

Locus Coeruleus Volume is Reduced in Early Parkinson Disease-Related Orthostatic Hypotension.

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Research

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Abstract

Background

Orthostatic hypotension (OH) is common in Parkinson disease (PD) and often coincident with cognitive impairment. The locus coeruleus (LC), a central autonomic and cognitive regulator, may be a common pathophysiological link. Here we tested whether LC structural pathology, measured by neuromelanin-sensitive MRI, is associated with OH, cognition, and OH symptom presence (OHSx) in PD.

Methods

PD motor exam, orthostatic vital signs (OVS), and depression, anxiety, and fatigue symptom scales were measured in 62 patients. Automated segmentation of LC and substantia nigra pars compacta (SNc, control region) took place using 3T MRI-based 2D T1-weighted and neuromelanin-sensitive sequences. LC/SNc volumes (mm^3) were compared between OH and no-OH patients (N=9 & 53) using MACOVA. One-tailed partial correlations (False discovery rate (FDR) corrected) between LC volume, OVS, and MoCA were measured. MANOVA tested for relationships between OHSx, LC/SNc volumes, OVS, and non-motor scales.

Results

LC, but not SNc, volumes were reduced in OH-patients, compared to no-OH (LC $p=0.01$; SNc $p=0.44$). LC volumes correlated with OVS (systolic blood pressure/SBP $r=0.24$, $p_{\text{FDR}}=0.043$; diastolic/DBP $r=0.25$, $p_{\text{FDR}}=0.043$; heart rate/HR $r=-0.32$, $p_{\text{FDR}}=0.024$) and with MoCA ($r=0.22$, $p_{\text{FDR}}=0.043$). OH-patients were more likely to endorse OHSx (Chi Sq. $p=0.047$). LC/SNc volumes were unrelated to OHSx but were associated with DBP change ($F=4.3$, $p=0.043$; SBP trended – $F=3.8$, $p=0.055$), and with greater depressive ($F=6.6$, $p=0.012$) and fatigue ($F=5.13$, $p=0.027$) symptoms.

Conclusions

This study supports LC as a neural substrate for OH and possibly cognitive decline in PD, but not OHSx, which were more associated with depressive and fatigue symptoms. A larger cohort of OH-patients is needed to validate these findings.

Introduction

Autonomic failure with orthostatic hypotension (OH) is common in Parkinson's disease (PD). While 50% of PD patients will develop OH at some point, upwards of at least 14% of early-stage patients develop OH (1–3). Despite only ~33% of patients with OH endorsing typical OH symptoms (OHSx) (4, 5), OH presence

confers increased morbidity and mortality, including risk of falls, impaired quality of life, and healthcare utilization (6, 7). Similarly, cognitive impairment, also a risk for quality of life reduction, is common in early PD (15-20% in de novo PD), with upwards of 80% of MCI-PD patients progressing to dementia (8–10). Interestingly, several studies have found those with OH, irrespective of OHSx, have a greater risk of cognitive impairment (11–14). Neuropathologic mechanisms underlying this link remain unclear.

Prevailing mechanistic understanding of PD-related OH relates to peripheral noradrenergic efferent alpha-synuclein neuropathology (15, 16), including denervation of sympathetic post-ganglionic myocardial and blood vessels nerves (17, 18). However, recent work has suggested a central contribution toward dysautonomia in PD, including OH (19–21). Such central substrates could also provide neuroanatomical links between PD-OH and cognitive impairment, for which the latter has been associated with altered central noradrenergic function (21, 22). A strong candidate link here could be the locus coeruleus (LC) (23), which is pathologically affected in PD early, progressively, and to greater degree than the substantia nigra pars compacta (SNc) (24, 25). The LC is the primary source of central noradrenergic signaling, with extensive cortical, subcortical, and spinal efferent projections; its functional roles are thus many, but importantly include autonomic regulation, arousal/attention, and learning/memory (26, 27). The LC exerts a net sympathoexcitatory effect on cardiovascular function, with positive chronotropic and vasopressor effects through its interaction with the baroreflex arc, including through direct inhibition of brainstem cardio-parasympathetic nuclei (26, 28). The LC's potential role for cognition likely involves modulation of cerebral blood flow (29) and attention/cognitive control (30, 31), and moderating medial temporal synaptic plasticity (32, 33).

Few studies have directly tested for relationships between LC structure/function, OH, and cognitive symptoms in PD. Those that have done so have primarily utilized PET imaging and neuromelanin sensitive (NM-)MRI. One study, by Sommerauer and colleagues(21), found that reduced norepinephrine transporter availability (^{11}C -MeNER PET) correlated with orthostatic vitals sign (OVS) changes in PD, but NM-MRI *structural* measures did not correlate with OVS; these findings suggest at least LC dysfunction is involved in PD-OH. Similarly, a brief pathological report found no LC structural relationship with OH presence (34). However, the NM-MRI study's negative result may have related to methodological issues, statistical power, and lack of a direct comparison between PD with/without OH. Additionally, in the pathological study, patients had advanced disease duration and OH-presence was based on chart diagnosis alone, which likely affected results. Cognitive changes associated with normal aging, Alzheimer's disease, and PD have also been linked to LC integrity (35–38), and two recent NM-MRI studies linked disrupted LC integrity in PD, compared to healthy controls, to worse cognitive performance (36, 38). Taken together there is a strong premise for involvement of the LC in PD-OH and cognitive decline and for use of NM-MRI to examine its role. Findings supporting this interrelationship could have practice changing implications for treatments targeting the LC-norepinephrine system.

Guided by the hypothesis that LC pathology contributes to OH in PD, and potentially to cognitive decline as well, we compared NM-MRI derived LC volumes in early-moderate PD patients with/without OH. We then looked for correlational relationships across subjects between LC volume and OVS. As a preliminary

assessment of the LC's role in cognition, we additionally correlated LC volumes with scores of the Montreal Cognitive Assessment (MoCA). We predicted a reduction in LC volumes in PD-OH, compared to PD with no OH. A secondary prediction was that LC volume would positively correlate with cognitive scores. Finally, recent work has found that PD-related OH, independent of OHSx, confers risk of cognitive decline (39). Some have proposed that OHSx may rely on function of adrenergic output by the LC (40). If true, this observation would indicate biomarker-based approaches may enhance general studies of PD-related OH. We thus also tested for relationships between OHSx, OVS, and LC volume; this analysis also included scales for depression, anxiety, and fatigue, as atypical OHSx may overlap with these non-motor symptoms. We predicted that LC volume may be associated with OHSx, but that OVS would be more so; additionally, we predicted significant associations between OHSx and those of depression, anxiety, and fatigue.

Methods

Participants and clinical evaluation:

This prospective study was approved by the Emory institutional review board. Data were collected between 2012 and 2017. All participants provided written informed consent. In this study, 62 PD participants were recruited from the Emory University Movement Disorders Clinic. All PD participants were diagnosed by a fellowship-trained movement disorders neurologist according to the United Kingdom Parkinson's Disease Society Brain Bank criteria (41). Study exclusion criteria were: (1) drug-induced or atypical parkinsonisms; (2) a history of multiple sclerosis, territorial ischemic stroke, hemorrhagic stroke, epilepsy, parenchymal brain tumor, moderate-to-severe head trauma, hydrocephalus, other neurodegenerative diseases; or (3) treatment with dopamine blocking drugs.

Demographic information including sex, age, and education was collected for each participant. Disease motor severity was evaluated using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III).(42) Dopaminergic medication strength and daily doses were recorded to calculate levodopa equivalent daily doses (LEDDs) using the Parkinson's measurement toolbox (<https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm>). Cognition was assessed using the Montreal Cognitive Assessment (MoCA) (43). The Non-motor Symptoms Questionnaire (NMSQ) (44) assessed general non-motor symptoms, including OHSx (question #20). Depressive and anxiety symptoms were assessed with the Beck Depression Inventory II (BDI) (45) and Beck Anxiety Inventory (BAI) (46), respectively. Symptoms of fatigue were assessed with the Fatigue Questionnaire (FatQ) (47, 48). Both motor symptoms and OVS were tested during the 'ON' medication state. OVS (systolic and diastolic blood pressure, SBP/DBP, and heart rate, HR) were measured after resting supine for several minutes and then repeated after one minute of active standing. Presence of OH was determined based on standard clinical criteria of either a drop in SBP of 20 or more mmHg or drop in DBP of 10 or more mmHg (49). Supine hypertension was determined based on supine SBP of 140 mmHg or higher or DBP of 90 mmHg or higher (14).

MRI scanning and Image analysis:

MRI data for 22 PD patients were acquired with a Siemens Trio 3 Tesla scanner (Siemens Medical Solutions, Malvern, PA, USA) at Emory University with a 12-channel receive-only head coil. NM-MRI data was acquired using a magnetization transfer (MT)-prepared 2D gradient echo (GRE) sequence (50–52) with parameters: echo time (TE)/repetition time (TR)=2.68ms/337ms, flip angle (FA)=40°, slice thickness=3mm, in plane resolution 0.39x0.39mm², field of view (FOV)=162x200mm², 15 contiguous slices, 7 measurements, 470 Hz/pixel bandwidth, MT-preparation pulse (FA=300°, 1.2kHz off resonance, 10ms duration), and scan time 16 minutes 17 seconds. A T₁-weighted magnetization-prepared rapid gradient echo (MP-RAGE) sequence (parameters: TE/TR=3.02ms/2600ms, inversion time=800ms, FA=8°, voxel size=1.0x1.0x1.0mm³) was used for common space registration.

The Trio scanner was upgraded to a Prisma-Fit scanner using the same transmitter, and MRI data of 40 more PD patients were acquired with this upgraded scanner at Emory University using a 64-channel receive-only coil. NM-MRI data were acquired using a MT-prepared 2D GRE sequence with the following parameters: TE/TR=3.10ms/354ms, 416x512 imaging matrix, 162x200mm (0.39x0.39x3mm³), 15 contiguous slices, 7 measurements, flip angle=40°, 470 Hz/pixel receiver bandwidth, and MTC pulses (300°, 1.2kHz off resonance, 10ms duration), scan time 17min-12s. A T₁-weighted magnetization-prepared MP-RAGE sequence (TE/TR=2.46ms/1900ms, inversion time=900ms, FA=9°, voxel size=0.8x0.8x0.8mm³) was used for common space registration.

On the sagittal T₁-weighted images for both cohorts, the GRE scan slices were positioned perpendicular to the dorsal edge of the brain stem at midline along the fourth ventricle, starting from the lower pons (below the most caudal extent of LC), covering the SNc and LC.

MRI data were processed using the FMRIB Software Library (FSL) (53) and MATLAB. NM-MRI images were motion corrected by registering the seven GRE measurements to the first image using the FMRIB Linear Image Registration Tool (FLIRT) (54, 55) and then averaged. These images were then used for analysis. Next, individual subject space and common space transformations took place using a previously published method from our group (50).

SNc and LC volumes were segmented with a semi-automated thresholding method as previously described (56). A reference region of interest (ROI) in each cerebral peduncle was transformed from standard space to individual subject space using the previously described transformations. The mean and standard deviation (SD) of the signal intensities were determined for the reference ROIs. Voxels that were three SD or four SD greater in intensity than the mean intensity in the reference region were identified as SNc or LC, respectively. Thresholding was restricted to the anatomic location of SNc and LC using dilations of previously reported probabilistic standard space masks (57).

Statistical Analysis:

Subject demographics between OH/no-OH were compared using either independent samples T-testing (continuous variables) or Chi-square testing (categorical variables). MANCOVA testing was used to compare LC and SNc volume differences between OH/no-OH groups. Covariates of non-interest in this model included demographic/clinical variables found to be significantly different, or closely trending, between groups as well as variables considered strong conceptual confounders. Next, we evaluated relationships between LC volume, OVS, and MoCA using one-tailed partial correlations based on the hypothesis that increasing neurodegeneration (i.e., neuromelanin loss) is associated with more symptoms. Age was included as a covariate in OVS partial correlation analyses, given the association between greater age and risk of OH (58), as was scanner type. Next, we examined associations between OHSx and other variables. First, we compared relative percentages of OHSx between OH/no-OH groups using responses to #20 of the NMSQ (“Feeling light-headed, dizzy or weak standing from sitting or lying”) using Chi-square testing. We then compared demographic and clinical variables between OHSx groups. We determined *a priori* to assess relationships between OHSx, LC/SNc volumes, OVS, and certain non-motor scales (BDI, BAI, FatQ) in a MANOVA model. The selected non-motor scales were chosen because some questions on these scales overlap with atypical symptoms of OH (15). For each analysis the threshold for significance was $p < 0.05$. Both uncorrected and false discovery rate (FDR) (59) corrected p-values are reported for correlational analyses.

Results

Subject clinicodemographic data, across and between OH groups, are found in Table 1. In general the OH/no-OH groups were well matched with respect to demographics; OH tended towards being slightly older, $p = 0.06$. There was no significant group difference between scanner type utilized, disease duration, LEDDs, or number of anti-hypertensives used. The OH group tended to have slightly higher motor scores ($p = 0.06$). No group differences were found for non-motor scale scores. OVS differed between groups for SBP (supine and standing, individually), standing DBP, and supine HR. The OH group tended toward a greater percentage of supine hypertension ($p = 0.08$).

One-tailed partial correlation results (age, scanner type covariates) between LC volume, OVS, and MoCA are visualized as scatter plots in **Figure 2**. In general, lower LC volumes correlated with greater orthostatic drop in SBP (**Fig. 2A**; $r = 0.24$, $p_{\text{unc}} = 0.033$, $p_{\text{FDR}} = 0.043$) and DBP (**Fig. 2B**; $r = 0.25$, $p_{\text{unc}} = 0.027$, $p_{\text{FDR}} = 0.043$). On the other hand, lower LC volumes correlated with greater degree of orthostatic HR *increase* (**Fig. 2C**; $r = -0.32$, $p_{\text{unc}} = 0.006$, $p_{\text{FDR}} = 0.024$). LC volume correlated positively MoCA score ($r = 0.22$, $p_{\text{unc}} = 0.043$, $p_{\text{FDR}} = 0.046$).

Subject demographics comparing OHSx groups (answering ‘yes/no’ on question 20 of the NMSQ) are found in Supplementary Table 1. These baseline characteristics were compared between these groups for consideration of inclusion into a MANOVA that would further examine characteristics of those with OHSx. No significant differences in demographics, scanner type, or clinical variables were found, with exception of BDI and FatQ results (greater in those with OSHx, independent T-test $p = 0.016$ and 0.029 , respectively), with standing DBP trending ($p = 0.08$). OH-patients were more likely to endorse OHSx (Chi Sq. $p = 0.047$).

Relative percentages of OHSx stratified by OH-groups, and factors underlying report of OHSx, are found in **Fig. 3**. Among OH, 66% reported OHSx, with the remainder denying symptoms. Conversely, 34% of no-OH endorsed OHSx. This reciprocal relationship is shown in **Fig. 3A**. MANOVA testing across all PD patients (N=62) found no relationship between OHSx and LC/SNc volumes (**Fig. 3B**). Regarding OVS changes and OHSx: orthostatic SBP change trended toward significance ($F=3.8, p=0.055$); DBP change was significantly associated with OHSx ($F=4.3, p=0.043$); HR change was not associated with OHSx. BAI scores were not associated with OHSx, but both BDI ($F=6.6, p=0.012$) and FatQ ($F=5.13, p=0.027$) were associated with OHSx.

Discussion

The mechanism underlying central contribution to OH in PD is unresolved. We hypothesized that LC is a strong candidate for a central substrate (23). To test this hypothesis, we derived LC volumes using NM-MRI and compared them between PD patients with and without OH; we subsequently assessed correlations between LC volume and OVS; correlations between LC volumes and cognitive testing (MoCA) was also explored to examine potential influence on cognition. Prior studies report cognitive decline occurs in PD-OH to greater degree than in those without OH, irrespective of OHSx (12,13,39); additionally a role for LC function has been proposed for occurrence of OHSx (40). We thus examined the relationship of OHSx with LC/SNc volume and OVS, with symptoms of depression, anxiety, and fatigue also included given similarity between these and atypical OHSx.

Our primary prediction, that LC volume would be reduced in the OH group, compared to the no-OH group, was confirmed; SNc volumes did not differ between groups. In line with our primary prediction, LC volumes were additionally correlated with OVS across subjects. We found a weaker correlation between LC volume and cognition. These findings provide further evidence that LC neurodegeneration is a substrate for autonomic dysfunction in PD. However, the weak LC-MoCA correlation suggests a need for more extensive testing in a larger cohort. Our main secondary prediction related to OHSx; namely that LC volume and OVS would be predictive of OHSx. This prediction was partly confirmed; while no relationship between structural measures (LC/SNc volume) and OHSx was found, OVS (namely DBP change, to a lesser extent SBP) were predictive of OHSx. However, compared to OVS, OHSx was better predicted by depressive and fatigue symptoms.

Neuropathologically, LC is affected very early in PD and to a greater extent than SNc (24,25), compromising the brain and spinal cord's primary source of noradrenergic innervation. The LC has several ascending and descending outputs that generally inhibit central preganglionic parasympathetic nuclei and activate preganglionic sympathetic pathways to result in a net sympathetic increase: projections to the hypothalamic paraventricular nucleus promote behavioral arousal and suppression of the baroreflex; descending alpha2-receptor activation in the vagal dorsal motor nucleus and nucleus ambiguus reduces parasympathetic cardiovascular effects; LC also provides alpha1-mediated excitatory influence to spinal preganglionic sympathetic intermediolateral nuclei (60). One exception to the LC's general role in increasing in sympathetic activation is its *inhibitory* (alpha2) effects on rostroventrolateral

medulla (RVLM) (60), which is the main sympathetic nucleus in the baroreflex arc (61). Nevertheless, it is logical that LC pathology, by impairing its overall sympathetic cardiovascular effects, contributes to cardiovascular dysautonomia in PD.

Our findings complement recent neuroimaging studies suggesting central contributions to dysautonomia in PD via structural (20) and functional alterations of central autonomic regulators (19,21). Indeed, a prior study by Sommerauer and colleagues found reduced cerebral norepinephrine transporter availability (via ^{11}C -MeNER PET) correlated with OVS changes in PD (21). Our results add to these findings, supporting the hypothesis that structural disruption of LC contributes to PD-OH; not only were LC volumes lower in OH patients, LC volumes also generally correlated with OVS across all PD subjects. Furthermore, our findings were specific to LC, as no such reduction was observed in the SNc for the OH group. One curious result was a negative correlation between LC volume and HR changes across all PD subjects; i.e., lower LC volume was associated with greater orthostatic HR increase, which could be inconsistent with role in neurogenic OH (6). However, this effect may relate to a 'release' of LC's typical inhibitory effects on RVLM (60), which could then contribute to an orthostatic HR increase. Interestingly, OH groups differed with respect to supine HR (lower in the OH group) but not standing HR. It is thus possible that LC pathology in PD may primarily affect orthostatic pressor response, with the blunted orthostatic HR change typical of neurogenic OH perhaps resulting from an alternative autonomic lesion, such as post-ganglionic cardiac sympathetic denervation (62).

Of note, our findings do contrast somewhat with structural findings by Sommerauer and colleagues (21), whose NM-MRI LC measures did not correlate with OVS. These differences likely relate to study methodology. The prior NM-MRI study did not directly compare OH vs. no-OH, utilizing only correlational analyses. Their protocol also restricted analysis to the 10 highest intensity voxels after manual region of interest (ROI) placement; this approach is subject to impacts from noise and operator-dependent variability. In contrast, we utilized semi-automated ROI placement and volume measurement using methods with high scan-rescan reproducibility (63,64). Similarly, a brief pathological report found no relationship between LC pathology and charted presence vs. absence of OH (34). However, this study utilized a cohort with advanced disease duration (averaging more than a decade), and OH designation was based on chart diagnosis alone; both of these factors likely affected results.

The LC has a well-established role with respect to attention and learning/memory via modulation of cerebral blood flow, frontal attentional/cognitive control mechanisms, and effects on memory and related synaptic plasticity (29,30,33,57,65,66). Prior work examining LC-related effects on PD cognitive impairment is limited, but supportive of LC playing a role: LC-related neuronal loss occurs earlier and to a greater degree than Meyert's nucleus in PD (25); pharmacologic increase in NE levels improve cognitive performance in PD (67); NM-MRI based LC structural integrity correlated with cognition in PD (38) and is lower in PD patients with mild cognitive impairment (MCI), in comparison to those without MCI and healthy controls (36). The correlation we observed between MoCA score and LC volume is consistent with these findings, but will require replication with more extensive cognitive testing and a larger cohort of patients with OH.

Establishing a role for the LC in the pathophysiology of OH, and potentially cognitive impairment, in PD has implications for treatment, as centrally acting, noradrenergic medications may benefit patients from both perspectives. Atomoxetine, a norepinephrine transport inhibitor, is one example of a centrally and peripherally acting noradrenergic agent that has been examined in PD for effects on OH and cognition, though separately; multiple studies have found atomoxetine safe and effective for OH treatment, with better performance than the peripherally acting standard of care, α_1 agonist midodrine (68,69). Additionally, atomoxetine's effects are greater in patients with central, rather than peripherally-based, autonomic failure (70). Atomoxetine has been experimentally used to improve measures of somnolence, impulsivity and frontal function, and global cognition in PD (67,71,72), and the response in this regard varies as a function of LC integrity (73). These cognitive effects have been posited to relate to greater noradrenergically mediated prefrontal top-down control and more effective coherence of cortico-coeruleal circuits particularly involving the subthalamic nucleus (74). Based on these observations in treatment trials of atomoxetine, our findings would suggest the need for further investigation of this or similar drugs as candidate treatments for OH and cognitive impairment in PD.

Accurate definition of OH is essential to establish mechanistic understanding of OH in PD. However, for unclear reasons, relatively few patients (~33%) with OH endorse typical OHSx (4,5). Interestingly, we observed a reciprocal pattern of typical OHSx in those with and without OH (Fig. 3A). The significant proportion of PD patients without OH that report putative OHSx, and vice versa, is clinically important; this is particularly the case given we found no relationship between LC volumes and OHSx (Fig. 3B), contrasting prior postulation on a role for the LC in this regard (40). Additionally, while OVS did significantly predict OHSx they did so less robustly than depressive and fatigue-related symptoms (Fig. 3B), which were not different in occurrence between OH groups (Table 1). Interpretation of these findings is challenging given a lack of mechanistic understanding of hypotension perception. However, results may relate to the frequent non-specificity of atypical OHSx, which can include several fatigue or depression scale symptoms (15). Our results may reflect some of this overlap, particularly given a significant number of no-OH patients endorsing OHSx. Our findings are additionally similar to those seen in orthostatic intolerance patients, in which OHSx correlates highly with those of depression and fatigue (75,76). It is possible that a more specific/in-depth questionnaire for OHSx would have led to findings more specific to OVS.

There are limitations to this study. First, though we have similar numbers of OH patients compared to prior work involving NM-MRI, our findings would be strengthened by greater numbers of OH patients. Future work would benefit from comparison of LC volumes in the PD population with those of healthy controls as well. Similarly, our cognition-related results may have been more robust with a wider range of cognitive performance or more in-depth testing. Patient OVS may have been influenced by measurement during the ON-medication state; comparison of OFF and ON-state measures would potentially provide assurance of PD-mediated OH. It is notable, though, that our OH group generally had lower LEDDs. We performed no formal autonomic testing to confirm neurogenic OH, using instead clinically relevant bedside measures. Nevertheless, it is notable that our OH group's average orthostatic HR change, divided

by SBP change (12bpm,30mmHg), meets neurogenic OH criteria determined by Norcliffe-Kaufman and colleagues (77). We additionally included anti-hypertensive use in our models comparing groups. Measuring OVS by only one minute could have affected findings; however, one-minute measures are clinically relevant to OHSx and adverse OH events (78).

Conclusions

Using NM-MRI we found that LC volumes were lower in PD patients with OH, compared to no-OH, and that LC volumes correlated with OVS across subjects; a preliminary weaker correlation between LC volume and cognition was also found. In contrast, LC volumes were not associated with OHSx; instead, OHSx was related to OVS and, to a greater extent, depressive and fatigue-related symptoms. Future work will need to validate these findings in a larger cohort of PD patients with OH, during OFF-medication state, with a wider range of cognitive ability and testing, and for a greater duration of orthostatic challenge. Nevertheless, these findings support the notion that central autonomic dysfunction plays a role in PD-related dysautonomia and suggest that LC may serve as a common central substrate connecting OH and cognitive function in PD. Centrally acting noradrenergic treatments may thus benefit patients suffering from these non-motor symptoms. Our findings also support the need to undertake more in-depth clinical screening for OH, as symptoms may be infrequent and non-specific.

Abbreviations

OH=Orthostatic hypotension; PD=Parkinson disease; LC=Locus coeruleus; OHSx=Orthostatic hypotension symptoms; OVS=orthostatic vital signs; SNc=Substantia nigra pars compacta; FDR=False discovery rate; NM-MRI=Neuromelanin sensitive magnetic resonance imaging; LEDDs=Levodopa equivalent daily doses; MoCA=Montreal Cognitive Assessment; BDI=Beck Depression Inventory II; BAI=Beck Anxiety Inventory; FatQ=Fatigue Questionnaire; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; HR=Heart rate; FDR=False discovery rate; RVLM=Rostrolateral medulla

Declarations

Ethics approval and consent to participate:

This study received approval from the Emory University Institutional Review Board. All subjects provided informed consent prior to inclusion.

Consent for publication

All authors have read the manuscript as submitted for publication and have provided consent for publishing.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

Dr. Paul A. Beach: None

Dr. Nithin Kurra: None

Dr. Kristy Hwang: None

Dr. Xiaoping Hu: None

Dr. Jason Langley: None

Dr. Daniel E Huddleston: inventor on an issued patent (U.S. patent #9600881, 3/21/17) which covers aspects of the NM-MRI methods discussed here.

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Authors' contributions

Dr. Paul A. Beach: All rounds of manuscript drafting, statistical analysis design and execution, conception of the project.

Dr. Nithin Kurra: Data collection and collation, review of manuscript.

Dr. Kristy Hwang: Review and critique of the manuscript.

Dr. Xiaoping Hu: Organization and execution of research project, review and critique of manuscript.

Dr. Jason Langley: Organization and execution of research project, review and critique of manuscript, data analysis and image processing.

Dr. Daniel E Huddleston: Conception of research project, study organization and data collection management, review and critique of statistical analysis, review and critique of manuscript.

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Tables

Table 1 - Subject demographics

	All PD (N=62)	OH (N=9)	No-OH (N=53)	<i>p</i> (OH v no-OH)
	mean (SEM) or %			
Age (years)	62.2 (1.2)	67.4 (3.0)	61.3 (8.9)	0.06
Gender (% F)	43.5	44.4	43.4	0.95
Race (%)				0.47
Caucasian	91.9	88.9	92.5	
African American	3.2	11.1	1.9	
Hispanic	1.6	0	3.8	
other	1.6	0	1.9	
Education (years) [§]	16.6 (0.44)	15.4 (0.78)	16.8 (0.49)	0.29
Scanner Type (% Trio Prisma)	35.5 64.5	44.4 55.6	34 66	0.54
Disease Duration (years) [^]	4.9 (0.52)	3.4 (1.1)	5.2 (0.57)	0.26
LEDDs (mg)	671.7 (53.8)	497.8 (106.1)	701.3 (59.7)	0.19
UPDRS-III	19.1 (1.0)	23.9 (2.7)	18.28 (1.1)	0.06
Number anti-hypertensives	0.31 (0.082)	0.44 (0.34)	0.28 (0.078)	0.49
MoCA	27.6 (0.27)	27.8 (0.85)	27.8 (0.28)	0.15
BDI	6.7 (0.73)	7.1 (2.2)	6.7 (0.78)	0.85
FatQ	26.1 (1.5)	25.4 (3.6)	26.3 (1.7)	0.85
NMSQ total	8.1 (0.62)	8.8 (2.0)	8.0 (0.65)	0.67
BAI	7.4 (0.88)	8.7 (2.8)	7.1 (0.92)	0.55
Systolic BP supine (mmHg)	129.7 (2.0)	141.1 (5.7)	127.8 (2.0)	0.017*
Systolic BP stand (mmHg)	121.11 (2.0)	109.9 (6.4)	123.0 (2.0)	0.019*
Diastolic BP supine (mmHg)	77.2 (0.96)	80.2 (2.9)	76.7 (1.0)	0.2
Diastolic BP stand (mmHg)	77.3 (1.3)	67.1 (4.8)	79.1 (1.1)	0.04*
HR supine (BPM)	71.8 (1.6)	64.4 (2.3)	73.0 (1.7)	0.05*
HR stand (BPM)	80.8 (1.4)	76.2 (2.7)	81.5 (1.6)	0.2
Supine Hypertension Presence (%)	30.6	55.6	26.4	0.08

Figures

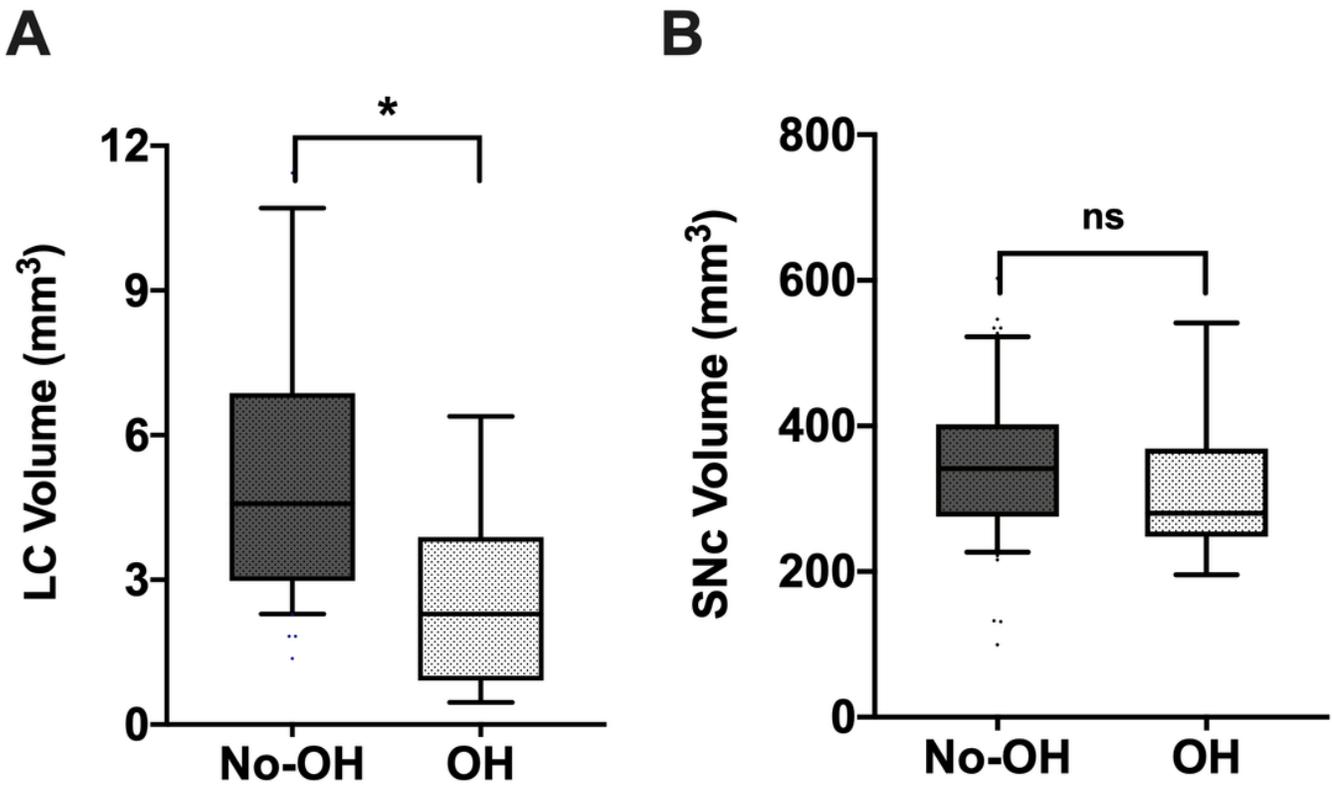


Figure 1

Comparison of LC and SNc volumes (mm³) between PD with and without OH. A) Mean LC volume (+/- SEM; N) in PD without OH (no-OH) was 5.4 (+/- 0.44; 53) and, in PD with OH, LC volume was 2.7 (+/- 0.63; 9). B) Mean SNc volume in the no-OH group was 350.3 (+/- 14.7; 53) and in the OH group SNc volume was 313.4 (+/- 35.9; 9). Box midline represents median volumes per group and whisker lines represent 10th to 90th percentiles. * Significant finding (p<0.05); ns = non-significant (p>0.05).

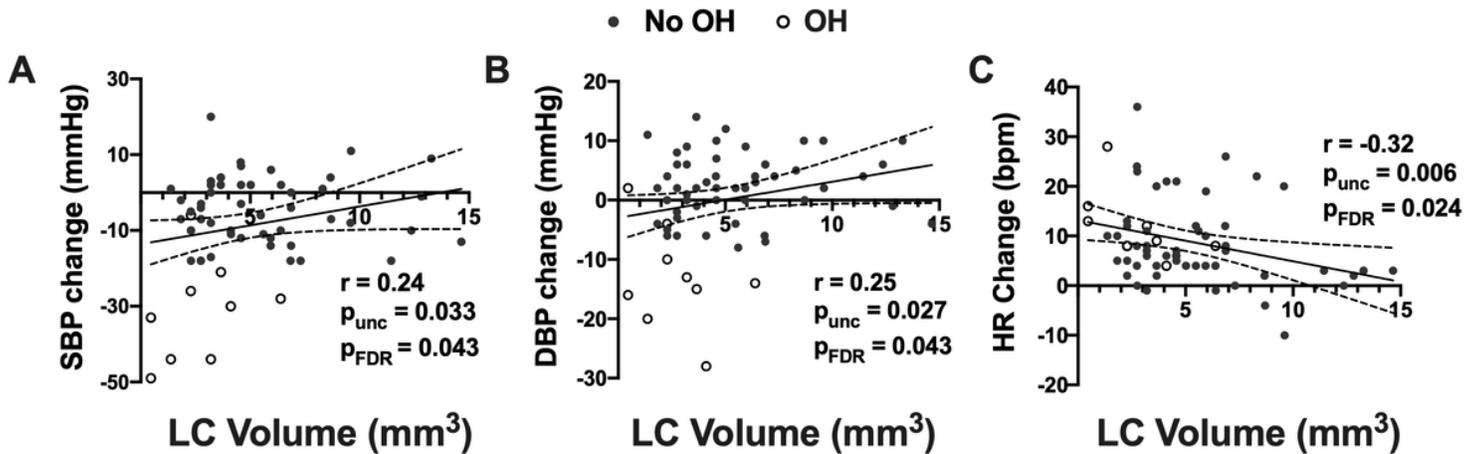


Figure 2

Partial correlations between LC volumes, OVS changes from lying to standing. Scatter plots represent one-tailed partial correlations (age & scanner type covariates) color stratified by presence or not of OH. OVS changes reflect standing - supine calculations (negative BP change = an orthostatic drop, positive HR change = orthostatic increase). r = partial correlation coefficients; punc = uncorrected p-values; pFDR = FDR corrected p-values. Solid line represents linear regression line across subjects with dotted lines representing 95% confidence intervals.

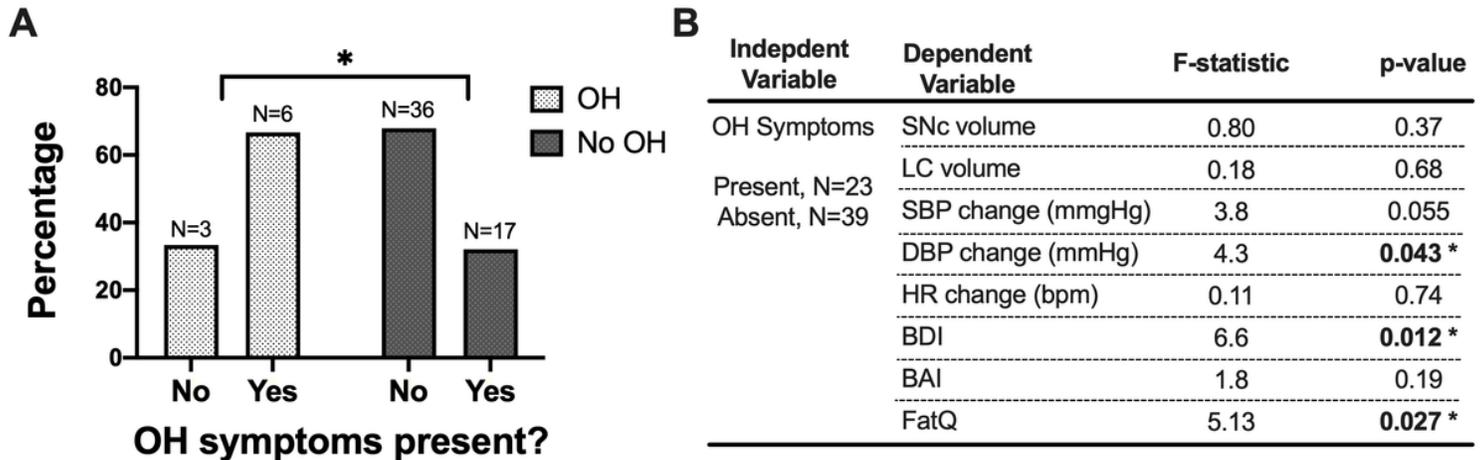


Figure 3

Characteristics of OH symptom presence across subjects. A) OH symptom presence was more likely in OH (66%) compared to no-OH (32%); B) Results of MANOVA findings for OH symptom presence across all PD subjects (N=62). Symptoms were more likely to occur based on greater orthostatic diastolic blood pressure drop (a trend was found for systolic blood pressure), greater degree of depressive symptoms (BDI), and greater degree of fatigue symptoms (FatQ). * Statistical threshold $p < 0.05$ met for Chi-Square testing (left) and MANOVA results (right).

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