Sleep Medicine 61 (2019) 57–62

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Sleep microstructure in Parkinson's disease: cycling alternating pattern (CAP) as a sensitive marker of early NREM sleep instability

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ARTICLE INFO

Article history:
Received 6 January 2019
Received in revised form
26 March 2019
Accepted 27 March 2019
Available online 20 April 2019

Keywords:
Sleep
Parkinson's disease
Cycling alternating pattern
NREM sleep
Sleep microstructure

ABSTRACT

Background: Sleep disorders are frequent in Parkinson's disease (PD). Apart from the occurrence of REM behavior disorders, in the early phase of the disease standard sleep macrostructure evaluation was inconclusive.
Objective: We analyzed non-rapid eye movement (NREM) sleep microstructure (CAP) in a group of PD patients to provide an objective measure of sleep disruption.
Methods: We recruited 31 PD patients [mean age 59.5 ± 12.4 years; mean Hoehn-Yahr (H-Y) stage: 3.4 ± 1.8] and 34 age-matched non-parkinsonian subjects (mean age 61.5 ± 15.2 years) as a control group. All patients underwent full-night laboratory polysomnography (PSG). Conventional sleep macro/microstructure analysis was performed. Patients were then divided into two groups: group 1 (H-Y stage $\leq$ 2) and group 2 (H-Y stage $\geq$ 3).
Results: In group 2 PD patients compared to controls, alterations of both sleep macrostructure and microstructure were found. The PD subgroup with milder disease (group 1) presented sleep macrostructure, movements and respiratory parameters not significantly different from controls, although their CAP rate was significantly higher and the proportion of the A1 phase of CAP was reduced ($p = 0.03$). Multivariate logistic regression showed that disease duration, disease severity, and arousal index emerged as independent predictive factors for CAP rate $\geq$55% and the A1 phase of CAP $\leq$40% ($p < 0.05$).
Conclusion: The main result of our study consists in the disclosure of altered NREM sleep microstructure in PD even at an early stage of the disease, suggesting an early alteration of the central pathways involved in the NREM sleep building-up and stability.

1. Introduction

Sleep disorders are frequent in Parkinson's disease (PD) and have multifactorial origin [1]. These sleep disorders may lead to sleep fragmentation and excessive daytime somnolence [2]. In Parkinson's disease, sleep fragmentation with frequent awakenings and micro-arousals, concurrent with excessive daytime somnolence, can be caused by REM sleep behavior disorder (RBD) [3], periodic limb movements in sleep (PLM) [4], re-emergence of parkinsonian symptoms [5], sleep-disordered breathing [6], effect of medications [7,8], or psychiatric disorders such as depression or anxiety [9]. Of particular interest is REM sleep behavior disorder (RBD), a parasomnia characterized by violent movements and increased motor activity during REM sleep that may be either idiopathic or coupled with neurodegenerative disorders, typically synucleinopathies [10,11].

Currently, polysomnographic studies have been directed to investigate sleep macrostructure together with disease-related

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https://doi.org/10.1016/j.sleep.2019.03.025
1389-9457/

changes [12–21], nocturnal motor symptoms [22–24], sleep-related breathing disorders [25–28], PLM disorder [29–32] and RBD [33–39]. Case-control polysomnographic studies using sleep standard scoring give inconclusive results [14,15]. Concerning REM sleep, most studies find no difference in the percentage of total REM sleep time, although a few authors report some reductions; moreover, non-rapid eye movement (NREM) sleep including slow wave sleep (SWS) proves to be quantitatively unaffected in the majority of the studies, compared to healthy people [12]. Disease severity and medication are all factors that impact the macro-structure of sleep. For example, dopaminergic drugs promote SWS and REM sleep at low doses, while at higher doses they reduce SWS and promote alertness [40–42].

On the contrary, little effort has been directed to investigate transient EEG phenomena lasting less than the scoring epoch and Cycling Alternating Pattern (CAP), to describe what is known as the microstructure of sleep [43]. In particular, CAP analysis adds valuable information and provides more insights into sleep disorders pathogenesis, as it reflects the building-up and stability of NREM sleep. Furthermore, it is more sensitive in detecting subtle sleep alterations not recognizable by standard scoring of sleep stages [44].

In our study, we analyzed sleep microstructure utilizing CAP analysis in a group of PD patients compared to age-matched healthy people, to provide an objective measure of NREM sleep instability and its relationship with disease severity.

2. Material and methods

We recruited 31 PD patients [mean age 59.5 ± 12.4 years; mean Hoehn-Yahr (H-Y) stage: 3.4 ± 1.8] from among our PD outpatients with a diagnosis of PD according to standard criteria, after therapy optimization. Thirty-four age-matched non-parkinsonian subjects (Elderly Controls; mean age 61.5 ± 15.2 years) coming from the same geographic area were selected from our database to serve as controls. Exclusion criteria for both groups included moderate or severe depression, significant pain disturbances, and cognitive impairment.

All patients underwent an adaptation night and then full-night polysomnography (PSG) in the sleep laboratory in a quiet room with video monitoring. Patients were allowed to maintain their regular sleep habits and timing. Only two patients and none of the elderly controls were under treatment with low doses of benzodiazepines and neuroleptics. This therapy was discontinued one week before PSG. The following parameters were recorded: EEG using C3-A2, C4-A1, O2-A1, O1-A2 derivations integrated by bipolar montages Fp2-F4, F4-C4, C4-P4, P4-02; Fp1-F3, F3-C3, C3-P3, P3-01; Fz-Cz, Cz-Pz of the 10–20 international placement system; electrooculogram (bipolar montage: right ocular canthus-left ocular canthus); electrocardiogram; respiratory effort by thoracic and abdominal strain gauges, nasal air-flow by nasal cannula, snoring by a microphone, arterial oxyhemoglobin (SaO_2) using a pulse oximeter with finger probe; submental and tibialis anterior muscles electromyogram. Conventional sleep analysis, respiratory parameters, and arousals were performed independently by two evaluators experienced in sleep staging according to the literature [45] and based on the guidelines defined by Terzano and colleagues for CAP scoring [46]. Levodopa equivalent dose was calculated, and daily motor performances were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS-part III).

We then divided the patients into two groups according to their H-Y stage: group 1 (H-Y stage ≤ 2) and group 2 (H-Y stage ≥ 3). Data were examined for normality using visual histograms and the Kolmogorov-Smirnov test. Means were compared using unpaired t-tests or ANOVA (normally distributed data). Comparisons between the control group and the whole parkinsonian group were performed using Student t-Test, while comparisons between the control group and the parkinsonian groups 1 and 2 were performed using ANOVA for independent samples and post hoc Duncan correction. Correlations were calculated using Spearman Rank test, and logistic regression analysis was performed to assess predictive variables and to control for covariates (eg, age). The statistica[l TM] software package, StaSoft Inc. [TM] was used for these analyses. Our study was intended to be a preliminary exploratory, not confirmatory study so that the threshold of significance was set at $p < 0.05$.

The protocol was approved by the Ethics Committee of the IRCCS Istituto Auxologico Italiano. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The study was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from study participants.

3. Results

Compared to controls, polysomnographic analysis of the whole group of PD patients showed a significant increase of sleep onset latency, wake periods after sleep onset (WASO), arousal index and N2 sleep stage percentage together with a significant decrease of both sleep efficiency and slow wave sleep. PLMs index was increased in PD patients compared to elderly controls, although at the limit of statistical significance. In PD patients there was evidence of tremor persistence during N1 and N2 sleep stages in 22.5% of patients. RBD and PLMs disorders were diagnosed in 29% and 6% of PD patients, respectively. Taking into account the microstructural parameters of sleep in the whole group of PD patients, it was found that their mean CAP rate was increased compared to controls. Conversely, the A1 phase proportion was significantly reduced in PD patients compared to age-matched controls (Table 1).

The subgroup of 17 patients with more advanced disease (group 2), showed, as expected, a significant increase of sleep onset latency, decreased sleep efficiency, decreased slow wave sleep, increased CAP rate and decreased A1 phases, compared to controls. Conversely, the subgroup of 14 patients (group 1) with H-Y stage ≤ 2 presented sleep macrostructure parameters not statistically different from controls, even if a tendency to decreased sleep efficiency, decreased slow wave sleep and increased arousal index was noted. Somewhat unexpectedly, in this group the CAP rate was significantly higher than controls, while the proportion of the A1 phase of CAP was reduced (Table 1).

Considering the whole group of PD patients, sleep efficiency and stage N3 sleep showed mild correlations with age, H-Y stage, UPDRS or disease duration. CAP rate showed a moderate correlation with disease severity and disease duration, while the A1 phase of CAP showed a moderate negative correlation with disease duration and a mild negative correlation with disease severity (Table 2). In our group of PD patients, levodopa equivalent dose showed a wide dispersion of data and did not correlate with sleep parameters.

Considering only the subgroup of PD patients with H-Y stage ≤ 2, CAP rate and A1 phase of CAP correlated only with disease duration ($r = 0.67$, $p = 0.03$, and $r = -0.59$, $p = 0.04$ respectively). Plots regarding these relations are displayed in Fig. 1. Patients with a higher CAP rate presented lower A1 phase proportions; this relationship was statistically significant ($r = -0.76$, $p = 0.01$). No statistical significant correlation between CAP parameters and disease severity [Group 1: UPDRS – III (on): 19.2 ± 10.9; Group 2: UPDRS – III (on): 28.3 ± 14.5], levodopa equivalent dose (Group 1: 532.8 ± 275.8; Group 2: 885.8 ± 435.2) and age was observed.

Table 1
Sleep parameters in PD patients compared to elderly controls.

	Elderly controls		PD patients (total)		p	PD patients (group 1)		p^1	PD patients (group 2)		p^2
	Mean	SD	Mean	SD		Mean	SD		Mean	SD	
Total sleep time (min)	384.3	78.6	377.5	95.6	NS	395	88.2	NS	353	89.5	NS
Sleep efficiency (%)	81.4	21.6	65.5	31.2	0.04*	75.3	16.2	NS	56.4	26.8	<0.01*
WASO (min)	58.5	24.9	67.5	37.8	0.04*	64.6	26.8	NS	71.2	36.4	NS
Sleep latency (min)	18.2	14.2	34.6	27.2	0.01*	24.3	23.2	NS	43.6	25.4	<0.01*
REM sleep latency (min)	81.2	28.8	92.1	44.2	NS	88.8	27.4	NS	95.6	36.7	NS
REM periods (n)	6.3	2.1	8.1	5.8	NS	7.9	4.7	NS	8.6	5.6	NS
Stage N1 (%)	4.7	5.2	4.2	5.3	NS	3.9	4.9	NS	4.5	5.2	NS
Stage N2 (%)	47.4	16.1	61.2	21.3	0.01*	51.2	18.2	NS	68.5	16.2	<0.01*
Stage N3 (%)	28.4	12.1	15.8	14.6	<0.01*	23.7	13.6	NS	10.2	12.3	<0.01*
Stage R (%)	18.5	13.8	18.8	13.6	NS	20.8	11.6	NS	15.8	12.4	NS
Total NREM (%)	80.5	19.5	81.2	23.7	NS	78.8	21.2	NS	83.2	18.4	NS
Arousal index (n/h)	15.8	16.8	28.8	24.9	0.03*	26.8	14.2	NS	33.2	21.5	<0.01*
PLM index (n/h)	5.7	6.3	11.8	12.4	0.05	11.3	9.6	NS	12.5	11.6	0.04*
AHI (n/h)	2.8	2.3	3.5	1.8	NS	2.7	1.6	NS	3.6	1.6	NS
Central apnea index (n/h)	1	0.8	1.5	1.4	NS	1.2	0.9	NS	1.9	1.3	NS
RBD (n)	1 (0.04%)		9 (29%)			4 (28.5%)			5 (29.4%)		
Tremor persistence in stage 1 and 2 (n)	–		7 (22.5%)			2 (14.2%)			5 (29.4%)		
CAP rate (% of total NREM)	50.8	8.2	57.7	13.2	0.02*	56.8	7.1	0.04*	59.2	11.8	0.03*
A1 (% of total A phases)	68.4	13.6	50.5	21.5	<0.01*	56.7	14.2	0.03*	40.3	15.8	<0.01*
A2 (% of total A phases)	22.4	10.2	32.3	17.3	<0.01*	29.1	10.8	NS	36.9	13.2	<0.01*
A3 (% of total A phases)	9.2	6.7	17.2	14.1	<0.01*	14,2	8.8	0.03*	22,8	12.6	<0.01*

Sleep stages expressed as % of total sleep time. PD: Parkinson's disease. WASO: wake after sleep onset; PLM: periodic limb movements during sleep. RBD: REM behavior disorder. CAP: cycling alternating pattern. A1: A1 phases of CAP. SD: standard deviation.
Comparisons between the control group and the whole parkinsonian group are performed using Student t-Test; p-value indicated when significant (*). NS: not significant. Comparisons between the control group and parkinsonian groups 1 and 2 were performed using ANOVA for independent samples and post hoc Duncan correction; p^1 values indicated when the difference between group 1 and elderly controls is significant (*), p^2 values indicated when the difference between group 2 and elderly controls is significant (*). NS: not significant.

Table 2
Correlations between clinical data and sleep parameters in PD patients.

	Age	Hoehn-Yahr stage	Disease duration	UPDRS (on)	UPDRS (off)
Sleep latency	0.27	0.19	0.21	0.28	0.21
REM sleep latency	0.16	0.12	0.09	0.21	0.25
Sleep efficiency	−0.31	−0.4	−0.27	−0.37	−0.36
Stage N3 sleep	−0.34	−0.45*	−0.34	−0.21	−0.33
PLM index	0.26	0.15	0.21	0.11	0.18
CAP rate	0.18	0.64**	0.49*	0.54*	0.51*
A1 phases	−0.23	−0.35	−0.56**	−0.33	−0.36

(*) $p < 0.05$; (**) $p < 0.01$; Spearman Rank correlation test.

Multivariate logistic regression showed that disease duration and disease severity (H-Y $\geq$ 3) emerged as independent predictive factors for CAP rate $\geq$ 55% (disease duration $p = 0.01$; disease severity $p = 0.002$), and for A1 phase of CAP $\leq$ 40% (disease duration $p = 0.001$; disease severity $p = 0.04$). These CAP parameter cut-offs were chosen, following published CAP rate distribution in healthy people of comparable age [43].

4. Discussion

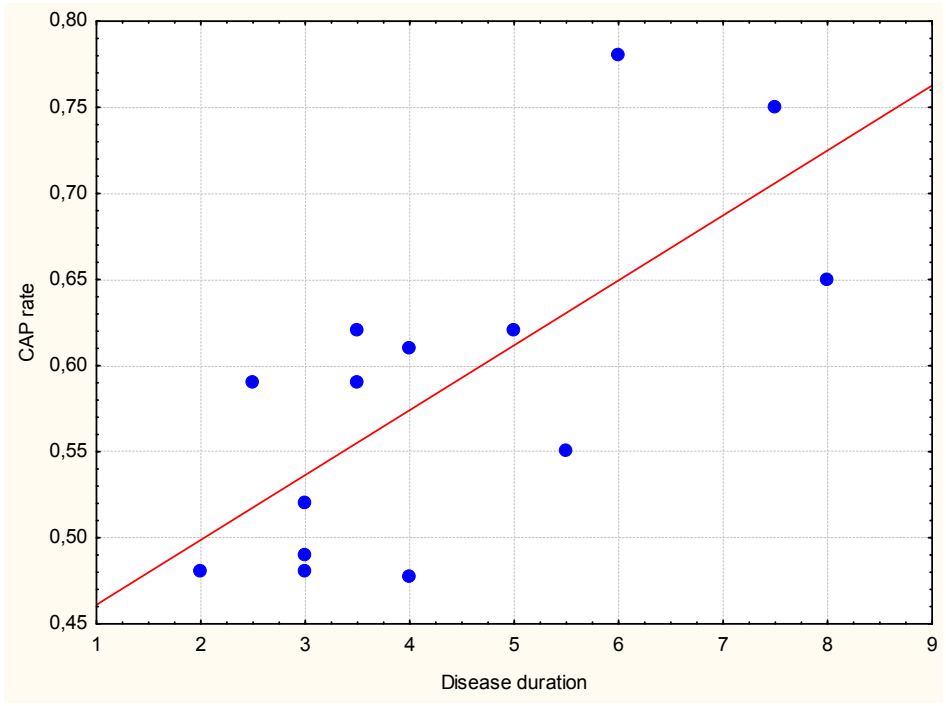
Sleep disorders have a high prevalence in PD patients and, together with the underlying motor symptoms, are leading causes of disability, having a substantial impact on the quality of life [47].

REM sleep alterations are well documented in PD, while NREM sleep abnormalities, in particular, sleep microstructure including CAP, still remain poorly investigated.

CAP constitutes a repetitive biphasic pattern of NREM sleep in which sequences of transient synchronized and/or desynchronized EEG sequences (phase A) recur at intervals from background theta or delta rhythms (phase B). CAP components corresponding to EEG synchrony represent the cortical expression of cortical–subcortical interactions mediated by thalamocortical pathways and modulated by hypothalamic and brainstem nuclei, among which the locus coeruleus and raphe nuclei play an essential role [44–48]. Subtype A1 consisting of an EEG synchronized pattern (irregular alpha rhythms in S1, K-complex sequences, and delta bursts), is most common in the transition from light to SWS and seems to be linked to the activity of REM-off neurons [44]. CAP is supposed to play the primary role in the building-up of EEG synchronization during NREM sleep, and in the flexible adaptation against perturbations, so that its increase is considered to be related to NREM difficulties in proceeding towards stable SWS [44]. In this view, sleep EEG spectral pattern investigations showed alterations during NREM phases in PD patients, even at the earlier stages of the disease, which may present evidence for altered electrophysiological mechanisms leading to sleep-wake instability [50].

Our study shows, as expected, worse sleep macrostructure parameters, increased CAP rate and decreased A1 phases of CAP in PD patients compared to age-matched controls. CAP alterations, in particular, are frequent in disease characterized by frequent arousals and typically suggest sleep instability and difficulty in the building-up of SWS [44]. As shown by subgroup analysis and multivariate logistic regression, considering the whole group of PD patients, CAP rate increase and A1 phases decrease in PD patients

(a)



(b)

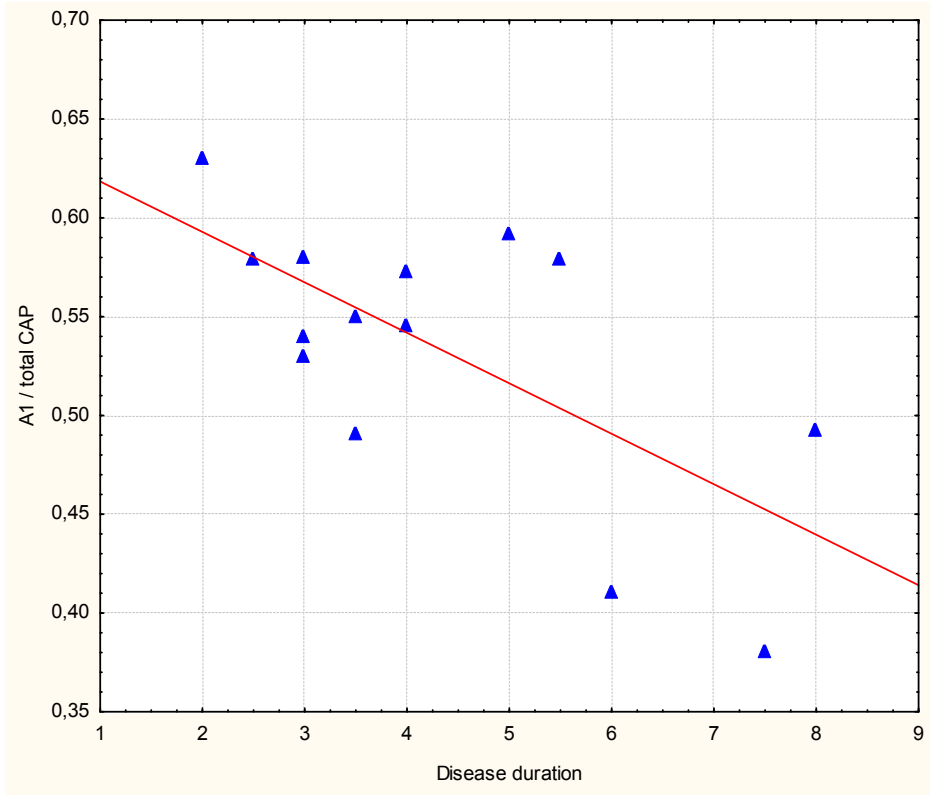


Fig. 1. Relationship of disease duration (in years) with CAP rate (a) or A1 proportion of CAP (b) in the subgroup of PD patients with less advanced disease stage (Group 1, Hoehn-Yahr stage ≤ 2).

are mainly correlated with disease duration and severity. In the subgroup of patients at a milder disease stage, it is not macrostructure abnormalities, but CAP alterations that are detected. Moreover, these CAP alterations appear to be related to disease duration, independently from disease severity. These data are the most relevant findings of our study, not yet reported in the literature, to our knowledge. Considering neuropathology studies [51], it seems that the neurodegenerative process spreads sequentially in a caudal-rostral direction (for example, pathological cases with cortical involvement always exhibit brainstem involvement). So, reasonably, patients with more advanced and/or longer duration of Parkinson's disease should display more pronounced NREM alterations.

Concerning CAP analysis in sleep disorders and neurodegenerative diseases, a 2013 study performed in Rem Sleep Behavior Disorder (RBD) showed an increased CAP rate in RBD patients compared to healthy controls, with a significant positive correlation between disease duration with total CAP time [52]. Moreover, the increase in CAP sequences was observed in phase A2 and A3 subtypes, while phase A1 subtype was significantly lower in RBD patients, as found in our PD patients. In the same perspective, in another study, CAP slow components (A1 index) were decreased in MCI subjects and, to a greater extent, in AD patients, compared to cognitively intact controls [53]. However in this last study CAP rate was decreased in MCI and AD patients, suggesting a correlation between a decreased sleep instability and cognitive decline. Worthy of mention, this finding was related to AD pathology in term of cognitive performance, rather than neurodegenerative processes themselves.

Our study confirms this hypothesis, suggesting that NREM sleep instability is present even in the early stages of Parkinson's disease, independently from concurrent motor symptoms or age. These alterations could only be detected by microstructure analysis, as standard sleep stage scoring did not prove to be adequate nor sufficiently sensitive. Precocious NREM sleep instability could reflect early alterations of neural pathways involved in NREM building-up and maintenance. In line with these results, greater sleep fragmentation was found to be associated with PD pathology, particularly Lewy Body deposition in the CNS and neuron loss in the Substantia Nigra, in older adults with pathological diagnosis of PD, independently of motor features of Parkinsonism, demographic characteristics or medical co-morbidities [54].

Moreover, neuropathology studies show that Lewy pathology increases with each advancing stage and progresses caudal-rostrally from the dorsal motor nucleus of the vagus nerve and olfactory bulb (stage 1) to the lower brainstem (stage 2), midforebrain (stage 3) and, eventually, cerebral cortex (stage 4–6) [51]. In neuropathologically defined stages 2 and 3, associated with the clinically premotor phase, Lewy body pathology is evident in the lower raphe group, the gigantocellular nucleus of the reticular formation and locus coeruleus–subcoeruleus complex. These nuclei are part of the NREM and REM sleep network, and its dysfunction could lead to REM sleep behavior disorder, a disease that frequently occurs in and can predate by decades the occurrence of PD [10]. NREM and REM sleep and wakefulness systems are mutually inhibitory and interact through a flip-flop switch model; therefore, dysfunction in one system can destabilize activity in the opposing one [55]. From this point of view, dysfunction in the NREM-promoting cell network as well as in the REM and orexyn systems could lead to NREM sleep alterations, in line with the REM/NREM instability seen in RBD and PD patients [56].

Dopaminergic medications also may play a role in sleep structure, even if data in the literature are not conclusive about NREM sleep architecture [40,41] and EEG spectral power changes [58]. In this context, our study is still not conclusive, as it does not provide evidence of any relationship between levodopa equivalent doses and sleep microstructure alterations, possibly due to the high dispersion of data and small sample.

5. Conclusion

In conclusion, polysomnography is a useful tool to evaluate the presence of sleep disorders, but standard sleep stage scoring may be not adequate to detect subtle changes in sleep microarchitecture. In this context, to our knowledge, our study is the first investigation of sleep microstructure, based on CAP analysis, in PD patients. Our main result is the demonstration of NREM sleep instability at an earlier stage of the disease and independently from concurrent motor symptoms or age. Further studies are needed to confirm these preliminary data, in particular with the evaluation of a large sample of de-novo patients that are devoid of pharmacological and motor symptoms bias.

Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.03.025.

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