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# Sleep abnormalities across different clinical stages of Bipolar Disorder:

# A review of EEG studies

Caroline Zangani[a*], Cecilia Casetta[a], Alejandro Serrano Saunders[b],

Francesco Donati[a], Eleonora Maggioni[c], Armando D'Agostino[a]

[a]Department of Health Sciences, University of Milan, Milan, Italy

[b]School of Psychology, University of Glasgow, Glasgow, United Kingdom

[c]Department of Neurosciences and Mental Health, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

* Corresponding author: caroline.zangani@unimi.it

Highlights:

- Total sleep time and Sleep latency are impaired in all stages of Bipolar Disorder.
- Increased REM density may precede the onset of the disease.
- Microarchitecture is a poorly studied, especially sleep spindles.
- Psychotic versus non-psychotic subjects and within-subject analyses are required.

**ABSTRACT**

Sleep disturbances are highly prevalent across all stages of Bipolar Disorder. Despite a wealth of research on the neurophysiological features of sleep in this population, progress in this field has been slow. We aimed to review the literature on sleep electroencephalography (EEG) studies in Bipolar Disorder, considering sleep architecture and microstructural oscillatory activity.

We included a total of 22 studies: six on sleep during manic episodes, seven during depressive episodes, seven in euthymic patients and two in high-risk individuals. The most consistent findings were increased SOL and REM density across all stages of the disorder. Only two studies reported a reduced spindle count during bipolar depression and euthymia, respectively. Although not specific for Bipolar Disorder, SOL and REM density have been repeatedly found to be increased across all stages of illness in this population. Whereas the former reflects a difficulty initiating sleep, the latter can be considered a neurophysiological signature of patients' overall reduced sleep need, independent of illness stage.

**Keywords**: Sleep need; REM density; Insomnia; Circadian rhythms; Bipolar Depression; Sleep oscillations

## 1. Introduction

Bipolar Disorder (BD) is a chronic and disabling psychiatric illness, characterized by the recurrence of depressive and manic and/or hypomanic episodes. Sleep disturbances in BD are highly prevalent during all stages of illness, namely prodromal, relapse and remission periods (Jackson et al., 2003; Bauer et al., 2006; Harvey, 2009), and change in sleep need is among the diagnostic criteria of BD (American Psychiatric Association, 2013). Sleep disturbances have been significantly correlated with a more severe and chronic illness course (Eidelman et al., 2010), and they have a negative impact on quality of life, symptom burden, treatment outcomes and overall functioning (Giglio et al., 2010; Sylvia et al., 2012).

The close inter-relation between sleep and BD can be illustrated by several research and clinical findings. Sleep disturbances are frequently early signs of relapse in BD and often precede a mood episode recurrence. A recent meta-analysis concluded that changes in sleep, mainly insomnia and decreased need for sleep, were among the most prevalent prodromal symptoms of mood episodes, with the former anticipating almost 60% of manic and 20% of depressive recurrences, and the latter almost 40% and 10%, respectively (Van Meter et al., 2016). Of interest, experimentally induced sleep deprivation is associated with the onset of hypomania or mania in BD (Wehr, Sack, & Rosenthal, 1987; Lewis et al., 2017), and sleep deprivation has been explored as a potential treatment for bipolar depression with promising results (Boland et al., 2017). Circadian cycle disturbances have also been investigated in BD with a focus on sleep-wake patterns, alterations in melatonin, body temperature, cortisol rhythms, variations of clock genes and chronotype (Abreu et al., 2015).

Among the most common tools employed to explore sleep and circadian abnormalities, subjective reports such as sleep diaries are probably the easiest and most widely used. However, their reliability in detecting sleep variation is limited by recollection bias. Instead, actigraphy offers prolonged and objective measures of sleep/wake activity through wrist movements. Actigraphic findings in BD have recently been reviewed and meta-analysed in two studies. Geoffroy et al. (2015) concluded that compared to healthy subjects, during euthymic phases BD patients show significant differences in sleep latency, increased awakenings after sleep onset (WASO), greater variability of sleep–wake parameters and reduced sleep efficiency. The lack of consistency in the methodology employed to assess sleep and circadian rhythms was highlighted

amongst the limitations of their study. De Crescenzo et al. (2017) found that BD patients have reduced mean day activity, increased sleep duration and a more disturbed pattern of sleep compared to healthy controls. These differences appear to occur during both mood relapses and remission phases.

Despite its unequivocal utility, actigraphy cannot be used for the investigation of sleep architecture, thereby limiting insight into the neurobiological pathways of mental disorders. Indeed, the study of the sleeping brain can shed light on complex pathophysiological mechanisms of clinical syndromes, offering the opportunity to investigate neural activity while minimizing wake-related confounds such as fluctuating attention and motivation, external stimuli, cognitive processes and interfering symptoms such as hallucinations. As an objective, non-invasive and low-cost procedure, electroencephalography (EEG) is considered an invaluable tool to investigate sleep brain activity, and it remains a gold-standard for sleep assessment. EEG abnormalities have been studied extensively in depressive disorders, with conflicting results. Observed architectural differences in Major Depression include impaired sleep continuity (i.e. increased sleep latency, sleep fragmentation, early morning awakenings, reduced sleep efficiency, decreased total sleep time; Benca et al., 1992) and altered sleep architecture. The latter includes decreased REM latency and increased REM density, modifications in non-REM sleep, such as reduced slow wave sleep (SWS), slow wave activity (SWA) and sleep stage 2 (N2) (Borbély et al., 1984; Kupfer et al., 1984; Kupfer et al., 1986; Armitage et al., 1995; Benca et al., 1997).

Advances in EEG technology also fostered a new wave of sleep EEG studies in Schizophrenia. After decades of conflicting findings, high-density EEG was recently used to identify significantly impaired sleep spindle activity during NREM in Schizophrenia (Ferrarelli et al., 2007) as well as in

unaffected first-degree relatives (Schilling et al., 2017; D'Agostino et al., 2018). Altered sleep spindle activity is now considered a stable trait reflecting dysfunctional thalamocortical communication that can be studied as a new candidate endophenotype of the disorder (Ferrarelli & Tononi, 2017). More recently, abnormality of SWA has also been identified as a potential marker in Schizophrenia research (D'Agostino et al., 2018; Kaskie et al., 2019). Given the role of spindling and slow oscillations in plasticity and memory consolidation mechanisms, a link with cognitive symptoms of Schizophrenia has been hypothesized (Manoach & Stickgold, 2019). Indeed, there is considerable evidence that Schizophrenia and BD may share overlapping aetiological determinants, pathophysiological mechanisms and phenotypical presentation, suggesting disorders should not be viewed as separate categorical entities but rather on a diagnostic continuum (Sorella et al., 2019). Beyond the specificity of its clinical presentation, BD can be conceptually distinguished from Schizophrenia by its phasic and relapsing course. Although many studies have addressed the EEG characteristics of sleep in the different phases of BD, a comprehensive review to identify trait- or state-dependent features is lacking.

In order to clarify available evidence, we reviewed the literature on sleep patterns, architecture and micro-architecture from sleep EEG studies in BD during prodromal, manic, depressive and euthymic phases, as well as in high-risk subjects such as unaffected relatives.

## 2. Methods

### 2.1 Search strategy

A narrative review of the literature was undertaken to identify all of the relevant studies concerning patients with bipolar disorder and EEG evaluation of their sleep pattern. An electronic search up to 30th June 2019 was performed on PubMed. The following search terms were variously combined "bipolar", "mania", "manic" and "depression", "EEG", "electroencephalography", "sleep", "REM", "NREM", "nonREM".

A manual search was performed from the reference lists of included studies and reviews on the topic to identify potentially eligible publications.

2.2 Inclusion criteria

Studies which fulfilled the following three criteria were included: 1) recruitment of patients with BD, regardless of disease state (i.e. manic episode, depressive episode, mixed state, euthymia), or high-risk individuals, as defined by the original authors; 2) execution of sleep-EEG; and 3) evaluation of sleep pattern. No restriction on the type of study, manuscript language or publication year was applied.

Studies evaluating sleep only by means of actigraphy or subjective parameters (e.g. scales or questionnaires) were excluded. Studies presenting data on mixed populations, i.e. patients with different diagnoses, were only included when data on bipolar patients could clearly be retrieved.

2.3 Study selection and data extraction

Three authors (CC, FD, CZ) performed title/abstract and full text screening against eligibility criteria. Any issue was resolved by discussion with a senior author (ADA). All included studies were read in order to collect relevant details, and the following information were extracted by

two authors (AS, CZ): first author, year, diagnosis, state, comparator (if applicable), sample size, presence or absence of medication, main EEG findings.

## 3. Results

### 3.1 Overview of the included studies

After the screening process, a total of 22 studies (n= 309) were included (Table 1). Of these, six investigated sleep in cases of mania, seven in cases of depression, seven in euthymic patients and two in high-risk individuals. Of them, 13 studies had less than 20 participants, while the largest sample size was of 28 individuals.

The majority of the studies (n=17) compared BD patients to healthy controls, while 12 reported comparisons with individuals with other psychiatric disorders. In particular, one study compared BD patients to patients with Attention Deficit Hyperactivity Disorder (ADHD) (Estrada-Prat et al., 2019), while 11 studies compared bipolar patients during different states to depressed patients (Asaad et al., 2016; de Maertelaer et al., 1987; Duncan et al., 1979; Fossion et al., 1998; Giles et al., 1986; Hudson et al., 1992; Linkowski et al., 1986; Mendelson et al., 1987; Mendels et al., 1971; Nakamura et al., 1993; Rao et al., 2002). Moreover, one study investigated differences between BD types I and II (Giles et al., 1986). We also included a study comparing eight depressed patients to matched healthy controls, although one patient was reported to have unipolar depression (Mendelson et al., 1987).

Of all 22 studies, four studies (Hudson et al., 1988; Hudson et al., 1992; Modell et al., 2003; Friess et al., 2008) used the DSM-III-R, two studies (Asaad et al., 2016; Eidelman et al., 2010) used the

DSM-IV, three studies (Talbot et al., 2009; Soehner et al., 2018; Ritter et al., 2018) used the DSM-IV-TR, one study (Estrada-Prat et al., 2019) used the DSM-V, seven studies (Linkowski et al., 1986; Duncan et al., 1979; Giles et al., 1986; Mendelson et al., 1987; de Maertelaer et al., 1987; Foisson et al., 1998; Rao et al., 2002) used the Research Diagnostic Criteria (Spitzer et al., 1978), one study (Sitaram et al., 1982) used a modified version of the Research Diagnostic Criteria and four studies made no mention of any diagnostic criteria used (Mendels et al., 1971; Jernajczyk, 1986; Knowles et al., 1986; Nakamura et al., 1993).

Across the 20 studies of this review investigating phases of BD, six studies recruited patients during the course of pharmacological treatment (Nakamura et al., 1993; Talbot et al., 2009; Eidelman et al., 2010, Soehner et al., 2018; Ritter et al., 2018; Estrada-Prat et al., 2019) and 14 studies measured EEG characteristics during a medication-free period (Mendels et al., 1971; Linkowski et al., 1986; Hudson et al., 1988; Hudson et al., 1992; Assad et al., 2016; Duncan et al., 1979; Jernajczyk, 1986; Giles et al., 1986; Mendelson et al., 1987; de Maertelaer et al., 1987; Foisson et al., 1998; Rao et al., 2002; Sitaram et al., 1982; Knowles et al., 1986).

## 3.2 Sleep architecture in euthymic patients

### 3.2.1 Total sleep time

The only included study reporting data on Total Sleep Time (TST) in euthymic bipolar patients fails to find any different between recruited patients and HC (Soehner et al., 2018).

### 3.2.2 Sleep onset latency

Only two studies reported Sleep Onset Latency (SOL) in cases of euthymic BD (Knowles et al., 1986; Talbot et al., 2009). In patients recovering from a depressive episode, Knowles et al. (1986) observed significantly greater between-subject variance for SOL, as well as for total minutes awake after sleep onset, as compared to control subjects. The original authors argued that this finding may be attributed to an unusually low between-subject variance in the control group. Talbot et al. (2009) measured laboratory sleep in twenty-four BDI patients, four BDII patients and twenty-four healthy controls, for two baseline nights as well as one happy and one sad mood induction nights. In comparison to healthy controls, BD patients showed respectively a significantly longer SOL within the happy mood induction night, while both groups presented a significantly shorter SOL within the sad mood induction night. In baseline nights, no significant differences were observed between either group.

### 3.2.3 Non–REM sleep

Findings from Knowles et al. (1986) suggested that in BD patients recovering from a depressive episode there was a greater between-subject variance for percentage of N1 when compared to healthy controls. However, this same observation was not present in all other sleep stages. In cases of euthymic BD amongst adolescents, the BD patients have shown a significantly shorter N2 than healthy controls (Estrada-Prat et al., 2019).

In Eidelman et al. (2010) the amount of N2 sleep was negatively correlated with symptoms of mania and mood-regulated functional impairment at three months. Conversely, amount of SWS

was positively associated with the same parameters. No association was found for healthy controls.

Furthermore, in a recent EEG study, BD patients and healthy controls underwent mood induction nights, including a neutral, happy and sad induction night (Soehner et al., 2018). Over the course of the mood induction nights, overnight mood regulation in BD was not significantly different from the controls. However, the induction of a positive mood state prior to sleep increased SWA relative to baseline (i.e. neutral mood induction) across all participants. Moreover, lower SWA was linked to a reduced regulation of negative mood overnight in BD patients.

3.2.4 REM sleep

When comparing patients with remitted BD to healthy controls, Sitaram et al. (1982) observed a greater total percentage of REM sleep in BD patients. Findings from Eidelman et al. (2010) suggested that the duration of the first REM period was positively correlated to manic symptoms and mood-related functional impairment in BD patients at three months, though sleep architecture was not correlated with any concurrent mood symptoms. In comparison to patients with ADHD, BD patients have been reported to exhibit a longer duration of the first episode of REM sleep (Estrada-Prat et al., 2019). In the same study, no difference was reported between ADHD or BD patients and healthy controls for REM latency. Notably, Eidelman et al. (2010) reported that patients who took a medication which suppressed REM exhibited longer latency to the first REM stage than patients whose medications enhanced REM or had no effect on REM at all.

Within the first period of REM sleep, Sitaram et al. (1982) reported significantly greater density of eye movements in BD patients as compared to healthy controls. REM density was also found to be heightened in euthymic BD as compared to both ADHD patients and healthy controls (Estrada-Prat et al., 2019) confirming the previous findings by Eidelman et al (2010). In the latter study, REM density was reported to be positively correlated with depressive symptoms and mood-related functional impairment at three months of follow-up. In contrast to this, the control group exhibited a negative correlation between REM density and impairment following a three-month follow-up. In an investigation measuring the effects of pre-sleep mood inductions, Talbot et al. (2009) observed increased REM density in both BD patients and healthy controls on the night of sad mood induction when compared to baseline nights. However, as compared to controls, BD patients showed higher REM density on both nights of happy and sad mood induction.

### 3.3 Sleep spindles in euthymic patients

Only one study has so far investigated prevalence of sleep spindles in euthymic BD patients (Ritter et al., 2018). The authors observed a reduced density and a lower mean frequency of fast spindles in patients compared to controls. In both frontal and central derivations, BD patients had lower fast spindles (density >13 Hz) within N2 sleep as compared to controls. In addition, BD patients exhibited a reduced mean spindle frequency for fast spindles in derivation F4, as well as in both central derivations. When analysing fast spindle amplitude and duration, no significant differences were found. Amongst lithium-treated patients, no association was found between

treatment and fast spindle parameters. In terms of slow spindles (density <13 Hz), no significant differences were found across all parameters. Spectral analysis showed lower EEG power in the high sigma band in BD patients compared to HC, only in central derivation C3-M2.

### 3.4 Sleep architecture in manic patients

#### 3.4.1 Total Sleep Time

Three studies reported shorter TST for manic BD patients compared to healthy controls (Hudson et al., 1992; Mendels, 1971; Linkowski et al., 1986). When compared to MDD and controls, BD manic patients exhibit the least amount of TST (Hudson et al., 1992). However, the comparison of TST across phases of BD showed no significant difference between manic and depressed patients (Linkowski et al., 1986).

#### 3.4.2 Sleep onset latency

Only three studies investigated sleep continuity and sleep latency in manic patients (Assad et al., 2016; Hudson et al., 1992; Linkowski et al., 1986). Sleep continuity is shown to be notably disturbed in the manic phase of BD (Linkowski et al., 1986; Hudson et al., 1992). Manic patients were characterized by lower sleep efficiency than healthy subjects and had considerably longer latency compared to healthy controls and unipolar depressed subjects but not bipolar depressed patients (Linkowski et al. 1986). In this line, one study reported an increase of sleep latency in hypomanic patients as compared to controls (Assad et al., 2016).

#### 3.4.3 Non–REM sleep

In a study by Hudson et al. (1988), no significant differences were reported between sleep architecture in patients with mania. Conversely, in a study by the same author (Hudson et al., 1992), a greater percentage of both N1 and N3 was found in cases of manic BD in comparison with healthy controls. No significant differences in N4 were reported. Finally, studies of hypomanic patients reported a reduction in N3-N4 sleep compared to healthy controls (Mendels et al., 1971; Assad et al., 2016).

3.4.4 REM sleep

When comparing onset of REM latency across BD patients, Linkowski et al. (1986) observed normal REM latencies in both manic and bipolar depressed groups compared to healthy controls. However, subsequent studies (Hudson et al., 1988; Assad et al., 2016) on slightly bigger samples of hypomanic/manic BD patients reported a significantly shortened REM latency. These findings were further supported by Hudson et al. (1992), with patients of BD and MDD showing similarly decreased REM latency compared to controls. On the other hand, more recent evidence (Assad et al., 2016; Nakamura et al., 1993) found BD hypomanic patients to show a longer REM latency than unipolar depressed patients.

As for REM density, it was found higher in comparison to healthy controls (Asaad et al., 2016; Hudson et al., 1988; 1992) while differences between BD and MDD are unclear. Indeed, Hudson and colleagues (1992) reported no significant differences between the two groups, while Assad et al. (2016) found that patients with MDD showed greater REM density than hypomanic BD patients. Furthermore, Linkowski et al. (1986) found no significant differences in REM density

among patients with bipolar depression and unipolar depression, and healthy controls. Unipolar patients however showed a trend towards a higher REM density.

### 3.5 Sleep architecture in depressed patients

#### 3.5.1 Total Sleep Time

Mendelson et al. (1987) reported less TST in depressed patients compared to healthy controls. A trend towards reduced TST was also observed in Linkowski et al. (1986). Compared to MDD, BDII patients showed greater TST (Fossion et al., 1998; Giles et al., 1986), with total non-REM (NREM) time suggested to account for the increased sleep time (Giles et al., 1986).

#### 3.5.2 Sleep continuity and sleep onset latency

One study (Linkowski et al., 1986) found disturbed sleep continuity in depressed bipolar individuals.

Research into SOL of bipolar depression features in three studies (Duncan et al., 1979; Mendelson et al., 1987; de Maertelaer et al., 1987). BD depressed patients showed longer SOL (de Maertelaer et al., 1987; Duncan et al., 1987; Mendelson et al., 1987) and more early morning awakening in comparison to healthy controls (Duncan et al., 1987). Similarly, de Maertelaer et al. (1987) reported longer SOL in BD patients as compared to patients with MDD.

Finally, two studies (Linkowski et al., 1986; Mendelson et al., 1987) reported less efficient sleep in subjects with bipolar depression.

#### 3.5.3 Non–REM Sleep

De Maertelaer et al. (1987) reported that in depressed patients, the duration of N2 sleep was lower than in healthy controls. There was no reported difference between unipolar and bipolar depressed patients. A reduction in NREM and delta sleep was reported also by Mendelson et al. (1987).

Amongst adolescents with a depressive episode retested after 7 years, Rao et al. (2002) observed more N1 sleep and a trend towards diminished N4 sleep in BD, though not in MDD, suggesting a SWS deficit only in Bipolar patients. In a study comparing four separate subgroups (i.e. mania, bipolar depression, unipolar depression and healthy controls), although a decreasing trend for SWS was observed in both bipolar and unipolar depression groups, Linkowski et al. (1986) reported no significant differences in percentage of NREM stages 1-4 (N1-N4). This is in line with the report of Giles et al. (1986) that found no significant differences in any stages comparing BDI, BDII and unipolar depressed individuals.

3.5.4 REM sleep

Lower REM efficiency (i.e. minute of actual REM sleep in a REM period divided by the time of the total REM period) was found in BD compared to both HC and unipolar patients (Duncan et al., 1979).

Findings on REM latency are more uncertain. Indeed, two studies found a reduced REM latency in BD when compared to controls (de Maertelaer et al., 1987; Duncan et al., 1979), but findings from Jernajczyk (1986) and Mendelson et al. (1987) failed to prove significant differences in REM latencies. The former attributes this to the minor intensity of depressive symptoms, as previously

observed by Duncan et al. (1979), who found REM latencies to be less affected in milder cases of depression. In addition to this, REM latencies in BD and MDD patients were found similar (de Maertelaer et al., 1987; Duncan et al., 1979). Furthermore, Foisson et al. (1998) reported REM latency distribution in BDI to differ significantly from both BDII and unipolar patients, having more similar lower latencies. The authors suggested this may be due to more extreme REM latency values within the BDI group. However, in a prior study, patients with BDII showed greater REM latency as compared to cases of unipolar depression (Giles et al., 1986). Moreover, Rao et al. (2002) reported that BD depressed adolescents showed longer REM latency compared to MDD subjects, as well as to healthy controls.

No differences between the length of the first REM period in depressed patients as compared to healthy controls were found. Interestingly, the authors also reported that number and density of sleep spindles were negatively correlated with REM latency in BD, though not in unipolar depression.

Few studies have investigated REM densities either within phases of BD or across patient groups of other disorders. Within the literature, findings from de Maertelaer et al. (1987) suggested REM density to be higher in depressed patients in comparison to healthy controls. Furthermore, Rao et al. (2002) observed that subjects with MDD exhibit greater REM density than depressed adolescents which later converted to BD. Mendelson et al. (1987) on the other hand, found no differences in REM density between patients with BD and healthy controls. Across BDI and BDII, Giles et al. (1986) found no significant differences in REM density. In depressed BD compared to MDD as well as healthy controls, Duncan et al. (1979) also found no such significant differences in REM density.

### 3.5.6 Sleep spindles in depressed patients

The only study that reported a specific analysis of sleep spindles in bipolar depressed patients found a lower number and density of spindles in depressed patients compared to controls (de Maertelaer et al., 1987).

## 3.6 Sleep architecture in High-Risk Subjects

### 3.6.1 NREM sleep

Only one study reported on NREM sleep variables in high-risk subjects (Friess et al., 2008). A marginally significant increase of sigma power in NREM sleep was observed, in the low sigma frequency range, compared to the control group. No significant differences were observed between the two groups for the SWS parameters analysed.

### 3.6.2 REM sleep

In an investigation by Modell et al. (2003), relatives of unipolar depressed patients showed higher REM density indices in comparison to relatives of BD patients, as well as healthy controls. Beyond REM density, no significant differences were observed between relatives of unipolar and BD patients. Friess et al. (2008) similarly reported no significant differences in sleep architecture variables between high-risk and control subjects, apart from increased REM density in high-risk subjects over an entire night's sleep. In the first sleep cycle, a trend towards higher REM density and shorter REM sleep period was also suggested.

## 4. Discussion

Our review summarised the available evidence on sleep pattern, architecture and micro-architecture of patients with BD and high-risk subjects. Disturbances in sleep pattern are frequent in every stage of BD. In particular, findings suggest differences in TST across phases of BD, with shorter TST in mania in comparison to healthy controls, bipolar depression and MDD. Moreover, patients during both manic and depressive episodes showed an increased sleep latency compared to healthy controls. This consolidates the view that difficulty in initiating sleep is a common prodromal sign of any mood episode (Van Meter et al., 2016). Intriguingly, increased SOL was also found in euthymic patients after an induced happy mood state but not after an induced sad mood state (Talbot et al., 2009). Although further research is needed, this might depend on state-dependent affective regulatory processes that are known to be impaired in BD (Krueger et al., 2003; Johnson, 2005).

In terms of architecture, a large discrepancy was found between findings on REM latency in BD patients compared to MDD patients and healthy controls. This probably reflects the limited sample size across studies. Conversely, consistent results are observed in REM density in BD, with higher REM density observed in euthymia, mania, and depression. Included studies also consistently reported a higher REM density in MDD compared to BD. Notably, increased REM density was also observed in high-risk individuals, suggesting this alteration may precede the onset of the disease. Some authors suggested that REM density can be used as a measure of sleep need, with a higher density associated with a reduction in sleep need in healthy subjects (Lucidi et al., 1996). Moreover, using a forced desynchrony protocol, which is capable of distinguishing sleep- and circadian-dependent modulation, Khalsa and colleagues (2002) found

that REM density is not related to circadian rhythm, but it changes as a function of sleep time. This supports the idea of REM density as a marker of sleep satiety (Aserinsky,1969). Further research is needed to clarify the clinical significance of this neurophysiological marker, which appears to be shared with PTSD and MDD (Simor et al., 2019). Although increased REM density might reflect a reduction of sleep need in individual patients with BD, hypersomnia and insomnia across stages are both highly prevalent at a population level (Steinan et al., 2016; Grigolon et al., 2019; Kanady et al., 2015). Therefore, available evidence on the relationship between sleep need and REM density cannot be considered conclusive.

The reported length of sleep stages (most notably SWS during N3-N4) presents markedly mixed findings both within and between phases, compared across studies. No relevant differences were observed comparing BD with MDD and high-risk probands. SWS modifications appear to be associated with mood induction and mood-regulated functional impairment in euthymia. Eidelman et al. (2010) offer the possible explanation that SWS could potentially be influential in BD, overcompensating for the need of regularization of depressed mood and causing a shift along the mood spectrum where manic symptoms are more present. This suggestion lends support to the S-deficiency hypothesis (Borbély, 1987) which posits that deficient SWS may sustain depressed mood. Further, less SWS sleep on the night of a sad mood induction in BD patients observed by Soehner et al. (2018) was associated with variations in overnight mood regulation and may have a specific role in overnight regulation of negative mood and impoverished negative effect (Soehner et al., 2018; Cheng et al., 2015).

Despite few studies investigating sleep spindles in BD, results from euthymic and depressed patients suggest reduced density and frequency of fast and slow spindles in BD as compared to

healthy controls. No spindle analysis has been conducted in manic patients so far. One study failed to observe differences in spindle parameters with healthy control subjects when 10 BD patients were pooled together with 4 MDD, 2 Post-Traumatic Stress Disorder (PTSD), 2 Panic Disorder and 2 Generalized Anxiety Disorder patients (Ferrarelli et al., 2010). The same study confirmed a marked, whole-night deficit of sleep spindle activity in Schizophrenia patients (Ferrarelli et al., 2010). Although these findings were not reviewed because no information was given on phase of illness nor subgroup spindle parameters, they suggest further research is needed to clarify whether spindle abnormalities are shared between BD and Schizophrenia. Despite significant rates (16%-50%) of psychotic symptoms in patients with bipolar depression (Endicott et al., 1985; Dilsaver et al., 1997; Black & Nasrallah, 1989; Serretti et al., 1999), only one sleep study (Hudson et al., 1992) compared psychotic and non-psychotic bipolar patients. While diagnostic manuals categorically diagnose BD patients into distinct phases of the disorder (APA, 2013), research has suggested bipolar symptomatology to lie on a dimensional spectrum (Akiskal & Pinto, 1999; Angst, 2007), with different degrees of severity plresent across different clinical cases (Möller, 2003). In spite of the unresolved debate between dimensional and categorical diagnoses in psychiatry, many evidences suggest BD and Schizophrenia patients to exhibit psychotic symptoms on a continuum. Many authors proposed that such a continuum may be shared between both disorders (Möller, 2003; Kuswanto et al., 2013; Tamminga et al., 2014; Keshavan et al., 2011). Given the preliminary evidence that slow wave abnormalities are associated with the severity of positive symptoms in early–stage psychosis (Kaskie et al., 2019), future studies should investigate sleep oscillations in BD in relationship to patients' illness stage and history of psychotic symptoms.

Moreover, none of the studies included in this review use a within-subjects paradigm to compare sleep in BD across different phases, which may reduce the confounding effects of medication that characterize between-subject studies. As patients diagnosed with BD usually undergo different phases throughout their lives, more research should focus on comparing sleep within-subjects at different clinical stages of the disorder. This approach would allow a more thorough assessment of whether sleep disturbances change accordingly with the phase of the disease and the symptomatology. Finally, the impact of circadian rhythm and chronotype, known for being disrupted in BD patients (Takaesu, 2018), should be further analysed to understand their impact on the sleep pattern and architecture.

**4.1 Limitation**

The main limitation of this work is the heterogeneity of methods applied and findings reported in the included studies. First of all, in six studies patients were not drug-free. Additionally, of the studies investigating patients in a medication-free period, not all studies used the same timeframe for such period. This could have differently affected the sleep pattern, contributing to the variety of the EEG findings between studies. Indeed, psychotropic medication has been identified as a confounder of sleep research in BD (Harvey et al., 2009). Second, the sample size of many studies was relatively small, with the majority of the studies recruiting less than 20 individuals. Third, EEG techniques widely improved over time with the introduction of more accurate and sophisticated instruments and methods of analysis, such as high-density EEG.

Fourth, sleep staging also changed over time with a modification in the American Association of Sleep Medicine (AASM) criteria. From 2007, N3 and N4 of NREM sleep have been considered together as SWS (AASM, 2007). Hence, differences in the used instrument or in the applied scoring criteria might partly explain the heterogeneity among the collected evidence. Fifth, since the reports were published between 1979 and 2019, diagnostic criteria used over time varied considerably. Although the majority of studies used DSM, diagnostic criteria changed among different versions. Most notably, the distinction made between BDI and BDII was introduced in DSM-IV, therefore former studies (which used the DSM-III) did not perform this separation. Although BDI and BDII present differences in their clinical presentation and courses, only one study so far compared EEG sleep characteristics between BDI and BDII depressed patients, finding no differences (Giles et al., 1986). Regarding stage of illness, several studies adopted similar criteria, although some variability might have limited the possibility of comparing findings overall. As shown in Table 1, some older studies considered clinical judgment rather than structured criteria and euthymia in particular was variously defined on the basis of rating scales, structured interviews, or remission from the prior episode.

Future studies should specify the exact nature of the diagnosis of patients to further investigate possible differences between these subtypes.

Finally, current uncertainty on the association and the direction of causality between circadian rhythm disruption, mood and functioning (Bradley et al., 2017) is likely to complicate the interpretation of sleep EEG findings between individual patients and across cohorts.

## 5. Conclusion

Sleep is a complex phenomenon and most BD studies thus far have employed a broad lens to analyse macrostructural abnormalities in sleep architecture. The results of this review indicate the majority of findings to be inconsistent, with the exception of increased SOL and REM density across all stages of illness, suggesting the method employed to detect biomarkers in BD sleep might not have sufficient sensitivity. However, preliminary evidence on sleep spindle abnormalities suggests the use of emerging novel techniques which provide a more accurate evaluation of microstructures of sleep may yield valuable findings in future research.

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Figure 1. Significant sleep abnormalities in different stages of Bipolar Disorder.

Abnormalities are grouped according to three categories and connecting arrows are dashed or continuous to reflect the strength of reported findings. Simple dashed line: only one study reporting abnormality. Continuous line: at least two studies reported the abnormality. Dot-and-line dash: more than two studies with opposite findings. Red = Increased in BD; Blue = Decreased in BD; Grey: Uncertain.

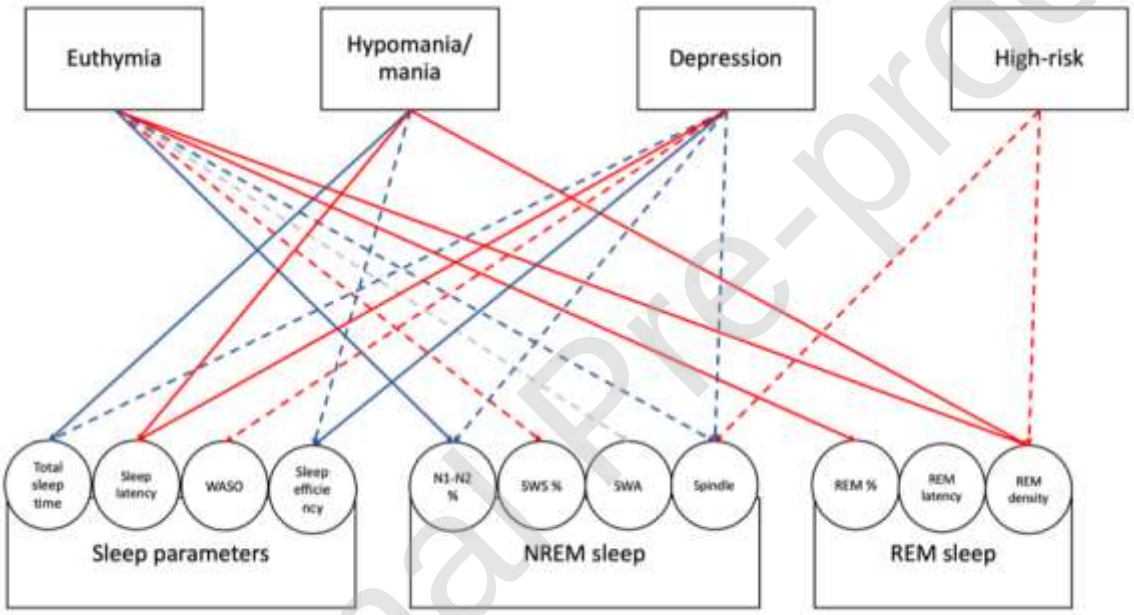

**Table 1 EEG characteristics of individuals with Bipolar Disorder.**

*Table 1a EEG characteristics of euthymic patients. BD= Bipolar Disorder type I (BDI) and type II (BDII); HC= Healthy Controls; HR = High Risk individuals; P= Patients; ADHD= Attention Deficit Hyperactivity Disorder; SWA= Slow Wave Activity; N2= non-REM sleep Stage 2. BDI = Beck Depression Inventory; IDS-C = Inventory of Depressive Symptomatology–Clinician Rating; Y-MRS = Young Mania Rating Scale; Altman Self Rating Scale (ASRM); CDI: Children´s Depression; Inventory; CMRS-P: Child Mania Rating Scale – Parent version; CMAS-R: Children's Manifest Anxiety Scale - Revised.*

| STUDY | YEAR | PATIENTS | STATE | STATE DEFINITION | CLINICAL RATING | VERSUS | CLINICAL RATING | FINDINGS | SAMPLE SIZE | DRUGS |
|---|---|---|---|---|---|---|---|---|---|---|
| SITARAM | 1982 | BD | EUTHYMIA | Clinical remission for at least 3 months. | n.a. | HC/HR | n.a. | Higher density of eye movements during first REM period.<br>Higher %REM sleep. | 14 BD + 15 HC + 5 HR | Drug free for 2 weeks. |
| KNOWLES | 1986 | BD | EUTHYMIA (RECOVERY FROM DEPRESSIVE EPISODE) | Recovery from a major depressive episode. | BDI = 1.4 ± 1.8<br>HAM–D = 2.4 ± 2.2 | HC | BDI = 0.8 ± 1.1<br>HAM–D = 3.2 ± 4.0 | Between-subjects variance greater in BD for sleep onset latency, minutes awake after sleep onset and %stage 1 sleep. | 10 P + 10 HC | Drug free for 3 weeks. |
| TALBOT | 2009 | BD | EUTHYMIA | A score of less than 7 on the Young Mania Rating Scale and a score of less than 12 on the Inventory of Depressive Symptomatology–Clinician Rating. | IDSC–C = 7.00 ± 3.71<br>Y–MRS = 0.88 ± 1.40 | HC | IDSC–C = 2.67 ± 2.39<br>Y–MRS = 2.81 ± 2.17 | Longer sleep onset latency after happy mood induction in BD and shorter in HC.<br>Shorter sleep onset latency after sad mood induction in both groups.<br>Increased REM density after sad mood induction in both groups.<br>Increased REM density in BD in both nights. | 28 P (24 BDI + 4 BDII) + 28 HC | Yes |
| EIDELMAN | 2010 | BDI/BDII | EUTHYMIA | A score of less than 7 on the Young Mania Rating Scale and a score of less than 12 on the Inventory of Depressive Symptomatology–Clinician Rating. | IDSC–C = 5.55 ± 5.11<br>Y–MRS = 2.09 ± 2.20 | HC | IDSC–C = 2.36 ± 1.79<br>Y–MRS = 0.55 ± 1.06 | Higher REM density in BD.<br>SWS and duration of first REM period related with manic symptoms at 3 months follow up.<br>REM density related with depressive symptoms at 3 months follow up. | 22 P + 22 HC | Yes |
| SOEHNER | 2018 | BD | EUTHYMIA | A score of less than 7 on the Young Mania Rating Scale and a score of less than 12 on the Inventory of Depressive Symptomatology–Clinician Rating. | IDSC–C = 2.80 ± 2.60<br>Y–MRS = 5.59 ± 6.23 | HC | IDSC–C = 0.56 ± 0.92<br>Y–MRS = 1.65 ± 1.60 | No differences in total sleep time.<br>Overnight mood regulation in interepisode BD did not significantly differ from healthy adults.<br>Inducing a positive mood state prior to sleep increased SWA relative to baseline across all participants.<br>Lower SWA was associated with attenuated overnight regulation of negative mood, but not positive mood, in bipolar patients. | 20 P + 23 HC | Yes |
| RITTER | 2018 | BDI/BDII | EUTHYMIA | Exclusion of a current episode using Structured Clinical Interview for DSM, affective disorder section. | ASRM <5<br>BDI <8 | HC | ASRM <5<br>BDI <8 | Lower fast spindles (>13 Hz) density within N2 sleep in both frontal and central derivations in BD compared to HC.<br>Reduced mean spindle frequency for fast spindles in derivation F4 and both central derivations in BD.<br>No significant differences in fast spindle amplitude and duration.<br>No significant differences in slow spindle parameters.<br>Lower EEG power in the high sigma band for BD in central derivation C3-M2.<br>No association between lithium treatment and fast-spindles parameters. | 23 P + 25 HC | Yes |
| ESTRADA-PRAT | 2019 | BDI/BDII/BD NOS (Adolescents) | EUTHYMIA | Defined as euthymic; Children's Depression inventory and the Child Mania Rating Scale-Parent version were used to assess depressive and manic symptoms. | CDI = 24.3 ± 3.49<br>CMRS-P = 21.92 ± 2.48<br>CMAS-R = 16.23 ± 1.91 | HC/ADHD | HC: n.a.<br>ADHD: CDI = 12.15 ± 1.82<br>CMRS-P = 16.46 ± 2.23<br>CMAS-R = 14.46 ± 1.49 | Shorter N2 time in BD compared to HC and ADHD.<br>Higher REM density in BD compared to HC and ADHD.<br>No differences in REM latency.<br>Longer first episode of REM duration in BD compared to ADHD. | 13 P + 13 ADHD + 26 HC | Yes |

*Table 1b EEG characteristics of manic patients. BD= Bipolar Disorder type I (BDI) and type II (BDII); HC= Healthy Controls; MDD = Major Depressive Disorder; UD=Unipolar Depression; P= Patients; REM= Rapid Eye Movement; NREM: Non-Rapid Eye Movement; BMS = Beigel-Murphy scale; HAM-D = Hamilton Depression Scale; BPRS-A = Brief Psychiatric Rating Scale with 9 additional items for mania; BDI = Beck's Depression Inventory.*

| STUDY | YEAR | PATIENTS | STATE | STATE DEFINITION | CLINICAL RATING | VERSUS | CLINICAL RATING | FINDINGS | SAMPLE SIZE | DRUGS |
|---|---|---|---|---|---|---|---|---|---|---|
| MENDELS | 1971 | BDII | HYPOMANIA | Clinical judgment. | n.a. | HC | n.a. | Shorter total sleep time.<br>Reduction in stage 3 and 4.<br>Reduction in REM sleep. | 1 BDII + 15 HC + 4 psychotic depression | No drugs during 2 weeks of registration. |
| | | | | | | Depression | n.a. | Similar changes in total sleep time and sleep architecture. | | |
| LINKOWSKI | 1986 | BD/MDD | MANIA/ DEPRESSION | Research Diagnostic Criteria for manic episode. | BMS = 196 ± 88 (manic patients)<br>HAM-D = 35 ± 3 (depressed patients). | HC | n.a. | Shorter total sleep time.<br>Decreased sleep efficiency in all 3 groups of patients.<br>Longer sleep time in manic and unipolar depressed patients.<br>Normal REM latencies both in manic and bipolar depressed groups.<br>No differences in REM density. | 18 P (6 manic + 6 bipolar depressed + 6 unipolar depressed) + 6 HC | Manic, drug free for 1 week. Depressed, drug free for 2 weeks. |
| HUDSON | 1988 | BD | MANIA | Structured Clinical Interview for DSM-III-R for manic episode. | BPRS-A = 48-105 | HC | n.a. | Shortened REM latency.<br>Higher total REM density and for all each REM period.<br>No reduction in delta sleep. | 9 P + 18 HC | Alcohol and drug free for 2 weeks. |
| HUDSON | 1992 | BD | MANIA | Structured Clinical Interview for DSM-III-R for manic episode. | BPRS-A = 61.7±15.5<br>HAM-D = 10.2±5.4 | MDD/HC | HC: n.a.<br>MDD:<br>BPRS-A = 61.2±15.0<br>HAM-D = 23.6±9.9 | Both BD and MDD show disturbed sleep continuity.<br>Shorter total sleep time in BD than MDD.<br>Both BD and MDD show increased percentage of stage 1 sleep.<br>Higher percentage of stage 3 in BD, but no difference in total stage 3 time.<br>Both BD and MDD show shortened REM latency and increased REM density<br>No differences between psychotic and non-psychotic patients. | 19 BD + 19 MDD + 19 HC | Alcohol and drug free for 1 week. |
| NAKAMURA | 1993 | MDI | MANIA/ EUTHYMIA | Clinical judgment. | n.a. | UD | n.a. | Longer REM latencies in mania (but not in recovery) in MDI than UD. | 1 BD + 1 UD | Yes |
| ASAAD | 2016 | BD II | HYPOMANIA | Structured Clinical Interview for DSM-IV for hypomanic episode. | Y-MRS = 22.00 ± 1.777. | HC | n.a. | Increased sleep latency.<br>Increased percentage of stages 1 and 2, decreased percentage of stage 3–4.<br>Increased REM density, density of first (1st) REM, decreased REM latency and increased apnea appendix. | 20 BDII + 20 MDD + 20 HC | Alcohol and drug free for 1 week. |
| | | | | | | MDD | HAM-D= 22.10 ± 5.409. | Abnormalities in BDII are intermediate between HC and patients with MDD. | | |

*Table 1c EEG characteristics of patients during depression state. BD= Bipolar Disorder type I (BDI) and type II (BDII); HC= Healthy Controls; MDD = Major Depressive Disorder; P= Patients; SWS= Slow Waves Sleep; REM= Rapid Eye Movement; NREM: Non-Rapid Eye Movement.*

| STUDY | YEAR | PATIENTS | STATE | STATE DEFINITION | CLINICAL RATING | VERSUS | CLINICAL RATING | FINDINGS | SAMPLE SIZE | DRUGS |
|---|---|---|---|---|---|---|---|---|---|---|
| DUNCAN | 1979 | BD | DEPRESSION | Clinical judgment. | n.a. | HC | n.a. | Longer sleep latency and more early morning wake.<br>Reduce REM efficiency (i.e. minute of REM sleep in a REM period divided by the time of the total REM period).<br>Shorter first NREM period. | 22 BD+ 36 MDD + 36 HC | Drug free for 2 weeks. |
| | | | | | | MDD | n.a. | No difference in sleep architecture between MDD and BD. | | |
| JERNAJCZYK | 1986 | BD | DEPRESSION | Clinical judgment. | BDI = 13 - 37<br>HAM-D = 12 - 29 | HC | n.a. | No differences in REM latency maybe due to mild depression symptoms. | 10 P + 10 HC | Drug free for 2 weeks. |
| GILES | 1986 | BDII | DEPRESSION | Research Diagnostic Criteria for bipolar depressive episode. | HAM-D = 22.1 ± 5.0 | BDI | HAM-D = 25.9 ± 5.2 | No differences. | 10 BD I + 12 BDII + 22 MDD | Drug free for 2 weeks. |
| | | | | | | MDD | HAM-D = 26.3 ± 4.3 (group 1)<br>24.4 ± 4.8 (group 2) | More total sleep time in BDII.<br>More NREM sleep.<br>Longer REM sleep latency. | | |
| MENDELSON | 1987 | BDI/BDII/UD | DEPRESSION | Research Diagnostic Criteria for bipolar depressive episode. | HAM-D = 25.4 ± 4.1 | HC | n.a. | Less total sleep time.<br>Increased sleep latency.<br>Less NREM sleep. | 8 P (4 BDI + 3 BDII + 1 UD) + 8 HC | Alcohol and drug free for 2 weeks. |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | No differences in REM density, latency and length of first REM period.<br>Less delta sleep. | | |
| DE MAERTELAER | 1987 | BD/UD | DEPRESSION | Research Diagnostic Criteria for bipolar depressive episode. | HAM-D = 33 ± 8 | HC | HAM-D = 37 ± 2 | Longer sleep onset in patients vs HC (BD > MDD)<br>Decreased stage 2 in patients. No difference between unipolar/bipolar.<br>Shorter REM latencies but higher REM density. No difference between unipolar/bipolar.<br>Lower number and density of sleep spindles in patients vs HC. (MDD < BD) | 19 P (11 BD + 8 UD) + 9 HC | Stop AP, Lithium and IMAO for at least 1 months and TCA for at least 2 weeks. |
| FOSSION | 1998 | BDI/BDII/UD | DEPRESSION | Research Diagnostic Criteria for bipolar depressive episode. | BDI: HAM-D = 27.4 ±8.7<br>BDII: HAM-D = 26.2 ± 7.6<br>UD: HAM-D = 24.5 ±4.4 | | | Longer SPT in BDII vs MDD<br>REM sleep more fragmented in BDI vs BDII.<br>Higher REM latencies in BDI. | 14 BDI + 14 BDII + 14 UD | Alcohol and drug free for 2 weeks. |
| RAO | 2002 | BD | Adolescent with depressive episode retest after 7 years | Clinical judgment. | n.a. | MDD/HC | n.a. | More stage 1 sleep and diminished stage 4 in BD but not in MDD.<br>Reduced REM latency, higher REM density, and more REM sleep (specifically in the early part of the night) in unipolar patients than adolescents who converted to BD and HC<br>SWS deficit in BD but not in MDD. | 28 P + 35 HC | Alcohol and drug free for 2 weeks. |

*Table 1d EEG characteristics of individuals at high risk (HR) of developing bipolar disorder. BD= Bipolar Disorder type I (BDI) and type II (BDII); HC= Healthy Controls; MDD = Major Depressive Disorder; SWS= Slow Waves Sleep; REM= Rapid Eye Movement; NREM: Non-Rapid Eye Movement.*

| STUDY | YEAR | PATIENTS | STATE DEFINITION | CLINICAL RATING | VERSUS | CLINICAL RATING | FINDINGS | SAMPLE SIZE | DRUGS |
|---|---|---|---|---|---|---|---|---|---|
| MODELL | 2003 | HR | First-degree relatives of BD/MDD patients, without current/lifetime diagnosis of any psychiatric disorder | n.a. | HC | n.a. | Elevated REM density indices in relatives of unipolar patients compared to both the relatives of bipolar patients and HC. | 75 HR (48 HR-MDD + 27 HR-BD) + 49 HC | No |
| FRIESS | 2007 | HR | First-degree relatives of BD patients, without current/lifetime diagnosis of any psychiatric disorder | n.a. | HC | n.a. | Increased REM density.<br>Increased sigma power during NREM sleep.<br>No differences in SWS. | 21 HR + 13 HC | No |