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Original Article

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Nocturnal sleep dynamics alterations in the early stages of behavioral variant frontotemporal dementia

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Abstract

Study Objectives: Sleep disorders have been recognized as an integral component of the clinical syndrome in several neurodegenerative diseases, including Alzheimer's disease (AD). However, limited data exist for rarer types of neurodegenerative diseases, such as behavioral variant frontotemporal dementia (bvFTD). This study aims to analyze EEG power spectra and sleep stage transitions in bvFTD patients, hypothesizing that bvFTD may show distinctive sleep stage transitions compared to patients with AD.

Methods: Eighteen probable bvFTD patients and 18 age- and sex-matched probable patients with AD underwent overnight polysomnography (PSG) and completed sleep disorders questionnaires. Sleep questionnaires, full-night EEG spectra, and sleep stage transition indexes were compared between groups.

Results: bvFTD patients had higher Insomnia Severity Index (ISI) scores (95% confidence intervals [CI]: 0, 5) and reported poorer sleep quality than AD patients ($p < .01$). Compared to AD, bvFTD patients showed higher N1 percentage (95% CI: 0.1, 6), lower N3 percentage (95% CI: –13.6, –0.6), higher sleep–wake transitions (95% CI: 1.49, 8.86) and N1 sleep–wake transitions (95% CI: 0.32, 6.1). EEG spectral analysis revealed higher spectral power in bvFTD compared to patients with AD in faster rhythms, especially sigma rhythm, across all sleep stages. In bvFTD patients, sleep–wake transitions were positively associated with ISI.

Conclusions: Patients with bvFTD present higher rates of transitions between wake and sleep than patients with AD. The increased frequency of sleep transitions indicates a higher degree of sleep instability in bvFTD, which may reflect an imbalance in sleep–wake-promoting systems. Sleep stage transitions analysis may provide novel insights into the sleep alterations of patients with bvFTD.

Key words: behavioral variant frontotemporal dementia; Alzheimer's disease; EEG spectra; sleep stage transitions; sleep questionnaires

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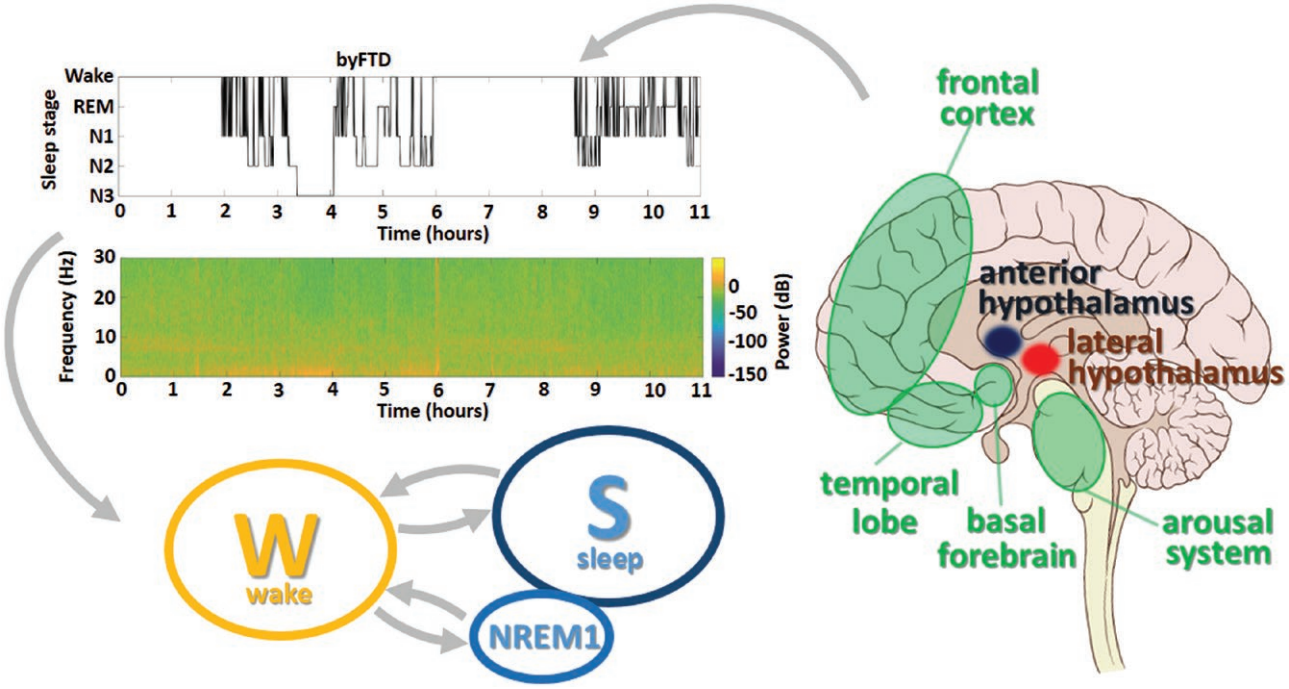
Graphical Abstract



Statement of Significance

Sleep alterations remain poorly understood in rare conditions like behavioral variant frontotemporal dementia (bvFTD). We conducted a comprehensive sleep assessment comparing patients with bvFTD and AD in the early stages of the diseases, focusing on sleep dynamics analyses, a sleep feature scarcely investigated in neurodegenerative disorders. BvFTD exhibited a higher occurrence of transitions between wakefulness and sleep, indicating greater sleep instability likely due to alterations in sleep–wake regulation mechanisms, possibly involving also the orexinergic system. Sleep dynamics analyses may serve as a potential diagnostic tool to characterize bvFTD. Further studies are warranted to confirm these findings, enabling novel therapeutic strategies that may also target the orexinergic system, with the possibility of improving sleep and consequently the quality of life for both patients and caregivers.

Frontotemporal lobar degeneration (FTLD) encompasses a spectrum of neuropathological conditions characterized by neurodegeneration and atrophy, primarily affecting the frontal and temporal lobes [1]. Recent evidence has shown that FTLD is more common than previously described [2]. Current diagnostic criteria recognize three main clinical syndromes of FTLD: the behavioral variant of frontotemporal dementia (bvFTD), the semantic variant of primary progressive aphasia, and the non-fluent variant of primary progressive aphasia [3, 4]. bvFTD is the most common clinical subtype of FTLD, with an estimated incidence rate of 0.83 per 100 000 person-years, and clinically presents with behavioral and personality changes, and dysexecutive symptoms [2, 5]. Specifically, patients with bvFTD present with disinhibition, apathy, loss of sympathy or empathy, perseverative or compulsive behaviors, and hyperorality [5]. The diagnosis of bvFTD remains challenging due to the absence of reliable disease biomarkers and the high variability in clinical presentation, which may lead to misdiagnosis with psychiatric disorders [5]. Recent studies have highlighted a high prevalence of sleep disorders in bvFTD, in addition to the typical behavioral and cognitive symptoms [6, 7]. Sleep and circadian rest–activity rhythm alterations have been recognized as a crucial component of the clinical syndrome in several neurodegenerative disorders, posing significant impacts on both patients and caregivers [7]. Disruptions in sleep and rest–activity rhythm may precede the onset of motor and/or cognitive symptoms, as documented in neurodegenerative diseases characterized by abnormal accumulation of alpha-synuclein protein (i.e. α-Synucleinopathies) [8], and may contribute to accelerating cognitive decline in Alzheimer's disease-related pathology [9, 10]. However, while sleep alterations have been extensively investigated in Alzheimer's disease (AD) and α-Synucleinopathies (Parkinson's disease, multiple system atrophy, and Lewy body dementia), there is sparse knowledge regarding sleep alterations in FTLD [10, 11]. Preliminary studies indicated that patients with FTLD commonly report complaints of insomnia, sleep-disordered breathing, and excessive daytime sleepiness, and presented with peculiar alterations in sleep patterns and rest–activity rhythm [6–14]. Additionally, it has been reported that patients with FTLD displayed a two-fold higher prevalence of sleep disturbances compared to AD [15]. Nonetheless, the majority of studies have used sleep questionnaires or clinical interviews to characterize sleep alterations in patients with FTLD, while studies utilizing

objective sleep measures, such as polysomnography (PSG) or actigraphy, are rare [12–19]. Collectively, the few available PSG studies conducted on FTLD have shown various alterations in sleep parameters [16–19]. These studies documented reduced total sleep time, sleep efficiency, and number of NREM–REM cycles in patients with FTLD compared to AD and controls, along with decreased percentages of NREM sleep stages 1 and an increased percentage of NREM stage 2 compared to the patients with AD [16, 17]. Notwithstanding this, alterations in sleep macrostructure measured by PSG are insufficient to fully characterize the complexity of sleep alterations experienced by patients with FTLD [16–18]. Thus, conventional sleep parameters analyses may fail to delineate the dynamic fluctuation of overnight sleep and its continuity providing only a static picture of sleep. Recently, some complementary and potentially more sensitive analyses have been proposed to characterize sleep fragmentation such as cyclic alternating pattern (CAP) analyses. CAP analyses assess sleep continuity beyond traditional sleep macrostructure metrics. Maestri et al. investigated CAP in patients with FTLD and revealed a peculiar pattern of sustained sleep instability characterized by fewer but longer CAP sequences, decreased CAP slow components (A1 phases), and an increase in fast CAP components (A2 and A3 phases), compared to controls [19]. In recent years, another approach that has emerged as a complementary method for assessing sleep continuity and quality beyond traditional sleep macrostructure metrics is the analysis of nocturnal sleep stage sequences and transitions [20–24]. This analytical framework involves computing transitions between and within all sleep stages to identify overall sleep–wake instability, sleep phase-specific instability, and sleep stage-specific instability, with the key advantage of utilizing already available data derived from sleep macrostructure [20–24]. Sleep stage transition analyses have successfully characterized sleep continuity alterations among patients with fibromyalgia and primary sleep disorders such as those with narcolepsy and insomnia who are known to experience a high degree of sleep fragmentation [21–26]. However, to the best of our knowledge, sleep stage transitions have never been investigated in patients with neurodegenerative diseases. The aim of this study was to analyze nocturnal sleep stage sequences and transitions in patients with bvFTD and AD hypothesizing that individuals with bvFTD may exhibit a distinctive organization of sleep stage sequences. In particular, we hypothesized that bvfTD may have increased sleep transitions compared to patients with AD. As a secondary aim, we assessed whether EEG spectral features could discriminate between bvFTD and AD patients. Finally, we investigated the relationship between sleep stage transitions and the sleep disturbances subjectively reported by patients with bvFTD.

Methods

Participants

Eighteen patients with probable bvFTD (9 men, mean age 70.11 ± 8.23 years) and 18 patients with probable Alzheimer's dementia (6 men, mean age 69.34 ± 8.14 years) were recruited from the Center for Neurodegenerative Diseases and Aging Brain in Tricase, between July 2022 and September 2023. Patients underwent a standardized diagnostic protocol that comprised neurologic evaluation, and neuropsychological assessment (including administration of the Mini-Mental State Examination [MMSE] and the Neuropsychiatric Inventory [NPI]). The NPI was developed to assess neuropsychiatric symptoms in patients with neurodegenerative disorders but has also been used in a variety of neurological diseases [27]. The NPI is based on responses from primary caregivers and It encompasses several questions assessing 12 main domains including delusions, hallucinations agitations, depression, anxiety, euphoria, apathy disinhibition irritability aberrant motor behaviors, sleep disorders, and eating disorders [27]. Furthermore, patients underwent 3-Tesla brain MRI, and lumbar puncture for the CSF biomarkers of neurodegeneration assay. All patients fulfilled the current research and diagnostic criteria for probable bvFTD and probable AD [3, 28]. We enrolled bvFTD and AD patients with comparable age at onset and dementia severity, as assessed by the clinical dementia rating scale (all patients' CDR global score between 0.5 and 1) [29], to reduce the potential confounding effects of these clinical features. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local health trust's ethics committee. Written informed consent was obtained from all participants.

Hypnological evaluation

All patients underwent a comprehensive sleep evaluation performed by a certified somnologist and completed sleep questionnaires. The Epworth Sleepiness Scale was used to assess excessive daytime sleepiness, the Insomnia Severity Index (ISI) to evaluate insomnia severity, and the Pittsburgh Sleep Quality Index (PSQI) to assess overall sleep quality [30–32]. Obstructive sleep apnea risk was evaluated using the STOP-Bang questionnaire while REM sleep behavior disorder (RBD) risk was assessed through the REM sleep behavior disorder screening questionnaire [33, 34]. Restless legs syndrome was clinically evaluated based on the International Restless Legs Syndrome Study Group criteria [35]. Finally, the reduced Morningness–Eveningness Questionnaire (rMEQ) was used to assess chronotype [36]. All questionnaires were completed by the patients with the support of the patient's primary caregivers.

Sleep macrostructure

All patients underwent an overnight, home-based PSG. PSG was performed using the Embletta MPR Sleep System plus ST proxy, which included EEG (F3, F4, C3, C4, O1, and O2 referred to bilateral mastoids), electrooculography (EOG), submental-electromyography (EMG), respiratory inductance plethysmography with chest and abdominal belts, nasal pressure sensor, pulse-oximeter, two-lead electrocardiogram (ECG), body position detector, and bilateral EMG of anterior tibialis and flexor digitorum superficialis. Patients were asked to go to bed and rise at their habitual time. Recordings were manually scored using the Remlogic software according to the AASM scoring rules [37]. The following sleep macrostructure parameters were computed: time in bed, total sleep time (TST), sleep onset latency (SOL, time difference between lights out and the first sleep stage epoch), wake after sleep onset (WASO), awakenings number (Awk), percentage of TST spent in NREM sleep stage 1 (N1%), NREM sleep stage 2 (N2%), slow-wave sleep (N3%), and REM sleep (REM%), periodic limb movement index (PLM) and limb movement index (LM).

Arousals were scored according to AASM rules and reported as arousal index, PLM-arousal index, and respiratory arousal index. Finally, the following respiratory-related sleep metrics were computed: apnea–hypopnea index, oxygen desaturation index (oxygen desaturation events ≥3%/TST an hour), mean oxygen saturation (mean SpO2%) and lowest SpO2 saturation (Lowest SpO2%).

Sleep stage shifts and transitions

Sleep stage shifts and transitions were calculated following the procedure described in previous studies [21, 36]. Specifically, we computed the absolute number of shifts between and within all stages (N1 shift, N2 shift, N3 shift, REM shift, and wake shift) and the following sleep transition indexes: transitions between wake and sleep (tWS), transitions between N1 sleep and wake (tN1-W), transitions between wake, NREM (any stage), and REM sleep (tW-NREM-REM), transition between wake, N1, N2, N3, and REM sleep (tW-N1-N2-N3-REM), and transitions between N1, N2, N3, and REM sleep (tN1-N2-N3-REM).

EEG spectral analysis

PSG recordings were visually inspected by an experienced sleep technician to identify noisy epochs. Full-night spectral analysis was carried out epoch-wise, by considering 2-second nonoverlapping segments in the Fast Fourier transform analysis. Spectral analysis was conducted using HypnoLab v.1.2 software (SWS Soft, Italy), considering the following EEG rhythms: slow oscillation (0.5–1 Hz), delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–15 Hz), and beta (15–20 Hz).

Relative spectral power was estimated in each epoch and for each rhythm on the F3-C3 channel. Subsequently, the median value was computed across all the epochs to provide a more reliable estimate per participant. Finally, relative power distributions were then derived for each rhythm and sleep stage.

Statistical analysis

Data were reported as median and interquartile range (IQR). Differences in demographic, clinical data, questionnaire scores, sleep macrostructure sleep dynamics, and EEG spectral features between patients with bvFTD and AD were analyzed by means of chi-squared and Mann–Whitney U tests. The relationship between clinical data, questionnaire scores, and sleep transition indexes was analyzed, separately for each group, through Spearman's rank correlation coefficient analysis. Statistical analyses were conducted using SPSS 19.0 and R. p-values < .05 were considered statistically significant.

Results

Demographic, clinical, and sleep questionnaires

Demographic, clinical data, and questionnaire scores of bvFTD and AD patients are reported in Table 1, along with the corresponding test statistics (chi-squared or Mann–Whitney U), p-values, and 95% confidence intervals (CI) for the difference between medians.

No significant group differences emerged in sex distribution ($\chi^2_{(1)} = 1.03$, p = ns), age, age at disease onset, disease duration, education, and BMI (all p = ns). There was no difference in the CDR-FTD total score between groups (Mann–Whitney $U = 136.5$, p = ns), but patients with bvFTD showed higher CDR-FTD Sum of Boxes scores (Mann–Whitney $U = 230$, $p < .05$) and higher scores in the CDR-FTD behavior domain (Mann–Whitney $U = 313$, $p < .0001$). Moreover, bvFTD patients showed higher NPI scores (Mann–Whitney $U = 245.5$, $p < .005$) and MMSE (Mann–Whitney $U = 234.5$, $p < .05$) than AD patients.

Regarding sleep questionnaires, patients with bvFTD had lower rMEQ scores (Mann–Whitney $U = 98$, $p < 0.05$), higher ISI scores (Mann–Whitney $U = 224.5$, $p < .05$), higher PSQI total scores (Mann–Whitney $U = 253.5$, $p < .005$), and were more likely to report poor sleep quality compared to AD patients ($\chi^2_{(1)} = 7.02$, $p < .01$).

Sleep macrostructure

Sleep macrostructure data are reported in Table 2. Patients with bvFTD exhibited higher N1% (Mann–Whitney $U = 227$, $p < .05$) and lower N3% (Mann–Whitney $U = 96$, $p < .05$) compared to AD patients. No further statistically significant differences were observed.

Sleep stage shifts and transitions

Sleep stage shifts and sleep transition indexes are reported in Table 3. Patients with bvFTD had a lower number of N3 shifts (Mann–Whitney $U = 53.5$, $p < .001$), a higher tWS index (Mann–Whitney $U = 244$, $p < .01$), and a higher tN1-W index (Mann–Whitney $U = 232$, $p < .05$) compared to patients with AD. Concerning correlation analysis, age in bvFTD was negatively associated with tW-N1-N2-N3-REM ($r_s = -.53$, $p < .05$) and tN1-N2-N3-REM ($r_s = -.56$, $p < .01$), while ISI score showed a positive association with tWS ($r_s = .51$, $p < .05$). We further investigated this association by means of Spearman's rank correlation coefficient analyses between tWS and ISI items reflecting difficulty falling asleep (ISI item 1), difficulty staying asleep (ISI Item 2), and early morning awakenings (ISI Item 3). tWS showed a positive association with ISI Item 2 ($r_s = .66$, $p < .005$) while no association emerged with ISI Item 1 ($r_s = .07$, p = ns) and ISI Item 3 ($r_s = .19$, p = ns). No significant associations were found between clinical data, questionnaire scores, and sleep transition indexes in AD patients.

Spectral analysis

Results of full-night spectral analysis are shown in Figures 1 and 2. Significant differences emerged in the sigma rhythm, with bvFTD patients showing higher spectral power compared to patients with AD in N1 sleep (Mann–Whitney $U = 218$, $p < .05$), N2 sleep (Mann–Whitney $U = 243$, $p < .005$), N3 sleep (Mann–Whitney $U = 229$, $p < .05$), and REM sleep (Mann–Whitney $U = 238$, $p < .01$). The same trend of differences was observed for the spectral power of beta rhythm in N2 sleep (Mann–Whitney $U = 216$, $p < .05$) and in REM sleep (Mann–Whitney $U = 233$, $p < .01$) and for the alpha rhythm in REM sleep (Mann–Whitney $U = 228$, $p < .05$). No group differences emerged in slow oscillation, delta, and theta rhythms.

Discussion

In this study, we compared sleep disorders questionnaires, sleep macrostructure, EEG spectral power in different frequency bands, and sleep stage sequences and transitions in patients with bvFTD and AD in the early stages of the disease. Only a few studies assessed the sleep of bvFTD patients with polysomnography and, to the best of our knowledge, our cohort represents the largest sleep study of bvFTD and the first to assess nocturnal sleep dynamics in these patients. Previous studies have documented that patients with FTLD often experience disturbed sleep and have an increased prevalence of sleep disorders. Nonetheless, these studies assessed mixed samples of FTLD patients (e.g. bvFTD and PPA) or patients at different disease stages [16–19].

The main result of our study is that bvFTD patients had a significantly higher frequency of stage transitions between wake and sleep and between light sleep and wake (indicated by higher tWS index and higher tN1-W index) compared to patients with AD with similar age at onset and dementia severity, a finding which suggests higher sleep instability in bvFTD.

Concerning sleep disorders questionnaires, bvFTD patients had significantly higher ISI and PSQI scores and were more likely to report poor sleep quality than AD patients.

Table 1. Demographic, Clinical Data, and Sleep Disorder Questionnaires of Patients With bvFTD and AD

	bvFTD *n* = 18 Median (IQR)	AD *n* = 18 Median (IQR)	χ^2 or Mann–Whitney *U*	*P*	95% CI for the difference between median	
					Lower	Upper
Male gender (%)	9 (50%)	6 (33.3%)	1.03	*ns*		
Age, years	73.09 (11.29)	71.02 (12.77)	181.5	*ns*	−5.05	6.98
Age at onset, years	68.78 (12)	67 (15.11)	170	*ns*	−5.95	6.49
Disease duration, years	3.06 (3.01)	3.55 (3.2)	156	*ns*	−1.91	1.97
Education, years	8 (6)	8 (8)	150.2	*ns*	−5	3
BMI	26.29 (9.96)	24.05 (4.5)	177	*ns*	−0.86	6.49
CDR	1 (0.38)	1 (0)	136.5	*ns*	−0	0
CDR-SoB	6.5 (2.38)	4.5 (1)	230	<.05	0.5	3
CDR-behavior	2 (1)	0.5 (0.5)	313	<.0001	1	2
MMSE	22 (7.75)	16.5 (8.75)	234.5	<.05	1	10
NPI	32 (8)	14 (15.75)	245.5	<.005	6	24
STOP-Bang	4 (2.75)	3.50 (2)	204	*ns*	−0	2
OSA risk						
Low risk (%)	4 (22.2%)	7 (38.9%)				
Intermediate risk (%)	8 (44.4%)	9 (50%)	2.88	*ns*		
High risk (%)	6 (33.3%)	2 (11.1%)				
ISI	6 (5.75)	3 (3.5)	224.5	<.05	0	5
Insomnia severity						
No Insomnia (%)	11 (61.1%)	15 (83.3)				
Subthreshold Insomnia (%)	5 (27.8%)	2 (11.1%)				
Moderate insomnia (%)	1 (5.6%)	1 (5.6%)	2.9	*ns*		
Severe insomnia (%)	1 (5.6%)	0				
ESS	5 (3.5)	5.5 (5.5)	157.5	*ns*	−3	3
EDS (%)	4 (22.2%)	2 (11.1%)	0.8	*ns*		
rMEQ	19 (2)	20 (2)	98	<.05	−3	-0
Chronotype						
Morning type (%)	9 (50%)	14 (77.8%)	3.1	*ns*		
Intermediate type (%)	9 (50%)	4 (22.2%)				
PSQI	8.5 (7)	5 (2.75)	253.5	<.005	1	6
Poor sleep quality (%)	14 (77.8%)	6 (33.3%)	7.2	<.01		
RBDSQ	3 (4)	2 (3)	186	*ns*	−1	2
Probable RBD (%)	3 (16.7%)	3 (16.7%)	0	*ns*		
RLS (%)	7 (38.9%)	6 (33.3%)	0.12	*ns*		

bvFTD, behavioral variant Frontotemporal Dementia; AD, Alzheimer's disease; IQR, interquartile range; CI, confidence interval; BMI, body mass index; CDR, clinical dementia rating scale; CDR-SoB, clinical dementia rating scale—sum of boxes; MMSE, Mini-Mental State Examination; NPI, neuropsychiatric inventory; OSA, obstructive sleep apnea; ISI, insomnia severity index; ESS, Epworth sleepiness scale; EDS, excessive daytime sleepiness; rMEQ, reduced Morningness–Eveningness questionnaire; PSQI, Pittsburgh sleep quality index; RBDSQ, REM sleep Behavior Disorder screening questionnaire; RBD, REM sleep behavior disorder; RLS, restless leg syndrome.

These findings align with those of previous studies by Bonakis et al. and Guarneri et al., who did not find differences in the prevalence of self-reported sleep disorders (i.e. excessive daytime sleepiness, RSL, RBD, NREM parasomnia, and sleep-disordered breathing) between bvFTD and AD patients [15, 16]. However, in contrast to our findings, these studies found no difference in insomnia prevalence between bvFTD and AD patients. This discrepancy may stem from the different approaches adopted to assess insomnia between studies (i.e. clinical interview vs psychometrically validated questionnaires).

In terms of sleep macrostructure, we found no significant differences regarding sleep duration (TIB and TST) and quality (SE%, SOL, WASO, and awakening frequency) between bvFTD and AD patients and no significant differences in respiratory parameters and PLM index, despite both bvFTD and AD patients showing a high PLM index (i.e. >15/hour).

Table 2. Sleep Macrostructure Data of Patients With bvFTD and AD

	bvFTD *n* = 18 Median (IQR)	AD *n* = 18 Median (IQR)	Mann–Whitney *U*	*P*	95% CI for the difference between the median	
					Lower	Upper
TIB, min	562.6 (114.5)	559.65 (46.25)	157.5	*ns*	−71.8	47.1
TST, min	330.25 (114.55)	410 (96.07)	122	*ns*	−107.5	30.5
SOL, min	14.15 (37.97)	4.15 (14.32)	219.5	*ns*	−0.1	23.4
WASO, min	147.5 (59.17)	132.65 (81.6)	194	*ns*	−22.5	70.5
SE, %	68.5 (15.67)	76.15 (16.8)	113	*ns*	−16.4	2
Awk. *n*°	40.5 (20.5)	26.5 (20.75)	221	*ns*	−1	23
N1%	12.3 (3.45)	9.65 (6.65)	227	<.05	0.1	6
N2%	32 (9.08)	33.8 (7.3)	115	*ns*	−9.1	1.2
N3%	17.5 (12.2)	20.6 (13.85)	96	<.05	−13.6	−0.6
REM%	11.65 (5.62)	9.05 (5.77)	222.5	*ns*	−0	6.7
Wake%	29.78 (12.12)	23.10 (17.2)	201	*ns*	−3.2	14.55
PLM index	28.65 (38.37)	28 (27.07)	164	*ns*	−14.7	17.4
LM index	40.15 (50.12)	51 (30.25)	155	*ns*	−21.2	18.1
Arousal index	12.75 (23.64)	8.12 (4.51)	113	*ns*	−1.32	14.05
PLM-arousal index	1.59 (3.60)	1.29 (0.67)	183	*ns*	−0.47	1.34
Respiratory arousal index	1.49 (3.21)	0.88 (3.61)	173	*ns*	−1.07	1.73
AHI	8.7 (8.90)	9.1 (11.72)	154	*ns*	−6.3	6.1
ODI	7.7 (9.45)	8.2 (10.32)	153.5	*ns*	−6	5
Mean SpO2%	94 (2.57)	94.45 (1.67)	100.5	*ns*	−2.3	0
Lowest SpO2%	84.5 (7.75)	86.5 (6)	109	*ns*	−7	1

bvFTD, behavioral variant Frontotemporal Dementia; AD, Alzheimer's disease; IQR, interquartile range; CI, confidence interval; TIB, time in bed; TST, total sleep time; SOL, sleep onset latency; WASO, wake after sleep onset; SE, sleep efficiency; Awk, nocturnal awakenings; N1, NREM sleep stage 1; N2, NREM sleep stage 2; N3, NREM sleep stage 3, REM, rapid eye movement; PLM, periodic limb movement; LM, limb movement; AHI, apnea–hypopnea index; ODI, oxygen desaturation index.

Table 3. Sleep Stage Shifts and Sleep Transition Index of Patients With bvFTD and AD

	bvFTD *n* = 18 Median (IQR)	AD *n* = 18 Median (IQR)	Mann–Whitney *U*	*P*	95% CI for the difference between median	
					Lower	Upper
Sleep dynamics						
N1 shifts, *n*°	71 (30)	52 (31.75)	217.5	*ns*	−3	34
N2 shift, *n*°	40.5 (27.25)	46 (16)	125	*ns*	−17	4
N3 shift, *n*°	7.5 (5.75)	15 (7.5)	53.5	<.001	−9	−3
REM shift, *n*°	12.5 (7.75)	11 (8)	174.5	*ns*	−4	5
Wake shift, *n*°	41.5 (20.25)	27.5 (21.5)	222.5	*ns*	−0	23
Transition indexes						
tWS	13.75 (7)	7.27 (6.7)	244	<.01	1.49	8.86
tN1-W	11.05 (4.72)	7.71 (4.22)	232	<.05	0.32	6.1
tW-NREM-REM	90.97 (33.4)	73.27 (40.79)	221	*ns*	−2.6	46.84
tW-N1-N2-N3-REM	140.29 (45.01)	111.92 (71.05)	205	*ns*	−9.8	57.04
tN1-N2-N3-REM	83.41 (52.70)	78.90 (26.45)	149	*ns*	−28.89	20.33

bvFTD, behavioral variant Frontotemporal Dementia; AD, Alzheimer's disease; IQR, interquartile range; CI, confidence interval; tWS, transitions between wake and sleep; tN1-W, transitions between N1 sleep and wake; tW-NREM-REM, transitions between wake, NREM sleep (any stage), and REM sleep; tW-N1-N2-N3-REM, transition between wake, N1, N2, N3, and REM sleep; tN1-N2-N3-REM, transitions between N1, N2, N3, and REM sleep.

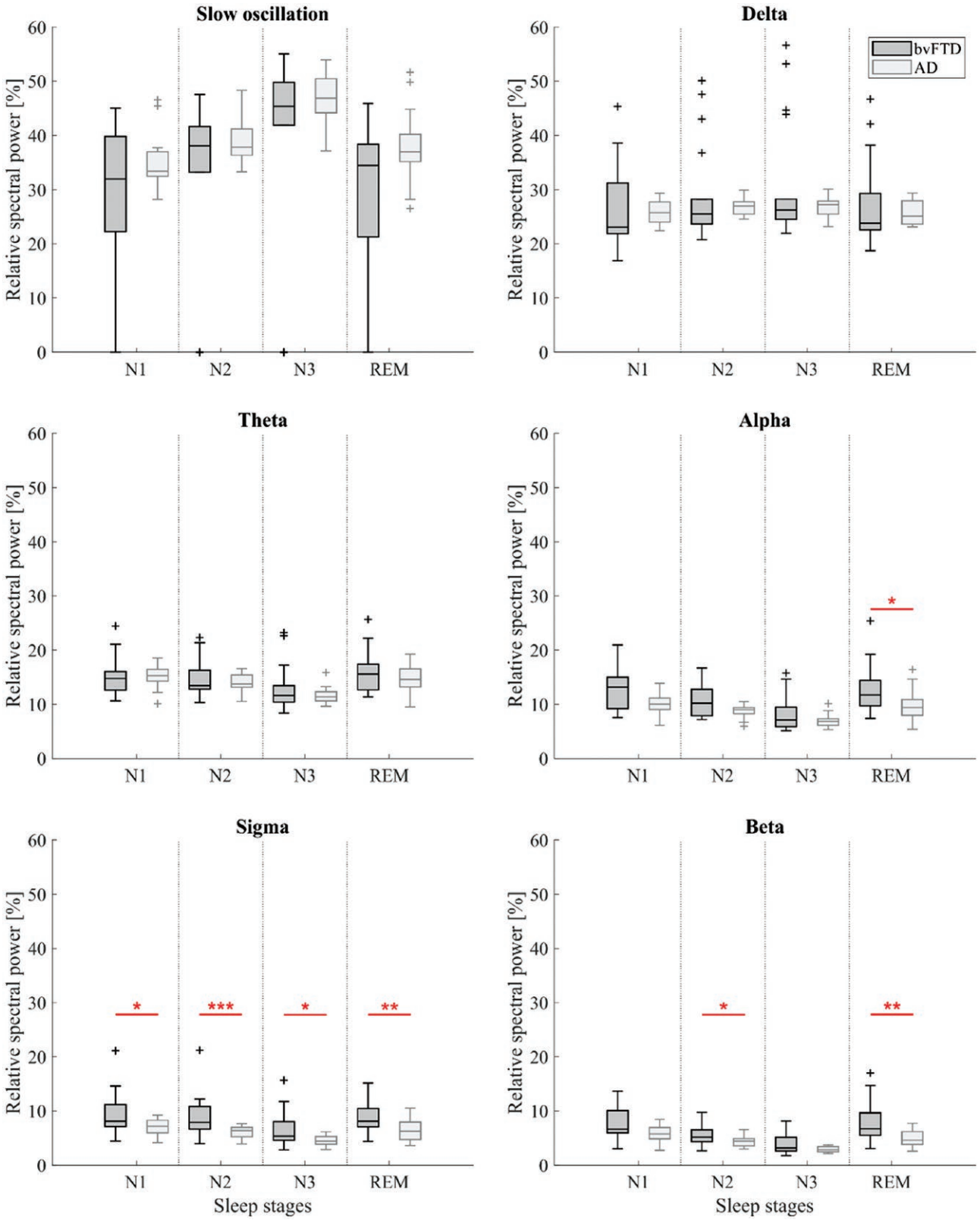


Figure 1. Relative spectral power for each sleep stage of bvFTD (dark gray) and AD (light gray). bvFTD, behavioral variant Frontotemporal Dementia; AD, Alzheimer's Disease. N1, NREM sleep stage 1; N2, NREM sleep stage 2; N3, NREM sleep stage 3; REM, rapid eye movement; * ($p < .05$), ** ($p < .01$), *** ($p < .005$).

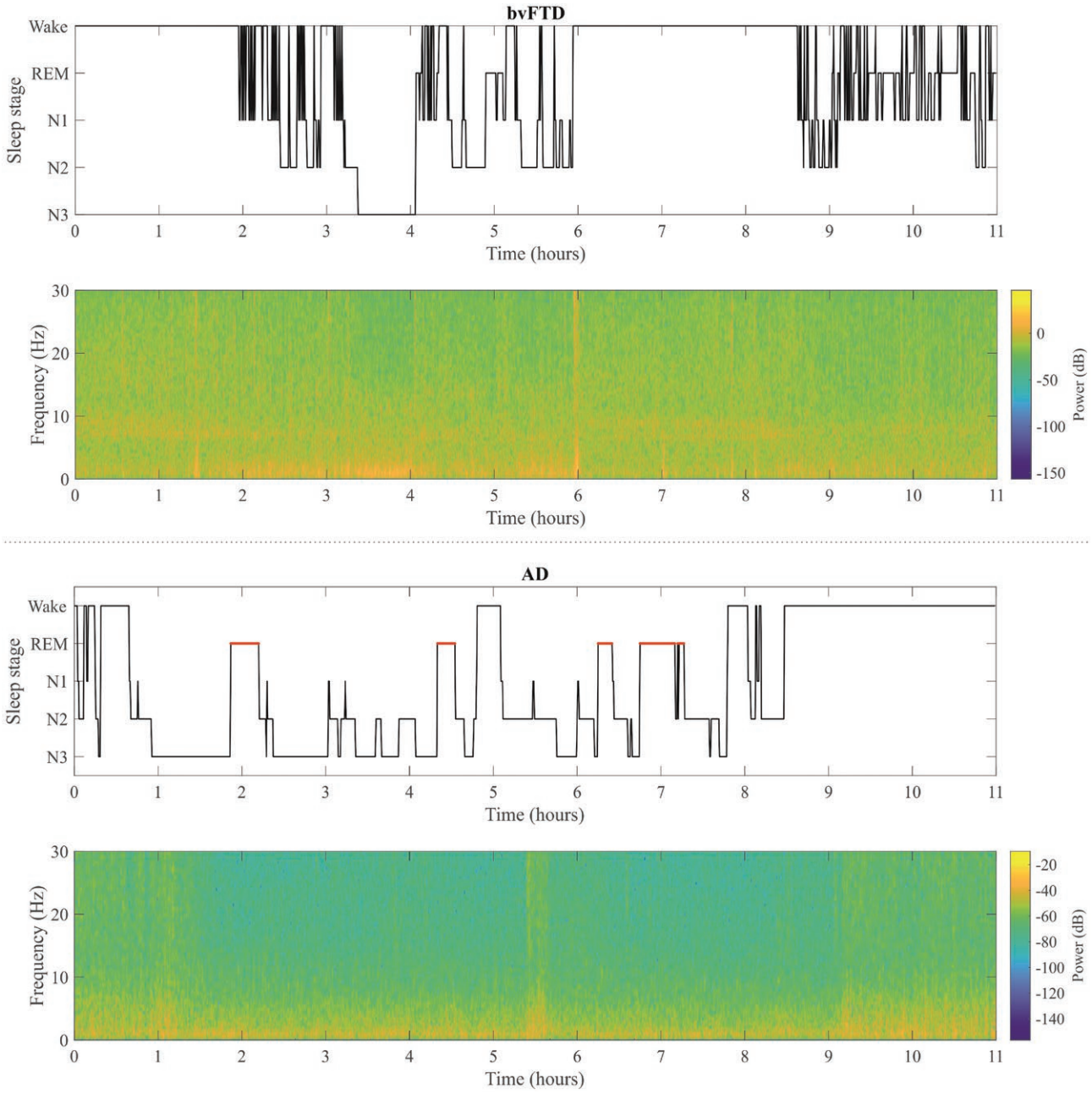


Figure 2. Illustrative full-night spectrograms (lower panels) and corresponding hypnograms (upper panels) of a patient with bvFTD and a patient with AD. bvFTD, behavioral variant Frontotemporal Dementia; AD, Alzheimer's disease.

Our results are consistent with those of Kundermann et al. who reported no differences in traditional sleep macrostructure metrics in a smaller sample of bvFTD and AD patients [17]. However, we found that bvFTD patients spent more time in N1 sleep and less time in N3 sleep compared to AD patients. These findings contrast with the study by Bonakis et al., which found that the only difference between bvFTD and AD patients was a lower number of NREM–REM cycles in bvFTD patients. Additionally, their study showed that both bvFTD and AD patients spent more time in N1 sleep, less time in N2 sleep, and had increased apnea–hypopnea index compared to controls [16]. Unfortunately, our study lacks a control group primarily due to the inherent challenge of enrolling healthy individuals over 65 years old among participants referred to a center specialized in neurodegenerative diseases, thereby preventing us from directly assessing where patients with bvFTD stand in terms of sleep alterations compared to the general population.

Nonetheless, when comparing the sleep macrostructure data of our bvFTD patient cohort with those of the Multi-Ethnic Study of Atherosclerosis sleep cohort, bvFTD patients showed longer total sleep time ($p < .0001$, 95% CI: 36.02, 112.64), lower sleep efficiency ($p < .05$, 95% CI: −14.39, −1.85), and higher WASO ($p < .0005$, 95% CI: 26.68, 87.33) [38, 39]. Noteworthy, this pattern of increased sleep duration and reduced sleep quality aligns with the results of a recent study that investigated sleep alterations in patients with bvFTD and controls through actigraphy [12].

Regarding EEG spectral analysis, the spectral power of high-frequency bands was significantly increased in bvFTD compared to AD patients. Specifically, bvFTD patients showed higher spectral power of the alpha and beta bands during REM sleep, higher

spectral power of the beta band in N2 sleep, and higher spectral power of the sigma band across all sleep stages compared to AD patients.

Over the past few decades, alterations in brain oscillations have been extensively studied in AD, both in animal models and humans, particularly through resting-state EEG (rsEEG), and have been correlated with cognitive dysfunction as well as the accumulation of amyloid-beta and tau proteins [40]. In AD, several studies have also shown alterations in EEG frequency components during sleep [41]. Reduced slow-wave activity, spindles, and K-complexes density during NREM sleep, along with increased low-frequency rhythms coupled with a reduction of high-frequencies during REM sleep, are among the most consistent quantitative EEG findings in AD patients [42, 43]. These alterations have been associated with the degree of cognitive decline and atrophy in the brain regions most affected during the course of AD [42, 43]. Some studies have also shown differences in quantitative rsEEG between AD, FTLD, and controls [44, 45]. Conversely, quantitative EEG abnormalities during sleep have not been investigated so far in patients with FTLD. This, coupled with the absence of a control group of healthy individuals in our study, prevents us from drawing definitive conclusions about quantitative EEG could represent a promising method to characterize sleep alterations in patients with bvFTD. Nevertheless, it is possible to hypothesize that the alterations we found in the spectral analysis between the two groups reflect EEG alterations specific to AD. Accordingly, the difference in sigma power between bvFTD and AD patients, particularly evident in NREM stage 2 sleep observed in our study, is likely to result from the reduction in spindle density consistently documented in AD patients [46].

Finally, regarding nocturnal sleep dynamics, our study shows that bvFTD patients display fewer shifts between N3 sleep and any other stages, and a higher frequency of transitions between sleep and wakefulness, as well as between N1 sleep and wakefulness, compared to AD patients. Conversely, no significant differences were observed in either the frequency of transitions between the cycles NREM–REM sleep or in the frequency of transitions between wakefulness, NREM sleep, and REM sleep. The increased shift between sleep and wakefulness in bvFTD indicates a more pronounced instability between the two systems, resulting in difficulty maintaining sleep and subsequently progressing to deeper sleep stages. This difficulty is particularly evident in the instability of N1 sleep, which is a transitional stage between wakefulness and deeper sleep stages and typically initiates sleep cycles. Thereafter, the patients with bvFTD show a relatively normal tendency to remain in the N3 and REM stages once these stages are achieved. These findings therefore highlight a specific impairment of state transitional mechanisms between wakefulness and sleep. To the best of our knowledge, only the study by Maestri et al. has analyzed sleep metrics beyond traditional sleep macrostructure reporting notable differences between bvFTD patients and healthy controls [19]. Specifically, the authors analyzed CAP which represents a protective, short-term homeostatic mechanism of NREM sleep [47], and found that bvFTD exhibits higher sleep instability compared to controls characterized by reduced CAP-A1 phases, increased CAP-A3 phases, and reduced but longer CAP sequences [19]. Our results align with those of Maestri et al. and extend these findings by showing that sleep continuity disruption is more severe in bvFTD than in AD patients.

This increased sleep instability in bvFTD compared to AD might reflect the impairment of different etiopathogenetic mechanisms and the atrophy of different involved brain areas. Liu et al. investigated the neuroanatomical correlates of sleep disorders, assessed through the NPI, in patients with the frontal variant of FTLD, temporal variant of FTLD, and AD, reporting a higher prevalence of sleep disturbances in patients with temporal variant FTLD compared to frontal variant FTLD and AD [48]. More recently, Perry et al. demonstrated that atrophy in the anterior cingulate, frontoinsula, striatum, and amygdala are associated with behavioral symptoms, including sleep disorders, in bvFTD patients [49]. Additionally, Warren and Clark have hypothesized that the differences in sleep disturbances observed in bvfTD compared to AD may stem from the distinct neurodegenerative process targeting specific neural systems, whereas in AD cholinergic pathways primarily affect more posterior areas whereas in FTLD proteinopathies primarily target more anterior areas [50]. The authors also proposed that sleep disturbances in both pathologies may lead to synaptic dysfunction in disease-targeted brain regions, contributing to further sleep disruption and neuronal damage involved in sleep and circadian rhythms [50]. Thus, neurodegeneration in bvFTD spreading throughout cerebral areas may impair essential nuclei and connections in sleep–wake mechanisms from the arousal system in the brainstem to the frontal cortex. Our findings therefore suggest that the altered transitions between wakefulness and sleep in bvFTD reflect disruptions in the mechanisms governing sleep maintenance, indicating an imbalance between sleep and wake-promoting systems [51, 52]. The frontal cortex, particularly the prefrontal regions, plays a key role in promoting and maintaining wakefulness and in the transition from wakefulness to NREM sleep [53–56]. It inputs from the thalamus and other brain regions, allowing it to evaluate sensory information and internal cues and can trigger an arousal response, leading to wakefulness [53, 54]. Moreover, all components of the arousal system extensively connect with the prefrontal cortex, which reciprocally sends signals to the basal forebrain, hypothalamus, and the brainstem elements of the arousal system [53–57]. Dysfunction of the frontal cortex as a modulator of sleep state switching may therefore actively influence the mechanisms of mutual inhibitory circuits that regulate sleep and wakefulness [56, 57]. On the other hand, although less studied, degeneration of the brainstem has also been noted in FTLD [58]. This degeneration is believed to impact the reticular activating system, which regulates wakefulness, attention, and alertness [58, 59]. It has also been shown that patients with FTLD compared to controls had smaller volumes of the midbrain, pontine tegmentum, and colliculi (especially in bvFTD) [60]. Future studies should investigate the neuroimaging correlates of sleep instability in bvFTD patients to better understand the neuroanatomical underpinnings involved.

This study represents the first to employ metrics of sleep dynamics analysis in the context of neurodegenerative disorders. Prior investigations have predominantly concentrated on primary sleep disorders [20–26]. A higher rate of stage transitions is characteristic of patients experiencing hypersomnia [25, 26]. Specifically, it has been found that patients with narcolepsy and low orexin levels exhibit a significantly higher frequency of sleep–wake transitions compared to those with narcolepsy with normal orexin levels [25]. However, these patients also experience higher rates of REM–NREM sleep transitions [25]. Another study demonstrated that patients with narcolepsy type 1 with orexin deficiency had the highest number of awakenings, sleep stage transitions, and spent more time in N1 compared to those with idiopathic hypersomnia, narcolepsy type 2, and subjective hypersomnolence [26]. Taken together, these studies indicate that the increased transitional rates found in patients with narcolepsy support the complaints of nocturnal fragmented sleep and also that dysfunction of orexin plays a central role in the increased

sleep–wake transitions and other sleep stage abnormalities seen in these conditions [25, 26]. Although the transition abnormalities in narcoleptics are more pronounced and involve all sleep stages, the similarity between bvFTD and narcoleptic patients allows us to hypothesize a potential alteration in the orexin system in bvFTD as well. It is well established that orexin regulates REM sleep and sustains wakefulness and sleep once these states are reached stabilizing the "flip-flop" switch [61]. In recent years, several hypotheses have been advanced regarding orexin system dysfunction in neurodegenerative diseases [62]. In bvFTD, impairment of the hypothalamus has been suggested, with specific dysfunction of the orexin system [63]. Notably, orexin is also involved in other crucial functions [61, 62]. Orexinergic neurons through their connections to several brain areas and various monoaminergic and cholinergic systems, regulate not only sleep but also other homeostatic functions such as appetite, and energy metabolism and are also involved in reward mechanisms and cognition [61, 62]. Notably, these functions are all altered in bvFTD patients, who typically present with behavioral disinhibition, impulsive, reward-seeking behaviors, and appetite dysregulation with binge eating [3, 63]. Some authors have reported abnormal orexin levels in patients with bvFTD [63–65]. For instance, plasma orexin-A levels were significantly lower in patients with FTLD compared to controls in a study by Coban et al. [64]. However, plasma orexin levels are considered an unreliable indicator of orexin activity in the central nervous system [66]. Conversely, in the study by Liguori et al., no differences were found in CSF orexin concentrations between FTLD patients and controls [65]. Interestingly, in this study, a negative correlation was observed between CSF orexin levels and daytime sleepiness severity in FTLD, which supports the hypotheses that orexin may be a key factor in maintaining wakefulness in bvFTD [65]. However, to date, research data on orexin in bvFTD remain inconclusive likely due to different methodologies of orexin measurement used across studies and also to the fluctuation of the orexin concentration throughout the day. Additionally, it is possible that the impairment of the orexin system is more closely related to its connections with other areas affected by neurodegenerative processes, including neural circuits specifically involved in the wake–sleep switch and the interconnected anterior (frontal) brain regions. In bvFTD, the increased wake–sleep transitions due to the alteration in the mechanisms that regulate wakefulness and sleep may be the result of the orexinergic dysfunction affecting the "flip- flop" switch between the stages. Therefore, further research on the orexinergic system in bvFTD is warranted.

Higher sleep stage transition rates were also found in the general populations among individuals complaining of light sleep overrepresentation [20]. More recently, Wei et al. demonstrated that patients with insomnia showed significantly higher empirical probabilities of transitioning from stage N2 to the lighter sleep stage (i.e. N1) or wakefulness [22].

Finally, another noteworthy finding of this study is the positive association between ISI scores and transitions between wake and sleep, which was observed exclusively in bvFTD patients. Accordingly, it is, therefore, possible to speculate that insomnia complaints in bvFTD are not the result of alterations in standard sleep macrostructure metrics but instead originate from disruptions in state transitions, particularly in the mechanisms regulating the transition between wakefulness and sleep. These hypotheses are supported by the results of correlation analysis between tWS and the individual ISI items, which showed that tWS is positively associated with the scores of ISI items reflecting difficulties in sleep maintenance, while no association emerged with items reflecting difficulty falling asleep or early morning awakening. A connection between insomnia and atrophy of the frontal lobe has been hypothesized. Specifically, it has been demonstrated that patients with insomnia exhibit reduced gray matter volume in the left orbitofrontal cortex, and similar reductions in the anterior and posterior precuneus in patients with insomnia [67].

This study has several limitations. First, while it represents the largest PSG study in patients with bvFTD, the sample size is relatively small, thus our results need to be confirmed and expanded in future studies on larger samples of bvFTD patients. Additionally, including a comparison with a healthy control group, which was not available in this study, would further enhance our understanding of the findings. Furthermore, in this study, positron emission tomography data were available only for some patients, preventing us from conducting specific correlations, which would be highly beneficial for future studies.

The role of sleep dynamics alterations in the diagnostic process of bvFTD needs to be investigated in future studies. Understanding these alterations could provide valuable insights into the disease's progression and ultimately contribute to better patient care and management.

In conclusion, our analysis of nocturnal sleep dynamics provides novel insights into sleep alterations associated with bvFTD and may serve as an additional tool beyond standard analysis to help delineate bvFTD and differentiate it from other pathologies. In particular, this study offers evidence that sleep is more disrupted and unstable in bvFTD compared to AD and the altered sleep stage transition rates may reflect the subjective experience of poor sleep quality reported by bvFTD patients. It is plausible that the pathological changes affecting sleep–wake-promoting systems, and their connections with more anterior brain areas in bvFTD as compared to AD, may underlie these observed differences. The role of the orexinergic system cannot be ruled out and deserves deeper investigations. Further investigations should delve deeper into the intricacies of sleep microstructure and sleep dynamics to enhance our understanding of sleep disturbances in bvFTD.

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Data Availability

The dataset supporting the conclusions of this article is available from the corresponding author, upon reasonable request.

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