

## Review article

# Electroencephalography findings in menstrually-related mood disorders: A critical review

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## ABSTRACT

The female reproductive years are characterized by fluctuations in ovarian hormones across the menstrual cycle, which have the potential to modulate neurophysiological and behavioral dynamics. Menstrually-related mood disorders (MRMDs) comprise cognitive-affective or somatic symptoms that are thought to be triggered by the rapid fluctuations in ovarian hormones in the luteal phase of the menstrual cycle. MRMDs include premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), and premenstrual exacerbation (PME) of other psychiatric disorders. Electroencephalography (EEG) non-invasively records *in vivo* synchronous activity from populations of neurons with high temporal resolution. The present overview sought to systematically review the current state of task-related and resting-state EEG investigations on MRMDs. Preliminary evidence indicates lower alpha asymmetry at rest being associated with MRMDs, while one study points to the effect being luteal-phase specific. Moreover, higher luteal spontaneous frontal brain activity (slow/fast wave ratio as measured by the delta/beta power ratio) has been observed in persons with MRMDs, while sleep architecture results point to potential circadian rhythm disturbances. In this review, we discuss the quality of study designs as well as future perspectives and challenges of supplementing the diagnostic and scientific toolbox for MRMDs with EEG.

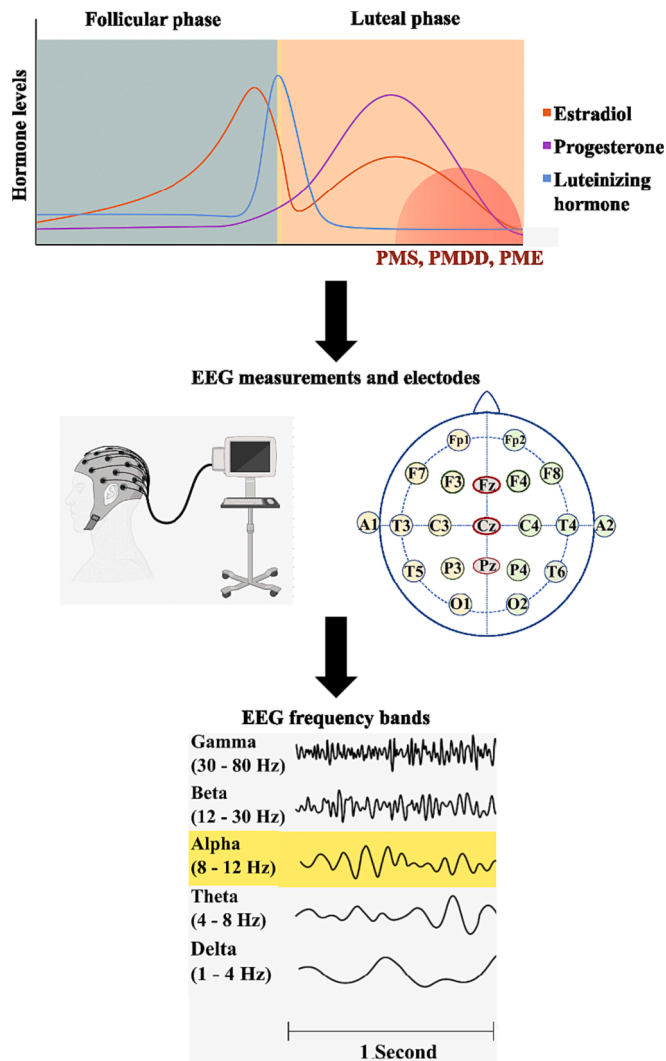
## 1. Introduction

### 1.1. The menstrual cycle and menstrually-related mood disorders (MRMDs)

Major changes in ovarian hormone concentrations occur throughout the female lifespan, such as during puberty, pregnancy, postpartum, and menopause. The menstrual cycle involves considerable fluctuations in ovarian hormones, namely a follicular surge and decline in estradiol during the periovulatory period, and a sustained peak in estradiol and progesterone in the mid-luteal phase, followed by a decrease in both ovarian hormones shortly before menstruation (Fig. 1). These ovarian hormones can influence the brain via slow genomic (Tetel and Acharya, 2013) and fast non-genomic mechanisms (Cornil et al., 2012; Mani et al.,

2012; Singh et al., 2013). Indeed, several behaviourally-relevant brain regions have been shown to be modulated by ovarian hormones in females with regular menstrual cycles (Dubol et al., 2021; Bixo et al., 1997; Barth et al., 2015). For instance, functional neuroimaging studies have pointed to menstrual cycle effects on the hippocampus (Lisofsky et al., 2015; Barth et al., 2016), amygdala (Ossewaarde et al., 2013; van Wingen et al., 2008; Dan et al., 2019; Pletzer et al., 2016), insula (De Bondt et al., 2016; De Bondt et al., 2013; Arnoni-Bauer et al., 2017), anterior cingulate cortex (Arnoni-Bauer et al., 2017; Diekhof and Ratnayake, 2016; Bayer et al., 2013), and prefrontal cortex (De Bondt et al., 2013; Engman et al., 2018; Arélin et al., 2015; Syan et al., 2017), all regions critical for emotional and cognitive processing (Dubol et al., 2021). In fact, as part of the neuroendocrine system, ovarian hormones critically regulate a wide array of psycho-behavioural functions, from

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**Fig. 1. Summary of the main electrophysiological measurements in relation to MRMDs.** Upon daily mood symptom monitoring across the menstrual cycle, premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), and premenstrual exacerbation of another medical condition (PME) are diagnosed if their occurrence is concomitant with the premenstrual phase. The electroencephalogram (EEG) permits the measurement of oscillatory activity of large populations of neurons as electrophysiological signals, detected via scalp electrodes on the head. Signals are captured as microvolt ( $\mu\text{V}$ ) differences in charge in the temporal range of milliseconds, commonly reported in the frequency domain (range 0.5–40 Hz). Up to 256 electrodes can be placed on the scalp with a peripheral reference electrode. Electrodes are commonly placed according to the 10–20 system with the following coding: A, auricle; C, central; F, frontal; Fp, frontal pole; O, occipital; P, parietal; T, temporal. Electrophysiological rhythms are associated with patterns of behaviour and information processing (e.g., level of alertness, arousal, sleep, and memory) in a frequency-specific manner. More specifically, EEG is commonly assessed along the constraints of the following frequency margins: Gamma: 30–80 Hz; Beta: 12–30 Hz; Alpha: 8–12 Hz; Theta: 4–8 Hz; Delta: 1–4 Hz. To date, nine studies investigated the relationship between MRMDs and EEG, predominantly alpha asymmetry in the frontal region. The results, limited by the sparsity of studies and hampered by study design limitations, are inconclusive.

circadian rhythms to stress resilience (Pyle and Martino, 2018; Sen and Hoffmann, 2020; Shao et al., 2021).

Ovarian hormone fluctuations play a prominent role in the pathophysiological mechanisms of menstrual-related mood disorders (MRMDs) (Rubinow and Schmidt, 2018). MRMDs include premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), and

premenstrual exacerbation (PME) of other psychiatric disorders (Yonkers and Simoni, 2018). MRMDs can lead to severe psychological symptoms, as well as functional and interpersonal impairment, which can foster suicidal ideation and behaviour (Wikman et al., 2022; Eisenlohr-Moul, 2022). The premenstrual symptoms associated with MRMDs most commonly entail emotional distress, social, and occupational impairments, partly overlapping with those of major mood disorders, anxiety, and post-traumatic stress disorders (Halbreich, 2003; Epperson et al., 2012).

PMS has been described as a variety of psychological and physical symptoms, experienced during the late luteal phase of the cycle, that subside shortly following subsequent menstruation, if not better explained by other diagnosis (Biggs and Demuth, 2011). A severe form of PMS, known as premenstrual dysphoric disorder (PMDD) has been categorized as a depressive disorder and recently added to the DSM-5 (Epperson et al., 2012). On the other hand, significant worsening of the emotional and behavioural symptoms underlying an affective disorder during the luteal phase is classified as PME. Due to lack of comprehensive diagnostic schemes (Halbreich, 2004) and poor awareness in the medical and research field (Eisenlohr-Moul, 2019), individuals with PMDD are often misdiagnosed with a non-cyclical affective disorder or PME (Hantsoo et al., 2022). Several clinical conditions have been linked to PME such as depression (Kuehner and Nayman, 2021; Handy et al., 2022), bipolar disorder (Payne, 2011; Pearlstein, 2022), and schizophrenia (Seeman, 2012), although the syndrome is not yet defined as a diagnostic entity, with its prevalence and neurobiological underpinnings being even less investigated than those of PMDD.

A main characteristic of the hormonal fluctuation-related symptomatology in MRMDs is the temporal variance in affective, cognitive, or somatic states (Rubinow and Schmidt, 2003). This cluster of symptoms poses several methodological challenges, likely complicating the identification of the psychobiology of MRMDs. In fact, knowledge of the neurophysiological mechanisms of MRMDs is scarce. Symptomatology or symptom exacerbation is temporally linked to the luteal phase of the cycle and thus likely the luteal-phase specific surge in progesterone and estradiol (Eisenlohr-Moul, 2019). Considering that ovarian hormone concentrations in persons with PMS and PMDD have been reported to lay within standard ranges (Backstrom et al., 1983; Hantsoo and Epperson, 2015; Schmidt et al., 1994), current evidence suggests an altered central sensitivity to physiological phasic hormone fluctuations in individuals affected by MRMDs (Schmidt et al., 1998; Schmidt et al., 2017). Indeed, pharmacological suppression of these fluctuations with gonadotropin-releasing hormone (GnRH) agonists leads to significant remission of premenstrual symptoms in persons with PMS or PMDD (Schmidt et al., 1998; Wyatt et al., 2004; Sundström et al., 1999; Segebladh et al., 2009). Albeit, the distinct effects of estradiol and progesterone on premenstrual symptomatology and the surrounding contribution of other phenomena such as receptor plasticity and dynamics have not yet been disentangled.

Different mechanisms have been suggested to underlie the ovarian hormone sensitivity hypothesized for MRMDs, one of which is highlighting the contribution of luteal progesterone fluctuations to premenstrual symptoms (Wyatt et al., 2004; Comasco et al., 2021), or those of its neuroactive metabolite allopregnanolone (Bixo et al., 2018). This has been corroborated by preliminary evidence indicating altered  $\gamma$ -Aminobutyric acid (GABA) function in PMDD in comparison with healthy controls. Namely, lower GABA concentrations have been found in subjects with PMDD in the luteal phase compared with healthy controls (Liu et al., 2015). Further evidence demonstrates an increase in GABA concentrations from the follicular to the mid- and late luteal phase for individuals with PMDD, while their follicular cortical GABA levels were also higher compared with controls (Bixo et al., 2018; Epperson et al., 2002). Complementary to this, a recent clinical trial showed that progesterone antagonism through the use of a selective progesterone receptor modulator treatment, which leads to stable and low levels of

progesterone and mid-follicular levels of estrogen, alleviates the mood symptoms of PMDD, in particular irritability and depression (Comasco et al., 2021). In a functional neuroimaging investigation, greater fronto-cingulate activity during aggressive response to provocation was associated with this treatment in comparison with placebo (Kaltsouni et al., 2021). This can be interpreted as a potential beneficial enhancement of top-down regulation, namely better executive control on emotional reactivity, a mechanism that has been suggested to be altered in PMDD and to underlie poor emotional regulation in mood and anxiety disorders (Huang et al., 2014; Blair et al., 2012; Rive et al., 2013). Further, another line of research highlights the involvement of serotonergic neurotransmission in premenstrual suffering (Roca et al., 2002; Halbreich and Tworek, 1993; Rapkin and Akopians, 2012), especially supported by the efficacy of intermittent dosing with serotonergic antidepressants as treatment for PMDD (Marjoribanks et al., 2013). Further evidence for an interplay between ovarian hormone fluctuations and the serotonergic system in MRMDs comes from a hormonal manipulation study that pharmacologically induced fluctuations in estradiol (Frokjaer et al., 2015). Decreases in estradiol were associated with depressive responses in healthy women, where worse symptom severity was correlated with both the magnitude of estradiol decline and increase in neocortical serotonin transporter binding (Frokjaer et al., 2015), suggesting less available extracellular serotonin. In individuals with PMDD, positron emission tomography (PET) studies have provided *in vivo* evidence of a relationship with serotonergic neurotransmission markers (Eriksson et al., 2006; Jovanovic et al., 2006). Most recently, serotonin transporter binding increase from the periovulatory to the premenstrual phase was noted in patients with PMDD, in which increased binding correlated with greater symptom severity, corroborating the hypothesis on serotonin depletion impacting depressive mood (Sacher et al., 2023). Nevertheless, evidence on the precise mechanism by which serotonergic neurotransmission may be related to MRMDs symptomatology is scarce.

Altered neurophysiological response to canonical ovarian hormones fluctuations likely induces premenstrual distress (Bäckström et al., 2003; Dubol et al., 2020; Sundstrom-Poromaa et al., 2020). To date, neuroimaging techniques with high spatial resolution have been sparsely employed to study the neural signatures of MRMDs and have been mainly focused on PMDD. These include structural magnetic resonance imaging (sMRI), functional MRI (fMRI), diffusion tensor imaging (DTI) (Gu et al., 2022), and molecular imaging methods such as PET as well as single photon emission computed tomography (SPECT) (Dubol et al., 2020; Dubol et al., 2022; Dubol et al., 2022). Regarding anatomical differences, contradictory findings have been found in small samples with regards to PMDD (Syau et al., 2018; Protopopescu et al., 2008; Berman et al., 2013; Jeong et al., 2012). A recent multi-scale investigation in a relatively large sample, accounting for potential covariates, found differential anatomy of top-down control regions, such as the medial prefrontal, superior prefrontal, and orbitofrontal cortex, as well as superior and inferior parietal lobules, influencing the limbic system and visual processing areas, as features of the PMDD brain (Dubol et al., 2022). These structural characteristics were additionally correlated with the severity of symptoms of PMDD during the luteal phase (Dubol et al., 2022). On the other hand, the sole study on white matter structure points to higher integrity and volume in tracts connected to the limbic brain in patients with PMDD during the symptomatic phase, in comparison with controls (Gu et al., 2022). However, it remains to be investigated whether these are state- or trait-features of the PMDD brain. Moreover, to the best of our knowledge, no studies have thus far been conducted on the structural correlates of PMS and PME.

Functional neuroimaging studies have found differences between females with and without PMDD during emotion processing and cognitive tasks; these differences include altered activity of cortico-limbic structures, such as lower activity in the anterior cingulate cortex (ACC) and prefrontal cortex (PFC) subregions, and higher amygdala

reactivity to emotional stimuli pointing to increased bottom-up reactivity and depleted top-down cognitive control (Dubol et al., 2020). Menstrual cycle dependent reactivity to different emotion processing or cognitive tasks has been reported to differ in several corticolimbic regions, although the direction of effects greatly depends on the nature of the task used (Dubol et al., 2020). Moreover, current evidence suggests altered functional connectivity patterns between regions of the default mode network (DMN) in persons with PMS compared to healthy controls (De Bondt et al., 2015; Liu et al., 2015), along with some alterations of amplitude in low frequency fluctuations within the precuneus, hippocampal, and inferior temporal cortex in persons with PMS compared with healthy controls (Liao et al., 2017). Preliminary evidence on altered network dynamics has been found, exemplified as increased hippocampal-frontocortical and decreased hippocampal-premotor resting state connectivity associated with PME of bipolar disorder (Syau et al., 2018), as well as with menstrual cycle phase-independent increased functional temporal connectivity with the executive control network in patients with PMDD (Petersen et al., 2019). Nevertheless, despite the recent efforts to document menstrual cycle-dependent variations in intrinsic brain dynamics, alternatively known as functional brain organization (Friston, 2002), in healthy females (Hidalgo-Lopez et al., 2020; Pritschet et al., 2020), the overall literature on dynamic functional connectivity in MRMDs falls short.

Furthermore, functional magnetic resonance imaging relies on signals derived from hemodynamic activity, which (i) is merely an indirect proxy for brain activity and (ii) demonstrates only moderate temporal resolution while incurring (iii) highly non-stationary noise at (iv) high imaging acquisition costs. While spatial resolution is limited for subcortical brain areas as the amygdala, electroencephalography (EEG) recordings afford the measurement of instantaneous neuronal electrical activity, deriving from multi-source synaptic *trans*-membrane currents with high temporal resolution (Michel and Murray, 2012).

## 1.2. Electroencephalography

In MRMDs, psychological symptoms coincide with phases of the menstrual cycle, providing an opportunity to systematically study the modulation of affective and cognitive state changes (Rubinow, 2021). Mental and behavioural states are implemented in the brain via the synchronous activity of neuronal populations, which represent direct substrates of neural information processing (Mathalon and Sohal, 2015). With EEG, electrodes are fixed to the scalp (Fig. 1) and each channel records electrical activity (Louis et al., 2016). In order for the brain to produce and electrical signal that is detectable at the scalp, computational modelling has revealed it requires 10,000–50,000 synchronously active, apically projecting, neurons (Murakami and Okada, 2006). Thus EEG non-invasively records electrical activity in the brain, made up of primarily excitatory and inhibitory postsynaptic potentials *in vivo*, with high temporal and moderate spatial resolution (Biasiucci et al., 2019). This provides the opportunity to non-invasively explore the neural syntax underlying cognitive, affective, and behavioural dynamics in MRMDs. Interestingly, albeit not consistent, menstrual cycle dependent variations in the oscillatory activity has been shown (Thériault and Prereault, 2019).

Time or phase-locked cortical activity, (i.e. the neuronal activity that spontaneously arises at a specific time after a stimulus or falls into phase synchronicity as part of an ongoing oscillation) can be assessed by analysing event related potentials (ERPs), recorded with EEG. ERPs are high voltage fluctuations detected at the scalp relative to a reference electrode and studied based on their polarity and latency and spatial distribution or topography. ERPs provide a direct link between behaviour and stimulus- or task-related activation changes in mental processes such as memory, attention, emotion regulation, and beyond (Bridwell et al., 2018). Alternatively, the EEG can detect amplitude and frequency changes in oscillations while the brain is at rest (task-free), or when evoked (phase-locked) or induced (non-phase-locked). Neural

oscillation amplitude and frequency changes are currently most often at a single source or based on coherence between sources. EEG may, therefore, serve as a candidate tool to disentangle neural markers of state retention and transition for MRMDs in a real-time fashion during task performance or at rest (Lee and Dan, 2012; da Silva, 2013).

### 1.3. Potential for EEG in MRMDs

An advantage of EEG for future translation of scientific findings to use as a clinical measurement for MRMDs includes the fact that EEG recordings are noninvasive, painless, and relatively cost effective compared to other brain imaging/recording techniques (for example, PET, MRI and magnetoencephalography (MEG)). Advancements in both EEG hardware and analysis pipelines have increased the robustness of detecting brain signal in the recorded data relative to sources of noise; indeed, physical movement, muscle, and electrical line noise, can interfere with and present challenges for interpreting EEG data if not controlled. With such advancements, portable and wireless systems present a growing potential for bedside, outpatient or even home-based monitoring of the functioning brain (Niso et al., 2023).

Because EEG provides a direct index of neuronal activity, it is particularly well suited for accessing cyclical changes in neurotransmission. For example, changes in the power and peak frequency of resting state spectral bands across menstrual cycle phases have been found in several studies (Solís-Ortiz et al., 1994; Brötznner et al., 2014; Creutzfeldt et al., 1976; Bazanova et al., 2014; Makarchouk et al., 2011), with the most commonly reported observation being increased alpha power in the luteal phase (Bazanova et al., 2014; Brötznner et al., 2014). Evoked response paradigms (roving mismatch negativity and visually induced long-term potentiation) have shown that EEG is sensitive to changes in plasticity over the menstrual cycle (Sumner et al., 2018). Studies also show that EEG detects shifts in interhemispheric-transfer time; specifically, in the luteal phase there is an increase in the latency of visually evoked potentials in the hemisphere contralateral to the stimulated visual field (Hausmann et al., 2013). Induced changes in the EEG spectra include statistically significant increases in visually induced gamma oscillation frequency by ~5 Hz in the luteal phase of healthy females (Sumner et al., 2018). Additionally, an MEG study showed reduced suppression response to induced gamma oscillations triggered by moving gratings in PMDD (Manyukhina et al., 2022). Of relevance, induced gamma oscillations have an established relationship with excitation and inhibition (Manyukhina et al., 2022) changes in the brain.

When the above EEG studies on changes in both evoked and induced signal over the menstrual cycle are considered alongside TMS based research (Inghilleri et al., 2004; Smith et al., 2002; Smith et al., 1999), the interpretations consistently point to increased GABAergic inhibition in the healthy luteal phase. This is because the TMS studies cited (Inghilleri et al., 2004; Smith et al., 2002; Smith et al., 1999) discuss their results in light of non-menstrual cycle related TMS findings based on GABAergic and glutamatergic drug interventions. The increase in GABAergic inhibition is hypothesized to be driven by progesterone's metabolite allopregnanolone's effects on the GABA-A receptor  $\alpha 4\beta\delta$  subunit (Bäckström et al., 2014), which could play an important role in tonic inhibition and neuronal excitability variations. Allopregnanolone/oestradiol mediation of excitation and inhibition is one of the putative mechanisms implicated in the pathophysiology of MRMDs (Sundstrom-Poromaa et al., 2020; Clemens et al., 2019). However, further research, particularly using interventions, is required to deepen the potential inferences drawn from these data.

EEG can also be used beyond direct neurophysiological effects to study emotion and cognition. A common conceptual model in studying emotion regulation and vulnerability in psychopathology is frontal alpha asymmetry, already investigated in relation with the risk for, and treatment outcomes in, depression and anxiety disorders, among other psychopathologies (Allen and Reznik, 2015; Allen et al., 2018). Frontal

alpha asymmetry is most often calculated as the right-left difference in log-transformed spectral power in the alpha frequency band (8–13 Hz) between directly bilateral, frontal electrodes (Davidson, 1988). It has been studied in the context of motivation differences (defined as approach vs. avoidance behaviour in relation to some tasks) (Davidson, 1984; Kelley et al., 2017). High alpha asymmetry refers to lower frontal alpha power in the left relative to the right hemisphere and has been related to approach behavior, namely the willingness to explore reward sensitivity and related to increased positive affect. Low alpha asymmetry refers to the opposite pattern, namely higher left relative to right alpha power, and has been related to withdrawal and negative affect (Davidson, 1984; Kelley et al., 2017).

In a meta-analysis, lower alpha asymmetry has been associated with depression, and dysphoric symptoms generally (Thibodeau et al., 2006). However, caution is advised over its reliability, with subsequent reviews arguing that alpha asymmetry is unlikely to become diagnostically useful despite the large numbers of studies using it (van der Vinne et al., 2017). It is suggested that, with future research, alpha asymmetry may instead be a marker for specific symptoms, such as suicidal ideation, or for differentiating depressive disorders (van der Vinne et al., 2017), or treatment response prognosis (van der Vinne et al., 2017; Baskaran et al., 2012). Furthermore, lower alpha asymmetry has been consistently documented as a response to trauma-related stimuli in people with post-traumatic stress disorder (Meyer et al., 2015). Of relevance to the present review, changes in alpha asymmetry have also been documented across the menstrual cycle (Makarchouk et al., 2011; Huang et al., 2015).

There are numerous other examples of markers of mood disorders in the EEG literature related to clinically relevant phenotypes for MRMDs. Though not an exhaustive list, relevant examples include the reward positivity ERP in anhedonic depression (Proudfit, 2015), and the error-related negativity evoked response in anxiety disorders (Meyer, 2016). Alternatively, insight can be drawn from changes in EEG data features related to underlying neurobiological mechanisms. For example, bidirectional involvement of gamma and theta band activity as diagnostic classifiers or predictors of treatment response (Baskaran et al., 2012; de Aguiar Neto and Rosa, 2019).

While it is not within the scope of this review to consider all of the literature on EEG markers of mood disorders, it is of relevance to MRMDs that there is empirical evidence demonstrating the sensitivity of EEG to psychiatric symptomatology. Further, that there is a wealth of literature attempting to find the parameters of reliable and specific markers upon which future EEG research on MRMDs can draw, as the symptomatology profile partly overlaps with the one of mood and anxiety disorders (Halbreich, 2010). The current critical literature review aimed to summarize EEG findings on MRMDs (Fig. 1), to identify gaps in this field of research, and to discuss future perspective in utilizing EEG biomarkers as diagnostic or prognostic indicators.

## 2. Method

A literature search was performed using PubMed to identify articles investigating the neurophysiological correlates of MRMDs. The following keywords, along with their derivatives, were used for the search: "MRMDs", "menstrual", "mood disorders", "electrophysiology", "EEG", "electroencephalogram", "mood disorders", "PMDD", "PMS", "PME", and "premenstrual mood". We considered studies published in peer-reviewed journals until November 2022. Moreover, we screened the references cited in the included results. All publications meeting the following criteria were included in this critical review: (1) samples with MRMDs alone or in comparison to healthy controls and (2) papers written in English and indexed in PubMed.

### 3. Results

#### 3.1. Study characteristics

##### 3.1.1. Sample

To date, nine studies have investigated MRMDs with EEG (Tables 1–4): five focused on PMS and four on PMDD (of which two potentially on PME of major depression). The sample size ranged from 10 to 113 females ( $M_d = 41.2$ ,  $IQR = 29$ ), with participants being on average  $M_d = 22.5$ ,  $IQR = 8.8$ , years old. All studies were case-control studies (Parry et al., 1999; Baehr et al., 2004; Baker et al., 2007; Baker and Colrain, 2010; Accortt et al., 2011; Lin et al., 2013; Deng et al., 2019; Liu et al., 2017), except for one that compared participants with high PMS symptoms to those with low PMS symptoms (Hou et al., 2022).

##### 3.1.2. Inclusion and exclusion criteria

The extent and depth in evaluating subject features differed substantially across studies and inhomogeneous eligibility criteria were applied. Among the most common inclusion criteria were regular menstrual cycle length and absence of concurrent psychoactive drug use, hormonal contraceptive (HC) use, and neuropsychiatric conditions other than MRMDs. Regarding HC use, six studies excluded participants who reported current use (Parry et al., 1999; Baker et al., 2007; Baker and Colrain, 2010; Deng et al., 2019; Liu et al., 2017; Hou et al., 2022) or

use within the past three months (Baker et al., 2007). Two studies provided no information about HC use (Baehr et al., 2004; Lin et al., 2013), while one study included participants that were using HC and did not provide information on the type of HC (Accortt et al., 2011).

##### 3.1.3. MRMDs screening

In the selected papers, MRMDs screening was implemented in various ways, ranging from retrospective self-reports to standardised or non-standardised scales. Several studies opted for structured clinical interviews and prospective self-reported mood ratings (Parry et al., 1999; Baker and Colrain, 2010; Accortt et al., 2011; Deng et al., 2019). One assessed depression symptoms, not targeting MRMD-specific symptomatology (Parry et al., 1999); while two relied on retrospective methods (Lin et al., 2013; Hou et al., 2022). Baehr and colleagues did not provide enough information on the screening process to establish what their method was (Baehr et al., 2004). In two studies using overlapping cohorts, PMS and PMDD were not clearly distinguished, as the authors included persons with both PMDD and severe PMS (Baker et al., 2007; Baker and Colrain, 2010).

More specifically, to establish the MRMD diagnosis, as summarized in Tables 1–4, two studies applied the SCID based on the DSM-IV, using the custom module on PMS symptoms to confirm PMDD diagnosis, and requested the participants to record their symptoms for two menstrual cycles (Baker et al., 2007; Baker and Colrain, 2010). Another study utilized a battery of interviews, including the SCID, Hamilton

**Table 1**

Summary of the study characteristics and findings on EEG measurements in relation to MRMDs: frontal alpha band asymmetry studies.

Study	Sample (N)	Age (years)	Design	Comorbidities	MRMD diagnosis	Menstrual cycle	EEG method	Findings
(Deng et al., 2019)	113 (61 PMS, 52 CT)	21 ± 1.4	1x FP, 1x LP	<i>n.a.</i>	Prospective; 2-month self-recorded symptoms based on ACOG PMS diagnosis criteria	Self-report, salivary hormonal levels	Averaged frontal alpha asymmetry of 12 ch EEG at rest and during emotional picture task; open and closed eyes counterbalanced	Lower resting alpha asymmetry in PMS vs. CT regardless of MC phase Lower alpha asymmetry in LP vs. FP at rest Higher alpha asymmetry regardless of MC phase for positive than negative pictures in CT, but not in PMS
(Lin et al., 2013)	24 (12 PMDD, 12 CT)	20 ± 1.2	1x FP, 1x LP	<i>n.a.</i>	Retrospective; MDQ, BDI-II	Self-report from menses onset.	Frontal alpha asymmetry of 2 ch EEG (F3/F4) at (i) rest, (ii) depressive induction, (iii) recall, (iv) recovery and (v) relaxation. Participants were instructed to have their eyes closed.	Higher alpha asymmetry in PMDD vs. CT in LP during a task (specifically ii and v)
(Accortt et al., 2011)	50 (25 PMDD, 25 CT)	18 ± 1.2	4x during 2-weeks, irrespective of MC phase	Lifetime MDD or dysthymia	Prospective; DRSP based on DSM IV criteria	Self-report from menses onset.	Frontal alpha asymmetry for respective 8 ch EEG at rest. 64 ch EEG set up for modeling of reference montage: linked mastoid, average ref., current source density	Lower alpha asymmetry in PMDD vs. CT irrespective of MC phase Lower alpha asymmetry in PMDD with MDD vs. PMDD without MDD
(Baehr et al., 2004)	10 (5 PMDD, 5 CT)	43 ± 6.7	3x during 2 cycles for PMDD and 1 MC for CT irrespective of MC phase	MDD	<i>n.a.</i>	Self-report from menses onset for 5 PMDD and 1 CT. Experimenter guess for 4 CT.	Frontal alpha asymmetry of 2 ch EEG (F3/F4), assessed as percentage of time with scores > 0; no information on whether participants' eyes were open or closed.	Decrease in alpha asymmetry in PMDD in LP compared to "non-LP", but not in CT

ACOG: American College of Obstetrics and Gynecology; BDI-II: Beck Depression Inventory II; CT: controls; ch: channel; DRSP: Daily Record of Severity of Problems; EEG: electroencephalography; EMG: electromyography; EOG: electrooculogram; FP: follicular phase; LH: luteinizing hormone; LP: luteal phase; MC: menstrual cycle; MDD: major depressive disorder; MDQ: Moos Menstrual Distress Questionnaire; PME: premenstrual exacerbation; PMS: premenstrual syndrome.

**Table 2**  
Summary of the study characteristics and findings on EEG measurements in relation to MRMDs: stress reactivity study.

Study	Sample (N)	Age (years)	Design	Comorbidities	MRMD diagnosis	Menstrual cycle	EEG methods	Findings
(Liu et al., 2017)	30 (15 PMS, 15 CT)	22 ± 1.5	1x; MC phase modeled as covariate	n.a.	Prospective and retrospective; Self-compiled history and "PMS scales"	Self-report, gynecological examination, ultrasound	1 ch (Cz) EEG; 1 ch facial EMG, skin conductance, finger heart rate sensor, respiratory rate to assess stress reactivity and emotional state; no information on whether participants' eyes were open or closed.	Higher alpha power, lower positive affect and higher negative affect in PMS vs. CT Higher alpha power in PMS vs. CT under resting, attention and cognition test conditions

CT: controls; EEG: electroencephalography; Cz: midline central; EMG: Electromyography; MC: menstrual cycle.

Depression Rating Scale (HDRS), a custom PMDD interview, and the Daily Record of Severity of Problems (DRSP) scale for reporting of PMDD symptoms (Accortt et al., 2011). In another study focusing on PMS, the participants self-documented their symptoms for two months to confirm the diagnosis, criteria were defined in accordance with the American College of Obstetrics and Gynecology guidelines (Deng et al., 2019). Lastly, three studies used retrospective premenstrual symptom recording, one used the official Premenstrual Syndrome Scale (PMSS) (Hou et al., 2022), another through self-compiled history accompanied by a PMS scale (Liu et al., 2017), and, lastly, one by use of MDQ and BDI-II to confirm PMDD diagnosis (Lin et al., 2013).

### 3.1.4. Psychiatric comorbidities

Systematic interviews to assess eligibility criteria regarding mental health were described in seven studies (Parry et al., 1999; Baker et al., 2007; Baker and Colrain, 2010; Accortt et al., 2011; Lin et al., 2013; Deng et al., 2019), with six among them explicitly stating the use of standardised questionnaires (i.e., the Structured Clinical Interview for DSM-IV (SCID), Menstrual Distress Questionnaire (MDQ), and Beck Depression Inventory II (BDI-II)) (Parry et al., 1999; Baker et al., 2007; Baker and Colrain, 2010; Accortt et al., 2011; Lin et al., 2013). Six studies excluded participants with ongoing psychiatric conditions (Parry et al., 1999; Baker et al., 2007; Baker and Colrain, 2010; Deng et al., 2019; Liu et al., 2017; Hou et al., 2022), with two of these including individuals with a past history of psychiatric diagnosis or substance abuse (Baker et al., 2007; Baker and Colrain, 2010). Two studies included participants with ongoing comorbid disorders, that is major depressive disorder (MDD) (Baehr et al., 2004) or MDD and dysthymia (Accortt et al., 2011). Two studies stated a history of mental or other serious medical illness in their exclusion criteria (Lin et al., 2013; Deng et al., 2019). In their PMS sample, Baker and colleagues included severe cases that had a history of psychiatric illness or substance abuse during the past year (Baker et al., 2007).

### 3.1.5. Menstrual cycle assessment

Menstrual cycle regularity was an inclusion criterion in seven studies (Parry et al., 1999; Baker et al., 2007; Baker and Colrain, 2010; Lin et al., 2013; Deng et al., 2019; Liu et al., 2017; Hou et al., 2022). One study did not report information about menstrual cycle regularity assessment (Baehr et al., 2004), while another study did not include regular menstrual cycles in the inclusion criteria (Accortt et al., 2011). Furthermore, high variability was found in the type of menstrual cycle assessments and reporting (Tables 1–4), with some studies using saliva, blood, or urine testing, and others self-reports of menses onset. Baehr and colleagues (Baehr et al., 2004) did not have menses start dates for the majority of their control group, instead separated their EEG sessions by seven days.

## 3.2. Study design

### 3.2.1. Experimental settings and protocol

As presented in Tables 1–4, one study employed a cross-sectional design (Liu et al., 2017) and the other eight studies used within-subject measurements to assess the effects of menstrual cycle phase (Parry et al., 1999; Baehr et al., 2004; Baker et al., 2007; Baker and Colrain, 2010; Accortt et al., 2011; Lin et al., 2013; Deng et al., 2019; Hou et al., 2022) with the strongest focus on the late luteal phase (Parry et al., 1999; Baker et al., 2007; Baker and Colrain, 2010; Deng et al., 2019; Liu et al., 2017; Hou et al., 2022). In two of the studies, alpha asymmetry measurements were collected for cases and controls irrespective of menstrual cycle phase (Baehr et al., 2004; Accortt et al., 2011), one collected data three times over two cycles for the PMDD cases and over one cycle for the controls (Baehr et al., 2004), while the other study acquired data on four occasions within a two-week period (Accortt et al., 2011). Resting and task-related EEG activity was measured by Liu and colleagues only once with the menstrual cycle phase being modeled

**Table 3**  
Summary of the study characteristics and findings on EEG measurements in relation to MRMDs: circadian characteristics studies.

Study	Sample (N)	Age (years)	Design	Comorbidities in sample	MRMD diagnosis	Menstrual cycle	EEG methods	Findings
* (Baker and Colrain, 2010)	17 (9 PMS and PMDD, 8 CT)	30 ( $\pm 5$ )	2x, FP and LP	>1 year of psychiatric illness or alcohol/substance abuse	Prospective, PDSRF and retrospective; SCID for DSM-IV custom PMS module, 2-month Daily Symptom Rating Form	Blood estrogen and progesterone levels	Waking EEG, ERP recording; eyes open during the wakefulness task, but closed during a psychomotor task	Increased delta, theta and high alpha power in LP to FP for both groups. Across phases of the menstrual cycle severe PMS showed higher power across spectral bands in the low-beta range (12–16 Hz). Lower P300 amplitude in response to auditory and visual stimuli. Fatigue and mood deteriorate from FP to LP in PMDD vs. CT. Slower RTs and increased number of lapses in PVT during LP in PMDD vs. CT.
* (Baker et al., 2007)	21 (9 PMS and PMDD, 12 CT)	24.7 ( $\pm 5.5$ )	2x, FP and late-LP	>1 year of major psychiatric diagnosis	Prospective; SCID for DSM-IV custom PMS module	Urinary LH levels	Polysomnography (8 e EEG, EOG, EMG) in PMS and CT	Poorer sleep quality in PMS compared with CT. Decreased delta and increased theta incidence and amplitude in PMS vs. CT regardless of MC phase. Differences in beta power and theta amplitude in PMS vs. CT regardless of MC phase.
(Parry et al., 1999)	41 (23 PMDD, 18 CT)	36.6 ( $\pm 4.95$ )	4x, mid-FP, late-LP, late luteal sleep deprivation, recovery	none	Prospective; 2 month twice daily mood ratings – 21-item HRSD and BDI	Urinary LH levels	Sleep EEG during early and late partial sleep deprivation between PMDD and CT	MC phase effect on REM latencies in PMS and CT. Sleep architecture differences in PMDD vs. CT. Improved sleep quality in recovery nights for PMDD.

BDI: Beck Depression Inventory; CT: controls; Cz: midline central; DSM: Diagnostic and Statistical Manual of Mental Disorders; EEG: electroencephalography; EMG: Electromyography; EOG: electrooculogram; ERP: event-related potential; FP: follicular phase; HRSD: Hamilton Depression Scale; LH: luteinizing hormone; LP: luteal phase; MC: menstrual cycle; MDD: major depressive disorder; MWT: maintenance of wakefulness test; PDSRF: Penn Daily Symptom Rating Form; PMDD: premenstrual dysphoric disorder; PMS: premenstrual syndrome; PVT: psychomotor vigilance task; RT: reaction time. \*Overlapping cohorts.

Table 4

Summary of the study characteristics and findings on EEG measurements in relation to MRMDs: resting spectral dynamics.

Study	Sample (N)	Age (years)	Design	Comorbidities	MRMD diagnosis	Menstrual cycle	EEG methods	Findings
Hou et al., 2022	65 (32 hPMS, 33 IPMS)	21.2 ( $\pm 3.2$ )	2x, FP and late-LP	none	Retrospective; PMSS	Salivary estrogen and progesterone levels	Resting-state EEG; SW/FW (including TBR and DBR) ratio, averaged for frontal (F3, FZ, and F4), central (C3, CZ, and C4), and parietal electrodes (P3, PZ, and P4).	Delta-beta power ratio higher in LP vs. FP in hPMS, which positively correlated with symptoms, but not in IPMS

CT: controls; DBR: delta/beta power ratio; EEG: electroencephalography; FP: follicular phase; hPMS: high PMS; LP: luteal phase; IPMS: low PMS; PMS: premenstrual syndrome; PMSS: Premenstrual Syndrome Scale; SW/FW: slow wave/fast wave ratio; TBR: delta/beta power ratio.

as a covariate (Liu et al., 2017). Finally, five studies collected EEG data twice, once in the follicular and once during the luteal phase of the menstrual cycle (Baker et al., 2007; Baker and Colrain, 2010; Lin et al., 2013; Deng et al., 2019; Hou et al., 2022).

One of the studies assessed frontal alpha asymmetry differences between PMDD and controls under depressive induction, recall, recovery and relaxation (Lin et al., 2013). In the depressive induction condition, participants were guided to bring to mind an event that was followed by depressive feelings and active processing of depressive thoughts; evidence of the effectiveness of the depressive induction paradigm was not provided (Lin et al., 2013). Deng and colleagues (Deng et al., 2019) collected data both at rest and during an emotional picture task. Liu and colleagues (Liu et al., 2017) employed a stress reactivity task to assess changes in alpha activity, as well as the positive affect and negative affect scale, and a physiological stress evaluation scale. Baker and Colrain used a polysomnographic investigation as well as probed daytime sleepiness in cases and controls in a multimodal setting, using a maintenance of wakefulness test, a psychomotor vigilance task, auditory and visual recording of event-related potentials, as well as psychological scales for mood and sleepiness, in combination with waking EEG measurements (Baker and Colrain, 2010). Features of the sleep EEG were investigated once in the follicular and once in the luteal phase through the same aforementioned polysomnographic investigation, including EEG, electrooculography, and electromyographic recordings (Baker et al., 2007). Daytime was specified to have been set approximately 90–120 min after waking and typically between 9:00 and 10:00 am (Baker and Colrain, 2010). Last, to study the effects of sleep deprivation in PMDD and controls, Parry and colleagues (Parry et al., 1999) collected EEG measurements based on a partial sleep deprivation protocol on three occasions: a baseline sleep recording during the mid-follicular phase, during early (sleep between 3:00–7:00 am) or late (21:00–1:00 am) sleep deprivation in the late luteal phase, and on a recovery night, entailing a session of full night (22:30–6:30 am) sleep during the late luteal phase.

### 3.2.2. EEG measurement and processing

The extent to which the experimental arrangements and EEG settings were detailed varied substantially between studies affecting comparability. For example, in the frontal alpha asymmetry studies, the most common reference was the central electrode  $C_z$  (Fig. 1), but not always (Accortt et al., 2011). Analog sampling rates ranged from 128 Hz (Baehr et al., 2004; Baker et al., 2007; Lin et al., 2013) to 1 kHz (Baker and Colrain, 2010; Accortt et al., 2011; Deng et al., 2019; Hou et al., 2022). Some reports lacked a precise enough depiction of the task settings and conditions to permit replication or between study comparison (Lin et al., 2013; Liu et al., 2017). All studies included information about recording times and lengths and/or epoch segmentation procedures. Only three explained their methods for the spectral analysis in sufficient detail to permit replication (Baehr et al., 2004; Baker et al., 2007; Accortt et al., 2011).

### 3.3. EEG findings in MRMDs

The objective in four papers was centered around frontal oscillatory alpha asymmetry at rest (Baehr et al., 2004; Accortt et al., 2011) or during a task (Lin et al., 2013; Deng et al., 2019) (Table 1). One study focused on stress reactivity (Liu et al., 2018) (Table 2), while three studies investigated circadian electrophysiological characteristics (Parry et al., 1999; Baker et al., 2007; Baker and Colrain, 2010) (Table 3). Finally, one study assessed spontaneous brain activity, as measured by delta, theta, and beta power, and slow/fast (delta/beta and theta/beta) wave ratios in relation to PMS and emotion regulation (Hou et al., 2022).

#### 3.3.1. Frontal alpha band asymmetry

Four studies investigated alpha asymmetry as defined above. The evidence suggests lower anterior alpha asymmetry at rest in individuals with PMS or PMDD compared with controls (Table 1). Deng and colleagues (Deng et al., 2019) compared alpha asymmetry at 8–12 Hz between mid-late follicular and late luteal phases, and evaluated the mean of respective differences in spectral power of frontal electrode pairs (FP1/2, AF3/4, F1/2, F3/4, F5/6, F7/8). The authors found a main effect of group, with lower alpha asymmetry at rest (regardless of menstrual cycle phase, here defined as trait) in persons with PMS compared to healthy controls, and a main effect of phase with relatively lower asymmetry scores comparing luteal to follicular phase scores in both groups ( $\eta^2 = 0.11$ – $0.25$ ). No group by phase interaction effect was found. Upon visual presentation of emotional pictures (here defined as state), healthy controls presented higher asymmetry to positive than negative pictures, while no such effect was found in the PMS group (Deng et al., 2019).

Adding to the task-related findings in (Deng et al., 2019), Lin and colleagues investigated frontal alpha asymmetry when comparing patients with PMDD to healthy controls, during both the luteal and follicular phase (Lin et al., 2013). The authors describe higher asymmetry between F4-F3 channels in PMDD as compared with control subjects, only in the luteal phase during depressive induction and a subsequent relaxation period of three minutes. A similar but less pronounced effect was found in the follicular phase (Lin et al., 2013).

Accortt et al. (Accortt et al., 2011) also found lower resting alpha asymmetry indices for frontal channel pairs F1/2, F3/4, F5/6, F7/8 in patients with PMDD versus controls. In this study, measurements were on four occasions within a two-week period, regardless of menstrual cycle phase. Additionally, PMDD accompanied by lifetime MDD diagnosis was associated with lower alpha asymmetry compared to PMDD without MDD (Accortt et al., 2011). However, no effect size was reported for these results. Lastly, Baehr and co-workers (Baehr et al., 2004) analysed the percent of time that the absolute alpha asymmetry (F4–F3)/(F4+F3) was above null at rest in PMDD versus controls during the luteal and “non-luteal” phase. The authors found alpha asymmetry to be lower and self-reported negative affect to be higher than positive affect in the luteal compared to the “non-luteal” phase for only PMDD cases, although no effect size was reported (Baehr et al., 2004).

To summarise, both studies recording resting state EEG show lower



alpha asymmetry in subjects with PMS and PMDD (Accortt et al., 2011; Deng et al., 2019), with one study pointing to a luteal phase-specific effect (Baehr et al., 2004). Task related asymmetry produced mixed results that cannot be compared across the tasks and menstrual cycle phases, thus needing replication to determine reliability.

### 3.3.2. Stress reactivity

As reported in Table 2, one study focused on the EEG signatures of stress reactivity in PMS. To assess central stress reactivity using a biofeedback system and a stress evaluation test battery, Liu and colleagues (Liu et al., 2017) compared one channel (C<sub>z</sub>) 8–13 Hz alpha band power between persons with and without PMS, accounting for menstrual cycle phase (follicular and luteal phases) as a covariate. The authors found higher alpha power, higher negative affect, and lower positive affect in individuals with PMS compared to healthy controls. A main effect of group (PMS vs. controls  $\eta^2 = 0.410$ ) and an interaction of group-by-test condition on alpha activity during the EEG stress evaluation paradigm were found ( $\eta^2 = 0.117$ ), driven by higher alpha power under rest as well as during the attention and cognition tests in the PMS group compared with the controls (Liu et al., 2017).

### 3.3.3. Circadian characteristics

Regarding sleep architecture and circadian rhythmicity, three studies investigated sleep characteristics in regular sleep and after sleep deprivation, as well as alterations in daytime wakefulness, in PMS and PMDD (Table 3). The results can be seen as complementary, suggesting menstrual cycle phase-independent alterations, including higher low range spectral power (Baker and Colrain, 2010), decreased delta or theta incidence (Baker et al., 2007), and increased sleep quality as a response to sleep deprivation in MRMDs (Parry et al., 1999).

Comparing the EEG sleep architecture in a group of persons with either PMS or PMDD to healthy controls in the follicular and late luteal phase, power spectral and period amplitude analyses of two channel recordings (C3-A2, C4-A1) yielded menstrual cycle-dependent changes, in both directions in non-rapid eye movement (REM) EEG features (Baker et al., 2007). For instance, absolute and relative luteal spectral power were elevated in low beta (15 ≤ 23 Hz) and sleep spindle range sigma (12 ≤ 15 Hz), namely the rhythmic sigma waves characterizing stage 2 sleep (De Gennaro and Ferrara, 2003), frequency bins in both groups compared to the follicular phase. Sigma wave incidence (waves per epoch) and amplitude were increased in the luteal phase for all subjects, while the PMS/PMDD group displayed lower incidence in delta (0.3–≤4 Hz) activity and higher incidence in theta (4–≤8 Hz) oscillations, regardless of menstrual cycle phase. Moreover, sleep efficiency, measured as the percentage of sleep time during time in bed, was significantly worse in participants with PMS/PMDD and REM-sleep onset latency was longer compared to controls, independent of cycle phase. Both groups showed more frequent wakefulness after sleep onset and increased microarousal in the luteal phase compared to the follicular phase, while no difference between the two groups was noted in total time in bed (Baker et al., 2007).

Data from the latter experiment was then used to test whether individuals with PMS/PMDD display electrophysiological and behavioural differences in daytime sleepiness compared to healthy controls, across cycle phases (Baker and Colrain, 2010). Both groups displayed increased power in the delta/theta and alpha luteal phase frequencies when compared to the follicular phase. Mood and fatigue ratings indicated premenstrual deterioration in patients with “severe PMS” compared to controls. Though an effect of severe PMS was not found between the menstrual cycle phases (state), differences regardless of phase were found (trait). Participants with severe PMS performed worse on a psychomotor vigilance task (slower reaction time and more lapses). Using EEG, significantly higher power across spectral bands in the low-beta range (12–16 Hz) and lower P300 amplitude in response to auditory and visual stimuli were observed. The relationship between EEG and behavioural findings was not explored in this paper.

Lastly, a cross-over experiment investigated the EEG sleep architecture in an early (sleeping time 3:00 am–7:00 am) and late (sleeping time 9:00 pm–1:00 am) sleep deprivation intervention in healthy controls and patients with PMDD. The authors demonstrated facilitated recovery in PMDD after partial sleep loss intervention (Parry et al., 1999). Comparing baseline luteal recordings and post-sleep deprivation recovery nights, patients with PMDD showed augmented sleep efficiency, shorter sleep onset latency, fewer time awake independent of sleep deprivation type. When compared with controls, the PMDD sample was found to have increased sleep time and efficiency, shorter sleep latency, less time spent in the light sleep stage (stage 1), and less awake time. Positive correlations between changes in depressive scores (HDRS) from baseline, and changes in EEG (sleep variables) from baseline to the sleep deprivation recording were also observed in 9 out of 16 PMDD intervention responders between the luteal baseline and early sleep deprivation recovery night. Sleep variables comprised (a) fast REM sleep latency, (b) time awake after sleep onset, (c) stage 2 sleep, and (d) REM density during first REM phase. Complementary to the findings in (Baker et al., 2007), both case and control subjects were found to display longer REM latencies and reduced REM sleep in the luteal with the follicular phase, while only healthy controls showed increased stage 1 sleep in the luteal compared to the follicular phase (Parry et al., 1999).

In summary, three studies assessed the circadian and sleep characteristics in MRMDs. Baker and colleagues observed higher power in the low-beta spectral range in individuals with severe PMS compared with controls, irrespective of menstrual cycle phase (Baker et al., 2007; Baker and Colrain, 2010). Additionally, higher incidence and amplitude in theta and lower in delta oscillations, regardless of menstrual cycle phase, were noted in the PMS/PMDD sample compared with the control subjects (Baker et al., 2007), while after a night of sleep or sleep deprivation, EEG revealed higher luteal phase spectral power in PMDD patients for the low frequency bands, delta, theta, and alpha, along with fatigue and mood deterioration compared with the follicular phase (Baker and Colrain, 2010). Longer REM latencies and reduced REM sleep were found in the PMDD sample in the luteal compared with the follicular phase, while sleep efficiency and recovery after sleep deprivation were improved in females with PMDD compared with controls (Parry et al., 1999).

### 3.3.4. Resting spectral dynamics

One study (Table 4) examined the spontaneous variation in delta (1–3 Hz), theta (4–7 Hz), and beta (13–30 Hz) power, as well as the changes in relative slow/fast wave proportions from follicular to luteal phase, along with differences between individuals with moderate versus severe PMS (Hou et al., 2022). Hou and colleagues report a higher frontal and central delta/beta ratio (DBR) in persons with severe PMS in the luteal phase compared to the follicular (Table 4). No such result was found for theta/beta ratios and overall differences between the high and moderate PMS group were insignificant. The luteal DBRs in the high PMS group were further found to be positively correlated with scores of self-blame and rumination (Hou et al., 2022).

## 4. Discussion

The present review presents the current EEG findings in MRMDs, while highlighting the variability in the methodology of the few existing studies. Categorised by diagnosis, four studies focused only on PMDD (with two of them potentially recruiting subjects with PME of MDD rather than comorbid PMDD with MDD), three on PMS only, and two on PMS and PMDD. In general, syndrome definitions, diagnostic procedures and recording settings were not comprehensively described in all reviewed papers, and greatly varied, which makes it difficult to compare the findings.

As a major focus of the reviewed studies has been on interhemispheric frontal alpha asymmetry, and consistent results are beginning to emerge in the literature, these results are discussed first. In general,

power of alpha oscillations plays a functional role in cortical inhibition (Klimesch et al., 2007), where alpha power is inversely related to cortical activity. Frontal alpha asymmetry has been reliably used as an electrophysiology marker that can capture state and trait indices of emotion processes (Coan and Allen, 2003), with higher asymmetry values reflecting greater left frontal activity and lower values reflecting greater right frontal activity. Interpreted as balancing approach-avoidance motivation (Davidson, 1998), high frontal alpha asymmetry scores are understood to be an indicator of positive affect and approach drive (Davidson, 1984). On the other hand, low alpha asymmetry scores have been related to avoidance and negative emotional state (Harmon-Jones and Allen, 1997). While previous studies have demonstrated consistent frontal EEG alpha asymmetries in depressed individuals (Allen and Kline, 2004; Hagemann et al., 2002; Tomarken et al., 1992), our review aimed to extend this literature to studies specific to MRMDs. The two studies published so far suggest lower alpha asymmetry, assessed at rest using frontal electrodes, between persons with PMS/PMDD versus healthy controls (Accortt et al., 2011; Deng et al., 2019) and luteal alpha asymmetry did not vary depending on emotional stimuli (Deng et al., 2019). In one study, alpha asymmetry was found to decline from the follicular to the luteal phase, exclusively in the MRMD group (Baehr et al., 2004). However, in one of the studies assessing alpha asymmetry, the opposite pattern was observed, with higher alpha asymmetry in the luteal phase, potentially attributed to the fact that this was noted under a depressive induction state (Lin et al., 2013). The authors further discussed that sample-related factors could have influenced this result, indicating that PMDD diagnosis was retrospectively confirmed and diagnosis cannot be assured, thus highlighting the complexity of MRMD research (Lin et al., 2013). Overall, albeit limited, lower alpha asymmetry in persons with MRMDs seems to reflect both a general (Accortt et al., 2011; Deng et al., 2019) but also luteal phase-specific (Baehr et al., 2004) sensitivity in the avoidance motivational system.

Although the neural mechanism of alpha asymmetry is not conclusively defined, the main assumption, is that alpha power is inversely related to frontal cortical activity (Smith et al., 2017). Functional MRI studies focusing mainly on depression and emotional regulation have investigated the neurovasculature of the lateralized motivation-approach model described in (Davidson, 1984; Davidson, 1998) and observed effects on regions such as the dorsolateral PFC, insula, amygdala, ACC, amongst others (Zotov et al., 2016; Herrington et al., 2010). These regions are abundant in estrogen and progesterone receptors (Brinton et al., 2008; McEwen, 2002). Further, ovarian hormone levels have repeatedly been shown to impact some of the main neurotransmission pathways, like the GABAergic, glutamatergic, dopaminergic, and serotonergic, whose receptors are also widespread in the aforementioned regions (Barth et al., 2015). Even though the neuro-pathophysiological mechanism underlying the psychological symptomatology of MRMDs is not yet fully clarified, altered prefrontal activation patterns observed in MRMDs could be translated as reward-motivation and cognitive control deficiencies that relate to negative bias towards negative stimuli and poorer coping skills coupled with attentional shifting.

When discussing frontal alpha asymmetry as a potential index of altered emotional processing in MRMDs, limitations found in the wider literature on mood and anxiety disorders have to be considered. As a construct, alpha asymmetry is sensitive to factors such as the diagnostic and psychiatric properties of the sample, electrophysiological recording settings and study design (Thibodeau et al., 2006; van der Vinne et al., 2017). As a result, the low number of studies into MRMDs and the variability in methodologies poses a challenge in reliably inferring a causal relationship between frontal asymmetry and negative affect in MRMDs. The majority of studies have been conducted with a low number of participants (Baehr et al., 2004; Baker and Colrain, 2010; Lin et al., 2013) and within a narrow age range (Liao et al., 2017; Accortt et al., 2011; Lin et al., 2013; Deng et al., 2019). The studies also showed

substantial diversity in sample symptomatology and clinical characteristics (Baehr et al., 2004; Baker et al., 2007; Baker and Colrain, 2010; Accortt et al., 2011). Diagnostic criteria varied broadly in two studies including patients with PMDD comorbid with MDD, potentially reflecting PME (Baehr et al., 2004; Accortt et al., 2011). The different studies might have thus covered different combinations of mood symptoms on the MRDM spectrum.

Addressing specifically the contradictory results from Lin and colleagues (Lin et al., 2013), as the authors mention, the task might have not specifically induced depressive mood, and instead induced a stress response. Therefore, it is plausible that asymmetry as an index of emotional state could possibly vary depending on symptom category; inconsistencies in frontal asymmetry results are also present in studies on depression (van der Vinne et al., 2017). Future EEG studies could experimentally manipulate states of emotional processing to resolve this, by using standardized measurements with more consistent symptom profile. Altogether, these findings (Baehr et al., 2004; Accortt et al., 2011; Lin et al., 2013; Deng et al., 2019) warrant replication on larger scale to confirm the direction of alpha asymmetry at rest and during tasks as a possible feature of MRMDs.

Sleep EEG findings demonstrate menstrual cycle-related changes and group differences in spectral properties. On the one hand, the luteal phase might generally represent a phase of increased vulnerability to wakefulness and arousal, reflected by incremented power in fast waves (Baker et al., 2007) and longer REM sleep duration and latency (Parry et al., 1999). On the other hand, alterations in theta and delta wave incidence (waves per epoch) (Baker et al., 2007) might reflect global impairments in sleep quality, as reported by persons with severe PMS but not controls. In particular, altered patterns of delta wave sleep would largely affect homeostatic regulation of synaptic scaling (Tononi and Cirelli, 2006) and glymphatic activity (Hablitz et al., 2019) in the sleeping brain. Disturbance of night sleep might result in compromised daytime wakefulness and increased fatigue in persons with severe PMS, leading to functionally impaired behavioural performance (Baker and Colrain, 2010). Maladaptive task activity could be the result, putatively represented by increased cortical idling (Liu et al., 2017) and disturbances in resting-state spectral dynamics (Hou et al., 2022). Complex regulative behaviour and stress resilience might depend on adaptive tuning of fast and slow oscillatory activity (Ivaskevych et al., 2019; Snyder and Hall, 2006; Knyazev, 2007), which could potentially be recovered through luteal sleep intervention in PMS/PMDD (Baker et al., 2007). However, a realistic representation of stress has to be modelled and evaluated experimentally to systematically assess the response to stress and premenstrual adversity. This could ultimately help to tailor prevention and rehabilitation strategies in persons with MRMDs.

Interestingly, in two of the reviewed studies, potential sleep quality disruptions in MRMDs do not seem to be an effect of menstrual cycle phase (Parry et al., 1999; Baker et al., 2007). This means that the observed effects could presumably be disorder-specific (trait-like) and not necessarily attributable to the ovarian hormone cyclicity throughout the cycle. Nevertheless, considering the inconsistencies in methods between studies, this interpretation needs to be supported by further investigation. However, functional neuroimaging findings also support this trait-like vulnerability in relation to neural correlates of PMDD; indeed, independently of menstrual cycle phase, differential dorsolateral prefrontal activation has been observed in PMDD patients compared with controls (Baller and M.S., Shau-Ming Wei, B.S., Philip D. Kohn, M. S., David R. Rubinow, M.D., Gabriela Alarcón, B.A., Peter J. Schmidt, M. D., and Karen F. Berman, M.D., 2013; Toffoletto et al., 2014). Taking it one step further, lower relative delta, theta, and alpha power have been found in perimenopausal subjects compared to non-depressed controls, with those alterations being associated with vigilance and depression scores (Saletu et al., 1996), which would imply an overall female vulnerability to depressive states and not necessarily to cycle-dependent fluctuations. At present, findings on regularly cycling individuals and rodents indicate menstrual/estrous cycle phase effects on

low-frequency band oscillations, such as on the theta, alpha, or delta bands, although the pattern of change is not consistently related to one cycle phase or endocrine state (Thériault and Perreault, 2019).

Taken together, these findings provide first evidence for alterations in electrophysiological markers of menstrual cycle related mood disorders. Further replication and methodological advancement could test the robustness and the scope of this first evidence. The following critical discussion aims to facilitate appraisal of the presented evidence and highlights pivotal aspects in the complex study of females psychoneuroendocrinology.

#### 4.1. Methodological considerations

##### 4.1.1. MRMD symptom assessment

Regarding the requirements for studying and diagnosing MRMDs (Epperson et al., 2012; Schmalenberger et al., 2021), the reviewed studies did not consistently apply validated questionnaires, specifically targeting MRMDs symptomatology and its cyclical nature, such as the validated DRSP (Endicott et al., 2006) and diagnostic protocols as the Carolina Premenstrual Assessment Scoring System (C-PASS) (Eisenlohr-Moul et al., 2017). It is thus important for future studies to consider the nature and timing of symptoms in MRMDs, including individual differences in symptom profiles, and to employ appropriate inclusion and exclusion criteria (Gehlert et al., 2009). Even though the included studies were categorized according to diagnosis, how diagnosis was determined was unclear in four studies. While two studies focused on PMDD comorbid with MDD, it is highly likely that the participants could have been suffering from PME, according to literature definitions of the term (Kuehner and Nayman, 2021). Other than mentioning the comorbidity type included in their samples, the authors did not distinguish between PMDD and MDD nor did they provide additional information on the cyclicity and possible overlap in the symptoms of the two disorders (Baehr et al., 2004; Accortt et al., 2011). Similarly, in two other studies, even though participants were given a PMDD diagnosis, there were subjects included in the sample that did not meet the criteria, but instead had pronounced PMS symptomatology (Baker et al., 2007; Baker and Colrain, 2010). To what degree, however, this impacted the results is difficult to assess. Future research in the field of biological psychiatry might also have to consolidate features of the control groups to adequately interpret the results.

##### 4.1.2. EEG methods

In the presented studies, the comparability of EEG assessments between experiments is hampered due to high variability in EEG methods as well as sparse and variable reporting practices. For example, for the alpha asymmetry work in particular, there are differences in referencing. Given referencing methods affect the spatial and amplitude-based features of the EEG activity, it also impacts comparability of outcomes (van der Vinne et al., 2017). Further, re-referencing to the average is more common and in fact recommended for alpha asymmetry research going forward (van der Vinne et al., 2017), which ought to include MRMD studies. This issue of methodological and reporting variability in biological psychiatry research is not limited to the field of MRMDs or even EEG, however, in order to translate future work into potential clinical biomarkers for MRMDs, more consistency in approach and reporting is needed (Bixo et al., 2018; Liu et al., 2015; Epperson et al., 2002; Halbreich and Tworek, 1993; Sundstrom-Poromaa et al., 2020; Muthukumaraswamy, 2014; Hantsoo and Epperson, 2020).

#### 4.2. Strengths, limitations, and potential of EEG for future use in MRMD research

The current literature on MRMDs and EEG provides a basis to leverage the potential strengths of this technique. One of the major advantages of EEG is that it is a direct measure of neurophysiology and has demonstrated sensitivity to the dynamic and phasic sex hormone

fluctuations throughout the menstrual cycle. The variations in excitatory and inhibitory neurophysiology mediated by the major neurotransmitter systems glutamate and GABA, respectively, throughout the menstrual cycle, have been described (Smith et al., 2002; Harada et al., 2011). This review demonstrates that the potential of EEG to make detailed inferences on the biological mechanisms underlying MRMDs has not yet been fully realized. Future studies could draw upon the psychopharmacology research literature that manipulates key systems implicated in MRMDs like serotonin, GABA, and glutamate.

Currently, the most utilized imaging tool in discerning the emotion- and cognition-centered neural correlates of MRMDs has primarily been fMRI, followed by sMRI. Recent advances in psychiatric neuroscience have suggested alterations in resting-state network activity to characterize certain psychiatric disorders (Canario et al., 2021; Sha et al., 2019) in a symptom-domain specific manner (Andreano et al., 2018; Doucet et al., 2020; Xu et al., 2019) with sensitivity to sex hormone fluctuations (Dubol et al., 2021; Creutzfeldt et al., 1976; Huang et al., 2015; Andreano et al., 2018). In alignment with contemporary views of the emotional brain (Pessoa, 2018), the study of large-scale functional networks might help to elaborate the understanding of menstrual cycle related mood disorders, given ever changing endocrine states along the reproductive lifespan of a woman (Dubol et al., 2021; Andreano et al., 2018; Brinton et al., 2015; Hare et al., 2020).

Though sparse, the majority of fMRI results on PMDD report alterations within regions of the corticolimbic system activation during affective tasks, as reviewed in (Dubol et al., 2020). Similar evidence suggests that network dynamics may play a role in PMS, as confirmed by recent evidence on altered thalamocortical connectivity in persons with PMS (Liu et al., 2018; Meng et al., 2021; Long et al., 2022; Liu et al., 2022); however, studies on PME are even scarcer. As EEG lacks spatial resolution for subcortical regions that are suspected to have etiological relevance for MRMDs, EEG can complement research in this context, though it is unlikely to replace the need for further MRI studies. Future MRMDs research using EEG could focus on cycle-related electrophysiological changes in the dorsolateral PFC, given that frontal regions serve as a hub for mood regulation (Ray and Zald, 2012) and are highly accessible to surface EEG. Speculatively, potential clinical translation opportunities in PMDD include alpha waves in the PFC, which could be a potential target for EEG neurofeedback. Differential corticolimbic activation in response to emotional stimuli is proposed to distinguish the PMDD brain, namely enhanced amygdala and diminished fronto-cortical function (Dubol et al., 2020). Moreover, the most efficacious target for FDA-approved TMS-treatment for treatment-resistant depression is the dorsolateral PFC (Cantone et al., 2017), thus this brain region may be most responsive to fast neuroplastic changes in patients with a disorder of overlapping symptomatology. In line, Riddle and colleagues by employing an alternating alpha-power current stimulation paradigm on patients with PMDD, observed a decreased prefrontal alpha amplitude in the luteal phase relative to the follicular, thus corroborating phase-specific neural activity alterations as a feature of PMDD (Riddle et al., 2022).

Alternatively, if future studies use higher density EEG systems than the ones employed in many of the studies investigating MRMDs so far, spectral analyses on MRMDs could become more advanced employing source based, effective, and functional connectivity measures. For instance, resting-state functional connectivity alterations using EEG have already been widely reported in research on depression (Petersen et al., 2019; Kaiser et al., 2016; Syan et al., 2018; Lanius et al., 2010; Miljevic et al., 2023). In addition to resting-state studies, ERP studies in response to emotional or cognitive based tasks may also assist in disentangling the shared and unique phenomenology between MRMDs themselves and when compared to other mood disorders.

#### 4.3. Conclusion

In conclusion, the present overview systematically assessed the

current state of EEG research on MRMDs. Findings on frontal asymmetry in the alpha frequency were rather consistent; two out of two studies showed preliminary evidence for lower asymmetry at rest associated with MRMDs in the luteal phase. In terms of sleep and circadian rhythms, the results from the three reviewed studies point to generalized differential sleep dynamics being associated with MRMDs regardless of menstrual cycle phase. Recent evidence demonstrates differences in other frequency bands, as measured by slow-to-fast wave ratios between low and high severity individuals with MRMDs. This pioneering work could be followed up by well-powered studies using cutting edge methodology and analysis designs to expand the nascent literature on EEG spectral, ERP, and connectivity changes in MRMDs across the menstrual cycle in comparison with healthy controls. The conjunct implementation of psychophysiological and behavioural paradigms will contribute to advance our understanding of MRMDs.

#### CRedit authorship contribution statement

**Elisavet Kaltsouni:** Data curation, Visualization, Writing – original draft. **Felix Schmidt:** Data curation, Writing – original draft. **Rachel G. Zsido:** Methodology, Writing – original draft, Writing – review & editing. **Allison Eriksson:** Data curation, Writing – original draft, Writing – review & editing. **Julia Sacher:** Supervision, Writing – review & editing. **Inger Sundström-Poromaa:** Supervision, Writing – review & editing. **Rachael L. Sumner:** Methodology, Writing – original draft, Writing – review & editing. **Erika Comasco:** Conceptualization, Funding acquisition, Supervision, Visualization, Writing – original draft, Writing – review & editing.

#### Data availability

No data was used for the research described in the article.

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