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Autonomic Dysregulation During Sleep in Parkinsonian Spectrum Disorders - A Proof of Concept

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Authorship Contributions:

YC, DJL and DT designed the study, YC, DJL, GM, and EKSL analyzed and interpreted the data, CMW, DT, JKLI, CB, DS, JMH, BFB, TCN, and EKSL supervised data acquisition, and all authors contributed in the writing, review, and approval of the manuscript.

Declaration of Conflicts of Interest:

Mr. Levendowski and Ms. Berka as shareholders in Advanced Brain Monitoring, Inc., would benefit financially if the Sleep Profiler intellectual property was sold to a third party. Dr. Lee-Iannotti serves as a paid advisor to and speaker for Jazz Pharmaceuticals.

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Abstract

Introduction: Autonomic dysfunction is common in α-synucleinopathies such as Lewy Body dementias (LBD), Parkinson's disease (PD), and isolated REM Sleep Behavior Disorder (iRBD). We analyzed pulse-rate changes during sleep to index autonomic nervous system (ANS) dysfunction in patients with α-synucleinopathies vs. non-synucleinopathy groups expected to have normal ANS function.

Methods: Patients with LBD (n=16), PD (PD, n=14) or iRBD (n=12) were compared to the non-synucleinopathy groups Alzheimers disease dementia (ADem, n=26), mild cognitive impairment (MCI, n=34) or controls (CG, n=54). Sleep Profiler was used to derive a sleep autonomic activation index (AAI), i.e., ≥6 beat-per-minute increase/decrease, pulse rate coefficient of variation (PR-CV), and automated sleep staging with sleep-spindles and non-REM hypertonia (NRH). Analysis included statistical group comparisons and receiver operating characteristics curves to determine optimal classification of groups.

Results: AAI and PR-CV were moderately correlated across all recordings (r_s=0.58, P<0.0001), except in the LBD and PD groups. AAI but not PR-CV differentiated the LBD, PD and iRBD from non-Parkinsonian groups. AAI was decreased in LBD and PD patients compared to the CG (p<0.003) and MCI (p<0.03). AAI decreased based on age and its receiver operating characteristic area under the curve ranged from 0.63 to 0.75. AAI had a weak negative correlation to NRH ($r_s \leq -0.26$) but not sleep-spindles.

Conclusion: Synucleinopathy-related ANS dysfunction can reasonably discriminate prodromal and manifest PD/LBD diseased groups from non-synucleinopathies. Further studies incorporating AAI into a multivariate classifier of neurodegenerative disorders based on sleep characteristics acquired in the patient's home are planned.

Keywords

Autonomic dysfunction; Parkinsonian disorders; Alzheimer's disease dementia; sleep; neurodegenerative disorder

Introduction:

The α-synucleinopathies including Parkinson's disease (PD), Dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) are a group of neurodegenerative disorders (NDD) characterized by abnormal accumulation of aggregates of alpha-synuclein, a synaptic protein in neurons and glial cells. These disorders share features of parkinsonism, impaired cognition, fluctuation, prominent sleep disorders and variable other neuropsychiatric symptoms including visual hallucinations.

An important feature of α-synucleinopathies is autonomic nervous system (ANS) dysfunction caused by the functional or structural impairment of peripheral nerves of the ANS, and/or the central autonomic network [1, 2]. Although ANS dysfunction can be manifested in various α-synucleinopathies in any stage of the disease, ANS dysfunction can precede or follow other characteristic motor or cognitive symptoms. For example, attenuated heart rate variability (HRV) is an objective measurement of ANS dysfunction found in α-synucleinopathies and may manifest in prodromal stages, especially in isolated rapid eye movement (REM) sleep behavior disorder (iRBD) [3–5]. Specifically, abnormal sympathetic nervous activity has been reported in both wakefulness and sleep in these conditions [4]. Sympathetic surge may be observed with any interruption of sleep, including spontaneous, respiratory, or movement-related microarousals [6,7]. Pulse rate change occurring in sleep is an indirect marker of sympathetic response. Thus, abnormal pulse rate change during sleep could be another indicator of ANS dysfunction. We recently demonstrated that pulse rate variability associated with sleep apnea events discriminated ANS dysfunction in patients with multiple system atrophy from controls [8].

Previously, our consortium identified two sleep biomarkers, sleep spindle duration and non-REM hypertonia (NRH), which distinguished patients with Parkinsonian spectrum disorders from other non-synucleinopathy neurodegenerative disorders [9,10]. The objective of this study was to examine ANS dysfunction across a spectrum of α-synucleinopathy phenotypes in the prodromal and manifest stages, as compared to presumed neurodegenerative disorder groups without suspected synucleinopathy expected to have normal ANS functioning [11]. We hypothesized that pulse rate changes are more attenuated in α-synucleinopathies than in Alzheimer's dementia (ADem) and controls.

Methods:

Participants:

To participate in the study, participants provided informed consent in accordance with the Declaration of Helsinki. Local institutional review boards approved the study protocol for human subjects research at six participating centers.

Patients broadly characterized as presumed Parkinsonian spectrum disorders including Lewy body dementia (LBD, i.e., DLB or PD dementia, n=20), Parkinson disease (PD, n=14), and isolated REM sleep behavior disorder (iRBD, n=15) were compared with non-Parkinsonian groups that included ADem (n=27), mild cognitive impairment (MCI, n=37), and a control group (CG, n=58). Selection criteria for the LBD, PD, ADem, MCI and CG groups was described previously [10]. The iRBD group includes patients with a history of dream enactment behavior with REM sleep without atonia confirmed by polysomnography. Further inclusion criteria required at least one night with pulse quality ≥ 70% of recording time and/or not receiving beta blockers or non-dihydropyridine calcium channel blockers. As a result, 15 available records were rejected (PD=2, ADem=2, MCI=4, iRBD=4, CG=3).

Recordings:

Sleep Profiler (SP) recordings were acquired from EEG sensor sites AF7-AF8, AF7-Fpz and AF8-Fpz (Advanced Brain Monitoring, Carlsbad, CA, USA) with self-application in all participants, except those with RBD, who were studied simultaneously during in-laboratory PSG. The SP records were auto-staged using within-epoch temporal power spectral characterization with combined detection of individual slow waves, sleep spindles and cortical arousals, followed by technical review for final sleep stage assignments [7].

SP measured the pulse rate from the forehead using a reflectance emitter and detector, sampled at 100 Hz, low and high pass filtered prior to extraction of the beat-to-beat intervals, which were four-beat weight averaged, and interpolated to 1 Hz values [7].

Autonomic activation was based on the detection of ≥ 6 beat per minute (BPM) increase and/or decrease compared to the previous and/or subsequent 10^{th} second. AAI The autonomic activation index (AAI) reflected the number of events detected per hour of sleep. The AAI was described, and an abnormal threshold selected (i.e., 11.4 events/h) based on 48 healthy controls with ages ranging from 24 – 89 years [7]. For this proof-of-concept study, characterization of blunted AAI was empirically set to <10 events per hour of sleep.

The pulse rate coefficient of variation (PR-CV) was computed by dividing the standard deviation of the pulse rate by the mean pulse rate across epochs staged as sleep. The blunted PR-CV threshold (≤ 0.055) was empirically selected to optimize the area under the curve (AUC).

Sleep spindles were auto-detected based on temporal excursions in the absolute and relative sigma power in combination with simultaneous bursts of alpha power of at least 250 milliseconds. During the sigma and alpha power bursts, the beta and EMG power were tested to ensure relative suppression. Spindle lengths were restricted to 0.5-to 3.0-sec in length and spindle duration reflected the sum of all spindle lengths [9].

NRH was auto-detected based on previously described patterns of persistently elevated electromyographic (EMG) power relative to delta, theta, and sigma bands [10]. Variability thresholds were applied across a minimum of four consecutive 30-sec epochs to ensure EMG bursts attributed to sleep-disordered breathing arousals were not mischaracterized as NRH. The percent-time NRH was based solely on auto-detected blocks. No edits were made to add or remove NRH.

Data Analysis:

The sleep and heart rate measures were averaged across nights with weighting based on the total sleep time per night. When applicable, LBD, PD and iRBD patients were combined into the Parkinsonian spectrum disorders (PSD) group, while the ADem, MCI and CG were included in the non-Parkinsonian group (non-PSD). One-way Analysis of Variance (ANOVA) and multiple logistic regressions were used to test the capability for group differentiation. Pairwise group differences in demographic, sleep, and autonomic regulation measures were assessed using Mann-Whitney U tests. Between group differences in the distributions in blunted autonomic regulation were measured with Chi-square and

Fisher exact probability tests. Spearman ranked correlations were used to assess across-group associations between AAI and PR-CV, and to evaluate the association between the AAI values vs. spindle duration and NRH. For individual variable pairwise comparisons, statistical significance was set at $P \leq 0.03$ using a Bonferroni correction. The areas under the curve (AUC) derived from receiver operating characteristic curve plots were used to evaluate the capability of blunted AAI to characterize group differences.

Results:

The demographic, sleep and heart rate metrics are presented in Table 1. Based on one-way ANOVA differences were observed between PSD and non-PSD groups for AAI, PR-CV, REM time and NRH (all $p<0.01$) and for age, REM time, and NRH ($p<0.0001$) across the six groups.

The ADem group was older than the PD, CG, iRBD (all $p<0.01$), LBD and MCI (both $p<0.025$). The CG was younger than the LBD and MCI groups ($p \leq 0.01$). The iRBD group exhibited less NREM sleep time compared to LBD, ADem, and MCI (all $p<0.025$) patients. LBD patients exhibited less REM time vs. the PD, iRBD, ADem, MCI and CG groups (all $P<0.025$). ADem had less REM time compared to the CG ($p<0.01$) and MCI ($p<0.025$).

The AAI values for the LBD and PD patients were decreased compared to the CG ($p<0.003$) and MCI ($p<0.03$) while the PR-CVs were lower in the PD patients compared to CG and ADem (both $p<0.02$).

A moderate correlation was observed between the AAI and PR-CV across all groups ($r_S=0.58$, $p<0.0001$), with group associations ranging from LBD ($r_S=0.69$, $p<0.005$), MCI ($r_S=0.68$, $p<0.0001$), ADem ($r_S=0.58$, $p=0.01$), iRBD ($r_S=0.53$, $p=0.077$), CG ($r_S=0.49$, $p=0.0005$), and PD ($r_S=0.28$, $p=0.33$).

Using multiple logistic regression, sex ($p=0.02$) and AAI ($p<0.025$) but not age ($p=0.08$) or CV-PR ($p=0.24$) distinguished those with a Parkinsonian spectrum disorder from non-Parkinsonian groups. A second regression model determined age ($p=0.039$) rather than sex ($p=0.68$) predicted blunted AAI using the <10 events/h threshold.

With blunted AAI, the ROC-AUC values achieved specificity of 0.87 with (AUC, sensitivity) for each group contrast: CG vs. LBD (0.75, 0.63), CG vs. LBD+PD (0.72, 0.57), and CG vs. LBD+PD+iRBD (0.70, 0.52). A slightly less robust specificity of 0.73 with (AUC, sensitivity) was observed for contrasts between AD vs. LBD (0.68, 0.63), CG vs. LBD+PD (0.65, 0.57), and CG vs. LBD+PD+iRBD (0.63, 0.52).

Figure 1 presents the proportions of cases with blunted AAI values for each group. The proportion of the blunted AAI was greatest in LBD patients (63%), and greater than ADem (27%) and MCI (29%)($p<0.05$) and CG (13%, $p<0.0002$), while AAI in CG was less than the PD (50%, $p<0.006$) and iRBD (42%, $p<0.05$).

A weak negative association was observed between AAI and percent time NRH ($r_S=-0.26$, $p<0.002$) but not between AAI and spindle duration ($r_S=0.14$, $p<0.072$).

Discussion:

Our study demonstrated that synucleinopathy-related ANS dysfunction can be indexed by high resolution forehead-based reflectance pulse rate signals. As expected, the AAI characterized ANS dysfunction in the Parkinsonian spectrum disorder groups and distinguished LBD and PD from MCI and CG. AAI appeared to be relatively independent of spindle duration and non-REM hypertonia sleep, two previously identified biomarkers that appear capable of differentiating PSD from non-PSD groups and/or patients with dementia.

The decrease in AAI sensitivity in detection of ANS dysfunction when PD and then iRBD cases were included with the LBD was likely due to variability in the expression of compromised ANS dysfunction in patients between the prodromal iRBD and manifest PD stages of disease. Further characterization of the severity and temporal emergence of autonomic insufficiency through the Lewy body disease spectrum by prospective longitudinal cohort studies is needed.

The night-to-night stability of AAI, differences during REM and NREM consistent with low- to high-frequency heart rate variability, and the influence of antihypertensive medications in a cohort of insomnia patients with a range of comorbidities and medications were previously described [7]. The previously suggested threshold for blunted AAI (i.e., 11.4 events/h) was reduced to <10 in this proof-of-concept study to adjust for a CG that was older with no controls for comorbidities and non-hypertensive medications. Our finding that age was associated with suppressed cardiovascular responses to microarousals during sleep was consistent with what Goff et al. reported in healthy subjects [12]. Disproportionate distributions of males and females in the CG and LBD groups limited our ability to draw conclusions related to a potential interaction between sex, group and ANS dysfunction.

Lower REM sleep in the LBD patients limited our ability to apply conventional heart rate variability frequency windows and evaluate group parasympathetic and sympathetic nervous system activity differences between non-REM and REM sleep [7]. Our study was also limited by lack of assessment for obstructive sleep apnea (OSA) which could contribute to pulse rate variability. Group-wise differences between LBD and PD vs. CG remained after six CG cases (10%) with AAI values ≥60 events/h were excluded. Additionally, AAI outliers would not have impacted the AUC measures associated with lower values. Further research is needed to fully characterize potential covariates and confounding influences on AAI in OSA and periodic limb movements of sleep.

This study was limited in that the number of subjects in each of the NDD groups were relatively small and without control for non-antihypertensive medications and comorbidities. Acquisition of independent data sets with a longitudinal component is currently underway to provide cross validation of these findings.

Conclusions:

Our findings demonstrate that the AAI may be useful to characterize autonomic dysfunction and differentiate Parkinsonian spectrum disorders from other neurodegenerative phenotypic groups. The association between the AAI values and previously validated SP biomarkers

non-REM hypertonia and sleep spindles was limited, suggesting that each of these three sleep biomarkers may independently differentiate LBD, PD and iRBD from ADem and CG. These findings support development of machine learning algorithms using these and other sleep biomarkers that could more fully characterize neurodegenerative disorder groups and shed light on disease trajectory longitudinally.

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Data Statement:

The data underlying this article will be shared on reasonable request to the corresponding author.

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Highlights:

- The autonomic activation index (AAI) detects sharp changes in pulse rate
- The AAI is generally blunted in patients with Parkinsonian spectrum disorders
- The proportion with blunted AAI is consistent with disease progression
- AAI during sleep is unrelated to sleep spindles
- AAI is weakly negatively correlated with non-REM hypertonia (NRH)

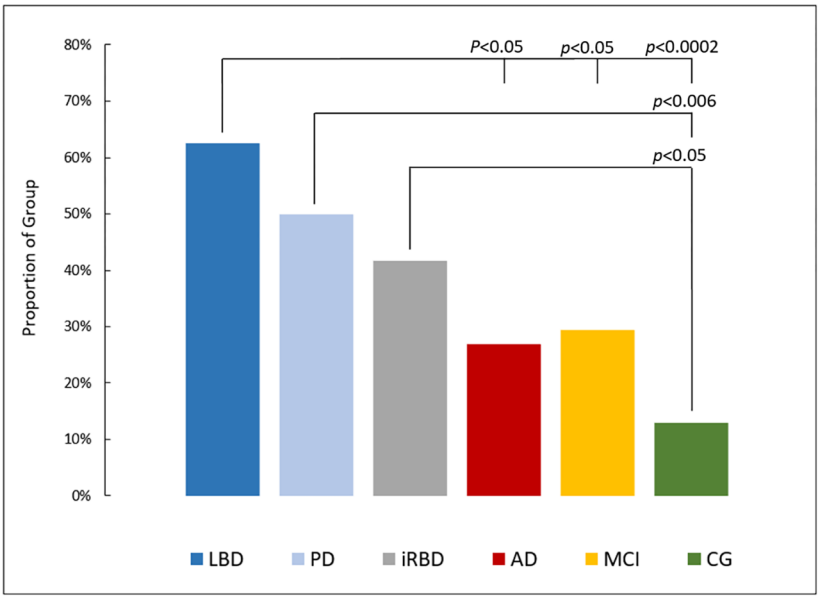

Figure 1.

Distributions of blunted AAI values by group: LBD=Lewy body dementia, PD=Parkinson disease, iRBD=isolated REM sleep behavior disorder, ADem=Alzheimers disease dementia, MCI=mild cognitive impairment, CG=control group.

Table 1:

Demographics, sleep architecture, and heart rate measures for Parkinsonian spectrum disorder (PSD) and non-PSD groups

Mean + SD	PSD	Non-PSD	PSD vs Non-PSD ANOVA F (p)	PSD Groups			Non-PSD Groups			Across Groups ANOVA F (p)
				LBD	PD	iRBD	ADem	MCI	CG	
Demographic										
Group size	42	114		16	14	12	26	34	54	
Female, %	26.2	42.1		12.5	35.7	33.3	23.1	38.2	53.7	
Age, years	67.3 ± 8.5	68.3 ± 9.2	0.36 (0.547)	69.8 ± 5.7	67.3 ± 8.6	63.9 ± 10.8	74.7 ± 7.0	69.8 ± 8.6	64.2 ± 8.6	6.73 (<0.001)
Heart Rate Measures										
AAI, hour	14.2 ± 13.9	23.7 ± 19.0	8.73 (0.004)	12.8 ± 13.7	12.5 ± 14.8	18.0 ± 13.6	21.6 ± 19.4	21.9 ± 18.0	25.8 ± 19.5	2.16 (0.061)
PR-CV, %	6.1 ± 1.6	7.0 ± 1.9	7.25 (0.008)	6.0 ± 2.0	5.8± 1.0	6.5 ± 1.6	6.9 ± 1.8	6.9 ± 2.0	7.1 ± 2.0	1.66 (0.148)
Pulse rate, BPM	61.5 ± 7.7	62.1 ± 8.2	0.16 (0.687)	61.3 ± 8.7	60.8 ± 7.1	62.5 ± 7.5	58.6 ± 6.5	61.5 ± 7.4	64.1 ± 8.9	1.78 (0.119)
Sleep Architecture										
REM, hour	0.9 ± 0.7	1.2 ± 0.5	11.07 (0.001)	0.6 ± 0.6	1.0 ± 0.6	1.2 ± 0.9	1.0 ± 0.4	1.3 ± 0.5	1.3 ± 0.4	6.15 (<0.001)
NREM, hour	5.0 ± 1.4	5.2 ± 1.0	0.66 (0.416)	5.5 ± 1.6	5.2 ± 0.9	4.2 ± 1.2	5.4 ± 1.2	5.3 ± 1.1	5.0 ± 0.8	2.69 (0.023)
Spindle duration, min	4.0 ± 7.1	6.9 ± 10.1	2.73 (0.100)	4.0 ± 9.5	5.2 ± 6.5	2.7 ± 3.0	3.7 ± 6.6	6.1 ± 9.9	8.8 ± 11.4	1.76 (0.125)
NRH, % sleep time	13.4 ± 12.2	3.3 ± 4.9	54.3 (<0.001)	14.7 ± 13.4	10.8 ± 10.2	14.7 ± 13.3	3.0 ± 4.1	3.8 ± 4.8	3.1 ± 5.3	11.3 (<0.001)