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ORIGINAL ARTICLE

Sleep stability in isolated rapid eye movement sleep behavior disorder, Parkinson's disease, and dementia with Lewy bodies

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Background: Non-REM sleep symptoms remain poorly understood in alpha-synucleinopathies.

Aims: The aims of the study were to compare sleep stability and transitions, arousals, and sleep cycle structure between isolated rapid eye movement (REM) sleep behavior disorder (iRBD), Parkinson's disease (PD), and dementia with Lewy Bodies (DLB).

Materials and Methods: Sleep transition and stability measures were assessed in one-night video-polysomnography records. Transition measures were the number of shifts between Wake and REM, Wake and NREM, and REM and NREM. Stability measures were the number of passages within the same sleep stage. We assessed arousals, the number/duration of sleep cycles (defined as a sequence of any NREM stage to REM), and the duration of N3 and REM sleep in each cycle. These variables were compared between two sets of groups (PD vs. DLB vs. iRBD and RDB+ vs. RBD−).

Results: We assessed 54 PD, 24 DLB, and 21 iRBD patients (54 RBD+, 22 RBD−). There were no significant differences regarding sleep stability measures. Arousal indices in N1 and N2 stages were significantly higher in PD compared with iRBD. 24% of the sample did not have any sleep cycle. PD had significantly fewer cycles than iRBD. Differences became non-significant when adjusting for medication. There was no effect of group or time of night in REM or N3 duration. There were no significant differences between RBD+ and RBD−.

Discussion: There were no significant differences in stability/transition measures. Arousals and disturbance in sleep cycling were higher in PD, but the difference was no longer significant after adjusting for medication.

Conclusion: Different alpha-synucleinopathies have a similar degree of non-REM sleep instability, but medication could worsen symptoms in PD.

KEYWORDS
arousals, dementia with Lewy bodies, Parkinson's disease, REM sleep behavior disorder, sleep cycles, sleep stability

1 | INTRODUCTION

Parkinson's disease (PD) and dementia with Lewy bodies (DLB) are related to alpha-synuclein deposition and share common symptoms (parkinsonism, behavioral disturbance, sleep disorders), the distinction relying upon the relative preponderance and onset of cognitive symptoms, predominant in DLB and probably related to cortical degeneration in late-stage disease.[1] Both disorders have in common

a high prevalence of rapid eye movement (REM) sleep behavior disorder (RBD), a parasomnia defined by the presence of dream enacting and loss of normal REM sleep muscle atonia. RBD frequently predates the appearance of the cognitive and motor symptoms that permit the diagnosis of PD and DLB, at which stage is denominated as isolated RBD (iRBD). iRBD has been connected to early alpha-synuclein accumulation in the brain stem, involving the locus coeruleus/subcoeruleus complex,[2] and most patients present with subtle clinical signs that will eventually progress to a full-blown alpha-synucleinopathy.[3] Thus, PD, DLB, and iRBD could be considered different stages of the same neuropathological process. Not all PD and DLB patients present with RBD, this parasomnia corresponds to a more severe cognitive and motor phenotype.[4–6]

Although most of the attention has been focused on REM sleep features, there is some suggestion that there are other alterations in sleep functions in alpha-synucleinopathies, including sleep fragmentation in PD[7] and DLB,[8,9] reduction or abolition of REM sleep in PD and DLB,[8,10,11] changes in NREM sleep spindles, K complexes and slow-wave activity in PD, iRBD[12,13] and DLB.[9] The hypothesis that overall sleep architecture could be altered, encompassing sleep functions beyond REM sleep, is in accordance with neuropathological findings in alpha-synucleinopathies[14] showing affection of brainstem structures responsible for maintaining the flip-flop system that controls shifting between states of consciousness, including the reticular activation system and connected mesopontine structures.[15] A study performed in a small group of iRBD patients has suggested alteration in Cyclic Alternating Pattern, more frequent arousals, and a decrease in the normal reduction of N3 across sleep cycles, suggesting alterations in sleep homeostasis.[16] Christensen et al.[17] have found REM and NREM sleep stability to be diminished in PD and iRBD patients compared with controls. Abnormal arousal characteristics were found in PD and iRBD.[18] However, we have found no studies that can provide a direct comparison between these three disorders regarding non-REM sleep features. Because not all PD and DLB patients have RBD, it is also important to understand to which categorical division sleep structure changes should be ascribed: presence/absence of RBD versus disease type (iRBD, PD, DLB).

Thus, the objective of the present study was to compare sleep stability, arousals, and cycle structure between two sets of diagnoses: iRBD versus PD versus DLB; RBD versus non-RBD. We hypothesize that: (1) sleep instability, arousals, and cycle structure changes would increase in severity from iRBD to PD to DLB patients, given that these disorders represent stages of increasingly advanced alpha-synuclein deposition and/or that (2) changes in sleep structure would be more severe in patients with RBD (RBD+) compared with patients without RBD (RBD−), given that RBD corresponds to a worse phenotype.

2 | METHODS

2.1 | Subject selection and diagnosis

We included all DLB, PD, and iRBD patients that underwent video-polysomnography (PSG) in a tertiary center covering part of Lisbon's metropolitan area, between January 2015 and June 2021. DLB was diagnosed according to the Fourth consensus report of the DLB Consortium and PD according to UK brain bank criteria. Information was collected regarding age, gender, disease duration in years, and use of medication with influence on sleep structure. We gathered information on the use, at the time of PSG, of any drugs with central nervous system (CNS) influence and divided them into the four major groups in this population: dopaminergics, selective serotonin reuptake inhibitors, clonazepam and acetylcholinesterase inhibitors (less frequently used CNS drugs were reported together on the same general category).

The International Classification of Sleep Disorders III criteria were used for RBD diagnosis (both needed):

1. repeated episodes of behavior or vocalization that are either documented by PSG to arise from REM or are presumed to arise from REM based on reports of dream enactment
2. evidence of REM sleep without atonia (RSWA) on PSG

Tonic excessive muscular activity was assessed in 30 s epochs and considered when sub-mental Electromyography (EMG) activity exceeded twice that of background activity for more than 50% of the epoch. Phasic excessive muscular activity was measured in 3 s mini-epochs and defined as sub-mental EMG activity bursts lasting 0.1–5 s and exceeding four times that of the background. Phasic and tonic activities indexes were calculated by dividing the number of epochs with excessive activity by the total number of REM epochs. According to the work by Frauscher et al.,[19] the cutoff for excessive muscular activity was 16% for phasic activity and 10% for tonic excessive EMG activity in the mentalis muscle. Besides quantifying phasic and tonic REM sleep without atonia, global measurement of RBD severity was also used, according to the method proposed by Sixel-Döring et al,[20] which is based on video-file observation of the patient's behavior during REM sleep.

Patients attended dementia, sleep, or the movement disorders outpatient clinics and were proposed PSG during routine clinical follow-up, whenever sleep symptoms demanded an objective evaluation of sleep parameters (e.g., hypersomnolence not explained by medication, RBD symptoms).

2.2 | Video-polysomnography

All subjects underwent one-night, in lab, video-PSG. PSG was performed with a digital polygraph (XLTEK-TREX; Natus Medical, Inc.) and included electrooculography, electroencephalography (EEG; six channels F1-A1, F2-A2, C4-A1, C3-A2, O1-A2, O2-A1,) electrocardiography, electromyography of the mentalis, right and left tibial muscles, recording of nasal airflow, thoracic and abdominal respiratory effort, oxygen saturation, microphone, and digital EEG-synchronized videography with infrared camera. Sleep staging was performed according to the American Academy of Sleep Medicine (AASM) recommendations (except for REM sleep, which we allowed to be scored in the presence of increased EMG activity in the mentalis muscle).

The following sleep parameters were registered: Total sleep time, Sleep efficiency, Awakenings Index, Wake after sleep onset, Sleep latency, REM sleep latency, Stage N1%, Stage N2%, Stage N3%, Stage R %, Apnea–Hypopnea Index, Desaturation Index, Periodic Limb Movements of Sleep index.

2.3 | Definitions of sleep stability, arousals, and cycle structure measures

We manually counted the number of shifts between Wake and REM, Wake and NREM, REM and NREM during PSG registry, yielding three transition variables (R-W, N-W, R-N). These variables were defined as frequency per minute of total time in bed. We also counted all the passages (toggles) within the same sleep stage N-N (any stage), R-R, and W-W, yielding three stability measures. Stability measures were defined as frequency per minute spent in the correspondent stage.

Arousals were scored in 30 s epochs according to the AASM manual rules: abrupt shift of EEG frequency including alpha, theta, and/or frequencies greater than 16 Hz (but not spindles), lasting at least 3 s, with at least 10 s of stable sleep preceding the change; scoring of arousals during REM required a concurrent increase in submental EMG lasting at least 1 s. We calculated the total number of arousals, expressed as events per hour of total sleep, and the number of arousals in each sleep stage, expressed as number of events divided by the total time, in hours, passed in each stage.

A sleep cycle was defined as the sequence of NREM (stages N1 to N2 to N3, or just N1 toN2) to REM. Cycles always began with NREM and were not considered if they lacked REM sleep. Absence of N3 was admitted. In other words, a cycle was only considered if a stage N1, N2, or N3 was followed by a period of REM sleep. Periods that were not followed by REM were incorporated in the next one, in order to have REM sleep, if they were not interrupted by one or more Wake epochs (in which case there not considered as belonging to any sleep cycle). We calculated the total number of sleep cycles and mean sleep cycle duration per patient. We also assessed the duration of N3 and REM sleep in each cycle.

2.4 | Data analysis

We formed two sets of groups. In one set, patients were divided according to disease type, into PD, DLB (irrespective of RBD diagnosis), and iRBD groups. In the other, patients were divided according to the presence or absence of RBD, irrespective of disease type. RBD+ group was formed by iRBD and PD and DLB patients that had criteria for RBD. RBD− was formed by PD and DLB patients that did not have RBD. DLB and PD patients in whom the PSG results were inconclusive regarding RBD, due to absence of REM sleep, were excluded from this second analysis.

ANCOVA analysis was used to compare clinical features, PSG data, sleep stability measures, arousals, and the total number of sleep cycles between groups in each set, using demographic variables as covariates whenever these differed between groups. A second ANCOVA analysis was performed, adjusting also for medication variables, to test if these influenced the differences found between groups.

Repeated measure ANOVA was used to compare sleep stages durations in groups in both sets, using group as a between-subjects factor and cycle sleep duration variables (total, N3, and REM) as the dependent variable. We calculated the significance of between-subjects (group) and within-subjects (sleep duration variables) differences and the interaction between group and sleep duration. Post hoc analysis with Bonferroni correction was used to compare duration in-between cycles.

2.5 | Ethics

Patients signed informed consent forms. The ethics committee of the institution approved the investigation protocol.

3 | RESULTS

We assessed 54 PD, 24 DLB, and 21 iRBD patients. Within the PD and DLB groups, 21 and 12 had RBD, respectively (in 13 and 6, respectively, RBD status could not be ascertained, due to lack of REM sleep during PSG). Adding those to the number of patients with iRBD, the study yielded a total of 54 patients with RBD (RBD+) and 22 without RBD (RBD−) (a total of 76). One PD patient fulfilled criteria for PD with dementia. Demographic and medication data for all groups are presented in Table 1. In the comparison between disease types, there were significant differences regarding gender (males were comparatively more frequent in the iRBD group) and age (DLB patients were significantly older). There were not significant differences in age or gender between RBD+ and RBD. Regarding the comparisons between disease types, there were significant differences in the use of dopaminergic medication (more frequent in PD) and acetylcholinesterase inhibitors (more frequent in DLB). When comparing patients with and without RBD, the former showed more frequent use of clonazepam and dopaminergics.

Regarding PSG variables (Table 2), there were no significant differences between diagnostic categories, after correcting for age, except for mean REM sleep duration, which was significantly lower in PD patients compared with iRBD and RBD severity, which was higher in iRBD patients. Comparison between RBD+ and RBD− groups also did not yield significant differences (except for RBD severity, as by definition).

Figure 1 depicts the comparison of sleep stability and transition variables between groups in the two sets. There were no significant differences between groups in either set, neither regarding transition nor stability measures.

Arousal indices in NREM sleep (total and N2) sleep were significantly higher in PD compared with iRBD (significance of N1 differences became trend level in post hoc analysis). There were no other

TABLE 1 Demographic and medication features in patients' groups

	iRBD ($n = 21$)	PD ($n = 54$)	DLB ($n = 24$)	p	RBD+ ($n = 54$)	RBD− ($n = 22$)	p
Age (years)	69.33 (8.78)	70.20 (9.21)	79.25 (6.85)	.00006	70.72 (10.30)	72.73 (8.57)	.423
Gender (male)	18 (85.7)	29 (53.7)	16 (66.7)	.033	54 (70.4)	13 (59.1)	.422
Disease duration (years)	7.75 (5.65)	8.41 (7.07)	5.64 (3.10)	.375	6.83 (4.08)	8.09 (10.77)	.713
Medication							
Clonazepam	3 (15.8)	5 (9.3)	7 (30.4)	.064	10 (19.6)	0	.025
Dopaminergics	0	52 (96.3)	5 (20.8)	<.00001	24 (44.4)	16 (72.7)	.025
SSRI	7 (36.8)	20 (37.0)	13 (56.5)	.253	21 (41.2)	6 (27.3)	.259
Acetilcoli. inhi.	2 (9.5)	2 (3.7)	11 (47.8)	.00004	7 (13.2)	4 (18.2)	.253
Other drugs w/ CNS action	7 (36.8)	14 (25.9)	7 (30.4)	.659	14 (27.5)	5 (22.7)	.673

Note: Values are mean (standard deviation) or number (percentage).

Abbreviations: CNS, central nervous system; DLB, dementia with Lewy bodies; iRBD, idiopathic REM sleep behavior disorder; PD, Parkinson's disease; RBD+, patients with RBD; SSRI, selective serotonin reuptake inhibitor.

TABLE 2 Video-PSG data by group

	iRBD ($n = 21$)	PD ($n = 54$)	DLB ($n = 24$)	p	RBD+ ($n = 54$)	RBD− ($n = 22$)	p
Total sleep time (min)	326.21 (96.83)	327.92 (103.52)	256.06 (90.84)	.368	330.01 (93.96)	314.00 (99.41)	.510
Sleep efficiency (%)	73.40 (43.66)	57.90 (18.12)	51.09 (17.81)	.056	65.77 (31.11)	58.23 (14.53)	.281
Awakenings Index	4.95 (4.50)	5.76 (4.59)	6.85 (3.90)	.500	5.22 (3.53)	5.99 (2.84)	.372
WASO (min)	131.23 (104.59)	157.56 (68.22)	233.34 (338.54)	.315	144.84 (84.96)	157.52 (67.05)	.535
Sleep latency (min)	49.07 (89.47)	40.17 (40. 28)	68.69 (93.05)	.374	46.81 (65.97)	35.96 (32.27)	.465
REM sleep latency (min)	186.44 (112.80)	193.15 (125.59)	204.74 (157.27)	.972	190.57 (113.66)	210.93 (153.03)	.525
Stage N1 (%)	10.05 (6.71)	10.87 (10.94)	10.38 (9.10)	.931	9.42 (9.16)	9.73 (8. 88)	.894
Stage N2 (%)	60.29 (10.58)	68.11 (16.24)	65.68 (16. 75)	.146	64.26 (12.64)	62.58 (20.83)	.668
Stage N3 (%)	15.38 (10.62)	12.49 (12.13)	14.75 (16. 97)	.650	13.71 (11. 20)	14.35 (15.38)	.840
Stage R (%)	14.28 (5.99)	7.45 (6.96)	9.55 (9.71)	.003[a]	12.75 (6.75)	10.41 (7.64)	.191
AHI	15.23 (16.89)	18.57 (19.00)	13.69 (10. 17)	.129	17.50 (17.68)	17.40 (17.17)	.981
PLMS index	6.00 (9.05)	5.39 (10.09)	14.42 (18.97)	.098	8.16 (12. 29)	5.50 (9.21)	.364
RSWA (tonic)	0.206 (0.140)	0. 217 (0.254)	0.180 (3.280)	.201	0.260 (0.205)	0.006 (0.019)	.0001
RSWA (phasic)	0.364 (0.167)	0.158 (0.214)	0.225 (0.225)	.004[b]	0.310 (0.331)	0.006 (0.020)	.0001
RBD severity	1.701 (0.588)	0.770 (0.815)	1.000 (0.943)	.005[c]	1.301 (0.793)	0.000 (0. 000)	.0001

Note: Values are mean (standard deviation).

Abbreviations: AHI, apnea–hypopnea index; DLB, dementia with Lewy bodies; iRBD, idiopathic REM sleep behavior disorder; PD, Parkinson's disease; PLMS, periodic limb movements of sleep; RBD+, patients with RBD; RSWA, REM sleep without atonia; WASO, wake after sleep onset.

[a]PD versus DLB, $p = .280$; PD versus iRBD $p = .002$; iRBD versus DLB, $p = .517$.

[b]PD versus DLB, $p = 1.000$; PD versus iRBD $p = .003$; iRBD versus DLB, $p = .148$.

[c]PD versus DLB, $p = 1.000$; PD versus iRBD $p = 0.004$; iRBD versus DLB, $p = 0.178$.

significant differences between diagnostic categories. There were no significant differences in arousal indices between RBD+ and RBD− groups (Table 3).

When repeating ANCOVA analysis with medication as a covariate, the differences in sleep stability measures between iRBD, PD, and DLB remained non-significant. The differences in arousals indices between iRBD and PD were no longer significant. In this second analysis, differences between RBD+ and RBD− comparisons remained non-significant.

The mean number of sleep cycles (standard deviation) for iRBD, PD, and DLB were the following (respectively): 2.90 (1.34); 1.39 (1.43), and 2.25 (2.56). ANOVA showed significant differences between the

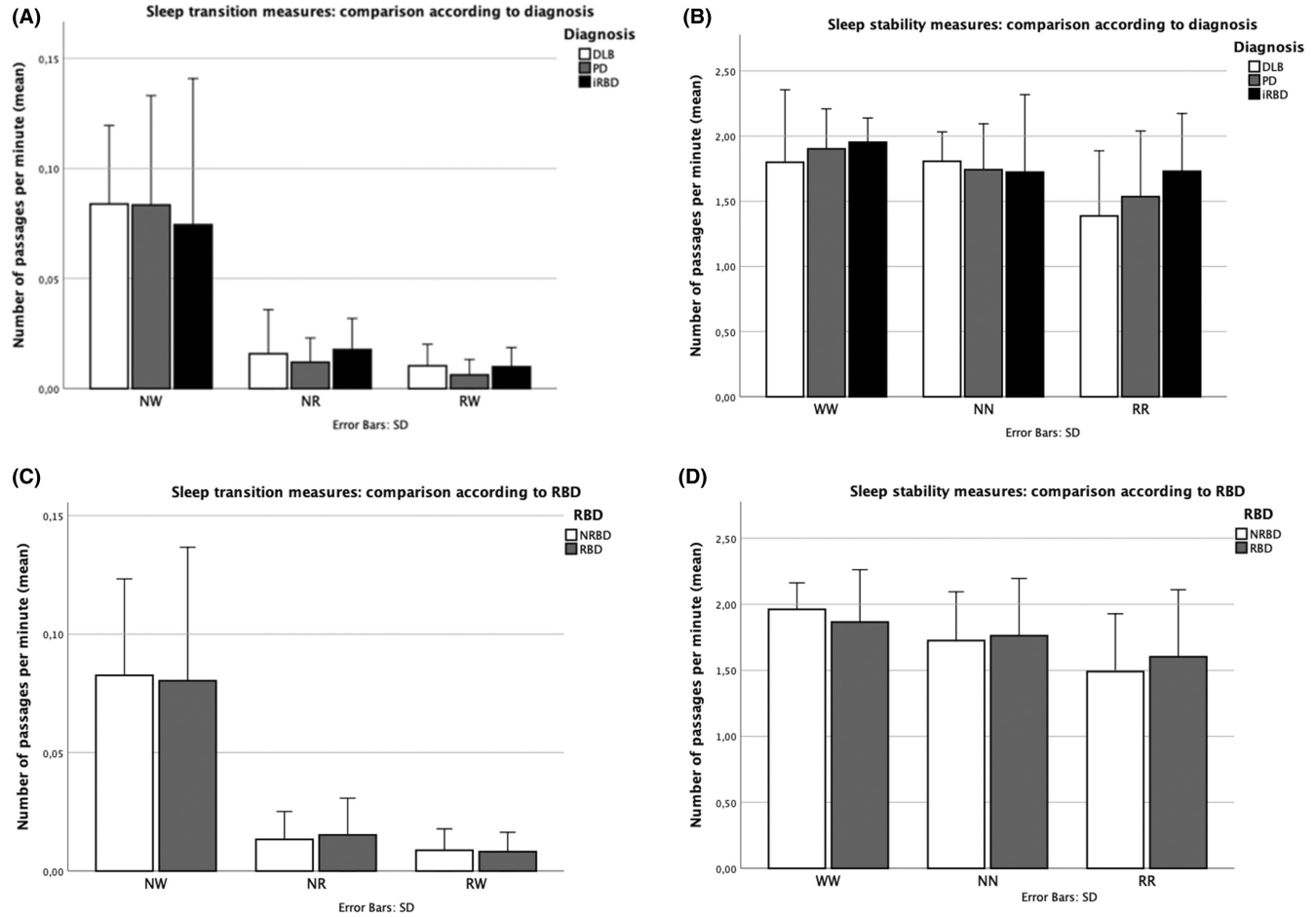

FIGURE 1 Sleep stability/transition measures: group comparison. Values are mean number of shifts between different stages (NW, NR, RW) or passages between the same stage (NN, RR, WW) per hour of sleep. DLB, dementia with Lewy bodies; iRBD, idiopathic REM sleep behavior disorder; PD, Parkinson's disease; RBD+, patients with RBD.

TABLE 3 Arousals indices by group (number of arousals per hour of sleep in each stage)

	iRBD ($n = 21$)	PD ($n = 54$)	DLB ($n = 24$)	p	RBD+ ($n = 54$)	RBD− ($n = 22$)	p
Total	12.19 (8.59)	24.63 (24.03)	14.27 (13.57)	.053	16.72 (17.97)	19.42 (19.13)	.627
N1	15.02 (10. 84)	31.47 (29. 15)	18.20 (20. 03)	.041[a]	20.39 (23.20)	28.71 (24.30)	.425
N2	11.34 (8.59)	26.05 (27. 00)	13.63 (12. 62)	.035[b]	15.57 (17.66)	22.35 (25.51)	.504
N3	11.09 (14.19)	12.62 (18.23)	5.78 (10. 11)	.762	9.52 (15.40)	10.42 (12.30)	.746
NREM total	11.61 (8.33)	24.55 (24.65)	13.82 (12.75)	.031[c]	15.49 (16.7)	21.09 (22.22)	.543
R	16.15 (12. 41)	15.92 (43.71)	15.04 (22.87)	.786	25.33 (42.2)	9.47 (13.77)	.299

Note: Values are mean arousal index (standard deviation).

Abbreviations: DLB, dementia with Lewy bodies; iRBD, idiopathic REM sleep behavior disorder; PD, Parkinson's disease; RBD+, patients with RBD; RSWA, REM sleep without atonia.

[a]PD versus DLB, $p = .446$; PD versus iRBD $p = .051$; iRBD versus DLB, $p = 1.000$.

[b]PD versus DLB, $p = .624$; PD versus iRBD $p = .036$; iRBD versus DLB, $p = .886$.

[c]PD versus DLB, $p = .563$; PD versus iRBD $p = .031$; iRBD versus DLB, $p = .821$.

groups ($p = .002$). Post hoc analysis showed iRBD patients to have significantly more sleep cycles than PD patients ($p = .004$), non-significant differences between iRBD and DLB ($p = 1.000$), and a trend to fewer sleep cycles in PD version DLB ($p = .052$). Repeating the analysis after excluding patients that did not have REM sleep showed significant differences between the groups ($p = .007$), with post hoc comparisons showing significant fewer sleep cycles in PD compared with DLB ($p = .013$) and a tendency ($p = .096$) to fewer sleep cycles in PD compared with iRBD. Differences between RBD+ and RBD− were significant only at trend level (2.70 [1.89] vs. 1.95

[1.17], respectively, $p = .089$). When repeating the ANCOVA analysis with medication as co-variate, the differences between iRBD, PD, and DLB were no longer significant. Differences regarding RBD+ versus RBD− comparisons remained non-significant.

Twenty-four percent of the sample did not have any sleep cycle, another 54.24% had only one or two sleep cycles. Only patients with at least three cycles ($n = 31$) were included in sleep stage duration analysis, and only the first three cycles were considered. Repeated measures ANOVA using disease type as a between-subject factor and cycle total sleep time as the dependent variable showed a significant effect of time, with decreasing cycle length with increasing sleep time, a difference which in post hoc analyses was significant only at trend level, between cycle 1 and 3 ($p = .076$). There was no significant interaction between diagnosis and time and no significant differences between groups (Figure 2A). The same analysis, using N3 (Figure 2B) or REM (Figure 2C) sleep cycle duration as the dependent variable showed no significant interactions or differences. Repeated measure analysis using RBD+/RBD− as a between-subject factor did not show significant results (Figure 2D–F).

4 | DISCUSSION

Our study has found significant differences in age, gender, and RBD severity between iRBD, PD, and DLB patients. This agrees with previous studies by our group. Several explanations have been proposed, involving both referral bias and the nature of the degenerative process itself, which are discussed in detail elsewhere.[8,21] Differences in medication reflect habitual differences in therapeutic options concerning each disorder.

Contrary to our expectations, there were no significant differences in sleep transition and sleep stability measures between diagnosis groups. This suggests that the three different disorders are equally affected by changes in the flip-flop mechanism involved in maintaining and switching between states of consciousness. This is in accordance with a previous study, performed only in PD and iRBD groups that showed no differences between these two groups.[17] Given that this same study showed significant differences between iRBD and PD, on one side, and controls on the other, and their values are similar to ours, we can admit that all three alfa-synucleinopathies present with a similarly abnormal degree of sleep stability. This could be due to floor-effect caused by early affection of lower brain-stem regions, meaning that sleep control nuclei are strongly deranged since the early stages of the disease and that the latter stages of the disease, affecting superior areas of the CNS, do not add to sleep dysfunction the same as to cognitive and motor dysfunction. That the systems affected in sleep stability/transition are not coincident with those involved in RBD is suggested by the lack of significant differences between RBD and non-RBD patients, shown in our study and also suggested by Christensen et al.,[17] which showed no correlation between the severity of RBD symptoms and these measures.

Arousals are caused by attenuation of thalamus-driven, cortical inhibition that predominates during sleep, mainly by the action of cholinergic activating pathways that originate in mesopontine nuclei. Although an excessive frequency of arousals can be detrimental to sleep, causing fragmentation, their presence could

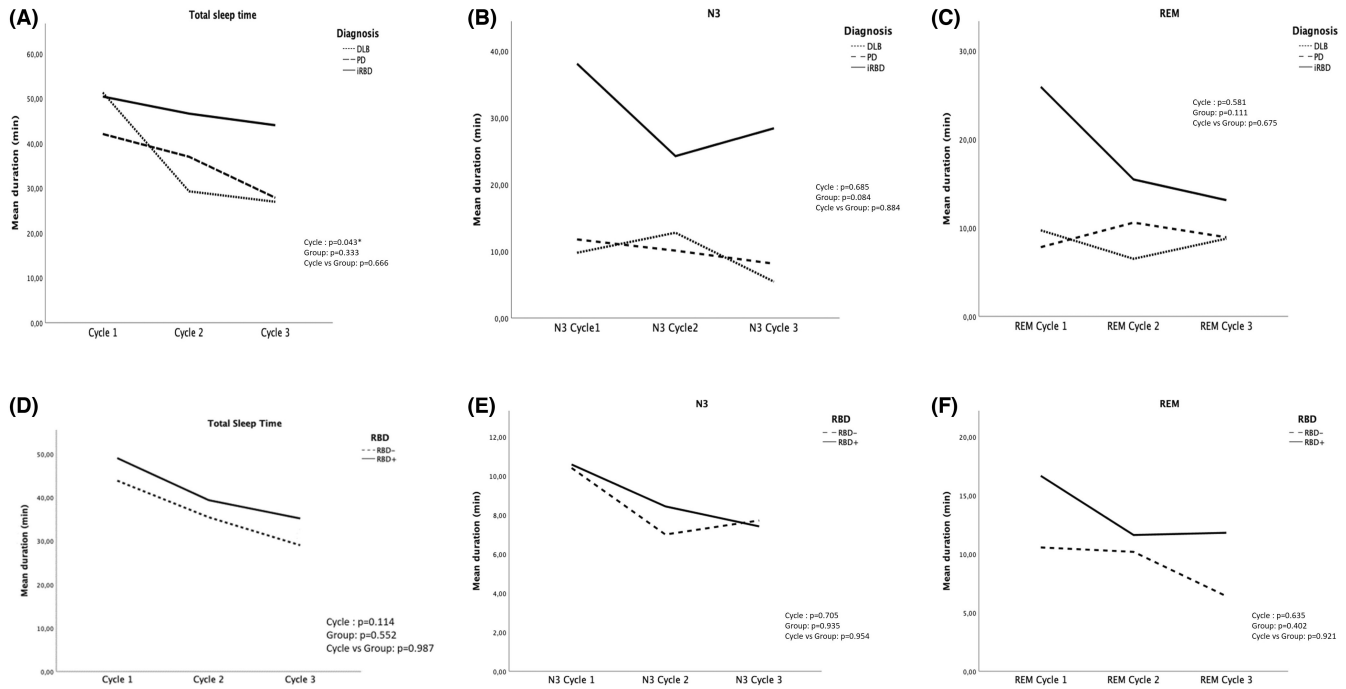

FIGURE 2 Sleep cycles duration: group comparison. Values in graphic are mean duration of total, N3 and R3 for the first, second, and third sleep cycle. *p* values are the result of repeated measures ANOVA.

represent a physiological mechanism ensuring sleep reversibility and adequate response to endangering stimuli requiring prompt awake reaction.[22] In the present study, PD presented more frequent arousals than iRBD patients in N1 and N2 sleep, with no differences regarding REM sleep. This suggests higher susceptibility of PD patients to cortical activation during the lighter stages of sleep. Although it is difficult to make comparisons, because of different methodologies, this finding seems in discordance with studies reporting an inferior number of arousals in NREM sleep in PD compared with controls.[18,23] On one hand, if we could consider, as Sommerauer et al.,[23] that the response to arousing stimuli is pathologically low in PD, possibly due to a failure in autonomic control caused by neurodegeneration of pontine nuclei, our finding could suggest that PD patients are less altered, in this regard, than patients with iRBD and DLB. On the other hand, a higher frequency of arousals could be connected to an increase of arousing stimuli in PD patients, suggesting that other factors, particular to this disorder, like motor dysfunction or the effects of dopaminergic drugs, could be contributing to more severe sleep fragmentation, as discussed below. There were no significant differences when comparing patients according to RBD status. This goes against a previous study that has found a higher frequency of arousals during REM sleep in iRBD and PD patients with RBD.[18] On the contrary, differences in arousal indices were no longer significant after adjusting for medication differences. This could mean that dopaminergics, more frequently used in PD, could promote arousals in this disorder, while acetylcholinesterase inhibitors, more frequently used in DLB, could have a protective effect on arousal in this population.

Sleep progression across the night obeys to the repetition of cycles, from progressively deepening NREM sleep to REM sleep. An 8 h night's sleep usually comprehends 4–6 cycles. Cycle duration tends to decrease as the night advances; REM sleep duration increases and N3 duration decreases. N3 duration is considered a marker of sleep homeostasis, decreases with age, and could be absent in older, non-diseased patients; REM sleep duration depends mostly on circadian rhythm regulation and its absence is considered pathological.[15] In our study, sleep architecture analysis showed significant structuration defects in all groups, describing a global pattern of sleep fragmentation. A quarter of the patients did not have any sleep cycle, mostly due to the total absence of REM sleep in PD and DLB patients, a phenomenon that has been described before in patients with alpha-synucleinopathies.[5,8,9] Most patients had only one or two cycles, with PD patients showing significantly fewer cycles than iRBD and DLB. The discrepancy suggests that specific factors could interfere with PD cycle structure: this could include differences in medication, particularly dopaminergics, which are used more frequently in PD patients and are known to cause dose-dependent sleep fragmentation,[7] or the effect of motor dysfunction, which is usually more intense in this population than in DLB patients. Differences in the mean number of sleep cycles were no longer significant after adjustment for medication, which is in favor of the hypothesis that dopaminergics, which were more frequently used in PD patients (as expected, this being the mainstay of therapeutical intervention in this disorder, contrary to DLB and iRBD) could be a deleterious influence in sleep stability in these patients. Sleep cycle duration decreased significantly through the night, although this significance did not persist in post hoc analysis and there were no significant changes when analyzing REM and N3 separately, pointing to a malfunction of the mechanisms that regulate circadian time system and sleep homeostasis,[15] as hypothesized, and previously reported, in studies performed in iRBD patients regarding N3[16] and in iRBD and PD patients regarding REM sleep duration.[24] There was no significant effect of group, indicating that these changes could be present in their full-blown state since the first stages of the disease, represented by iRBD.

Some limitations should be acknowledged, one being the absence of a control group of patients without PD, DLB, or iRBD, which would have allowed us to assess the differences between patients with and without neurological disorders. Also, our sample was formed by patients with sleep complaints who presented clinical indication for PSG and might not be representative of the entire population of PD and DLB patients. Finally, the lack of motor function measurements could also be considered a limitation, as this would allow us to investigate the impact of this variable on sleep fragmentation.

In conclusion, our study did not find significant differences in sleep stability/transition variables between iRBD, PD, and DLB, which could signify that these disorders have the same degree of sleep stability dysfunction, possibly concerning an early derangement of mesopontine structures responsible for both NREM and REM regulation—a preliminary finding that would benefit from confirmation by studies powered by larger samples, in which subtler differences could become significant. Arousal analysis did show a higher susceptibility in PD patients, regarding N1 and N2 NREM stages. Sleep cycling was significantly impaired in all three disorders, but more pronounced, regarding the number of sleep cycles, in PD patients. These differences could be due to the specificities of the neuropathological progression in PD, but the fact that they did not persist after adjusting for differences in medication suggests that other factors, particularly dopaminergic medication, should be contributing specifically to sleep fragmentation in PD patients. RBD+ versus RBD− comparisons revealed no significant differences, which suggests that disease differences could play a larger role in arousals and sleep cycle duration changes than the presence of RBD de per se, a hypothesis that could merit confirmation from larger sample studies and comparison with a non-neurological control group.

AUTHOR CONTRIBUTIONS

Paulo Bugalho was responsible for conceiving the project and designing the methodology. Paulo Bugalho and Marta Magriço retrieved the data and completed the database. Paulo Bugalho analyzed the data and wrote the first version of the manuscript. The manuscript was reviewed by Paulo Bugalho and Marta Magriço.

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CONFLICT OF INTEREST

None.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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