Short Communication

Sleep actigraphic patterns and cognitive status

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We performed an actigraphic assessment of sleep characteristics in healthy subjects and patients with cognitive impairment. Thirty subjects were included and classified into controls (10 subjects), mild cognitive impairment (10 patients) and mild-to-moderate Alzheimer's disease (10 patients). Sleep quality was assessed using the Pittsburgh Sleep Quality Index. Participants had a 7-day actigraphic record. Sleep parameters collected were time in bed, total sleep time, sleep efficiency, sleep latency, wakefulness after sleep onset, number of awakenings, and mean motor activity. Significant differences between mild cognitive impairment and controls patients were found for sleep latency ($p = 0.05$); Alzheimer's disease patients had significantly worse scores for Pittsburgh Sleep Quality Index ($p = 0.01$), time in bed ($p = 0.001$), total sleep time ($p = 0.04$), sleep latency, sleep efficiency, motor activity ($p = 0.0001$) and wakefulness after sleep onset ($p = 0.001$) compared to controls. When comparing Alzheimer's disease and mild cognitive impairment, differences were significant for sleep latency ($p = 0.01$), wakefulness after sleep onset ($p = 0.004$), sleep efficiency, number of awakenings and motor activity ($p = 0.0001$). In addition to showing a high prevalence of sleep alterations in subjects with cognitive impairment, our data suggest that they are evident from the earliest stages of cognitive decline. Further studies are needed to assess whether early correction of sleep alterations can positively influence the evolution of cognitive impairment. The opportunity to provide clinically meaningful information with a simple assessment of sleep characteristics based on actigraphy suggests that wider use of the approach in patients with cognitive decline should be considered.

Keywords

Sleep; Actigraphy; Cognitive impairment; Dementia; Apnea

1. Introduction

Sleep is an active phenomenon regulated by a highly integrated network of cortical and subcortical structures. The efficiency of this complex pattern may be compromised at various levels during physiological aging [1]. About half of elderly subjects report disturbed sleep, and there is extensive evidence that sleep alterations are closely linked to neurodegenerative disorders [2, 3]. Sleep and wake disturbances are common among people with dementia. Up to 70% of patients with early-stage dementia report sleep disturbances [4]. Among patients with Alzheimer's disease (AD), disturbed sleep is associated with poorer daily functioning, aggression and agitation. In general, sleep alterations seem to begin in the early stages of cognitive impairment and tend to worsen as the disease progresses [5, 6].

The association between sleep and dementia is complex and probably bidirectional [4, 7]. Sleep is involved in maintaining the anatomical integrity of the brain through different and complex mechanisms. Sleep problems may contribute to neurodegenerative changes. Consequently, the preservation of restorative sleep is strategic for memory consolidation through the transfer of information from the hippocampus to the anterior regions of the brain [7]. In addition, the role of sleep in synaptic plasticity and the promotion of amyloid (AB) removal has been demonstrated [4, 8].

Neurodegenerative processes can lead to disturbed sleep, and the coexistence of sleep disorders and dementia has been associated with a more rapid decline in cognitive performance [8]. Therefore, the demonstration that potentially correctable sleep disturbances can be recognized at an early stage of cognitive decline would be of interest because of possible implications in developing treatment strategies [9].

Actigraphic assessment allows a simple determination of objective sleep changes. For example, it has been shown that in approximately half of the general population of older adults, sleep structure tends to become progressively disorganized [8], and actigraphic studies in community-dwelling people with AD have shown a deterioration of rest-activity cycles [10].

In this preliminary research, we evaluated actigraphic patterns in three populations of subjects with a distinct state of cognitive efficiency to test whether the characterization of sleep parameters can be specifically associated with the extent of cognitive decline.

2. Materials and methods

2.1 Patients

Patients were selected from consecutive subjects referred to the cognitive impairment outpatient service of the Neurological Department of the University Hospital of Ancona, Italy, over 6 months (January 2019–June 2019). Only pa-

tients with a baseline score >19 on the Mini-Mental Status Examination (MMSE) test were considered [11, 12]. All eligible patients underwent neurological examination; blood tests (including vitamin B12 and folic acid levels, homocysteine, thyroid function and syphilis screening); neuropsychological assessment and magnetic resonance imaging (MRI). In addition, all subjects underwent a detailed neuropsychological assessment [13]. Functional status was assessed through the Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL) [14, 15]. The Neuropsychiatric Inventory [16, 17] was also performed to assess dementia-related behavioral symptoms.

Inclusion criteria were: age 65–75 years; diagnosis of probable mild-to-moderate Alzheimer's disease (AD) according to the National Institute on Aging and the Alzheimer's Association diagnostic criteria, NINCDS-ADRDA [18] or mild cognitive impairment (MCI) according to the criteria of Albert *et al.* [19].

To select a more homogeneous sample, we considered only the amnesic form of MCI.

Healthy elderly subjects of the same age group were recruited. They were selected among the patients' relatives. As caregiver status can be considered a highly stressful condition potentially associated with secondary sleep disorders [20], we avoided including relatives directly involved in the daily management of patients.

Exclusion criteria were the demonstration of MRI lesions compatible with a diagnosis of secondary dementia; language other than Italian; education <3 years; familiarity for cognitive impairment documented by positive genetic testing in at least one family member; exposure to toxic substances or history of substance abuse, excluding nicotine and including alcohol dependence (according to DSM V diagnostic criteria) in the last 12 months; and ongoing therapy with drugs that reduce cognitive function. In addition, a clinical history collection was performed along with a thorough review of clinical records to exclude patients and controls with other neurological diseases, including previous head trauma, epilepsy, neurodegenerative diseases, hydrocephalus; the presence of mental retardation or psychiatric disorders reducing neuropsychological performance; history of neoplastic and/or autoimmune diseases; the presence of other medical conditions not mentioned above that interfere with neuropsychological performance; the presence of diseases that cause cognitive impairment (thyroidism, syphilis, deficiency diseases such as vitamin B deficiency, brain neoplasms, paraneoplastic syndromes, severe liver and kidney diseases, HIV infection); focal neurological signs on physical examination; institutionalization of patients; sleep disorders or ongoing therapies that change the sleep profile. In this regard, a thorough history has been taken to highlight symptoms suggestive of insomnia, sleep apnea syndrome, restless legs syndrome and periodic limb movement [21, 22]. In case of consumption of supplements or drugs with a possible excitatory effect, including homotaurine, citicoline and piracetam, patients and

controls were asked to discontinue them for at least 10 days before inclusion in the study.

According to emerging evidence that both sleep disturbances and the APOE ε4 allele are associated with an increased risk of dementia and considering that previous research suggested that the presence of the APOE ε4 allele in subjects at increased risk of AD was associated with more inferior sleep quality, we identified the APOE4 genotype (ε3/ε4 or ε4/ε4) in all MCI/AD patients [23]. However, to avoid any invasive approach in control subjects, the APOE4 genotype was not studied in this group.

All enrolled patients were treated with centrally acting anticholinesterases. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), a self-administered questionnaire used to assess sleep quality in the previous month. It contains 19 self-assessment questions and 5 optional questions. Each item is assembled into 7 components: 1 = subjective sleep quality, 2 = sleep onset latency, 3 = sleep duration, 4 = sleep efficiency, 5 = sleep disturbance, 6 = hypnotic medication use, and 7 = diurnal dysfunction. Each component is rated from 0 to 3, with a PSQI range from 0 to 21: the higher the score, the lower the sleep quality. A cut-off score of 5 is used to divide good sleepers (<5) from bad sleepers (≥5). Several studies have confirmed the validity of the PSQI score in different patient populations [24, 25]. The Italian version validated in the general population was used [26]. Depending on the mental status, the questionnaire was completed with partial or full supervision of caregivers. The reliability and ability of the caregivers to complete the questionnaire were carefully examined to minimize possible errors or misinterpretation of the questions.

For each participant, we considered age, sex, PSQI score and the presence of hypertension, diabetes, dyslipidemia, smoking and obesity.

All participants wore an actigraphy device on their non-dominant wrist (Philips Respironics Actiwatch Spectrum or Philips Respironics Actiwatch-2, set to the same parameters) for seven consecutive days. The reliability of these devices for the study of sleep disorders has been previously demonstrated [27, 28]. Special attention was paid to obtain a similar distribution of the two devices among the three study groups. Healthy subjects and patients were asked to maintain their usual sleep/wake schedules, leaving them free to take naps during the day to consider the impact of circadian rhythm dysregulation on nocturnal actigraphic parameters. A particular recommendation for this was made in the case of AD patients to caregivers. Subjects and caregivers were encouraged to report as accurately as possible when lights were turned off and on and any intermediate periods out of bed. In addition, to avoid intra-individual variability, we contacted patients and caregivers to exclude from the analysis nights potentially affected by particular contingent life changes, extending the recording to seven standard night recordings.

We considered the following sleep measures: (i) time in bed (TIB): time in minutes spent in bed; (ii) sleep latency (SL):

Table 1. Scores were obtained at the Pittsburgh Sleep Quality Index (PSQI) in control subjects (CS), mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients. Multiple comparisons were performed with ANOVA with Bonferroni correction.

	CS	MCI	AD	CS vs MCI	CS vs AD	MCI vs AD
1 = subjective sleep quality	0.3 ($\pm$0.67)	0.4 ($\pm$0.84)	0.5 ($\pm$1.08)			
2 = sleep onset latency	0	1 ($\pm$1.24)	2 ($\pm$1.24)			
3 = sleep duration	1.4 ($\pm$0.96)	1.5 ($\pm$0.97)	1.3 ($\pm$0.94)			
4 = sleep efficiency	0.4 ($\pm$0.52)	1 ($\pm$1.15)	2 ($\pm$1.41)			
5 = sleep disturbance	0.3 ($\pm$0.48)	0.3 ($\pm$0.67)	0.5 ($\pm$0.52)			
6 = hypnotics use	0	0	0			
7 = diurnal dysfunction	0.2 ($\pm$0.42)	0.4 ($\pm$0.52)	0.3 ($\pm$0.48)			
				p	p	p
PSQI total score	2.8 ($\pm$1.39)	4.7 ($\pm$3.26)	7.0 ($\pm$4.14)	0.565	0.018	0.342

interval, in minutes, between turning off the light and the onset of sleep; (iii) total sleep time (TST): sum, in minutes, of all sleep epochs between sleep onset and sleep end; (iv) wake after sleep onset (WASO): sum, in minutes, of all wakefulness epochs between sleep onset and sleep end; (v) sleep efficiency percentage (SE%): the ratio of total sleep time to time in bed multiplied by 100; (vi) number of waking episodes (NA): the total number of awakenings in the sleep intervals; (vii) mean motor activity (MA): average number of movements in one minute calculated for the TIB. In all groups, data were collected using 1-minute epochs. Actigraphy data were processed in Philips Actiware 6 software.

All data were automatically evaluated in the software using the predefined scoring algorithm, with sleep time evaluated considering minutes of immobility. The analysis criteria of the algorithm were set as follows for all subjects: wakefulness threshold value of 40 activity counts, 10 minutes of immobility for the beginning and end of sleep, white light threshold of 1000 lux. A trained technician visually inspected the automatic scoring, and scores were modified if necessary based on sleep diary data to reconcile unclear records. In addition, SL, WASO, SE and TST duration were extracted.

We did not make any correction in the activity parameters of the patients, as cognitive impairments were mild even in AD, and this condition did not affect movements compared to healthy controls of the same age.

The study was conducted according to the 1975 Declaration of Helsinki (and as revised in 1983) and was approved by the Ethics Committee of the Polytechnic University of Marche. All participants provided written informed consent.

2.2 Statistical analysis

Subjects were classified into three groups, adopting a categorical grouping variable: control subjects (CS), MCI patients and AD patients.

Age, PSQI, TIB, TST, SL, SE, WASO, NA and MA were collected as continuous variables. In addition, sex, hypertension, diabetes, dyslipidemia, smoking, obesity, and the APOE 4 allele were collected as dichotomous variables.

We performed a *post hoc* power analysis considering an F-test analysis of variance (ANOVA) model, the overall number of enrolled patients, 3 groups, and α error probability of 0.05 and an f-effect size of 0.6.

Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Normally distributed variables were summarised as mean and standard deviation (SD) and compared with ANOVA. In contrast, non-normally distributed variables were presented as the median and interquartile range (IQR) compared with the Kruskal-Wallis H test. Dichotomous variables were recorded as numbers and percentages and compared with the chi-square test. The significance level of multiple comparisons was checked with the Bonferroni correction.

Finally, we prepared a GLM/multivariate model considering the PSQI and actigraphic variables as dependent variables. The grouping variable was independent and age, sex, hypertension, smoking status, diabetes, dyslipidemia, and obesity covariates. We then assessed the differences between the estimated marginal means.

Power analysis was performed with G*Power 3.1 for MacOS systems [29].

Statistical analysis was performed with SPSS 13.0 for Windows systems (SPSS Statistics for Windows, version 13.0, SPSS Inc., Chicago, Ill., USA).

3. Results

Of 59 patients initially recruited from among those with mild cognitive impairment, 36 were excluded due to the presence of one or more exclusion criteria while three refused to participate or discontinued the actigraphic assessment. In particular, 5 patients with MCI and 4 with AD were excluded due to the presence of sleep disturbances. Twenty patients, 10 with MCI and 10 with AD were included together with ten controls. We had no missing values for any of the measurements taken. All included subjects were able to complete the 7-day actigraphic study without any extension of the recording. The results obtained at PSQI with the detailed description of the 7 components are reported in Table 1. The power analysis resulted in an 80% probability of rejecting the H0 hypothesis when it was false. When analysing age, PSQI, TIB, TST, SL, SE, WASO, NA and MA with the

Table 2. Baseline characteristics of the sample: control subjects (CS), mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients. Multiple comparisons were performed with ANOVA with Bonferroni correction.

Variable	CS	MCI	AD	CS vs MCI	CS vs AD	MCI vs AD
				p	*p*	*p*
Demographic characteristics						
Age (± SD), years	70.60 (±3.65)	70.70 (±3.47)	70.50 (±2.95)	n.s.	n.s.	n.s.
Sex (n, %), males	5 (16.7%)	5 (16.7%)	5 (16.7%)	n.s.	n.s.	n.s.
Comorbidities						
Hypertension (n, %)	5 (16.7%)	4 (13.3%)	6 (20.0%)	n.s.	n.s.	n.s.
Diabetes (n, %)	2 (6.7%)	3 (10.0%)	2 (6.7%)	n.s.	n.s.	n.s.
Dyslipidaemia (n, %)	4 (13.3%)	4 (13.3%)	3 (10.0%)	n.s.	n.s.	n.s.
Smoke (n, %)	3 (10%)	3 (10%)	2 (6.7%)	n.s.	n.s.	n.s.
Obesity (n, %)	3 (10.0%)	2 (6.7%)	4 (13.3%)	n.s.	n.s.	n.s.
$\varepsilon 4$ allele (n, %)	–	4 (20%)	7 (35%)	–	–	n.s.
Actigraphy data (± SD)						
Time in bed, min	467.8 (±72.51)	529.3 (±108.1)	616.9 (±103.9)	0.488	0.005	0.152
Total sleep time, min	426.29 (±69.4)	469.40 (±99.8)	511.34 (±76.6)	0.766	0.090	0.805
Sleep latency, min	10.06 (±3.12)	26.44 (±9.03)	49.48 (±28.40)	0.131	0.000	0.018
Sleep efficiency %	91.02 (±1.50)	88.58 (±1.54)	83.64 (±4.06)	0.000	0.000	0.006
Wake after sleep onset, min	31.44 (±7.69)	33.45 (±5.89)	52.48 (±17.58)	1.000	0.001	0.003
Number of awakenings	18.8 (±4.99)	20.9 (±8.02)	59.52 (±26.32)	1.000	0.000	0.000
Mean motor activity/min	14.5 (±3.27)	11.9 (±4.32)	34.19 (±15.96)	1.000	0.000	0.000

Legend: PSQI, Pittsburg Sleep Quality Index; SD, standard deviation.

Kolmogorov-Smirnov test in three groups of patients, we observed that this test was non-significant in all three groups for each variable analysed, suggesting a normal distribution. The three groups resulted similar for baseline characteristics, as sex (chi-squared = 0.000; df = 2; *p* = 1.000), hypertension (chi-squared = 0.800; df = 2; *p* = 0.670), diabetes (chi-squared = 0.373; df = 2; *p* = 0.830), dyslipidaemia (chi-squared = 0.287; df = 2; *p* = 0.866), smoke (chi-squared = 0.341; df = 2; *p* = 0.843) and BMI (chi-squared = 0.952; df = 2; *p* = 0.621), as shown in Table 2. MCI and AD patients did not significantly differ for the prevalence of APOE $\epsilon 4$ allele (chi-squared = 1.818; df = 1; *p* = 0.178). ANOVA showed a significant difference between CS and MCI in SL (F = 13.095; *p* = 0.0001). CS and AD resulted significantly different in PSQI score (F = 4.461; *p* = 0.021), TIB (F = 6.113; *p* = 0.006), SE (F = 20.028; *p* = 0.0001), WASO (F = 10.030; *p* = 0.001), NA (F = 20.111; *p* = 0.0001), MA (F = 15.681; *p* = 0.0001), while TST did not reach statistical significance (F = 2.627; *p* = 0.091). MCI patients differed significantly from AD patients in SL, SE, WASO, NA and MA.

The GLM/Multivariate model resulted significantly, and we were able to reject the H_0 hypothesis that the model explained zero variance in the dependent variables. The leading independent grouping variable resulted significantly both at multivariate test (*p* < 0.0001). In contrast, the included covariates (age, sex, hypertension, smoking status, diabetes, dyslipidemia and obesity) did not significantly associate with the dependent variables at the multivariate test in this model. Estimated marginal means derived from the multivariate model are synthesized in Table 3, while the comparison among groups in the multivariate model is shown in Table 4.

Differences between MCI patients and CS were significant for SL (*p* = 0.05); AD patients had significantly worse score for PSQI (*p* = 0.01), TIB (*p* = 0.001), TST (*p* = 0.04), SL, SE, WASO, e MA (*p* = 0.0001) when compared to CS. When comparing AD and MCI, the differences was significant for SL (*p* = 0.01), WAS0 (*p* = 0.004), SE, NA and MA (*p* = 0.0001).

4. Discussion

The results show that an actigraphic assessment can allow rapid and non-invasive detection of sleep changes in subjects with impaired cognitive performance. According to our results, reduced sleep quality may already be evident in patients with MCI. In agreement with the results of previous studies, the presence and extent of different sleep changes have become more frequent and severe in patients with AD [30, 31]. In particular, we found a progressive negative evolution of changes in SL and SE from CS to MCI to AD patients. Moreover, AD patients showed a higher prevalence of other alterations in actigraphic parameters, thus confirming that the evolution of cognitive impairment is associated with a reduction in sleep quality. The increase in the number of NA in cognitive impairment patients, besides underlining the relevance of actigraphy in detecting and defining the extent of motor hyperactivity [32], further emphasizes that sleep deprivation is a common feature in patients with dementia [33–35].

Some sleep alterations have been described in normal aging and reflect changes in sleep regulation processes [9]. Neurodegeneration may include neurons involved in sleep regulation. The alternation between sleep and wakefulness is reg-

Table 3. Estimated marginal means derived from multivariate model for control subjects (CS), mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients.

Dependent variables	CS (95% CI)	MCI (95% CI)	AD (95% CI)
	n = 10	n = 10	n = 10
PSQI	2.73 (0.72–4.75)	5.10 (3.03–7.17)	6.66 (4.59–8.73)
Time in bed, min	472.92 (419.87–525.96)	536.68 (482.22–591.13)	604.40 (550.01–658.80)
Total sleep time, min	430.27 (383.11–477.43)	476.18 (427.76–524.59)	500.59 (452.22–548.95)
Sleep latency, min	10.57 (0.88–22.02)	26.58 (14.83–38.34)	48.82 (37.07–60.56)
Sleep efficiency %	90.97 (89.17–92.77)	88.68 (86.83–90.52)	83.59 (81.75–85.43)
Wake after sleep onset, min	31.99 (24.21–39.76)	33.66 (25.68–41.63)	51.74 (43.77–59.71)
Number of awakenings	18.76 (8.21–29.31)	20.44 (9.61–31.27)	60.10 (49.28–70.92)
Mean motor activity/min	14.55 (7.27–21.82)	11.74 (4.27–19.20)	34.34 (26.88–41.79)

Legend: 95% CI, 95% Confidence Interval; PSQI, Pittsburg Sleep Quality Index; n, number of subjects.

ulated by a homeostatic component that considers the need for sleep in proportion to the duration of the waking state. On the other hand, the circadian process organizes the temporal distribution of wakefulness and sleep [9]. In the present study, we found a gradual increase in SL from controls to AD patients. This may suggest the occurrence of progressive alterations in the circadian process.

Sleep architecture is altered in the presence of sleep disorders. Therefore, in the present work, we excluded subjects with suspected primary sleep disorders [36].

The design of our study does not allow us to determine whether sleep alterations can be considered secondary or whether they may be involved in influencing the risk of cognitive impairment in patients. The interaction between sleep alterations and neurodegeneration is complex and bidirectional [4, 9]. The presence of sleep disorders in subjects with cognitive impairment, regardless of their interpretation as primary or secondary conditions, deserves attention for the pathophysiological implications. A correct approach and early diagnosis of sleep alterations are relevant to managing subjects at risk of developing dementia. In this regard, an interesting aspect that emerges from our study concerns the fact that the administration of the PSQI, a validated scale to assess sleep quality in the last month, was not able to detect significant differences between CS and MCI. Due to the low sample size, we did not perform a specific analysis to assess whether there were any differences in the different components of the PSQI between the two groups of patients. The different results between PSQI and actigraphy may be due to several reasons. First, the two approaches allow the acquisition of different data. Actigraphy information is based on objective data provided over 7 days, whereas PSQI supports subjective data over 1 month.

The advantage of providing objective data in a clinical setting where cognitive impairment may reduce the reliability of information based on patients' ability to offer full cooperation is significant. Our data support the need to consider a multimodal approach in investigating sleep disorders in patients with cognitive impairment. Actigraphy seems to be a promising diagnostic approach for a fast, sim-

ple and widely available possibility to investigate and objectively detect sleep disorders, especially in the early stage of cognitive impairment. In agreement with our findings, the results of a recent survey of patients referred to a memory clinic showed that objective data supported by actigraphy are more reliable than self-reported information for assessing correlations between sleep disturbances and cognitive dysfunction [37]. Polysomnography remains the gold standard approach for definitive and accurate characterization of the sleep profile. Wider use of polysomnography is, however, limited for several reasons, including reduced patient compliance. In this regard, rapid screening with a more straightforward approach may be advantageous. Actigraphy, although mainly dedicated to the assessment of circadian rhythm alterations, providing reliable information on aspects related to the amount of sleep, could support the indication of the possibility of correcting parameters potentially implicated in the progression of cognitive impairment [10].

Our work has some limitations. The small sample size did not allow us to consider the possible influence of sex and age on sleep alteration even though the different groups of subjects in the study were comparable for these variables. Furthermore, the careful selection of subjects, mainly the exclusion of patients with sleep disorders, does not allow us to generalize our results to the entire population of patients with cognitive impairment. However, we wanted to obtain some preliminary indications on the possibility of extending the use of actigraphic assessments to obtain information on the association between sleep alterations and cognitive impairment. For this reason, we tried to select a relatively homogeneous group of patients. The fact that the subjects were not studied simultaneously must be considered to define our results as preliminary and capable of raising hypotheses and suggesting the need for further investigation into possible practical implications. For instance, the possibility that early correction of sleep disturbances in patients with MCI may reduce the risk of dementia conversion should be carefully considered when planning specifically designated investigations. It would be essential to assess sleep over 24 hours. We only evaluated sleep during the night without consider-

Table 4. Comparison between estimated marginal means derived from a multivariate model in control subjects (CS), mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients.

Dependent variable	(I) Group	(J) Group	I–J	Se	p	95% Confidence Interval	
						Lower bound	Upper bound
PSQI	CS	MCI	−2.37	1.39	0.10	−5.26	0.522
		AD	−3.93	1.38	0.01	−6.82	−1.04
	MCI	AD	−1.56	1.44	0.29	−4.56	1.44
Time in bed, min	CS	MCI	−63.76	36.51	0.09	−139.92	12.40
		AD	−131.49	36.45	0.001	−207.52	−55.45
	MCI	AD	−67.73	37.85	0.088	−146.70	11.24
Total sleep time, min	CS	MCI	−45.91	32.46	0.17	−113.63	21.81
		AD	−70.31	32.41	0.04	−137.92	−2.71
	MCI	AD	−24.41	33.66	0.47	−94.62	45.81
Sleep latency, min	CS	MCI	−16.0	7.88	0.05	−32.46	0.43
		AD	−38.26	7.87	0.0001	−54.67	−21.84
	MCI	AD	−22.24	8.17	0.01	−39.29	−5.19
Sleep efficiency %	CS	MCI	2.29	1.24	0.08	−0.29	4.87
		AD	7.38	1.23	0.0001	4.80	9.95
	MCI	AD	5.09	1.28	0.0001	2.41	7.76
Wake after sleep onset, min	CS	MCI	−1.67	5.35	0.76	−12.83	9.49
		AD	−19.7	5.34	0.001	−30.89	−8.61
	MCI	AD	−18.08	5.55	0.004	−29.65	−6.51
Number of awakenings	CS	MCI	−1.67	7.26	0.82	−16.83	13.47
		AD	−41.33	7.25	0.0001	−56.46	−26.21
	MCI	AD	−39.65	7.53	0.0001	−55.37	−23.95
Mean motor activity/min	CS	MCI	2.81	5.00	0.58	−7.63	13.25
		AD	−19.79	4.99	0.0001	−30.21	−9.37
	MCI	AD	−22.60	5.19	0.0001	−33.42	−11.78

Legend: PSQI, Pittsburg Sleep Quality Index.

ing the 24-hour TST and the occurrence of naps, affecting the quality of the patients' nightly sleep. In this regard, it has been reported that AD patients may have sleep episodes during the day [38]. Therefore, future studies should be performed that do not focus exclusively on changes in nocturnal sleep architecture. The delivery of information via PSQI, a self-administered questionnaire was obtained, in the case of AD patients, with the collaboration of caregivers responsible for assisting patients to correctly interpret each question. This approach can be considered at the potential risk of introducing inaccuracies. However, we have paid particular attention to minimize this possible bias by carefully monitoring the reliability of the caregivers and explaining in detail the meaning of the questions. Because subjective and objective measures can affect different aspects of sleep quality, each providing valuable insights, we recommend that both approaches, when examining sleep quality in older adults, be considered even in the presence of cognitive impairment [39]. The presence of mood disorders may significantly influence sleep characteristics. Their possible interference was not assessed in our study. Although the presence of a history of psychiatric illness was among the exclusion criteria, we cannot exclude the possibility that some sleep alterations observed in cognitively impaired patients may be related to a higher prevalence of anxiety and/or depression. Finally,

all AD patients were on centrally acting anticholinesterasic drugs. According to a double-blind placebo-controlled study, drugs with cholinergic action may influence REM sleep [40].

Moreover, a possible effect is related to changes in respiratory parameters in AD patients with obstructive sleep apnea. Indeed, cholinergic activity influences the functional status of the upper airways through central and peripheral mechanisms [41]. This aspect should be considered as a potential confounding factor for the possible action of this type of treatment on the sleep profile. However, it is essential to point out that pharmacological activation of central cholinergic systems may improve abnormalities in sleep patterns [42]. Therefore, it is likely that the negative changes in sleep actigraphic parameters in our AD patients can be considered independent of the drug's influence. Some of the limitations mentioned above, especially the low sample size, can probably explain some of our results that seem to be at odds with previously reported findings. Our data obtained in MCI did not confirm a reduction in TST [43].

Furthermore, we could not confirm an influence of APOE genotype on sleep patterns [23]. As a further limitation of our study, we did not obtain data on APOE4 genotype in control subjects. On the other hand, our data confirm that actigraphy is a reliable approach to detect circadian rhythm alteration [44, 45].

Actigraphy is not suitable for a detailed description of sleep's macro and microstructure and defines some particular alterations, including reducing slow sleep waves that characterize neurodegenerative changes. For this reason, a detailed sleep assessment capable of supporting strategic information to define the relationship between sleep and cognitive decline requires polysomnographic evaluation. The selection of patients with sleep disorders, especially in the early phase of cognitive impairment, may be relevant for an early attempt to precisely correct alterations potentially interfering with the evolution of cognitive decline. In this regard, reduced sleep efficiency may be linked to several specific alterations that require a differentiated pharmacological approach. For example, an increase in SL can be corrected by a chronobiotic treatment, while a sleep stabilizer can correct an increase in fragmentation. The possibility of obtaining early objective information with a simple and non-invasive approach may be relevant and expand the potential use of actigraphy to monitor the evolution of sleep disorders with repeated recordings.

5. Conclusions

The relevance of early assessment and correction of risk factors in the management of cognitive impairment suggests the potential importance of careful assessment of sleep characteristics in patients with cognitive impairment. According to our results, actigraphy should be considered for a simple and non-invasive approach capable of supporting adequate information to guide specific therapeutic approaches and to select patients in whom more specific diagnostic assessments are needed.

Abbreviations

AB, amyloid; AD, Alzheimer's disease; ADL, Activities of Daily Living; CS, control subjects; IADL, Instrumental Activities of Daily Living; MA, mean motor activity; MCI, mild cognitive impairment; MMSE, Mini-Mental Status Examination; MRI, magnetic resonance imaging; NA, number of awakenings; PSQI, Pittsburgh Sleep Quality Index; SE, sleep efficiency; SL, sleep latency; TIB, time in bed; TST, total sleep time; WASO, wakefulness after sleep onset.

Author contributions

LB: drafting/revising the manuscript, study concept or design, analysis and interpretation of data; RC, AP, CR, GV, SB, CF: drafting/revising the manuscript, acquisition of data; LF: drafting/revising the manuscript, analysis and interpretation of data; MS: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All participants provided written informed consent. The Institutional Review Board of the Department of Experimen-

tal and Clinical Medicine, Marche Polytechnic University, approved the study, code 2019/37.

Conflict of interest

The authors declare no conflict of interest.

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