

2017-11-14

Author response: Effects of orthostatic hypotension on cognition in Parkinson disease

Justin Centi, Roy Freeman, Christopher H Gibbons, Sandy Neargarder, Alexander O Canova, Alice Cronin-Golomb. 2017. "Author response: Effects of orthostatic hypotension on cognition in Parkinson disease." *Neurology*, Volume 89, Issue 20, pp. 2122 - 2122. <https://doi.org/10.1212/WNL.0000000000004658>
<https://hdl.handle.net/2144/39256>

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The Effects of Orthostatic Hypotension on Cognition in Parkinson's Disease

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Search Terms: [165] Parkinson's disease/Parkinsonism; [1] Autonomic diseases;
[199] All Neuropsychology/Behavior

Running Title: Effects of Orthostatic Hypotension on Cognition in Parkinson's
Disease

Study funding: Supported by NIH-NINDS 1F31NS074801-01 (JC) and
R01NS067128 (ACG)

Word Count: (3294/abstract)

This study was supported by a Ruth L. Kirschstein National Research Service Award
(F31NS074801) (JC) and R01NS067128 (ACG) from the National Institute of
Neurological Disorders and Stroke (NINDS).

AUTHOR DISCLOSURES

Dr. Centi reports no disclosures.
Dr. Freeman reports no disclosures
Dr. Gibbons reports no disclosures
Alex Canova reports no disclosures.
Dr. Cronin-Golomb reports no disclosures.

AUTHOR CONTRIBUTIONS

Dr. Centi contributed to the design and conceptualization of the study, the collection,
analysis, and interpretation of the data, and primary preparation of the manuscript.
Dr. Freeman contributed to the design and conceptualization of the study,
interpretation of the data and manuscript preparation.
Dr. Gibbons contributed to the design and conceptualization of the study,
interpretation of the data and manuscript preparation.
Alex Canova contributed to data analysis and interpretation and manuscript
preparation.
Dr. Cronin-Golomb contributed to design and conceptualization of the study,
interpretation of data and manuscript preparation.

ACKNOWLEDGMENTS

The authors would like to thank all of the patients for their participation in this study. For support with clinical referrals, we would like to thank Dr. Daniel Tarsy, Dr. Ludy Shih, Dr. Katherine Czarnecki, and Dr. David Simon. Steven Dewitte of the "Moving Forward" support group and its members deserve appreciation for help in organizing participant travel and collaboration. The authors would like to thank Rachel Lavoie for her help in data collection and entry.

ABSTRACT

Objective: To investigate the relation between orthostatic hypotension (OH) and posture-mediated cognitive impairment in persons with Parkinson's disease (PD) without dementia.

Methods: There were 55 participants: 37 non-demented individuals with idiopathic PD, including 18 with OH (PDOH), and 19 without (PDWOH), and 18 control participants (C). All participants completed neuropsychological tests in the supine and in the upright tilted position. Blood pressure was assessed in each posture using a standardized oscillometric cuff at the right brachial artery.

Results: The two PD groups performed similarly while supine, with a profile notable for executive dysfunction consisting of deficits in sustained attention, response inhibition, and semantic verbal fluency, as well as reduced verbal memory encoding and retention. When upright, these deficits were exacerbated and broadened to include additional cognitive functions in the PDOH group: deficits in phonemic verbal fluency, psychomotor speed, and both basic and complex aspects of auditory working memory. When group-specific supine scores were used as baseline anchors, both PD groups showed cognitive changes following tilt, though the PDOH group had a wider range of deficits in the executive functioning and memory domains and was the only group to show significant changes in visuospatial skills.

Conclusions: Cognitive deficits in idiopathic PD have been widely reported, though assessments are typically performed in the supine position. While both PD groups had supine deficits that aligned with prior studies and clinical findings, we demonstrated that those with PD and orthostatic hypotension had transient, posture-mediated changes in excess of those found in PD without autonomic failure. These observed changes suggest an acute, reversible effect, and as orthostatic hypotension is a significant comorbid factor in PD, an independent target for clinical intervention. Further understanding of the effects of autonomic failure on cognition in other disorders is desirable, particularly in the context of neuroimaging studies and clinical assessments where data are collected only in the supine or seated positions. Identification of a distinct neuropsychological profile in PD with autonomic failure also has implications for functional activities of daily living and overall quality of life.

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; **DRT**=dopamine replacement therapy; **GDS**=Geriatric Depression Scale; **HR**=heart rate; **HY**=Hoehn and Yahr motor symptom stage scale; **MMSE**=Mini-Mental State Examination; **C**=normal control; **OH**=orthostatic hypotension; **PD**=Parkinson's Disease; **PDWOH**=Parkinson's Disease without orthostatic hypotension; **PDOH**=Parkinson's Disease with orthostatic hypotension; **SBP**=systolic blood pressure; **WTAR**=Wechsler Test of Adult Reading

Over the past two decades, there has been an increase in attention to non-motor symptoms of Parkinson's disease (PD). Of these, orthostatic hypotension (OH) is among the most commonly reported, with prevalence as high as 53%.¹ Consensus criteria for diagnosing OH include a reduction in systolic blood pressure (SBP) of at least 20 mmHg or in diastolic blood pressure (DBP) of at least 10 mmHg within the first three minutes after a change in posture from supine to either the standing or upright-tilted position.² Symptoms include lightheadedness, fatigue, neck pain, presyncope, and syncope.^{3, 4} However, asymptomatic OH is common and is itself a risk factor for mortality and cardiovascular disease.⁵ In PD, the causes of OH are multiple, and can include both central and peripheral degeneration.⁶ Dopamine replacement therapies have been implicated as well, though these effects are likely disease-modulated and not directly caused by the drugs themselves.⁷

Orthostatic hypotension is associated with cognitive impairment. Even when controlling for SBP, elderly individuals with OH score lower on bedside cognitive screening measures relative to matched controls.⁸ In younger adults without comorbid neurological disorders and when tested in the seated position, those 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.⁹

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.¹⁰ However, deficits across executive functions, including metacognitive and regulatory aspects of goal-directed behavior have also been shown, even in cases without significant motor slowing.¹¹ Executive dysfunction in PD is caused by an alteration of connectivity between prefrontal and striatal regions, whose networks contain dense dopaminergic and cholinergic projections.¹²⁻¹⁵ Thus, an updated model of cognitive decline in PD is now appropriately characterized as a disconnection syndrome.¹⁶

While both OH and PD are linked to cognitive decrements, few studies have considered the independent contribution of each towards specific impairments. Of those that have included OH as a factor influencing neuropsychological test performance, those with OH have scored lower on screening measures and have showed modest relative deficits in sustained attention, visuospatial processing and visual episodic memory relative to those with normal hemodynamics.¹⁷⁻¹⁹ Importantly, cognitive testing in these studies was conducted only in the seated position, yet deficits OH-related deficits emerged nonetheless.

The mechanism by which OH worsens cognition in PD is not fully elucidated. Structural imaging studies with cognitive variables have thus far failed to support the notion that such vulnerability is the result of anoxic changes to white matter integrity or of overall vascular burden.¹⁸ An alternative explanation suggests that disease-specific deficits are exacerbated during periods of sympathetic stress due to autoregulatory failure in those regions which are already compromised. In Lewy body disease, selective hypoperfusion is generally seen within the temporal and occipital lobes independent of autonomic dysfunction and visuospatial deficits are indeed pathognomonic. In those with concomitant OH, however, postural change is followed by further hypoperfusion but only in posterior regions, and those that show the

greatest relative change have more significant deficits in visuospatial cognition. This pattern of selective hypoperfusion in response to sympathetic stress would suggest that cognition may also vary across supine and upright positions. To our knowledge, however, no studies have utilized this format to determine the effects of OH on cognition in PD or other synucleinopathies.

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

METHODS 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 non-demented individuals participated in the study: 18 patients with both PD and neurogenic OH (PDOH), 19 normotensive PD patients (PDWOH), and 18 control participants (C). OH was defined as a sustained reduction in systolic blood pressure (SBP) of at least 20 mmHg and/or a reduction in diastolic blood pressure (DBP) of at least 10 mmHg during the first three minutes of standing or head-up tilt on a sixty-degree tilt table.² All groups were matched on age, education, and male:female ratio. Control participants were not excluded if maintained on anti-hypertensive 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 C 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.²⁰ Participants also received the Beck Depression Inventory (BDI-II),²¹ the Geriatric Depression Scale (GDS),²² and the Beck Anxiety Inventory (BAI).²³ For those with PD, side of symptom onset, Hoehn and Yahr motor stage, and treatment history were obtained. All met clinical criteria for mild to moderate idiopathic PD (Hoehn and Yahr stages I-III). Dopaminergic therapies were converted to levodopa equivalent dosages (LED).²⁴

Autonomic assessment. Assessment of autonomic functioning was completed in accordance with standardized clinical protocols. Participants were instructed to eat a light breakfast two hours prior to testing. Upon arrival, they were allowed a 20-minute rest in the supine position to attain psychological and physiological 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 five minutes in the supine position, followed by 15 minutes in the 60-degree tilted position. Exclusion criteria included any subjective symptoms associated with orthostasis (lightheadedness, dizziness, etc.) 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 were excluded using these criteria. During the testing session, arterial pressure was measured for three minutes at one-minute intervals while supine. A battery of neuropsychological tests was then administered. Participants were then tilted to 60

degrees at a rate of 6 degrees/sec. Arterial pressures were again measured at one-minute intervals for three 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 mmHg of baseline, this sequence (supine-tilt) was repeated for sessions three and four. 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.²⁵ 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 and/or motor components were adapted for projection on a large screen at approximately 53-degree visual angle with responses given orally.²⁶ Specific tests included:

Attention/Executive Functioning. A Stroop test was used as a measure of sustained attention and response inhibition;²⁷ The Digit Span Test to assess basic auditory attention and working memory; the Arithmetic test to assess working memory and logical reasoning;²⁸ the Verbal Fluency Test (phonemic and semantic) to assess retrieval processes;²⁹ and the Symbol Search Test to assess visual scanning and psychomotor speeds.²⁸

Memory. The CERAD VLT 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.³⁰

Visuospatial Functioning. The Hemifield Lines Test was used to measure right/left biases in two 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.³¹ The Line Bisection Test was used to determine egocentric reference points, and the Visual Dependence Test was used to assess line orientation and angle judgment.³¹

Statistical Analysis. Statistical analysis was performed using SPSS v17.0 (SPSS Inc.). Analyses of variance with Tukey post-hoc analysis were used to examine group differences on clinical measures except for median Hoehn&Yahr score (chi square 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 on within-group cognitive performance, and change in z-score performance from supine to tilted positions was used as an index of relative impairment. Alpha 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 premorbid verbal IQ. PD groups were similar with regard to left/right side of symptom onset, disease stage/duration and LED. (Table 1). PDOH patients were more likely to be on anti-hypotensive medications than the C and PDWOH groups. C were more

likely to be on anti-hypertensive medications than PDOH but not PDWOH. Both PDWOH and PDOH scored higher on the BDI-II than did C ($p < 0.05$, both groups) and PDOH scored higher than PDWOH ($p < 0.05$). PDOH scored higher on the GDS than did C ($p < 0.05$), while differences between PD groups were not significant. On the BAI, both PD groups scored higher than C ($p < 0.05$) 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 mmHg and/or DBP > 100) was found in 6 of 19 PDOH, 5 of 18 PDWOH, and 4 of 18 C (Table 2).

Cognitive Measures. *Supine.* Compared to C, both PD groups showed impaired cognition (Table 3). PDWOH performed more poorly than C 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. PDOH was impaired relative to C on several executive tasks including Digit Span Backwards, Symbol Search, both fluency tests, and the Stroop test. They were also impaired on all memory sub-measures, but not on any visuospatial measures. There were no differences between PD groups on any cognitive measure.

Upright Tilt. Compared to C, PDWOH was impaired on several executive measures and had poorer memory encoding (Table 4). PDOH participants, however, performed more poorly than C on nearly all executive measures, including several that did not elicit differences between C and PDWOH. PDOH also had a worse memory encoding than PDWOH and showed a trend towards weaker recall after a delay. There were no significant differences between groups on any measure of visuospatial functioning, though PDOH showed a trend towards relative impairment on Visual Dependence.

Changes in Performance. *Within-group, following tilt.* C had no within-group changes when supine and upright performances were compared. PDWOH demonstrated deficits when upright relative to supine on Symbol Search and two CERAD subtests (Learning and Delayed Recall, $p < 0.001$). PDOH showed posturally-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 ($p < 0.01$). Trends were observed for Digit Span Backward ($p = 0.043$), learning slope ($p = 0.038$), and both conditions of Hemifield Lines (Hemifield-left, $p = 0.028$; Hemifield-right, $p = 0.041$).

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 1). There were no significant differences in the effect of postural change on cognition between the C and PDWOH groups. By contrast, PDOH showed a greater posture-mediated impairment than C on several tests, including Arithmetic, Symbol Search, Semantic Fluency, Digit Span Backward (with a trend on Digit Span Forward $p = 0.05$), the Stroop test, memory encoding ($p < 0.01$) and Visual Dependence ($p = 0.01$). Compared to PDWOH, 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 Ours is the first study to assess cross-sectional and within-group, posture-specific neuropsychological performance to determine the effects of OH on cognition in PD. We found broader executive dysfunction and visuospatial impairments

in PDOH as part of an overall exacerbated deficit profile when cognition was assessed in the upright position, with a subsequent return to baseline performance following supination. This transient change was not observed in PDWOH or C participants and would thus imply a direct effect of autonomic failure.

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 is limited to the peripheral autonomic nervous system, suggest that hemodynamics do indeed play a role. Cognitive deficits have also been observed in autonomic autoimmune ganglionopathy, a rare disorder where nicotinic acetylcholine receptor antibodies disrupt transmission across autonomic ganglia, leading to autonomic failure. Following plasma exchange and titer reduction, OH resolves and cognition improves. These antibodies appear to not be acting centrally, thus the associated cognitive impairment is more likely related to either a global reduction in peripheral sympathetic activation or, in the setting of normal large-vessel cerebral blood flow, the attenuation of peripheral neurovascular regulation in a regionally-specific response to cognitive demand.^{32, 33}

As expected, PD groups displayed frontostriatal and visuospatial cognitive deficits relative to C. This pattern is observed in as many as 55% of all individuals with PD and is the result functional disconnectivity. Specifically, the basal ganglia and its dense dopaminergic and cholinergic projections to multiple cortical regions as well as the thalamus are selectively affected in a progressive and disease-specific process.³⁴ It is this central degeneration that causes global alterations of neurotransmission and the emergence of numerous motor and non-motor signs that associated with the disease. It is notable that we found no meaningful differences across PD groups while supine, as this contrasts with at least one previous report.³⁵ However, the prevalence of supine hypertension in the OH group was significantly lower in the present study. By ensuring normal supine pressures across groups, we reduced the likelihood of comorbid white-matter angiopathy, a known and independent risk factor for cognitive impairment.³⁶⁻³⁸ PD groups were also matched across measures of disease duration, motor symptom severity, and LED. There is considerable support, therefore, that these transient decrements following postural change are independently related to a failure of cerebral autoregulation during orthostatic stress.

As the overwhelming majority of clinical neuropsychological tests, if not all, are administered in the seated position, it would be reasonable to modify assessment methodology in PD to include testing in a variety of postures. In this study, only those with mild-to-moderate symptoms of OH (and many who were asymptomatic) were included, though cognitive impairments emerged nonetheless. Clinicians should therefore consider 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 alpha-synucleinopathies, clinicians should also be mindful of this manifestation for those individuals who show normal hemodynamics within the first three minutes of standing.

A multiphasic cognitive profile 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. This would not be appreciated in a private office setting, but perhaps when conducting affairs in public spaces, where sitting is not an option. Impairments in visual processing could lead to problems in the marketplace, where searching for wanted items among a varied array of goods would be a particular challenge. Similarly, difficulties with judging line orientation would likely increase the risk of falls, and as postural instability is already a core feature of PD, a provider might not consider such cognitive impairment as contributive. Working memory problems might lead to difficulties with tracking conversations or when counting change, further complicating interactions about town and possibly eliciting symptoms of social anxiety. There are also implications for functional neuroimaging studies, in which data are collected without consideration of postural hemodynamics. 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, prior studies may have failed to fully demonstrate the neurophysiological underpinnings of cognitive decline, particularly in diseases where OH is a common finding. Finally, as delayed OH is common in patients with PD and other alpha-synucleinopathies, clinicians should be mindful of this manifestation for those individuals who show normal hemodynamics within the first three minutes of standing.

It is 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.^{39,40} We also addressed potential confounds that would otherwise affected interpretation of our neuropsychological test findings. As noted, we excluded those with salient symptoms during tilt, and while reliance on the subjective report of such symptoms has inherent flaws, we are confident that the cognitive changes as observed in this study were not symptom-driven. With regard to the potential threats to validity following repeated neuropsychological assessment, several methodological 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 the supine position.

Table 1 - Demographic and clinical information characteristics

	C (n=18)	PDWOH (n=19)	PDOH (n=18)
Men : Women (#)	9:9	11:8	11:7
Age (years)	62.9 ± 7.6	65.6 ± 9.5	64.3 ± 6.5
Education (years)	17.9 ± 1.3	17.5 ± 1.4	16.9 ± 1.6
Disease stage (HY score)	N/A	2 (1-3)	2(1-3)
Disease duration (years)	N/A	5.7 ± 2.0	6.7 ± 2.3
On DRT (#)	N/A	17	17
LED (mg)	N/A	591 ± 329	513 ± 303
On Anti-hypertensive (#)	6 ^c	4	1 ^a
On Anti-hypotensive (#)	0 ^c	0 ^c	4 ^a
WTAR (raw score)	46.9 ± 1.3	46.1 ± 3.2	45.7 ± 2.2
MMSE (raw score)	28.9 ± 1.1 ^c	28.4 ± 1.1 ^c	27.1 ± 1.4 ^a

Abbreviations: HY=Hoehn&Yahr, DRT=dopamine replacement therapy, LED=levodopa equivalent dose, WTAR=Wechsler Test of Adult Reading, MMSE=Mini-Mental State Exam.

Reported as means ±SD, except HY score, which is reported as median (range).

^aSignificant at p<0.05 vs. C

^bSignificant at p<0.05 vs. PDWOH

^cSignificant at p<0.05 vs. PDOH

Table 2 - Hemodynamic information

	C (n=18)	PDWOH (n=19)	PDOH (n=18)
Supine hemodynamics			
SBP (mmHg)	125.5 ± 11.7	125.2 ± 16.3	130.9 ± 14.6
DBP (mmHg)	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 (mmHg)	-2.3 ± 10.9 ^c	-4.6 ± 6.9 ^c	-30.4 ± 7.9 ^{a,b}
DBP (mmHg)	2.6 ± 7.0 ^c	1.2 ± 8.9 ^c	-12.2 ± 8.7 ^{a,b}
HR (bpm)	7.9 ± 4.6	8.5 ± 5.9	8.6 ± 5.7

Abbreviations: SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate (beats per minute).

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

^aSignificant at p<0.05 vs. C

^bSignificant at p<0.05 vs. PDWOH

^cSignificant at p<0.05 vs. PDOH

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

	C (n=18)	PDWOH (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 ^c	7.9 ± 1.7	7.2 ± 1.5 ^a
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 ^c	28.9 ± 5.4	26.2 ± 4.9 ^a
Phonemic Fluency (words/min)	21.1 ± 4.2	17.1 ± 3.6	17.1 ± 4.4
Semantic Fluency (words/min)	25.5 ± 3.5 ^{b,c}	20.2 ± 5.1 ^a	20.0 ± 5.2 ^a
Stroop Color (total correct)	261 ± 35 ^{b,c}	213 ± 41 ^a	218 ± 37 ^a
Stroop Color-word (total correct)	120 ± 25 ^b	90 ± 20 ^a	98 ± 24
CERAD Trial 1 (words recalled)	6.1 ± 1.5 ^c	5.2 ± 1.2	4.5 ± 1.2 ^a
CERAD Trial 2 (words recalled)	8.3 ± 1.2 ^{b,c}	6.4 ± 1.5 ^a	6.1 ± 0.8 ^a
CERAD Trial 3 (words recalled)	8.9 ± 1.1 ^{b,c}	7.1 ± 1.0 ^a	7.2 ± 1.3 ^a
CERAD Total Score (T1+T2+T3)	23.3 ± 3.2 ^{b,c}	18.6 ± 3.5 ^a	17.8 ± 2.8 ^a
CERAD Total Learning (T3 -T1)	2.8 ± 1.5 ^b	1.9 ± 0.7 ^{a,c}	2.7 ± 1.1 ^{a,b}
CERAD Recall (words recalled)	7.3 ± 1.6 ^{b,c}	4.7 ± 1.6 ^a	4.6 ± 2.4 ^a
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.

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

^aSignificant at p<0.01 vs. C

^bSignificant at p<0.01 vs. PDWOH

^cSignificant at p<0.01 vs. PDOH

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

	C (n=18)	PDWOH (n=19)	PDOH (n=18)
Digit Span Forward (total score)	12.1 ± 2.7 ^c	10.8 ± 1.6	9.9 ± 1.6 ^a
Digit Span Backward (total score)	8.1 ± 1.6 ^c	7.7 ± 1.3 ^c	5.7 ± 1.1 ^{a,b}
Arithmetic (split half total score)	6.2 ± 1.3 ^c	5.5 ± 1.5 ^c	4.2 ± 1.0 ^{a,b}
Symbol Search (total score)	31.6 ± 5.5 ^{b,c}	27.2 ± 5.6 ^c	21.9 ± 3.7 ^{a,b}
Phonemic Fluency (words/min)	20.2 ± 4.3 ^{b,c}	16.1 ± 3.5 ^{a,c}	12.8 ± 3.5 ^a
Semantic Fluency (words/min)	23.3 ± 4.4 ^{b,c}	18.2 ± 4.2 ^a	14.9 ± 4.7 ^a
Stroop Color (total correct)	261 ± 34 ^{b,c}	194 ± 46 ^a	195 ± 40 ^a
Stroop Color-word (total correct)	127 ± 16 ^{b,c}	94 ± 18 ^a	86 ± 19.2 ^a
CERAD Trial 1 (words recalled)	5.9 ± 1.3 ^c	5.1 ± 1.1 ^c	3.8 ± 0.6 ^{a,b}
CERAD Trial 2 (words recalled)	7.8 ± 0.9 ^{b,c}	6.1 ± 1.1 ^{a,c}	4.8 ± 0.9 ^{a,b}
CERAD Trial 3 (words recalled)	8.7 ± 1.3 ^{b,c}	7.0 ± 1.3 ^{a,c}	5.8 ± 1.2 ^a
CERAD Total Score (T1+T2+T3)	22.4 ± 2.4 ^{b,c}	18.1 ± 3.1 ^{a,c}	14.3 ± 2.3 ^{a,b}
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 ^{b,c}	4.3 ± 1.7 ^a	2.9 ± 2.9 ^a
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 ^c	0.71 ± 0.6 ^c	1.35 ± 1.0 ^{a,b}

Abbreviations: CERAD=Consortium to Establish a Registry for Alzheimer's Disease verbal learning test, Hemi=Hemifield lines test

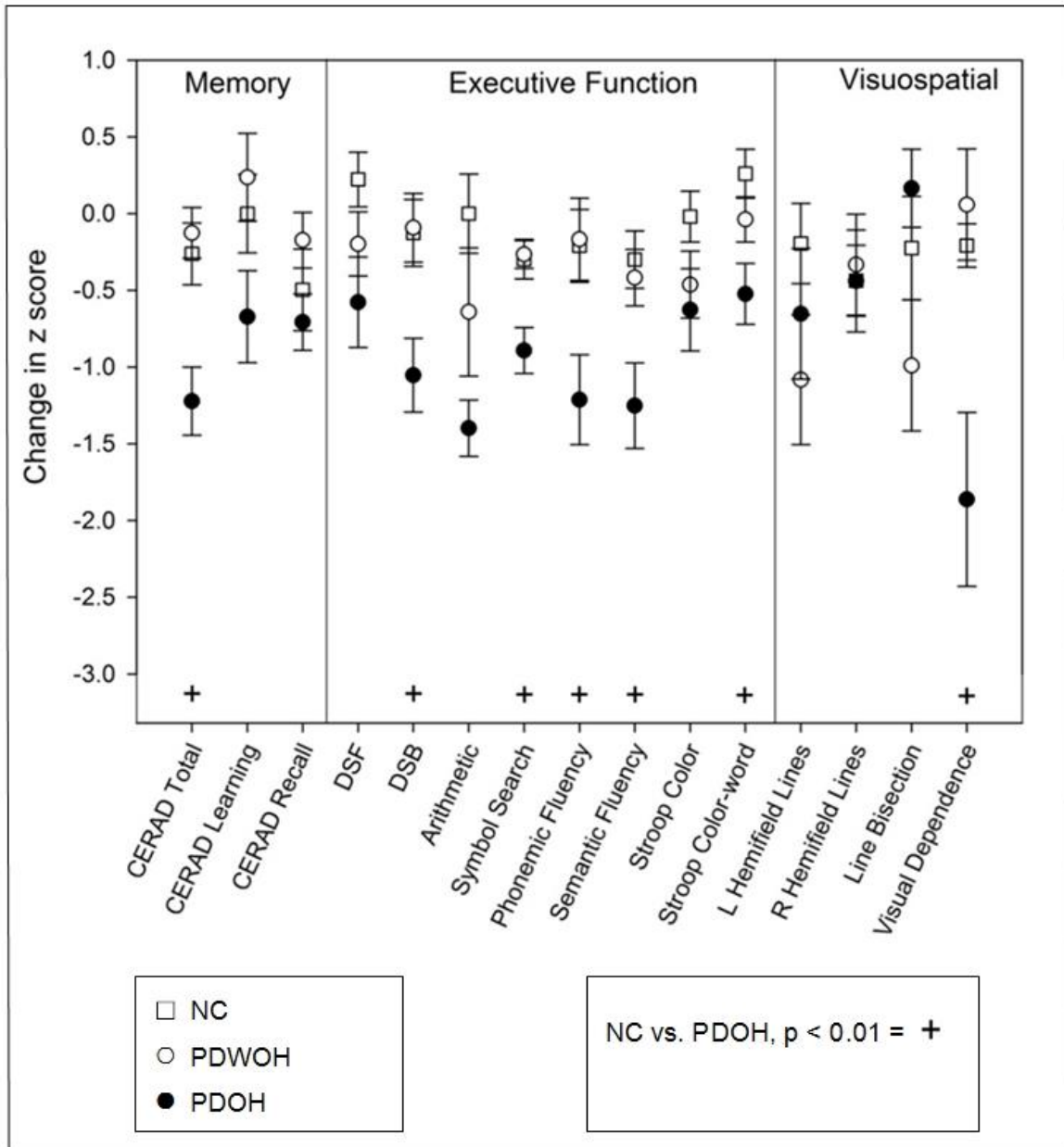
Scores are reported as raw values ± standard deviations for each individual measure and within neuropsychological domains.

^aSignificant at p<0.01 vs. C

^bSignificant at p<0.01 vs. PDWOH

^cSignificant at p<0.01 vs. PDOH

Figure 1 - Cognitive performance reflected as group-specific (ex. C, PDWOH, 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 standard deviation in the supine position of each specific group (C, PDWOH, 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.

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