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RESEARCH ARTICLE

Temporal progression of sleep electroencephalography features in isolated rapid eye movement sleep behaviour disorder

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Summary

Previous studies indicated that patients with isolated rapid eye movement (REM) sleep behaviour disorder (iRBD) exhibit alterations in spectral electroencephalographic (EEG), spindle, and slow-wave features. As it is currently unknown how these EEG features evolve over time, this study aimed to evaluate their temporal progression in patients with iRBD in comparison to controls. We included 23 patients with iRBD and 23 controls. Two polysomnographies (baseline and follow-up) were recorded with a mean (standard deviation) interval of 4.0 (2.5) years and were automatically analysed for sleep stages, spectral bandpower, spindles, and slow waves. We used linear models to evaluate differences at each time point, and linear mixed-effects models to analyse differences in temporal progression between the groups. At baseline, patients with iRBD presented EEG slowing both in REM (expressed as significantly reduced α-bandpower and increased δ-bandpower in frontal channels) and in non-REM (NREM) sleep (significantly increased slow-to-fast ratio in central channels). These differences vanished at follow-up. In both REM and NREM sleep, γ-bandpower was increased at follow-up in patients with iRBD, resulting in significantly different temporal progression between groups (in occipital channels during REM sleep and frontal channels during NREM sleep). Relative power of sleep spindles was significantly higher at baseline in patients with iRBD in frontal channels, but we observed a significant reduction over time in central channels. Finally, slow waves were significantly shorter in patients with iRBD at both time-points. Our results underscore the need of considering longitudinal data when analysing sleep EEG features in patients with iRBD. The observed temporal changes as markers of progression of neurodegeneration require further investigations.

KEYWORDS
computerised methods, electrophysiology, prodromal alpha-synucleinopathy

1 | INTRODUCTION

Rapid eye movement (REM) sleep behaviour disorder (RBD) is characterised by dream enactment behaviours during REM sleep and the loss of the physiological REM-sleep atonia (Schenck et al., 1986). When occurring in the absence of other neurological disorders, it is called isolated RBD (iRBD), and represents the prodromal stage of α-synuclein-related neurodegenerative disorders, namely Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multi-system atrophy (MSA) (Iranzo et al., 2014; Schenck et al., 2013).

Several investigations have shown that alterations in sleep electroencephalogram (EEG) are present in patients with iRBD. Some studies reported a shift in the power spectral density from high- to low-frequency bands during REM sleep (Fantini et al., 2003; Iranzo et al., 2010; Massicotte-Marquez et al., 2005; Sasai et al., 2013). However, others did not report such changes (Valomon et al., 2021). Similar EEG alterations were discovered during non-REM (NREM) sleep (Massicotte-Marquez et al., 2005), although these findings could not consistently be replicated (Latreille et al., 2011; Sasai et al., 2013; Valomon et al., 2021). Other studies investigated sleep spindles, i.e., sporadic cortical oscillatory events with a frequency of 11–16 Hz and duration of 0.5–2 s (Berry et al., 2020). Previous works reported decreased density of fast spindles (O'Reilly et al., 2015), lower relative power (Sunwoo et al., 2021) and decreased overall density (Christensen et al., 2014; O'Reilly et al., 2015) in patients with iRBD compared to controls, although changes in density could not always be reproduced (Sunwoo et al., 2021). Similarly, slow waves, i.e. waves of frequency 0.5–2 Hz and peak-to-peak amplitude >75 μV occurring during NREM sleep (Berry et al., 2020), were previously investigated in patients with iRBD. One study found that the decline of overnight slow-wave activity present in controls does not occur in patients with iRBD (Valomon et al., 2021). Additionally, frontal slow oscillations with a frequency <1 Hz showed a decrease in amplitude and an increase in duration in patients with iRBD compared to controls (Sunwoo et al., 2021). However, these findings were not in line with a previous study, where no differences in slow waves were observed between patients with iRBD and controls (Latreille et al., 2011).

Due to the cross-sectional nature of these previous studies, it is currently unknown how these EEG features progress over time in patients with iRBD. To the best of the authors' knowledge, only one study investigated the temporal progression of EEG features in patients with iRBD, but resting-state EEG was analysed in that work (Roascio et al., 2022). Missing information on the changes in sleep EEG over time limits our understanding of how these features may describe the disorder's progression and may cause discrepancies in the literature. Understanding the time progression of sleep EEG features in patients with iRBD is also very important in light of recent findings showing that EEG features, such as slow waves, can predict motor progression in patients with PD (Schreiner et al., 2019; Tao et al., 2024). Therefore, this study aimed to investigate the temporal progression of sleep EEG features in patients with iRBD, as compared to a control group.

2 | METHODS

2.1 | Study design and participant selection

This retrospective longitudinal case-control study was performed using a dataset of 23 patients with iRBD and 23 age- and sex-matched controls. All subjects underwent one baseline and one follow-up video-polysomnography (v-PSG) at the Sleep Disorder Clinic, Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria. The interval between the baseline and follow-up PSGs was at least 2 years. RBD diagnosis was given according to the International Classification of Sleep Disorders third edition criteria (American Academy of Sleep Medicine, 2014) and to the diagnostic criteria of the International RBD Study Group (Cesari et al., 2022). All patients with iRBD did not have any sign of overt neurodegeneration, both at baseline as well as follow-up v-PSG. The control group consisted of patients who were admitted to the Sleep Disorder Clinic, Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria, either for (i) suspicion of sleep-related breathing disorder (two subjects at baseline PSG), or (ii) titration of positive air pressure therapy (one subject at baseline), or (iii) control of their positive air pressure therapy (20 subjects at baseline and all subjects at follow-up). All the subjects in the control group did not have, both at baseline and at follow-up, any neurodegenerative disease or any relevant neurological diagnosis and did not show any abnormal finding at the neurological examination. Patients with iRBD and controls were enrolled regardless of the presence of drug therapy. To minimise the influence of respiratory events on our analyses, only v-PSGs with either an apnea–hypopnea index <15 events/h or those recorded with positive airway pressure therapy were included in our analyses.

Both baseline and follow-up recordings were performed in accordance with the international guidelines adopted at the time of the recordings (Berry et al., 2012; Iber et al., 2007). Signals obtained during v-PSG recordings included at least six EEG channels (F3-M2, F4-M1, C3-M2, C4-M1, O1-M2 and O2-M1), vertical and horizontal electro-oculogram, chin and bilateral tibialis anterior electromyography (EMG), and cardio-respiratory signals. EEG signals were sampled using a frequency of 250 Hz.

The study was approved by the ethics committee of the Medical University of Innsbruck (1054/2020).

2.2 | Automatic sleep stage detection

To improve reproducibility and overcome inter-rater variability (Cesari et al., 2021), sleep stage scoring was performed automatically using the previously validated 'Yet Another Spindle Algorithm' (YASA) algorithm (Vallat & Walker, 2021). The C4-M1 EEG signal was fed to the algorithm, and every 30-s epoch was classified as either wakefulness, N1 sleep, N2 sleep, N3 sleep, or REM sleep. Cohen's kappa (κ) coefficient between the manually and automatically determined sleep stages was calculated to ensure the validity of the automatic scoring. For automatic sleep stage scoring, we chose a central derivation, as

the YASA algorithm was trained on central EEG channels (Vallat & Walker, 2021). The quality of the C4-M1 derivation was visually checked for all PSGs included in the study.

2.3 | Electroencephalogram feature extraction

As first step of feature extraction, EEG signals were pre-processed as follows. First, we removed from analyses 4-s windows where EEG signals were affected by EMG artefacts, by applying a previously validated automatic method (Brunner et al., 1996). Second, artefacts induced by rapid eye movements in REM sleep were removed by applying a previously validated adaptive filtering algorithm (He et al., 2004), which has been used several times also in the context of sleep recordings (Cesari et al., 2019).

For power analyses, EEG signals were bandpass filtered between 0.5 and 40 Hz. Power spectral densities were derived using the Welch method applied to sliding 4-s windows in REM and NREM sleep, the latter being defined as the combination of N2 and N3 sleep. For each channel and subject, the average relative power in REM and NREM sleep in δ (0.5–4 Hz), θ (4–8 Hz), α (8–13 Hz), σ (11–16 Hz), β (13-30 Hz) and γ (30–40 Hz) bands were derived. Finally, the slow-to-fast ratio ($[\delta + \theta]/[\alpha + \beta]$) was calculated for each channel. For each topographic location (i.e., frontal, central and occipital), the average of relative band powers and the slow-to-fast ratio between the left and right channels was obtained.

In N2 sleep, sleep spindles were automatically detected using a validated algorithm (Lacourse et al., 2019; Vallat & Walker, 2021), solely in the frontal and central channels. For each channel, the following spindle features were extracted: spindle density (expressed as the number of spindles/min of N2 sleep), the average spindle amplitude, the average number of oscillations in the spindles, the average frequency of spindles, average absolute and relative powers, and the average root-mean-square of the amplitude. Averages of each feature over channels and hemispheres were obtained.

Finally, slow waves were automatically detected in NREM sleep (defined as the combination of N2 and N3 sleep) with an automatic algorithm (Massimini et al., 2004; Vallat & Walker, 2021). For each EEG channel, the following slow-wave features were derived: slow-wave density (expressed as the number of slow waves/min of NREM sleep), the average duration, the average relative position of the mid-crossing (in relation to the start and end of the slow waves), the average peak-to-peak amplitude, the average slope between the peaks, the average values of the negative and positive peaks, and the relative positions of the negative and positive peaks (in relation to the start and end of the slow waves). Averages of each feature over channels and hemispheres were obtained.

2.4 | Statistical analyses

In a first step, the differences in the EEG features between patients with iRBD and controls at baseline and follow-up were investigated. For these analyses, linear models were built in R by considering each feature as a dependent variable, while group (i.e., iRBD or control), age, sex, use of antidepressants and use of either benzodiazepines (including clonazepam) or hypnotics were considered independent variables. The assumption of linearity was tested by visual inspection of the residuals and was met for all the performed analyses.

To investigate differences between patients with iRBD and controls on how each EEG feature progresses over time, linear mixed-effects regressions were employed (the 'lme4' library in R was used for this). Each EEG variable was set as the dependent variable, with each subject as a random effect and group-time interaction as a fixed effect. Age, sex and medication use, as defined above, were set as co-factors. The assumption of linearity was tested by visual inspection of the residuals and was met for all performed analyses. The primary outcome variable was the group-time interaction term, which detects differences in the progression over time between the two groups.

Due to the study's exploratory nature, multiple comparison correction was not applied in the statistical analyses (Althouse, 2016; Bender & Lange, 2001).

3 | RESULTS

3.1 | Demographic information

Table 1 summarises the included subjects' demographic, medication and sleep diagnosis information. The mean (standard deviation [SD]) interval between the baseline and follow-up v-PSGs was 4.0 (2.5) years. Sex, age and body mass index did not differ significantly between the groups. The use of antidepressant medication and clonazepam was significantly more common in patients with iRBD than in controls. No other significant difference between groups was observed in terms of medication intake.

3.2 | Automatic sleep staging

On average, the automatic sleep stage classification agreed with human observers (overall mean [SD] $\kappa = 0.63$ [0.13]). Good agreement was also found for each individual sleep stage used in analysis (Figure S1). Table 2 reports details in sleep macrostructure for patients with iRBD and controls both at baseline, as well as follow-up. No sleep macrostructure feature, including apnea–hypopnea index and periodic leg movement index in sleep, was significantly different between patients with iRBD and controls at either time-point.

3.3 | Electroencephalogram features

Table 2 reports the minutes excluded from the analysis due to intrusion of EMG artefacts in the EMG. Both at baseline as well as at follow-up, significantly more 4-s windows were affected by EMG artefacts for patients with iRBD than for controls. Due to the many

TABLE 1 Demographic, clinical and medication information of the included subjects. For each variable, the values for each group (i.e., isolated rapid eye movement behaviour disorder and controls) are compared at baseline and at follow-up.

	Baseline			Follow-up		
Variable	**Ctrl ($n = 23$)**	**iRBD ($n = 23$)**	***p***	**Ctrl ($n = 23$)**	**iRBD ($n = 23$)**	***p***
Sex, male, *n* (%)	21 (91.3)	21 (91.3)	1.000	21 (91.3)	21 (91.3)	1.000
Age, years, mean (SD)	65.1 (8.9)	65.0 (9.1)	0.987	68.7 (8.9)	68.7 (9.1)	1.000
Body mass index, kg/m^2, mean (SD)	32.4 (5.7)	31.0 (7.0)	0.517	32.0 (5.8)	31.2 (7.3)	0.698
Antidepressants, *n* (%)	4 (17.4)	9 (39.1)	0.101	3 (13.0)	10 (43.5)	**0.022**
Melatonin, *n* (%)	0 (0)	1 (4.3)	0.312	0 (0)	2 (8.7)	0.148
Clonazepam, *n* (%)	0 (0)	4 (17.4)	**0.036**	0 (0)	5 (21.7)	**0.018**
Other benzodiazepines than clonazepam, *n* (%)	0 (0)	1 (4.3)	0.312	0 (0)	1 (4.3)	0.312
Hypnotics, *n* (%)	0 (0)	1 (4.3)	0.312	0 (0)	2 (8.7)	0.148
Antipsychotics, *n* (%)	3 (13.0)	1 (4.3)	0.295	3 (13.0)	2 (8.7)	0.636
Beta-Blockers, *n* (%)	7 (30.4)	4 (17.4)	0.299	9 (39.1)	5 (21.7)	0.199
Antiepileptics, *n* (%)	2 (8.7)	0 (0)	0.148	3 (13.0)	0 (0)	0.073
Sleep-related breathing disorders, *n* (%)	23 (100.0)	18 (78.3)	**0.017**	23 (100.0)	18 (78.3)	**0.017**
Restless leg syndrome, *n* (%)	4 (17.4)	2 (8.7)	0.381	5 (21.7)	6 (26.1)	0.729
Excessive fragmentary myoclonus, *n* (%)	8 (34.8)	10 (43.5)	0.545	11 (47.8)	13 (56.5)	0.628
Hypertension, *n* (%)	15 (65.2)	14 (60.9)	0.760	18 (78.3)	17 (73.9)	0.730
Dyslipidaemia, *n* (%)	6 (26.1)	8 (34.8)	0.522	8 (34.8)	9 (39.1)	0.760
Coronary artery disease, *n* (%)	2 (8.7)	8 (34.8)	**0.032**	2 (8.7)	9 (9.1)	**0.016**
Diabetes mellitus, *n* (%)	5 (21.7)	8 (34.8)	0.326	6 (26.1)	8 (34.8)	0.522
COPD, *n* (%)	1 (4.3)	2 (8.7)	0.550	2 (8.7)	3 (13.0)	0.636
Thyroid disease, *n* (%)	3 (13.0)	3 (13.0)	1.000	3 (13.0)	3 (13.0)	1.000
Past stroke, *n* (%)	4 (17.4)	0 (0)	**0.036**	4 (17.4)	0 (0)	**0.036**
Depression, *n* (%)	1 (4.3)	10 (43.5)	**0.002**	2 (8.7)	11 (47.8)	**0.003**

Note: normality was checked for continuous variables with Shapiro–Wilk test and Student's *t*-test employed for comparisons. Categorical variables were compared with chi-squared tests. Significant *p* values ($p < 0.05$) are highlighted in bold.
Abbreviations: COPD, chronic obstructive pulmonary disease; Ctrl, controls; iRBD, isolated rapid eye movement sleep behaviour disorder; SD, standard deviation.

features tested, only variables that showed significant differences are reported, with the remaining results available in the supporting information (Tables S1–S4).

3.3.1 | REM spectral bandpowers

Table 3 shows the results of spectral analyses in REM sleep. Relative δ-bandpower was increased for patients with iRBD in the frontal region, while there was no significant difference at follow-up (Figure 1a). Patients with iRBD showed also significantly reduced relative α-bandpower at baseline in the frontal channels, but not at follow-up (Figure 1b). For both δ- and α-bandpowers, there was no significant difference in the time-progression between the groups. Relative γ-bandpower, on the other hand, did not differ at baseline, but was significantly increased at follow-up in the central and occipital electrodes, resulting in a significant difference in the time progression in the occipital area only (Figure 1c).

3.3.2 | NREM spectral bandpowers

Table 3 also reports the significant results of the spectral analysis of NREM sleep. At baseline, patients with iRBD showed significantly increased slow-to-fast ratio compared to controls in the central electrodes (Figure 2c). This difference vanished at follow-up. No other difference was observed between the groups in the baseline recordings. Relative γ-bandpower was significantly increased at follow-up in patients with iRBD in all brain areas, resulting in a significant difference in the time progression in the frontal area (Figure 2a,b).

3.3.3 | Sleep spindles

The relative power of sleep spindles was found to be significantly increased in the frontal area in patients with iRBD at baseline, but not at follow-up (Table 3 and Figure 3). On the other side,

TABLE 2 Sleep information of the included subjects. For each variable, the values for each group (i.e., isolated rapid eye movement behaviour disorder and controls) are compared at baseline and at follow-up.

	Baseline			Follow-up		
Variable, mean (SD)	**Ctrl ($n = 23$)**	**iRBD ($n = 23$)**	***p***	**Ctrl ($n = 23$)**	**iRBD ($n = 23$)**	***p***
Time in bed, min	475.8 (22.7)	489.9 (27.7)	0.072	484.3 (24.3)	490.0 (25.1)	0.443
TST, min	343.8 (77.7)	355.5 (49.1)	0.552	360.4 (58.4)	357.1 (33.9)	0.820
Sleep efficiency, %	72.4 (16.0)	72.4 (8.0)	0.981	74.4 (11.3)	73.1 (7.8)	0.651
Sleep latency, min	27.4 (27.3)	31.2 (22.6)	0.615	29.3 (36.6)	28.9 (17.5)	0.971
Wake after sleep onset, min	93.3 (67.8)	98.9 (42.4)	0.738	84.6 (36.05)	101.7 (40.0)	0.139
N1, %TST	6.7 (3.8)	8.2 (3.3)	0.173	7.1 (4.6)	10.4 (5.5)	0.032
N2, %TST	57.8 (102)	57.2 (8.4)	0.847	56.9 (8.7)	58.6 (9.5)	0.546
N3, %TST	14.6 (9.9)	14.2 (7.3)	0.874	15.4 (9.0)	13.0 (7.5)	0.333
REM, %TST	21.0 (7.7)	20.5 (7.6)	0.818	20.6 (5.9)	18.0 (8.1)	0.230
AHI, events/h[a]	4.8 (6.7)	3.9 (3.2)	0.533	4.0 (3.4)	3.7 (3.2)	0.745
PLMS index, events/h[a]	32.7 (33.5)	31.5 (33.5)	0.904	31.1 (34.6)	41.0 (44.0)	0.403
EMG artefacts removed from analysis, min	8.0 (4.2)	12.6 (5.3)	**0.003**	7.5 (3.06)	9.9 (2.7)	**0.009**

Note: normality was checked for continuous variables with Shapiro–Wilk test and Student's *t*-test employed for comparisons. Significant *p* values ($p < 0.05$) are highlighted in bold.
Abbreviations: AHI, apnea–hypopnea index; Ctrl, controls; EMG, electromyography; iRBD, isolated REM sleep behaviour disorder; PLMS, periodic leg movements in sleep; REM, rapid eye movement; TST, total sleep time.
[a]AHI and PLMS index value are obtained based on manual sleep stage scoring.

TABLE 3 Electroencephalogram features showing significant results. For each feature, the values in patients with isolated rapid eye movement behaviour disorder and in controls are reported for both baseline and follow-up video-polysomnography.

			Controls, mean (SD)		iRBD, mean (SD)		*p*		
Category	**Feature**	**Location**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**	**Temporal progression**
REM sleep	Relative δ-bandpower [–]	Frontal	0.512 (0.06)	0.515 (0.053)	0.553 (0.051)	0.538 (0.059)	**0.023**	0.167	0.200
	Relative α-bandpower [–]	Frontal	0.138 (0.049)	0.133 (0.037)	0.116 (0.022)	0.117 (0.024)	**0.049**	0.110	0.284
	Relative γ-bandpower [–]	Central	0.012 (0.004)	0.011 (0.004)	0.014 (0.004)	0.015 (0.006)	0.078	**0.029**	0.290
		Occipital	0.012 (0.005)	0.011 (0.004)	0.014 (0.004)	0.016 (0.007)	0.194	**0.005**	**0.032**
NREM sleep	Relative γ-bandpower [–]	Central	0.003 (0.003)	0.002 (0.001)	0.003 (0.001)	0.004 (0.002)	0.957	**<0.001**	0.070
		Frontal	0.002 (0.003)	0.002 (0.001)	0.002 (0.001)	0.003 (0.002)	0.922	**0.001**	**0.042**
		Occipital	0.004 (0.004)	0.003 (0.002)	0.004 (0.002)	0.006 (0.006)	0.862	**0.010**	0.054
	Slow-to-fast ratio [–]	Central	8.259 (2.494)	8.84 (2.832)	9.867 (3.373)	9.561 (3.439)	**0.037**	0.402	0.262
Spindles	Relative power [–]	Central	0.33 (0.032)	0.332 (0.035)	0.332 (0.036)	0.321 (0.035)	0.808	0.288	**0.040**
		Frontal	0.315 (0.023)	0.312 (0.029)	0.328 (0.025)	0.312 (0.036)	**0.049**	0.962	0.197
Slow waves	Duration [s]	Central	1.447 (0.111)	1.504 (0.107)	1.388 (0.102)	1.432 (0.111)	**0.048**	**0.021**	0.571
		Frontal	1.387 (0.105)	1.425 (0.092)	1.287 (0.098)	1.356 (0.116)	**0.001**	**0.032**	0.347

Note: The *p* values describe the significance of the difference at baseline, follow-up, and over time. Significant *p* values ($p < 0.05$) are highlighted in bold.
Abbreviations: iRBD, isolated REM sleep behaviour disorder; PSG, polysomnography; (N)REM, (non-)rapid eye movement; SD, standard deviation.

in the central electrodes, the relative power, while not being significantly different neither at baseline nor at follow-up, showed a significant difference in the time-progression, as it decreased in patients with iRBD and remained stable in controls (Table 3 and Figure 3).

3.3.4 | Slow waves

Slow waves were significantly shorter, both at baseline and at follow-up, in patients with iRBD compared to controls in the frontal as well as in the central areas (Table 3 and Figure 4). Interestingly,

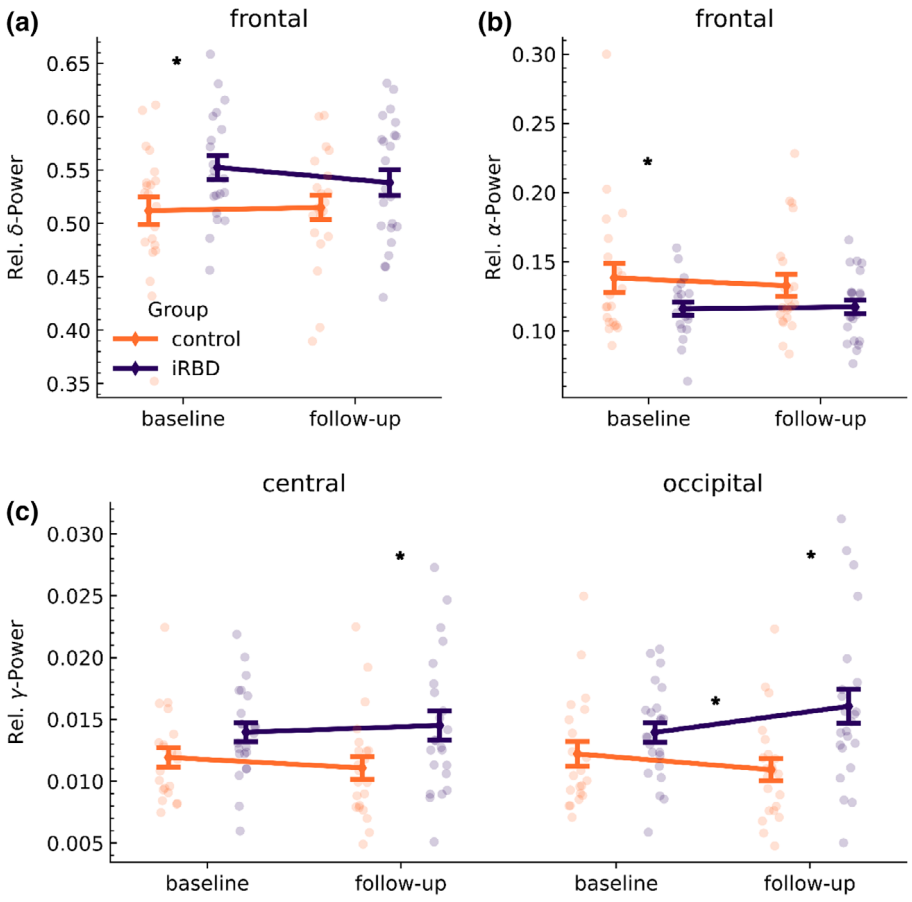

FIGURE 1 Electroencephalogram features in rapid eye movement (REM) sleep. The figure reports bandpower values measured during REM sleep for which a significant difference at baseline, follow-up or in the temporal progression between groups was observed: (a) δ-bandpower, (b) α-bandpower, and (c) γ-bandpower. For each graph, the brain region where the difference was observed is specified on top of the graph. Translucent points represent the values of each individual subject, while error bars showing the standard error are centred at the mean. Stars denote significant differences at baseline or follow-up. Stars in between baseline and follow-up denote significant difference in change over time. iRBD, isolated REM sleep behaviour disorder; Rel., relative.

Figure 4 shows that slow-wave duration seems to increase over time at the same rate in both groups. No other difference for slow-wave features were found between the groups.

4 | DISCUSSION

To the best of the authors' knowledge, this is the first study investigating the temporal evolution of sleep EEG features in patients with iRBD. At baseline, patients with iRBD showed significantly lower relative α-bandpower and significantly higher relative δ-bandpower during REM sleep in frontal channels. These differences disappeared at follow-up. Additionally, γ-bandpower was increased at follow-up in central and occipital channels. During NREM sleep, solely the slow-to-fast ratio was increased in patients with iRBD in central channels at baseline. Whilst, γ-bandpower was increased at follow-up in all channels in the iRBD group, with a significant difference in time progression in frontal channels. Sleep spindle relative power was increased in frontal channels in patients with iRBD at baseline but not at follow-up. In central channels, the relative spindle power showed a significant different time progression between groups, as it decreased over time in patients with iRBD and remained stable in controls. Slow-wave duration was decreased in patients with iRBD at both time-points.

4.1 | Slowing during REM and NREM

During REM sleep, δ-bandpower was increased at baseline in frontal channels in patients with iRBD, whereas α-bandpower was found to be decreased. The slow-to-fast ratio at baseline in central channels was the only bandpower feature measured during NREM that showed significant differences between groups. All in all, these results hint at slowing of the EEG at baseline, a result in line with literature (Fantini et al., 2003; Iranzo et al., 2010; Massicotte-Marquez et al., 2005; Sasai et al., 2013), although the slow-to-fast ratio did not significantly differ between groups in REM sleep. These differences were not significant at follow-up indicating that values in both groups become more similar over time. These results imply that, contrary to expectations, EEG slowing does not undergo progression in patients with iRBD. Several works showed that there is a bidirectional relationship between sleep-related breathing disorder and neurodegeneration (Ibrahim et al., 2024). In particular, patients with sleep-related breathing disorders showed increased values of plasma alpha-synuclein (Sun et al., 2019), increased amyloid burden (Sharma et al., 2018), as well as neuroimaging biomarkers of cognitive impairment and dementia (Carvalho et al., 2023). As all the subjects in the control group had a diagnosis of sleep-related breathing disorder, the lack of difference in slowing between groups at follow-up could be potentially ascribable to this. In other words, our control group might also show abnormal slowing over time, which could be the cause of the lack of significant difference at follow-up between the groups.

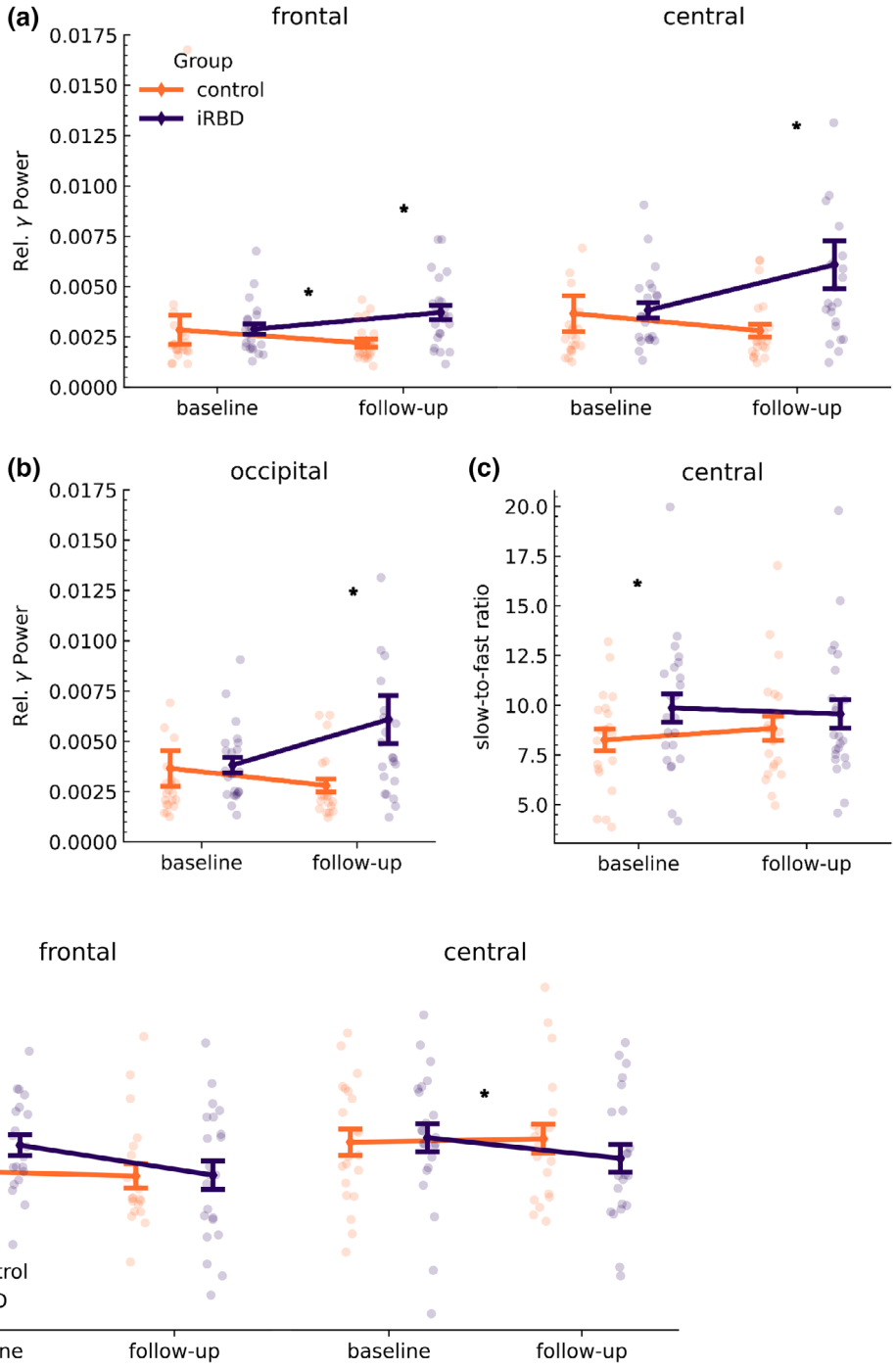

FIGURE 2 Electroencephalogram features in non-rapid eye movement (NREM) sleep. The figure reports bandpower values measured during NREM sleep for which a significant difference at baseline, follow-up or in the temporal progression between groups was observed: (a,b) γ-bandpower and (c) slow-to-fast ratio. For each graph, the brain region where the difference was observed is specified on top of the graph. Translucent points represent the values of each individual subject, while error bars showing the standard error are centred at the mean. Stars denote significant differences at baseline or follow-up. Stars in between baseline and follow-up denote significant difference in change over time. iRBD, isolated REM sleep behaviour disorder; Rel., relative.

FIGURE 3 Spindle features. The figure reports relative spindle power, the only feature for which a significant difference at baseline, or in the temporal progression between groups was observed. For each graph, the brain region where the difference was observed is specified on top of the graph. Translucent points represent the values of each individual subject, while error bars showing the standard error are centred at the mean. Stars denote significant differences at baseline. Stars in between baseline and follow-up denote significant difference in change over time. iRBD, isolated rapid eye movement sleep behaviour disorder; Rel., relative.

4.2 | The γ-bandpower

During both REM and NREM sleep, relative γ-bandpower showed a peculiar temporal progression, not differing at baseline and showing significant increases in the iRBD group at follow-up. Very little is known about the role of changes in the γ-band during REM or NREM sleep in iRBD, as most studies use a lowpass filter with a threshold below this frequency band. One study recorded increased absolute γ-bandpower during NREM in patients with iRBD and found that its absolute power is increased in phasic compared to tonic REM sleep (Valomon et al., 2021). In theory, these findings could support the results of our study, if an increase in the proportional duration of

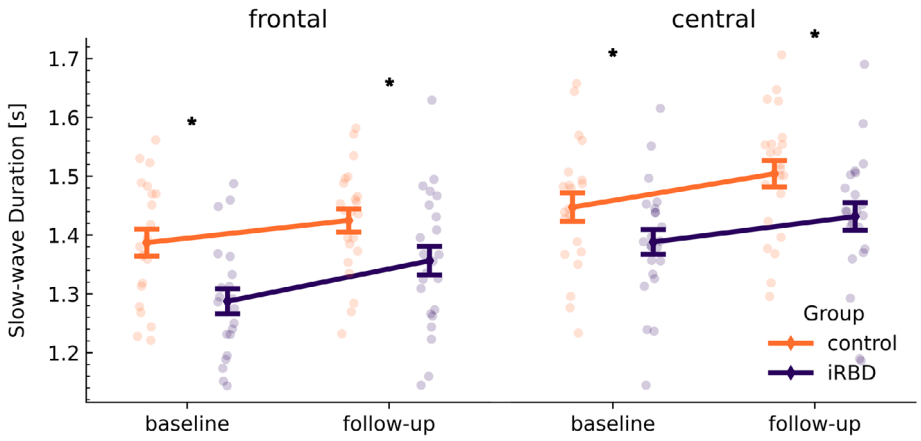

FIGURE 4 Slow wave features. The figure reports relative slow wave duration, the only feature for which a significant difference at baseline or follow-up between groups was observed. For each graph, the brain region where the difference was observed is specified on top of the graph. Translucent points represent the values of each individual subject, while error bars showing the standard error are centred at the mean. Stars denote significant differences at baseline or follow-up. iRBD, isolated rapid eye movement sleep behaviour disorder.

phasic REM sleep occurred over time in patients with iRBD. As the durations of tonic and phasic REM sleep were not measured, such an assertion cannot be made, and remains to be explored in a future study. As to the biological significance of these findings, one could argue that the recorded increase of relative γ-power over time might instead be due to the presence of high-frequency noise due to muscular artefacts caused by the loss of REM atonia in patients with iRBD. However, this is unlikely to be the case, as segments with muscular artefacts were specifically excluded with artefact removal, and the effect is present during NREM sleep as well. Activity in the γ-frequency band is known for its association with memory formation through the theta–gamma phase-amplitude coupling, caused by synchronised activity from the hippocampus (Bragin et al., 1995; Buzsáki et al., 1983), which results in a low-frequency wave with high-frequency ripples at the peak (Colgin, 2015; Tort et al., 2009). While it might be intuitive to think that increased power in the γ-frequency band predicts better memory formation ability, a study using a mouse model of DLB found increased power in the γ-frequency (Stylianou et al., 2020). It could be hypothesised that the increase in this frequency is associated with the development of dementia, representing a disturbance of hippocampal-cortical communication or a compensatory mechanism as reported in Alzheimer's disease (Gaubert et al., 2019). If confirmed, γ-activity may prove to be a useful biomarker for tracking the progression of α-synuclein-dependent neurodegeneration. However, more conclusive research comparing γ-bandpower during sleep to cognitive performance in prodromal and overt neurodegenerative disorders is needed. Furthermore, as it was shown that patients with iRBD have increased delta–gamma coupling in phasic REM sleep (Tea-Gon et al., 2024), future work should explore these aspects as well.

4.3 | Other considerations on spectral bandpowers

Next to δ-bandpower, previous works showed increased absolute θ-power in patients with iRBD, both in REM and NREM sleep (Fantini et al., 2003; Iranzo et al., 2010). This study did not find any significant differences between groups in this band. Similarly, β-bandpower, which some studies found to be decreased in patients with iRBD (Fantini et al., 2003; Sasai et al., 2013), was not found to be significantly differing between the patients with iRBD and controls in this work. Reasons for these discrepancies compared to previous works could be low power due to the sample size, as well as the use of investigating in this study relative powers, where slight changes in one band might be overshadowed by stronger changes in other frequency ranges.

Interestingly, our findings reveal some topological dependence. Slowing was found at baseline in REM sleep in frontal channels, while in NREM sleep in central channels. On the other side, the increase of γ-bandpower appears to be a more generalised brain phenomenon both in REM and in NREM sleep.

4.4 | Spindle features

Relative power of sleep spindles in frontal channels differed at baseline between the groups, showing an increase in power in patients with iRBD. This is remarkable as the opposite was shown previously (Sunwoo et al., 2021). While the relative power of spindles in central channels did not differ between the groups, the time dependent development did so significantly, with relative power decreasing over time in patients with iRBD as opposed to controls, where this value remained stable. This may imply that the detection of a difference in spindle relative power might depend on the time-point of the measurement. In other words, the more advanced the neurodegeneration, the more likely it might be to detect differences in relative spindle power. Despite the changes in relative power of spindles, overall σ-bandpower was not different at either time-point or in time-progression between the groups. Notably, spindle density did not differ between the patient groups, contrary to previous data (Christensen et al., 2014; O'Reilly et al., 2015), but in line with one study, where also no difference was found (Sunwoo et al., 2021).

4.5 | Slow-wave features

The only slow-wave features showing significant differences between the groups was slow-wave duration in frontal and central channels, with duration being decreased in patients with iRBD at baseline and

follow-up. Additionally, slow-wave duration seems to increase over time at the same rate in both groups. The former result runs contrary to a previous study, which found this variable to be increased in patients with iRBD (Sunwoo et al., 2021). However, in that previous work, only slow oscillations (i.e., with a frequency <1 Hz) were analysed. The concomitant increase of slow-wave duration in both groups over time might be an effect of ageing. In fact, previous research indicated such an effect, by finding an increase in the duration of both positive and negative peaks in older individuals (Carrier et al., 2011). As a fixed minimum peak-to-peak amplitude of 75 μV was used to detect slow waves, the algorithm may have excluded low-amplitude waves of shorter duration, thus introducing a bias towards higher slow-wave duration values (Muehlroth & Werkle-Bergner, 2020). When analysing our results, we also observed that amplitude values were on average lower at follow-up in this study, though not reaching statistical difference (Supplemental Table S4). Similarly, slow-wave density, while being lower at follow-up in both groups, did not differ between time-points and groups (Table S4). These findings are in line with a previous study (Latreille et al., 2011), but not with the mentioned study on slow oscillations (Sunwoo et al., 2021). Slow waves have been shown to be protective for neurodegeneration (Ju et al., 2017) and for progression of motor symptoms in patients with PD (Schreiner et al., 2019; Tao et al., 2024). As none of the patients with iRBD converted to an overt neurodegenerative disease in the timeframe of the study, future studies should investigate the role of slow waves and of K-complexes (as forerunners of slow waves; Galbiati et al., 2021) as predictors of phenoconversion.

4.6 | Strengths and weaknesses

Our study has several strengths. First, the use of previously validated automatised detection algorithms for sleep stages, artefacts, spectral powers, sleep spindles and slow waves increases the reproducibility of the results and may serve as a starting point for future investigations. Additionally, the employment of linear-mixed effects models allowed for the detection of differences in temporal progression. Another strength of this study is the similarity in clinical and demographic characteristics as well as v-PSG indices between groups and time-points.

Due to its retrospective nature, an important limitation of our study is the absence of systematic assessment of cognition with standardised cognitive batteries. Future studies should evaluate the correlation between the time progression of sleep EEG features and cognition in patients with iRBD. The low sample size and the retrospective construction of the two groups are other significant limitations of this study. As the control group consisted of patients with sleep-related breathing disorders, which might also be at higher risk of neurodegeneration compared to a healthy population (Ibrahim et al., 2024), our analyses might suffer from a bias. The retrospective design might be the cause of inhomogeneities in the groups. The use of only six EEG electrodes, furthermore, prevented us from doing a finer analysis on changes of EEG features in several brain regions. Additionally, as the study was exploratory, we decided not to perform multiple test corrections, as proposed in literature (Althouse, 2016; Bender & Lange, 2001). This implies that future confirmatory studies are needed to verify our findings in other cohorts. A follow-up study with more subjects and a more limited selection of tested features could solidify the results obtained in this study. Additionally, such a study could incorporate more time-points and thereby further investigate sleep EEG changes over time. Another limitation of the study is the high amount of medication use both in the iRBD group, as well as in controls. Although antidepressants might unmask RBD, depression is frequent in iRBD and is a non-motor early symptom of alpha-synucleinopathies, therefore excluding patients taking antidepressant may results in a selection bias. Our statistical analyses were corrected for antidepressants, benzodiazepines (including clonazepam), and hypnotics use. We are aware that some of our subjects were taking medications like antipsychotics and antiepileptics, which might have an influence on the EEG. However, due to the low sample size, the low number of patients taking them, as well as the lack of significant difference in their intake between groups, we decided not to include them in the statistical analyses. Future studies with larger cohorts should investigate their effects. Finally, studies investigating the correlation between the progression of these features and clinical symptoms could provide valuable insights into the biological and clinical relevance of temporal changes in sleep EEG.

5 | CONCLUSIONS

In conclusion, this study represents a pioneering investigation into the temporal evolution of sleep EEG features in patients with iRBD, revealing novel findings especially regarding the significant increase in γ-bandpower over time in patients with iRBD. The study underscores the importance of considering longitudinal changes over time of these features when attempting to understand the progression of iRBD to overt neurodegenerative disorders.

AUTHOR CONTRIBUTIONS

Raphael Angerbauer: Methodology; software; formal analysis; data curation; writing – original draft. **Ambra Stefani:** Data curation; supervision; writing – review and editing. **Jennifer Zitser:** Writing – review and editing. **Abubaker Ibrahim:** Data curation; writing – review and editing. **Victoria Anselmi:** Data curation; writing – review and editing. **Merve Aktan Süzgün:** Data curation; writing – review and editing. **Kristin Egger:** Data curation; writing – review and editing. **Elisabeth Brandauer:** Writing – review and editing. **Birgit Högl:** Supervision; writing – review and editing. **Matteo Cesari:** Conceptualization; methodology; writing – review and editing; funding acquisition; supervision.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

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

ETHICS APPROVAL STATEMENT

The study was approved by the ethics committee of the Medical University of Innsbruck (1054/2020).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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