TITLE

Autonomic dysfunction is associated with neuropsychological and neuropsychiatric impairment in patients with Lewy body diseases

AUTHORS

Rocío Del Pino, PhD [1,2], Ane Murueta-Goyena, PhD [1], Marian Acera, MSc[1], Mar Carmona, MD, PhD[1], Beatriz Tijero, MD, PhD[1,3], Olaia Lucas-Jiménez, MSc[4], Natalia Ojeda, PhD[4], Naroa Ibarretxe-Bilbao, PhD[4], Javier Peña, PhD[4], Iñigo Gabilondo, MD, PhD[1,5], Juan Carlos Gómez-Esteban, MD, PhD [1,3,6]

[1]Neurodegenerative Diseases Group, Biocruces Bizkaia Health Research Institute, Barakaldo, Bizkaia, Spain; [2]International University of La Rioja, La Rioja, Spain; [3]Neurology Department, Cruces University Hospital, Barakaldo, Bizkaia, Spain; [4]Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Spain; [5]Ikerbasque: The Basque Foundation for Science, Bilbao, Spain; [6]Department of Neurosciences, University of the Basque Country (UPV/EHU), Leioa, Spain.

Corresponding author:

Rocío Del Pino, Neurodegenerative Diseases Group, Biocruces-Bizkaia Health Research Institute, Plaza de Cruces 12, Barakaldo (Bizkaia), CP 48903, Spain

Corresponding author's phone and fax: +34 946006000 ext. 7961

Corresponding author's e-mail: delpinorocio@gmail.com

Running head: Dysautonomia and cognition in Lewy body diseases

Word count: Abstract: 249; Main text: 4109; No. of references: 39; Figures: 3; Tables: 2;

Supplementary material: 1 table.

ABSTRACT

Objective: This study aimed to analyze the association of autonomic dysfunction with cognition, depression, apathy, and fatigue in Lewy body disease (LBD). **Methods**: We included 61 patients [49 with idiopathic Parkinson's disease, 7 with dementia with Lewy bodies, and 5 E46KSNCA mutation carriers] and 22 healthy controls. All participants underwent a comprehensive battery of neuropsychological and clinical measures, autonomic symptom assessment with the SCOPA-AUT, analysis of non-invasive hemodynamic parameters during deep breathing, the Valsalva maneuver, and a 20-min tilt test, and electrochemical skin conductance measurement at rest (Sudoscan). Student's t tests were used to assess group differences, and bivariate correlations and stepwise linear regressions to explore associations between autonomic function, cognition, depression, apathy, and fatigue. **Results:** Compared to controls, patients who had significant impairment ($p < 0.05$) in cognition, higher depression, apathy, and fatigue, more autonomic symptoms and objective autonomic dysfunction, reduced deep breathing heart rate variability [expiratory-to-inspiratory (E/I) ratio], prolonged pressure recovery time, and lower blood pressure in Valsalva late phase II and phase IV, while 24.1% had orthostatic hypotension in the tilt test. Autonomic parameters significantly correlated with cognitive and neuropsychiatric outcomes, systolic blood pressure during the Valsalva maneuver predicting apathy and depression. The E/I ratio was the main predictor of cognitive performance (17.6% for verbal fluency to 32.8% for visual memory). **Conclusion**: Cardiovascular autonomic dysfunction is associated with cognitive and neuropsychiatric impairment in LBD, heart rate variability during deep breathing and systolic blood pressure changes during the Valsalva procedure are the main predictors of neuropsychological performance and depression/apathy symptoms, respectively.

Keywords: Apathy, Autonomic dysfunction, Cognition, Depression, Lewy Body Disease, Parkinson Disease.

INTRODUCTION

The presence of resting tremor, bradykinesia, rigidity or postural instability are defining features of Parkinson's disease (PD) and other Lewy body diseases (LBD). Besides suchmotor manifestations, patients with LBD can develop a wide variety of non-motor abnormalities, such as sleep disorders, cognitive impairment, neuropsychiatric symptoms and autonomic dysfunction, that usually precede motor features and significantly affect quality of life (Bernal-Pacheco et al., 2012; Tijero et al., 2013; Berganzo et al., 2016; Schapira et al., 2017). Cognitive dysfunction is a cardinal non-motor feature of LBD (Emre, 2003; Bosboom et al., 2004; Goldman et al., 2014; Gomperts, 2016). In fact, the prevalence of dementia in PD patients is two to six times greater than in the general population and it increases in relation to disease duration (Emre, 2003; Bosboom et al., 2004).

In recent years, cognitive research has focused the attention in pre-dementia stages of PD, referred as mild cognitive impairment (MCI) (Aarsland et al., 2017), when the decline is more evident in some cognitive domains such as attention, executive function, visual and verbal memory, and visual functions (Aarsland et al., 2017; Hansch et al., 1982; Peña et al., 2014; Pillon, Dubois, & Agid, 1996). Regarding neuropsychiatric symptoms, apathy or depression are very frequent symptoms in PD patients and they are related to cognitive impairment. Depression can affect up to 72% of PD patients in the first 10 years of the disease and apathy appears in 38% to 51% of patients affecting their quality of life and the activities of daily living (Pluck and Brown, 2002; Jasinska-Myga et al., 2010; Bernal-Pacheco et al., 2012).

Autonomic abnormalities have been reported in 14 to 80% of PD patients, depending on the design and methodology of studies (Jost, 2003), with constipation, symptomatic hypotension and erectile and urinary dysfunction now being considered diagnostic markers of prodromal PD (Berg et al., 2015). More specifically, cardiovascular autonomic dysfunction has aroused major interest in clinical research as a potential mechanism to understand clinical deterioration of patients and as a source of development for biomarkers in PD (Kaufmann and Goldstein, 2013).Orthostatic hypotension (OH), the main manifestation of cardiovascular autonomic dysfunction in PD, has an estimated prevalence of 30-58% (Low, 2008; Velseboer et al., 2011;

Bernal-Pacheco et al., 2012; Palma et al., 2015; Cutsforth-Gregory and Low, 2019), and its association with cognitive impairment has been documented in the literature (Fanciulli et al., 2013; Centi et al., 2017; De Pablo-Fernandez et al., 2017; Sforza et al., 2018; Guo et al., 2019; Stankovic et al., 2019). Moreover, even in the absence of OH, patients with LBD have additional well-defined cardiovascular autonomic abnormalities in several parameters extracted from non-invasive hemodynamic tests(Oka et al., 2011; Perez et al., 2015; Rocchi et al., 2015), but, intriguingly, their clinical implications and their potential relation with cognitive or neuropsychiatric symptoms of LBD has not been determined (Wang et al., 2013). Thus, in the present study we aimed to evaluate the association of a collection of cardiovascular autonomic function measures with cognitive performance, depression, apathy, and fatigue in patients with LBD.

METHODS

Participants, demographical and PD-related data

We consecutively recruited 83 participants, including 61 patients with LBD[49 idiopathic PD (iPD), 7 patients with dementia with Lewy bodies (DLB) and 5 E46K-SNCA mutation carriers] through the Department of Neurology at Cruces University Hospital and the Biscay PD Association (ASPARBI), and 22 healthy controls (HC). Participants in HC group were matched with patients in age, education, and sex. Patients with iPD fulfilled Parkinson's UK Brain Bank criteria for the diagnosis of PD (Hughes et al., 1992), and DLB patients had a diagnosis of probable DLB by 2016 revised criteria for the clinical diagnosis of DLB (McKeith et al., 1996). Participants with diabetes mellitus, heart diseases potentially influencing hemodynamic measures, or any other neurological disorder were excluded. Age, sex and years of education were registered for all participants. Patients were studied in an on-medication condition and in their optimal on-motor situation to complete the study. Two neurologists experienced in the field of movement disorders recorded age at disease onset, disease duration, scores for Hoehn &Yahr scale and Unified Parkinson's Disease Rating scale (UPDRS I-IV), and Levodopa Equivalent Daily Dose (LEDD). The study protocol was approved by the regional Basque Clinical Research Ethics Committee. All participants gave written informed consent prior to their participation in the study, in accordance with the tenets of the Declaration of Helsinki.

Cognitive and neuropsychiatric assessment

All neuropsychological evaluations were performed by experienced neuropsychologists and they were conducted before autonomic function testing. Overall cognition screening was performed with the Montreal Cognitive Assessment (MoCA). A comprehensive battery of neuropsychological tests (see Supplementary Table 1) was used to evaluate specific cognitive domains: perception, attention, executive functions, verbal fluency, verbal memory, visual memory, and visuospatial abilities. All neuropsychological outcome variables were converted to z-scores and averaged to create composite scores of all cognitive domains. For visual memory and visuospatial abilities composites, only 35 out of 61 patients successfully completed all the neuropsychological tests. Based on neuropsychological testing and following the recommended Movement Disorder Society criteria for the diagnosis of MCI in PD (Litvan et al., 2012), patients were categorized as cognitively normal, single-domain PD-MCI or multiple-domain PD-MCI. The neuropsychiatric status was assessed with questionnaires measuring depression [Geriatric Depression Scale (GDS)], apathy [Lille Apathy Rating Scale (LARS)], fatigue [Fatigue Severity Scale questionnaire (FSS)], and Instrumental Activities of Daily Living (IADL). The apathy scale was only completed by 27 patients.

Autonomic function test protocol

Autonomic symptoms were evaluated using the Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT) that assesses patient-reported manifestations from six dimensions of autonomic function: digestive, urinary cardiovascular, pupillary, thermoregulatory, and sexual (Evatt et al., 2009). Non-invasive quantitative measures for cardiovascular autonomic function were obtained with Task Force Monitor (TFM) (CNSystems, Graz, Austria) following standard procedures for quantitative autonomic testing (Novak, 2011). In brief, we continuously monitored heart rate and blood pressure variability at rest in supine position for 10 minutes and in response to deep breathing, the Valsalva maneuver and the 20-minute Tilt Test (TT). Four-lead electrocardiography (ECG) was used to measure the heart rate and the inter-beat interval. The expiratory-to-inspiratory ratio (E/I) was calculated using results from a deep breathing test which consisted of a series of six successive deep breath cycles in a supine position. This was followed by the Valsalva maneuver performed at an expiratory pressure of 40 mm Hg for 15 seconds. We only considered hemodynamic parameters from phase II, late

phase II, and phase IV of Valsalva, which allowed us to calculate blood pressure recovery time (PRT) [recovery time of systolic blood pressure (SBP) from the bottom of phase III to baseline], and the Valsalva ratio (duration of the longest R-R interval in phase IV divided by the duration of the shortest R-R interval between phase II and the very beginning of phase III). After Valsalva, patients were instructed to breath at a normal and comfortable rate. Finally, a 20-minute TT at an inclination of 60º was performed. Orthostatic hypotension was defined as a drop in SBP ≥20 mmHg and/or a reduction in diastolic blood pressure (DBP) ≥10 mmHg after five minutes of inclination, according to the criteria from The Consensus Committee of the American Autonomic Society and the American Academy of Neurology (1996). Sudomotor function was quantified non-invasively with Sudoscan (Impeto Medical; Paris, France), a commercial device able to quantify in a simple, fast and painless way electrochemical skin conductance (ESC) in palms and sores. ESC is automatically calculated by the equipment for skin of palms and soles, and results are expressed in microSiemens (µS) (Casellini et al., 2013).

Statistical analysis

Statistical analyses were carried out with IBM SPSS Statistics for Windows, version 21.0 (IBM SPSS, Armonk, NY, USA). Group differences for continuous and categorical variables were analyzed with two-tailed Student's t tests for independent samples and with pairwise Fisher's exact tests, respectively. First, we computed bivariate correlations to explore the relationship between the autonomic function parameters and cognitive performance, separately in controls and patients. Then, we used significantly correlated autonomic variables to perform stepwise linear regression analyses, setting autonomic parameters as independent predictors and composites of cognitive tests and neuropsychiatric scores as dependent variables. The variance-inflating factor (VIF) was calculated to check for multicollinearity. Statistical significance was set at $p < 0.05$ (two-tailed).

RESULTS

Demographical and PD-related clinical features

The general characteristics of study participants are summarized in Table 1. There were no statistically significant differences between groups in sociodemographic characteristics. The

mean disease duration of patients was 6.8 ± 4.3 years and they had a mild to moderate bilateral motor disability (median Hoehn and Yahr score of 2.5 and mean UPDRS III score of 28.2 ± 12.7). A total of 51 patients (83.6%) had MCI, of which 47 (92.2%) met Movement Disorder Society criteria for multiple-domain MCI. Regarding data on the apathy scale, there were no significant differences between participants who completed this scale and those who did not in sociodemographic and clinical variables (age, disease duration, UPDRS, depression or fatigue).

Neuropsychological and neuropsychiatric status

Compared to controls, patients showed significantly worse performance in general cognition (MoCA) (t = 4.65, p < 0.001) and the composites of all cognitive domains tested (perception: t = 4.17, p < 0.001; executive functions: t = 3.85, p < 0.001; attention: t = 2.46, p = 0.017; verbal fluency: t = 3.48, p < 0.001; verbal memory: t = 4.01, p < 0.001; visual memory: t = 4.36, p < 0.001; and visuospatial abilities: t = 4.74, p < 0.001) (Fig. 1a). Patients also had significantly poorer neuropsychiatric outcomes, with higher scores for depression (t = 3.25, p = 0.002), fatigue (t = 3.48, p = 0.001) and apathy (t = 2.34, p = 0.025), and reported worse status in terms of instrumental activities of daily living (t = 4.26, p < 0.001).

Autonomic manifestations and quantitative autonomic testing

Table 2 summarizes the main autonomic function findings and the differences between LBD patients and controls. The presence and severity of autonomic symptoms, assessed through the SCOPA-AUT questionnaire, were significantly greater in LBD patients than in controls for all autonomic domains, except for cardiovascular manifestations. Interestingly, several significant differences were found between patients and controls in quantitative cardiovascular autonomic testing. While in the supine resting state, baseline SBP, DBP, and heart rate were comparable in the two groups; however, during deep breathing, and the Valsalva and tilt tests, the variability of these parameters differed significantly (Fig. 1b). First, we observed that heart rate variability during deep breathing, as measured by the E/I ratio, was significantly lower in LBD patients (p = 0.006). Second, in the Valsalva maneuver, LBD patients displayed significantly lower (p < 0.05) DBP in late phase II and phase IV, lower SPB in phase IV, and prolonged blood PRT. Third, in

the tilt test, after 20 min in an upright position, LBD patients had significantly lower SBP than controls (p = 0.004). Regarding the presence of OH, 20% of patients and 9.1% of controls met the criteria for OH after 5 min, while delayed OH was observed in 24.1% of patients versus 13.1% of controls at 10 min, and in 36.5% versus 22.7% at 20 min, respectively. Notably, most patients with objective OH did not report symptoms during the tilt test and there were no significant differences in the SCOPA-AUT cardiovascular domain between such patients and those without objective OH, indicating that OH may have been subclinical in all cases. Lastly, we did not observe significant differences in sudomotor function between LBD patients and controls, or in left–right averages or left–right asymmetry of ESC values for the hands and feet.

Relation of autonomic measures with cognitive and neuropsychiatric status

Several autonomic variables significantly correlated (p < 0.05) with cognitive and neuropsychiatric outcomes in LBD patients. First, we observed a modest to moderate negative correlation between overall autonomic symptoms (higher total SCOPA-AUT score) and lower cognitive performance in most neuropsychological domains, ranging from r = − 0.28 (p = 0.04) for visuospatial abilities to r = − 0.46 (p = 0.01) for visual memory. Several SCOPA-AUT domains were also correlated with depression (gastrointestinal, r = 0.36, p = 0.008; thermoregulatory, r = 0.50, p < 0.001; and pupillomotor, r = 0.35, p = 0.01), but not with apathy. Fatigue mainly correlated with the gastrointestinal domain of the SCOPA-AUT (r = 0.38, p = 0.008).

Second, we found significant correlations between several parameters obtained from non-invasive quantitative autonomic testing and cognitive and neuropsychiatric outcomes. Lower magnitudes of SBP change in phase IV of the Valsalva maneuver, the Valsalva ratio, and the E/I ratio were correlated with lower composite scores in most cognitive domains (perception, executive functions, attention, verbal fluency and verbal memory) (Fig. 2). Such correlations were especially strong between the magnitude of the SBP change in Valsalva phase IV and both executive functions (r = 0.48, p < 0.001) and attention (r = 0.45, p < 0.001); between the E/I ratio and visual memory (r = 0.57, p < 0.001); and between the Valsalva ratio and visuospatial ability (r = 0.45, p < 0.01). In addition, SBP after 5 min of tilt correlated with

attention (r = 0.26, p = 0.047), DBP after 5 min of tilt with visuospatial abilities (r = 0.38, p = 0.028), and DBP after 10 min of tilt with verbal fluency (r = 0.30, p = 0.023). Moreover, scores of apathy and depression were negatively correlated with the E/I ratio (r = -0.40, p = 0.04; and r = −0.26, p = 0.047, respectively), and SBP at phase II and late phase II with apathy (r = −0.41; p < 0.05, and r = −0.47; p < 0.05, respectively), suggesting that the low E/I ratio and hemodynamic parameters during such Valsalva phases are linked to apathy and depression in LBD patients. Nonetheless, the fatigue score was not significantly correlated with any autonomic parameters.

Lastly, none of the electrochemical skin conductance parameters measured with Sudoscan significantly correlated with cognitive or neuropsychiatric variables. Regarding the correlations in the control group, only general cognition significantly correlated with PRT during the Valsalva maneuver (rho = rho 0.52, p = 0.01), participants with poorer general cognitive performance obtained longer PRTs.

To quantify the association of autonomic parameters with cognitive and neuropsychiatric status, we performed stepwise hierarchical linear regression analyses including the autonomic variables that were the most significant in correlation analyses as independent predictors: the E/I ratio from the deep breathing test and SPB change in late phase II and phase IV, the Valsalva ratio, and PRT from the Valsalva maneuver (Fig. 3a). In this analysis, we found that a lower E/I ratio was significantly associated with poorer performance in practically all cognitive domains except visuospatial abilities, explaining 17.6–32.8% of the variance. Interestingly, for executive functions and attention domains, in addition to the effect of the E/I ratio, SBP change in phase IV of the Valsalva maneuver was also an important contributing factor (R2 change 10%). In addition, lower Valsalva ratios were significantly associated with lower scores in the visuospatial ability domain, explaining 20.4% of its variance. On the other hand, we observed that PRT from the Valsalva maneuver and parameters from the tilt test were not significantly associated with cognition or neuropsychiatric variables (Fig. 3a). In a second step, to control the effect of disease-related confounding factors, we incorporated additional independent predictors in the regression, the motor scores from the UPDRS III and disease duration (Fig.

3b). Although cognitive and neuropsychiatric outcomes were clearly related to UPDRS III scores and disease duration (these variables explaining between 8.0 and 38.5% of their variance), the analysis confirmed that the E/I ratio remained a significant predictor of cognitive performance in most domains, especially visual memory (30.8% of variance) (Fig. 3b). In addition, the Valsalva ratio also persisted as a significant factor influencing the visuospatial ability domain and contributing to 10.3% of its variance. In contrast, after controlling the effects of UPDRS III scores and disease duration, the association between SBP change in Valsalva phase IV and attention and executive function domains no longer reached significance.

DISCUSSION

The present study investigated the association between autonomic function, and neuropsychological and neuropsychiatric status in patients with LBD. We included a comprehensive collection of neuropsychological and neuropsychiatric variables and a wide variety of autonomic parameters derived from patient-reported questionnaires and non-invasive cardiovascular and sudomotor tests. The main findings of the present work were: (1) compared to controls, patients with LBD showed significantly reduced E/I ratio in deep breathing, prolonged PRT and lower blood pressures in phase II late and IV of Valsalva Maneuver and 24.1% of patients had objective OH at 10 minutes of tilt; (2) LBD patients had poorer general cognition and cognitive impairment related to perception, attention and executive functions, verbal memory and fluency, visual memory and visuospatial abilities, and presented more symptoms of depression, apathy, and fatigue. (3) Non-invasive cardiovascular autonomic parameters, especially those obtained during deep breathing test and Valsalva maneuver, significantly influenced neuropsychological performance in most cognitive domains, being the E/I ratio from deep breathing test the main autonomic predictor of cognitive status in LBD. Furthermore, this together with the absence of significant differences between controls and LBD patients regarding cardiovascular manifestations on SCOPA-AUT supports the idea that subclinical autonomic abnormalities may be silently contributing to cognitive deterioration in LBD.

10

To our knowledge, this is the first study specifically analyzing the relation of neuropsychological and neuropsychiatric status of LBD patients with a complete set of non-invasive cardiovascular autonomic parameters. An association between OH and cognitive impairment has been documented (Allcock et al., 2006; Peralta et al., 2007; De Pablo-Fernandez et al., 2017; Sforza et al., 2018) but not well established in LBD. A recent meta-analysis suggests that OH increases the relative risk of cognitive impairment by 2.98 in PD (Guo et al., 2019), and it seems that OH has a causal role in cognitive alterations (Centi et al., 2017). Although the pathophysiological underpinnings of this relationship are yet to be determined, it has been claimed that brain hypoperfusion is a central mediator. Further, it has been proposed that altered cerebrovascular perfusion with lower occipitoparietal perfusion in LBD plays an important role in visuospatial, attentional, and executive deficits (Robertson et al., 2016), and cognitive impairment is related to the magnitude of the decrease in brain perfusion as the disease progresses (Paschali et al., 2010). The vascular hypothesis suggests that recurrent episodic hypotension could result in white matter lesions, which in turn could induce cognitive impairment. A recent study (Chung et al., 2019) showed that in PD patients with moderate to severe dysautonomia [assessed by Composite Autonomic Severity Score (CASS)], the cognitive performance was significantly poorer than in PD patients without autonomic dysfunction, mainly involving frontal and executive functions. According to their results, the reported symptoms correlated with fronto-subcortical and posterior cortical white matter connectivity disruption.

Whereas OH typically occurs late in the course of the disease, other subtle autonomic function alterations appear earlier in disease progression (Perez et al., 2015). Additional manifestations of autonomic dysfunction beyond OH in patients with LBD include decreased E/I ratio in deep breathing and altered regulation of blood pressure in the Valsalva maneuver. Parasympathetic and sympathetic dysfunction in LBD is well-established, and our results support previous findings. Metronomic breathing assesses parasympathetic baroreflex function, and pathological responses have been described in PD patients with a mean disease duration of 4.3±4.5 years (Rocchi et al., 2015), which is in line with our results. Interestingly, a significant I/E difference at deep breathing is also observed in patients with idiopathic REM sleep behavior disorder – a prodromic stage of α-synucleinopathies (Rocchi et al., 2018).

The Valsalva maneuver is used as an autonomic function test that can detect sympathetic and parasympathetic autonomic dysfunction. The Valsalva ratio is as a parameter of cardiovagal function, whereas PRT evaluates the adrenergic component of the baroreflex. In this work, the reduced SBP in phase II late and phase IV in LBD patients indicated an absence of reflex vasoconstriction and, in combination with a prolonged PRT, indicated that the adrenergic baroreflex was markedly impaired in LBD. Previous hemodynamic studies using Valsalva maneuver have also described impaired blood pressure regulation in PD patients in phase II and phase IV, and longer PRT duration compared to controls (Schmidt et al., 2009; Oka et al., 2011). In our cohort, 24% of patients presented OH at 10 minutes of 60º tilt, which is lower than the 30% prevalence reported in previous studies (Velseboer et al., 2011; Fereshtehnejad and Lökk, 2014). However, the percentage of patients with OH increased up to 36.5% at 20 minutes, suggesting that prolonged periods of Tilt Test protocol might be needed to unravel OH in LBD with shorter disease durations. The cardiovascular symptoms were comparable between patients and controls, indicating that OH was subclinical.

Although some studies have shown a link between OH and cognitive impairment, the association between subclinical sympathetic and parasympathetic dysfunction and cognition has not been extensively studied in LBD. Cognitive impairment as well as autonomic alterations are considered premotor symptoms in LBD. A possible explanation for the relationship between dysautonomia and cognitive impairment in LBD is that they share common neuroanatomical structures and neural networks that are affected by Lewy body pathology. Inclusions of alpha-synuclein aggregates are found in autonomic small fibers (Siepmann et al., 2016; Carmona-Abellan et al., 2019), but also in several nuclei of the brainstem that modulate the autonomic nervous system, including dorsal motor nucleus of the vagus, the reticular formation, the raphe nuclei or the locus coeruleus, from early stages of LBD (Seidel et al., 2015). Alternatively, the association between autonomic pathology and cognition could reflect that the abnormal cardiovascular findings are risk factors for cognitive decline. Our results reinforce this assertion that some of the autonomic parameters were significant predictors of cognitive performance, after controlling for the effect of disease duration and motor severity. Heart rate variability with respiratory cycles was the autonomic parameter most frequently associated with cognitive

performance. Moreover, the Valsalva ratio was associated with visuospatial abilities. In combination, the parameters of parasympathetic activity predicted cognitive performance in our sample.

Altered parasympathetic innervation of the vertebrobasilar or carotid arteries could contribute to neurocirculatory abnormalities that have been described to occur early in PD and are known to be related to cognitive impairment (Kim et al., 2012). Nonetheless, it remains challenging to understand its precise contribution to cerebral perfusion as a causal factor for cognitive impairment, since cerebral blood flow is highly complex, and there are likely to be contributions from neurogenic, hemodynamic, metabolic and autoregulatory factors. A recent review that included 19,431 participants concluded that heart rate variability could be considered a promising early biomarker for cognitive impairment (Forte et al., 2019). This contrasts with sudomotor function, which was not significantly reduced in our LBD patients and did not correlate with any cognitive function. Nonetheless, sudomotor function is commonly altered in advanced stages of the disease, and the electrochemical skin conductance as a tool to measure sudomotor function in LBD still lacks robustness.

A considerable percentage of symptoms of depression and apathy were explained by SBP in phase II late and phase IV of Valsalva maneuver, and were therefore associated with sympathetic function. This finding is in agreement with studies using Magnetic Resonance Imaging (MRI) with neuromelanin-sensitive measurements, in which the degeneration of locus coeruleus, the main source of noradrenalin in the brain, has been related to depression symptoms severity (Remy et al., 2005; Solopchuk et al., 2018). Although the relationship between apathy and noradrenalin is less clear, the deficiency of noradrenalin has been proposed a plausible factor contributing to apathy and cognitive decline (Loued-Khenissi and Preuschoff, 2015). We did not find a correlation between fatigue and E/I ratio in deep breathing test, contrary to previous findings(Olivola et al., 2018), nor between fatigue and autonomic function parameters attributable to sympathetic innervation, which is in line with the results of Solopchuk et al., (Solopchuk et al., 2018). However, fatigue was correlated with autonomic symptoms, a link that has been previously reported (Chou et al., 2017).

One of the limitations of the current study is that we studied patients with LBD including patients with idiopathic PD, DLB and genetic PD simultaneouslywithout stratifying patients according to the severity of their autonomic dysfunction. However, having patients with variable disease durations, autonomic dysfunction and severity of symptoms allowed as to unravel the link between the severity of cognitive impairment and dysautonomia. Moreover, control participants with OH were not excluded from the analysis. The OH incidence in elderly people is about 5-30% (Sambati et al., 2014), and including controls with OH might better reflect the specific autonomic alterations that occur in LBD compared to the general population. Despite these limitations, our results are consistent with previous studies regarding the autonomic parameters that are altered in LBD, and further extends the available literature by showing the association of E/I ratio and Valsalva ratio with cognitive impairment.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

REFERENCES

(1996). Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* 46(5), 1470. doi: 10.1212/wnl.46.5.1470.

Allcock, L.M., Kenny, R.A., Mosimann, U.P., Tordoff, S., Wesnes, K.A., Hildreth, A.J., et al. (2006). Orthostatic hypotension in Parkinson's disease: association with cognitive decline? *Int J Geriatr Psychiatry* 21(8), 778-783. doi: 10.1002/gps.1562.

Berg, D., Postuma, R.B., Adler, C.H., Bloem, B.R., Chan, P., Dubois, B., et al. (2015). MDS research criteria for prodromal Parkinson's disease. *Mov Disord* 30(12), 1600-1611. doi: 10.1002/mds.26431.

Berganzo, K., Tijero, B., Gonzalez-Eizaguirre, A., Somme, J., Lezcano, E., Gabilondo, I., et al. (2016). Motor and non-motor symptoms of Parkinson's disease and their impact on quality of life and on different clinical subgroups. *Neurologia* 31(9), 585-591. doi: 10.1016/j.nrl.2014.10.010.

Bernal-Pacheco, O., Limotai, N., Go, C.L., and Fernandez, H.H. (2012). Nonmotor manifestations in Parkinson disease. *Neurologist* 18(1), 1-16. doi: 10.1097/NRL.0b013e31823d7abb.

Bosboom, J.L., Stoffers, D., and Wolters, E. (2004). Cognitive dysfunction and dementia in Parkinson's disease. *J Neural Transm (Vienna)* 111(10-11), 1303-1315. doi: 10.1007/s00702-004-0168-1.

Carmona-Abellan, M., Gabilondo, I., Murueta-Goyena, A., Khurana, V., Tijero, B., Luquin, M.R., et al. (2019). Small fiber neuropathy and phosphorylated alpha-synuclein in the skin of E46K-SNCA mutation carriers. *Parkinsonism Relat Disord* 65, 139-145. doi: 10.1016/j.parkreldis.2019.05.038.

Casellini, C.M., Parson, H.K., Richardson, M.S., Nevoret, M.L., and Vinik, A.I. (2013). Sudoscan, a noninvasive tool for detecting diabetic small fiber neuropathy and autonomic dysfunction. *Diabetes Technol Ther* 15(11), 948-953. doi: 10.1089/dia.2013.0129.

Centi, J., Freeman, R., Gibbons, C.H., Neargarder, S., Canova, A.O., and Cronin-Golomb, A. (2017). Effects of orthostatic hypotension on cognition in Parkinson disease. *Neurology* 88(1), 17-24. doi: 10.1212/wnl.0000000000003452.

Chou, K.L., Gilman, S., and Bohnen, N.I. (2017). Association between autonomic dysfunction and fatigue in Parkinson disease. *J Neurol Sci* 377, 190-192. doi: 10.1016/j.jns.2017.04.023.

Chung, S.J., Bae, Y.J., Jun, S., Yoo, H.S., Kim, S.W., Lee, Y.H., et al. (2019). Dysautonomia is associated with structural and functional alterations in Parkinson disease. *Neurology* 92(13), e1456-e1467. doi: 10.1212/wnl.0000000000007181.

De Pablo-Fernandez, E., Tur, C., Revesz, T., Lees, A.J., Holton, J.L., and Warner, T.T. (2017). Association of Autonomic Dysfunction With Disease Progression and Survival in Parkinson Disease. *JAMA Neurol* 74(8), 970-976. doi: 10.1001/jamaneurol.2017.1125.

Emre, M. (2003). Dementia associated with Parkinson's disease. *Lancet Neurol* 2(4), 229-237.

Evatt, M.L., Chaudhuri, K.R., Chou, K.L., Cubo, E., Hinson, V., Kompoliti, K., et al. (2009). Dysautonomia rating scales in Parkinson's disease: sialorrhea, dysphagia, and constipation--critique and recommendations by movement disorders task force on rating scales for Parkinson's disease. *Mov Disord* 24(5), 635-646. doi: 10.1002/mds.22260.

Fanciulli, A., Strano, S., Colosimo, C., Caltagirone, C., Spalletta, G., and Pontieri, F.E. (2013). The potential prognostic role of cardiovascular autonomic failure in alpha-synucleinopathies. *Eur J Neurol* 20(2), 231-235. doi: 10.1111/j.1468-1331.2012.03819.x.

Fereshtehnejad, S.M., and Lökk, J. (2014). Orthostatic hypotension in patients with Parkinson's disease and atypical parkinsonism. *Parkinsons Dis* 2014, 475854. doi: 10.1155/2014/475854.

Forte, G., Favieri, F., and Casagrande, M. (2019). Heart Rate Variability and Cognitive Function: A Systematic Review. *Front Neurosci* 13, 710. doi: 10.3389/fnins.2019.00710.

Goldman, J.G., Williams-Gray, C., Barker, R.A., Duda, J.E., and Galvin, J.E. (2014). The spectrum of cognitive impairment in Lewy body diseases. *Mov Disord* 29(5), 608-621. doi: 10.1002/mds.25866.

Gomperts, S.N. (2016). Lewy Body Dementias: Dementia With Lewy Bodies and Parkinson Disease Dementia. *Continuum (Minneap Minn)* 22(2 Dementia)**,** 435-463. doi: 10.1212/con.0000000000000309.

Guo, Y., Xu, W., Liu, F.T., Li, J.Q., Cao, X.P., Tan, L., et al. (2019). Modifiable risk factors for cognitive impairment in Parkinson's disease: A systematic review and meta-analysis of prospective cohort studies. *Mov Disord* 34(6)**,** 876-883. doi: 10.1002/mds.27665.

Hughes, A.J., Daniel, S.E., Kilford, L., and Lees, A.J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 55(3)**,** 181-184. doi: 10.1136/jnnp.55.3.181.

Jasinska-Myga, B., Putzke, J.D., Wider, C., Wszolek, Z.K., and Uitti, R.J. (2010). Depression in Parkinson's disease. *Can J Neurol Sci* 37(1)**,** 61-66. doi: 10.1017/s0317167100009665.

Jost, W.H. (2003). Autonomic dysfunctions in idiopathic Parkinson's disease. *J Neurol* 250 Suppl 1**,** I28-30. doi: 10.1007/s00415-003-1105-z.

Kaufmann, H., and Goldstein, D.S. (2013). Autonomic dysfunction in Parkinson disease. *Handb Clin Neurol* 117**,** 259-278. doi: 10.1016/b978-0-444-53491-0.00021-3.

Kim, J.S., Oh, Y.S., Lee, K.S., Kim, Y.I., Yang, D.W., and Goldstein, D.S. (2012). Association of cognitive dysfunction with neurocirculatory abnormalities in early Parkinson disease. *Neurology* 79(13)**,** 1323-1331. doi: 10.1212/WNL.0b013e31826c1acd.

Litvan, I., Goldman, J.G., Troster, A.I., Schmand, B.A., Weintraub, D., Petersen, R.C., et al. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord* 27(3)**,** 349-356. doi: 10.1002/mds.24893.

Loued-Khenissi, L., and Preuschoff, K. (2015). Apathy and noradrenaline: silent partners to mild cognitive impairment in Parkinson's disease? *Curr Opin Neurol* 28(4)**,** 344-350. doi: 10.1097/wco.0000000000000218.

McKeith, I.G., Galasko, D., Kosaka, K., Perry, E.K., Dickson, D.W., Hansen, L.A., et al. (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 47(5)**,** 1113-1124. doi: 10.1212/wnl.47.5.1113.

Novak, P. (2011). Quantitative autonomic testing. *J Vis Exp* (53). doi: 10.3791/2502.

Oka, H., Toyoda, C., Yogo, M., and Mochio, S. (2011). Cardiovascular dysautonomia in de novo Parkinson's disease without orthostatic hypotension. *Eur J Neurol* 18(2)**,** 286-292. doi: 10.1111/j.1468-1331.2010.03135.x.

Olivola, E., Brusa, L., Rocchi, C., Schillaci, O., Liguori, C., Cerroni, R., et al. (2018). Does fatigue in Parkinson's disease correlate with autonomic nervous system dysfunction? *Neurol Sci* 39(12)**,** 2169-2174. doi: 10.1007/s10072-018-3569-x.

Paschali, A., Messinis, L., Kargiotis, O., Lakiotis, V., Kefalopoulou, Z., Constantoyannis, C., et al. (2010). SPECT neuroimaging and neuropsychological functions in different stages of Parkinson's disease. *Eur J Nucl Med Mol Imaging* 37(6)**,** 1128-1140. doi: 10.1007/s00259-010-1381-9.

Peralta, C., Stampfer-Kountchev, M., Karner, E., Kollensperger, M., Geser, F., Wolf, E., et al. (2007). Orthostatic hypotension and attention in Parkinson's disease with and without dementia. *J Neural Transm (Vienna)* 114(5)**,** 585-588. doi: 10.1007/s00702-006-0615-2.

Perez, T., Tijero, B., Gabilondo, I., Luna, A., Llorens, V., Berganzo, K., et al. (2015). Cardiocirculatory manifestations in Parkinson's disease patients without orthostatic hypotension. *J Hum Hypertens* 29(10)**,** 604-609. doi: 10.1038/jhh.2014.131.

Pluck, G.C., and Brown, R.G. (2002). Apathy in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 73(6)**,** 636-642. doi: 10.1136/jnnp.73.6.636.

Remy, P., Doder, M., Lees, A., Turjanski, N., and Brooks, D. (2005). Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain* 128(Pt 6)**,** 1314-1322. doi: 10.1093/brain/awh445.

Robertson, A.D., Messner, M.A., Shirzadi, Z., Kleiner-Fisman, G., Lee, J., Hopyan, J., et al. (2016). Orthostatic hypotension, cerebral hypoperfusion, and visuospatial deficits in Lewy body disorders. *Parkinsonism Relat Disord* 22**,** 80-86. doi: 10.1016/j.parkreldis.2015.11.019.

Rocchi, C., Pierantozzi, M., Galati, S., Chiaravalloti, A., Pisani, V., Prosperetti, C., et al. (2015). Autonomic Function Tests and MIBG in Parkinson's Disease: Correlation to Disease Duration and Motor Symptoms. *CNS Neurosci Ther* 21(9)**,** 727-732. doi: 10.1111/cns.12437.

Rocchi, C., Placidi, F., Liguori, C., Del Bianco, C., Lauretti, B., Diomedi, M., et al. (2018). Daytime autonomic activity in idiopathic rapid eye movement sleep behavior disorder: a preliminary study. *Sleep Med* 52**,** 163-167. doi: 10.1016/j.sleep.2018.08.023.

Sambati, L., Calandra-Buonaura, G., Poda, R., Guaraldi, P., and Cortelli, P. (2014). Orthostatic hypotension and cognitive impairment: a dangerous association? *Neurol Sci* 35(6)**,** 951-957. doi: 10.1007/s10072-014-1686-8.

Schapira, A.H.V., Chaudhuri, K.R., and Jenner, P. (2017). Non-motor features of Parkinson disease. *Nat Rev Neurosci* 18(7)**,** 435-450. doi: 10.1038/nrn.2017.62.

Schmidt, C., Herting, B., Prieur, S., Junghanns, S., Schweitzer, K., Globas, C., et al. (2009). Valsalva manoeuvre in patients with different Parkinsonian disorders. *J Neural Transm (Vienna)* 116(7)**,** 875-880. doi: 10.1007/s00702-009-0239-4.

Seidel, K., Mahlke, J., Siswanto, S., Kruger, R., Heinsen, H., Auburger, G., et al. (2015). The brainstem pathologies of Parkinson's disease and dementia with Lewy bodies. *Brain Pathol* 25(2)**,** 121-135. doi: 10.1111/bpa.12168.

Sforza, M., Assogna, F., Rinaldi, D., Sette, G., Tagliente, S., and Pontieri, F.E. (2018). Orthostatic hypotension acutely impairs executive functions in Parkinson's disease. *Neurol Sci* 39(8)**,** 1459-1462. doi: 10.1007/s10072-018-3394-2.

Siepmann, T., Illigens, B.M.-W., and Barlinn, K. (2016). Alpha-synuclein in cutaneous small nerve fibers. *Neuropsychiatric disease and treatment* 12**,** 2731-2735. doi: 10.2147/NDT.S117423.

Solopchuk, O., Sebti, M., Bouvy, C., Benoit, C.E., Warlop, T., Jeanjean, A., et al. (2018). Locus Coeruleus atrophy doesn't relate to fatigue in Parkinson's disease. *Sci Rep* 8(1)**,** 12381. doi: 10.1038/s41598-018-30128-y.

Stankovic, I., Petrovic, I., Pekmezovic, T., Markovic, V., Stojkovic, T., Dragasevic-Miskovic, N., et al. (2019). Longitudinal assessment of autonomic dysfunction in early Parkinson's disease. *Parkinsonism Relat Disord*. doi: 10.1016/j.parkreldis.2019.07.008.

Tijero, B., Gomez-Esteban, J.C., Lezcano, E., Fernandez-Gonzalez, C., Somme, J., Llorens, V., et al. (2013). Cardiac sympathetic denervation in symptomatic and asymptomatic carriers of the E46K mutation in the alpha synuclein gene. *Parkinsonism Relat Disord* 19(1)**,** 95-100. doi: 10.1016/j.parkreldis.2012.08.001.

Velseboer, D.C., de Haan, R.J., Wieling, W., Goldstein, D.S., and de Bie, R.M. (2011). Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord* 17(10)**,** 724-729. doi: 10.1016/j.parkreldis.2011.04.016.

Wang, Y., Zhao, X., O'Neil, A., Turner, A., Liu, X., and Berk, M. (2013). Altered cardiac autonomic nervous function in depression. *BMC Psychiatry* 13**,** 187. doi: 10.1186/1471-244x-13-187.
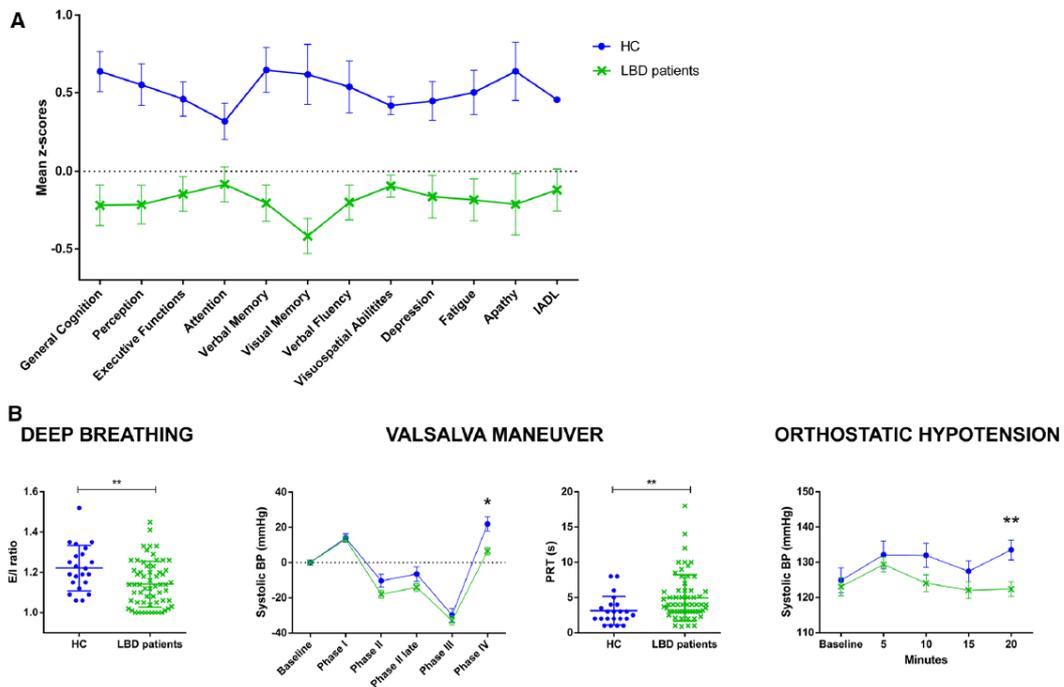
Figure 1. Cognitive and autonomic measures in LBD patients and healthy controls. A) Differences in neuropsychological performance and neuropsychiatric symptoms between LBD patients and controls. The results of cognitive composites and questionnaires are expressed as z scores. B) Quantitative autonomic function testing. Under deep breathing, the ratio between heart rate during expiration and heart rate during inspiration (E/I ratio) was calculated. For the Valsalva maneuver, systolic blood pressure changes during the maneuver and systolic blood pressure recovery time (PRT) are presented. Orthostatic hypotension was monitored by measuring systolic blood pressure at baseline, and at 5, 10, 15, and 20 min in the tilt-table test. BP blood pressure, HC healthy control, IADL Instrumental Activities of Daily Living.
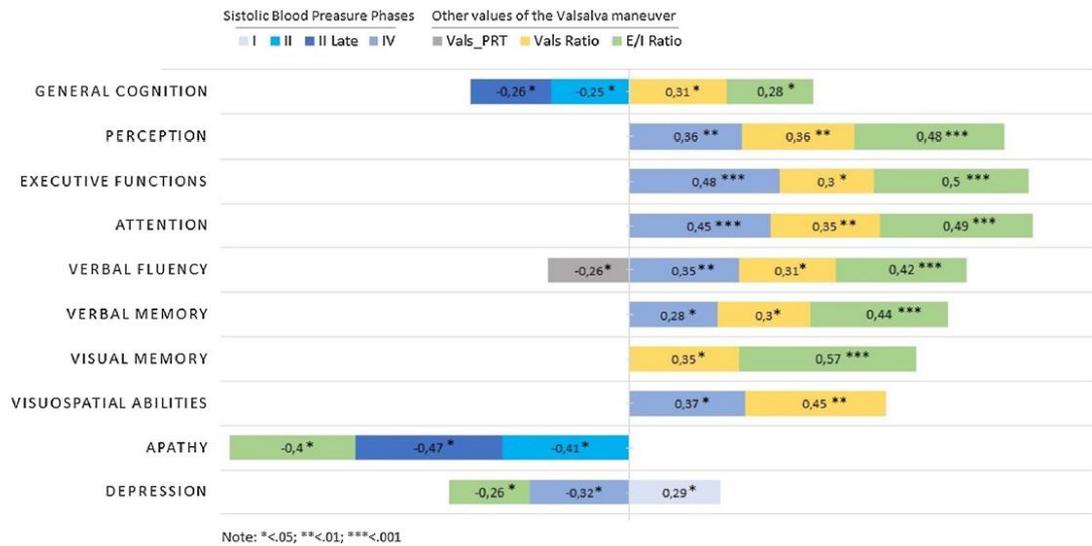
Figure 2. Correlations between neuropsychological performance and neuropsychiatric symptoms with autonomic function in LBD patients.
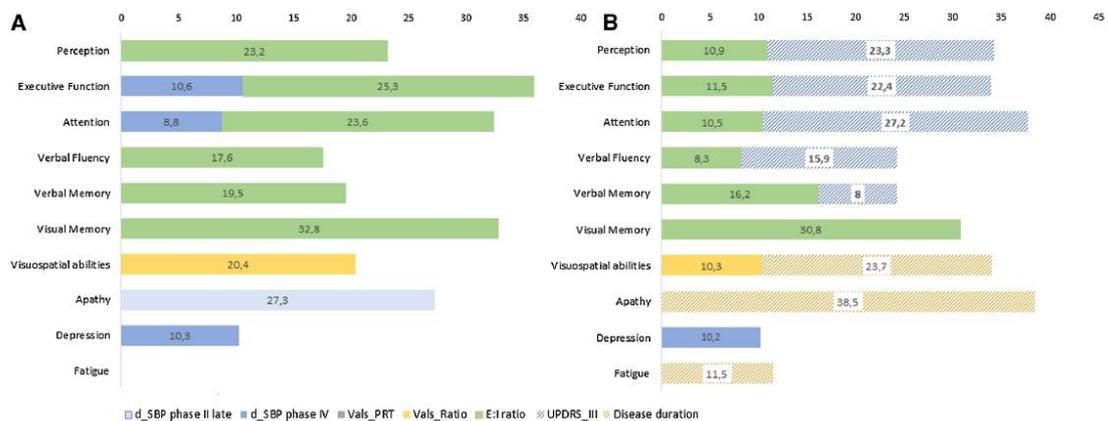
Figure 3. Predicted effects of autonomic function in cognition, depression, apathy and fatigue in patients with LBD. A) Autonomic variables as predictors of the regression analyses. B) Autonomic variables and disease related factors (disease duration and motor performance from the UPDRS-III) as predictors of the regression analyses.

Table 1. Demographics and PD characteristics of study participants

	HC (n=22)	LBD patients (n=61)	Statistics (p)
Age, years	57.9 (5.9)	61.5 (8.9)	$t = -1.74$ (0.08)
Males, n (%)	10 (45.5)	38 (62.3)	$X^2 = 1.88$ (0.17)
Education, years	12.5 (4.0)	10.5 (4.1)	$t = 1.92$ (0.06)
Age at onset, years		47.7 (55.9)	
Disease duration, years		6.8 (4.3)	
Hoehn &Yahr		2.2 (.72)	
UPDRS I		2.7 (2.1)	
UPDRS II		12.8 (7.0)	
UPDRS III		28.2 (12.7)	
UPDRS IV		4.3 (3.7)	
LEDD		654.58 (426.1)	
No PD-MCI (%)	13 (61.9)	10 (16.4)	$X^2 = 17.96$ (0.00)
Single-domain PD-MCI, n (%)		4 (7.8)	
Multiple-domain PD-MCI, n (%)		47 (92.2)	

The results are displayed as mean (standard deviation) except for sex, PD–MCI and Hoehn and Yahr score, which are shown, respectively, as number of males (% of males), number of participants with PD–MCI (% of total patients with PD–MCI within the group) and median (range). See methods for references on MCI classification criteria. Abbreviations: HC healthy controls, LBD Lewy body disease, PD-MCI Parkinson's disease with Mild Cognitive Impairment, UPDRS Unified Parkinson Disease Rating Scale, LEDD Levodopa Equivalent Daily dose.

Table 2. Autonomic manifestations and quantitative autonomic tests

	HC (n = 22)	LBD patients (n = 61)	Statistics t (p)	95% CI LL	95% CI UL	Cohen's d
SCOPA-AUT scores	5.3 (4.9)	13.0 (7.6)	− 5.2 (0.000)	− 11.16	− 4.24	− 1.10
Autonomic function tests						
Deep breathing						
E/I ratio	1.2 (0.1)	1.1 (0.1)	2.8 (0.006)	0.05	0.15	1.10
Valsalva Maneuver (BP difference from baseline)						
ΔSBP phase II late	− 6.4 (19.3)	− 13.9 (17.2)				
ΔDBP phase II late	12.0 (16.5)	1.7 (15.8)	2.5 (0.012)	2.39	18.21	0.64
ΔSBP phase IV	21.8 (18.9)	6.5 (16.0)	3.6 (0.000)	6.00	23.61	0.91
ΔDBP phase IV	11.5 (15.7)	4.3 (13.6)	2.0 (0.042)	0.19	14.21	0.51
Valsalva PRT (s)	3.1 (2.0)	4.9 (3.2)	− 2.4 (0.017)	− 3.25	− 0.35	− 0.61
Valsalva Ratio	1.4 (0.3)	1.3 (0.2)				
Hemodynamic responses to tilt						
Supine						
SBP	124.8 (16.5)	123 (19.9)				
DBP	79.5 (16.3)	80.7 (17.3)				
HR	68 (11.4)	70 (10.6)				
5 min						
SBP	132.1 (18.4)	129.3 (16.1)				
DBP	89.8 (18.3)	88.7 (13.4)				
HR	79 (13.5)	79 (11.4)				
10 min						
SBP	131.9 (15.9)	124 (17.9)				
DBP	86.3 (12.0)	81.4 (14.5)				
HR	77 (13.5)	79 (11.8)				

15 min						
SBP	127.4 (13.9)	122.0 (17.8)				
DBP	84.56(11.9)	80.8 (12.7)				
HR	78 (14.2)	79 (11.5)				
20 min						
SBP	133.50 (13.3)	122.4 (15.0)	t = 3.0 (0.004)	3.89	18.31	0.76
DBP	82.7(14.7)	80.4 (12.8)				
HR	78 (14.4)	80 (12.0)				
Sudoscan Electrochemical skin conductance (ESC)						
Feet (µS)	71.5 (11.3)	72.5 (13.0)				
Hands (µS)	63.7 (16.7)	68.9 (13.3)				

The results are displayed as mean (standard deviation). Units for each variable are detailed in the first column of the table, except for unitless parameters.

See "Methods" for details on calculations of variables in table.

Abbreviations: HC healthy controls, LBD Lewy body disease, SCOPA-AUT Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire, E/I ratio expiratory-to-inspiratory ratio for heart rate variability, SBP systolic blood pressure, DBP diastolic blood pressure, HR heart rate, sg seconds, bpm beats per minute, mmHg millimeters of mercury, ΔSBP phase II late change of SBP from baseline to phase II late of Valsalva, ΔDBP phase II late change of DBP from baseline to phase II late of Valsalva, ΔSBP phase IV change of SBP from baseline to phase IV of Valsalva, ΔDBP phase IV change of DBP from baseline to phase IV of Valsalva, PRT pressure recovery time, ESC electrochemical skin conductance, µS micro- Siemens