Journal of Integrative Neuroscience

J. Integr. Neurosci. **2025**; 24(3): 26397
https://doi.org/10.31083/JIN26397

Original Research

Cyclic Alternating Pattern of EEG Activities and Heart Rate Variability in Parkinson's Disease Patients during Deep Sleep

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Academic Editor: Luigi De Gennaro
Submitted: 2 September 2024 Revised: 22 December 2024 Accepted: 25 December 2024 Published: 21 March 2025

Abstract

Background:Sleep disturbance and autonomic dysfunction are often found in Parkinson's disease (PD) patients, but little is known about changes in cyclic alternating patterns (CAPs) of electroencephalographic (EEG) activities and heart rate variability (HRV) during deep sleep in PD patients. **Objectives**: To investigate changes in EEG activities and HRV during CAPs and non-CAPs (NCAPs) of N3 sleep in PD patients. **Methods**: Polysomnographic (PSG) examinations were carried out on 18 PD patients and 18 healthy controls, and power spectral analysis of EEG activities and HRV during CAPs and NCAPs (the segment of sleep without CAPs for more than 60 seconds) of N3 sleep were carried out. **Results**: The percentages of N3 sleep with CAPs and CAP A1, as well as the CAP A1 index in the PD patients, were significantly smaller compared with the healthy controls. In addition, the power of α waves in NCAPs was significantly higher, while the powers of δ waves in Phase A and B of CAP A1 and A3, and NCAPs were significantly smaller. Furthermore, the durations of total δ waves and δ waves with an amplitude $\geq$75 µV were significantly shorter, and the low frequency (LF) power of HRV during CAPs and the LF/high frequency (HF) HRV ratio during both CAPs and NCAPs were significantly smaller. **Conclusions**: The changes documented in EEG activities and HRV in PD patients during CAPs and NCAPs of N3 sleep compared with healthy controls suggest that N3 sleep quality and sympathetic function are compromised in PD patients.

Keywords: Parkinson's disease; cyclic alternating pattern; heart rate variability; α wave intrusion; non-rapid eye movement sleep; autonomic nervous system

1. Introduction

Parkinson's disease (PD), one of the most common movement disorders caused by neurodegeneration, affects more than 1% of the population over the age of 60 [1]. As a typical neurodegenerative disease, PD patients often present with motor and also non-motor symptoms. It has been reported that nocturnal sleep disturbances including insomnia, reductions in rapid eye movement (REM) sleep and slow wave sleep (SWS) sleep, REM sleep behavior disorder (RBD), and excessive daytime sleepiness in most PD patients [2,3]. Additionally, autonomic dysfunction in PD patients often manifests as typical PD symptoms of constipation, cardiac arrhythmias, and orthostatic hypotension, which significantly impact patients' life quality [4,5].

A staggering 80% of PD patients might experience cognitive dysfunction over the disease course, which is attributed to the impaired quantity and quality of Non-rapid eye movement sleep stage 3 (N3) sleep [6]. In addition, alterations in N3 sleep are also correlated with a progression of PD motor symptoms [7,8]. Cyclic alternating patterns (CAPs) are periodic oscillations in non-rapid eye movement (NREM) sleep, comprising high-amplitude slow waves with a mixture of low-amplitude fast waves in Phase A and the background rhythm in Phase B. CAP A1 indicates a stable sleep while subtype A2 and A3 suggests sleep stability might be disrupted, which leads to arousals. The segment of sleep without CAPs longer than 60 seconds is regarded as non-CAP (NCAP), which is characterized by stable electroencephalographic (EEG) rhythm and fewer events associated with arousals [9]. In addition, changes in N3 sleep including a reduction in N3 sleep duration were often reported in PD patients [2,10] and there were preliminary findings of changes in CAPs during sleep in previous studies [11–13].

The autonomic system (ANS) plays crucial roles in regulating various activities such as blood pressure, digestion, stress reactions and metabolisms [14], and many non-motor symptoms of PD, such as constipation, orthostatic hypotension, and cardiac arrhythmias in PD patients, are closely associated with autonomic impairments [4,5,15]. Heart rate variability (HRV) serves as a non-invasive tool to evaluate the autonomic function and has increasingly gained attentions these days [16]. In patients with stroke, epilepsy, brain infarctions, and PD, HRV was diminished [17–19]. Further studies showed shorter mean R-R intervals and reduction of sympathetic regulation during sleep in PD patients [20,21]. However, it is still not elucidated whether the changes in HRV in PD patients were related to CAPs.

Given that EEG activities and HRV might be changed in PD patients during N3 sleep, the aims of this study were to investigate changes in EEG activities and HRV during CAPs and NCAPs of N3 sleep in PD patients.

2. Methods

2.1 Subjects

A total of 46 PD patients with main extrapyramidal symptoms and 54 healthy controls were recruited and clinically examined at the Department of Neurology of the Jiangxi Provincial People's Hospital between January 2019 to December 2022. The patients were diagnosed based on the UK Parkinson's Disease Society Brain Bank clinical criteria and graded by Hoehn and Yahr staging (1–3) [22].

Inclusion criteria included: (1) 50–70 years old; (2) apnea-hypopnea index (AHI) $<$10; (3) without dementia; (4) no sleep-related respiratory disorders; (5) no depression, anxiety and other neurological and mental disorders; (6) no sleep disorders, such as bruxism, insomnia, and narcolepsy; (7) no arrhythmia; (8) no diabetes mellitus, polyneuropathies or other disorders that could affect autonomic function; (9) without taking medications that may affect sleep and autonomic function. The subjects were not allowed to drink tea, coffee, and any beverages containing stimulants within 24 hours (Hrs) before polysomnographic (PSG) examination.

The healthy controls and patients were excluded if they had the following conditions: (1) obstructive sleep apnea with AHI $\geq$10; (2) respiratory diseases; (3) hypertension (Stage II or higher); (4) heart diseases with New York Heart Association Functional Class II or worse; (5) diabetes mellitus; (6) sleep disorders; (7) brain trauma; (8) alcohol and other substance abuses.

2.2 Polysomnographic Recordings

A computer recording system (Pro Fusion 4 system, Compumedics Limited, Abbotsford, Australia) was used to record EEG (O1-M2, O2-M1, C3-M2, C4-M1, F3-M2, F4-M1, sampling rate: 512 Hz), electrocardiographic (ECG, sampling rate: 1024 Hz), and electrooculographic (EOG; sampling rate: 512 Hz) activities. At the same time, electromyographic (EMG; sampling rate: 512 Hz) activities from jaw muscles, bilateral upper (flexors and extensor carpi radialis) and lower limb muscles (tibialis anterior muscle and gastrocnemius), peripheral oxygen saturation (SpO2) in index finger via a finger pulse oximeter (sampling rate: 16 Hz, Nonin Medical Inc, Plymouth, MN, USA), body posture via a position sensor (sampling rate: 16 Hz), snore via a snore sensor (sampling rate: 256 Hz) as well as respiration via nasal thermistor (sampling rate: 32 Hz), pressure transducer (sampling rate: 256 Hz), and thoracoabdominal plethysmography (sampling rate: 32 Hz) were also recorded during sleep overnight as previous studies [23–25]. Two infrared video recorders, which were focusing on the head and entire body, respectively, were used to monitor and record movements in the mouth, limbs, and other parts of the body during sleep to aid data analysis.

2.3 General Sleep Data Analysis

Sleep data were scored in 30 s epochs, and sleep efficiency, total sleep time, durations of NREM sleep stage 1–3 (N1-N3) and REM sleep were scored by one expert clinician and confirmed by another according to the standards established by the American Academy of Sleep Medicine (AASM) [26]. Besides, the sleep bruxism index (SBI; the number of SB events/Hr of sleep), and arousal index, periodic leg movements index (PLMI), as well as mean and minimal SpO_2, were also determined as described in previous studies [23,24]. EEG or ECG recordings were separately exacted at the preprocessing stage and analyzed using different software (see below).

2.4 CAP Scoring and Power Spectral Analysis

CAP scoring was carried out in accordance with the standards described by Parrino *et al.* [27,28]. CAPs were typically observed during NREM sleep, although they could be observed during REM sleep in severe obstructive sleep apnea patients [9,23]. Each CAP sequence lasted for 2–60 seconds and consisted of phase A (phasic EEG activities) and phase B (background EEG activities). Before the onset of CAP, there must be greater than 60 seconds of continuous NREM sleep without any CAP, except (1) before the first CAP, (2) after the transition from arousal to sleep, and (3) after the transition from REM sleep to NREM sleep. The absence of CAPs in EEG tracings for more than 60 seconds was considered to reflect NCAP [9,23].

CAPs can be divided into three subtypes, namely CAP A1, A2 and A3 based on the criteria described by Parrino *et al.* [27]. Phase A in CAP A1 (Phase A1) consisted of EEG synchrony (slow waves with high amplitudes, such as δ bursts, K-complexes, vertex sharp transients, and polyphasic bursts) accounting for 80% or more and EEG desynchrony (fast waves with low amplitudes) accounting for below 20%. Phase A in CAP A2 (Phase A2) comprised a mixture of slow and fast EEG rhythms, with EEG desynchrony (including EEG arousals) accounting for 20–50% of phase A2. Phase A in CAP A3 (Phase A3) was dominated by fast, low-voltage rhythms, with EEG desynchrony accounting for greater than 50% of phase A3, and CAP sequences containing motor artifacts have also been categorized as CAP A3 [9,23]. Since CAP A1 is usually considered to be associated with stable sleep while CAP A2 and A3 are often considered to be associated with unstable sleep, combine

Table 1. Main parameters of NCAP and CAP in N3 sleep.

Parameters	Definitions
CAP index	# of CAPs/Hr of N3 sleep
CAP A1 index	# of CAP A1/Hr of N3 sleep
CAP A2 index	# of CAP A2/Hr of N3 sleep
CAP A3 index	# of CAP A3/Hr of N3 sleep
CAP A1/CAP (%)	CAP A1 as the proportion of total # of CAPs
CAP (A2+A3)/CAP (%)	CAP A2 and A3 as the proportion of total # of CAPs
Total CAP Duration	A sum of all CAPs in duration in N3 sleep
Total NCAP Duration	A sum of all NCAPs in duration in N3 sleep
NCAP/N3 (%)	Total duration of NCAPs as the percentage of N3 sleep time
CAP/N3 (%)	Total duration of CAPs as the percentage of N3 sleep time
Phase A/N3 (%)	Total duration of phase A of CAPs over N3 sleep time in percentage
Phase B/N3 (%)	Total duration of phase B of CAPs over N3 sleep time in percentage
CAP A1/N3 (%)	Total duration of CAP A1 over N3 sleep time in percentage
CAP (A2+A3)/N3 (%)	Total duration of CAPs A2 and A3 over N3 sleep time in percentage
A1/A (%)	Phase A1 duration over total phase A duration in percentage
(A2+A3)/A (%)	Phase A2 and A3 duration of over the total phase A duration in percentage
B1/B (%)	Phase B1 duration over total phase B duration in percentage
(B2+B3)/B (%)	Phase B2 and B3 duration of over total phase B duration in percentage
Phase A1/B1	Ratio of duration of phase A1 to phase B1
Phase A2/B2	Ratio of duration of phase A2 to phase B2
Phase A3/B3	Ratio of duration of phase A3 to phase B3
K complex Index (events/h)	
Index in CAP A1	# of K complexes in CAP A1/Hr of N3 sleep
Index in CAP A2	# of K complexes in CAP A2/Hr of N3 sleep
Index in CAP A3	# of K complexes in CAP A3/Hr of N3 sleep
Index in NCAP	# of K complexes in NCAP/Hr of N3 sleep
Total index	# of K complexes during N3 sleep/Hr of N3 sleep

CAP, Cyclic alternating pattern; Hr, Hour; NCAP, Non-cyclic alternating pattern; N3, Non-rapid eye movement sleep stage 3; #, Number.

A2 and A3, as well as B2 and B3 are carried out [23,27]. Some CAP parameters were shown in Table 1.

The EEG data were filtered with a high-pass filter and a low-pass filter (Pro Fusion 4 system, Compumedics Limited, Abbotsford, Australia) set at 0.01 Hz and 35 Hz, respectively, and EEG segments obscured by movements and EMG artifacts were excluded [23]. The power spectral analysis of CAP sequences and NCAPs was based on Fast Fourier transform with 0.25 Hz resolution and cosine window smoothing, and was carried out with the Brainstorm program version 2.0 (GNU GPLv2, McGill University, Montréal, Québec, Canada).

Frontal EEG activities were reported to be more sensitive for evaluation of changes in EEG activities caused by aging [29], CPAP treatment [29,30], and neurodegenerative diseases [31]. In addition, previous study did not find any significant lateralization of EEG activity [32]. Therefore, EEG activities recorded from left frontal cortex (F3-A2) were selected for further analysis as previously described [32–34]. The power spectral density of frontal EEG activities associated with N3 sleep was analyzed and the absolute and relative power of δ (0–3.99 Hz), θ (4–7.99 Hz), α (8–13 Hz) and β (13.01–30 Hz) waves were calculated [35]. The relative EEG power was calculated with the absolute power of a particular type of EEG waves divided by the total absolute power of four types of EEG waves, since it has been reported that this calculation may reflect the contribution of the activities of a particular type of EEG wave to the sum of the absolute powers of the four types of EEG waves [35]. In accordance with a previous study [36], three or more oscillations of α waves in a series (longer than 0.3 s) with amplitudes exceeding 0.8 µV were analyzed to examine changes in α waves in the PD patients. In addition, δ waves (with frequency from 0 to 3.99 Hz) in N3 sleep were manually selected and marked according to their amplitudes (i.e., $<$75 µV and $\geq$75 µV), given that N3 scoring requires the presence of δ wave activity with an amplitude of at least 75 µV in at least 20% of the epoch according to the criteria established by the AASM [26], and the duration of δ waves with different amplitudes were calculated. Then, the duration of δ waves with amplitudes of $<$75 µV, and $\geq$75 µV divided by the duration of N3 sleep were determined as the percentage of N3 sleep occupied by δ waves with amplitudes of $<$75 µV and $\geq$75 µV, respectively.

2.5 HRV Frequency Domain Analysis

The R-R intervals were determined by using the software HRV analysis version 1.1 (SNA-EPIS laboratory, Jean Monnet University, Saint-Etienne, France). HRV was analyzed in the frequency domain by using the Fast Fourier transform and power spectral analysis of HRV was carried out using the Welch periodogram algorithm with a Hamming window of 256 points, an overlap of 50%, and an accuracy of 256 points/Hz as described by Pichot *et al.* [37]. The spectral HRV components were divided into two frequency bands: (1) high frequency (HF) band (0.15 to 0.40 Hz), (2) low frequency (LF) band (0.04 to 0.15 Hz). The normalized spectral indices were defined as LFnu = LF/(LF + HF) and HFnu = HF/(LF + HF) [38]. The LF of HRV mainly reflects sympathetic regulation and the HF of HRV reflected parasympathetic regulation, plus the LF/HF ratio reflects sympathovagal balance [39,40].

2.6 Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) (Version 26, IBM, Armonk, NY, USA). Data with normal distributions in the PD patients and healthy controls were expressed as mean $\pm$ standard error of the mean (SEM) and the Student's t-test was used for comparisons between the two groups. On the other hand, data with skew distributions in the PD patients and healthy controls were expressed as median (minimum-maximum) and the Mann-Whitney U test was used for comparisons between the two groups. $p < 0.05$ was considered to be statistically significant.

3. Results

3.1 Demographics and Sleep Characteristics

A total of 100 subjects were recruited and 64 subjects (28 PD patients and 36 healthy controls) including 18 subjects with insomnia, 43 subjects with obstructive sleep apnea, and 3 subjects with arrhythmia were excluded. Thus, 18 early-stage PD patients (8 males and 10 females) aged 58–69 (median: 62) with H-Y staging of 1–3, and 18 healthy controls (9 males and 9 females) aged 55–67 (median: 60) were included in the study. PD patients were under regular dopaminergic medications (L-dopa/carbidopa, or plus either ropinirole, pramipexole or entacapone). Daily L-dopa equivalent dose was calculated according to the previous study [41]. The PD patients had a disease duration of 2.5 $\pm$ 0.5 years (mean $\pm$ SEM) from the first symptom appearance. Besides, three PD patients also had rapid eye movement sleep behavior disorder (RBD).

Table 2 summarizes demographic data and general sleep parameters of the PD patients and healthy controls. No significant differences in BMI and AHI were found between the two groups. The total sleep time, sleep efficiency, durations of N3 and REM sleep, and the ratio of REM sleep duration to total sleep time in percentage in the PD patients were significantly shorter or smaller than those in the healthy controls while the wakefulness after sleep onset (WASO) and the ratio of N2 sleep duration to total sleep time in the PD patients were significantly longer or higher than those in the healthy controls.

3.2 CAP Parameters in the PD Patients

As shown in Table 3, CAP index and CAP subtype A1 index in the PD patients were significantly lower, while subtype A2 and A3 indices in the PD patients were significantly higher than those in the healthy controls. In addition, the total CAP duration and CAP/N3 during N3 sleep in the PD patients were significantly shorter or smaller. In contrast, NCAP duration and NCAP/N3 were significantly longer and higher in the PD patients, respectively, than those in healthy controls.

In the PD patients, phase A/N3, phase B/N3 and CAP A1/N3 were significantly smaller while CAP (A2+A3)/N3 was significantly greater than those in the healthy controls. Similarly, in the PD patients, CAP A1/CAP, A1/A and B1/B were significantly smaller and CAP (A2+A3)/CAP, A2+A3)/A and (B2+B3)/B were significantly greater than those in the healthy controls. In addition, phase A2/B2 and phase A3/B3 in the PD patients were significantly greater than those in the healthy controls. Furthermore, the durations of phase A2 and phase A3, but not phase A1, were significantly longer in the PD patients than those in the healthy controls while the durations of phase B1, B2 and B3 were not significantly different between the two groups (Table 3).

The K complex index in CAP A3 was significantly higher in the PD patients, but there were no significant differences in K complex index, K complex index in CAP A1 and A2 as well as K complex index in NCAP of the PD patients compared to the healthy controls (Table 3).

3.3 EEG Power in CAPs in the PD Patients during N3 Sleep

As shown in Fig. 1, in phases A1, B1 and A3, the absolute power of δ waves was significantly smaller in the PD patients than that in the healthy controls, but in phase A2, B2 and B3, it was not significantly different between the two groups. In contrast, in phases A3, B2, and B3, the absolute power of θ waves was significantly greater in the PD patients than that in the healthy controls, but in phases A1, A2, and B1, it was not significantly different between the two groups.

The absolute power of α waves in any phases of CAPs, unlike that of other EEG waves in the PD patients was not significantly different from that in the healthy controls. In contrast, in phases A1–A2 and B1–B3, the absolute power of β waves in the PD patients was significantly greater than that in the healthy controls, but in phase A3, it was not significantly different between the two groups.

In phases A1, B1–B2 and A3, relative power of δ waves in the PD patients was significantly smaller and rel-

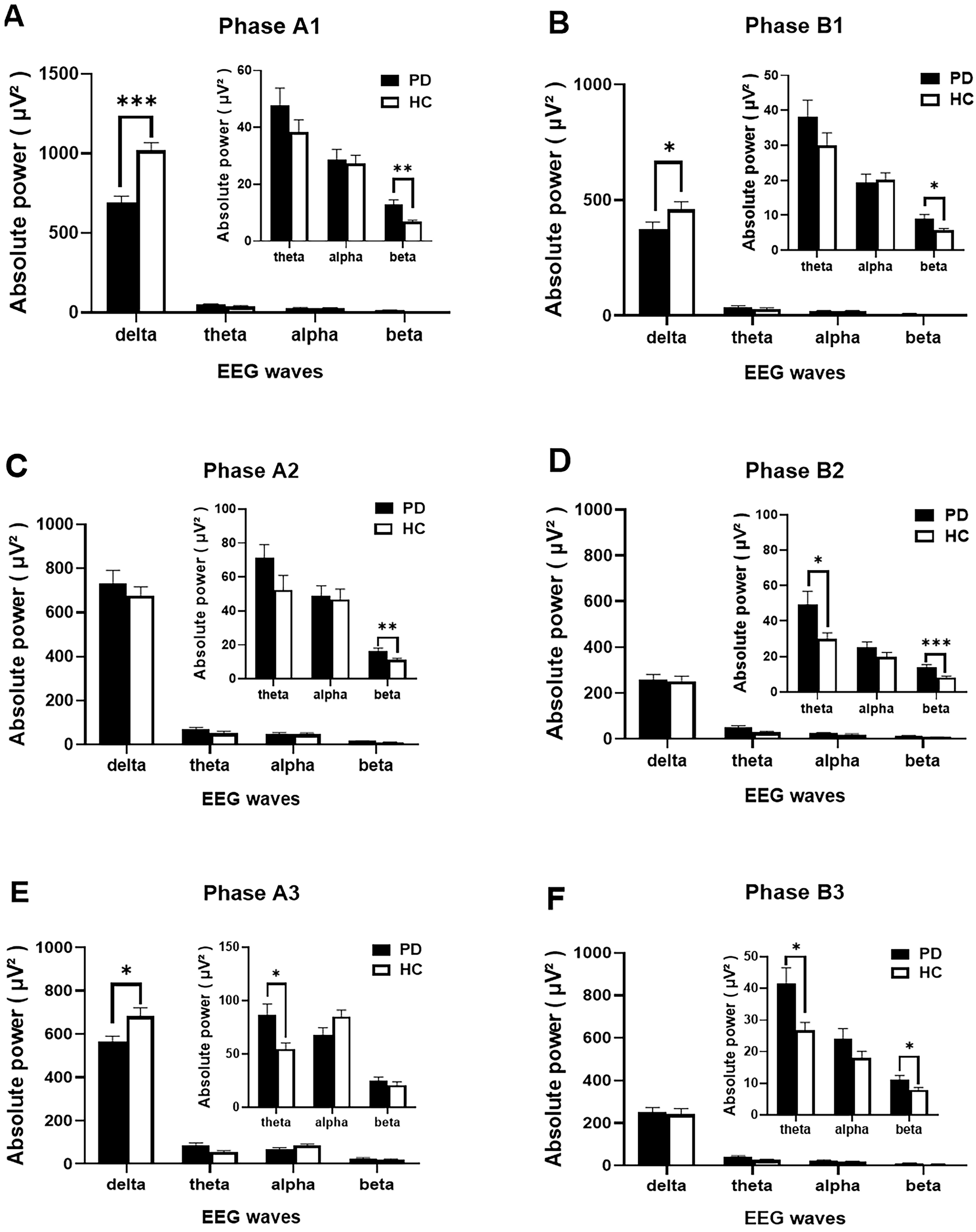

Fig. 1. Comparisons of the absolute power of δ, θ, α and β waves in phases A1–A3 (A,C,E) and B1–B3 (B,D,F) of CAPs during N3 sleep in the Parkinson's disease (PD) patients and healthy controls (HC). EEG, Electroencephalographic; Student's *t*-test. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

ative power of θ waves in the PD patients was significantly greater than those in the healthy controls, but in phases A2 and B3, both were not significantly different between the two groups. The relative power of α in the PD patients was not significantly different from that in the healthy controls during any phases of CAPs (Fig. 2). However, the relative power of β waves in phase A1 and B1, but not other phases of CAPs, was significantly greater in the PD patients.

Table 2. Demographic and general sleep characteristics in the PD patients and healthy controls.

Variables	PD patients	Healthy controls	*p*
Age (years)	62 (58–70)	60 (55–67)	0.10
Male	8	9	
Female	10	9	
BMI, Kg/m^2	22.14 ± 0.49	23.67 ± 0.58	0.21
H-Y stage	2 (1–3)		
Duration of disease from being diagnosed (years)	2.5 ± 0.5		
L-Dopa equivalent dose (mg/day)	454.7 ± 54.9		
AHI (events/h)	2.0 (0.3–8.3)	2.2 (0.2–7.4)	0.61
Mean heart rate during sleep	62 (53–75)	65 (57–75)	0.46
Total sleep time (min)	360.7 ± 12.2	421.3 ± 15.7	<0.01
N1 (min)	27.0 ± 3.6	36.6 ± 4.2	0.11
N2 (min)	189.4 ± 10.7	192.0 ± 12.3	0.87
N3 (min)	87.5 ± 7.6	107.5 ± 5.8	<0.05
REM (min)	56.8 ± 4.7	85.3 ± 2.4	<0.001
N1 (%)	7.5 ± 1.0	8.6 ± 0.9	0.44
N2 (%)	52.2 ± 1.9	45.0 ± 1.7	<0.01
N3 (%)	24.5 ± 2.0	25.9 ± 1.5	0.55
REM (%)	15.8 ± 1.3	20.5 ± 0.7	<0.01
WASO, min	67.6 ± 6.0	38.8 ± 3.4	<0.001
Sleep efficiency (%)	80.3 ± 1.6	88.5 ± 1.2	<0.001
Arousal index	20.1 ± 1.5	15.2 ± 1.3	<0.05
SBI (events/h)	2.7 ± 0.3	3.2 ± 0.4	0.39
PLMI (events/h)	14.9 ± 3.0	10.7 ± 2.0	0.33
Mean SpO2 (%)	96 (93–98)	97 (95–98)	0.25
Minimal SpO2 (%)	90 (87–93)	91 (89–93)	0.17

Data are expressed as mean ± SEM for variables with a normal distribution and examined with the Student's *t*-test, and data are expressed as median (min–max) for variables with a skewed distribution and examined with the Mann-Whitney U test.

AHI, Apnea-hypopnea index; BMI, Body Mass Index; N1–N3, Non-rapid eye movement sleep stage 1-3; PD, Parkinson's disease; PLMI, Periodic leg movements index; REM, Rapid eye movement sleep; SBI, Sleep bruxism index; WASO, Wakefulness after sleep onset; SpO2, oxygen saturation of peripheral capillary blood.

3.4 EEG Power in NCAP Phase in the PD Patients during N3 Sleep

In the PD patients, the absolute power of δ waves was significantly smaller while the absolute power of θ waves was not significantly different, and the absolute power of α and β waves was significantly greater in NCAP phase of N3 sleep in comparison with those in the healthy controls (Fig. 3). Meanwhile, the relative power of δ waves was significantly smaller while the relative power of θ, α, and β waves was significantly greater in NCAP of N3 sleep in the PD patients.

3.5 Alpha Waves during N3 Sleep in the PD Patients

As described in the previous study [42], α waves were observed in the PD patients to be present throughout N3 sleep, independent of δ wave activities, which was considered to reflect a tonic α pattern in the PD patients, while low α wave activity was observed in the healthy controls.

The total duration of the selected α waves (i.e., three or more oscillations of α waves in a series, longer than 0.3 s, >0.8 µV) and the proportion of N3 sleep with the α waves in the PD patients were significantly greater than those in the healthy controls. In addition, the mean frequency of the selected α waves in the PD patients was significantly faster than that in the healthy controls (Table 4).

3.6 Delta Wave Amplitude in PD Patients During NREM Sleep Stage 3

As shown in Fig. 4, the percentage of N3 sleep containing δ waves with amplitudes ≥75 µV, but not <75 µV, was significantly smaller in the PD patients compared with that in the healthy controls (Fig. 4A). In addition, the proportion of N3 sleep occupied by total δ waves was also significantly smaller in the PD patients (Fig. 4B).

Table 3. CAPs parameters during N3 sleep in the PD patients.

CAP parameters	PD patients	Healthy controls	*p*
CAP index (events/h)	60.84 ± 4.42	75.39 ± 3.43	<0.05
CAP A1 index (events/hr)	48.37 ± 3.87	74.34 ± 3.68	<0.001
CAP A2 index (events/hr)	7.25 (1.05–18.00)	0 (0–1.74)	<0.001
CAP A3 index (events/hr)	2.61 (0.64–11.68)	0 (0–1.60)	<0.001
CAP A1/CAP (%)	88.56 ± 2.81	99.08 ± 0.30	<0.001
CAP (A2+A3)/CAP (%)	11.44 ± 2.81	0.92 ± 0.30	<0.001
Total CAP Duration (min)	52.75 ± 5.43	81.04 ± 7.01	<0.01
Total NCAP Duration (min)	28.45 ± 4.45	16.66 ± 2.25	<0.001
NCAP/N3 (%)	32.51 ± 2.90	15.59 ± 1.90	<0.001
CAP/N3 (%)	59.72 ± 2.33	74.28 ± 3.92	<0.01
Phase A/N3 (%)	24.34 ± 1.68	35.46 ± 2.03	<0.001
Phase B/N3 (%)	35.38 ± 1.83	38.82 ± 2.70	0.31
CAP A1/N3 (%)	47.98 ± 2.98	73.63 ± 3.96	<0.001
CAP (A2+A3)/N3 (%)	11.74 ± 1.51	0.64 ± 0.21	<0.001
Total Duration (min)			
Phase A	21.01 ± 2.06	38.30 ± 2.97	<0.001
Phase A1	17.11 ± 1.73	38.03 ± 2.94	<0.001
Phase A2	2.64 ± 0.36	0.12 ± 0.04	<0.001
Phase A3	1.27 ± 0.31	0.15 ± 0.05	<0.01
Phase B	31.74 ± 3.68	42.74 ± 4.56	<0.05
Phase B1	25.48 ± 3.48	42.25 ± 4.66	<0.01
Phase B2	4.73 ± 1.04	0.26 ± 0.10	<0.001
Phase B3	1.52 ± 0.42	0.24 ± 0.08	<0.001
Average Duration (s)			
Phase A1	12.66 ± 0.98	11.87 ± 0.57	0.49
Phase A2	10.70 ± 0.82	6.70 ± 1.38	<0.05
Phase A3	10.35 ± 0.92	6.04 ± 1.44	<0.05
Phase B1	22.31 ± 2.38	18.07 ± 1.41	0.13
Phase B2	17.40 ±2.47	11.93 ± 2.56	0.24
Phase B3	15.68 ± 2.15	11.68 ± 2.27	0.30
A1/A (%)	81.16 ± 2.23	99.29 ± 0.23	<0.001
(A2+A3)/A (%)	18.84 ± 2.23	0.71 ± 0.23	<0.001
B1/B (%)	78.17 ± 3.55	98.81 ± 0.42	<0.001
(B2+B3)/B (%)	21.83 ± 3.55	1.19 ± 0.42	<0.001
Phase A/B (%)	72.13 ± 6.72	96.54 ± 6.63	<0.05
Phase A1/B1 (%)	77.16 ± 8.22	97.17 ± 6.79	< 0.05
Phase A2/B2 (%)	74.13 ± 8.85	50.24 ± 6.83	0.12
Phase A3/B3 (%)	81.23 ± 7.11	66.16 ± 3.47	0.25
K complex Index (events/hr)			
Index in CAP A1	16.21 (2.85–41.00)	20.94 (4.44–33.96)	0.24
Index in CAP A2	0.75 (0–6.34)	0.61 (0–2.79)	0.68
Index in CAP A3	1.64 (0–5.92)	0.51 (0–3.58)	<0.05
Index in NCAP	5.50 (1.24–19.65)	2.93 (0–10.80)	0.10
Total index	25.90 (4.59–50.76)	25.29 (7.27–39.01)	0.85

Student's *t*-test was used to compare data with a normal distribution (shown as mean ± SEM), and Mann-Whitney U test was used to compare data with a skewed distribution [shown as median (min–max)].

3.7 HRV During CAPs and NCAPs, and N3 Sleep in the PD Patients

As shown in Table 5, there were no significant differences in RR intervals and HF power of HRV in all CAP subtypes between the PD patients and healthy controls. In contrast, LF power of HRV during CAP A1-A3 in the PD patients was significantly lower than that in the healthy controls. In addition, LFnu and HFnu of HRV during CAP A1

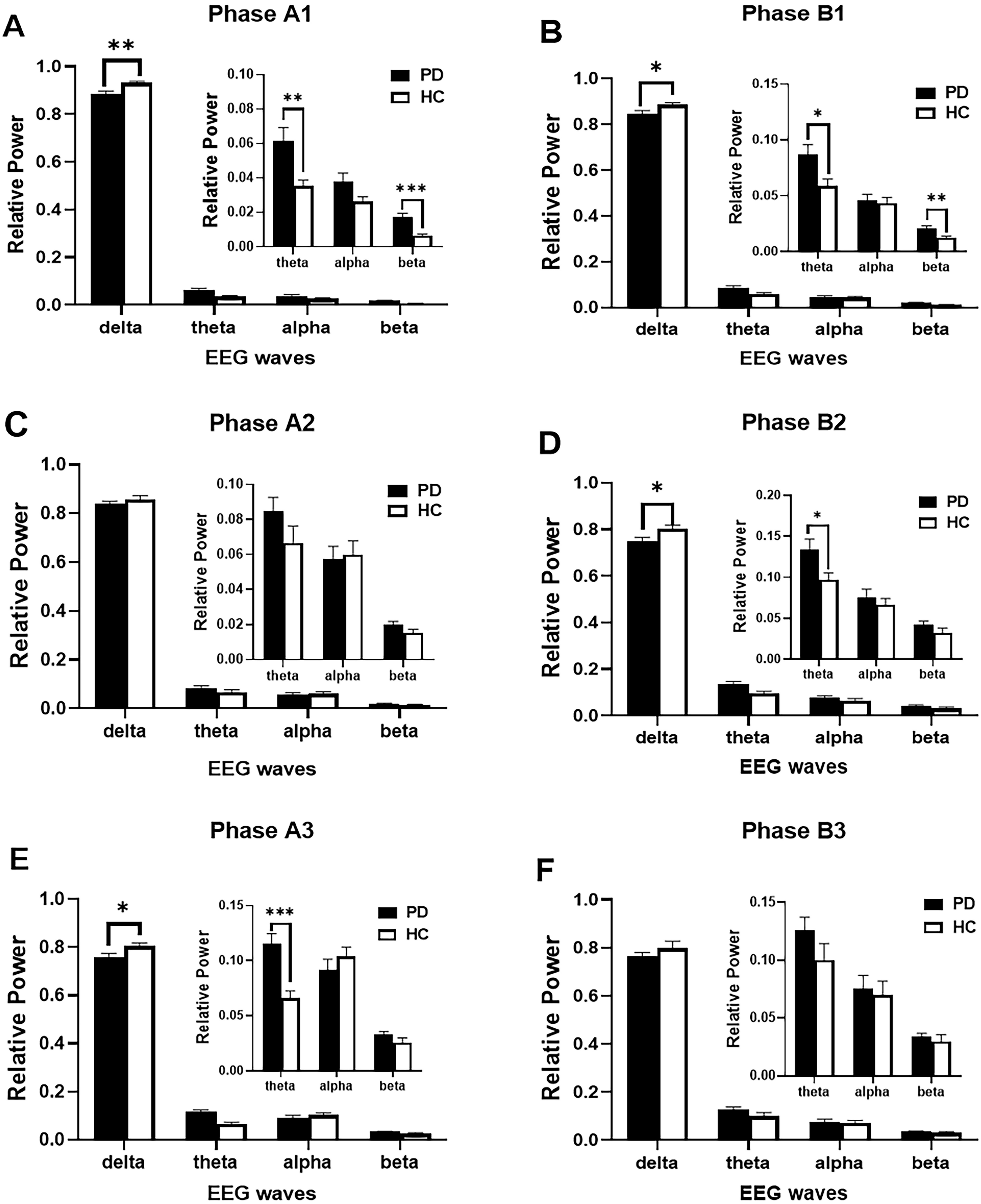

Fig. 2. Comparisons of the relative power of δ, θ, α and β waves in phases A1–A3 (A,C,E) and B1–B3 (B,D,F) of CAPs during N3 sleep in the PD patients and HC). Student's *t*-test. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

and A2 was significantly lower and higher than those in the healthy controls, respectively. Nevertheless, no significant differences in LFnu and HFnu during CAP A3 were found between the two groups. Furthermore, the LF/HF ratio during CAP A1-A3 in the PD patients was significantly lower than that in the healthy controls.

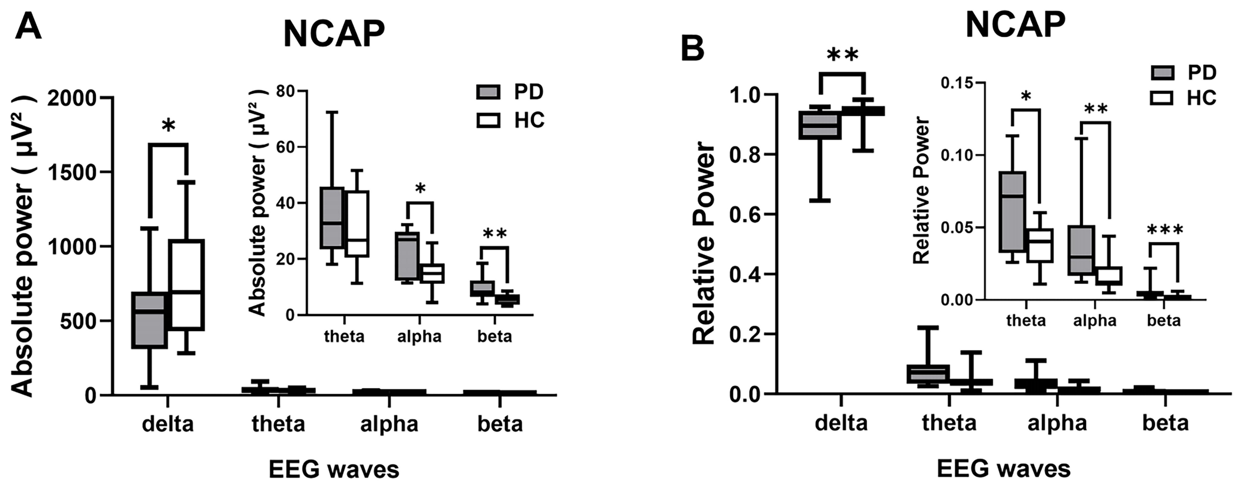

Fig. 3. Comparisons of the absolute (A) and relative power (B) of δ, θ, α and β waves in NCAP phase of N3 sleep in the PD patients and HC. Mann-Whitney U test. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 4. Alpha waves during N3 sleep in the PD patients.

Alpha waves	PD patients	Healthy controls	p
Total duration, min	55.3 (20.9–104.7)	8.5 (2.8–29.3)	<0.001
N3 sleep with α waves, %	62.37 $\pm$ 3.11	14.61 $\pm$ 1.68	<0.001
Mean frequency, Hz	10.98 (10.38–11.55)	10.40 (9.29–10.70)	<0.001

Student's t-test was used for comparisons of data with a normal distribution (shown as mean $\pm$ SEM), and Mann-Whitney U test was used for comparisons of data with a skewed distribution [shown as median (min-max)].

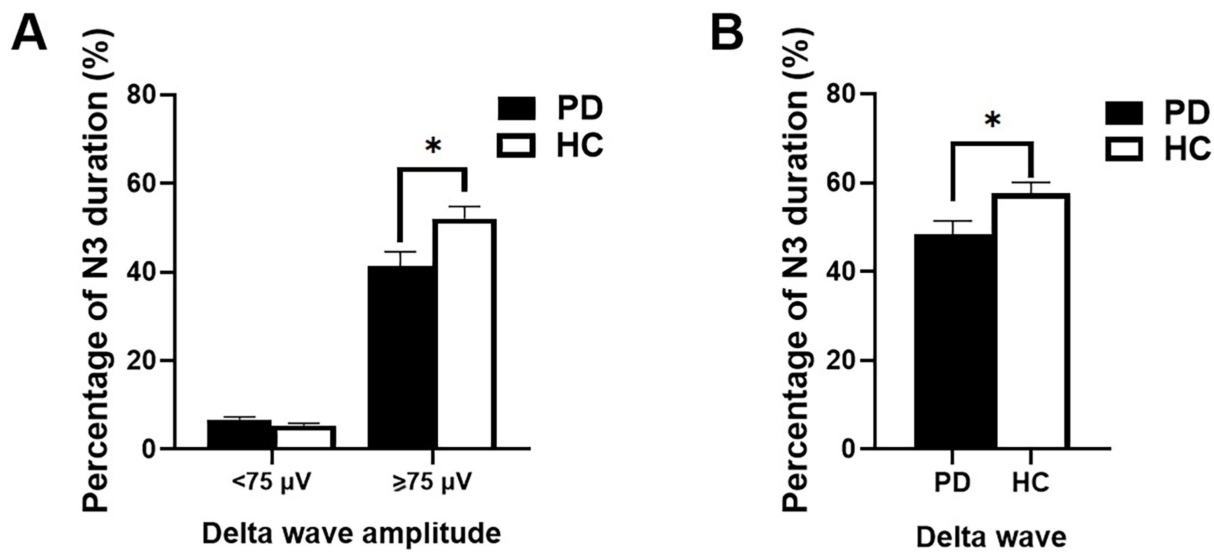

Fig. 4. Percentages of N3 sleep containing δ waves with amplitudes of <75 µV and $\geq$75 µV, respectively (A), and by all δ waves (B) in the PD patients and HC. Student's t-test. *$p < 0.05$.

During NCAP and N3 sleep, RR intervals, and HF and LF power of HRV in the PD patients were not significantly different from those in the healthy controls. In contrast, LFnu was significantly lower and HFnu was significantly higher in the PD patients than those in the healthy controls. Furthermore, the LF/HF ratio was significantly lower in the PD patients than that in the healthy controls.

4. Discussion

Sleep disturbance is prevalent in PD patients, and greatly decreases their life quality [1]. In this study, the authors systematically examined N3 sleep especially CAPs and NCAPs and their associated EEG activities and HRV in the PD patients compared to the healthy controls and found

Table 5. Comparisons of HRV parameters between the PD patients and healthy controls.

	Variable	PD patients	Healthy controls	*p*
CAP				
A1		971.5 (719.4–1107.9)	964.0 (831.4–1243.6)	0.59
A2	RR, ms	973.2 (726.0–1145.9)	967.3 (775.2–1300.0)	0.88
A3		962.3 (777.3–1139.1)	974.5 (842.4–1147.0)	0.78
A1		833.8 (265.3–1527.6)	955.3 (241.7–1761.5)	0.14
A2	HF, ms^2	646.6 (310.6–1694.1)	790.3 (215.3–1574.1)	0.47
A3		850.6 (266.9–1555.3)	837.5 (231.0–1789.6)	0.58
A1		360.1 (58.0–760.4)	848.0 (233.3–1058.2)	<0.01
A2	LF, ms^2	160.1 (34.5–282.2)	430.4 (47.0–582.9)	<0.01
A3		224.0 (65.6–513.1)	296.3 (109.5–714.7)	<0.05
A1		86.6 (60.6– 96.7)	64.3 (31.5–83.7)	<0.01
A2	HFnu, %	81.7 (57.4– 93.7)	60.0 (6.2–85.5)	<0.001
A3		73.9 (51.4– 94.2)	72.9 (41.1–85.7)	0.32
A1		13.4 (3.3–39.4)	35.7 (16.3–68.5)	<0.01
A2	LFnu, %	18.3 (6.3–42.7)	40.0 (14.5–93.8)	<0.001
A3		26.1 (5.8–48.5)	27.1 (14.3–85.7)	0.32
A1		0.22 (0.04–0.63)	0.41 (0.15–1.46)	<0.05
A2	LF/HF	0.23 (0.05–0.45)	0.59 (0.18–1.63)	<0.01
A3		0.25 (0.10–0.80)	0.36 (0.21–1.02)	<0.05
NCAP				
	RR, ms	930.4 (779.5–1055.2)	933.7 (797.1–1114.5)	0.67
	HF, ms^2	680.7 (280.0–1381.1)	572.5 (287.3–1254.0)	0.63
	LF, ms^2	120.8 (31.4–295.5)	217.2 (60.7–318.8)	0.25
	HFnu, %	85.2 (77.2–94.8)	80.3 (42.2–82.1)	<0.05
	LFnu, %	14.8 (5.2–22.8)	19.7 (17.9–57.8)	<0.05
	LF/HF	0.18 (0.17–0.31)	0.32 (0.23– 0.92)	<0.001
N3 Sleep				
	RR, ms	1003.8 (819.1–1109.7)	932.4 (827.1–1261.2)	0.53
	HF, ms^2	783.8 (200.8–1584.0)	743.3 (510.2–1439.8)	0.77
	LF, ms^2	226.3 (133.8–526.0)	298.1 (77.7–772.5)	0.13
	HFnu, %	80.7 (65.0–91.0)	72.2 (56.7–84.7)	<0.01
	LFnu, %	19.3 (9.0–35.0)	27.8 (15.3–43.3)	<0.01
	LF/HF	0.30 (0.11–0.6)	0.52 (0.16–0.98)	<0.05

Data were shown as median (min–max) and examined with the Mann-Whitney U test. RR, RR interval; HRV, heart rate variability; HF, high frequency; LF, low frequency; LFnu, low frequency power of heart rate variability expressed in normal units; HFnu, high frequency power of heart rate variability expressed in normal units.

in the PD patients, the N3 sleep duration, proportion of N3 sleep occupied by CAPs and CAP A1, as well as CAP A1 index were significantly smaller while the proportion of N3 sleep occupied by CAP A2 and A3, and NCAP, as well as CAP A2 and A3 indices were significantly greater. In addition, α waves intrusion in NCAP and greater β wave power in most of CAP phases and NCAP were found, and δ wave powers in CAP A1 and A3 and δ wave amplitudes were significantly smaller. Furthermore, LF power of HRV during CAPs and LF/HF ratio during CAPs and NCAPs in N3 sleep were significantly smaller than those in the healthy controls. These findings suggest quality of N3 sleep and sympathetic function are compromised in the PD patients.

The current study has documented sleep disturbance in the PD patients such as shorter total sleep time and N3 and REM sleep, longer WASO and N2 sleep, and lower sleep efficiency (Table 2). These findings are in line with previous studies [3,13,43] and indicate that sleep disturbance, as a non-motor symptom in the PD patients, is very common. In addition to shorter N3 sleep, the proportion of N3 sleep containing CAPs and CAP A1, as well as CAP A1 index in the PD patients was significantly smaller in the current study (Table 3). CAP is a form of periodic EEG activity that may signify sleep disturbance or sleep instability and contribute to arousals in both physiological and pathological conditions [9,27]. CAP A1 is thought to be associated with deeper and more efficient SWS, which promotes phase-amplitude coupling and synaptic plasticity processes, as well as the brain's efforts to maintain stable sleep [23,27]. It has been reported that a positive correlation occurs between CAP A1 and frontal cognitive functions such as language learning and memory processes [5,7]. Decreased CAP A1 indicate that N3 sleep in the patients is disturbed and becomes less stable. Previous studies have shown alternation in sleep microstructure such as CAPs and CAP A indices even in patients with an early stage of PD [11–13]. For example, it was found that CAP rate (Duration of CAPs/Duration of NREM sleep) as well as CAP index in the PD patients were significantly decreased, and CAP metrics in the PD patients were significantly correlated with reduced norepinephrine transporter density in arousal prompting nuclei (i.e., locus coeruleus, raphe nuclei) in the brainstem as well as arousal propagating brain structures such as temporal cortex and thalamus. These findings suggest a more severely altered microstructure than macrostructure of sleep in PD patients, which might be associated with widespread dysfunction of the noradrenergic arousal system [12]. Furthermore, the proportion of N3 sleep containing CAP A2 and A3, and NCAP, as well as CAP A2 and A3 indices were found to be significantly greater in the PD patients (Table 3). CAP A2 and A3 (especially CAP A3) are positively correlated with AHI in obstructive sleep apnea (OSA) patients, SB index in SB patients, and periodic limbic movement index in restless leg patients [44,45], and are always linked with activities that promote arousals and sleep segmentations [46,47]. These findings further indicate sleep instability in PD patients.

CAP A1 is generally considered to be related to the establishment and maintenance of stable sleep that facilitates phase-amplitude coupling and synaptic plasticity processes, and phase A1 predominantly comprises slow EEG waves in the frontal cortex, which is associated with a strengthened network and enhanced cognitive function. Phase A1 was found to be positively correlated with cognitive functions such as memory and language learning, and δ oscillation during N3 sleep might contribute to memory consolidation [23,27]. In the current study, the powers of δ waves in CAP A1 and NCAP (Figs. 1,2,3), and durations and amplitudes of δ waves in N3 sleep (Fig. 4) were all significantly reduced. These findings suggest that decreased δ wave duration and amplitude in N3 sleep, and decreased δ power of CAP A1 and NCAP of N3 sleep in PD patients might have a negative effect on the patients' cognitive functions.

CAP A2 is a form of CAP occurring between unstable sleep related to CAP A3 and stable sleep related to CAP A1. In the current study, it was found in the PD patients significantly greater CAP A2 index (Table 3) and β wave power, but not significantly different δ, θ and α wave power, in CAP A2 compared to the healthy controls (Figs. 1,2). These changes might be associated with poor sleep quality in PD patients.

CAP A3 is often related to incidents during sleep that increase sleep fragments and arousals such as movements and OSA [23,27]. In the current study, significantly more CAP A3 and greater absolute and relative power of θ waves of CAP A3, smaller absolute power of δ waves were found in the PD patients. Phase A3 is inversely related to motor sequences and planning while phase A2 is inversely correlated with cognitive task performance [48]. The decrease in CAP A1 and the increase in CAP A2 and A3 were consistent with decreases in cognitive functions in the PD patients.

In the current study, α wave intrusion [42] as a demonstration of prolonged duration of α waves and a significantly higher proportion of N3 sleep containing α waves was found in the PD patients (Table 4). Alpha waves appear most predominant over occipital areas and have been well studied during wakefulness, with increased activities by eye closing and decreased by eye-opening. During sleep, α waves usually appear during unstable sleep, which recur periodically over sleep [49,50]. Increased α activity can directly result from abnormal inputs to thalamocortical loops from disrupted basal ganglia [51] and in this case, an episodic α rhythm occurs simultaneously with δ activity (phasic α sleep pattern). This type of α intrusion into stage N3 is often associated with psychiatric diseases, which commonly manifests with a general feeling of chronic, somatic malaise and fatigue [52]. However, no phasic α sleep pattern [42] was observed in the present study. Instead, a tonic α pattern was found in the PD patients and a low α pattern in the healthy controls. All of these patterns were first defined in fibromyalgia patients and the degree of α intrusion has been shown to correlate with pain and psychological distress [42]. Such continuous α intrusion might contribute to sleep instability and mental disturbance in PD patients.

In the current study, increased α spectral power was only found in NCAP, but not in CAPs although the duration of α waves and proportion of N3 containing α waves were increased in the PD patients. NCAP in N3 sleep is considered a stable sleep pattern associated with many functions such as clearing waste from the brain [27,53]. Alpha waves intrusion and reduction in the number and amplitude of δ waves might impair clearance of wastes (e.g., β amyloid) from the brain and other brain functions [54]. Furthermore, the frequency of α waves during N3 sleep in the PD patients was significantly higher than that in the healthy controls, which might represent disturbed SWS in the PD patients. A previous finding showed increased α and sigma activities during N2 sleep in drug-naive PD patients, which were at three main frequencies: around 8.6 Hz (slow α), around 12.5 Hz (fast α/slow sigma), and around 15 Hz (fast sigma) [51]. Consistent with the previous study [51], the current study showed abundant α wave intrusions with higher frequencies during N3 sleep in the PD patients treated with L-dopa/carbidopa, or plus either ropinirole, pramipexole or entacapone. Both of the studies implied a disrupted NREM sleep in early-stage PD patients. Similarly, the α wave intrusion was also reported to present in patients with depression, anxiety, and chronic pain disorders like fibromyalgia, even with COVID-19 survivors [42,55,56]. The increased α wave frequency would further cause sleep instability and EEG desynchronization in N3 sleep, which might lead to reduced abilities for removal of wastes from the brain and promotion of PD progression.

At the same time, a significantly greater power of β waves was found in CAP A1, A2, and NCAP of N3 sleep in the PD patients. Beta wave activities were found to be linked to motor impairment and dopaminergic tone in PD patients [57,58], which could be suppressed by dopaminergic medications and deep brain stimulation. The degree of suppression of β waves has been found to be correlated with motor symptom improvement [59,60]. Previous studies showed physiological β wave activities consisted of short-lived phasic bursts in the cortico-basal ganglia motor loop [61,62], and pathological β wave activities in PD patients consisted of phasic bursts with longer durations, which was less frequently found in the PD patients with dopaminergic medications [63]. Excessive EEG desynchronization, along with increased CAP A3 during N3 sleep might reflect worsened sleep instability in the PD patients.

HRV is a noninvasive tool to evaluate the autonomic functions [16]. Attenuated HRV has been found during daytime and night in PD patients, strongly reflecting the blunted autonomic nervous system [21]. Orthostatic hypotension is a common symptom reflecting impairments in the autonomic system in PD patients [64]. In addition, exercise-evoked sympathetic activation is decreased in PD patients irrespective of dopaminergic mediations. Finally, PD patients show reduced LF power of HRV, which can be considered to reflect compromised sympathetic modulation of vascular tone [65,66]. HRV impairment could also be more overt in PD patients with worse motor symptoms [67], reminding concomitant changes of the autonomic system with motor system. In the present study, the authors focused on HRV during N3 with consideration of CAPs and found a significantly lower LFnu and LF/HF ratio but no significant differences in RR interval, LF and HF power of HRV during N3 sleep and NCAP in the PD patients compared to the healthy controls. In addition, smaller LF power of HRV was also found during CAPs (Table 5). The HF HRV is considered to reflect the parasympathetic activity mediated by vagal nerve, while the LF power of HRV reflects the baroreflex modulation of the autonomic outflow mediated by both sympathetic and parasympathetic system [39,40]. Sympathetic regulation was found to be blunted while parasympathetic regulation was relatively intact during N3 sleep in the PD patients in the current study, which was consistent with previous findings showing blunted sympathetic regulation during REM and NREM sleep [21]. In PD patients, accumulation of α-synuclein and neurodegeneration were found throughout peripheral and central autonomic networks for regulation of cardiovascular function [68,69]. In addition, an early cardiac noradrenergic postganglionic denervation was found in PD patients using *in vivo* imaging with the radioligand ^{123}I metaiodobenzylguanidine (MIBG-SPECT) [70,71]. Together with the findings in previous studies, the current study supports the view that the autonomic system especially the sympathetic system is impaired in PD patients.

In summary, in N3 sleep, significantly fewer CAP A1, more CAP A2 and A3, smaller LF power of HRV and LF/HF ratio during CAPs and NCAPs, smaller power of δ waves during CAP A1 and A3, and NCAPs, more α waves in NCAPs were found in the PD patients compared to the healthy controls. These findings suggest changes in N3 sleep EEG microstructure, decreased N3 sleep quality, and damaged autonomic function in the PD patients.

5. Limitations

While the current study showed changes in sleep especially CAPs and NCAP of N3 sleep and associated changes in HRV in the PD patients compared to the healthy controls, there are some limitations to be considered. First, it was possible that dopaminergic drugs might have impacted the results since the PD patients in the present study were not drug naïve, but were taking dopaminergic medications such as L-dopa, ropinirole and pramipexole. However, application of controlled-release Co-beneldopa (200/50 mg) before sleep has been reported to increase the total SWS time by about 10% without significant influences on other sleep stages [72]. In addition, dopamine agonist pramipexole does not affect CAPs and most sleep parameters except for prolonged N2 sleep and increased sleep efficiency, decreased WASO, which might be considered as a result of relief of pre-sleep restless leg syndrome (RLS) symptoms and abolition of periodic limb movements, not action on sleep abnormalities in RLS patients [73]. Moreover, acute or chronic usage of dopamine agonist pramipexole has been reported not to change HRV parameters and tonic sympathovagal regulation [74,75]. Thus, future studies need to include anti-PD medication naïve PD patients. Secondly, the number of subjects was also relatively small as the standards for inclusion of healthy controls and PD patients were quite strict. Nevertheless, the power of each test with $p > 0.05$ was examined to make sure it was acceptable (i.e., >0.8), but more subjects would be desirable in future studies. Thirdly, only one night PSG data were analyzed in the current study and more nights of PSG data are needed to investigate gradual changes in sleep EEG and HRV over time in PD patients. Last, CAPs and NCAP only in N3 sleep were analyzed in this study, and further investigation is necessary to examine possible alteration of EEG activities and associated HRV in CAPs and NCAP in other sleep stages.

6. Conclusions

In the PD patients, it was found in the current study that N3 sleep duration, percentage of N3 sleep occupied by CAPs and CAP A1, as well as CAP A1 index during N3 sleep were significantly shorter or smaller compared to healthy controls. In addition, α wave intrusion in NCAP and greater β wave power, and smaller δ wave power in CAP A1 and A3, and δ wave amplitudes were also found during N3 sleep. Furthermore, significantly smaller LF power of HRV and LF/HF ratio in CAPs and NCAPs of N3 sleep in the PD patients than those in healthy controls were shown. These findings suggest that N3 sleep quality and sympathetic function are compromised in PD patients.

Availability of Data and Materials

The data used to support the findings of this study are included in the article.

Author Contributions

DY conceived and supervised the study, and ZC finalized the data analysis and drafted the article. ZC, QL, XZ, ZZ, QOuyang, CG, FY, YL, YM, and DY contributed to study design and execution, recruiting Parkinson's disease patients and healthy controls, data acquisition, analysis and interpretation, sort references, preparation of the figures and tables, critically reviewing and editing the manuscript, and read and approved the final manuscript. All the authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All research protocols and experimental procedures were reviewed and approved by the Jiangxi Provincial People's Hospital Research Ethics Committee (No. 2019-014) in compliance with the principles of the Declaration of Helsinki. Informed consent was acquired from all the subjects.

Acknowledgment

The authors are grateful to Professor Barry Sessle of the University of Toronto for his assistance in editing this article and helpful discussions, and also wish to thank all the subjects for participating in the study.

Funding

This research was supported by the Jiangxi Provincial People's Hospital Grant 2019-009, and Jiangxi Province Key Laboratory of Neurology Grant (No. 2024SSY06081).

Conflict of Interest

The authors declare no conflict of interest.

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