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REVIEW PAPER

The key role of insomnia and sleep loss in the dysregulation of multiple systems involved in mood disorders: A proposed model

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Summary

Mood disorders are amongst the most prevalent and severe disorders worldwide, with a tendency to be recurrent and disabling. Although multiple mechanisms have been hypothesized to be involved in their pathogenesis, just a few integrative theoretical frameworks have been proposed and have yet to integrate comprehensively all available findings. As such, a comprehensive framework would be quite useful from a clinical and therapeutic point of view in order to identify elements to evaluate and target in the clinical practice. Because conditions of sleep loss, which include reduced sleep duration and insomnia, are constant alterations in mood disorders, the aim of this paper was to review the literature on their potential role in the pathogenesis of mood disorders and to propose a novel theoretical model. According to this hypothesis, sleep should be considered the main regulator of several systems and processes whose dysregulation is involved in the pathogenesis of mood disorders. The model may help explain why sleep disturbances are so strikingly linked to mood disorders, and underscores the need to evaluate, assess and target sleep disturbances in clinical practice, as a priority, in order to prevent and treat mood disorders.

KEYWORDS

circadian system, emotion regulation, insomnia, monoamine neurotransmission, mood disorders, neurobiological mechanisms, neuronal plasticity-connectivity, sleep loss, stress-inflammatory system

1 | INTRODUCTION

Mood disorders include a spectrum of conditions that can encompass elevated mood, such as mania/hypomania and depressed mood; major forms, such as major depressive unipolar and bipolar disorders, are amongst the most prevalent and serious diseases with a tendency to be recurrent, chronic and disabling (American Psychiatric Association, 2013; Kupfer, Frank, & Phillips, 2012; Wittchen, 2012). These disorders constitute a major public health concern and are the leading conditions in the global burden of disease in terms of disability, morbidity and premature mortality conferring high suicidality risk (American Psychiatric Association, 2013; Ferrari et al., 2014; Kupfer et al., 2012; Whiteford et al., 2013; Wittchen, 2012). The study and understanding of the mechanisms involved in the development and maintenance of mood disorders should thus be a priority to better identify potential early markers, which may inform preventive strategies and/or improve treatment outcomes in those affected by reducing morbidity and mortality. Sleep disturbances, particularly insomnia and conditions of sleep loss such as shortened sleep duration, may be such ideal candidates for this endeavour.

Insomnia is a clinically significant feature of mood disorders, and it was listed as a diagnostic criterion for mood disorders according

to the Diagnostic and Statistical Manual of Mental Disorders-DSM, starting as early as 1980 (American Psychiatric Association, 1980). It is highly prevalent across the course of mood disorders, as many as 80%–100% of people during the depressive episode and 45%–55% during the bipolar inter-episode period experience insomnia (Riemann, 2007; Dolsen, Asarnow, & Harvey, 2014; Geoffroy et al., 2015; Ng et al., 2015; Rumble, White, & Benca, 2015). It is positively related to mood disorder severity, cognitive dysfunctions, levels of hopelessness, increased risk of substance abuse, aggressive and impulsive behaviours, emotional dysregulation and increased risk of suicidality (Baglioni, Spiegelhalder, Lombardo, & Riemann, 2010; Ritter et al., 2011; Boudebesse & Henry, 2012; Ritter et al., 2012; Conroy & Arnedt, 2014; Kamphuis, Dijk, Spreen, & Lancel, 2014; Schaffer et al., 2015; Kanady, Soehner, Klein, & Harvey, 2017; Ng et al., 2015; Woosley, Lichstein, Taylor, Riedel, & Bush, 2014; Woznica, Carney, Kuo, & Moss, 2015). Insomnia plays an important role in relapses and recurrences of mood disorders, it is an independent risk factor for mood disorders, and a frequent early sign occurring prior to both depressive and manic episodes (Baglioni et al., 2011; Ellis, Perlis, Gardani, Bastien, & Espie, 2014; Gruber et al., 2011; Kanady, Soehnera, & Harvey, 2015; Pigeon, Bishop, & Krueger, 2017; Ritter et al., 2015; Rumble et al., 2015; Sakurai, Suzuki, Yoshimura, Mimura, & Uchida, 2017). Recently, it has been shown that targeting insomnia may improve not only insomnia symptoms but favourably impacts on the trajectory of mood disorders (Franzen & Buysse, 2008; Geoffroy et al., 2017; Jansson-Fröjmark & Norell-Clarke, 2016; Manber et al., 2011) and, by reducing depressive symptoms, it may even prevent major depressive forms (Christensen et al., 2016).

Sleep loss, such as for example reduced sleep duration and insufficient sleep, has particular importance in the emergence of mood dysregulation characteristic of bipolar disorders. Reduced sleep need is a unique and highly prevalent feature of mania (American Psychiatric Association, 2013; Harvey, 2008), experimental sleep deprivation can trigger mania in subjects with bipolar disorder and sleep loss predicts subsequent manic symptoms (Bauer et al., 2006; Colombo, Benedetti, Barbini, Campori, & Smeraldi, 1999). Links between reduced sleep duration/insufficient sleep and mood disturbance, impulsive and aggressive behaviours have also been observed in community samples and across affective disorders (Barnes & Meldrum, 2015; Clinkinbeard, Simi, Evans, & Anderson, 2011; Raniti et al., 2017; Sivertsen, Harvey, Lundervold, & Hysing, 2014).

Several potential mechanisms, through which these conditions of disrupted sleep might increase the risk or perpetuation of mood disorders, have been hypothesized. Indeed, sleep has important regulatory functions that are involved in most of the mechanisms that have been hypothesized to sustain mood disorders, including altered monoamine neurotransmission, hypothalamic–pituitary–adrenal (HPA)-axis abnormalities involved in chronic stress and inflammation, glutamatergic and orexinergic dysregulation, altered brain neurotrophic factors, brain neuroplasticity dysfunction and circadian systems dysregulations (Hashimoto, 2010; Leboyer et al., 2012; Mahar, Bambico, Mechawar, & Nobrega, 2014; McClung, 2013; aan het Rot et al., 2009; Yeoh, Campbell, James, Graham, & Dayas, 2014). In addition, sleep affects emotions, motivation, decision-making and cognition (Altena et al., 2016; Walker, 2009, 2010; Walker & van der Helm, 2009), which are implicated in the development and maintenance of mood disorders (Baskin-Sommers & Foti, 2015; Hofmann, Sawyer, Fang, & Asnaani, 2012; Whitton, Treadway, & Pizzagalli, 2015).

In spite of the availability of a huge amount of data about the pathogenesis of mood disorders, just a few integrative theories have been proposed. Therefore, the aim of this paper was to review the evidence on the potential role of these sleep disturbances, particularly insomnia and conditions of sleep loss, in the pathogenesis of mood disorders in order to propose a comprehensive model that might unify all these different mechanisms proposed for mood disorders through sleep impairment. These models may help to explain why sleep disturbances and the trajectory of mood disorders are so strikingly related and bidirectionally linked, and why to evaluate, assess and target sleep disturbances in clinical practice should be a priority in order to prevent and treat mood disorders.

2 | METHODS

The PubMed, PsycINFO and Embase electronic databases were searched for literature published until January 2018 on the neurobiology of mood disorders in relation with insomnia and conditions of sleep loss, including short sleep duration, chronic sleep deprivation, sleep restriction, insufficient sleep and such conditions experimentally induced, according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) method (Moher, Liberati, Tetzlaff, & Altman, 2009).

Several combinations of search terms were used, such as “monoamine and mood disorders” or “HPA-axis/stress system and mood disorders” or “inflammatory system/inflammation and mood disorders” or “neurotrophic factors and mood disorders” or “brain plasticity and mood disorders” or “glutamatergic system and mood disorders” or “circadian dysregulation and mood disorders” or “orexinegic system and mood disorder” or “emotion dysregulation and mood disorders” and “insomnia” or “sleep deprivation” or “sleep restriction” or “sleep loss” or “short sleep duration” or “insufficient sleep”. Inclusion criteria were investigative works on animals and humans on the association between these factors. Studies were included if they: (a) involved human adults aged > 18 years or animals; (b) were longitudinal observational case–control or cross-sectional studies or reviews; (c) analysed the relationship between insomnia, short sleep, conditions of sleep loss and those mechanisms identified for mood disorders; (d) were published until January 2018. Studies were excluded if: (a) they did not control for confounding factors such as other sleep disorders (i.e. other sleep disorders, narcolepsy, sleep-disordered breathing and restless leg syndrome); (b) they were not available in full text; or (c) they were not available in English. Seventy-eight articles containing original concepts and hypotheses

about the role of insomnia, sleep loss, sleep restriction and deprivation, short sleep duration in mood disorders' dysregulation were selected. Specifically, these related to eight different potential pathways whose dysregulation has been proposed for mood disorders – (a) monoamine neurotransmission (*N* = 15), (b) stress system, neuronal plasticity-connectivity (*N* = 12), (c) inflammatory system (*N* = 4), (d) neurotrophic support (*N* = 6), (e) glutamatergic system (*N* = 5), (f) circadian system (*N* = 6), (g) orexinergic system (*N* = 4), and (h) emotion dysregulation (*N* = 26). The data were integrated in a narrative review to construct a hypothesis. The evidence outlining the importance of sleep for each of these pathways is preceded by a brief summary of the neurobiological mechanisms that have been hypothesized to underlie mood disorders.

2.1 | Monoamine hypothesis of mood disorders

2.1.1 | Summary of evidence

The "monoamine or biogenic amine hypothesis" of mood disorders – the predominant theory for mood disorders for the last 50 years – states that the main symptoms of depression are due to a functional deficiency of the brain monoaminergic transmitters: norepinephrine, serotonin and/or dopamine, whereas mania is caused by a functional excess of monoamines at critical synapses in the brain (for review, see Muneer, 2016; aan het Rot, Mathew, & Charney, 2009). Although recently some observations have challenged the legitimacy of this theory (for an overview, see Ruhe, Mason, & Schene, 2007), a dysregulation in monoamine production and transmission is still considered an important factor in the regulation of mood, emotions, cognition, motivational behaviours and stress responses (Chaudhury, Liu, & Han, 2015; Muneer, 2016; aan het Rot et al., 2009). Recent studies have shown that an increased vulnerability for developing mood disorders, especially in response to stress, is associated with a polymorphism in the 5-HT transporter (Kenna et al., 2012) and in the dopamine type 2 receptor (aan het Rot et al., 2009), which has been related to reduced levels of serotonin and dopamine being available for transmission. Additionally, a decrease in both sensitivity and numbers of serotonin receptors and serotonin$_{1A}$ (5-HT1A) auto-receptors has been proposed as an endophenotypic hallmark for developing mood disorders (for an overview, see Mahar et al., 2014; Nautiyal & Hen, 2017).

2.1.2 | Role of insomnia and experimentally induced sleep loss

It is widely accepted that serotonin, norepinephrine and dopamine are involved in sleep–wake regulation (Monti & Jantos, 2008; Monti, 2010) and while short-term sleep deprivation has shown therapeutic properties for those with mood disorders (Adrien, 2002), long-term/chronic sleep deprivation and disruption have instead been related to the development of mood disorders via monoamine activity dysregulation.

A decrease in monoamines production has been shown in experimental studies of chronic sleep deprivation in animals. In fact, a decreased production of norepinephrine in the medial preoptic area, and of dopamine and serotonin in the medial preoptic area and in the cortex has been described (Monti, 2010). Especially, long-term rapid eye movement (REM) sleep deprivation has been shown to be related to a dysregulation in monoamine activity. As such, mice deprived of REM sleep for 5 days showed depressive-like behaviours 1 week following, with these behaviours being moderated by the monoaminergic system in the amygdala and hippocampus (Wang, Chen, Zhang, & Wang, 2017).

The role of sleep disturbances of the serotonin 5-HT transporter comes predominately from human studies. Brummett et al. (2007) compared the sleep quality of adult primary caregivers for a parent with dementia against non-caregiver controls. The authors found the short allele of the 5-HT transporter was related to caregivers' poor sleep quality and hypothesized that the short 5-HT allele moderates sleep disturbance in response to chronic stress. Deuschle et al. (2010) conducted a study in a group of individuals suffering from chronic insomnia, and found that the short allele of the 5-HT transporter was significantly more frequent in patients suffering from insomnia than in good sleepers (Deuschle et al., 2010). Taken together, these data may suggest that a polymorphism in the 5-HT transporter, which may be more frequent in individuals suffering from chronic insomnia, may favour sleep disturbances in response to stress by altering serotonin transmission. This dysregulation may contribute to mood disorders by sensitizing the stress system, thus predisposing to the development of mood disorders (see Methods).

The effect of sleep disruption on serotonin receptor sensitivity has been tested experimentally in animals and confirms the data obtained in humans. Chronic sleep restriction causes a gradual and persistent desensitization of the 5-HT1A receptor system (Novati et al., 2008; Roman, Walstra, Luiten, & Meerlo, 2005). In one study, rats were restricted to 4 hr of sleep per day for either 2 or 8 days. Following 8 days of sleep restriction, a significant desensitization of the serotonin receptor led to a decrease in serotonin levels (Novati et al., 2008), which is consistent with responses found in depressed individuals. Roman et al. (2005) suggested that chronic sleep restriction may increase an individual's vulnerability to develop mood disorders by impairing serotoninergic transmission throughout the activation of the stress system, and this hypothesis was later confirmed (Meerlo et al., 2009; Meerlo, Havekes, & Steiger, 2015; Novati et al., 2008, 2015). There are also some emerging findings about the role of sleep disruption on dopamine system dysregulation. The genetic makeup of the dopamine system involved in vulnerability to mood disorders (aan het Rot et al., 2009) has also been shown to be involved in the response to sleep loss and in alterations in responses to reward in humans (Greer, Goldstein, Knutson, & Walker, 2016; Holst et al., 2017). A polymorphism in the dopamine 2 receptor, more commonly in the dopamine transporter system, has been related to a vulnerability to psychiatric disorders in the presence of sleep deprivation

in humans (Holst et al., 2017). Sleep deprivation in humans has been associated with increasing response in brain areas sensitive to reward choices with a disinhibition of mesolimbic dopaminergic networks mediating reactivity to pleasurable and rewarding experiences (Gujar, Yoo, Hu, & Walker, 2011; Perogamvros & Schwartz, 2015). The role of sleep disruption on norepinephrine regulation has been studied less extensively. The activity of the noradrenergic system of the locus coeruleus promotes arousal and electroencephalogram activation, as well as attention, working memory and cognitive flexibility (Killgore, 2010). These functions rely on the prefrontal cortex and have been shown to be impaired by sleep deprivation (for an overview, see Killgore, 2010). Recently, an experimental study conducted in mice by Bellesi, Tononi, Cirelli, and Serra (2016) suggested that the impairment in the locus coeruleus neurons targeting prefrontal cortex during sleep deprivation could be one of the mechanisms underlying the cognitive impairment related to sleep deprivation. As such, these mechanisms of insomnia/sleep deprivation/sleep restriction may contribute to the vulnerability and maintenance of mood disorders by altering monoamine transmission (Figure 1).

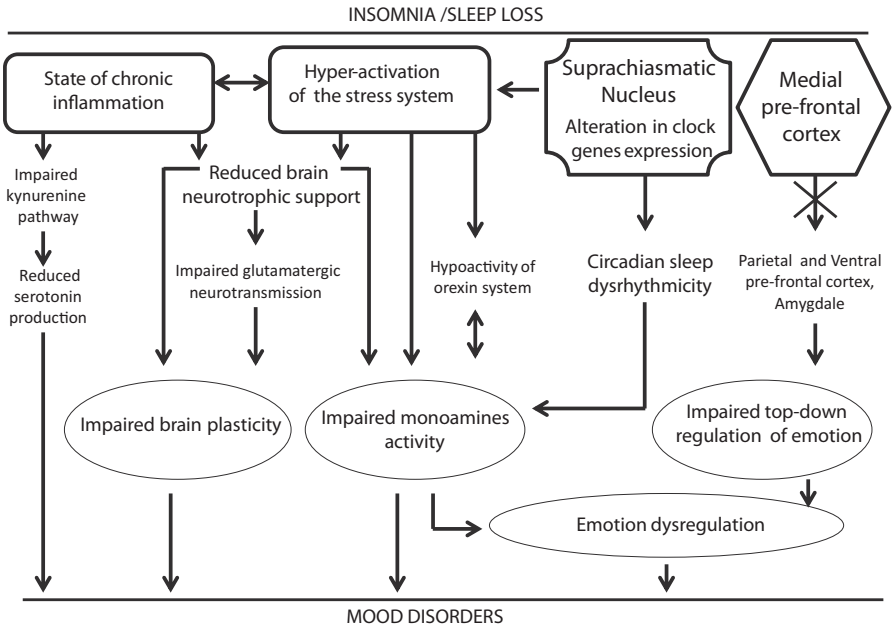

FIGURE 1 A proposed model: role of insomnia and sleep loss in mood disorders. Sleep plays a key role in the regulation of those multiple systems whose dysregulation is involved in the pathogenesis of mood disorders. Particularly sleep disruption due to insomnia or to sleep restriction/deprivation/loss seems to contribute to mood disorders essentially through three mechanisms. (1) Sleep disruption acts as a neurobiological stressor leading to different and multiple consequences: (a) an overactivation of the stress system that may negatively influence hippocampal neurogenesis, brain plasticity and connectivity in the prefrontal cortex and in the brain regions that regulate mood, emotion and cognition, thus contributing to the vulnerability and maintenance of mood disorders; (b) a dysregulation of the inflammatory system, thus establishing a state of chronic inflammation that may consequently have a negative effect on serotonin production via impairment of the kynurenine pathway, a reduction in neurotropic brain support, and via feedforward cascade of hypothalamic-pituitary-adrenal (HPA)-axis and stress system dysregulation; (c) monoaminergic system dysregulation with alterations in serotonin production via impairment of the kynurenine pathway and the desensitization of the 5-HT1A receptors thus altering serotonin production, alterations in dopamine system with a disinhibition of mesolimbic dopaminergic networks that mediate reactivity to pleasurable and rewarding experiences, and alterations in norepinephrine functions due to an impairment in the locus coeruleus neurons targeting the prefrontal cortex and regulating cognitive functions; (d) a reduction in neurotrophic factors, especially, brain-derived neurotrophic factor (BDNF) thus impairing synaptic plasticity and neurogenesis, and may have a negative influence on serotonin and glutamatergic regulation; (e) increased levels of glutamate that may downregulate glutamate receptors expression which, in turn, may lead to improper functioning and disrupted neuronal plasticity being associated to dendritic retraction, loss of spines and dendritic atrophy in some brain structures, including the hippocampus; (f) elevated levels of orexin peptides that downregulate the orexin system in the long term, thus affecting behavioural and neuroendocrine responses to stress, reward-seeking behaviours, learning and memory being thus involved in the development and maintenance of mood disorders. (2) Sleep disruption may impair circadian rhythmicity by altering the rhythmic expression of core clock genes in the suprachiasmatic nucleus (SCN) and in turn altering, amongst others, the circadian regulation of stress, inflammatory and monoaminergic systems and neurotrophic support. These effects induced by sleep disruption may favour the development of a circadian dysregulation, which is a key factor in mood disorders. (3) Sleep disruption may impair the emotion regulatory machine by impairing the functional connectivity of the prefrontal cortex and the top-down modulation of emotional processing. Sleep disruption may impair the entire process of decision-making by altering the functional connectivity of parietal and medial prefrontal cortices with a loss in emotional control, a tendency to risky decisions, impulsive and aggressive behaviours that may contribute to perpetuate mood disorders. Sleep disruption has been related to a disinhibition of the mesolimbic dopaminergic networks thus disturbing the reactivity to pleasurable and rewarding experiences

2.2 | Stress system, neuronal plasticity-connectivity alterations in mood disorders

2.2.1 | Summary of evidence

Stress has long been identified as both a risk factor and precipitating factor for the development of mood disorders (for an overview, see Mahar et al., 2014; Muneer, 2016; aan het Rot et al., 2009). An individual's capacity to deal with stress has been hypothesized to be largely controlled by the HPA-axis. In mood disorders, the HPA-axis has been shown to be hyperactivated as evidenced by a hyperactivation of corticotropic-releasing hormone neurons in the hypothalamus and an increase in cortisol production. Because of the inhibitory control of the hippocampus on the HPA-axis, challenge to this structure is expected to disinhibit the HPA-axis and to cause a positive feedforward cascade of increasing glucocorticoid levels over time (Bao, Meynen, & Swaab, 2008; Lee, Reif, & Schmitt, 2013b; Lee et al., 2013a). Glucocorticoid cascades during stress may play a contributing role towards neuron death and hippocampal atrophy, thus contributing to mood dysregulation. In fact, the "neurogenic hypothesis of mood disorders" postulates that humans suffering from depression have a decreased neurogenesis that could be at the core of smaller hippocampi (Lee et al., 2013a, 2013b). HPA-axis dysregulation and chronic stress have deleterious effects on neurogenesis, synaptic plasticity and the connectivity of brain structures regulating mood. For instance, the orbital/ventrolateral prefrontal cortex, corpus callosum, caudate head, putamen, accumbens nuclei and the hippocampus are reduced in volume, while the amygdala volume has been reported to be increased in mood disorders (Drevets, Price, & Furey, 2008; McEwen & Gianaros, 2011; McKenna & Eyler, 2012).

2.2.2 | Role of insomnia and experimentally induced sleep loss

It has been widely shown that individuals suffering from insomnia display hyperactivation of the HPA-axis at both brain and peripheral levels (for review, see Morin et al., 2017; Riemann et al., 2010, 2015). Increases in norepinephrine, epinephrine and other markers of sympathetic outflow have been related to cognitive and emotional arousal and somatic hyperarousal in individuals suffering from insomnia: it is the key pathophysiological mechanism of insomnia (Morin et al., 2017; Riemann et al., 2010, 2015). Changes observed in brain structures in individuals suffering from insomnia include a reduction in the volume of the prefrontal cortex, caudate head and hippocampus, as well as an increase in the amygdala volume (for an overview, see Riemann et al., 2010, 2015), modifications resembling those described in individuals suffering mood disorders. Given these similarities, it has been hypothesized that insomnia may influence the development and maintenance of a mood disorder throughout the activation of the stress system and of its negative consequences on the brain, including hippocampal neurogenesis, synaptic plasticity and connectivity (McEwen & Gianaros, 2011; Meerlo et al., 2008, 2015; Raven, Van der Zee, Meerlo, & Havekes, 2017).

Recent research has shown that sleep disruption should be considered as a neurobiological and physiological stressor with consequences that impair brain functions and contribute to the cumulative wear and tear on body systems caused by too much stress and/or inefficient management of the systems promoting adaptation (for an overview, see McEwen, 2006; Meerlo et al., 2008, 2015).

Experimental animal studies have also shown that chronic restriction of sleep may gradually induce neurobiological changes very similar to those observed in depressed patients. It has been hypothesized that mechanisms through which insufficient sleep increases the risk for depression may include effects of sleep disruption on the neuroendocrine stress system (Kreutzmann, Havekes, Abel, & Meerlo, 2015; Meerlo et al., 2008, 2015; Raven et al., 2017). Meerlo et al. (2009) hypothesized that sleep loss may not only have a direct activating effect, but in the long term may also affect the reactivity of these systems to other stressors and challenges. According to this hypothesis, chronic sleep restriction may alter the fundamental properties of neuroendocrine stress systems, gradually changing certain brain systems and neuroendocrine systems in a way that may sensitize individuals to stress-related disorders such as depression (Meerlo et al., 2009). In particular, when restricted sleep occurs chronically, it has been shown to cause a reduction of hippocampal cell proliferation and neurogenesis, which may eventually lead to a reduction in hippocampal volume. As such, by impairing hippocampal plasticity and function, chronically restricted and disrupted sleep may contribute to mood disorders (Kreutzmann et al., 2015; Meerlo et al., 2008, 2015; Raven et al., 2017). Because sleep is considered to play a crucial role in regulating neuronal plasticity and synaptic strength (Tononi & Cirelli, 2014), chronic insufficient sleep may contribute to mood disorders through impairments of plasticity processes leading to altered connectivity and communication within and between brain regions involved in the regulation of mood (for an overview, see Benedetti et al., 2017; Kreutzmann et al., 2015; Meerlo et al., 2009, 2015; Raven et al., 2017). In summary, insomnia and conditions of sleep loss may act as neurobiological stressors, which, by over-activating the stress system, may negatively influence the brain regions that regulate mood, emotion and cognition, thus contributing to the vulnerability and maintenance of mood disorders (Figure 1).

2.3 | Inflammation hypothesis of mood disorders

2.3.1 | Summary of evidence

Another proposed mechanism for the pathogenesis of mood disorders has been related to the finding that elevated immune-inflammatory signalling may contribute to mood dysregulation (for an overview, see Leboyer et al., 2012; Wohleb, Franklin, Iwata, & Duman, 2016). The "monocyte-T-lymphocyte theory" of depression, proposed in the early 1990s, suggests that increased pro-inflammatory cytokine

secretion may contribute to the initiation and maintenance of mood disorders by creating a feedforward cascade of multiple systems dysregulation (Leboyer et al., 2012; Wohleb et al., 2016). Recently, a growing body of evidence hypothesized that pro-inflammatory cytokines in the form of interleukin (IL)-6 or IL-10, tumour necrosis factor-α (TNFα), interferon gamma (IFNγ) and C-reactive protein (CRP) are responsible for the initiation and maintenance of mood disorders (Leboyer et al., 2012; Wohleb et al., 2016). The "inflammation hypothesis of mood disorders" recognizes the key role of chronic stress: it is thought to impact negatively on the inflammatory response system, potentially culminating in the manifestation of mood disorders. A chronic inflammatory state may alter serotoninergic neurotransmission via the depletion of tryptophan throughout the impairment of the kynurenine pathway (Leboyer et al., 2012; Won & Kim, 2016). Stress-induced immune activation is also thought to contribute to the induction of HPA-axis hyperactivity, which, in turn, may lead to a feedforward cascade of HPA-axis dysregulation (for an overview, see Leboyer et al., 2012; Wohleb et al., 2016; Won & Kim, 2016). Cytokine dysregulations have also been shown to decrease neurotrophic support and inhibit neurogenesis in several brain areas, particularly in the hippocampus (Williamson & Bilbo, 2013). Immune dysregulation and subsequent alterations in monoaminergic neurotransmission, stress response and neurotrophic system have been hypothesized to have a detrimental impact on normal brain functioning, contributing to both the development and maintenance of mood disorders (Leboyer et al., 2012; Won & Kim, 2016).

2.3.2 | Role of insomnia and experimentally induced sleep loss

A reciprocal interaction of inflammatory mediators and the homeostatic regulation of sleep has been described previously (for an overview, see Irwin & Cole, 2011; Irwin, 2015; Irwin & Opp, 2017). In particular, chronic sleep deprivation and insomnia may lead to an over-activation of the HPA-axis and sympathetic nervous system pathway, together contributing to an increased pro-inflammatory cytokine activity (Irwin, 2015; Irwin & Cole, 2011; Irwin, Olmstead, & Carroll, 2016; Irwin & Opp, 2017). Insomnia is associated with: (a) alterations in the relative distribution of immune cells; (b) marked decreases in the numbers of T-cells; and (c) higher levels of CRP (Irwin, 2015; Irwin & Cole, 2011; Irwin et al., 2016). Higher levels of IL-6 have been observed in individuals with poor sleep quality, and individuals with short sleep durations have shown high levels of both IL-6 and TNF (Irwin & Opp, 2017; Irwin et al., 2016). In a recent study conducted in a group of depressed individuals, poor sleep quality was associated with an increase in CRP and with an alteration in kynurenine metabolism. The authors hypothesized that the latter finding may be the molecular link between poor sleep quality and depression (Cho et al., 2017). These findings are also supported by experimental sleep deprivation studies in humans. Data have shown that prolonged partial-night sleep deprivation produces increase in CRP and IL-6, and even short periods of sleep restriction result in an increase in TNF in men, and IL-1β, IL-6 and IL-17 in both sexes (Irwin, 2015; Irwin & Opp, 2017). Prolonged total sleep deprivation has also been shown to result in increases in circulating markers of inflammation with an increase of CRP, TNF and IL (Irwin, 2015; Irwin & Opp, 2017). On this basis, a role for insomnia and prolonged sleep deprivation has been hypothesized in the initiation and maintenance of mood disorders by establishing a state of chronic activation of the inflammatory system (Irwin & Opp, 2017; Irwin et al., 2016). As such, disturbed sleep may contribute to the development and maintenance of mood disorders through dysregulation of the inflammatory system and its impact on serotonin production via the kynurenine pathway, on brain neurotrophic support system and via feedforward cascade of HPA-axis dysregulation (Figure 1).

2.4 | Neurotrophic hypothesis of mood disorders

2.4.1 | Summary of evidence

The "neurotrophic hypothesis of mood disorders" proposes that mood disorders may result from decreased neurotrophic support, leading to neuronal atrophy, decreased hippocampal neurogenesis and loss of glia (for an overview, see Duman & Monteggia, 2006; Hashimoto, 2010; aan het Rot et al., 2009). Especially, brain-derived neurotrophic factor (BDNF) has been proposed as a potential biomarker of mood disorders: BDNF has emerged as a key regulator of synaptic plasticity and neurogenesis (Duman & Monteggia, 2006; Hashimoto, 2010; aan het Rot et al., 2009). Decreased serum BDNF levels have been found in patients with major depression and bipolar disorder (Duman & Monteggia, 2006; Hashimoto, 2010; aan het Rot et al., 2009). Decreased levels of BDNF could contribute to the atrophy of certain brain structures, including the hippocampus and prefrontal cortex by causing neuronal atrophy, impairing serotonin function and glutamatergic regulation (Duman & Monteggia, 2006; Hashimoto, 2010; aan het Rot et al., 2009; Sanacora, Treccani, & Popoli, 2012). BDNF has been increasingly accepted as a central mediator of the effects of stress on neuronal plasticity and thus being implicated in mood disorders (Duman & Monteggia, 2006; Hashimoto, 2010; aan het Rot et al., 2009).

2.4.2 | Role of insomnia and experimentally induced sleep loss

Brain-derived neurotrophic factor is involved in the homeostatic regulation of sleep (Faraguna, Vyazovskiy, Nelson, Tononi, & Cirelli, 2008). BDNF levels have been studied in individuals with insomnia symptoms in two studies: both of which demonstrated reduced BDNF serum levels in this group (Giese et al., 2013, 2014). These authors hypothesized a mediating role in the link between stress experience and serum BDNF levels in these individuals (Giese et al., 2013, 2014). These findings, obtained from clinical samples, are supported by experimental studies showing reduced BDNF levels in subjects with prolonged sleep deprivation (Meerlo et al., 2015; Schmitt, Holsboer-Trachsler, & Eckert, 2016).

Meerlo et al. (2015) hypothesized that sleep restriction may act as a neurobiological stressor throughout the activation of the stress system, thus impairing BDNF levels with a negative effect on serotonin signalling and on synaptic plasticity and neurogenesis (for an overview, see Meerlo et al., 2015). Concluding, insomnia and sleep deprivation have been shown to be related to a reduction in neurotrophic factors in the brain that are essential for synaptic plasticity and neurogenesis, and may have a negative influence on serotonin and glutamatergic regulation and the stress system (Figure 1).

2.5 | The glutamate hypothesis of mood disorders

2.5.1 | Summary of evidence

In recent years, there has been considerable interest in the role of glutamate in mood disorders, even if the roots of a "glutamate hypothesis of mood disorders" can be traced back to the early 1990s, when findings showed that *N*-methyl-D-aspartate receptor (NMDA-R) antagonists possess antidepressant-like action (for an overview, see Sanacora et al., 2012). The amino acid glutamate is now accepted as the major excitatory neurotransmitter in the nervous system. Abnormal levels of glutamate have been found in individuals suffering from mood disorders (Sanacora et al., 2012). Elevated glutamatergic function is thought to support the neurophysiological activation of amygdala and limbic-thalamo-cortical circuits involved in mood disorders. Higher glutamate levels have been noted in plasma, serum, cerebrospinal fluid and brain tissue in individuals with mood disorders, as well as in suicide completers when compared with healthy controls. Given that glutamate is necessary for the normal development of dendritic branching, it has been speculated that excessive glutamatergic neurotransmission, via exposure to chronic stress, may cause dendritic retraction, loss of spines and dendritic atrophy in some brain structures (for an overview, see Sanacora et al., 2012), especially in limbic and cortical areas (Drevets et al., 2008; Sanacora et al., 2012). These dendritic reshaping processes seem to depend on interactions between the increased NMDA-R stimulation and glucocorticoid secretion associated with repeated stress (Yasmin, Saxena, McEwen, & Chattarji, 2016). While there are several types of glutamate receptors in the brain, research has especially focused on the NMDA-R. Hyperfunction of NMDA-Rs in subcortical regions such as the hippocampus, locus coeruleus and amygdale, and hypofunction in the prefrontal and temporal cortices is thought to play a key role in development of mood disorders (Yasmin et al., 2016).

2.5.2 | Role of insomnia and experimentally induced sleep loss

Glutamate has also been implicated in sleep–wake homeostasis, and the activity of NMDA-Rs fluctuates through the sleep–wake cycle (for a review, see Havekes, Vecsey, & Abel, 2012; Kreutzmann et al., 2015). Experimental studies examining the effects of sleep deprivation on glutamate have found that glutamate levels increase after sleep deprivation in the hippocampus and in the cortex (Havekes et al., 2012; Kreutzmann et al., 2015). Specifically, sleep restriction has been shown to impair the function and expression of glutamate receptors (Havekes et al., 2012; Kreutzmann et al., 2015). For example, 24 hr of REM sleep deprivation in mice has been shown to impair the function of NMDA-R in the dentate gyrus (Chen, Hardy, Zhang, LaHoste, & Bazan, 2006), and 72 hr of REM deprivation in rats to impair the NMDA-R function in the hippocampus. Abnormal NMDA-R function appears to be a contributor to the hippocampal plasticity deficits observed after longer periods of sleep deprivation that resemble those found in mood disorders (for review, see Havekes et al., 2012; Kreutzmann et al., 2015). Kreutzmann et al. (2015) speculated that elevated levels of glutamate, in response to prolonged wakefulness, through the activation of the stress system may downregulate NMDA and other glutamate receptor expression which, in turn, may lead to improper functioning and eventually disrupted neuronal plasticity. In conclusion, sleep deprivation/restriction has been shown to negatively influence glutamatergic functions, and this may contribute to mood disorders (Kreutzmann et al., 2015; Meerlo et al., 2008, 2015; Figure 1). However, studies are needed in a clinical sample of individuals with insomnia to determine if this is the case in that population.

2.6 | The circadian disrhythmicity hypothesis of mood disorders

2.6.1 | Summary of evidence

Compelling evidence has suggested that mood disorders arise in part from a malfunction of the circadian system. The "circadian hypothesis of mood disorders" states that in individuals with mood disorders, there is a desynchronization of the central pacemaker and that circadian rhythm dysregulation constitutes a hallmark of mood disorders (Dallaspezia & Benedetti, 2015; Harvey, 2008, 2011; McClung, 2013). Physiological, biochemical processes and behavioural patterns have a circadian rhythmicity orchestrated by the master biological clock of the hypothalamus: the suprachiasmatic nuclei (SCN). The expression of many genes changes rhythmically over 24 hr: specific circadian genes such as CLOCK, BMAL1 and PER are responsible for the main SCN clock-working machinery as well as subsidiary clocks in other parts of the body (McClung, 2013). The SCN is also synchronized daily by environmental signals – mainly by light but also by some behaviours such as food intake, activities or social cues (McClung, 2013). While receiving and integrating information, the SCN drives secretion of the hormone melatonin, via the pineal gland and many peripheral clocks and their outputs, and modulates the SCN through feedback or feedforward effects. Rhythmic clock gene expression regulates multiple monoaminergic brain regions that control mood and motivational behaviours, stress and inflammatory systems, reward circuits, arousal and sleep by interacting with the homeostatic regulation of sleep and wake (McClung, 2013). In individuals with mood disorders, mutations in the circadian clock genes might

predispose to mood disruption by impairing the capacity to adapt to environmental deviation in daily schedules. In particular, individuals with mood disorders have shown a circadian rigidity and the inability to adapt, especially to seasons, sleep deprivation, shift work, jet leg and stressful events, thus misaligning the internal biological clocks and in turn altering monoamine transmission, HPA-axis and immune functions, motivational behaviours, reward sensitivity, hippocampal neurogenesis and neuropeptide signalling (McClung, 2013).

2.6.2 | Role of insomnia and experimentally induced sleep loss

Circadian sleep regulation and homeostatic sleep processes are mutually linked in regulating sleep and wake (Borbély, Daan, Wirz-Justice, & Deboer, 2016). Recently, animal studies have provided strong evidence for the role of disrupted sleep in circadian dysregulation: it can have a profound influence on circadian sleep regulation by altering the rhythmic expression of clock genes (for a review, see Archer & Oster, 2015). In a study from Maret et al. (2007), sleep deprivation in mice was shown to lead to an 80% reduction in rhythmic transcripts in the brain. The effect of sleep loss/deprivation in humans has been revised from Archer and Oster (2015). The authors have shown that chronic sleep loss and insufficient sleep may have consequences on core clock gene expression. In particular, authors have shown that 1 week of insufficient sleep may alter core clock gene expression in human blood cells: the affected genes have shown to be particularly involved in transcription and translation, as well as in inflammatory and stress responses reducing the amplitude of circadian rhythms and intensifying the effects of subsequent acute total sleep loss on gene expression (Archer & Oster, 2015; Möller-Levet et al., 2013).

Therefore, sleep deprivation and/or insufficient sleep have been hypothesized to negatively influence circadian rhythmicity by altering the rhythmic expression of core clock genes associated with transcription, translation, inflammatory and stress responses. These effects induced by sleep restriction/deprivation may account, in part, for a vulnerability to develop circadian dysregulation and, in turn, to develop a mood disorder. A bidirectional relationship between daytime affect regulation and nighttime sleep has also been hypothesized such that an escalating vicious circle of disturbance in affect regulation during the day interferes with nighttime sleep/circadian functioning and vice versa (Harvey, 2008, 2011). Within this framework, sleep disruption may be related to both a vulnerability to develop mood disorders, by altering the expression of clock genes, but also to its maintenance by impairing sleep/circadian functioning (Figures 1 and 2).

2.7 | Orexinergic system dysregulation in mood disorders

2.7.1 | Summary of evidence

The results of several recent studies have led to propose the involvement of the orexinergic system in the pathophysiology of

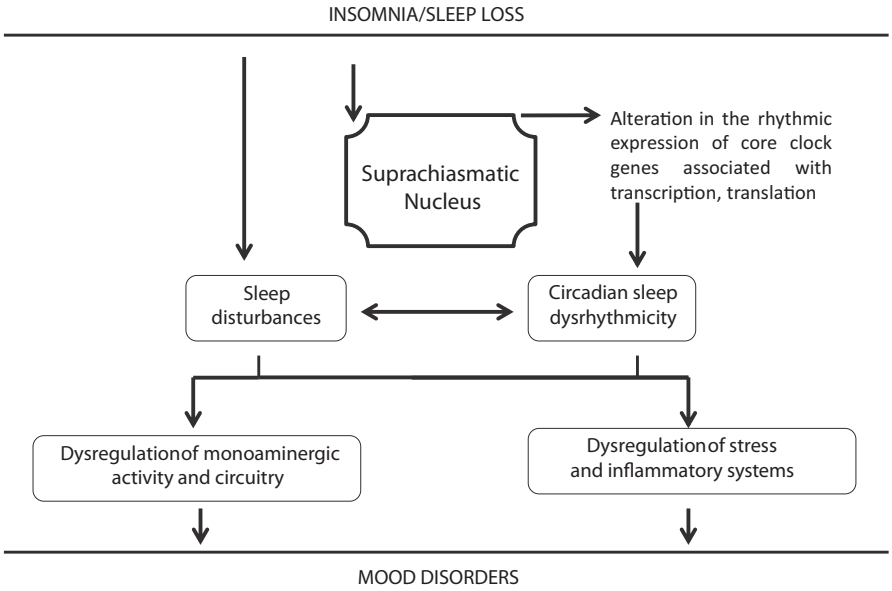

FIGURE 2 The circadian hypothesis of mood disorders: role of sleep loss. Sleep deprivation can negatively influence circadian rhythmicity by altering the rhythmic expression of core clock genes associated with transcription, translation, inflammatory and stress responses. These effects induced by sleep disruption dysregulate the circadian rhythmicity of monoamine, stress and inflammatory systems, and consequently of neurotrophic support and hippocampal neurogenesis. It has also been hypothesized that there is a bidirectional relationship between daytime affect regulation and nighttime sleep such that an escalating vicious circle of disturbance in affect regulation during the day interferes with nighttime sleep/circadian functioning and vice versa. Within this framework, sleep disruption may be related to both a vulnerability to develop mood disorders by altering the expression of clock genes and also to its maintenance by impairing the sleep/circadian functioning machine

mood disorders. The orexinergic system orchestrates various aspects disturbed in mood disorders, such as sleep and arousal, behavioural and neuroendocrine responses to stress, reward-seeking behaviours, energetic homeostasis, learning and memory, and in this is case this is achieved via direct projections to the medial prefrontal cortex (Chieffi et al., 2017; Li, Hu, & de Lecea, 2014a; Li et al., 2014b). Orexinergic neurons receive a variety of signals related to environmental, physiological and emotional stimuli, and project broadly to the entire central nervous system: the hypothalamic orexin system directly and strongly innervates and excites noradrenergic, dopaminergic, serotonergic, histaminergic and cholinergic neurons. Orexin also has a major role in modulating the release of glutamate and other amino acid transmitters, and in enhancing hippocampal neurogenesis (Chieffi et al., 2017; Li et al., 2014a,2014b). Orexin deficiency results in learning and memory deficits and mood dysregulation (Yeoh et al., 2014). In recent human studies, a polymorphism in Orx-1 receptor gene has been associated with major mood disorders, and hypoactivity of the orexin system has been found in subjects with mood disorders (Yeoh et al., 2014). Especially the interaction between chronic stress and orexin peptides appears to be involved in the pathogenesis of mood disorders. It has been hypothesized that chronic or repeated exposure to stress may downregulate orexin system function and, consequently, the hypoactivity of the orexin system may impair the ability to adapt to stress leading to dysregulated mood (Chieffi et al., 2017; Li et al., 2014a,2014b; Yeoh et al., 2014).

2.7.2 | Role of insomnia and experimentally induced sleep loss

Orexins have emerged as master regulators of the sleep–wake cycle (for an overview, see Mieda, 2017). The role of orexin in regulating the sleep–wake cycle was first discovered in relationship to narcolepsy: in fact, most people with narcolepsy (90%) are orexin-deficient. Conversely, overexpression of the orexinergic system has been shown to fragment and disrupt sleep leading to an inability to sustain sleep in animals (Mieda, 2017), and experimental sleep deprivation has been shown to lead to an overactivation of orexin peptides. Recently, a study conducted in individuals suffering insomnia showed elevated levels of orexin peptides in relation to the course and severity of insomnia (Tang et al., 2017). Based on clinical and experimental evidence, recent guidelines have suggested the use of the orexin receptor antagonist in the treatment of chronic insomnia (Sateia et al., 2017).

Summarizing these data within a framework relating sleep, stress and the orexin system, we may hypothesize that insomnia or sleep deprivation may act as a neurobiological stressor impairing the stress system (McEwen, 2006; McEwen & Karatsoreos, 2015; Meerlo et al., 2008, 2015) and downregulating the orexin system in the long term. A dysregulation in the orexin system may then affect arousal, behavioural and neuroendocrine responses to stress, reward-seeking behaviours, learning and memory being thus involved in the development and maintenance of mood disorders (Figure 1).

2.8 | Emotion dysregulation model of mood disorders

2.8.1 | Summary of evidence

Several models of mood disorders assume the crucial role of emotion dysregulation as a critical component in the development and maintenance of mood disorders (for an overview, see Gross & Thompson, 2011; Hofmann et al., 2012; Wessa & Linke, 2009). Emotional regulation is a complex process that includes the modulation of early emotional processes, the appraisal and evaluation of stimuli and emotional response with its behavioural and physiological components (for an overview, see Wessa & Linke, 2009). Emotion dysregulation, which occurs when there are problems with any of these regulatory dimensions in both the immediate context of the situation and in the long-term objectives/goals of individuals, has been proposed as a critical component of mood disorders by dynamic loop-reinforcing mood dysregulation (Gross & Thompson, 2011; Hofmann et al., 2012; Wessa & Linke, 2009). Particularly emotional hyper-reactivity has been related to mood instability, impaired decision-making, aggressive and impulsive behaviours, increased risk of substance abuse, and vulnerability to suicidal ideation and attempts in individuals with mood disorders (Gross & Thompson, 2011; Hofmann et al., 2012; Wessa & Linke, 2009). Cognitive control of emotion that is crucial for adaptive functioning (Crocker et al., 2013; Wessa & Linke, 2009) is impaired in mood disorders and may lead to an impairment in the decision-making process (Crocker et al., 2013; Marvel & Paradiso, 2004). Cognitive and emotional dysregulations also interact with reward-processing abnormalities in mood disorders, which drives goal-directed behaviours, reward learning and reward-based decision-making. In particular, depression is characterized by a reduced ability to modulate behaviour as a function of reward, and both mania and hypomania are positively related with reward hypersensitivity (for an overview, see Crocker et al., 2013; Whitton et al., 2015). Several neurobiological studies that have focused on the link between emotional dysregulation and mood disorders (Hofmann et al., 2012; Wessa & Linke, 2009) have shown dysfunction in the brain serotonergic and dopaminergic systems in both the pathophysiological mechanisms of mood disorders and in emotion dysregulation. Emotion regulation depends on the interaction between a complex circuit of brain structures consisting of the frontal cortex, amygdala, anterior cingulate cortex and several other interconnected regions. Particularly a dysfunction in the amygdala-frontal circuit has been related to emotion dysregulation observed in mood disorders due to a compromised connectivity between the prefrontal cortex and limbic regions such as the amygdala with impairment in the top-down regulation of emotions (Johnstone, Van Reekum, Urry, Kalin, & Davidson, 2007; Wessa & Linke, 2009). Studies of reward tasks have demonstrated alterations in the reward networks, including nucleus accumbens striatal areas, caudate and of the left prefrontal cortex orbitofrontal cortex and the anterior cingulate cortex in mood disorders, which are implicated in the assessment of risk and reward and in predicting response value (Chaudhury et al., 2015).

2.8.2 | Role of insomnia and experimentally induced sleep loss

Sleep has important functions that are fundamental for the regulation of emotion, reward system and cognition (Abel, Havekes, Saletin, & Walker, 2013; Fairholme & Mamber, 2015; Goldstein & Walker, 2014; Perogamvros & Schwartz, 2015; Raven et al., 2017; Van Someren et al., 2015; Walker, 2009, 2010; Walker & van der Helm, 2009). Insomnia and sleep loss have been proposed to lead to maladaptive emotional regulation, and consequently to exaggerated neural and behavioural reactivity to experiences and reward (Altena et al., 2016; Baglioni et al., 2010; Boudebesse & Henry, 2012; Gujar et al., 2011; Krause et al., 2017; McKenna & Eyler, 2012; Yoo, Gujar, Hu, Jolesz, & Walker, 2007). In addition, they are related to impairments in basic cognitive functions and higher-order cognitive processing of executive functions involved in supervisory control, problem-solving, flexibility, self-control and decision-making (Killgore, 2010; Krause et al., 2017; Ma, Dinges, Basner, & Rao, 2015; Pilcher, Morris, Donnelly, & Feigl, 2015; Raven et al., 2017; Rossa, Smith, Allan, & Sullivan, 2014; Simon et al., 2015; Venkatraman, Chuah, Huettel, & Chee, 2007), as well as to impulsive and aggressive behaviours (Acheson, Richards, & de Wit, 2007; Kamphuis et al., 2014; Rossa et al., 2014) and, consequently, to the increased risk of suicidality (for an overview, see Woznica et al., 2015). At the neural level, neuroimaging studies have revealed that emotional and reward networks are activated during sleep. Such activation may promote the reprocessing of emotional or rewarded information during sleep and dreaming, and optimize affective regulation and behavioural responses during wakefulness (Gujar et al., 2011; McKenna & Eyler, 2012; Perogamvros & Schwartz, 2015; Van Someren et al., 2015). Prolonged sleep deprivation instead has been associated with enhanced emotional reactivity signified by increased limbic activation in response to negative emotional stimuli, specifically within the amygdale, and also to a disinhibition of mesolimbic dopaminergic networks mediating reactivity to pleasurable and rewarding experiences (Gujar et al., 2011; Perogamvros & Schwartz, 2015; Van Someren et al., 2015; Venkatraman et al., 2007). Sleep deprivation may therefore be associated with amplified reactivity across the full range of affective valence, both positive and negative, thus potentially contributing to reported deficits in judgement and decision-making related to sleep disruption (Gujar et al., 2011; Perogamvros & Schwartz, 2015; Van Someren et al., 2015; Venkatraman et al., 2007). Impairment in the top-down modulation of emotional processing has been evidenced when sleep is disturbed (Gujar et al., 2011; Krause et al., 2017; Yoo et al., 2007): a dysfunction in the neural circuitry underlying emotion regulation has also been observed in individuals suffering from insomnia. Changes observed in brain structures in individuals with insomnia reveal a reduction in the volume of the prefrontal cortex and an increase in the amygdala volume (for an overview, see Riemann et al., 2015). There is considerable evidence to suggest that sleep disruption impairs cognitive functioning involved in the decision-making process, including simple tasks involving attention and vigilance and also high-order cognitive processes, especially executive functions that are largely controlled by the neural activity within the prefrontal cortex.

Further, there are data suggesting that in individuals suffering insomnia, there is reduced functional connectivity between parietal and medial prefrontal cortices that have been related with an impairment in executive function (Li et al., 2014a,2014b). This finding is substantiated through studies of experimental sleep loss that have shown that sleep disruption significantly reduces the functional connectivity in frontal brain regions, including the ventromedial regions involved in making decisions based on learning of reward and punishment contingencies (Ma et al., 2015; Raven et al., 2017; Van Someren et al., 2015). The relationship between insomnia and aggressive and impulsive behaviours may also be mediated by the negative effect of sleep loss on prefrontal cortical functioning (Kamphuis et al., 2014). It is likely that this impact on prefrontal cortical functioning contributes to loss of control over emotions, including loss of the regulation of aggressive impulses to context-appropriate behaviours (Kamphuis et al., 2014). In conclusion, insomnia and insomnia-related sleep disruption seem to negatively affect brain regions deputized to emotion, motivation and cognition regulation, thus contributing to emotional dysregulation and impaired decision-making processes leading to impulsive and aggressive behaviours, impairment in reward system and motivation, leading to disturbances in hedonic state and motivational behaviours, which, in turn, contribute to the development and maintenance of mood disorders (Figures 1 and 3).

3 | CONCLUSIONS

Because sleep disturbances, particularly insomnia and sleep loss, contribute to the development and maintenance of mood disorders, which are the most prevalent and severe diseases in psychiatric practice, the aim of this paper was to review the literature regarding their potential role in the pathogenesis of mood disorders. This overview provides a comprehensive model of the multiple hypotheses that have been suggested for mood disorders and may explain, in part, the considerable overlap between sleep disturbances and mood disorders that has emerged from clinical studies. We propose a model in which sleep plays a key role in the regulation of those multiple systems involved in the pathogenesis of mood disorders: these different mechanisms might fit together and contribute to mood disorders when the sleep machinery is impaired (Figure 1).

Particularly, sleep disruption due to either insomnia or sleep restriction/deprivation/loss seems to contribute to mood disorders essentially throughout three mechanisms.

Firstly, the to-date most acclaimed hypothesis, sleep disruption may act as a neurobiological stressor leading to different and multiple consequences, such as: (a) an overactivation of the stress system which may negatively influence hippocampal neurogenesis, brain plasticity and connectivity in the prefrontal cortex and in the brain regions that regulate mood, emotion and cognition; (b) a state of chronic inflammation that may have a negative effect on serotonin

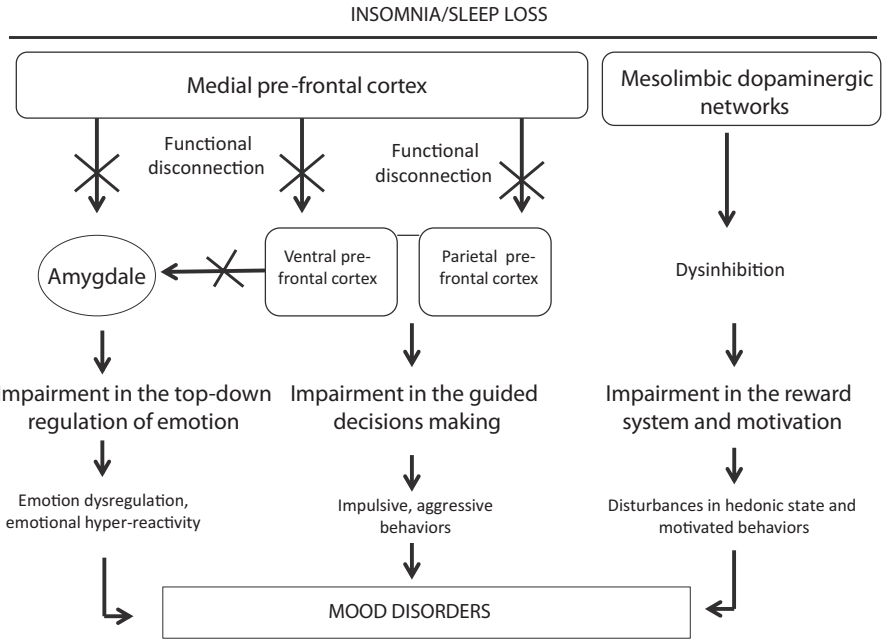

FIGURE 3 Emotion dysregulation model of mood disorders: role of insomnia and sleep loss. Insomnia and conditions of sleep deprivation have been hypothesized to be related to an impairment in the top-down modulation of emotional processing: a dysfunction in the neural circuitry underlying emotion regulation has been observed in subjects with insomnia. Changes that have been observed in brain structures in subjects with insomnia include in fact a reduction in the volume of the prefrontal cortex and an increase in the amygdala volume, and a functional disconnection between the prefrontal cortex and the amygdala has been hypothesized when sleep is disturbed. This may lead to an emotional hyper-reactivity and dysregulation that may contribute to maintain mood disorders. In subjects with insomnia, there is a brain reduced functional connectivity between parietal and medial prefrontal cortices, which has been related with an impairment in executive function. This finding is sustained by data from experimental sleep loss showing that sleep deprivation significantly reduces the functional connectivity in frontal brain regions, including the ventromedial regions involved in making decisions based on learning of reward and punishment contingencies. Insomnia may thus favour mood disorders development and maintenance by impairing the prefrontal cortex functionality and dysregulating cognitive functions involved in emotion and motivation regulation, in turn, impairing the decision-making process. These alterations have been related with a loss in emotional control, tendency to risky decisions, impulsive and aggressive behaviours that may contribute to perpetuate mood disorders. Sleep deprivation has been related to a disinhibition of the mesolimbic dopaminergic networks that mediate reactivity to pleasurable and rewarding experiences. We may have hypothesized that this mechanism may contribute to alterations in hedonic states and motivational behaviours, which are characteristics of mood disorders

production and neurotropic brain support with a feedforward cascade of HPA-axis and stress system; (c) monoaminergic system dysregulation with alterations in serotonin production and in the dopamine system; (d) a reduction in neurotrophic factors, especially BDNF, thus impairing synaptic plasticity and neurogenesis (Figure 1). Recently, some data supported the hypothesis that sleep disruption by acting as a neurobiological stressor may also act on the glutamate system, and by increasing levels of glutamate may impair brain plasticity. Indeed, this hypothesis needs to be confirmed in further studies that also involve human subjects with disturbed sleep. Also, some data in humans with insomnia and poor sleep quality indicated a role of disrupted sleep as a stressor on the orexinergic system: by elevating levels of orexin peptides the down regulation of the orexin system may affect the long-term behavioural and neuroendocrine responses to stress, reward-seeking behaviours, learning and memory (Figure 1). Indeed, these data may be considered as preliminary findings, and further empirical data need to be gathered to support this hypothesis.

Secondly, in the last few years, the role of sleep in emotion regulation has been widely studied, and it has emerged that emotion dysregulation is related to both insomnia and sleep loss. These conditions of disrupted sleep may impair the entire emotion regulatory machine, by weakening, functionally, the top-down modulation of emotional processing and the entire process of decision-making by altering the functional connectivity of parietal and medial prefrontal cortices. Furthermore, sleep disruption has been related to a disinhibition of the mesolimbic dopaminergic networks, thus disturbing the reactivity to pleasurable and rewarding experiences. Brain circuits that appear to undergo either a functional or structural impairment when sleep is disrupted are those whose alteration is also involved in the pathogenesis of mood disorders (Figures 1 and 3). Thirdly, sleep loss/deprivation may impair circadian rhythmicity by altering the rhythmic expression of core clock genes in the SCN and in turn altering, amongst others, the circadian regulation of stress, inflammatory and monoaminergic systems and neurotrophic support. These effects induced by sleep disruption may favour the development of a circadian dysregulation, which is a key factor in mood disorders (Figures 1 and 2). Indeed, the role of insomnia in circadian dysregulation needs to be further explored and should be a topic of interest in future research.

In conclusion, on the basis of the existent literature and under the light of the functions of sleep, we may hypothesize that such sleep disturbances may act as a causal factor in mood disorders, by particularly acting as a stressor or by altering the process of emotion regulation or modifying the circadian regulation of the body. Thus, to assess and target sleep disturbances in clinical practice should be a priority in order to prevent and treat mood disorders.

These evidences may also suppose that such sleep problems may be due to prodromal mood disorders. The trajectories of both sleep and mood disorders across the lifespan should be the topic of further studies in order to establish causality.

CONFLICT OF INTEREST

No conflicts of interest are declared.

AUTHORS' CONTRIBUTIONS

All authors have seen and approved the manuscript, and have contributed significantly to the paper.

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