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ORIGINAL RESEARCH

An Exploratory Study of Sleep-Wake Differences of Autonomic Activity in Patients with Mild Cognitive Impairment: The Role of Melatonin as a Modulating Factor

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Purpose: The objective of the present study was to assess sleep-wake differences of autonomic activity in patients with mild cognitive impairment (MCI) compared to control subjects. As a post-hoc objective, we sought to evaluate the mediating effect of melatonin on this association.

Patients and Methods: A total of 22 MCI patients (13 under melatonin treatment) and 12 control subjects were included in this study. Sleep-wake periods were identified by actigraphy and 24hr-heart rate variability measures were obtained to study sleep-wake autonomic activity.

Results: MCI patients did not show any significant differences in sleep-wake autonomic activity when compared to control subjects. Post-hoc analyses revealed that MCI patients not taking melatonin displayed lower parasympathetic sleep-wake amplitude than controls not taking melatonin (RMSSD -7 ± 1 vs 4 ± 4, $p = 0.004$). In addition, we observed that melatonin treatment was associated with greater parasympathetic activity during sleep (VLF 15.5 ± 0.1 vs 15.1 ± 0.1, $p = 0.010$) and in sleep-wake differences in MCI patients (VLF 0.5 ± 0.1 vs 0.2 ± 0.0, $p = 0.004$).

Conclusion: These preliminary findings hint at a possible sleep-related parasympathetic vulnerability in patients at prodromal stages of dementia as well as a potential protective effect of exogenous melatonin in this population.

Keywords: heart rate variability, actigraphy, circadian rhythms, wavelets

Introduction

Mild cognitive impairment (MCI) has been defined as an intermediate state between healthy ageing and dementia, where patients exhibit clinically significant mild cognitive decline from expected performance for subjects' age group, yet not severe enough to impact functional independence in activities of daily living.[1] MCI is present in 15–25% of older adults over 65 years old and 32% of MCI subjects convert to dementia due to Alzheimer's disease (AD) (the main cause for dementia) over a five-year period.[2] For this reason, MCI is a critical stage to assess subjects at risk of developing dementia and a promising target population to implement potential prevention and treatment interventions before neurodegeneration is more advanced.[1]

As a transitional phase to dementia, MCI due to AD already manifests some pathophysiological changes in the nervous system[1,3,4] such as accumulation of phosphorylated tau in the locus coeruleus and allocortical and diencephalic limbic structures involved in the autonomic nervous system regulation, along with a disrupted diurnal variation of multiple

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physiological processes.[5] Several cross-sectional and prospective studies have described associations between sleep disturbances and increased risk of cognitive decline.[6–9] Indeed, there is a high prevalence of sleep-aid medication use, such as zolpidem, benzodiazepines, and melatonin in this population.[10–14]

Sleep-wake cycle disruption is associated with abnormalities in the circadian regulation of the autonomic nervous system. Furthermore, cognitive function and sympathovagal cardiac modulation seem to influence each other in MCI and dementia patients, who exhibit reduced parasympathetic modulation.[15] It is believed that such anomalies in vagal tone are most likely caused to neurofibrillary degeneration and neuronal death in the insular cortex and brainstem.[16]

Heart rate variability (HRV) is considered an index of autonomic control of the heart[17] and represents a non-invasive, cost-effective method to assess cardiac autonomic function. HRV measures interval variations between successive heartbeats, reflecting the sympathetic and parasympathetic balance on the sinoatrial node.[18] Changes in HRV as a marker of autonomic activity have been associated with neuropsychiatric disorders and cognitive impairment, where high HRV is associated with better cognitive performance in healthy adults, older adults and patients with dementia.[19–21] However, the literature exploring this relationship specifically in MCI is surprisingly limited, and it reports mixed results.[15,16,22–25] Analysis of autonomic activity throughout the whole sleep-day cycle has been proposed as the better approach to study sleep-related changes in HRV,[26] yet only two studies explored autonomic function in MCI with 24hr HRV. One study did not assess the sleep-wake cycle.[27] The other publication explored HRV limited to time-domain analysis, which may explain why the authors found no significant results for the MCI group.[28] Therefore, the purpose of the present study was to assess sleep-wake differences of autonomic activity in patients with MCI through 24hr time- and frequency-domain HRV measures. Based upon previous literature,[5,16] we hypothesized that incipient neurodegeneration of limbic structures would induce changes in the circadian variation of the autonomic input to the heart. We specifically predicted that MCI would be associated with decreased vagal function, as defined by lower HRV measurements in the high-frequency domain. Finally, a post-hoc objective was to evaluate the mediating effect of melatonin on the relationship between MCI and vagal function.

Materials and Methods

Subjects and Design

A total of 39 outpatients with probable amnestic MCI and 12 control subjects comparable in gender, age and education level were examined at the facilities of the Centro de Neuropsiquiatría y Neurología de la Conducta (CENECON), Hospital de Clínicas "José de San Martín" and at the Service of Psychiatry of Fleni Foundation.

For this study, MCI was diagnosed by trained neuropsychiatrists and neurologists following Petersen's diagnostic criteria:[29] 1) cognitive complaint reported by the patient or by an informant, 2) objective cognitive impairment, 3) preserved independence in functional abilities, 4) no dementia. Clinical diagnosis was complemented with standardized neuropsychological assessment when available. Neuropsychological assessment included the following tests (only techniques common to all assessments available were included in the present study): Rey Auditory Verbal Learning Test (RAVLT) to assess verbal episodic memory and learning;[30] Semantic Fluency (SF, "animals") and Phonemic Fluency (PS, "P") to assess verbal fluency;[31] Trail Making Test A (TMT A) to assess sustained attention and Trail Making Test B (TMT B) to assess cognitive flexibility.[32]

Inclusion criteria for MCI subjects were as follows: 1) probable amnestic MCI diagnosis according to standard diagnostic criteria,[29] 2) >7 years of formal education. Exclusion criteria were as follows: 1) a diagnosis of dementia, neurological or other medical conditions known to affect cognition; 2) current alcohol or substance abuse; 3) diagnosis of a major psychiatric disorder (eg, psychosis); 4) cardiovascular conditions including stroke, transient ischemic attack, severe ischemic heart disease, unstable tachycardia, severe valvular heart disease, non-sinus rhythm including atrial fibrillation and other arrhythmias, paced rhythms; 5) regular use of beta-blockers.

From the total of 39 patients with probable MCI, nine subjects (17%) were excluded due to diagnosis of depression with memory complaint, and did not meet MCI diagnostic criteria, and eight (16%) due to undefined diagnosis. Thus, the final MCI sample consisted of 22 subjects.

Sleep-aiding medication information was collected. Of the MCI group (n = 22), ten subjects were under melatonin treatment (3 mg), three participants were under both melatonin (3 mg) and benzodiazepine treatment (0.5–2 mg), one subject was taking both a benzodiazepine (1 mg) and zolpidem (10 mg), and one subject was taking zolpidem (10 mg). Among control subjects (n = 12), six participants were under benzodiazepine treatment (0.25–1 mg), and two participants were taking melatonin (3–50 mg). All individuals under melatonin treatment took it approximately 30 minutes before the expected sleep time. All participants completed the Pittsburgh Sleep Quality Index (PSQI),[33] which is a sleep quality self-report questionnaire that assesses sleep problems in the last month to screen for sleep problems. MCI subjects reported a mean score of 8.4 ± 3.4, consistent with mild-to-moderate sleep problems, while control subjects reported a mean score of 5.8 ± 4.3, which reflects none to mild sleep problems. However, comparison between groups did not show significant differences.

The study was approved by the institutional review board at the School of Medicine, University of Buenos Aires and Fleni Foundation and was conducted according to the Declaration of Helsinki. All participants signed an informed consent to participate in the study.

Sleep Assessment

Wrist accelerometers (MicroMini Motionlogger Actigraphs, Ambulatory Monitoring Inc., Ardsley, NY) were used to assess the sleep-wake cycle. Subjects were asked to wear the actigraphs for seven days on their nondominant wrist and to complete a sleep diary. The following variables were derived using the software provided by the manufacturer (Action-W User's Guide, Version 2.4; Ambulatory Monitoring, Inc., Ardsley, NY): sleep onset (starting time of the first sleep episode after bedtime, as recorded by actigraphy), sleep offset (ending time of the last sleep episode before waking-up time, as recorded by actigraphy), sleep duration (elapsed time between sleep onset and sleep offset), sleep efficiency [(100 X (wake time during sleep / sleep duration)], and wake after sleep onset (WASO, wake minutes during sleep episode).[34]

Heart Rate Variability

A digital Holter device was used for the recording of the electrocardiogram signal for 24 hours. R waves (ventricular depolarizations) were detected through the device software. RR intervals (time elapsed between R waves) were then computed. Heart rate variability (HRV) indexes were calculated in 30 min bins. An automated filter was used to identify lost or ectopic beats, being replaced by RR intervals resulting from linear interpolation. Segments with more than 20% of missing intervals were excluded from further analysis.[30]

Time domain analyses were performed by assessing indexes of variation over time. Among these, RRm (mean duration of RR intervals in milliseconds) quantifies the mean heart rate, SDNN (standard deviation of RR intervals in milliseconds) represents a coarse quantification of global variability, and RMSSD (square root of the mean squared differences of successive normal RR) measures short-term heart rate variations. Frequency domain variables provide a measure of the amplitude of the frequencies contributing to the HRV signal. Its high-frequency (HF) component (0.15–0.4 Hz) is mediated by parasympathetic activity and related to respiratory sinus arrhythmia and its low-frequency (LF) component (0.04–0.15 Hz) relies on sympathetic and parasympathetic mechanisms and is related to baroreflex control. Its very low frequency (VLF) component (0.003–0.04 Hz) stems from the outflow of parasympathetic nervous system and its origin has been attributed to humoral factors such as the renin–angiotensin system and to thermoregulatory fluctuations in vasomotor tone.[17] Sympathetic predominance is usually reflected by a relative increase in the LF component, while parasympathetic predominance is reflected by an increase in the HF component (or RMSSD), either isolated or accompanied by increases in LF and VLF components as well.[35]

The Discrete Wavelet Transform (DWT) was chosen instead of the traditional Fast Fourier Transform (FFT) to analyze the frequency components of HRV because it is less sensitive to the presence of nonstationarities or discontinuities. The mean value and the linear trend were subtracted from the signal before applying the DWT. In addition, the signal was evenly sampled with a frequency of 2.4 Hz by means of a spline interpolation algorithm and zero padded to the next higher power of two. A Daubechies four-wavelet function and a nine-level wavelet decomposition were employed to analyze the signal. Using this decomposition, wavelet levels D2-D3 approximately correspond to the high-frequency band (HF, 0.15–0.6 Hz),

wavelet levels D4-D5 to the low-frequency band (LF, 0.0375–0.15 Hz), wavelet levels D6-D9 to the very low-frequency band (VLF, 0.0023–0.0375 Hz), and wavelet levels D2-D9 and A9 represent the total power (TP, 0–0.6 Hz). The spectral power of a level is concordant with the square of the standard deviation of wavelet coefficients at each level.[36,37]

Reported values are expressed as the natural logarithm of TP, HF, LF and VLF wavelet power coefficients (wpc); normalized units (nu) of HF [HF_{nu}= 100XHF/(TP – VLF)]; and the ratio between LF and HF. HRV bins were averaged along wake and sleep periods. Sleep periods were defined based on actigraphy data. HRV differences between sleep and wake averages were also calculated.[36]

Statistical Analysis

Values are presented as mean ± SEM for numerical variables or frequency and % for categorical variables. Several comparisons between groups and subgroups were conducted. First, demographics, clinical data, sleep-wake characteristics and autonomic activity were compared between MCI patients and controls. Comparisons between these groups were evaluated by means of a *t*-test for independent samples. For categorical variables "biological sex" and "higher education" a Fisher's exact test was used.

Post-hoc analyses were performed to assess a possible modulating effect of melatonin in autonomic activity when comparing MCI patients and controls. In order to remove the potential effect of melatonin, a further comparison was conducted excluding subjects under melatonin treatment. Additionally, we assessed MCI patients with or without melatonin treatment. Lastly, we assessed the independent effect of MCI and melatonin over sleep-wake characteristics and autonomic activity conducting two-way ANOVA models.

Exploratory studies in early stages such as the present work aim to discover new hypothesis,[38] so minimizing Type II errors is highly recommended.[39,40] Therefore, false discovery rate (FDR) correction[41] at a moderate q = 0.2 was applied to multiple intergroup comparisons and the significance level of two-tailed tests was established at $\alpha = 0.05$. The value q = 0.2 is a sensitive statistical threshold applied in various exploratory studies on different subjects with promising results.[42–45]

Results

Demographic and Clinical Data

Demographic and clinical characteristics are depicted in Table 1. Groups were comparable in terms of age, gender and education level. Statistically significant differences in favor of control subjects were observed in verbal episodic memory and learning (RAVLT total learning, RAVLT delayed recall, RAVLT recognition), verbal fluency (semantic fluency), and cognitive flexibility (Trail Making Test B), confirming MCI diagnosis.

Actigraphy

Table 2 shows the sleep-wake characteristics of the sample. The original sample was reduced to 29 subjects due to technical issues related to actigraphic signal. MCI patients exhibited greater sleep fragmentation (wake after sleep onset) than control subjects. However, this result did not survive correction for multiple comparisons (FDR).

Heart Rate Variability

Table 3 summarizes HRV analyses. The original sample was reduced to 28 subjects due to technical issues related to HRV signal quality. No significant differences were displayed between groups in wake, sleep or sleep-wake differences of HRV.

Post-Hoc Analyses: Melatonin Effect Assessment

Supplementary Table 1 shows demographic and clinical characteristics of controls and MCI patients without melatonin treatment. Removing subjects taking melatonin treatment did not affect the results: both groups remained comparable in terms of age, gender and education level, and controls not taking melatonin still exhibited better performance than MCI patients not taking melatonin in verbal episodic memory and learning (RAVLT delayed recall, RAVLT recognition), verbal fluency (semantic fluency, phonemic fluency) and cognitive flexibility (Trail Making Test B).

Table 1 Demographic Data

	Controls		MCI		Statistics	
	(n = 12)		(n = 22)		FET	*t*-test
Age (yrs: mean, SEM)	72	2	76	2	–	0.111
Female (n, %)	8	67	10	46	0.297	–
Higher education (n, %)	7	59	10	46	0.721	–
RAVLT TL (mean, SEM)	40	2	28	2	–	**0.001**[b]
RAVLT D (mean, SEM)	9	1	3	1	–	**<0.001**[b]
RAVLT R (mean, SEM)	14	0	10	1	–	**0.001**[b]
SF (mean, SEM)	20	1	13	1	–	**0.001**[b]
PF (mean, SEM)	15	1	10	1	–	**0.006**[b]
TMT A (sec: mean, SEM)	50	5	81	17	–	0.107
TMT B (sec: mean, SEM)	113	11	171	20	–	**0.024**[a]

Notes: [a]Statistical significance at $p < 0.05$; [b]Statistical significance at $p < 0.01$. Comparisons surviving FDR correction at q=0.2 are marked in bold.
Abbreviations: MCI, mild cognitive impairment; FET, Fisher's exact test; MEL, melatonin; RAVLT TL, Rey Auditory Verbal Learning Test - Total Learning; RAVLT D, Rey Auditory Verbal Learning Test – Delayed recall; RAVLT, Rey Auditory Verbal Learning Test – Recognition; SF, Semantic Fluency; PF, Phonemic Fluency; TMT A, Trail Making Test – part A; TMT B, Trail Making Test – part B.

Table 2 Actigraphy Analysis

	Controls (n = 10)		MCI (n = 19)		Statistics
	Mean	SEM	Mean	SEM	*t*-test
Sleep length (nights)	6.1	0.3	6.4	0.3	0.523
Sleep onset (hh:mm)	00:00	00:28	23:42	00:14	0.401
Sleep offset (hh:mm)	07:55	00:28	08:09	00:14	0.419
Sleep duration (m)	487	16	521	14	0.156
Sleep efficiency (%)	93	2	88	1	0.072
WASO (m)	34	11	64	8	0.037

Note: None of the comparisons survived FDR correction at q=0.2.
Abbreviations: MCI, mild cognitive impairment; MEL, melatonin; WASO, wake after sleep onset.

Supplementary Table 2 portrays demographic data of MCI patients with and without melatonin treatment. The MCI group under melatonin treatment showed lower education level. No significant differences were observed in cognitive performance.

Supplementary Table 3 shows sleep-wake characteristics in patients with MCI and controls without melatonin treatment. No significant differences were observed. Supplementary Table 4 shows sleep-wake characteristics in MCI patients with and without melatonin treatment. No significant differences were observed.

Table 4 shows the results of the independent effect of MCI and melatonin in sleep characteristics as evidenced by a two-way ANOVA model. No significant effect was observed relating to the presence of MCI or melatonin treatment in sleep characteristics.

Supplementary Table 5 displays HRV differences between MCI patients and controls without melatonin treatment. Sleep-wake differences of HRV (RMSSD and absolute values of LF) were decreased in MCI patients, denoting a diminished parasympathetic sleep-wake amplitude in this group.

Supplementary Table 6 shows HRV differences in patients with MCI with and without melatonin treatment. Results show an HRV pattern of greater parasympathetic activity during the night in patients that were taking melatonin as evidenced by the increased values of RRM, SDNN, TA, VLF and LF. Accordingly, sleep-wake differences of HRV were also significantly increased in this group of patients.

Table 3 HRV Analysis

	Controls (n = 12)		MCI (n = 16)		Statistics
	Mean	**SEM**	**Mean**	**SEM**	***t*-test**
Wake					
RRm (ms)	807	36	846	25	0.361
SDNN (ms)	57	6	52	4	0.407
RMSSD (ms)	28	4	40	6	0.153
TA (wpc)	17.9	0.1	17.97	0.06	0.321
VLF (wpc)	14.9	0.1	14.98	0.06	0.302
LF (wpc)	10.0	0.2	10.25	0.13	0.305
HF (wpc)	7.6	0.2	7.94	0.22	0.338
HF (nu)	0.089	0.006	10.4	1.5	0.413
L/H	11.7	0.7	12.0	1.2	0.886
Sleep					
RRm (ms)	935	41	1023	49	0.196
SDNN (ms)	57	6	58	6	0.896
RMSSD (ms)	34	4	40	8	0.537
TA (wpc)	18.2	0.1	18.3	0.1	0.270
VLF (wpc)	15.2	0.1	15.3	0.1	0.331
LF (wpc)	10.4	0.2	10.4	0.2	0.933
HF (wpc)	8	0.2	8.1	0.3	0.784
HF (nu)	0.089	0.009	9.8	1.5	0.625
L/H	13.2	1.5	12.3	1.3	0.666
Sleep - Wake					
RRm (ms)	128	23	186	32	0.174
SDNN (ms)	0	4	8	5	0.204
RMSSD (ms)	6	3	2	5	0.607
TA (wpc)	0.3	0.1	0.4	0.1	0.382
VLF (wpc)	0.3	0.1	0.4	0.1	0.531
LF (wpc)	0.4	0.1	0.2	0.1	0.453
HF (wpc)	0.3	0.2	0.2	0.1	0.450
HF (nu)	0.000	0.007	−0.8	0.9	0.499
L/H	1.4	1.2	0.6	0.8	0.548

Abbreviations: MCI, mild cognitive impairment; MEL, melatonin; RRm, mean of RR interval duration; SDNN, standard deviation of RR intervals; RMSSD, square root of the mean squared differences of successive normal RR; TA, total area power; VLF, very low frequency power; LF, low frequency power; HF, high frequency power; wpc, wavelet power coefficients; nu, normalized units.

Table 4 Actigraphy Multivariate Model

	Model		MCI		MEL	
	R2	**p**	**beta**	**p**	**beta**	**p**
Length	0.068	0.400	0.252	0.236	0.020	0.923
Onset	0.047	0.534	− 0.158	0.458	− 0.097	0.647
Offset	0.024	0.726	0.007	0.973	0.153	0.478
Duration	0.093	0.283	0.152	0.464	0.208	0.319
Efficiency	0.159	0.105	−0.231	0.252	−0.244	0.228
WASO	0.223	0.037[a]	0.296	0.131	0.267	0.171

Notes: [a]Statistical significance at p > 0.05. For each dependent variable (actigraphic parameters) a two-way ANOVA was conducted with Diagnostic and Melatonin use as fixed factors.
Abbreviations: MCI, mild cognitive impairment; MEL, melatonin; WASO, wake after sleep onset.

Table 5 HRV Multivariate Model

	Model		MCI		MEL	
	R2	**p**	**Beta**	**p**	**Beta**	**p**
Wake						
RRm (ms)	0.005	0.357	0.068	0.756	0.244	0.270
SDNN (ms)	0.031	0.677	−0.196	0.384	0.072	0.747
RMSSD (ms)	0.092	0.300	0.214	0.327	0.138	0.642
TA (wpc)	0.088	0.316	0.079	0.716	0.252	0.152
VLF (wpc)	0.064	0.438	0.124	0.574	0.171	0.440
LF (wpc)	0.049	0.534	0.153	0.492	0.104	0.639
HF (wpc)	0.045	0.560	0.137	0.540	0.113	0.613
HF (nu)	0.027	0.713	0.146	0.516	0.032	0.888
L/H	0.012	0.865	0.082	0.718	−0.117	0.606
Sleep						
RRm (ms)	0.264	0.025[a]	0.040	0.839	0.495	**0.018**[a]
SDNN (ms)	0.330	0.008[b]	−0.253	0.185	0.639	**0.002**[b]
RMSSD (ms)	0.138	0.169	−0.046	0.828	0.389	0.077
TA (wpc)	0.213	0.057	0.023	0.112	0.451	**0.035**[a]
VLF (wpc)	0.197	0.072	0.000	0.999	0.443	**0.039**[a]
LF (wpc)	0.357	0.005[b]	−0.274	0.145	0.665	**0.001**[b]
HF (wpc)	0.146	0.151	−0.129	0.545	0.420	0.057
HF (nu)	0.030	0.692	0.168	0.459	−0.159	0.484
L/H	0.018	0.804	−0.137	0.549	0.114	0.618
Sleep - Wake						
RRm (ms)	0.217	0.053	0.084	0.680	0.423	**0.046**[a]
SDNN (ms)	0.278	0.020[b]	0.026	0.137	0.516	**0.013**[a]
RMSSD (ms)	0.128	0.193	−0.271	0.214	0.381	0.085
TA (wpc)	0.106	0.259	0.041	0.849	0.306	0.167
VLF (wpc)	0.115	0.231	−0.027	0.899	0.350	0.114
LF (wpc)	0.493	<0.001[c]	−0.485	**0.006**[b]	0.763	**<0.001**[c]
HF (wpc)	0.178	0.096	−0.343	0.108	0.438	**0.044**[a]
HF (nu)	0.093	0.309	−0.003	0.990	−0.304	0.172
L/H	0.069	0.493	−0.235	0.294	0.260	0.247

Notes: [a]Statistical significance at $p < 0.05$; [b]Statistical significance at $p < 0.01$; [c]Statistical significance at $p < 0.001$. Comparisons surviving FDR correction at q=0.2 are marked in bold. For each dependent variable (HRV parameters) a two-way ANOVA was conducted with Diagnostic and Melatonin use as fixed factors.

Abbreviations: MCI, mild cognitive impairment; MEL, melatonin; RRm, mean of RR interval duration; SDNN, standard deviation of RR intervals; RMSSD, square root of the mean squared differences of successive normal RR; TA, total area power; VLF, very low frequency power; LF, low frequency power; HF, high frequency power; wpc, wavelet power coefficients; nu, normalized units.

Table 5 shows the results of the independent effect of MCI and melatonin in HRV as evidenced by the two-way ANOVA model. The effect of melatonin was confirmed for all variables exhibiting significant differences between MCI patients with and without melatonin treatment (Supplementary Table 6) during sleep and in sleep-wake differences. The effect of MCI was confirmed only for sleep-wake differences of LF.

Discussion

The present results add new information to the limited literature on sleep-wake differences of autonomic activity in MCI patients and the mediating effects of melatonin. The main findings of the present study are 1) MCI patients not taking melatonin displayed a reduced parasympathetic sleep-wake amplitude when compared to controls not taking melatonin during sleep and in sleep-wake differences, 2) the independent effect of MCI was confirmed for sleep-wake differences of LF HRV, and 3) the independent effect of melatonin was confirmed for all variables during sleep and in sleep-wake differences.

No significant findings related to sleep parameters were observed. This could be explained by multiple factors, many relating to the heterogeneous nature of MCI, either associated with severity and staging of the neurodegenerative process or regarding the underlying etiology of the MCI syndrome.[46] Therefore, additional sleep abnormalities might manifest at different stages or might not emerge at all in MCI.[47,48] MCI is considered a possible transitional stage to dementia in that not all subjects will develop dementia, and those who do, might have different underlying etiologies:[1] biomarker studies showed that about 25% of MCI subjects exhibit non-AD pathology.[49] Therefore, the various underlying pathologies of the MCI syndrome may not affect sleep equally or at all. Another possibility is that the limited sample size lacks statistical power to exhibit differences related to sleep parameters.

Initial analyses showed no differences in HRV measures, which is not entirely surprising, given the mixed and limited results in this field.[15,16,22–25,27,28] When comparing MCI and control subjects without melatonin treatment, a reduced parasympathetic amplitude (reduced RRm, SDNN and absolute values of TA, LF and VLF) was observed in the MCI group during sleep and in sleep-wake differences. Indeed, when performing multivariate analysis controlling for melatonin intake, a moderate negative association between MCI and LF sleep-wake differences was identified.

Our findings align with Kong et al's, who recently reported reduced parasympathetic function in MCI subjects during sleep.[25] It is not surprising that the only significant results observed in the current study were related to the sleep interval, given that MCI and dementia usually exhibit sleep disturbances very early on, even prior to cognitive symptoms[50–55] and sleep disorders are mostly related to decreased parasympathetic function during sleep.[56,57] Autonomic nervous system activity varies greatly between wakefulness and sleep, exhibiting parasympathetic predominance during sleep. Parasympathetic dysfunction at nighttime and during sleep has already been reported in AD patients,[28] which supports our results in MCI patients, arguing for a potential sleep-related parasympathetic vulnerability in this clinical population.[25]

In light of these observations, we were curious to explore whether melatonin might be mediating sleep-wake effects on the clinical sample, given that over half of the subjects were under melatonin treatment. Actigraphy analyses between MCI patients with versus without melatonin intake did not display significant differences, although actigraphic measures did show significant differences between MCI and control subjects related to sleep fragmentation. A possible explanation could be that patients under melatonin treatment had reported greater sleep difficulties, which is why they were prescribed melatonin in the first place. However, comparison of HRV measures showed MCI patients under melatonin treatment presented greater parasympathetic activity (RRm, SDNN, TA, VLF, LF, HF) during sleep and in sleep-wake differences than patients not taking melatonin. Additionally, two-way ANOVA analysis confirmed this effect of melatonin on HRV parasympathetic variables during sleep and sleep-wake differences, showing a protective effect of melatonin on parasympathetic function during sleep. These findings agree with the literature on the effect of exogenous melatonin on HRV, which suggests that melatonin administration increases parasympathetic activity and reduces sympathetic function,[58] and more specifically, that melatonin promotes parasympathetic activity during nighttime sleep.[59,60]

Limitations for this exploratory study include a small sample size, which may have lacked statistical power to detect additional differences in sleep parameters. Significant results observed in this work have been corrected for multiple comparisons with FDR method, with a moderate threshold of q=0.2 which is considered appropriate for preliminary studies.[39] However, subsequent studies with larger sample size should be developed to allow for multiple comparison correction with conservative methods like Bonferroni. Finally, another limitation is related to the potential heterogeneity within the MCI group due to lack of biomarkers to determine underlying pathology behind the MCI syndrome.[61]

Conclusion

Overall, the present study demonstrated parasympathetic reduction during sleep in MCI patients not taking melatonin. These findings hint at a possible sleep-related parasympathetic vulnerability in patients at prodromal stages of dementia as well as a potential protective effect of exogenous melatonin on such vulnerability. These results complement our previous observation of therapeutic effects of melatonin on cognitive function and depressive symptoms in a different MCI sample[62] and contribute to the burgeoning literature on melatonin as an adjunctive treatment in MCI, aiding sleep quality, sleep-wake cycle regulation, and cognition before brain function is too compromised by the underlying neurodegenerative processes of dementia.[63] To our knowledge, this is the first study reporting a relationship between

melatonin and HRV in MCI patients. Additional, more extensive, longitudinal studies should be performed to confirm the observed results in larger, culturally diverse populations.

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Disclosure

The authors report no conflicts of interest in this work.

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