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Research paper

Elevated gamma activity in left frontotemporal regions preceding sleep signals emotional arousal in Bipolar Disorders: Insights from a high-density EEG investigation

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ABSTRACT

Background: While changes in sleep architecture during depression and mania are well-established, the extent to which they persist during euthymia in Bipolar Disorders (BD) remains unclear. Here we investigate pre-sleep cortical arousal and its correlation with sleep architecture and subjective sleep quality in BD patients.
Methods: Subjective sleep measures and whole–night, high–density sleep electroencephalography (EEG) recordings were obtained from 16 euthymic BD patients and 16 age and sex-matched healthy control subjects. Sleep architecture was determined according to standard guidelines and power analysis was computed to compare mean group 0.5–80 Hz frequency bands in the EEG signal preceding sleep onset.
Results: Despite the absence of disturbances in subjective sleep, euthymic BD patients exhibited heightened sleep onset latency (52,91 ± 60,3 vs 21,76 ± 29,71, $p = 0{,}018$), REM density (2,65 ± 1,47 vs 1,52 ± 1,17, $p = 0{,}022$), and poorer sleep efficiency (0,64 ± 0,15 vs 0,74 ± 0,21, $p = 0{,}032$) compared to healthy controls. Total sleep time and durations of sleep substages did not differ between the groups. Additionally, our findings revealed increased pre-sleep gamma power in left frontotemporal areas among BD patients ($p = 0.005$), which exhibited an inverse relationship with sleep efficiency that approached significance ($r = -0.497$, $p = 0.050$).
Conclusion: Our findings suggest an alteration in sleep onset, efficiency, and REM density in euthymic BD patients, in the context of a preserved sleep duration. Some of these changes may be associated with a neural signature of cortical arousal that influences sleep quality.

1. Introduction

Bipolar disorders (BD) are persistent and recurring conditions impacting more than 1 % of the worldwide population (Merikangas et al., 2011). These conditions contribute to the burden of disability among young individuals, linked to cognitive and functional challenges, and heightened mortality risks, particularly from suicide and cardiovascular disease (Morton and Murray, 2020). BD encompass a range of

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conditions affecting emotion regulation, energy level, and thought processes that are distinguished by alternating mood episodes, including manic or hypomanic phases and depressive periods (American Psychiatric Association, 2013). These disorders manifest as recurrent episodes marked by fluctuations in energy levels and behaviour (Vieta et al., 2018). Sleep disturbances are prevalent across all stages of BD and have been repeatedly associated with the onset of the disease, severity of symptoms, treatment outcome and quality of life (Eidelman et al., 2010; Giglio et al., 2010; Morton and Murray, 2020). Furthermore, disruptions in the sleep-wake cycle are estimated to affect around 35 % of individuals with BD (Takaesu et al., 2016). Although the presence of sleep disturbances in BD is widely acknowledged (Kaplan, 2020; Harvey et al., 2015; Giglio et al., 2010), there is no agreement on the specific sleep stages and parameters that are disrupted (Zangani et al., 2020; Melo et al., 2017). One consistent observation, however, is that these disturbances occur throughout all stages of the illness, including mood episodes (depression and mania) as well as periods of remission (euthymia) (Marchetti et al., 2025; Zangani et al., 2020).

Mania and/or hypomania are usually characterized by a reduced need for sleep with a consequent reduction in Total Sleep Time (TST) Marchetti et al., 2025; Hudson et al., 1992), and increased Sleep Onset Latency (SOL) and Wake After Sleep Onset (WASO) (Asaad et al., 2016; Hudson et al., 1992). Findings on Non-Rapid-Eye Movement (NREM) sleep and Rapid Eye Movement (REM) during manic episodes are inconsistent and sometimes contradictory. Research shows variations ranging from no differences between manic BD patients and controls to alterations in NREM stages 1 (N1) and 3 (N3) (Hudson et al., 1992; Asaad et al., 2016). Additionally, manic patients often exhibit reduced REM latency (Asaad et al., 2016; Nakamura et al., 1993; Hudson et al., 1992). However, the most consistent finding is the increased REM density—measured by the number of eye movements during REM sleep—interpreted as a marker of sleep need and arousal (Rao et al., 2002).

During depressive phases, individuals with BD typically show alterations in TST compared to healthy controls and those with unipolar depression (Mendelson et al., 1987). Like manic phases, findings for NREM sleep characteristics are contradictory (Mendelson et al., 1987; Rao et al., 2002; Giles et al., 1986), particularly concerning REM duration and latency (Duncan et al., 1979; Jernajczyk, 1986; Mendelson et al., 1987). However, studies consistently indicate increased WASO and sleep onset latency (SOL) in depressive phases (Duncan et al., 1979; Mendelson et al., 1987). During remission (euthymia), sleep architecture appears generally preserved in terms of TST and NREM sleep (Soehner et al., 2018; Knowles et al., 1986; Estrada-Prat et al., 2019; Eidelman et al., 2010), although alterations in SOL and WASO may occur (Rocha et al., 2013; Geoffroy et al., 2015; Knowles et al., 1986; Talbot et al., 2009). Notably, REM sleep density remains significantly increased in euthymic patients (Sitaram et al., 1982; Eidelman et al., 2010; Estrada-Prat et al., 2019).

Together, these findings suggest that alterations in NREM sleep stages and REM latency/duration remain inconsistent across studies. These inconsistencies may reflect methodological differences (e.g., polysomnography vs. actigraphy), variability in sample characteristics (age, illness phase, medication status, comorbidities), and small sample sizes that limit generalizability. Conversely, parameters such as prolonged sleep onset latency (SOL), increased wake after sleep onset (WASO), and elevated REM density are more consistently observed (Gold and Sylvia, 2016; Tonon et al., 2024; Zangani et al., 2020), suggesting potential involvement of pre-sleep/sleep-related arousal mechanisms in BD (Barbato, 2023).

Of note, pre-sleep arousal has been widely associated with several indices of poorer sleep quality (Bean et al., 2021; Gorgoni et al., 2021; Gregory et al., 2008; Wuyts et al., 2012; Alfano et al., 2010; Tang and Harvey, 2004). However, while these studies emphasize cognitive and/or clinical arousal assessed through specific tasks and subjective scales, they often overlook a thorough exploration of the neural underpinnings and emotional implications of such arousal (Levy, 2013). Furthermore, it is acknowledged that during the remission phase, individuals with BD may still experience emotional hyper-reactivity, heightened sensitivity, and signs of emotion dysregulation (Henry et al., 2012; M'Bailara et al., 2015).

Previous research has shown that a normal transition from wakefulness to sleep is characterized by a decrease in alpha activity and an increase in low-frequency bands, such as theta and delta power, often accompanied by heightened sleepiness (De Gennaro et al., 2004; Ferrara and De Gennaro, 2011; Guerrero and Achermann, 2019; Strijkstra et al., 2003). In contrast, pre-sleep alertness appears to be marked by stable alpha band activity (Johnson, 1970; Chen et al., 2011) and may depend on arousal mechanisms, as reflected by the presence of higher frequency bands such as beta and gamma (Garcia-Rill et al., 2016; Chapotot et al., 2001).

To our knowledge, none of the available studies have explored the potential role of pre-sleep arousal by investigating spectral EEG signatures preceding sleep and their relationship with subsequent sleep in euthymic BD patients. Therefore, the present study aims to characterize neurophysiological markers of cortical emotional arousal prior to sleep onset and examine both objective sleep macrostructure and subjective sleep measures in BD patients during the euthymic phase.

2. Methods

2.1. Participants

In this case-control study, sixteen patients diagnosed with Bipolar I or Bipolar II disorder were recruited from the Mental Health Department of the ASST Santi Paolo e Carlo in Milan (Italy) over a 2–year period.

All participants completed the screening visit at the San Paolo University Hospital with a trained clinician to sign the informed consent and assess eligibility.

Patients were required to meet the following inclusion criteria: (1) between 18 and 65 years old; (2) Diagnosis of Bipolar I or Bipolar II disorder confirmed by trained clinicians using the Italian version of the Structured Clinical Interview for DSM-5 (SCID-5-CV, First et al., 2017); (3) current euthymic state, confirmed with the Italian versions of Hamilton Depression (HAM-D, Hamilton, 1960), Hamilton Anxiety (HAM-A, Hamilton, 1959) and Young Mania (YMRS, Young et al., 1978) Rating Scales (Conti, 1999); (4) proficiency in the Italian language; Sixteen age- and sex-matched healthy subjects were recruited as a control group.

Participants were excluded if any of the following conditions was present: (a) Substance Use Disorder within the previous 6 months; (b) Intellectual Disability; (c) diabetes; (d) severe cardiopathy, acute/subacute coronary or arrhythmic events within the previous 3 months; (e) neoplasia diagnosed within the previous 3 years, even in cases of negative follow-up; (f) engagement in working activities involving night shifts or airplane journeys with a 3-hour lag (or more) within the previous 3 weeks (g) major sleep disorders.

With the exception of the inclusion criteria 2 and 3, all the rest of criteria were uniformly applied to both individuals with BD and healthy controls (HC). Familiarity with psychiatric illness served as an additional exclusion criterion specifically applied to healthy control subjects. Screening included a structured sleep-focused clinical interview, review of medical history and medications for risk factors for sleep disorders. The study sample was recruited over two years based on stringent inclusion criteria and the ability to complete a technically demanding high-density sleep EEG protocol, reflecting common challenges in psychiatric electrophysiological research. The sample size aligns with prior clinical EEG studies and was justified by a post-hoc power analysis comparing our effect sizes (Cohen's d = 0. 93–1. 12) and statistical power (87–94 %) to those reported by Mitra et al. (2015), confirming sufficient power to detect large group differences in gamma power. Emphasis was placed on acquiring high-quality data under rigorously

controlled conditions to ensure robustness despite the limited sample. All procedures were approved by the Milan Area 1 Ethics Committee, and written informed consent was obtained from participants prior to any study activity.

2.2. EEG recording procedure

All participants were asked to arrive at the Regional Epilepsy Centre – Sleep Medicine unit of the San Paolo University Hospital 2 h before their usual sleeping time. Before starting the EEG set up, participants completed Italian versions (Conti, 1999) of the Pittsburgh Sleep Quality Index (PSQI) to assess subjective sleep quality (Buysse et al., 1989), and the Epworth Sleepiness Scale (ESS) to assess subjective feelings of daily sleepiness (Johns, 1991). No objective overnight measures specifically targeting sleep-disordered breathing or periodic limb movements (e.g., respiratory belts, nasal airflow sensors, pulse oximetry, leg EMG) were obtained, and anthropometric data such as body mass index (BMI) were not collected.

The EEG recording was performed using a 64-electrode EEG cap (BrainAmp DC, Brain Products, Germany) referenced to the FPz electrode. Additionally, two pairs of ocular electrodes were placed according to American Academy of Sleep Medicine (AASM) recommended rules for electrooculography (EOG) in sleep recordings. Impedances were kept below 10 k. The recording was performed in a dedicated video-polysomnography room, with participants allowed to begin sleep within approximately 1 h of their habitual bedtime. Bedtime ranged from 21:57 to 01:33 for healthy controls and from 21:27 to 00:39 for BD patients. For each participant, the recording was carried out for the whole night until spontaneous awakening.

2.3. Sleep architecture

Sleep staging was performed by two independent experts according to the American Academy of Sleep Medicine criteria, based on 30-second epochs for 6 EEG channels (F3/A2, F4/A1, C3/A2, C4/A1, O1/A2, O2/A1) (Berry et al., 2012), and electromyogram (EMG) was derived from channels around the neck and jaw, in line with previously published procedures (D'Agostino et al., 2018; Castelnovo et al., 2024). Consecutive epochs belonging to the same stage (i. e., wake, sleep N1, sleep N2, sleep N3, or REM sleep) were pooled together to determine their absolute duration as well as the duration against total sleep time. REM density was calculated according to Lucidi et al. (1996) and consisted of the number of eye movements per each 30-second epoch of REM sleep (Karamessinis et al., 2007). Sleep efficiency (SE) was computed as the ratio of TST to the total time spent in bed (SE = TST / Duration of Sleep Episode, DSE, in our case DSE coincides with Total Time of Recording, from light-off and final morning awakening) (Reed and Sacco, 2016). SOL was considered as the time between the start of EEG recording (lights-off) and the beginning of N1. WASO represented the number of minutes that a subject spent awake after falling asleep.

After filtering (bandpass 0.5–40 Hz), channels removal and interpolation, and artefactual epochs removal, signal from sleep stages N2 and N3 was extracted and used for power. Spectral analysis was performed using all clean 6-second epochs within N2–N3 sleep (Welch's averaged modified periodogram with a Hamming window, 8 s, 50 % overlap); average spectral density was computed for 6 frequency ranges (delta: 0.5–4 Hz; theta: 4–8 Hz; alpha: 8–12 Hz; sigma: 12–16 Hz; beta: 15–25 Hz; and low gamma: 25–40 Hz).

2.4. Pre-sleep EEG arousal

For each subject, we examined the EEG signal recorded during the wake eyes-closed pre-sleep period, that is the EEG signal included between start of the recording (participants lying in bed with the lights off) to sleep onset (beginning of first sleep epoch, namely N1 in all the participants). All pre-processing analyses were conducted using BrainVision Analyzer software (Brain Products, Gilching, Germany). Data were re-referenced to the common average, and the signal was bandpass-filtered between 0.5 and 80 Hz. A Notch filter was also applied to correct for main electrical noise. Ocular correction was conducted using the regression-based approach from Gratton et al. (1983) implemented in BrainVision Analyzer 2.2.

Afterwards, data were visually inspected for residual artefacts and segmented into 1 s segments. Only artifact-free trials were included in further analyses. EEG segments for the wake pre-sleep condition were then exported and analysed using customized Matlab routines (MathWorks, Natick, MA) and the EEGLAB toolbox (Delorme and Makeig, 2004).

EEG power spectrum was calculated for frequencies ranging from 0.5 to 80 Hz. A Morlet wavelet analysis was conducted using a one-cycle complex with an incremental factor of 0. 8. We examined the following frequency bands: delta (0.5–4 Hz), theta (4.5–7.5 Hz), alpha (8–12.5 Hz), beta (13–30 Hz), and gamma (30.5–80 Hz), as suggested by Saby and Marshall (2012).

2.5. Statistical analyses

To evaluate the differences between patients and controls concerning macrostructural sleep parameters, independent-sample *t*-tests tests were conducted. If the assumption of normality was violated, non-parametric equivalent tests were employed. Subsequently, all parameters were correlated with subjective sleep measures (i. e., PSQI and ESS scores) using Pearson's correlation. Sleep architecture analysis and statistical correlations were performed using version 27.0.2.0 of IBM SPSS Statistics (IBM Corp, 2020) and statistical significance level was set at $p < 0.05$.

Comparison of EEG power measures between groups involved permutation tests conducted on each frequency band, providing an initial overview of between-group differences. Unlike independent sample t-tests, permutation tests are non-parametric, offering increased reliability when the sample does not follow a normal distribution (Delorme and Makeig, 2004).

Subsequently, in accordance with Riha et al.'s approach (2020), we implemented a cluster-based subdivision of the electrodes. Accordingly, we identified specific clusters of interest for each frequency band, namely those clusters exhibiting relevant group differences in the first round of analyses. These were O1, C2 for delta; C2 for theta; T1, F1, C2 for beta; T1, F1, T2, F2, C2, O1 for gamma, as evident by applying Riha et al.'s cluster subdivision to our results in Fig. 1. For those clusters of interest, we conducted additional permutation analyses, selectively applying a Holm-Bonferroni correction (Aickin and Gensler, 1996). EEG power values associated with clusters of electrodes showing significant results were subsequently averaged across the electrodes within the same cluster.

To evaluate the relationship between cortical pre-sleep arousal and specific sleep parameters across both groups (Wuyts et al., 2012), we employed Pearson's correlation analysis. This approach examined correlations between EEG power in clusters that survived multiple comparison corrections and various macrostructural sleep parameters, along with subjective sleep measures, in both HC and BD The same analyses were also run separately within the two groups.

3. Results

3.1. Sleep architecture (macrostructure) and subjective sleep measures

The sleep architecture parameters for individuals with BD and healthy controls are presented in Table 1. In comparison to the control population, patients exhibited elevated REM density ($p = 0.022$) and SOL ($p = 0.018$), along with reduced sleep efficiency ($p = 0.032$). Furthermore a significant moderate positive correlation between REM density and SOL ($r = 0.51$, $p = 0.003$). Subgroup analyses revealed

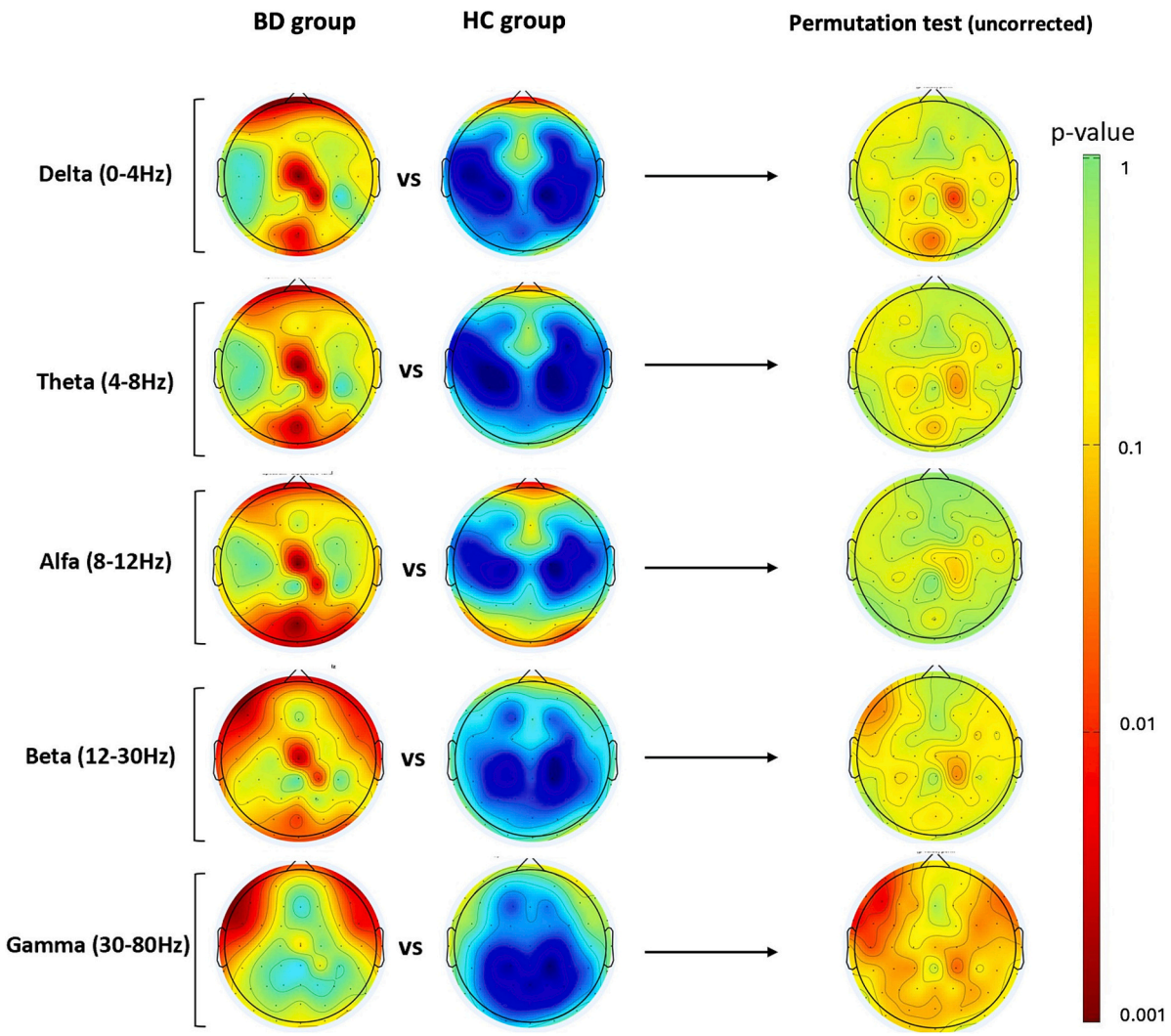

Fig. 1. Electrode-based permutation tests on the EEG power within each frequency band. From left to right: topographical plots showing BD's spectra, HC's spectra, and between-group differences spectra, respectively.

distinct patterns within the groups, with significant positive correlation in the BD group but not in the control individuals (BD: $r = 0.62$, $p = 0.010$ and HC: $r = -0.004$, $p = 0.989$). In healthy controls, the correlation between gamma power and sleep efficiency, as well as WASO, failed to reach significance (r = 0. 365, p = 0. 164 and r = −0. 111, p = 0. 681, respectively). No statistically significant between-group differences were observed in overall N2–N3 EEG power. However, a significantly lower peak in the Sigma band (which includes sleep spindles) was identified in BD patients compared to the control group. Further details on sleep spindles and slow waves from an overlapping dataset have been reported elsewhere (Sanguineti et al., under review). BD patients did not significantly differ from healthy control subjects in self-reported sleep quality (PSQI, $p = 0.776$) and subjective feelings of sleepiness in different contexts (ESS, $p = 0.959$).

3.2. Pre-sleep arousal (microstructure)

When considering the EEG frequency spectrum, all frequency bands displayed distinct power and scalp distribution patterns between BD patients and healthy controls, as shown in Fig. 1. The most notable differences were observed in the delta and gamma ranges, with patients exhibiting heightened delta power in Parieto-occipital areas and increased gamma power in frontotemporal regions.

3.3. Pre-sleep arousal and gamma power results

Permutation results applied to the cluster-based subdivision did not survive correction for multiple comparisons in the delta range (Supplementary Fig. 1). Consequently, any exploratory correlations between delta power and other sleep measures, reported only as supplementary information (Supplementary Table 2), should be interpreted with caution.

However, between-group differences within the gamma band remained significant and specifically in left frontotemporal regions, i.e., corresponding to the F1 and T1 clusters. Additionally, we computed the average EEG signal across electrodes within these clusters individually (F1 and T1) as well as collectively (F1 + T1) to evaluate the differences between BD patients and healthy control subjects in the amount of gamma power in front-temporal regions. Table 2 shows that BD patients exhibited significantly higher gamma power than healthy subjects on the averaged signal of the gamma clusters F1, T1, and F1-T1 separately ($p = 0.003$, $p = 0.010$, $p = 0.005$, respectively).

Given the evident between-group differences in both individual clusters and their pooled averages concerning macrostructural sleep parameters, we focused on the latter, which encompasses a larger scalp area. In the overall analysis, gamma power from the F1-T1 cluster significantly correlated with WASO ($r = 0. 403$, p = 0. 022) and sleep efficiency (SE) ($r = -0. 369$, p = 0. 038). This indicates that increased

Table 1
Between-group differences on demographics, subjective sleep measures (PSQI and ESS), psychopathology scores (HAM-D, HAM-A and YMRS) and macro-structural sleep parameters (SOL = sleep onset latency; TST = total sleep time; WASO = wake after sleep onset, TIB = Time in Bed (total recording time). Some *p*-values were obtained through Mann-Whitney *U* tests due to violation of the normality assumption (N1 min, N1%, REM density, SOL, TST min, Sleep efficiency). The remaining p-values were obtained through standard independent-sample *t*-tests. BD = bipolar disorder. HC = healthy controls. σ = standard deviation. *p-values indicate statistical significance. Percentages are expressed as % of total sleep time (mean ± SD).

	Healthy controls ($N = 16$) - Mean ± σ	Bipolar Disorders ($N = 16$) - Mean ± σ	Two-tailed p-value
Age	40.8 ± 12	42.2 ± 10.2	/
Gender (N)	6F, 10 M	6F, 10 M	/
Education (years)	16.93 ± 2.31	13.25 ± 3.04	0.001*
HAM-D	/	1.66 ± 1.83	/
HAM-A	/	2.13 ± 1.92	/
YMRS	/	2.06 ± 3.17	/
ESS	5.13 ± 3.27	5.19 ± 2.53	0.959
PSQI	4.93 ± 2.93	4.66 ± 2.05	0.776
N1 (min)	23.16 ± 14.96	38.5 ± 36.14	0.407
N1 (%)	9 ± 5	13 ± 11	0.474
N2 (min)	136.47 ± 71.93	140.5 ± 74.07	0.877
N2 (%)	49 ± 11	50 ± 12	0.815
N3 (min)	55.94 ± 44.22	46.56 ± 28.61	0.482
N3 (%)	20 ± 9	18 ± 17	0.879
REM (min)	71.19 ± 67.49	58.63 ± 39.12	0.524
REM (%)	22 ± 14	19 ± 6	0.432
REM density	1.52 ± 1.17	2.65 ± 1.47	0.022*
WASO (min)	72 ± 69.21	112.25 ± 83.19	0.147
WASO (%)	21 ± 21	25 ± 15	0.163
SOL	21.76 ± 29.71	52.91 ± 60.3	0.018*
TST (min)	282.63 ± 144.57	284.19 ± 124.42	0.880
Sleep efficiency (%)	74 ± 21	64 ± 15	0.032*
TIB (min)	522.84 ± 53.05	468.26 ± 67.02	0.089
Arousals (N)	56.72 ± 66.42	75.83 ± 105.53	0.839
Psychotropic treatment [N/sample (%)]			
Benzodiazepines		2/16 (12.5)	
Antipsychotics		9/16 (56.3)	
Antidepressants		3/16 (18.8)	
Mood stabilizers		13/16 (81.3)	
Anticonvulsants		3/16 (18.8)	
Lithium		10/16 (62.5)	

Table 2
Between-group differences on the two clusters of interests in the gamma range (F1, T1) as well as their pooled average (F1-T1). Each cluster of interest consists of the averaged EEG signal from the six adjacent electrodes within that cluster. *p-values indicate statistical significance.

Cluster of interest	Mean HC ± σ (N = 16)	Mean BD ± σ (N = 16)	p-Values
F1 gamma	36.68 ± 4.84	42.81 ± 6.01	0.003*
T1 gamma	37.00 ± 6.01	42.71 ± 6.33	0.010*
F1-T1 gamma	36.84 ± 4.90	42.76 ± 6.11	0.005*

left frontotemporal gamma activity during sleep transition is associated with reduced objective sleep quality across both groups (Fig. 2 and Table 1).

Subgroup analyses revealed distinct patterns within the groups, which did not reach statistical significance. In healthy controls, the correlation between gamma power and sleep efficiency, as well as WASO, failed to reach significance ($r = 0.365$, $p = 0.164$ and $r = -0.111$, $p = 0.681$, respectively). No correlation between gamma power and WASO ($r = 0.301$, $p = 0.258$) was observed for BD patients, whereas an inverse relationship with sleep efficiency approached significance ($r = -0.497$, $p = 0.050$).

4. Discussion

In the reported study we provide preliminary evidence of a possible link between sleep macrostructure and microstructural signs of cortical arousal in a euthymic BD sample. Patients maintained a preserved sleep architecture across most assessed parameters, including N1, N2, N3, and REM duration. Their TST did not differ from that of healthy control subjects. Additionally, subjective daytime sleepiness and subjective sleep quality, as measured by the PSQI and ESS scores, were comparable to those of healthy subjects. However, we observed a significant difference in sleep efficiency and SOL, indicating that patients took longer to fall asleep compared to healthy controls. This suggests a partial misalignment between objective and subjective sleep measures (as assessed by sleep questionnaires).

These results are coherent with previous studies on sleep during remitted periods of BD. In their meta-analysis of 248 studies, Geoffroy et al. (2015) found that euthymic BD patients tend to have increased SOL, and less sleep efficiency as compared to healthy individuals. Likewise, Rocha et al. (2013) administered the PSQI to 105 BD patients and 104 controls, and found that patients reported significantly higher SOL and poorer sleep efficiency. The sole inconsistency among these studies lies in the observation that, unlike the findings of Geoffroy et al. (2015), Rocha and colleagues reported no differences in TST between BD patients and healthy subjects. Our study aligns with the latter result, consistent with findings from other groups (Soehner et al., 2018; Verkooijen et al., 2017). These results collectively indicate a physiological sleep duration in euthymic BD, albeit more fragmented and characterized by difficulties in falling asleep.

Moreover, not only do our findings reveal no differences in TST but they also indicate comparable durations of sleep subphases across groups, as evidenced by similar N1, N2, N3, REM duration and number of arousals during sleep. This suggests that disruptions in overall sleep architecture, including its duration, may primarily occur during mood episodes rather than persisting across the entire course of the disease, as previously demonstrated by Verkooijen et al. (2017).

Consistent with previous findings, which demonstrated that SOL and REM density consistently tend to be higher in all stages of BD, including remission periods (Zangani et al., 2020), we also observed a significant increase in REM density among patients and additionally a significant positive correlation between SOL and REM density in the patients group. Since Aserinsky's seminal work in 1969, REM density is thought to depend on the amount of prior accumulated sleep, perhaps reflecting a form of “sleep satiety”. Accordingly, it increases across sleep cycles and reflects a growing pressure to awaken (Feinberg et al., 1967; Zimmerman et al., 1980; Wehr et al., 1993). While this explanation aligns with the clinically observed reduction in TST and sleep need during manic episodes, it is inconsistent with our results, which indicate that these parameters remain unaltered in euthymic phase.

An alternative interpretation is that increased REM density may reflect brain arousal (Barbato, 2023). The amount of rapid eye movements may accordingly result from arousing mechanisms that peak close to awakening (Achermann et al., 1993). Of note, not only do such mechanisms reflect upcoming awakening, but they may also indicate emotional arousal both in healthy individuals (van der Helm et al., 2011; Baekeland et al., 1968) and those with affective disorders (Nofzinger et al., 2004; Ho et al., 1996). Hence, increased REM density may point to limbic system activation reflecting emotional arousal (Weniger et al., 2006; Nofzinger et al., 2004). Given that BD is characterized by emotion dysregulation (De Prisco et al., 2022, for an updated overview) and heightened emotional susceptibility that persists during periods of remission (M'Bailara et al., 2009; M'bailara et al., 2015; Boudebesse and Henry, 2012; Henry et al., 2012), increased REM density may be considered a stable biomarker of BD reflecting emotional arousal carried overnight. This interpretation is coherent with our findings on the EEG signatures of pre-sleep arousal.

Regarding the latter, we did not observe the hypothesized difference

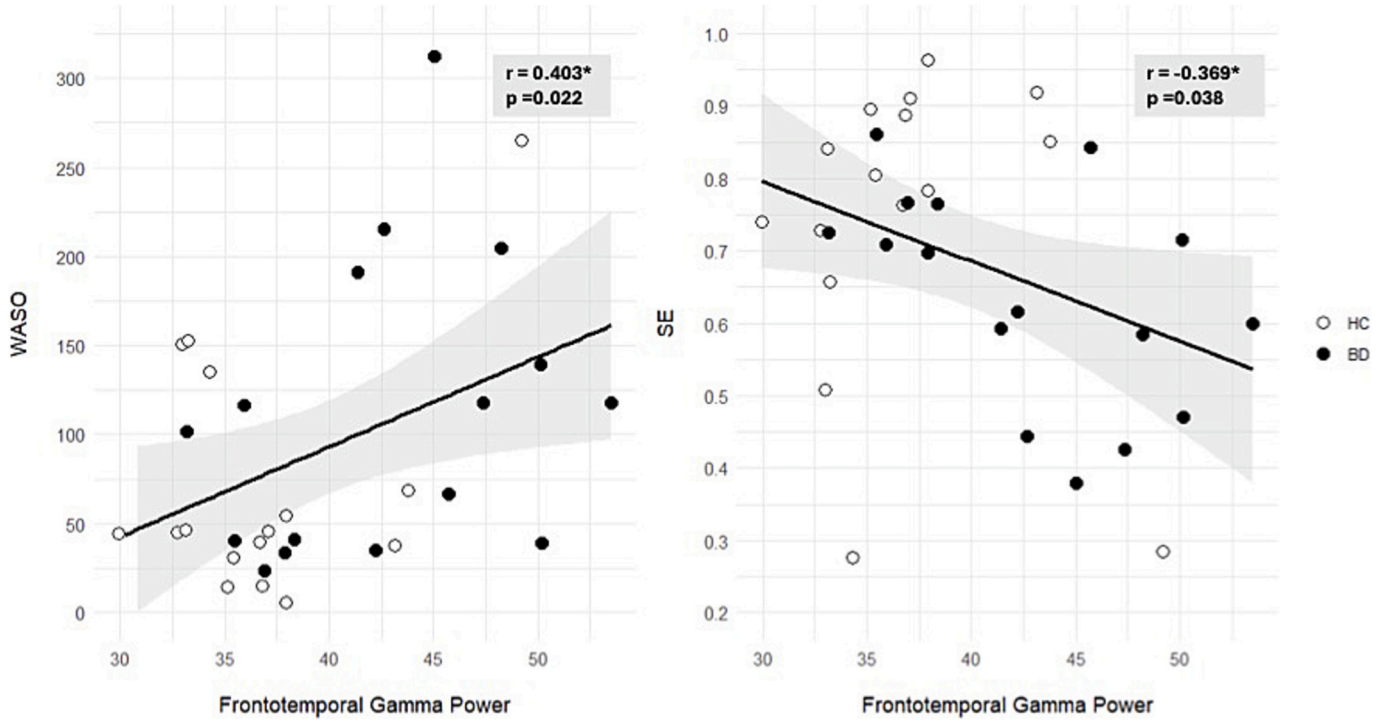

Fig. 2. The figure shows Pearson's correlation between EEG gamma power in left frontotemporal area (F1-T1) and sleep continuity (WASO, left panel) as well as sleep efficiency (SE, right panel) in the pooled study sample.

in alpha power between BD subjects and healthy controls, as suggested by previous studies on the wake-sleep transition (De Gennaro et al., 2004; Ferrara and De Gennaro, 2011; Guerrero and Achermann, 2019). However, according to other recent lines of evidence, there appears to be no (or even negative) relationship between arousal states and alpha activity (Barry et al., 2020; Schubring and Schupp, 2019, 2021). While increased alpha reflects alertness and vigilance, it may not necessarily point to cognitive and/or physiological arousal. Results on higher frequency bands, by contrast, suggest clearer signs of cortical arousal among our patients. More specifically, between-group differences emerged in the beta range (12 Hz–30 Hz) and peaked in the gamma range (30 Hz–80 Hz) (Fig. 1), although only the latter persisted after applying Bonferroni correction. Taken together, these results suggest increased cortical activation, especially in left frontotemporal areas, in the period preceding sleep onset in euthymic BD individuals.

Many previous studies converge on the close relationship between gamma power and pre-sleep cognitive arousal (Dressle et al., 2023), as well as emotional arousal in different contexts (Uribe et al., 2011; Knyazev et al., 2005) and populations, including BD (Liu et al., 2012). Negative emotional stimuli appear to elicit gamma oscillations during wakefulness, both in the neocortex and in the amygdala (Headley and Paré, 2013, for a comprehensive review). Furthermore, recent work suggests increased gamma phase synchrony between subcortical regions involved in emotional processing (e.g., the amygdala) and the neocortex (Muñoz-Torres et al., 2023). Importantly, this synchrony appears to be more pronounced during wakefulness compared to sleep. In other words, gamma frequencies may reflect emotional arousal spreading from limbic regions to the neocortex during wakefulness. While extreme caution is needed when inferring subcortical activity from scalp EEG (Fahimi Hnazaee et al., 2020), there is evidence of a high correlation between cortical activity close to a deep brain structure and the activity recorded from that structure (Seeber et al., 2019; Pizzo et al., 2019). Hence, further research may clarify whether the heightened pre-sleep frontotemporal gamma that we observed among BD is linked to increased activity in mesial temporal structures, such as the amygdala.

Gamma oscillations are widely understood to arise from interactions between excitatory pyramidal neurons and inhibitory fast-spiking parvalbumin-positive interneurons, producing rhythmic excitation–inhibition cycles that support local computation and interregional communication (Buzsáki and Wang, 2012). In the context of pre-sleep arousal, increased gamma may reflect (i) heightened local cortical excitability and reduced inhibitory tone, (ii) enhanced long-range synchrony driven by limbic-to-prefrontal projections (e.g., amygdala → orbitofrontal/temporo-frontal cortex), or (iii) state-dependent neuromodulatory influences (cholinergic upregulation and/or altered monoaminergic balance) that favor fast-frequency activity during the wake–sleep transition. Each of these mechanisms is compatible with our topography (left frontotemporal emphasis) and with the known role of these regions in emotional processing and rumination. However, scalp EEG cannot disambiguate local generation from volume-conducted deep sources; therefore, multimodal approaches (concurrent intracranial recordings, source imaging, or combined EEG-fMRI) are needed to test these mechanistic hypotheses.

At the current state of knowledge, a more plausible explanation is the one linking heightened frontal gamma to cognitive and/or emotional activation. This is supported by a large body of evidence showing an association between frontal fast frequencies and cognitive processing (Kaiser and Lutzenberger, 2005; Başar, 2013, for an overview) including that of negative emotional stimuli (Luther et al., 2023), as well as ruminative thinking (Wang et al., 2022). Considering that emotion dysregulation and rumination are typical phenomena in BD (Ghaznavi and Deckersbach, 2012), the heightened frontal gamma observed in our patients may mirror similar patterns during the pre-sleep period. This interpretation aligns with recent studies indicating a positive association between pre-sleep cognitive and physiological arousal on the one hand, and gamma oscillations across the sleep cycle on the other hand (Dressle et al., 2023; Pesonen et al., 2021). We speculate that these findings suggest that pre-sleep cognitive and emotional processing may unconsciously persist during night, influencing overall sleep quality. Indeed, pre-sleep arousal (indexed by pre-sleep gamma activity) was associated with modifications in WASO and sleep efficiency across the entire study population (Table 1). In line with previous empirical and conceptual

work (Perlis et al., 1997, 2001, 2010; Harvey and Tang, 2012; Dressle et al., 2023), our findings confirm that pre-sleep cortical activation is linked with more inefficient sleep. Remarkably, however, this association was primarily evident in the BD population, as we observed no significant relationship between pre-sleep gamma and sleep parameters in the healthy control group. Regarding NREM sleep, previous evidence suggests that pre-sleep affective arousal has no discernible impact on NREM architecture (for a comprehensive overview, see Ten Brink et al., 2023). Nevertheless, this body of evidence does indicate a relationship with REM sleep, encompassing its percentage and density (Ten Brink et al., 2023). According to this data, pre-sleep affective arousal might be carried over during the night and become manifest in sleep stages closer to wakefulness marked by higher emotional activation, such as REM stages. Interestingly, we did observe a positive correlation between REM density and pre-sleep gamma power, although it did not reach statistical significance.

From a translational standpoint, pre-sleep gamma has potential utility in three complementary domains: (1) as a state or trait biomarker for elevated nocturnal emotional arousal in BD (which could contribute to objective monitoring and risk stratification); (2) as a prognostic marker predicting short-term relapse risk or functional impairment if longitudinally validated; and (3) as a target engagement marker for interventions aimed at reducing pre-sleep arousal. Candidate interventions that could be tested include behavioral treatments (e.g., cognitive-behavioral therapy for insomnia [CBT-I] adapted to address rumination and affective arousal), psychological interventions that specifically target pre-sleep rumination (e.g., stimulus control, worry postponement, brief cognitive restructuring before bedtime), and pharmacological strategies that restore excitation-inhibition balance (for example, agents that augment GABAergic inhibition or modulate glutamatergic tone) might also reduce pathological gamma and improve sleep continuity. Importantly, any interventional study should predefine EEG-based target engagement outcomes (reduction in pre-sleep gamma and subsequent improvement in SOL/WASO/sleep efficiency) and evaluate clinical endpoints (mood stability, relapse rates).

Our findings must be interpreted within the framework of some study limitations. Even though the sample size is resource-intensive for a sleep study in chronic psychiatric population, it is still relatively small, with only 16 subjects per group. Although correction for multiple comparisons was applied, definitive conclusions cannot be drawn, and further studies with larger samples are needed to validate our results. An adaptation night was not included due to resource constraints and challenges in maintaining adherence among clinical participants over multiple nights. However, recent literature suggests the first-night effect may have limited impact in patients with psychiatric disorders (Sprajcer et al., 2022; Herbst et al., 2010; Toussaint et al., 2000). Additionally, our sample's sleep architecture closely matched normative data for the relevant age group, and the same protocol was applied to both groups, reducing potential bias. Moreover, we established an association between emotional arousal markers and sleep parameters through correlation analysis. This method does not enable us to infer any directionality, preventing us from conclusively stating that emotional arousal markers are the driving force behind the observed changes in sleep architecture. The lack of self-reported arousal or additional emotional arousal measures within the study did not allow us to assess subjective pre-sleep arousal or emotional state and link it to sleep changes.

Medication use in psychiatric populations influences brain activity during both wakefulness and sleep. Indeed, our BD sample was medicated with standard mood stabilizing treatments, many of which are known to impact sleep architecture. Lithium and valproate appear to play a regulatory role in sleep and often stabilize circadian rhythms, which are frequently disrupted in mood disorders. Additionally, they contribute to the restoration of slow-wave sleep and the regulation of REM sleep, both of which are typically impaired in these conditions. Carbamazepine might have similar effects, although more evidence is needed to confirm this. In contrast, the impact of lamotrigine, olanzapine, and quetiapine on sleep and circadian regulation remains unclear, underscoring the need for further investigation (Caruso et al., 2024). Although further stratification of our sample based on medication regimen would provide valuable insights, we could not perform analyses at the level of individual drugs or medication subgroups due to the limited sample size. We did not include spectral EEG analyses during REM sleep, but a substantial lack of overall between-group differences in N2–N3 band-wise power was reported, and detailed spindle and slow-wave metrics from an overlapping dataset are reported elsewhere (Sanguineti et al., under review). Pre-sleep EEG duration was not normalized across groups. Given the longer SOL observed in the BD group, patients may have may have contributed a larger number of pre-sleep epochs than controls. Although our frequency-domain metrics are computed as subject-level averages over artifact-free 1-s epochs—an approach that is relatively robust to unequal epoch counts —between-group differences in available data length could still bias estimates.. Moreover, while recordings were obtained during an eyes-closed pre-sleep interval, continuous behavioral/oculographic verification of eyes-closed compliance across the entire interval was not performed, so intermittent non-compliance cannot be excluded. Participants' habitual wake times or sleep duration were not systematically collected (only verbally during screening interviews). Therefore, we cannot exclude the possibility that interindividual differences in habitual sleep-wake patterns introduced additional variability, particularly given the relatively small sample size. By scheduling recordings in alignment with participants' self-reported habitual bedtimes, however, we aimed to minimize this source of bias. Lastly, although all participants were clinically screened by expert clinicians to exclude major sleep disorders and completed validated questionnaires (PSQI, ESS), we did not perform objective physiological testing to rule out conditions such as obstructive sleep apnoea (OSA) or periodic limb movement disorder (PLMD). Therefore, subclinical or undiagnosed sleep-disordered breathing or movement disorders cannot be formally excluded and may have influenced the sleep EEG measures. Despite these limitations, we provide evidence of increased SOL, REM density, and diminished sleep efficiency in BD patients during euthymia, even without subjective sleep disturbances. TST and sleep substages, on the contrary, appear to be unaltered. Moreover, we demonstrate that euthymic BD patients exhibit pre-sleep cortical activation as indexed by increased gamma power in left frontotemporal areas, and that this is associated with worse sleep efficiency and continuity in both samples suggesting a possible general mechanism for which the amount of high pre-sleep frequencies might impact subsequent sleep structure.

Future investigations may enhance our understanding of these findings by examining larger samples and potentially integrating self-reported and/or physiological measures of pre-sleep cognitive, emotional and somatic arousal as well as exploring the potential involvement of subcortical limbic activity. From a clinical perspective, it may be relevant to determine whether certain altered sleep parameters and levels of pre-sleep arousal act as predictive factors for relapse into mood episodes. This could facilitate the identification of specific biomarkers and support the development of sleep-tailored treatment options adapted to the particular illness phase (Kaplan, 2020). Finally, an important future direction is the recruitment of medication-free individuals with bipolar disorder to separate illness-intrinsic from treatment-related effects on sleep and EEG physiology. Although similar designs have been feasible in early psychosis (Castelnovo et al., 2020, 2024), to the best of our knowledge medication-naïve sleep studies in euthymic BD are not currently available.

5. Conclusion

This study investigated neurophysiological markers of pre-sleep cortical arousal in euthymic patients with BD. While overall sleep architecture was largely preserved, patients showed reduced sleep

efficiency and prolonged sleep onset latency, suggesting subtle objective impairments not reflected in subjective reports of sleep quality or daytime sleepiness. REM density was significantly elevated in the BD group, consistent with prior evidence of REM abnormalities in this population. BD patients also displayed heightened gamma power in left frontotemporal regions, pointing to increased cortical arousal during the transition to sleep. Taken together, these findings highlight a partial dissociation between objective and subjective sleep disturbances in BD and suggest that increased pre-sleep cortical activation may represent a physiological marker of arousal in euthymia.

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CRediT authorship contribution statement

Renata del Giudice: Methodology, Conceptualization. **Riccardo Stefanelli:** Writing – original draft, Visualization, Formal analysis. **Francesco Donati:** Methodology, Investigation, Data curation. **Veronica Nisticò:** Data curation. **Cecilia Casetta:** Investigation, Formal analysis. **Anna Castelnovo:** Supervision, Formal analysis. **Caroline Zangani:** Investigation. **Claudio Sanguineti:** Investigation, Formal analysis, Data curation. **Maddalena Sala:** Formal analysis, Data curation. **Elena Zambrelli:** Supervision. **Maria Paola Canevini:** Supervision, Resources. **Armando D'Agostino:** Writing – review & editing, Supervision, Project administration, Conceptualization.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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