~s |   .0133744    .047127     0.28   0.777    -.0789928    .1057416
  moca_score |    .182509   .0880134     2.07   0.038      .010006     .355012
  ageatonset |   .0042795   .0247293     0.17   0.863    -.0441891     .052748
   gds_total |   .0279053   .1214778     0.23   0.818    -.2101868    .2659974
       _cons |  -4.398394   3.661592    -1.20   0.230    -11.57498    2.778195
-------------+----------------------------------------------------------------
LO__T        |
vegetable~ss |   .0116285   .0399562     0.29   0.771    -.0666842    .0899411
fas_sum_no~s |  -.0140132   .0139524    -1.00   0.315    -.0413593    .0133329
shipley_2_~s |   .0367128   .0529782     0.69   0.488    -.0671225    .1405482
```

```
jolo_tota~ss |  -.0691694   .0668927    -1.03   0.301    -.2002766    .0619378
wais_digi~ss |   .0178636    .014687     1.22   0.224    -.0109223    .0466495
let_num_se~s |   .0338765   .0649504     0.52   0.602    -.0934239    .1611769
hvlt_total~s |  -.0682822   .0342211    -2.00   0.046    -.1353543   -.0012102
  moca_score |   .1170786   .0631838     1.85   0.064    -.0067594    .2409166
  ageatonset |  -.0226233   .0175992    -1.29   0.199    -.0571171    .0118706
   gds_total |  -.1721045    .094759    -1.82   0.069    -.3578287    .0136197
       _cons |   -.195143   2.490194    -0.08   0.938    -5.075833    4.685547
------------------------------------------------------------------------------
```

```
. logit tremor_group vegetables_nomiss fas_sum_nomiss shipley_2_nomiss jolo_tota

> l_correct_nomiss wais_digit_symbol_score_nomiss let_num_sequencing_total_nomis
> s   hvlt_total_recall_nomiss moca_score ageatonset gds_total

Iteration 0:   log likelihood =  -147.5918
Iteration 1:   log likelihood =  -144.4025
Iteration 2:   log likelihood = -144.37231
Iteration 3:   log likelihood = -144.37231

Logistic regression                                     Number of obs   =        269
                                                        LR chi2(10)     =       6.44
                                                        Prob > chi2     =     0.7771
Log likelihood = -144.37231                             Pseudo R2       =     0.0218

------------------------------------------------------------------------------
tremor_group |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
vegetable~ss |   .0235064   .0402749     0.58   0.559    -.0554309    .1024437
fas_sum_no~s |   .0027819   .0142187     0.20   0.845    -.0250862      .03065
shipley_2_~s |  -.0007883   .0538435    -0.01   0.988    -.1063196     .104743
jolo_tota~ss |    .016871   .0667231     0.25   0.800    -.1139038    .1476458
wais_digi~ss |   .0232536   .0145375     1.60   0.110    -.0052393    .0517465
let_num_se~s |  -.0175062   .0659706    -0.27   0.791    -.1468062    .1117939
hvlt_total~s |  -.0354231   .0339365    -1.04   0.297    -.1019373    .0310911
  moca_score |  -.0155774   .0622211    -0.25   0.802    -.1375284    .1063737
  ageatonset |   .0200312   .0179164     1.12   0.264    -.0150844    .0551468
   gds_total |   .0773169   .0935535     0.83   0.409    -.1060445    .2606784
       _cons |  -.6723123   2.533406    -0.27   0.791    -5.637697    4.293072
------------------------------------------------------------------------------

.
```

```
. logit left_group vegetables_nomiss fas_sum_nomiss shipley_2_nomiss jolo_total_
> correct_nomiss wais_digit_symbol_score_nomiss let_num_sequencing_total_nomiss
>    hvlt_total_recall_nomiss moca_score ageatonset gds_total

Iteration 0:   log likelihood = -186.23162
Iteration 1:   log likelihood = -179.65058
Iteration 2:   log likelihood = -179.63861
Iteration 3:   log likelihood = -179.63861

Logistic regression                                     Number of obs   =        269
                                                        LR chi2(10)     =      13.19
                                                        Prob > chi2     =     0.2135
Log likelihood = -179.63861                             Pseudo R2       =     0.0354

------------------------------------------------------------------------------
  left_group |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
vegetable~ss |     .00702    .034652     0.20   0.839    -.0608966    .0749366
fas_sum_no~s |  -.0019244   .0120977    -0.16   0.874    -.0256354    .0217867
shipley_2_~s |   .0296784   .0460709     0.64   0.519    -.0606188    .1199757
jolo_tota~ss |  -.1167424    .058269    -2.00   0.045    -.2309476   -.0025372
wais_digi~ss |   .0152064   .0126408     1.20   0.229    -.0095691    .0399819
let_num_se~s |  -.0134016    .056694    -0.24   0.813    -.1245198    .0977166
hvlt_total~s |  -.0472412   .0295282    -1.60   0.110    -.1051154    .0106329
  moca_score |   .1416641   .0548906     2.58   0.010     .0340804    .2492478
  ageatonset |  -.0023991   .0151077    -0.16   0.874    -.0320097    .0272114
   gds_total |  -.0406463   .0802055    -0.51   0.612    -.1978461    .1165536
       _cons |  -2.292591   2.163805    -1.06   0.289     -6.53357    1.948388
------------------------------------------------------------------------------
```