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RESEARCH ARTICLE

Sleep and circadian rhythm disruptions in behavioral variant frontotemporal dementia

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Abstract

INTRODUCTION: Sleep and rest–activity rhythm alterations are common in neurodegenerative diseases. However, their characterization in patients with behavioral variant frontotemporal dementia (bvFTD) has proven elusive. We investigated rest–activity rhythm alterations, sleep disturbances, and their neural correlates in bvFTD.

METHODS: Twenty-seven bvFTD patients and 25 healthy controls completed sleep questionnaires and underwent 7 days of actigraphy while concurrently maintaining a sleep diary. Cortical complexity and thickness were calculated from T1-weighted magnetic resonance (MR) images.

RESULTS: Compared to controls, bvFTD patients showed longer time in bed (95% confidence interval [CI]: 79.31, 321.83) and total sleep time (95% CI: 24.38, 321.88), lower sleep efficiency (95% CI: −12.58, −95.54), and rest–activity rhythm alterations in the morning and early afternoon. Increased sleep duration was associated with reduced cortical thickness in frontal regions.

DISCUSSION: Patients with bvFTD showed longer sleep duration, lower sleep quality, and rest–activity rhythm alterations. Actigraphy could serve as a cost-effective and accessible tool for ecologically monitoring changes in sleep duration in bvFTD patients.

KEYWORDS
actigraphy, behavioral variant frontotemporal dementia, cortical thickness, functional linear modeling, magnetic resonance imaging, rest-activity rhythm, sleep diary

Highlights

- We assessed sleep and circadian rhythms in behavioral variant frontotemporal dementia (bvFTD) using actigraphy.
- Patients with bvFTD show increased sleep duration and reduced sleep quality.
- Patients with bvFTD show rest–activity alterations in the morning and early afternoon.
- Sleep duration is associated with reduced cortical thickness in frontal regions.
- These alterations may represent an early sign of neurodegeneration.

1 | BACKGROUND

Frontotemporal lobar degeneration (FTLD) is an umbrella term for a heterogeneous group of neurodegenerative conditions characterized by the progressive atrophy of the frontal and temporal lobes of the brain.[1] FTLD is rare, with an estimated incidence rate in Europe of 2.36 cases per 100,000 person-years,[2] despite being the leading form of early-onset dementia.

The behavioral variant of frontotemporal dementia (bvFTD) is the most common presentation of FTLD, characterized by insidious changes in personality and behavior, usually manifesting as socially inappropriate conduct and emotional blunting.[3] Disinhibition, apathy, and changes in eating preferences complete the clinical picture of bvFTD, with some studies also indicating a high prevalence of sleep disorders.[4] Sleep and circadian rhythms disruption are common in neurodegenerative diseases, including FTLD; however, their objective characterization in patients with bvFTD has proven elusive.[5,6]

The few studies that investigated sleep in bvFTD using polysomnography (PSG) reported reduced total sleep time and sleep efficiency, along with macro- and microstructural sleep alterations.[7–9] The paucity of polysomnographic studies may be due to the behavioral and neuropsychiatric symptoms exhibited by patients, which make PSG challenging to perform. To overcome this issue, several studies have used actigraphs or wearable devices to record sleep and restactivity rhythms over extended periods in the subject's natural environment.[10]

Actigraphic studies that focused on sleep duration and quality in bvFTD reported lower sleep quality, consistently with PSG studies,[11] but also showed that when patients are studied at home, they spend significantly more time in bed compared to controls.[12] Studies that used actigraphy to assess restactivity rhythm in patients with bvFTD have also yielded conflicting results. Harper et al. reported a significantly more fragmented restactivity rhythm in institutionalized FTD patients compared to controls.[13] Conversely, Anderson et al. reported higher nocturnal motor activity and lower morning motor activity in non-institutionalized bvFTD patients compared to controls but found no difference in restactivity rhythm fragmentation (i.e., day-to-day variability of activity pattern).[11]

This study aims to obtain a clearer picture of sleep and restactivity rhythm alterations in bvFTD by investigating patients in at-home settings using actigraphy and sleep diary and examining the relationship between sleep disturbances and structural brain alterations. Specifically, the study's aims are the following: (1) to assess differences in both objective and subjective sleep quality and duration between bvFTD patients and age- and sex-matched healthy controls; (2) to assess differences in restactivity rhythm between bvFTD patients and healthy controls using a state-of-the-art analytical framework for actigraphic time series; and (3) to explore the association between structural brain proprieties and the sleep disturbances exhibited by patients.

RESEARCH IN CONTEXT

1. **Systematic review**: A systematic search of electronic databases (PubMed, Web of Science, and Scopus) was conducted to identify and review studies that examined sleep and rest–activity rhythm in behavioral variant frontotemporal dementia (bvFTD). Although sleep and rest–activity rhythm disruptions are common in neurodegenerative diseases, only a limited number of studies have investigated these disturbances in bvFTD. The relevant publications have been cited appropriately.
2. **Interpretation**: Our study presents compelling evidence that patients with bvFTD exhibit longer time in bed (95% confidence interval [CI]: 79.31, 321.83), increased total sleep time (95% CI: 24.38, 321.88), reduced sleep efficiency (95% CI: −12.58, −95.54), and rest–activity rhythm alterations in the morning and early afternoon. Increased sleep duration was associated with reduced cortical thickness over frontal brain regions typically affected by the disease.
3. **Future directions**: Prolonged sleep duration and rest–activity rhythm alterations are underrecognized symptoms in bvFTD. Further studies in patients with bvFTD close to disease onset will help clarify whether these alterations may represent early signs of neurodegeneration.

2 | METHODS

2.1 | Subjects

Twenty-seven consecutive subjects (17 male, mean age 68.58 ± 9.42 years, range 46–85 years) were evaluated at the Center for Neurodegenerative Diseases and the Aging Brain of the University of Bari, between December 2021 and December 2022, and received a final diagnosis of bvFTD according to the current diagnostic and research criteria.[14]

All patients underwent the following diagnostic protocol: (1) neurological examination; (2) comprehensive neuropsychological evaluation, including the assessment of main cognitive domains (attention, memory, executive functions, visuospatial abilities, language and social cognition),[15,16] personality and behavioral changes,[17] and functional disabilities; (3) 3-Tesla brain magnetic resonance imaging (MRI); and (4) lumbar puncture (in 21 of 27 patients) to assess cerebrospinal fluid (CSF) biomarkers of neurodegeneration. All cases fulfilled the current diagnostic criteria for probable bvFTD presenting with the core clinical features of bvFTD and frontal/temporal atrophy on MRI.[14] Twenty-five healthy controls (10 male, mean age 66.17 ± 6.72 years, range 56–82 years) were recruited from the local community. Participants were screened to rule out medical, neurological, and psychiatric

disorders. Healthy controls underwent the same assessment protocol as bvFTD patients, except for MRI and lumbar puncture. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local health trust's ethics committee (ASL Lecce verbale n°6, July 25th, 2017). Written informed consent was obtained from all participants.

2.2 | Hypnologic assessment

All participants underwent clinical interview with a board-certified somnologist and completed screening questionnaires for obstructive sleep apnea (OSA), rapid eye movement sleep behavior disorder (RBD), insomnia, and excessive daytime sleepiness (EDS). Relatives/caregivers were present during clinical interview and questionnaires administration and were allowed to assist the patients if necessary. The STOP-Bang questionnaire was used to screen for OSA, with scores ranging from 0 to 2 indicating low risk, scores from 3 to 4 indicating intermediate risk, and a score ≥5 indicating a high risk of OSA.[18] The RBD Screening Questionnaire (RBDSQ) was used to identify subjects at risk of RBD, with a score ≥6 indicating probable RBD.[19] The Insomnia Severity Index (ISI) was used to assess insomnia severity: scores <8 indicate no insomnia, 8–14 indicate subclinical insomnia, 15–21 indicate moderate insomnia, and a score ≥22 indicates severe insomnia.[20]

The Epworth Sleepiness Scale (ESS) was used to assess daytime sleepiness, with a score >10 indicating EDS.[21] The reduced Morningness-Eveningness Questionnaire (rMEQ) was used to assess the ideal time in bed (TIB) and circadian typology (i.e., chronotype). According to the rMEQ, scores between 4 and 10 indicate an evening-type chronotype, scores between 11 and 18 indicate an intermediate-type chronotype, and scores between 19 and 25 indicate a morning-type chronotype.[22,23]

Finally, the Pittsburgh Sleep Quality Index (PSQI) was used to assess habitual sleep duration and quality.[24] PSQI global score was computed using the original scoring system proposed by Buysse et al., with a score >5 indicating poor sleep quality.[25] In addition, we manually computed time in bed, total sleep time, sleep onset latency, and sleep efficiency based on the raw values reported in items 1–4 of the PSQI. Detailed information regarding PSQI-derived sleep metrics computation is provided in the supplementary materials.

2.3 | Sleep diary

The core consensus sleep diary (CSD), along with three items from the evening CSD (frequency and duration of naps and use of hypnotic drugs), was used to collect daily information on sleep quality/duration and daytime napping behavior.[26] Participants were asked to complete the sleep diary daily for seven consecutive days, in parallel with actigraphic assessment, and mean sleep metrics were computed across seven nights. Sleep diary instructions were provided to both participants and relatives/caregivers, who were instructed to assist the patient if necessary. The following CSD variables were considered: bedtime (BT), get up time (GUT), time in bed (TIB), total sleep time (TST), sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency (SE%), nocturnal awakenings (NWAK), terminal wakefulness (TWAK), nap frequency, and mean nap duration (NapD).

2.4 | Actigraphic nighttime and daytime sleep measures

Participants wore the Micro Motionlogger Watch actigraph (Ambulatory Monitoring Inc., Ardsley, NY) on the non-dominant wrist for seven consecutive days, which is necessary to obtain a reliable description of restactivity rhythm in elderly and patients with dementia.[27] The device consists of a triaxial accelerometer that quantifies motor activity above 0.01 *g*, a photodiode, a case temperature sensor, and an event-marker button. Epoch length was set at 1 minute. Actigraphy was performed during the subjects' regular week, outside of holidays and vacations. All participants were retired at the time of actigraphic assessment.

Subjects were instructed to retain their usual daily routine during the recording and to wear the device continuously over the 24-hours. Moreover, participants were instructed to signal periods in and out of bed and device removal via the event-marker button. Relatives/caregivers were allowed to assist the patients with the event-marker procedure, if necessary. To identify the major nocturnal rest period, an experienced scorer followed a hierarchical approach: first considering the event-marker points, then sleep diary data if event-marker points were absent, and if both sources of information were unavailable, relying on ambient light sensor data. Recordings were divided into nocturnal and diurnal periods based on individual bedtime and wake-up time and mean actigraphic parameters were computed across 7 days.

Actigraphic estimated sleep measures were obtained using the Cole-Kripke algorithm.[28] The following sleep timing variables were considered: BT, GUT, midpoint of sleep (MS, the time that split in half the TIB), and TIB. For the nocturnal period, the following variables were considered: estimated total sleep time (TST), estimated sleep onset latency (SOL), estimated sleep efficiency (SE%), estimated wake after sleep onset (WASO), estimated awakenings (NWAK) and prolonged (i.e., lasting more than 5 min) awakening (NWAK >5), estimated longest uninterrupted sleep (longest continuous episode scored as sleep), and sleep motor activity (SMA, mean activity counts during TIB). Finally, for the diurnal period, we considered diurnal total sleep time (DTST), nap frequency (with a nap defined as an interval of at least 10 min up to 3 h scored as sleep, preceded and followed by a period of at least 30 min scored as wake), mean nap duration (NapD), and mean diurnal motor activity (DMA).

2.5 | Rest–activity rhythm analysis

Rest–activity rhythm features were analyzed through functional linear modeling (FLM), a statistical framework developed specifically for the analysis of actigraphic time series.[29] The FLM framework involves

two steps: first, a basis function model converts the raw activity data into a functional form that captures the major trend and reduces data variability. Second, sets of functions are compared using a nonparametric permutation F-test, which derives a theoretical null distribution by randomly rearranging group assignments. Functional smoothing was preformed via a Fourier expansion model with $n = 23$ basis functions. Furthermore, the following conventional nonparametric actigraphy variables were computed: interdaily stability (IS), which reflects the day-to-day similarity of the rest-activity rhythm (higher value indicate a more stable rhythm); intradaily variability (IV), which reflects the day-to-day variability of the restactivity rhythm (higher values indicate a more fragmented rhythm); and the relative amplitude of the rest-activity rhythm (RA), defined as the difference between the most active 10 hours and the least active 5 hours divided by their sum.[10]

2.6 | MRI processing and analysis

Brain images were acquired on a high-field MRI scanner (Philips Ingenia 3.0 Tesla) using a fast-field echo T1-weighted sequence (repetition time = 8.2 ms, echo time = 3.8 ms, flip angle = 8°, resolution = 256 × 256, slices = 200, thickness = 1 mm). Brain images were inspected visually by an experienced neuroradiologist, and seven patients were excluded from the analysis due to poor image quality and/or excessive motion-related artifacts. Image quality was assessed by considering the Image Quality Rate (IQR) and grading provided by Computational Anatomy Toolbox (CAT12). Detailed image quality metrics and gradings for each subject are reported in the supplementary materials (Table S1). Voxel-based morphometry and surface-based morphometry analyses were performed using CAT12 version 12.8.[30] Cortical thickness was estimated using a projection-based thickness method.[31] To assess cortical complexity, we calculated the fractal dimension (FD) using a spherical harmonic reconstruction method.[32] FD captures the structural complexity of the cortex by assessing its self-similarity (i.e., morphological detail of a structure that remains consistent across different spatial scales) and has proven to be sensitive in characterizing brain changes associated with FTD.[33]

2.7 | Statistical analysis

Data are reported as mean ± standard deviation (SD) or frequency. Selection of the appropriate statistical test for each variable was determined by assessing normal distribution with the Shapiro–Wilk normality test. Group differences were examined using chi-square and two-tailed independent samples *t*-test, or Mann–Whitney *U* test, followed by effect size (Hedge's *g*) computation. False discovery rate (FDR) was used to account for multiple comparisons.[34] FDR-corrected *p*-values < 0.05 were considered statistically significant. Analyses were performed using IBM SPSS Statistics v.20 and R.[29] For FLM analysis, we considered both pointwise (proportion of 500 permutation F-values at each time point) and global (maximized F-value from each permutation) tests of significance. The association between gray matter density, cortical thickness, cortical complexity, and objective measures of sleep duration (TIB and TST) and quality (SE, WASO, and NWAK) was investigated through a whole-brain voxel-wise/vertex-wise multiple regression analysis corrected for age, gender, disease duration, and total intracranial volume (for voxel-based analysis). Whole-brain voxel-wise/vertex-wise statistical analyses were performed using a nonparametric permutation approach with 5000 permutations. Given the exploratory nature of this analysis α adjustments were not performed.

3 | RESULTS

3.1 | Demographic and sleep questionnaires

Demographic and sleep questionnaire data, along with the corresponding test statistic (*t*-test or Mann–Whitney *U*), FDR-adjusted *p*-values, Hedge's *g*, and 95% confidence interval, are reported in Table 1. No group differences emerged in age and gender distribution. Patients with bvFTD had fewer years of education than controls (Mann–Whitney $U = 133.5$, $p < 0.005$). No differences emerged in RBDSQ and ESS scores, nor in the percentage of subjects with EDS ($\chi^2_{(1)} = 0.42$, p = ns) or probable RBD ($\chi^2_{(1)} = 0.32$, p = ns). Patients with bvFTD displayed significantly higher ISI scores (Mann–Whitney $U = 177$, $p < 0.01$) and PSQI scores (Mann–Whitney $U = 179$, $p < 0.01$), and were more likely to be poor sleepers compared to controls ($\chi^2_{(1)} = 8.16$, $p < 0.01$). Furthermore, patients with bvFTD exhibited longer PSQI-derived time in bed compared to controls, while no significant differences were observed in PSQI-derived total sleep time, sleep-onset latency, or sleep efficiency.

Detailed results of PSQI-derived sleep metrics analysis are reported in the supplementary materials. Patients with bvFTD showed significantly higher STOP-Bang scores (Mann–Whitney $U = 215.50$, $p < 0.05$), but no significant difference emerged in OSA risk between bvFTD patients and controls ($\chi^2_{(2)} = 3.61$, p = ns). Finally, no difference emerged in rMEQ scores ($t_{(50)} = -2.08$, p = ns) and circadian typology distribution ($\chi^2_{(1)} = 2.40$, p = ns), but patients with bvFTD reported longer ideal TIB than controls ($t_{(50)} = 4.20$, $p < 0.0005$).

3.2 | Sleep diary

Sleep diary measures are shown in Table 2. Three patients returned incomplete/unintelligible diaries and were therefore excluded from analysis. Patients with bvFTD reported going to bed earlier ($t_{(47)} = -4.59$, $p < 0.0005$), waking up later ($t_{(47)} = 4.26$, $p < 0.0005$), and having a longer TIB ($t_{(47)} = 6.39$, $p < 0.0001$) and TST (Mann-Whitney $U = 41$, $p < 0.0001$) compared to controls. No differences emerged in sleep diary measures of SOL, WASO, SE%, NWAK, TWAK duration, nap frequency, and mean nap duration (all p = ns).

TABLE 1 Demographic, clinical data and sleep disorder questionnaires of patients with bvFTD and healthy controls.

	bvFTD ($n = 27$) Mean ± SD	HC ($n = 25$) Mean ± SD	$t_{(50)}$ or U	FDR p-value	Hedge's g	95% CI for the differences between means	
						Lower	Upper
Demographic and Clinical Data							
Male/female	17/10	10/15	2.74	ns			
Age, y	68.58 ± 9.42	66.17 ± 6.72	1.06	ns		−2.17	7.01
Education, y	8.96 ± 4.22	13.36 ± 4.25	133.5[b]	<0.005	−1.02	−6.71	−2.03
Disease duration, y	5.20 ± 4.63						
Aβ_{42}	987.43 ± 391.99[a]						
t-tau	411.05 ± 171.04[a]						
p-tau	45.46 ± 26.56[a]						
FBI	36.75 ± 12.16						
Mini-SEA	14.79 ± 4.29						
Sleep disorder questionnaires							
STOP-Bang	3.89 ± 1.76	2.76 ± 1.48	215.5[b]	<0.05	0.68	0.22	2.04
RBDSQ	2.81 ± 2.73	2.20 ± 2.25	301.5[b]	ns		−0.79	2.02
ISI	8.41 ± 6.28	4.08 ± 3.48	177[b]	<0.01	0.83	1.47	7.19
ESS	6.93 ± 4.63	4.88 ± 3.68	246[b]	ns		−0.30	4.39
PSQI	9.70 ± 4.60	6.24 ± 3.06	179[b]	<0.01	0.87	1.27	5.66
*r*MEQ	18.04 ± 2.93	19.48 ± 1.94	−2.08	ns		−2.84	−0.05
Ideal TIB, min	596.67 ± 95.08	493.40 ± 80.79	4.20	< 0.0005	1.15	53.92	152.61
OSA risk							
Low risk	9 (33.3%)	13 (52%)	3.61	ns			
Intermediate risk	6 (22.2%)	7 (28%)					
High risk	12 (44.4%)	5 (20%)					
RBD risk							
Excluded RBD	21 (77.8%)	21 (84%)	0.32	ns			
Probable RBD	6 (22.2%)	4 (16%)					
Insomnia severity							
No insomnia	15 (55.6%)	23 (92%)	9.40	<0.05			
Subthreshold insomnia	7 (25.9%)	2 (8%)					
Clinical insomnia, moderate	3 (11.1%)	0 (0%)					
Clinical insomnia, severe	2 (7.4%)	0 (0%)					
Sleepiness severity							
Normal sleepiness	22 (81.5%)	22 (88%)	0.42	ns			
Pathological sleepiness	5 (18.5%)	3 (12%)					
Sleep quality							
Normal sleep quality	4 (14.8%)	13 (52%)	8.16	<0.01			
Poor sleep quality	23 (85.2%)	12 (48%)					
Chronotype							
Morning type	15 (55.6%)	19 (76%)	2.40	ns			
Intermediate type	12 (44.4%)	6 (24%)					

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; CI, confidence interval; ESS, Epworth Sleepiness Scale; FBI, Frontal Behavioral Inventory; FRD, false discovery rate; HC, healthy controls; ISI, Insomnia Severity Index; Aβ_{42}, beta-amyloid 1-42; *t*-tau, total tau; p-tau, phosphorylated-tau 181; Mini-SEA, Mini Social Cognition & Emotional Assessment; OSA, obstructive sleep apnea; PSQI, Pittsburgh Sleep Quality Index; *r*MEQ, reduced Morningness-Eveningness Questionnaire; RBD, REM sleep Behaviour Disorder, RBDSQ, REM Sleep Behaviour Disorder Screening Questionnaire.

[a]Available in 21 of 27 patients.

[b]Mann–Whitney *U*.

TABLE 2 Sleep diary nighttime, daytime, and sleep timing measures of patients with bvFTD and healthy controls

	bvFTD ($n = 24$) Mean ± SD	HC ($n = 25$) Mean ± SD	$t_{(47)}$ or U	FDR p-value	Hedge's g	95% CI for the differences between means	
						Lower	Upper
Sleep timing							
Bedtime, hr:m	22:23 ± 1:04	23:35 ± 00:43	−4.59	<0.0005	−1.29	−1.72	−0.67
Get up time, hr:m	8:01 ± 01:24	6:43 ± 00:29	4.26	<0.0005	1.19	0.67	1.86
TIB, min	579.74 ± 108.02	426.52 ± 50.82	6.39	<0.0001	1.80	105.02	201.41
Nighttime period							
TST, min	507.75 ± 97.25	349 ± 67.09	41	<0.0001	1.88	110.90	206.59
SOL, min	16.13 ± 12.59	21.70 ± 21.73	269.5[a]	ns		−15.83	4.69
WASO, min	23.31 ± 21.71	31.22 ± 43.90	300[a]	ns		−27.95	12.13
SE, %	88.03 ± 8.53	82.15 ± 15.06	228[a]	ns		−1.20	12.95
NWAK, n°	1.45 ± 1.17	1.49 ± 1.28	298[a]	ns		−0.75	0.66
TWAK, min	32.76 ± 42.52	24.60 ± 19.47	277[a]	ns		−10.72	27.04
Daytime period							
Nap, n°	6.75 ± 6.22	5.96 ± 5.33	287[a]	ns		−2.53	4.11
NapD, min	88.15 ± 54.84	66.15 ± 39.04	115.5[a]	ns		−11.40	55.40

Note: Sleep metrics were computed across seven nights.
Abbreviations: bvFTD, behavioral variant frontotemporal dementia; CI, confidence interval; FRD, false discovery rate; HC, healthy controls; Nap, diurnal sleep episodes; NapD, mean nap duration, NWAK, nocturnal awakenings; SE, sleep efficiency; SOL, sleep-onset latency; TIB, time in bed; TST, total sleep time; TWAK, terminal wakefulness; WASO, wake after sleep onset.
[a]Mann–Whitney U.

3.3 | Actigraphic nighttime and daytime sleep measures

Nocturnal and diurnal actigraphic sleep estimates and nonparametric measures are shown in Table 3. Patients with bvFTD went to bed earlier (Mann–Whitney $U = 181.5$, $p < 0.01$), woke up later ($t_{(50)} = 4.67$, $p < 0.0005$), and spent more time in bed than controls ($t_{(50)} = 5.73$, $p < 0.0001$), without showing differences in the midpoint of sleep ($t_{(50)} = 0.61$, p = ns). Patients with bvFTD had longer TST ($t_{(50)} = 3.06$, $p < 0.01$), lower sleep efficiency (Mann–Whitney $U = 217$, $p < 0.05$), higher WASO (Mann–Whitney $U = 137.5$, $p < 0.005$), a higher occurrence of brief ($t_{(50)} = 3.22$, $p < 0.01$) and prolonged awakenings (Mann–Whitney $U = 171$, $p < 0.01$), and higher SMA (Mann–Whitney $U = 200$, $p < 0.05$) than controls. No group differences were observed in diurnal actigraphic measures (DTST, Nap, NapD, and DMA) and nonparametric measures (IS, IV, and RA)

3.4 | Rest–activity rhythm

Circadian motor activity profiles of patients with bvFTD and controls are shown in Figure 1 (Panel A), together with FLM results (Panel B). In Figure 1, the continuous red line corresponds to the observed statistics, the dashed blue line represents the global test of significance, and the dotted blue line represents the less conservative pointwise test of significance. Compared to controls, patients with bvFTD showed lower motor activity from 6:30 to 11:30 (6:30–10:00 global test of significance, 10:00–11:30 pointwise test of significance) and higher motor activity from 14:10 to 15:40 (pointwise test of significance) and from 2:00 to 5:20 (2:30–3:20 global test of significance, 3:20–5:20 pointwise test of significance).

3.5 | Neuroimaging correlates of sleep alterations

The association between cortical thickness, cortical complexity, and actigraphic measures of sleep duration (TIB and TST) is shown in Figures 2 and 3. TIB (Figure 2, Panel A) was negatively associated with cortical thickness ($p < 0.01$) bilaterally in the frontal regions (superior frontal gyrus, medial orbitofrontal cortex, rostral middle frontal cortex, lateral orbitofrontal cortex, precentral gyrus, and postcentral gyrus). On the right hemisphere, TIB was associated negatively with cortical thickness in the superior temporal sulcus, middle temporal gyrus, and superior temporal gyrus ($p < 0.05$). TIB showed a positive association with cortical complexity (Figure 2, Panel B) in the lateral orbitofrontal and medial orbitofrontal cortex of the left hemisphere ($p < 0.001$) and a negative association in the precentral and postcentral gyrus of the right hemisphere ($p < 0.05$). TST showed a negative

TABLE 3 Actigraphic nocturnal, diurnal, and nonparametric measures of patients with bvFTD and healthy controls.

	bvFTD ($n = 27$) Mean ± SD	HC ($n = 25$) Mean ± SD	$t_{(50)}$ or U	FDR p-value	Hedge's g	95% CI for the differences between means	
						Lower	Upper
Sleep timing							
BT, hr:m	22:22 ± 1:14	23:15 ± 00:49	181.5[a]	<0.01	−0.83	−1.53	−0.31
GUT, hr:m	7:48 ± 01:07	6:41 ± 00:25	4.67	<0.0005	1.27	0.64	1.60
MS, hr:m	3:06 ± 00:56	2:59 ± 00:28	0.61	ns		−0.29	0.54
TIB, min	565.96 ± 88.70	443.90 ± 61.08	5.73	<0.0001	1.57	79.31	164.82
Nighttime period							
TST, min	463.43 ± 103.96	392.66 ± 52.16	3.06	<0.01	0.84	24.38	117.17
SOL, min	29.53 ± 26.21	24.48 ± 17.98	321.5[a]	ns		−7.57	17.67
SE, %	81.94 ± 13.09	88.74 ± 6.19	217[a]	<0.05	−0.65	−12.58	−1.02
WASO, min	68.94 ± 55.69	28.72 ± 20.28	137.5[a]	<0.005	0.99	16.51	63.95
NWAK, n°	13.92 ± 5.55	9.47 ± 4.27	3.22	<0.01	0.88	1.67	7.22
Prolonged NWAK, n°	4.14 ± 2.46	2.21 ± 1.90	171[a]	<0.01	0.86	0.70	3.16
Longest sleep, min	153.46 ± 58.84	152.58 ± 56.17	320[a]	ns		−31.22	32.98
SMA, counts	25.73 ± 14.08	17.28 ± 5.69	200[a]	<0.05	0.76	2.38	14.52
Daytime period							
DMA, counts	195.64 ± 35.12	192.49 ± 22.42	0.38	ns		−13.41	19.71
DTST, min	71.48 ± 68.82	83.53 ± 56.04	274[a]	ns		−47.17	23.08
Nap, n°	9.74 ± 9.30	7.72 ± 7.29	299[a]	ns		−2.66	6.70
NapD, min	32.86 ± 25.11	39.31 ± 25.14	283[a]	ns		−20.46	7.55
Nonparametric measures							
IS	0.78 ± 0.11	0.81 ± 0.05	313[a]	ns		−0.08	0.02
IV	0.53 ± 0.18	0.53 ± 0.11	0.06	ns		−0.08	0.09
RA	0.81 ± 0.11	0.87 ± 0.06	251	ns		−0.10	0.00

Abbreviations: BT, clock time when subject goes to bed and turns off the light; bvFTD, behavioral variant frontotemporal dementia; CI, confidence interval; DMA, mean activity counts during daytime; DTST, estimated diurnal TST; FRD, false discovery rate; GUT, clock time when subject gets out of bed in the morning; HC, healthy controls; IS, interdaily stability; IV, intradaily variability; MS, clock time that split in half the TIB; Nap, diurnal sleep episodes; NapD, mean nap duration; NWAK, number of all epochs scored as wake during TIB; SE, estimated sleep efficiency; SMA, mean activity counts during TIB; RA, relative amplitude; SOL, estimated sleep-onset latency; TIB, time in bed; TST, estimated total sleep time; WASO, estimated wake after sleep onset; prolonged NWAK, number of all periods scored as wake during TIB lasting more than 5 min; longest sleep, mean duration of the longest uninterrupted sleep episode.
[a]Mann–Whitney U.

association with cortical thickness (Figure 3, Panel A) in the rostral anterior cingulate and medial orbitofrontal cortex ($p < 0.05$), and a positive association with cortical complexity (Figure 3, Panel B) in the postcentral and supramarginal gyrus of the left hemisphere ($p < 0.005$). No significant association emerged between cortical thickness, cortical complexity, and actigraphic measures of sleep quality (SE, WASO, and NWAK). Similarly, no significant associations emerged between gray matter volume and actigraphic measures of sleep duration and quality. Detailed information is reported in Table S2. The relationship between brain morphometric properties and nonparametric actigraphy variables describing rest–activity rhythm features (IS, IV, and RA), which did not show significant differences between bvFTD patients and controls, was not explored.

4 | DISCUSSION

In this study, we comprehensively analyzed sleep and rest–activity rhythm alterations, along with their neural correlates, in a sizeable group of bvFTD patients monitored in real-life setting.

Data from different sleep-assessment methods showed consistently that patients with bvFTD exhibit longer sleep duration and lower sleep quality than controls.

The most consistent finding is the longer TIB and TST in patients with bvFTD, which was both reported subjectively and objectively documented by actigraphy. The increase of sleep duration is not ascribable to an alteration in sleep timing. Indeed, patients with bvFTD and controls showed comparable sleep phase, and despite patients

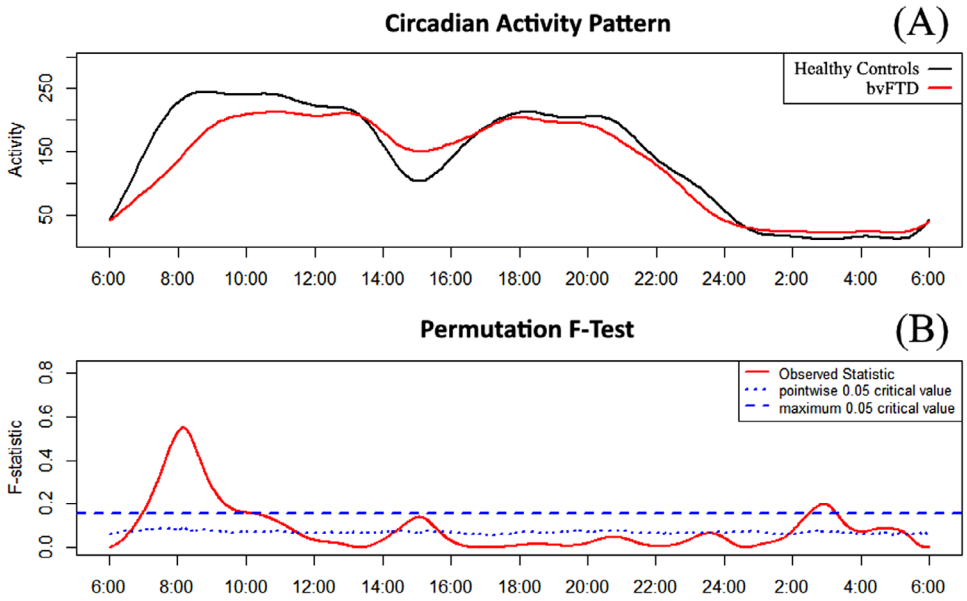

FIGURE 1 Circadian activity profile of patients with bvFTD and healthy controls. (A) Circadian activity patterns of patients with bvFTD (red line) and controls (black line). (B) Nonparametric permutation F-test result. The continuous red solid line corresponds to the observed statistics, the dashed blue line represents the global test of significance, and the dotted blue line represents the less conservative pointwise test of significance at $\alpha = 0.05$. Significant differences are observed whenever the observed statistic is above the pointwise or global threshold of significance.

going to bed earlier and waking up later than controls, no differences emerged in the midpoint of sleep. This finding contrasts with results of in-lab studies (i.e., PSG) that reported a reduction in total sleep time in bvFTD patients relative to controls,[8] but is in line with field studies, which instead reported a longer sleep duration in bvFTD patients (586.8 ± 95.4 min) compared to controls, similar to what was observed in our study (565.96 ± 88.7 min).[12] Furthermore, patients with bvFTD also reported longer ideal TIB, a measure computed from the rMEQ questionnaire that reflects sleep preferences rather than actual behavior.[23]

Prolonged nighttime sleep duration (i.e., >9 h) and the transition to extended sleep duration have been associated with neurodegeneration, lower total brain volume, impaired processing speed and executive functioning, and a higher risk of all-cause dementia.[35,36]

Nonetheless, the mechanisms linking increased sleep duration and neurodegeneration are still not fully understood. Candidate mechanisms for this association include neuroinflammation,[37] altered protein clearance,[38] and structural/functional changes in neural circuitry regulating sleep and wakefulness.[5] In our cohort of bvFTD patients, prolonged nighttime sleep duration was associated with decreased cortical thickness bilaterally in frontal brain regions (including the superior frontal, rostral middle frontal, anterior cingulate gyrus, and orbitofrontal cortex), and in precentral and postcentral gyrus of the right hemisphere. The association between increased sleep duration and decreased cortical thickness in frontal brain regions, particularly the superior frontal and middle frontal gyrus, has been reported previously in cognitively unimpaired elderly individuals and in patients with mild cognitive impairment.[39,40] Our study extends for the first time these findings to bvFTD, suggesting that structural changes in frontal brain regions may underlie extended sleep duration in both physiological and pathological aging. Regarding cortical complexity, longer sleep duration was associated with increased fractal dimension in frontal regions, particularly in the orbitofrontal cortex. Previous studies have documented reduced fractal dimension in the middle, inferior, frontal, and orbitofrontal cortex in patients with bvFTD compared to controls.[33] However, the relationship between cortical complexity and thickness is influenced by a complex interplay of various factors.[41] Moreover, in neurodegenerative diseases, changes in cortical complexity can be indicated by either an increased or decreased fractal dimension, depending on whether the neurodegenerative process reduces the folding area, resulting in a lower fractal dimension, or increases sulci depth, leading to a higher fractal dimension.[33]

Regarding screening questionnaires for primary sleep disorders, we found that patients with bvFTD were more likely to experience insomnia. Conversely, we did not observe an increased prevalence of EDS or risk of OSA. Although this latter finding contrasts with those of previous studies, it is important to note that these studies adopted different methodologies to assess OSA or investigated OSA in a mixed sample of FTD-spectrum patients.[8,42] bvFTD patients were more likely to report poor sleep quality compared to controls according to the PSQI, whereas no differences emerged in sleep quality as assessed by the sleep diary, indicating that the sleep diary may not be an optimal method for assessing sleep quality in bvFTD patients. Conversely, actigraphy objectively documented lower sleep efficiency, higher WASO, increased awakenings, and higher motor activity during sleep in bvFTD patients compared to controls. Noteworthy, the effect sizes for actigraphic estimates of sleep quality are significantly smaller than those observed for sleep duration, indicating that in bvFTD, alterations in sleep quality are, to some extent, more subtle than those in sleep duration. In this regard, polysomnographic

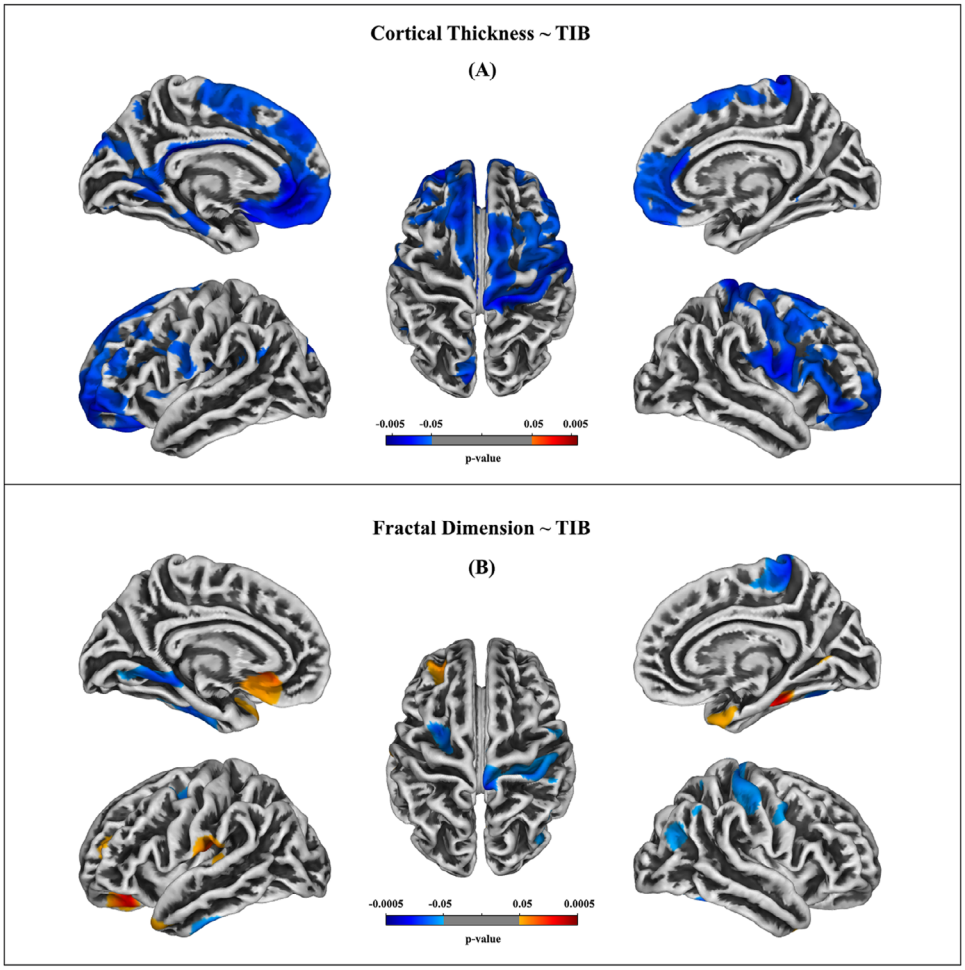

FIGURE 2 Association between cortical thickness, cortical complexity, and actigraphic TIB. (A) Association between cortical thickness and actigraphic TIB. (B) Association between cortical complexity (i.e., fractal dimension) and actigraphic TIB. Blue represents negative association and red represents positive association. The analysis is corrected for age, gender, and disease duration.

studies have highlighted several alterations of sleep macrostructure (higher N1 sleep percentage and lower non-REM (NREM)/REM cycles) and microstructure (lower slow component and higher arousal-related fast component of cyclic alternating pattern), whose evaluation is precluded to actigraphy.[7–9]

Taken together, our findings suggest that actigraphy may be an optimal method for assessing changes in sleep duration in bvFTD, whereas previous polysomnographic studies indicate that PSG might be more effective in detecting the subtle alterations in sleep quality experienced by bvFTD patients. These findings could have important clinical implications in the field of neurodegenerative diseases.

Given its cost-effectiveness and widespread accessibility, actigraphy can serve as an objective tool for longitudinally monitoring changes in sleep duration along the disease course and for ecologically assessing the effects of pharmacological interventions on the sleep/wake profile of bvFTD patients. Furthermore, it may have potential applications in other neurodegenerative diseases associated with extended sleep duration. However, no association was found between actigraphic metrics of sleep quality and brain morphometric properties, suggesting that actigraphic metrics may not be sufficiently sensitive to investigate the neuroimaging correlates of sleep quality alterations in bvFTD, whereas polysomnographic metrics may prove more informative in depicting the subtle sleep quality alterations experienced by bvFTD patients and their relationship with imaging biomarkers.

Concerning the rest–activity rhythm, when analyzing actigraphic data with a more advanced analytical framework (i.e., FLM), we found several differences between bvFTD patients and healthy controls. Patients with bvFTD and controls showed an overall preserved structure of rest–activity rhythm, showing lower motor activity during the nocturnal period and in the early afternoon in correspondence with the postprandial period. However, patients with bvFTD showed lower motor activity in the morning, a less pronounced postprandial dip, and a higher motor activity starting from the second half of the night until early morning hours, compared to controls.

Conversely, nonparametric measures (IS, IV, and RA) did not show significant differences between bvFTD patients and controls. The different outcomes of the two analyses highlight the advantages provided by FLM in detecting rest–activity rhythm alterations. Conventional nonparametric actigraphy measures describe the overall features of rest–activity rhythm by reducing the time series of activity data to a

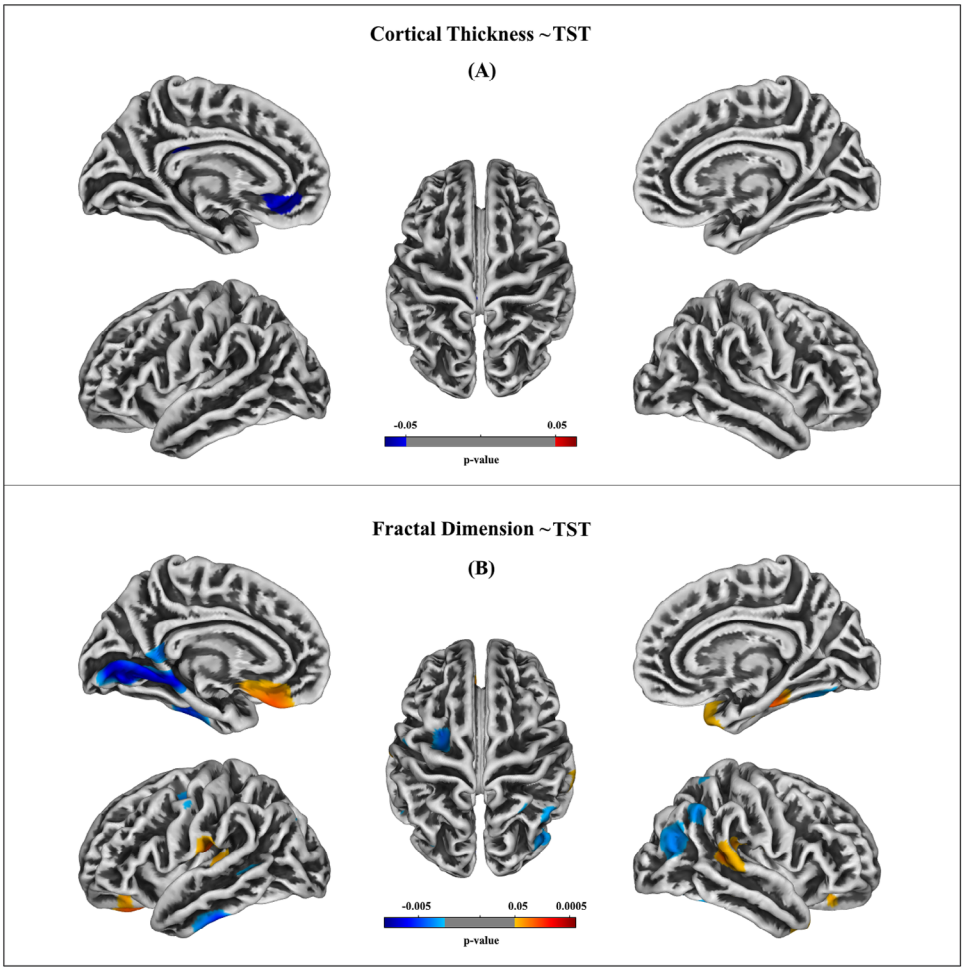

FIGURE 3 Association between cortical thickness, cortical complexity, and actigraphic TST. (A) Association between cortical thickness and actigraphic TST. (B) Association between cortical complexity (i.e., fractal dimension) and actigraphic TST. Blue represents negative association and red represents positive association. The analysis is corrected for age, gender, and disease duration.

single summary statistic, resulting in a significant loss of information. On the other hand, FLM analyzes the full time series of activity data, allowing the identification of specific time points within the 24-hour period when the activity patterns differ between bvFTD patients and controls. The reduction in morning activity levels is consistent with findings by Anderson et al., who documented lower motor activity levels (average motor activity values over a 30-min time period) from 9:00 to 11:00 in patients with FTD compared to controls.[11] Moreover, a similar pattern of increased afternoon motor activity has been documented in preclinical AD patients (i.e., cognitively unimpaired older adults with elevated amyloid beta 42 deposition).[43]

Recently several studies have hypothesized a potential involvement of the hypocretinergic system in bvFTD that could, at least in part, explain these alterations in motor activity pattern.[44] Hypocretin-producing neurons are located exclusively within the dorsolateral hypothalamus but project widely throughout the brain and play a key role in regulating sleep, motor activity, and a range of behaviors that are often altered in bvFTD patients, including hypersexuality, hyperorality, aberrant motor activity, and emotional blunting.[45] Structural alterations in the hypothalamus have been documented consistently in bvFTD patients; however, their relationship with hypocretin level has not yet been investigated.[46] Indeed, research in this area is still in its early stages, and the few studies that assessed hypocretin levels in bvFTD patients yielded conflicting results.[44] Further studies integrating both MRI data and CSF hypocretin levels are necessary to understand whether sleep disturbances in bvFTD are related to an alteration of the hypocretinergic system.

Several limitations of the present study should be acknowledged. First, the study used a cross-sectional design, which limits the ability to infer causality or determine the temporal sequence of observed associations. Second, although this cohort represents the largest sleep study on bvFTD, the sample size is still relatively small and may not be entirely representative of the bvFTD disease spectrum. Third, screening for mutations causative of FTLD was not routinely performed in our patients and therefore our sample may be heterogeneous from a genetic standpoint. Fourth, due to excessive motion during image acquisition, we were only able to process and analyze MRI data in a subset of patients. Finally, the imaging analysis was not corrected for multiple comparisons; therefore, these results should be interpreted with caution and require confirmation in subsequent studies.

In conclusion, our study showed that bvFTD patients present rest–activity rhythm alterations time-locked to the morning and early afternoon, a remarkable increase in sleep duration associated with decreased cortical thickness in frontal brain regions, and a slight alteration of sleep quality. Actigraphy may prove an optimal tool for ecologically assessing changes in sleep duration along the disease course and, possibly, for evaluating the effects of pharmacological interventions on the sleep/wake patterns of bvFTD patients. Further studies are needed to determine whether sleep alterations are detectable in patients with bvFTD close to disease onset, and their association with disease severity.

AUTHOR CONTRIBUTIONS

Conceptualization: M.F. and G.L. Methodology: M.F., V.G., L.T., and S.N. Formal analysis: M.F., S.N., and B.T. Investigation: V.G., L.T., D.U., D.V., A.G., R.D.B., and S.Z. Data curation: L.T., D.U., D.V., B.T., A.G., R.B.D., and S.Z. Supervision: M.F. and G.L. Funding acquisition: G.L. All authors contributed to the interpretation of the results and revised the manuscript for important intellectual content. All authors acknowledge full responsibility for the analyses and interpretation of the report and have read the manuscript and approved it as submitted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Anonymized data supporting the findings of this study not published within this article will be made available by the corresponding author, upon reasonable request, from any qualified investigator.

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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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