Effects of orthostatic hypotension on cognition in Parkinson disease

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ABSTRACT

Objective: To investigate the relation between orthostatic hypotension (OH) and posture-mediated cognitive impairment in Parkinson disease (PD) using a cross-sectional and within-group design.

Methods: Individuals without dementia with idiopathic PD included 18 with OH (PDOH) and 19 without OH; 18 control participants were also included. Neuropsychological tests were conducted in supine and upright-tilted positions. Blood pressure was assessed in each posture.

Results: The PD groups performed similarly while supine, demonstrating executive dysfunction in sustained attention and response inhibition, and reduced semantic fluency and verbal memory (encoding and retention). Upright posture exacerbated and broadened these deficits in the PDOH group to include phonemic fluency, psychomotor speed, and auditory working memory. When group-specific supine scores were used as baseline anchors, both PD groups showed cognitive changes following tilt, with the PDOH group exhibiting a wider range of deficits in executive function and memory as well as significant changes in visuospatial function.

Conclusions: Cognitive deficits in PD have been widely reported with assessments performed in the supine position, as seen in both our PD groups. Here we demonstrated that those with PDOH had transient, posture-mediated changes in excess of those found in PD without OH. These observed changes suggest an acute, reversible effect. Understanding the effects of OH due to autonomic failure on cognition is desirable, particularly as neuroimaging and clinical assessments collect data only in the supine or seated positions. Identification of a distinct neuropsychological profile in PD with OH has quality of life implications, and OH presents itself as a possible target for intervention in cognitive disturbance. *Neurology*® 2017;88:17-24

GLOSSARY

BAI = Beck Anxiety Index; **BDI-II** = Beck Depression Inventory II; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **DBP** = diastolic blood pressure; **DSB** = Digit Span Backward; **DSF** = Digit Span Forward; **GDS** = Geriatric Depression Scale; **OH** = orthostatic hypotension; **PD** = Parkinson disease; **PDOH** = Parkinson disease with orthostatic hypotension; **SBP** = systolic blood pressure; **WTAR** = Wechsler Test of Adult Reading.

Orthostatic hypotension (OH) is among the most commonly reported nonmotor manifestations in persons with Parkinson disease (PD), with prevalence as high as 53%.¹ Symptoms include lightheadedness, fatigue, neck pain, presyncope, and syncope.^{2,3} The causes can include both CNS and peripheral nervous system degeneration.⁴ Dopamine replacement therapies have been implicated as well.⁵

OH is associated with cognitive impairment. Even when controlling for systolic blood pressure (SBP), both elderly and younger individuals with OH show relative deficits in verbal memory and sustained attention, both of which are predictors of subsequent cognitive decline that is greater than would be expected in the context of normal aging.⁶

Idiopathic PD is itself associated with cognitive deficits. Historically, these were thought to be limited to psychomotor/information processing speeds and caused by disease-specific subcortical pathologies.⁷ However, deficits across executive functions are present, even in cases without

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significant motor slowing, and are attributed to an alteration of connectivity between prefrontal and striatal regions, where dopaminergic and cholinergic projections are abundant.^{8–12} An updated model of cognitive decline in PD is now appropriately characterized as a disconnection syndrome.¹³

We hypothesized that cognition is transiently impaired during OH in PD and that persons with PD and OH would have cognitive deficits that are more severe than those with PD without OH. We used standard autonomic assessment tools to determine whether OH would be associated with immediate effects on cognition as well as impairment independent of posture.

METHODS **Standard protocol approvals, registrations, and patient consents.** The study was approved by the Boston University and Beth Israel Deaconess Medical Center Institutional Review Boards. All participants provided written informed consent.

Study sample. Fifty-five individuals without dementia participated in the study: 18 patients with PD and neurogenic OH (PDOH), 19 normotensive patients with PD without OH (PD), and 18 control participants (controls). OH was defined as a sustained reduction in SBP of at least 20 mm Hg or a reduction in diastolic blood pressure (DBP) of at least 10 mm Hg during the first 3 minutes of standing or head-up tilt on a 60° tilt table.¹⁴ All groups were matched on age, education, and male:female ratio. Control participants were not excluded if maintained on antihypertensive medications, so long as they were normotensive at the time of testing and had no evidence of OH. The Mini-Mental State Examination was used as a general cognitive screening with a cutoff of 27 for controls and 25 for PD. The cutoff for PD was lower to account for disease-specific (i.e., motor) errors that are not associated with dementia.¹⁵ Participants also received the Beck Depression Inventory II (BDI-II),¹⁶ the Geriatric Depression Scale (GDS),¹⁷ and the Beck Anxiety Inventory (BAI).¹⁸ For those with PD, side of symptom onset, Hoehn & Yahr motor stage, and treatment history were obtained. All met clinical criteria for mild to moderate idiopathic PD (Hoehn & Yahr stages I–II). Dopaminergic therapies were converted to levodopa equivalent dosages.¹⁹

Autonomic assessment. Assessment of autonomic functioning was completed in accordance with standardized clinical protocols. Participants were instructed to remain on all medications as prescribed and to eat a light breakfast the morning of testing. Testing was scheduled for a 12:00 PM start time to minimize diurnal effects on hemodynamics. Upon arrival, participants were allowed a 20-minute rest in the supine position to attain psychological and physiologic equilibration. RR interval, beat-to-beat blood pressure (Finometer; FMS, Amsterdam, the Netherlands), and oscillometric blood pressure (Dinamap; Critikon Company, Tampa, FL) were measured for 5 minutes in the supine position, followed by 15 minutes in the 60-degree tilted position.

Prespecified exclusion criteria included any subjective symptoms associated with orthostasis (lightheadedness, dizziness) that were rated as severe (>8 on a 10-point Likert scale), significant tachycardia (>150 BPM), or SBP in the range associated with

presyncope/syncope. Of the 55 participants who met eligibility, none was excluded using these criteria. During the testing session, arterial pressure was measured for 3 minutes at 1-minute intervals while supine. A battery of neuropsychological tests was then administered. Participants were then tilted to 60° at a rate of 6°/s. Arterial pressures were again measured at 1-minute intervals for 3 minutes prior to the start of the second session of testing. Following test completion, participants were returned to the supine position. Once systolic pressure returned to within 10 mm Hg of baseline, this sequence (supine-tilt) was repeated for sessions 3 and 4. Throughout the assessment, participants reported subjective symptoms using the same 10-point Likert scale introduced during the initial screening. To control for the effects of subjective symptoms on cognitive performance, a score of 8 or higher was used to determine data exclusion; no participants met this criterion.

Cognitive assessment. The Wechsler Test of Adult Reading (WTAR) was administered prior to testing as a measure of premorbid verbal intelligence.²⁰ Each of the 4 testing sessions was completed in approximately 15 minutes. For each session, the order of test administration was counterbalanced, and validated alternate forms or split-halves were used in each subsequent session to maintain internal consistency. All tests with visual stimuli or motor components were adapted for projection on a large screen at approximately 53° visual angle with responses given orally.²¹ Specific tests included the following.

Attention/executive functioning. A Stroop test was used as a measure of sustained attention and response inhibition (color vs color-word conditions)²²; the Digit Span Test (forward [DSF], backward [DSB]) to assess basic auditory attention (DSF, DSB) and working memory (DSB); the Arithmetic test to assess working memory and logical reasoning²³; Verbal Fluency tests (phonemic and semantic) to assess lexical retrieval processes²⁴; and the Symbol Search Test to assess visual scanning and psychomotor speed.²³

Memory. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Verbal Learning Test was used to assess verbal memory. Variables analyzed included scores on the first recall trial, the total encoded words across trials (total score), learning slope, and delayed recall (assessed 10 minutes after the final learning trial).²⁵

Visuospatial functioning. The Hemifield Lines Test was used to measure right/left biases in 2 conditions. For this measure, a line presented in one hemifield changes incrementally in size until the participant perceives it to be the same size as a line of constant length in the opposite hemifield.²⁶ The Line Bisection test was used to determine egocentric reference point, and the Visual Dependence test was used to assess line orientation and angle judgment.²⁶

Statistical analysis. Statistical analysis was performed using SPSS v17.0 (SPSS Inc., Chicago, IL). Analyses of variance with Tukey post hoc analysis were used to examine group differences on clinical measures except for median Hoehn & Yahr score (χ^2 analysis). Group differences in baseline supine conditions were analyzed using one-way analysis of variance with Tukey post hoc analysis. Paired-samples *t* tests were used to detect differences from supine to tilted performance in within-group cognitive performance, and change in *z* score performance from supine to tilted positions was used as an index of relative impairment. The α for cognitive measures was 0.01 to correct for multiple comparisons.

RESULTS **Study sample.** None of the participants met criteria for dementia. There were no differences across groups with regard to age, male:female distribution, or

Table 1 Demographic and clinical characteristics

	Controls (n = 18)	PD (n = 19)	PDOH (n = 18)
M:F	9:9	11:8	11:7
Age, y	62.9 ± 7.6	65.6 ± 9.5	64.3 ± 6.5
Education, y	17.9 ± 1.3	17.5 ± 1.4	16.9 ± 1.6
Disease stage, H&Y score	NA	2 (1-3)	2 (1-3)
Disease duration, y	NA	5.7 ± 2.0	6.7 ± 2.3
On DRT	NA	17	17
LED, mg	NA	591 ± 329	513 ± 303
On antihypertensives	6 ^a	4	1 ^b
On antihypotensives	0 ^a	0 ^a	4 ^{b,c}
WTAR (raw score)	46.9 ± 1.3	46.1 ± 3.2	45.7 ± 2.2
MMSE (raw score)	28.9 ± 1.1 ^a	28.4 ± 1.1 ^a	27.1 ± 1.4 ^{b,c}

Abbreviations: DRT = dopamine replacement therapy; H&Y = Hoehn & Yahr; LED = levodopa equivalent dose; MMSE = Mini-Mental State Examination; NA = not applicable; PD = Parkinson disease; PDOH = Parkinson disease with orthostatic hypotension; WTAR = Wechsler Test of Adult Reading.

Values are means ± SD, except H&Y score, which is reported as median (range).

^a Significant at $p < 0.05$ vs PDOH.

^b Significant at $p < 0.05$ vs controls.

^c Significant at $p < 0.05$ vs PD.

premorbid verbal IQ. PD groups were similar with regard to left/right side of symptom onset, disease stage/duration, and levodopa equivalent dosages (table 1). Patients with PDOH were more likely to be on antihypotensive medications than control and PD groups. Controls were more likely to be on antihypertensive medications than patients with PDOH but not patients with PD. Both PD and PDOH groups scored higher on the BDI-II than did controls ($p < 0.05$, both groups) and patients with PDOH scored higher than patients with PD ($p < 0.05$). Patients with

PDOH scored higher on the GDS than did controls ($p < 0.05$), while differences between PD groups were not significant. On the BAI, both PD groups scored higher than controls ($p < 0.05$) but were similar to each other.

Hemodynamic measures. There were no significant group differences in baseline SBP, DBP, or heart rate. Supine hypertension (SPB >135 mm Hg or DBP >100) was found in 6 of 19 patients with PDOH, 5 of 18 patients with PD, and 4 of 18 controls (table 2).

Cognitive measures. Supine. Compared to controls, both PD groups showed impaired cognition (table 3). Patients with PD performed more poorly than controls on semantic fluency and on both Stroop conditions. They also displayed reduced memory encoding and delayed recall. There were no differences on any visuospatial measures. Patients with PDOH were impaired relative to controls on several executive tasks, including DSB, Symbol Search, both fluency tests, and the Stroop test. They were also impaired on all memory submeasures, but not on any visuospatial measures. There were no differences between PD groups on any cognitive measure.

Upright tilt. Compared to controls, patients with PD were impaired on several executive measures and had poorer memory encoding (table 4). Patients with PDOH, however, performed more poorly than controls on nearly all executive measures, including several that did not elicit differences between controls and patients with PD. Patients with PDOH also had worse memory encoding than patients with PD. There were no significant differences between groups on any measure of visuospatial functioning.

Changes in performance. Within-group, following tilt. Controls had no within-group changes when supine and upright performances were compared. Patients with PD demonstrated deficits when upright relative to supine on Symbol Search and 2 CERAD subtests (Learning and Delayed Recall, $p < 0.001$). Patients with PDOH showed posture-mediated impairment on nearly all measures of cognition, including Arithmetic ($p < 0.001$), Symbol Search ($p < 0.001$), both fluency conditions ($p < 0.01$), memory encoding and retention ($p < 0.01$), and Line Bisection ($p < 0.01$).

Across-group, following tilt. The change in group-specific z score following tilt was used as an index of relative performance (i.e., to control for baseline differences that may have skewed the effect of postural change) (figure). There were no significant differences in the effect of postural change on cognition between the controls and PD groups. By contrast, patients with PDOH showed a greater posture-mediated impairment than controls on several tests, including Arithmetic, Symbol Search, Phonemic Fluency, DSB, the

Table 2 Hemodynamic information

	Controls (n = 18)	PD (n = 19)	PDOH (n = 18)
Supine hemodynamics			
SBP, mm Hg	125.5 ± 11.7	125.2 ± 16.3	130.9 ± 14.6
DBP, mm Hg	72.6 ± 8.4	74.6 ± 16.5	78.0 ± 8.9
HR, bpm	66.6 ± 8.7	67.4 ± 9.0	66.0 ± 9.4
Change following tilt			
SBP, mm Hg	-2.3 ± 10.9 ^a	-4.6 ± 6.9 ^a	-30.4 ± 7.9 ^{b,c}
DBP, mm Hg	2.6 ± 7.0 ^a	1.2 ± 8.9 ^a	-12.2 ± 8.7 ^{b,c}
HR, bpm	7.9 ± 4.6	8.5 ± 5.9	8.6 ± 5.7

Abbreviations: DBP = diastolic blood pressure; HR = heart rate (beats per minute); PD = Parkinson disease; PDOH = Parkinson disease with orthostatic hypotension; SBP = systolic blood pressure.

Change refers to subsequent rise (+) or fall (-) in blood pressure after postural change from supine to upright tilt, reported as mean ± SD.

^a Significant at $p < 0.05$ vs PDOH.

^b Significant at $p < 0.05$ vs controls.

^c Significant at $p < 0.05$ vs PD.

Table 3 Across-group comparison of performance on cognitive measures while supine

	Controls (n = 18)	PD (n = 19)	PDOH (n = 18)
Digit Span Forward (total score)	11.6 ± 2.5	10.9 ± 1.7	10.9 ± 1.7
Digit Span Backward (total score)	8.9 ± 1.8 ^a	7.9 ± 1.7	7.2 ± 1.5 ^b
Arithmetic (split-half total score)	6.2 ± 1.2	6.1 ± 0.8	5.9 ± 1.2
Symbol Search (total score)	33.8 ± 6.7 ^a	28.9 ± 5.4	26.2 ± 4.9 ^b
Phonemic Fluency (words/min)	21.1 ± 4.2	17.1 ± 3.6	17.1 ± 4.4
Semantic Fluency (words/min)	25.5 ± 3.5 ^{a,c}	20.2 ± 5.1 ^b	20.0 ± 5.2 ^b
Stroop Color (total correct)	261 ± 35 ^{a,c}	213 ± 41 ^b	218 ± 37 ^b
Stroop Color-word (total correct)	120 ± 25 ^c	90 ± 20 ^b	98 ± 24
CERAD trial 1 (words recalled)	6.1 ± 1.5 ^c	5.2 ± 1.2	4.5 ± 1.2 ^b
CERAD trial 2 (words recalled)	8.3 ± 1.2 ^{a,c}	6.4 ± 1.5 ^b	6.1 ± 0.8 ^b
CERAD trial 3 (words recalled)	8.9 ± 1.1 ^{a,c}	7.1 ± 1.0 ^b	7.2 ± 1.3 ^b
CERAD total score (T1 + T2 + T3)	23.3 ± 3.2 ^{a,c}	18.6 ± 3.5 ^b	17.8 ± 2.8 ^b
CERAD total learning (T3 – T1)	2.8 ± 1.5 ^c	1.9 ± 0.7 ^{a,b}	2.7 ± 1.1 ^c
CERAD recall (words recalled)	7.3 ± 1.6 ^{a,c}	4.7 ± 1.6 ^b	4.6 ± 2.4 ^b
Hemi, L (deviation from equal size)	0.75 ± 0.7	0.64 ± 0.6	0.97 ± 0.8
Hemi, R (deviation from equal size)	0.79 ± 0.7	1.18 ± 1.9	1.18 ± 1.1
Line Bisection (deviation from midline)	0.57 ± 0.5	0.77 ± 0.5	0.95 ± 0.7
Visual Dependence (deviation from horizontal)	0.46 ± 0.5	0.72 ± 0.5	0.53 ± 0.4

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease verbal learning test; Hemi = Hemifield Lines test; PD = Parkinson disease; PDOH = Parkinson disease with orthostatic hypotension.

Scores are reported as raw values ± SD for each individual measure and within neuropsychological domains.

^a Significant at $p < 0.01$ vs PDOH.

^b Significant at $p < 0.01$ vs controls.

^c Significant at $p < 0.01$ vs PD.

Stroop test (color-word condition), memory encoding ($p < 0.01$), and Visual Dependence ($p = 0.01$). Compared to patients with PD, patients with PDOH showed a significantly greater effect of postural change on Symbol Search ($p < 0.01$), CERAD total score ($p < 0.01$), and Visual Dependence ($p < 0.01$).

DISCUSSION We assessed cross-sectional and within-group, posture-specific neuropsychological performance to determine the effects of OH on cognition in patients with PD. When cognition was assessed in the upright position, we found more widespread deficits in executive function and memory as well as visuospatial impairments in PDOH as part of an overall exacerbated deficit profile, with a subsequent return to baseline performance in the supine position. This transient change was not observed in patients with PD or control participants and would thus imply a direct effect of OH.

Cognitive deficits in PD are, at least in part, the result of central neurodegeneration. This presents a challenge when determining the relative contribution of other comorbidities. Reports of cognitive deficits in pure autonomic failure, where degeneration, at least in the early stages of the disease, is limited to the peripheral

autonomic nervous system, suggest that hemodynamic changes may indeed play a contributing role. Cognitive deficits centered in the domains of memory and executive functioning have also been observed in autonomic autoimmune ganglionopathy, a rare disorder in which nicotinic acetylcholine receptor antibodies disrupt transmission across autonomic ganglia, leading to autonomic failure. Following plasma exchange and titer reduction, OH resolves and cognition improves.^{27,28}

As expected, both PD groups displayed frontostriatal and visuospatial cognitive deficits relative to controls. This pattern is observed in as many as 55% of all individuals with PD and is most likely the result of a functional disconnection. Specifically, the basal ganglia and their dense dopaminergic and cholinergic projections to multiple cortical regions as well as the thalamus are selectively affected in a progressive and disease-specific process.²⁹ It is this central degeneration that causes global alterations of neurotransmission and the emergence of numerous motor and nonmotor signs that are associated with the disease.

We found no meaningful differences across PD groups while supine. This contrasts with at least one previous report.³⁰ Unlike this previous study, in which the participants with PD included those with

Table 4 Across-group comparison of performance on cognitive measures under upright tilt

	Controls (n = 18)	PD (n = 19)	PDOH (n = 18)
Digit Span Forward (total score)	12.1 ± 2.7 ^a	10.8 ± 1.6	9.9 ± 1.6 ^c
Digit Span Backward (total score)	8.1 ± 1.6 ^a	7.7 ± 1.3 ^a	5.7 ± 1.1 ^{b,c}
Arithmetic (split-half total score)	6.2 ± 1.3 ^a	5.5 ± 1.5 ^a	4.2 ± 1.0 ^{b,c}
Symbol Search (total score)	31.6 ± 5.5 ^{a,c}	27.2 ± 5.6 ^a	21.9 ± 3.7 ^{b,c}
Phonemic Fluency (words/min)	20.2 ± 4.3 ^{a,c}	16.1 ± 3.5 ^{a,b}	12.8 ± 3.5 ^{b,c}
Semantic Fluency (words/min)	23.3 ± 4.4 ^{a,c}	18.2 ± 4.2 ^b	14.9 ± 4.7 ^b
Stroop Color (total correct)	261 ± 34 ^{a,c}	194 ± 46 ^b	195 ± 40 ^b
Stroop Color-word (total correct)	127 ± 16 ^{a,c}	94 ± 18 ^b	86 ± 19.2 ^b
CERAD trial 1 (words recalled)	5.9 ± 1.3 ^a	5.1 ± 1.1 ^a	3.8 ± 0.6 ^{b,c}
CERAD trial 2 (words recalled)	7.8 ± 0.9 ^{a,c}	6.1 ± 1.1 ^{a,b}	4.8 ± 0.9 ^{b,c}
CERAD trial 3 (words recalled)	8.7 ± 1.3 ^{a,c}	7.0 ± 1.3 ^{a,b}	5.8 ± 1.2 ^{b,c}
CERAD total score (T1 + T2 + T3)	22.4 ± 2.4 ^{a,c}	18.1 ± 3.1 ^{a,b}	14.3 ± 2.3 ^{b,c}
CERAD total learning (T3 – T1)	2.8 ± 1.9	1.9 ± 1.0	2.0 ± 1.2
CERAD recall (words recalled)	6.2 ± 1.9 ^{a,c}	4.3 ± 1.7 ^b	2.9 ± 2.9 ^b
Hemi, L (deviation from equal size)	0.89 ± 0.7	1.20 ± 1.0	1.48 ± 1.3
Hemi, R (deviation from equal size)	1.11 ± 0.8	1.78 ± 1.5	1.67 ± 1.3
Line Bisection (deviation from midline)	0.68 ± 0.6	1.16 ± 0.8	0.84 ± 0.6
Visual Dependence (deviation from horizontal)	0.57 ± 0.5 ^a	0.71 ± 0.6 ^a	1.35 ± 1.0 ^{b,c}

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease verbal learning test; Hemi = Hemifield lines test; PD = Parkinson disease; PDOH = Parkinson disease with orthostatic hypotension.

Scores are reported as raw values ± SD for each individual measure and within neuropsychological domains.

^a Significant at $p < 0.01$ vs PDOH.

^b Significant at $p < 0.01$ vs controls.

^c Significant at $p < 0.01$ vs PD.

and without supine hypertension, our PD groups included only normotensive participants. Thus, we reduced the likelihood of comorbid white matter angiopathy, a known and independent risk factor for cognitive impairment.^{31–33} PD groups were also matched across measures of disease duration, motor symptom severity, and levodopa equivalent dosages. There is considerable support, therefore, that these transient decrements in cognition following postural change are independently related to a failure of cerebral autoregulation during orthostatic stress.

The overwhelming majority of clinical neuropsychological tests, if not all, are administered in the seated position. Based on these results, it seems reasonable to modify assessment methodology in PD to include testing in a variety of postures. Notably, none of our participants reported severe symptoms of OH and many were asymptomatic; nevertheless, cognitive deficits emerged. Clinicians should consider incorporating both autonomic and functional cognitive assessments in all persons with PD regardless of subjective concerns brought forth by the patient. Furthermore, as delayed OH is common in patients with PD and other α -synucleinopathies, clinicians should also be mindful of this manifestation of autonomic

failure in those individuals who show a normal hemodynamic response within the first 3 minutes of standing.^{34,35}

A multiphasic cognitive profile, if detected as part of a comprehensive assessment across postural changes, would be instructive for providers and would reveal otherwise unrecognized targets for intervention. For instance, impairments in verbal fluency, already noted in PD, could make it increasingly difficult to communicate effectively, particularly in the setting of already reduced nonverbal expression caused by declining motor functions. This might not be appreciated in a private office setting, but may manifest when conducting affairs in public spaces where sitting is not an option and the effects of social anxiety are perhaps more palpable. Impairments in visual and spatial processing could lead to problems in the marketplace, where searching for wanted items among a varied array of goods would be a particular challenge. Difficulties with judging line orientation and egocentric reference point could affect proprioception and other aspects of postural stability, thereby increasing the risk of falls that would otherwise be entirely attributed to motor features of PD. Again, clinical providers might miss an important target for intervention when not

Figure Cognitive performance reflected as group-specific (normal control [NC], Parkinson disease [PD], Parkinson disease with orthostatic hypotension [PDOH]) change from baseline following tilt

Prior to analysis of change, all raw scores on cognitive measures were converted to group-specific z scores, where the mean and SD in the supine position of each specific group (NC, PD, PDOH) were used to determine relative within-group performance while under upright tilt. Values reported are for within-group z score change for each measure. Error bars represent standard error. *NC vs PDOH, $p < 0.01$.

considering the contribution of such cognitive impairment. Working memory problems, along with lapses in self-monitoring and vigilance, might lead to difficulties in tracking conversations, counting change, or when processing pedestrian safety signals and other orienting markers, further complicating social interactions and possibly leading to withdrawal from meaningful activities.

There are also implications for functional neuroimaging studies, including those measuring regional metabolic activity and markers of network connectivity, as imaging data are collected while supine and thus without consideration of posture-induced hemodynamic changes. If the cause of cognitive change in OH is related to alterations in regional cerebral blood flow or task-specific metabolic activity as we suggest, these prior studies may have failed to demonstrate fully the neurophysiologic underpinnings of cognitive decline in diseases where OH is present.

It is, of course, difficult to fully rule out all potential confounds when assessing cognition, particularly

when utilizing repeat assessments and in disease states where multiple comorbidities are common. With regard to possible iatrogenic effects of dopamine agonists, which have been shown to produce or worsen OH and cause cognitive deficits, we controlled for levodopa equivalent dosages and found no associated differences in OH severity or cognitive performance.^{36,37} We also addressed potential confounds that would have otherwise affected interpretation of our neuropsychological test findings. As noted, we ensured that no participants had severe (hence distracting) symptoms during tilt, and while reliance on the subjective report has some inherent flaws, we are confident that the cognitive changes as observed in this study were not driven by state-based factors related to somatic stress. With regard to the potential threats to validity following repeated neuropsychological assessment, several methodologic safeguards were put in place. We counterbalanced the order of test administration, used alternate forms when available, and randomized split-halves when no alternate forms

existed. Perhaps more importantly, had any order or practice effects emerged, they would have served to mitigate our hypothesized differences across groups, as all participants were first tested in the supine position.

AUTHOR CONTRIBUTIONS

Dr. Centi: study design and conceptualization, data acquisition, analysis, and interpretation, primary preparation of manuscript. Dr. Freeman: study design and conceptualization, interpretation of the data, and manuscript preparation. Dr. Neargarder: primary statistical analysis and interpretation of the data, manuscript preparation. Dr. Gibbons: study design and conceptualization, interpretation of the data. Alex Canova: data acquisition, analysis and interpretation, manuscript preparation. Dr. Cronin-Golomb: study design and conceptualization, interpretation of the data, manuscript preparation.

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DISCLOSURE

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This Week's *Neurology*[®] Podcast

Effects of orthostatic hypotension on cognition in Parkinson disease (see p. 17)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the January 3, 2017, issue of *Neurology*. In the first segment, Dr. Matthew Barrett interviews Dr. Justin Centi about his paper on the effects of orthostatic hypotension on cognition in Parkinson disease. Dr. Andy Southerland talks with Dr. Seemant Chaturvedi about the urgent need for carotid surgery trials for our “What’s Trending” feature of the week. In the next part of the podcast, Dr. Ted Burns

focuses his interview with Dr. Michelle Mauermann on neuromuscular topics.

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