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BRIEF COMMUNICATION

Neuropsychological Test Performance in Parkinsonism Without Dopaminergic Deficiency on [123I]-FP-CIT SPECT Imaging

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Abstract

Objectives: To examine neuropsychological test performance among individuals clinically diagnosed with Parkinson's disease (PD) without evidence of dopaminergic deficiency on [123]I-CIT single photon emission computed tomography imaging. **Methods:** Data were obtained from the Parkinson's Progression Marker Initiative. The sample included 59 participants with scans without evidence of dopaminergic deficiency (SWEDD), 412 with PD, and 114 healthy controls (HC). Tests included Judgment of Line Orientation, Letter-Number Sequencing, Symbol Digit Modalities, Hopkins Verbal Learning Test-Revised, and Letter and Category Fluency. Multivariate analysis of variance was used to compare standardized scores between the groups. **Results:** There was a statistically significant difference in performances between the groups, $F(14,1155) = 5.04$; $p < .001$; partial $\eta^2 = .058$. Pairwise comparisons revealed significant differences in Category Fluency between SWEDD ($M = 0.22$; $SD = 1.08$) and HC ($M = 0.86$; $SD = 1.15$) and in Symbol Digit Modalities Test performance between SWEDD ($M = 45.09$; $SD = 11.54$) and HC ($M = 51.75$; $SD = 9.79$). No significant differences between SWEDD and PD were found. Using established criteria, approximately one in four participants in the SWEDD and PD groups met criteria for mild cognitive impairment (MCI). **Conclusions:** Individuals with SWEDD demonstrate significantly worse mental processing speed and semantic fluency than HC. The neuropsychological test performances and rates of MCI were similar between the SWEDD group and PD groups, which may reflect a common pathology outside of the nigrostriatal pathway. (*JINS*, 2018, *24*, 646–651)

Keywords: Cognition, Parkinsonism, SPECT, Subjects without evidence of dopaminergic deficiency

INTRODUCTION

The role of nigrostriatal dopamine deficits in Parkinson's disease (PD) has been firmly established (Perlmutter & Eidelberg, 2012). In recent years, dopamine transporter-single photon emission computed tomography (DaT-SPECT) has been used to detect degeneration of pre-synaptic dopamine receptors and neurons in the nigrostriatal structures (Ba & Martin, 2015; Perlmutter & Eidelberg, 2012). Of interest, multiple studies have shown that more than 10% of individuals who are thought to have PD based upon clinical criteria have normal DaT-SPECT findings (The Parkinson Study Group, 2004; Marek, Jennings, & Seibyl, 2005). When this occurs, the neuroimaging has been referred to as scans without evidence of dopaminergic deficit (SWEDD; Marek, Jennings & Seibyl, 2005).

The true etiology of the symptoms experienced by patients with SWEDD remains controversial, and it has been suggested that these individuals may represent a heterogeneous group comprised of different disorders (Erro et al., 2016). When patients with SWEDD were initially discovered, it was hypothesized that these patients might be within a prodromal phase of PD (Stoessl, 2010); however, subsequent research has demonstrated significant differences between patients with dopamine deficient scans and patients with SWEDD. Patients with SWEDD lack response to

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levodopa (The Parkinson Study Group, 2004) and do not demonstrate deficits in olfaction as frequently as patients with dopamine deficient PD (Silveira-Moriyama et al., 2009). Patients with SWEDD also have more significant cardiovascular and thermoregulatory dysfunction, orthostatic hypotension, sleep disturbances, and higher frequencies of daytime sleepiness than dopamine deficient PD patients (Sprenger et al., 2015).

Although patients with SWEDD can present with motor features similar to those patients with dopamine deficient PD, previous longitudinal research suggests that patients with SWEDD do not demonstrate progression of motor symptoms (Marshall, Patterson, Hadley, Grosset, & Grosset, 2006) and continue to have normal DaT-SPECT findings for up to 4 years after they are initially identified (Marek et al., 2014). In a 5-year follow-up study of 16 patients with SWEDD, only two patients demonstrated reduced dopamine uptake on DaT-SPECT, while 14 remained classified as SWEDD (Batla et al., 2014). These studies seem to indicate that individuals with SWEDD have a distinct pathology different from individuals with dopamine deficient PD (Erro, Schneider, Quinn, & Bhatia, 2016; Marek et al., 2014; Sprenger et al., 2015).

Researchers have demonstrated that cognitive impairment is frequently associated with idiopathic PD (Muslimovic, Post, Speelman, De Haan, & Schmand, 2009), and cognitive deficits can be identified in up to 34% of patients even in the early, untreated stages of the disease (Pfeiffer, Lokkegaard, Zoetmulder, Friberg, & Werdelin, 2014). This cognitive dysfunction may be related, in part, to dopaminergic deficit. While there are some inconsistent findings in the literature (Poletti & Bonuccelli, 2013), functional MRI (fMRI) studies with patients on and off levodopa indicate that higher levels of dopamine are associated with better cognitive performances on tasks of working memory and response accuracy (Mattay et al., 2002).

Additionally, recent fMRI and DaT-SPECT research has demonstrated a positive correlation between nigrostriatal dopaminergic function and performance on tests of executive functioning and memory (Lebedev et al., 2014). However, dopamine deficiency may not explain all of the cognitive deficits in PD, as some degree of cognitive impairment is common in patients diagnosed with related movement disorders such as dystonia (Scott et al., 2003) and essential tremor (Lombardi, Woolston Roberts, & Gross, 2001), conditions that are not associated with dopaminergic deficiency on imaging (Menéndez-González, Tavares, Zeidan, Salas-Pacheco, & Arias-Carrion, 2014).

Based on the aforementioned findings, one might expect patients with SWEDD to have some degree of cognitive decline, but these patients might have better cognitive functioning than patients with dopamine deficient PD, since dopamine uptake is intact in patients with SWEDD. Of interest, however, when Wyman-Chick, Martin, Minar, and Schroeder (2017) compared individuals with SWEDD and PD using the Montreal Cognitive Assessment (MoCA) screening test, the results were in the opposite direction. Specifically, the individuals with SWEDD were more likely to decline cognitively than individuals with dopamine deficient PD at a 2-year follow-up interval.

While Wyman-Chick et al. (2017) found that individuals with SWEDD had cognitive decline detected by a cognitive screening test, there are no published studies specifically comparing cognitive dysfunction in individuals with SWEDD, individuals with PD and abnormal DaT-SPECT findings, and healthy controls (HC) when measured by more comprehensive neuropsychological testing. As such, this study was conducted. Based upon the preliminary findings of Wyman-Chick et al. (2017), it was hypothesized that participants with SWEDD would demonstrate evidence of cognitive impairment on more comprehensive neuropsychological measures when compared to PD and HC groups.

METHODS

Participants were identified retrospectively from the Parkinson's Progression Marker Initiative (PPMI) archival database, and data from the baseline PPMI visit were obtained. Information about the aims of PPMI study and methodology have previously been published (Marek et al., 2011) and are available on the PPMI Web site (http:/www.ppmi-info.org/study-design). This study was approved by the institutional review board at each participating PPMI data collection site. The institutional review board at the University of Kansas School of Medicine – Wichita also reviewed the study. Written informed consent was obtained from all study participants before enrollment.

Participants

A total of 585 participants were included in the current study, which included 59 participants with SWEDD, 412 participants with PD, and 114 HC.

All participants in the PD group and the SWEDD group received clinical diagnoses of idiopathic PD within the previous 24-months, and they were not taking any PD medication at the time of enrollment in the PPMI. Participants diagnosed with non-PD related parkinsonism at the time of study enrollment were excluded from participation. Participants with excessive stroke risk factors were excluded from the study if the investigator determined the participant's parkinsonian features were better accounted for by vascular parkinsonism. Participants diagnosed with idiopathic PD at baseline were separated into two groups based on DaT-SPECT findings: PD participants with dopaminergic deficiency and PD participants with SWEDD. DaT-SPECT image processing protocols and procedures for calculation of striatal binding ratios are available on the PPMI Web site (http://www.ppmi-info.org).

HC participants were individuals with normal imaging findings (MRI and DaT-SPECT) and without history of neurologic disease, motor symptoms, first degree relative with PD, or cognitive impairment as defined by a cutoff score of ≤ 26 on the MoCA. Unlike the healthy control group, there was no set cutoff for inclusion for the group diagnosed with PD; however, patients who were determined to meet criteria

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for dementia by the PPMI site investigator were excluded from participation.

Assessment Measures

The PPMI study includes neuropsychological tests that are widely used in clinical practice which assess several domains including learning, memory, working memory, visuospatial ability, verbal fluency, and processing speed. The tests included in PPMI are discussed below.

The MoCA is a brief cognitive screening measure that has been validated for use among individuals with PD. The cutoff point for normal cognition is 26/30 in the general population (Nazreddine et al., 2005) and in PD (Hoops et al., 2009). The Hopkins Verbal Learning Test – Revised (HVLT-R) is a 12-item verbal memory task. Standard test administration includes three learning trials (immediate recall) and a 20- to 25-min delay where participants are asked to recall the words previously learned (delayed recall; Brandt, 1991). Letter Number Sequencing (LNS) is a test of attention and working memory, in which the participant is asked to listen to a series of numbers and letters of increasing lengths and repeat numbers and letters from the lowest in each series, providing numbers first, then the letters (Wechsler, 1997). Judgement of Line Orientation (JLO) is a test of visual perception where participants are asked to estimate the angle between two line segments (Benton, Varney, & Hamsher, 1978). For the verbal fluency task, participants were asked to name as many animals as they could within 60 s. They were also asked to name as many words that start with the letter F that they could think of in 60 seconds (Straus, Sherman, & Spreen, 2006). Finally, the participants were administered Symbol Digit Modalities Test (SDMT), which is a timed number-symbol transcription task in which participants are asked to match numbers to a unique symbols as quickly as they can in 90 s (Smith, 1982).

The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (off medication) was used to measure motor symptoms for the participants in the SWEDD and PD groups. Lower scores on the MDS-UPDRS reflect fewer and/or less severe motor symptoms (Goetz et al., 2008).

Statistical Methods

Age, education, and MoCA scores were compared overall using univariate analysis of variance (ANOVA) and pairwise using Tukey's studentized range procedure. A multivariate ANOVA (MANOVA) was conducted to compare standardized neuropsychological test scores between the three groups. *Post hoc* analyses were then conducted, as appropriate, using Tukey's studentized range procedure. Independent samples *t* tests were used to compare duration of motor symptoms in months (log-transformed to account for non-normality) and motor symptom severity in the SWEDD and PD groups. Statistical analysis was performed with SAS Version 9.4.

Finally, the proportion of individuals in the SWEDD and PD groups meeting criteria for mild cognitive impairment (MCI) was compared using a chi-square analysis. Based on the Movement Disorder Society Task Force Level I guidelines for classifying PD-MCI, (Litvan et al., 2012), participants in the current study were classified as MCI if they scored 1.5 standard deviations below the normative mean on 2 or more neuropsychological tests. Of note, impairment on both HVLT-R immediate memory and HVLT-R delayed recall was considered to be impairment on one test.

RESULTS

Demographics

Demographic information for each of the groups is displayed in Table 1. There were no significant differences between the SWEDD group, the dopamine deficient PD group, and the HC group in terms of education. However, the PD group was significantly older than the HC group ($p = .015$). The SWEDD group and PD group did not differ in their MoCA scores.

The SWEDD group ($M = 23.92$; $SD = 28.09$) and the PD group ($M = 22.84$; $SD = 23.83$) did not differ significantly in terms of months of disease duration ($p = .753$). However, the PD ($M = 20.84$; $SD = 8.79$) group demonstrated significantly worse motor symptoms than the SWEDD group ($M = 14.61$; $SD = 9.67$), $t(468) = 5.03$; $p < .001$), as measured by the MDS-UPDRS-III.

Neuropsychological Test Performances

We tested the model assumptions for a MANOVA (normality, linearity, and homogeneity of variance and covariance) and deemed that this was an appropriate analysis for our data. Box's Test of Equality of Covariance Matrices was significant ($p < .001$), therefore, Pillai's Trace was used. The multivariate effect reflected significant differences in performances between the three groups, $F(14,1155) = 5.04$; $p \leq .001$; $\eta^2 = 0.058$. Univariate analyses were conducted, which revealed significant group differences on category verbal fluency performances, $F(2,583) = 6.91$; $p = 0.001$; $\eta^2 = 0.023$, HVLT delay ($F(2,583) = 3.61$; $p = .028$; $\eta^2 = 0.009$; and SDMT performances, $F(2,583) = 24.09$; $p < .001$; $\eta^2 = 0.076$ (Table 2).

Tukey's studentized range procedure was used for pairwise comparisons. There were no significant differences between the SWEDD group and the dopamine deficient group on any neuropsychological test. Of the significant univariate models, the HC group performed better than the SWEDD group on category fluency ($p \leq .001$) and SDMT ($p \leq .001$). The HC group performed better than the dopamine deficient PD group on tests of category fluency ($p = .03$), SDMT ($p \leq .001$), and HVLT delay ($p = .10$).

Motor symptom severity among participants with PD was negatively correlated with MoCA ($r = -0.13$; $p = .007$), JLO ($r = -0.15$; $p = .003$), SDMT ($r = -0.20$; $p \leq .001$), HVLT immediate ($r = -0.16$; $p = .001$), and HVLT delay

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Table 1. Demographics

	SWEDD $n = 59$ *M* (*SD*)	PD $n = 412$ *M* (*SD*)	HC $n = 114$ *M* (*SD*)	*F*-Value (2, 582)	*p*-Value
Age	60.10 (1.19)	61.19 (9.73)	58.56 (11.82)	2.99	0.051*[a]
Education	14.85 (3.73)	15.58 (2.99)	15.88 (2.79)	2.26	0.106
MoCA	27.56 (2.50)	27.47 (2.39)	28.64 (1.30)	14.01	<0.001**[b]

Note. SWEDD = scans without evidence of dopaminergic deficiency; PD = Parkinson's disease; HC = healthy controls; MoCA = Montreal Cognitive Assessment; * $p \leq .05$; ** $p \leq .001$
[a]PD group was significantly older than the HC group.
[b]HC group had significantly higher mean MoCA score compared to both PD and SWEDD groups.

(r = –0.12; $p = .012$). Among the SWEDD group, motor symptom severity was negatively correlated with SDMT (r = –0.32; $p = .036$), category fluency (r = 0.36; $p = .005$), and letter fluency (r = –0.30; $p = .021$).

Rates of MCI

Using established criteria to define MCI, 27.12% ($n = 16$) of the participants with SWEDD and 26.94% ($n = 111$) of the participants with dopamine deficient PD met criteria for MCI. There was not a significant difference between the proportions of participants with MCI between the two groups ($p = .977$).

DISCUSSION

In this study, the SWEDD group demonstrated similar cognitive performances when compared to the dopamine deficient PD group, but demonstrated statistically significant weaknesses in mental processing speed and category fluency when compared to the HC group. There were also significant correlations between greater severity of motor symptoms and weaker performance on cognitive testing in both PD and SWEDD groups. Of note, the mean cognitive performances in both the SWEDD and HC groups were within the average range of functioning. This is likely due to the fact that these comparisons were based on group comparisons, which attenuated some of the cognitive findings in the SWEDD group.

Indeed, when looking at cognitive performances on the individual case level, it can be seen that approximately one quarter of the participants with SWEDD met established criteria for MCI. The rate of MCI occurrence was similar to the rate found in the participants with dopamine deficient PD. Such findings, in particular, are of clinical significance because they indicate that a sizeable proportion of individuals with SWEDD, even in the initial years after symptom onset, demonstrate cognitive dysfunction that is of the same magnitude as that which is seen with dopamine deficient PD.

Because cognitive profiles and rates of MCI in these two parkinsonian groups were not significantly different from each other, one might wonder if cognitive dysfunction in individuals with PD and some individuals with SWEDD might be due to a common pathology that is outside of the nigrostriatal dopaminergic circuit.

Menéndez-González and colleagues (2014) have hypothesized that a sub-group of patients with SWEDD may be experiencing a neurodegenerative disease process, which differentially affects frontosubcortical circuits and leads to parkinsonian symptoms. While the current study is unable to document the exact etiology of the SWEDD patients, this study

Table 2. Neuropsychological test performance

	SWEDD n = 59 *M* (*SD*)	PD n = 412 *M* (*SD*)	HC n = 114 *M* (*SD*)	*F*-Value (2, 582)	*p*-Value	***d***
JLO (scaled score)	12.85 (3.10)	12.77 (2.76)	13.39 (2.45)	2.31	.100[a]	0.18
LNS (scaled score)	10.47 (2.70)	11.47 (2.70)	11.78 (2.76)	4.67	.010[ab]	0.26
SDMT (T-score)	45.09 (11.54)	44.90 (8.98)	51.75 (9.79)	24.09	<.001*[ab]	0.57
HVLT-R Immediate (T-score)	46.75 (10.67)	46.42 (11.04)	49.03 (10.21)	2.60	.075[a]	0.19
HVLT-R Delay (T-score)	48.76 (13.27)	46.87 (11.80)	50.05 (10.21)	3.61	.028*[a]	0.22
Category Fluency (*Z*-score)	0.22 (1.08)	0.61 (1.05)	0.86 (1.15)	6.91	.001*[ab]	0.30
Letter Fluency (*Z*-score)	–0.36 (1.07)	–0.20 (1.55)	0.01 (0.91)	1.62	.198	0.16

Notes: SWEDD = scans without evidence of dopaminergic deficiency; PD = Parkinson's disease; HC = healthy controls; JLO = Judgment of Line Orientation; LNS = Letter Number Sequencing; SDMT = Symbol Digit Modalities Test; HVLT-R = Hopkins Verbal Learning Test-Revised.
*Statistically significant *p*-value = .05; JLO and LNS are noted in Scaled Scores ($M = 10$, $SD = 3$), SDMT and HVLT are noted in T-scores ($M = 50$, $SD = 10$), and Verbal Fluency are noted in *Z*-scores ($M = 0$, $SD = 1$).
[a] = HC group performed significantly better than the PD group.
[b] = HC group performed significantly better than the SWEDD group

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does demonstrate that individuals with SWEDD perform significantly worse than controls and similarly to individuals with PD. As such, some support for the hypothesis of Menéndez-González et al. might be inferred.

In conclusion, even though the exact etiology of symptoms of the PPMI SWEDD group is unknown at this time, this study provides evidence that SWEDD should not be considered "benign," as has been previously suggested (Marshall et al., 2006). Clinicians need to be aware of the potential for underlying cognitive dysfunction among these individuals. Future studies should examine neuropsychological functioning in SWEDD groups longitudinally.

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