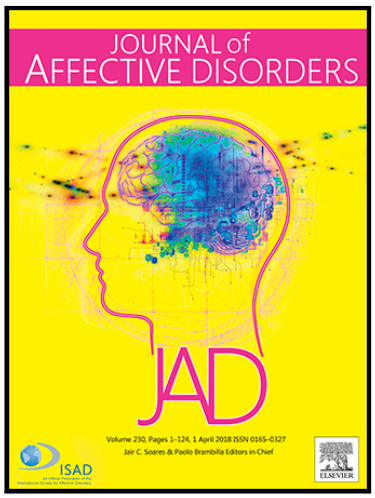

Developmental pathways towards mood disorders in adult life: is there a role for sleep disturbances?

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Highlights

- -Mood disorders rank high among to the leading global burdens of disease.
- -Developmental psychopathology can offer a life course perspective on them thus providing a basis for early prevention and intervention.
- -Sleep disturbances are risk factors for mood disorders across the entire life course and may constitute a developmental pathways towards mood disorders in adult life.
- -Studies revealed that exposure to prenatal/early life stress results in sleep disturbances and may predict or even precipitate mood disorders in adulthood.
- -Chronic sleep disruption may interfere with neuronal plasticity, connectivity and the developing brain thus contributing to the development of mood disorders.
- -Sleep and circadian dysregulations have been shown to be related to those temperaments, character and attachment styles which are considered precursors of mood disorders.
- -Sleep and circadian behaviours may serve as early targets regarding mood disorders.

Developmental pathways towards mood disorders in adult life: is there a role for sleep disturbances?

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Running head: **Sleep disturbances and developmental pathways towards mood disorders**

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Abstract

Introduction

Mood disorders are among the most prevalent and serious mental disorders and rank high among to the leading global burdens of disease. The developmental psychopathology framework can offer a life course perspective on them thus providing a basis for early prevention and intervention. Sleep disturbances, are considered risk factors for mood disorders across childhood, adolescence and adulthood. Assuming that sleep disturbances may play a pivotal role in the pathogenesis of mood disorders from a life course point of view, we reviewed the data on developmental pathways towards mood disorders in adult life in relation to sleep disturbances.

Method. From February 2017, a systematic search was conducted in PubMed, PsycINFO and Embase electronic databases for literature on developmental pathways to mood disorders in adult life in relation to sleep disturbances and to 1) pre-natal stress, 2) early brain developmental processes, and 3) temperaments, character and attachment style.

Results. Eleven, 54 and 15 articles were respectively selected.

Conclusions. Experimental and clinical studies revealed that exposure to prenatal/early life stress results in sleep disturbances such as poor sleep and altered circadian regulation phases and may predict or even precipitate mood disorders in adulthood. Chronic sleep disruption may interfere with neuronal plasticity, connectivity and the developing brain thus contributing to the development of mood disorders. In addition sleep and circadian dysregulations have been shown to be related to those temperaments, character and attachment styles which are considered precursors of mood disorders. Sleep and circadian behaviours may serve as early targets regarding mood disorders.

Declaration of interest: None

Key words: mood disorders, sleep disturbances, insomnia, circadian disorders, developmental pathways, pre-natal stress, early brain developmental processes, temperaments, character and attachment style

Introduction

Mood disorders refer to a group of diagnoses in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013) classification system with a disturbance of mood as central feature. Mood disorders which encompass symptoms of elevated mood, such as mania or hypomania, as well as depressed mood, have been grouped into several sub-types according to clinical presentation, dominant features and course of the disorder (American Psychiatric Association 2013). Mood disorders are characterized by severely and/or prolonged altered mood, and among the others emotion and motivation dysregulation, cognitive problems in attention, concentration and decision making, changes in sleep with mainly insomnia and have a high risk for suicidality and suicide (Hofmann et al. 2012; Herny et al. 2012; APA 2013; Croker et al. 2013; Whitton et al. 2015).

Major forms, such as depressive unipolar and bipolar disorders, are among the most prevalent and serious disorders with a tendency to be recurrent, chronic and disabling (Kupfer et al, 2012; APA 2013; Schaffer et al. 2015) and constitute major public health problems ranking very high concerning leading global burdens of disease in terms of disability, morbidity and premature mortality. They also pose a growing challenge for health systems due to the high frequency of medical comorbidities and suicides related to them (Whiteford et al. 2013; Ferrari et al. 2014; Schaffer et al. 2015).

Developmental psychopathology is considered a conceptual framework for developmental mechanisms in adult psychopathology taking into account the role of the biological-gene-epigenetic environmental interplay starting from early life and evaluating developmental trajectories in the continuity/discontinuity of psychopathology from childhood throughout adulthood (for an overview see Rutter and Sroufe 2000; Rutter 2013). Thus, insights emerging from developmental psychopathological approaches provide an excellent basis for prevention and early intervention (O'Connell 2009). Increasing evidence suggests considerable longitudinal links between childhood-adolescence and adulthood mood disorders (for an overview see Rutter and Sroufe 2000; Rutter et al. 2006; Youngstrom 2010; Rutter 2013).

There is an increasing consensus that mood disorders should be considered neurodevelopmental disorder conditions, which have been hypothesized to begin in the prenatal life, to emerge in early life and persist throughout the adult life within the framework of the stress-vulnerability-model (Rutter et al. 2006; Youngstrom 2010). In this model, risk markers for mood disorders in adulthood include genetic factors interacting with environmental stressors possibly moderated by epigenetic mechanisms, disturbances in early attachment and bonding experiences, diverse cultural influences that all shape the developing juvenile brain that is designed to learn from experience and to control emotion and cognition (Angst 2000; Alloy et al. 2006; Miklowitz and Chang 2008; Youngstrom 2010; Klein et al. 2011; Papoušek 2011; Domschke and Reif 2012; Rutter 2013; Duffy et al. 2015; Nolvi et al. 2016, Barate).

Insomnia and circadian sleep disorders are the sleep disturbances most frequently observed before and during an episode of mood disorder (Franzen and Buysse 2008; Harvey 2009; Harvey 2011). Hypersomnia may also be a clinical feature of mood disorders but less likely compared to insomnia being more commonly related to another sleep disorders including sleep disorders breathing (Barateau et al. 2017; Geoffry et al 2018). Notably, insomnia and circadian sleep disturbances are observed across childhood-adolescence and adulthood (Harvey et al. 2006; Franzen and Buysse 2008; Stanton 2008; Harvey 2009; Harvey 2011; Randler 2016) and found to be associated with an increased risk of developing depressive and bipolar disorders across the lifespan (Harvey 2006; Stanton 2008; Harvey 2009; Baglioni et al. 2011; Glozier et al. 2014; Steinan et al. 2016; Sivertsen et al. 2017; Pigeon et al. 2017). These sleep disturbances have been related to illness severity, relapse and recurrence, and symptoms such as cognitive impairment, aggressiveness, impulsive and risky behaviors, anxiety, emotional hyper-reactivity and increased risk of substance abuse and suicide rates (Benedetti et al. 2003; Stein and Friedmann 2005; Harvey et al. 2006; Franzen and Buysse 2008; Benedetti et al 2008; Harvey 2009; Gruber et al. 2011; Geoffry et al. 2015; Rumble et al. 2015; Benedetti et al 2015; Woznica et al. 2015; Lopes et al. 2016; Kanady et al. 2017).

Moreover, sleep is timed to occur at a specific phase in the circadian cycle, which is regulated by the hypothalamic body clock (Wulff 2012). This clock is functional before birth but needs to be entrained during the postnatal period, to be in synchrony with external rhythms, the most predictable being the environmental day-night cycle (Wulff and Siegmund 2002). All physiological body functions (i.e. rest/activity, core body temperature, feeding/metabolism, blood pressure, heart rate, immunity) follow cyclic patterns thereby striving for diurnal adaptation via local oscillators in the brain and body. Still, individuals can over-ride the clock's signal and act immediately to changes in the environment (so-called masking) which - depending on the temporal and spatial direction - can be beneficial or disruptive to the developing circadian timing system (Rietveld et al. 1993). Sleep is regulated by complex physiological processes where circadian mechanisms and homeostatic sleep processes are mutually linked (Borbely et al. 2016). Beyond, sleep itself serves

important regulatory functions and is considered a key factor in early Central Nervous System development implicated in normal brain connectivity and plasticity (Dahl 1996; Dang-Vu et al. 2006; Dahl 2007; Ringli and Huber 2011; Tononi and Cirelli 2014; Cirelli and Tononi 2015; Kurth et al. 2016; Cirelli and Tononi 2017). Additionally, sleep plays an important role in the regulation of emotions, motivation, decision-making and cognition (Gujar et al. 2011; McClung 2013; Abel et al. 2013; Goldstein and Walker 2014; Altena et al. 2014; Van Someren et al. 2015; Raven et al. 2017), the dysregulation of which is a key factor in mood disorders. Sleep disturbances as a reflection of allostatic load and the accumulation of stress-comprised regulatory processes (e.i. co-morbidities, neglect, maltreatment of children), are all implicated in the development and maintenance of mood disorders across the life span (Hoffmann et al 2012, McClung 2013; Harrison and Baune 2014; Whitton et al 2015; Dueck et al. 2017).

On the basis of these lines of evidence, the hypothesis of the review is that sleep disturbances, with focus on insomnia as a condition of sleep loss, and abnormal sleep timing may play a pivotal role in the development and maintenance of mood regulatory problems from a life course point of view by negatively influencing their developmental pathways starting from the pre-natal/-early life. To this aim we review the role of sleep disturbances on developmental pathways towards mood disorders in adult life in relation to 1) pre-natal stress which has been shown to negatively influence the individual stress-diatheses predisposing in the development of mood disorders (Bale et al. 2010; Kim et al. 2015; Syed and Nemeroff 2017); 2) early brain developmental processes (Paus et al. 2008; Arain et al. 2013) and 3) temperaments, character and attachment style which play a relevant role in the vulnerability/resilience to mood disorders (Cloninger et al 1993; Akiskal 1995; Bowlby 1988; Mikulincer and Shaver 2012).

This overview about the psychobiological and mechanistic role of sleep and circadian rhythm disruption for the developmental pathways of mood disorders is thought to provide an integrative framework to link childhood-adolescence and adulthood mood disorders. It may be useful from a clinical point of view to adopt this life course approach on mood disorders by

evaluating, assessing and treating sleep disturbances in a holistic approach thereby recognizing the potential for early interventive and preventive strategies.

Method

From February 2017 a systematic search was conducted in PubMed, PsycINFO and Embase electronic databases were searched for literature on developmental pathways to mood disorders in adult life in relation of sleep and sleep disturbances. The investigative approach aimed at including articles on human and animal models with extrapolative value for human mood disorders. An attempt was made to highlight original concepts in the developmental pathways to mood disorders across the life course in relation to insomnia and circadian sleep disturbances. Several combinations of search terms were used such as: “developmental pathways to mood disorders " or “pre-natal stress and mood disorders” or “early brain developmental processes and mood disorders” or “personality, temperament, character” or” attachment style” and mood disorders” and “sleep disruption” or “sleep deprivation” or “sleep restriction” or “sleep loss” or “insomnia” or “circadian sleep rhythms disorders”. Investigative work on animals and humans as well as review articles were assessed. Finally, the data were integrated into a narrative review. We reviewed the role of sleep disturbances on developmental pathways towards mood disorders in adult life in relation to 1) pre-natal stress (n. 11 articles), 2) early brain developmental processes (n. 54 articles), and 3) temperaments, character and attachment style (n. 15 articles). Each paragraph will be preceded by a brief summary of the hypotheses.

1) Prenatal/early life stress and mood disorders: may disturbed sleep be a link to mood disorders in later life?

Review of evidence

Research into the developmental pathways of neuropsychiatric disorders suggests that the underlying mechanisms are multifactorial, i.e. complex-genetic with an interplay of genetic factors (G) – with heritability estimates ranging from about 30 to 80% – and environmental (E) influences in a G x E interaction model (Domschke and Reif 2012; Guintivano and Kaminsky 2016 Ludwig and Dwivedi 2016; Syed and Nemeroff 2017). Within this framework, a key role of "pre-natal/early life programming" of mental health outcomes including mood disorders has been proposed (Bale et al. 2010; Kim et al. 2015; Syed and Nemeroff 2017): prenatal and postnatal periods are assumed to constitute highly important and sensitive periods during the development of an individual suggesting those periods as "windows of vulnerability" and extending the G x E model to a G x E x T (timing) concept (Lupien et al. 2009; Maccari et al. 2014; Schiele and Domschke 2017). Evidence from preclinical studies indicates that the developing brain is particularly sensitive to remodeling by environmental factors: adverse early-life experiences, such as stress exposure in the prenatal life or early life adverse experience, can have long-lasting negative consequences on mental health. Early life stress may negatively influence fetal brain plasticity, especially the pre-frontal cortex and the hypothalamic-pituitary-adrenal (HPA) axis and stress system regulation, which are critical for the modulation of physical growth and cortico-limbic processes related to the regulation of emotion and cognition (Chocyk et al. 2013; Bock et al. 2015). It has been hypothesized that prenatal/early life programming may in part occur throughout epigenetic mechanisms by which prenatal/early life environmental stressors may change genes expression during this highly sensitive time period for the developing brain (Provençal and Binder 2015). DNA methylation and histone modifications are the most commonly studied epigenetic mechanisms (Schuebel et al. 2016), by which cell structure and function can be altered during embryogenesis thus impairing early brain development with permanent changes in neuroendocrine functions that impact the child's capacity to manage stress, focus attention and flexibly adapt to the environment in later life (Talge et al. 2007; Lewis et al. 2014; Maccari et al. 2014; Kim et al. 2015; Bock et al. 2015).

Prenatal stress can be triggered by maternal psychological stressors such as maternal mental illness and sleep disturbances, both affecting the fetus' vagal tone nutritional problems and physiologic factors (Talge et al. 2007; Lewis et al. 2014; Palagini et al. 2014; Palagini et al. 2015; Kim et al. 2015). Continuous maternal stress during pregnancy exerts negative programming effects on the developing fetus by enhancing fetal exposure to glucocorticoids and inflammation, in turn negatively influencing fetal HPA axis and the stress system that are critical for the modulation of physical growth, sleep regulation, and limbic-pre frontal cortical processes (Dugovic et al. 1999; Koehl et al. 1999; Talge et al. 2007; Lewis et al. 2014; Kim et al. 2015; Palagini et al. 2015; Fatima et al 2017). Also, early postnatal periods are highly sensitive time periods for the developing brain. During this time window, exposure to adverse experiences has been hypothesized to lastingly impact cognitive and emotional development by HPA axis and stress system alteration impairing later hippocampal and prefrontal cortex functions, while increasing amygdala activity, sensitivity to stressors and emotional behavior later in life (Cicchetti 2016). Thereby, pre-natal/ early life exposure to adverse conditions may trigger epigenetic processes that increase the sensitivity to develop stress-related disorders in adult life, including anxiety and mood disorders (for an overview see Krugers et al. 2016).

Role of sleep and sleep disturbances

Sleep is an observable behaviour that happened to be influenced by pre-natal/early stress as evidenced by both animal and human research. Animal studies have shown that pre/postnatally-imposed early life stress may cause disrupted/fragmented sleep and circadian timing alterations by repeatedly impairing circadian and homeostatic regulation of sleep (Dugovic et al 1999; Koehl et al. 1999; Rao et al. 1999; Kennaway 2002; Mrdalj et al 2013).

Studies in humans have shown that prenatal stress may negatively influence sleep regulation in the newborns leading to disorganized sleep patterns, poor sleep and short sleep duration until 1-2 years

of age (Palagini et al 2014; Palagini et al. 2015). Early life adverse events, including maternal antenatal depression, family conflicts, poor mother or father relationships childhood maltreatment or abuse have been related to sleep disturbances in childhood throughout adulthood (Palagini et al 2014; Palagini et al. 2015).

Since sleep disturbances, especially insomnia and circadian sleep rhythms disorders, have been associated with an increased risk of developing depressive and bipolar disorders (Harvey 2009; Baglioni et al. 2011; Glozier et al. 2014; Steinan et al. 2016; Sivertsen et al. 2017), sleep problems have been suggested to be mediators between early adversities and the risk of the development of mood disorders (Aas et al. 2016; Duffy et al. 2016). Ongoing disturbed sleep after prenatal-/early life stress may be a warning sign reflecting vulnerability markers for stress-related disorders that can lead to clinically relevant anxiety and mood disorders. Exposure to early life stress may shape the developing central nervous system, thereby profoundly influencing major brain reorganization, which may include sleep regulation. Indeed, longitudinal data from a population-based cohort, the Generation R Study (Jaddoe et al. 2008), showed that sleep disturbances from parental reports declined from the age of 2 and 3 years to the age of 7, but a dose-response relationship with smaller grey matter volume was found across the sleep disturbance trajectories until the age of 7 years (Kocevska et al. 2017). Sleep is a fundamental process essential for many physiological and psychological functions including brain synaptic plasticity and connectivity (Dang-Vu et al. 2006; Tononi and Cirelli 2014; Raven et al. 2017; Cirelli and Tononi 2017), which are altered in mood disorders (for an overview see Drevets et al 2008; McKenna and Eyler 2012). These homeostatic sleep processes are mutually linked with circadian rhythms in regulating sleep and wake (Borbely et al. 2016) and interact in integrating sleep rhythms but also ultradian rhythmicity of hormone secretion, HPA axis and inflammatory system regulation, monoamine productions and neuronal plasticity. These systems are adversely affected by disrupted sleep and their dysregulation has been related to the pathophysiology of mood disorders (for an overview see McClung 2013; Frank 2016). We suggest that chronic sleep disturbances such as fragmented sleep, frequent awakenings and

circadian maladaptations related to early life stress contribute to the development of mood disorders via the impairment of underlying plasticity processes leading to altered connectivity and communication within and between brain regions involved in the regulation of mood (for an overview see Meerlo et al. 2015; Kreuzman et al. 2015; Raven et al. 2017). Poor sleep and circadian disruption have been suggested to be stressors themselves that may enhance the effect of other stressors, thus contributing to the cumulative wear and tear on body systems (McEwen and Karatsoreos 2015). Finally, in interacting with the above-mentioned environmental factors, sleep and sleep-related disorders are governed by genetic/epigenetic mechanisms, which partly overlap with those genetic/epigenetic risk factors for mood disorders (see Palagini, Biber et al. 2014). Within this theoretical framework, we may hypothesize that epigenetic processes following disturbed sleep due to pre-natal/ early life stress and possibly mediated by epigenetic processes may re-shape the individual's stress system, thereby contributing to an increased vulnerability to stress-related disorders in the long term. In addition, since sleep is vital for homeostatic and regulatory functions and plays a key role in fetal, early neonatal and teen brain development (Dahl 2007; Peirano and Algarín 2007; Frank 2011; Frank and Cantera 2014; Frank 2015), we may hypothesize that early life stress may predispose to mood disorders by also impairing brain development for which sleep plays a key function (Maggi etal. 2013). In the last few years, mood disorders have started to be considered complex brain disorder and neurodevelopmental factors have been implicated playing their part in their pathophysiology (Sanches et al. 2008; Gaffrey et al. 2013). On the basis of the existent literature we may hypothesize that prenatal/early life stress may predict mood disorders in adulthood via sleep disturbances such as insomnia, fragmented sleep, poor sleep and circadian sleep dysregulation (Fig 1).

Please insert figure 1 here

2) Brain development and mood disorders: role of sleep disturbances in a brain under construction

Review of evidence

Several lines of evidence have demonstrated that mood disorders are complex-genetic disorders which involve anatomical and functional changes that have been hypothesized to originate in early brain development. Mood disorders are believed to arise in part from subtle defects in the development of the cerebral cortex, hippocampus, and other forebrain regions implicated in an abnormal maturation of brain structures involved in affect regulation (Sances et al. 2008; Versace et al. 2010; Gaffrey et al. 2013; O'Shea and McInnis 2015; Cao et al 2017; Gałecki and Talarowska 2018). Studies carried out with magnetic resonance imaging in children and adolescents have allowed charting of trajectories of age-related changes in brain structures, activities, connectivity and neurochemistry (for an overview see Paus et al. 2008; Arain et al 2013): across childhood and adolescence, the brain undergoes massive morphological changes such as cortical refinement, synapse growth, pruning, and white matter myelination. Particularly, volumes of cortical grey-matter appear to increase during childhood, reaching peak levels around the time of the puberty onset, after which they gradually decline; this is the case mostly for the frontal and parietal lobes. Volumes of white matter show a linear increase throughout childhood and adolescence, with the maximum volumes reached often as late as in the third decade of life. Changes in "synaptic pruning", a process by which "redundant" synapses overproduced in the early years of life are being eliminated, and myelination have been the most popular explanations for the structural findings in adolescence, whereas age-related alterations in neural connectivity and neurotransmission might underlie the functional changes associated with adolescence (Paus et al. 2008; Arain et al. 2013).

Neurobehavioral, morphological, neurochemical, and pharmacological evidence has suggested that the brain remains "under construction" until adolescence and this is probably why mood disorders tend to emerge during this period of life (Paus et al. 2008; Arain et al. 2013;Miguel-Hidalgo et al. 2013). The forming brain is in fact extremely sensitive to environmental factors, nutritional and

sleep habits, drug use, sex hormones, and neurocircuitry remains structurally and functionally vulnerable from pre-natal life across adolescence (for an overview see Arain et al. 2013; Miguel-Hidalgo 2013; Sinclair et al. 2014). Structural magnetic resonance studies of adolescents with affective disorders have reported structural anomalies in the superior temporal gyrus, ventral prefrontal cortex and amygdala (Paus et al. 2008; Arain et al 2013; Miguel-Hidalgo 2013). Particularly significant changes occur in the frontal lobe and limbic system during adolescence which may impact self-control, decision making, emotional and motivational systems favoring the development of mood disorders (Paus et al. 2008; Arain et al 2013). There is an increasing consensus that mood disorders should be considered neurodevelopmental disorders which have been hypothesized to begin with disturbances in the developing juvenile brain that control emotion and cognition (Rutter and Sroufe 2000; Rutter et al. 2006; Miklowitz and Chang 2008; Youngstrom 2010; Strakowski et al 2012; Duffy et al. 2015). Moreover, converging evidence affirm that behavioral performance is related both, to cortical activity in multiple regions, and to the integrity of the fibers connecting them (Baird et al. 2005). Optimal cognition and behavior depend on synchronous function among neural networks, which is ensured by myelination of white matter tracts (Lu et al. 2013). Lifespan studies showed that structural brain changes of white matter continue lifelong, and follow rates and timing of development, degradation and repair that vary regionally and do not follow linear patterns (Bartzokis et al. 2012; Lebel et al. 2012). In the case of mood disorders, spread abnormalities of diffusion-tensor imaging measures of white matter integrity have been described in cortico-limbic networks, and associated with core psychopathological symptoms, including cognitive deficits and affective instability (Benedetti et al. 2011; Poletti et al. 2015; Johnston, Wang et al. 2017). These structural abnormalities which are evident in patients at the beginning of illness, reflect altered developmental trajectories of anterior gray and white matter during adolescence (Najt et al. 2016), and are negatively influenced both, by common genetic variation underlying risk to mood disorders (Whalley et al. 2013), and by exposure to adverse childhood experiences (Benedetti et al. 2014, Poletti et al. 2018).

Role of sleep and sleep disturbances

Sleep is increasingly recognized as a key process in neurodevelopment and in brain optimization processes (for an overview see Franck 2011). Both human and animal data have shown that sleep is essential for maturation of fundamental brain functions, and epidemiological findings increasingly indicate that children with early sleep disturbances suffer from later cognitive, attentional, and psychiatric problems. From birth throughout preschool and early school age, children spend more time asleep than awake, and the amount of sleep they require exceeds the physiological sleep requirements of young adults: these modifications have been related to differences in age-related brain activity (for a review see Schimidt et al. 2012). In fact, from birth throughout infancy and early childhood, sleep patterns undergo dramatic changes which include the gradual consolidation of sleep and waking cycles, the intensification of deep NREM sleep slow-wave activity (EEG power in the 1–4.5 Hz frequency range), and a progressive decrease of REM sleep proportion that reaches adult levels around the age of 5 years. It has been suggested that REM sleep is an inducer of brain development and of early myelination in the sensory processing areas in the fetus and the neonate and that it follows the maturational trajectory of the brain (Mirmiran and Van Someren 1993; Marks et al. 1995; Peirano and Algarín 2007; Frank 2011; Feinberg et al. 2012; Kurth et al. 2015). Animal studies have shown that REM sleep has multifaceted functions in brain development, including learning and memory consolidation by selectively eliminating and maintaining newly formed synapses (Li et al. 2017). Also, slow-wave activity has been shown to undergo maturation in parallel with brain cortical morphology (Buchmann et al. 2011). Slow-wave sleep and sleep spindles (10–14 Hz) seem to be involved in synaptic remodeling, being important for synaptic strength and synchronized neuronal firing, and it has been shown that while following the trajectory of brain maturation they may orchestrate synaptic plasticity and pruning during brain development (Feinberg and Campbell 2010; Campbell et al 2011; Buchmann et al. 2011; Ringli and Huber 2011; Feinberg et al. 2012, Feinberg and Campbell 2013; Cirelli and Tononi 2015; Lindemann et al.

2016). Particularly, Ringli and Huber (201l) hypothesized that slow wave sleep may contribute to cortical maturation by playing a role in the balance of brain synaptic strengthening/formation weakening/elimination that is titled during development (Ringli and Huber 201l). Sleep, especially slow wave activity, has been hypothesized to normalize synaptic strength and shape plastic brain processes (Frank 2011; Kayser et al. 2014; Kurth et al 2015). In particular animal studies have shown that during critical periods of life, sleep is required for plastic processes underlying the maturation of specific brain circuits (Ringli and Huber 201l; Kayser et al. 2014; Kurth et al. 2015). Sleep promotes myelination and oligodendrocyte precursor cell proliferation (Bellesi et al. 2013), enhances transcription of genes involved in synthesis and maintenance of membranes and myelin (Cirelli et al. 2004) too, and modulate the neuronal membrane homeostasis (Hinard et al. 2012). Since adequate sleep has been proposed to be fundamental for brain development (for overview Dahl 2007; Ringli and Huber 201l; Kurth et al. 2015) sleep has received considerable research attention, as it appears to be important in the study of developmental psychopathology (for a review Paus et al 2008; Reid et al. 2009; Ringli and Huber 201l; Gregory and Sadeh 2012; Sadeh et al 2014; Kurth et al. 2015). Extensive data has shown that poor sleep in childhood and adolescence is associated with both internalizing and externalizing problems, predicts the development of cognitive, attentional, emotional and behavioral problems, including risk-taking and aggression, as well as psychiatric conditions, attention deficit hyperactivity disorder and mood disorders emerging in childhood and adolescence, and is related to alterations in brain development (Dahal et al 1996; Sadeh et al 2007; Gregory et al 2005; Touchette et al 2007; Reid et al 2009; Ringli and Huber 2011; Geiger et al 2011; Gregory and Sadeh 2012; Tesler et al 2013; Vriend et al 2013; Simola et al 2014; Owens et al. 2014; Sadeh et al 2014; Volk and Huber 2015). Measuring brain activity of children, whose sleep had been restricted, Kurth et al. (2016) found that sleep restriction in children could affect NREM slow wave sleep activity in association with connective brain activity and that this may have an effect on brain development (Kurth et al. 2016). The study included 13 children aged between 5 and 12 years and compared the effects of a normal night's sleep with a restricted night's

sleep, both with the same wake-up time. It was found that sleep restriction was related to some NREM slow wave sleep activity which was linked with structural changes to the myelin sheath in the brain involved in planned movements, spatial reasoning, and attention. Authors suggested that sleep restriction could disrupt or slow down normal plasticity development (Kurth et al. 2016). Evidence from animal studies seems to support this hypothesis: sleep is required for neurodevelopmental processes in specific brain circuits during critical periods of life: chronic sleep restriction has been shown to affect adult brain connectivity during early adolescence (Jha et al. 2005; Kayser et al. 2014; Billeh et al. 2016). In fact, for preventing sleep disturbances and their negative consequences on health in general the American Academy of Pediatrics in 2014 (AAP 2014) supported the efforts of school districts to optimize sleep in students and by suggesting school start school times to change allowing and allowing students the opportunity to achieve optimal levels of sleep.

One study in 69 adult depressed patients with bipolar disorder associated the duration of night sleep with organization of myelin and axonal structures (Benedetti, Melloni et al. 2017), thus suggesting that sleep loss could contribute to the dysruption in key tracts contributing to the functional integrity of the brain which associates with mood disorders (Vai et al. 2014). Animal models showed that sleep loss causes neuroinflammation, due to increased secretion of pro-inflammatory cytokines, to increased blood-brain barrier permeability and to the activation of microglia (Muzio et al. 2016; Fernandes et al. 2017). Animal models suggest that early perturbations of microglial function lead to abnormal maturation of several braincellular processes, including synaptogenesis, synaptic pruning, axonal growth, and myelination, which result in behavioral abnormalities that emerge during the juvenile period (Johnson and Kaffman 2017); in humans, these pro-inflammatory phenotypes have been associated with worse outcomes of mood disorders (Steiner et al. 2013; Benedetti F, Poletti et al. 2017), and with white matter disruption (Benedetti et al. 2016). In sum, sleep disturbances experienced during early life may impair brain plasticity, thus contributing to the development of mood disorders (Fig 1).

3) Temperament, character, attachment style and mood disorders: is there a role for sleep disturbances?

Review of evidence

The hypothesis that mood disorders are linked to personality can be traced to antiquity, when Hippocrates, and later Galen, argued that particular "humors" were responsible for specific personality types and forms of psychopathology. Personality has traditionally been conceptualized as having two components: temperament, which refers to biologically based, early-emerging and stable individual differences in emotion and its regulation, and character, which refers to individual differences due to socialization (for an overview see Klein et al 2011). However, a large body of evidence has accumulated indicating that personality traits have all the characteristics of temperament, including strong genetic and biological underpinnings and substantial stability over the lifespan (for an overview see Klein et al. 2011). Some personality traits may represent a susceptibility factor for mood disorders (Cloninger et al 1993; Klein et al 2011; Zaninotto et al. 2016).

One of the most heuristic models of personality is the psychobiological model developed by Cloninger, includes four dimensions of temperament such as "novelty seeking", "harm avoidance", "reward dependence", and "persistence"(Cloninger et al. 1993). It also includes three dimensions of character such as "self-directedness" and "cooperativeness" measuring maturity traits and social adaptation, respectively and "self-transcendence" (Cloninger et al. 1993). Patients diagnosed with depressive disorders, even in euthymic phases, have very high harm avoidance scores that lend support to the hypothesis that harm avoidance may be pathogenic and represent a susceptibility factor for depression. A recent meta-analysis has concluded that high harm avoidance and low self-directedness may be trait markers for mood disorders, especially depression, while high novelty seeking and high self-transcendence may be specific to bipolar disorders (Zaninotto et al. 2016).

Additionally, the concept of affective temperaments, which refers to temporally stable behavioral traits with strong affective reactivity, has gained considerable research attention in the context of mood disorders starting from late 90s (Akiskal 1995). Origins of the modern concept for affective temperaments can be traced beginning from humoral theories described by Hippocrates (Akiskal 1995), while later on the four basic affective dispositions, depressive, manic, cyclothymic and irritable, by Emil Kraepelin (Kraepelin, 1921). Combining these ancient preliminary ideas with extensive modern scientific and clinical observation, Akiskal and collaborators developed the concept of affective temperaments which have a strong biological, particularly genetic basis (Chiaroni et al. 2005; Akiskal and Akiskal 2005; Akiskal 2007). Affective temperaments have been hypothesized to play a pathogenic role in mood disorders, determining and modeling the emergence and clinical evolution of affective disorders and several disease core features including predominant polarity, symptomatic expression, long-term course and consequences, and outcome as well (Mechri et al 2011, Pompili et al. 2012; Perugi et al. 2012; Perugi et al. 2018). Depressive temperament is usually more prevalent among major depressive patients, while hyperthymic as well as cyclothymic temperament are a particular affective characteristic for bipolar disorders (Iasevoli et al 2012; Mechri et al 2011, Perugi et al. 2012; Perugi et al. 2018), the latter are being associated with earlier age of onset, greater episodes severity, frequency of episodes, hospitalizations and suicidality and with poorer outcome (Mechri et al. 2011; Perugi et al. 2012; Perugi et al. 2018).

Insecure attachment styles have emerged as psychobiological traits that may predispose to psychopathology including mood disorders (Mikulincer and Shaver 2012), which was originally formulated to describe and explain infant-parent bonding (Bowlby 1988) and has been applied to the study of adult psychobiological processes, such as interpersonal functioning, emotional and stress-response regulation and mental health (Bowlby 1988; Mikulincer and Shaver 2012). Attachment theory posits that individuals develop stable cognitive schemas, based on their early experiences with attachment figures, such as a parent or a caregiver. While individual characteristics are shaped during infancy, they continue to guide behavior and expectations in

interpersonal relationships throughout life, showing a relative degree of stability and also incorporating temporary or long lasting changes. While secure attachment has been thought to promote healthy behaviors such as seeking support and comforting response to interpersonal challenges and distress, the two insecure attachment styles, anxious and avoidant attachment, are associated with less adaptive behaviors and with dysregulation in emotion, dysfunctional stress responses and psychopathology (Bowlby 1988; Mikulincer and Shaver 2012). In particular, attachment insecurity is considered as a cognitive vulnerability to mental disorders (Bowlby 1988; Mikulincer and Shaver 2012). Neuroanatomical structures that mediate attachment have been hypothesized to include limbic and cingulate-frontal regions which seem to play a special role in regulating adaptive and emotional behaviors—all important processes in the development of attachment (Insel and Young 2001)

Role of sleep disturbance

Studies which have examined associations between temperament and sleep problems in infants, toddlers and adolescents have shown that sleep disturbances in infants throughout adolescence are often associated with individual differences in temperament, including irritability, negative and great emotionality, high reactivity and impulsivity (for an overview Ednick et al. 2009, Schmidt et al 2015). In a longitudinal study conducted in 123 infants (63 male, 60 female) from the Washington, DC area (USA), maternal reports using the Infant Behavior Questionnaire and Brief Infant Sleep Questionnaire at 5, 9 and 12 months of age also revealed that negative temperament was associated with sleep problems, specifically longer sleep latency and more night wakefulness (Sorondo and Reeb-Sutherland 2015). Prospective, longitudinal data from two population-based cohorts, the Generation R Study (Jaddoe et al. 2008) and the Avon Longitudinal Study of Parents and Children (ALSPAC) (Boyd et al. 2013), showed that infant temperament and gender moderated the effect of antepartum depression on infant sleep at the age of 18 and 24 months, in particular

boys with more reactive temperament showed shorter sleep and more night awakenings (Netsi et al. 2015).

Temperament and character of subjects with insomnia have been studied according to the Cloninger model (Cloninger et al. 1993). In a cross-sectional study conducted in a group of 32 subjects with chronic insomnia, it has been shown that – compared with good sleepers – subjects with insomnia showed significantly greater harm avoidance and lower self-directedness (de Saint Hilaire et al. 2005). These data has been confirmed in further studies: in a study conducted in a group of 44 subjects with primary insomnia, insomnia severity was significantly and positively correlated with greater levels of harm avoidance and self-transcendence and negatively correlated with novelty seeking, reward dependence and cooperativeness (Park et al 2012). Another study conducted in a group of 25 subjects with primary insomnia and in a control group confirmed previous reports: subjects with insomnia have shown high levels of harm avoidance and low levels of self-directedness (Bravo-Ortiz et al 2013). These characteristics are similar to those of subjects with mood disorders. On the basis of existent literature we may hypothesize that insomnia may predispose to mood disorders by being related to personalities and characters that predispose to mood disorders.

Affective temperaments have been studied in relation to alterations of sleep patterns. In a web survey study by Ottoni et al. (2011), 5,129 subjects have been evaluated: cyclothymic and depressive temperaments were shown to endorse more ‘eveningness’ and to have impaired sleep profiles and circadian characteristics, particularly eveningness, compared to other temperaments especially into euthymic subjects. Subjects with cyclothymic temperament have also displayed prolonged sleep latency, fragmented sleep and poor sleep quality (Ottoni et al. 2011). In a study monitoring 56 healthy subjects via an actigraphy system to measure among other factors sleep time, greater fluctuation in sleep was related to hyperthymic temperament. Authors hypothesized that sleep may be crucial to understand hyperthymic temperament that is common in bipolar disorders (Hoaki et al. 2011). In another web survey, 6,436 subjects have been evaluated for temperaments

and sleep-based chronotype measures. Cyclothymic temperament, euphoric, apathetic, and disinhibited temperaments, showed pronounced eveningness, which has been related to less emotional control and more affective instability, a less adaptive emotional profile as compared to morning and intermediate types (Ottoni et al. 2012). In a cross-sectional study conducted in a group of 641 healthy young adults (376 male, 265 female), 'evening-type' subjects were more likely to display depressive, cyclothymic, irritable and anxious temperaments, whereas 'morning-types' were more likely to have a hyperthymic temperament (Park et al 2015) (Table 1).

Growing evidence has been accumulated for mood disorders to arise in part from abnormal malfunction of the timing within and between the circadian system and human behaviour (for an overview see Harvey 2009; Harvey 2011; Wulff et al. 2010; MClung 2013). The "circadian hypothesis of mood disorders" has suggested that there is disruption between endogenous rhythms controlled by de-synchronization of the body clock suprachiasmatic nuclei, the master biological clock of the hypothalamus and social zeitgebers such as personal relationships, caring responsibilities, work, travel, timing of outdoor activities, physical exercise or meals, which all have the potential to weaken the circadian internal phase regularity (for an overview see Foster and Wulff 2005; Harvey 2009; Harvey 2011; McClung et al. 2013; Dellaspezia et al. 2015). Rhythmic clock-controlled gene expression regulates multiple monoaminergic brain regions that control mood and motivated behaviors, stress and inflammatory systems, reward circuits, arousal and sleep by interacting with the homeostatic regulation of sleep and wake (Wulff et al 2010; McClung 2013). In subjects with mood disorders, mutation variants in the circadian clock genes might render an individual more vulnerable to mood disruption by impairing the capacity of the subjects to adapt to environmental changes especially to such as seasons, sleep deprivation, shift works, jet leg and or stressful events. thus misaligning the internal biological clocks and in turn altering monoamine transmission, HPA- axis and immune functions, motivated behaviors, reward sensitivity, hippocampal neurogenesis, and neuropeptide signaling can all be affected (for an overview see McClung 2013). On this basis we may hypothesize that an alteration in circadian sleep rhythms may

contribute to temperaments involved in the pathogenesis of mood disorders. Further studies are needed to better understand the interplay between personality, character, affective temperament and sleep/circadian phenotype disturbances in the pathogenesis of mood disorders.

Regarding attachment style evidence of its connection with sleep in early life has been provided by both animal studies, which have shown a disruption in REM sleep during mother–infant separation (Reite and Short 1978; Tiba et al. 2008) as well as numerous clinical studies documenting a significant association between sleep disorders in infants and insecure attachment (for an overview see Simard et al. 2017). A recent review of literature confirmed this association across the lifespan (for an overview see Adams et al 2014). Reviewing the literature on sleep and attachment McNamara (1996) and Zborowski and McNamara (1998) hypothesized that REM sleep may function, in part, to selectively influence and perhaps even promote attachment in the developing organism. On the other hand sleep disturbances experienced during early life may impair the developing brain including regions known to be important for regulation of emotional and social behaviors important for attachment (Zborowski and McNamara 1998). We hypothesize that disturbed sleep would contribute to alterations in the development of attachment involved in the pathogenesis of mood disorders probably by interfering with brain neurodevelopmental processes (Fig 1). Genetic, epigenetic and neuroendocrine mechanisms would drive the vulnerability or resilience towards certain sleep disturbances and, subsequently, mood disorders by favoring such personality, temperament, character and attachment style that predispose to mood disorders.

Please insert table 1 here

Conclusions

Since sleep disturbances, especially insomnia and circadian maladaptation, contribute to the development of mood disorders, which are the most prevalent disorders in the field of psychiatry,

the aim of this paper was to review the literature regarding the developmental trajectory of mood disorders in relation to these sleep disturbances. This life course perspective should be useful for clinicians by allowing to target sleep disturbances as preventive and early interventive measures regarding mood disorders. Developmental pathways towards mood disorders include a role of pre-natal/early life stress, early brain developmental processes (including sleep phase and circadian entrainment) as well as personality, temperament, character and attachment style. Research into the developmental pathways to mood disorders have suggested a key role of "pre-natal early life programming" of mental health, since prenatal and postnatal periods have been suggested as the most important and are very sensitive periods during which the evolutionary sensory susceptible brain learns immediately from environmental cues, such touch, smell, voice discrimination, mother-infant interaction, sleep and food intake routines. Along these lines, experimental and clinical studies have revealed that exposure to early life stress results in sleep disturbances that may predispose to mood disorders in adulthood. It has also been hypothesized that mood disorders may begin with disturbances in the developing juvenile brain regions that control emotion and cognition. Evidence from animal and human studies has shown that sleep is necessary for neurodevelopmental processes in specific brain circuits during critical periods of life. Chronic sleep disruption affects brain plasticity and connectivity, thus likely interfering with the processes of brain maturation and ultimately exposing individuals to develop mood disorders later on.

The hypothesis that mood disorders are linked to personality can be traced to antiquity and in the last years it has emerged the role of attachment style as psychobiological trait that may predispose to mood disorders. Studies conducted in subjects with insomnia have shown that they have high levels of harm avoidance as a temperamental trait and low self-directedness as a character trait, resembling the characteristics of subjects with mood disorders. Subjects with circadian maladaptations may have cyclotymic, hyperthymic and depressive affective temperaments. Subjects with sleep disturbances tend to present insecure attachment across the lifespan. These sleep disturbances have thus been suggested to be closely related to personality, temperament, character

and attachment styles that may constitute a risk factor for mood disorders. Genetic, epigenetic as well as neuroendocrine mechanisms may drive the vulnerability or resilience, respectively, towards certain sleep phenotypes and, subsequently, mood disorders by differentially shaping the sensitivity towards prenatal/early-life stress and/or negatively influencing early brain developmental processes and/or favoring such personality, temperament, character and attachment style that may predispose to mood disorders.

Consequently, assessing and targeting insomnia and abnormal circadian synchronisation as potentially modifiable behaviors by providing correctly timed cues should be a priority in daily clinical practice in order to intervene in the developmental trajectory of mood disorders by providing prevention and early treatment (Kaplan and Harvey 2013; Dallaspezia and Benedetti 2011; Hickie et al. 2013; Dallaspezia et al. 2015; Harvey et al. 2015; Jansson-Fröjmark and Norell-Clarke 2016; Riemann D, Baglioni et al. 2017). Particularly, Cognitive Behavioral Therapy for Insomnia (CBT-I) has shown great effects, which is the first line treatment for insomnia (Riemann D, Baum et al. 2017, Riemann D, Baglioni et al. 2017), could be ideal for the prevention of mood disorders and it has been shown to improve not only insomnia but mood disorders' trajectory when used as add-on within the context of mood disorder treatment in adults (Kaplan and Harvey 2013; Jansson-Fröjmark and Norell-Clarke 2016; Riemann D, Baglioni et al. 2017) but also children and adolescence (Paine and Gradisar 2011; de Bruin et al. 2014; Adolescent Sleep Working Group 2014; American Academy of Pediatrics 2014; Clarke et al 2015; Marx et al. 2017). Also the therapy for abnormal timing of circadian rhythm has been shown to improve the trajectory of mood disorders in adults (Dallaspezia and Benedetti 2011; Hickie et al. 2013; Dallaspezia et al. 2015; Harvey et al. 2015). These strategies, named chronotherapies are based on time-controlled exposures to environmental stimuli that act on biological rhythms, and demonstrate good efficacy in the treatment of illness abnormal timing and mood episodes. They include manipulations of the sleep-wake rhythm such as sleep phase timing modifications and manipulation of light/dark exposure, e.g. using bright light therapy and dark therapy. An increasing literature about the safety

and efficacy of non-pharmacological chronobiological therapies has supported the inclusion of these techniques among the first-line treatment strategies for patients affected by mood disorders (Wirz-Justice et al 2005, Harvey et al 2015) and they have been proven to be effective also in children and adolescence with circadian rhythm sleep disturbances (Gradisar et al 2011; American Academy of Pediatrics 2014; Adolescent Sleep Working Group 2014; Auger et al. 2015; Marx et al. 2017). Genetic, epigenetic and neuroendocrine markers may aid in individually tailoring these approaches in a precision medicine approach allowing for personalized and thus more effective preventive and therapeutic interventions (Domschke and Reif 2015).

Limitations. Although on the basis of the existent literature we may hypothesize that sleep disorders may act as a causal factor in mood disorders, particularly insomnia and mood disorders have been shown to be bidirectionally linked. Hence we may also suppose that sleep problems may be due to prodromal mood disorders. Further studies on the trajectories of both sleep and mood disorders are needed to establish a causality across the lifespan.

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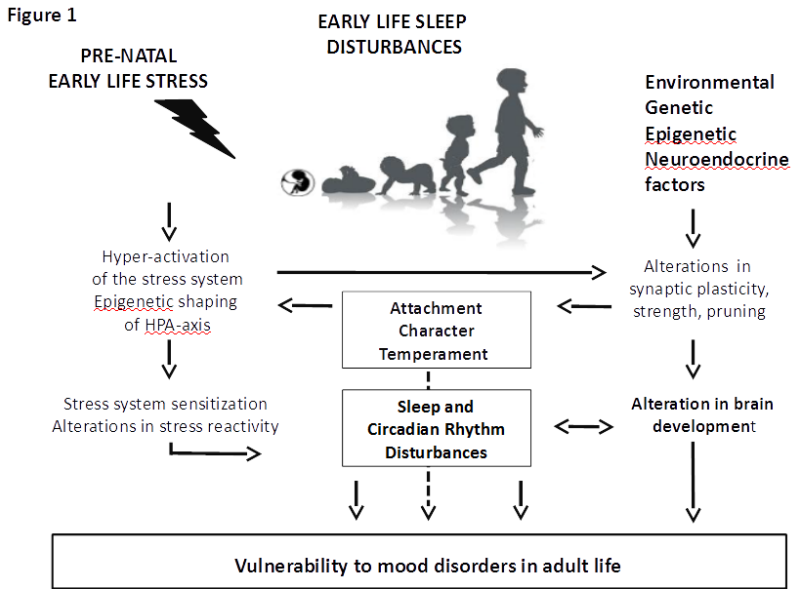
Legend

Figure 1. Sleep disturbances and pathways to mood disorders in adult life



Within the framework of the complex-genetic – and environmental model of mental disorders a key role of pre-natal/early life stress in the programming of the stress system of individuals is emerging. Prenatal and postnatal periods are in fact assumed to constitute highly sensitive periods during the development of an individual and may have negative consequence on later life mental health possibly through epigenetic mechanisms. Because disturbed sleep is one of the main consequences of early life stress we hypothesized that disturbed sleep due to pre-natal early life stress, possibly mediated by epigenetic processes, may re-shape the individual's stress system contributing to an increased vulnerability to stress-related disorders in the long term including mood disorders. Disturbed sleep due to early life stress may impair the regulation of HPA axis and stress system and has been hypothesized to be a stressor that may enhance the effect of other stressors, thus contributing to the cumulative wear and tear on body systems. Exposure to early life stress may also shape the developing central nervous system profoundly influencing major brain reorganization which may include sleep regulation. Within this theoretical framework, we hypothesize that disturbed sleep due to pre-natal early life stress and possibly mediated by epigenetic processes may re-shape the individual's stress system contributing to an increased vulnerability to stress-related disorders in the long term. We hypothesize that prenatal/early life stress may predict mood disorders in adulthood via sleep disturbances such as insomnia, fragmented sleep, poor sleep and circadian sleep dysregulation.

In the last few years, mood disorders have started to be considered complex brain disorders, and neurodevelopmental factors have been implicated in their pathophysiology. Because sleep has important regulatory functions and plays a key role in fetal, early neonatal and teen brain development, we hypothesize that a disturbed sleep may interfere with a normal brain development by favoring alterations in synaptic plasticity, pruning and strength thereby contributing to the development of mood disorders in adult life. The hypothesis that mood disorders are linked to personality can be traced to antiquity and in the last years it has emerged the role of attachment style as psychobiological trait that may predispose to mood disorders. Studies conducted in subjects

with insomnia have shown that they have high levels of harm avoidance as a temperament and low self-directedness as a character, resembling the characteristics of subjects with mood disorders. Subjects with circadian sleep dysregulation may have cyclotymic, hyperthymic and depressive affective temperaments. Subjects with sleep disturbances tend to have insecure attachment across the lifespan. These sleep disturbances have thus been suggested to be closely related to temperaments, character and attachment style which constitute a risk factor for mood disorders.

Genetic, epigenetic as well as neuroendocrine mechanisms may drive the vulnerability or resilience, respectively, towards certain sleep disturbances phenotypes and, subsequently, mood disorders by differentially shaping the sensitivity towards prenatal/early-life stress and/or negatively influencing early brain developmental processes and/or favoring such personality, temperament, character and attachment style that may favour mood disorders.

Table 1. Sleep dysregulation, temperament and character

Summary of the studies about the relationship between insomnia, circadian sleep dysregulation and temperament and character. **References 1**: Cloninger, C.,R., Przybeck, T.,R, Svrakic, D.,M., Wetzel, R.,D., Svrakic, D.,M.1994. The Temperament and Character Inventory (TCI): a guide to its development and use. Center for Psychobiology of Personality, Washington University; St. Louis.; **2**: Lara, D.,R., Bisol, L.,W., Brunstein, M.,G., Reppold, C.,T., de Carvalho, H.,W., Ottoni, G.,L. 2012.The Affective and Emotional Composite Temperament (AFECT) model and scale: a system-based integrative approach. J Affect Disord.140**,**14-37; **3**: Horne**,** J**.,**A**.**, Ostberg**,** O.1976. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 4, 97–110.; **4**: Morin, C. M., 1993. Insomnia: Psychological Assessment and Management. New York: Guilford Press; **5**: Ottoni, G.,L., Antoniolli, E., Lara,D.,R.2011.The Circadian Energy Scale (CIRENS): two simple questions for a reliable chronotype measurement based on energy.Chronobiol Int. 28, 229-37; **6**: Akiskal, H.,S., Akiskal, K.,K., Haykal, R.,F., Manning, J.,S., Connor, P.,D. 2005. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire.J Affect Disord. 85, 3-16.; **7:** Smith, C. S., Reilly, C., Midkiff, K. 1989. Evaluation of three circadian rhythm questionnaires with suggestions for an improved measure of morningness. J. Appl. Psychol. 74,728–738

Table 1 Sleep dysregulation, temperament and character

Authors	Study Design	Study Population	Evaluation of temperament, character and sleep	Main findings
de Saint Hilaire et al 2005	Cross-sectional	32 chronic insomniacs 30 good sleepers	Temperament and Character Inventory [1] polysomnography	Subjects with chronic insomnia show higher level of harm avoidance and lower self-directedness than good sleepers
Ottoni et al. 2011	Cross-sectional	web-survey 5129 subjects	Combined Emotional and Affective Temperament Scale [2] Morningness/Eveningness[3] Questionnaire	Cyclothymic and depressive temperaments have shown the worse sleep profile, particularly eveningness
Hoaki et al 2011	Cross-sectional	54 hyperthymics 30 healthy controls	Actigraphy	Subjects with hyperthymic temperament showed greater fluctuation in sleep patterns than healthy controls
Park et al 2012	Cross-sectional	44 chronic insomniacs 40 good sleepers	Temperament and Character Inventory [1] Insomnia Severity Index[4]	Insomnia severity was significantly and positively correlated with harm avoidance and self-transcendence and negatively correlated with novelty seeking, reward dependence, and cooperativeness.
Ottoni et al. 2012	Cross-sectional	web-survey 6436 subjects	Combined Emotional and Affective Temperament Scale[2] Circadian Energy Scale[5] Self reported chronotype measures	Cyclothymic, apathetic, and disinhibited temperaments showed evening chronotypes. Evening types showed less emotional control and more affective instability than morning and intermediate types
Bravo-Ortiz et al 2013	Cross-sectional	25 chronic insomniacs 25 good sleepers	Temperament and Character Inventory[1] Insomnia Severity Index[4]	Subjects with chronic insomnia show higher level of harm avoidance and lower self-directedness than good sleepers
Park et al 2015	Cross-sectional	640 college students	Temperament Scale of Memphis, Pisa, Paris and San Diego - Autoquestionnaire (TEMPS-A) [6] Composite Scale of Morningness[7]	Evening-types showed more likely depressive, cyclothymic, irritable and anxious temperaments, whereas morning-types were more likely to have hyperthymic temperament

Note. Summary of the studies about the relationship between insomnia, circadian sleep dysregulation and temperament

and character. **References 1**: Cloninger, C.,R., Przybeck, T.,R, Svrakic, D.,M., Wetzel, R.,D., Svrakic, D.,M.1994. The Temperament and Character Inventory (TCI): a guide to its development and use. Center for Psychobiology of Personality, Washington University; St. Louis.; **2**: Lara, D.,R., Bisol, L.,W., Brunstein, M.,G., Reppold, C.,T., de Carvalho, H.,W., Ottoni, G.,L. 2012.The Affective and Emotional Composite Temperament (AFECT) model and scale: a system-based integrative approach. J Affect Disord.140**,**14-37; **3**: Horne**,** J**.,**A**.**, Ostberg**,** O.1976. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 4, 97–110.; **4**: Morin, C. M., 1993. Insomnia: Psychological Assessment and Management. New York: Guilford Press; **5**: Ottoni, G.,L., Antoniolli, E., Lara,D.,R.2011.The Circadian Energy Scale (CIRENS): two simple questions for a reliable chronotype measurement based on energy.Chronobiol Int. 28, 229-37; **6**: Akiskal, H.,S., Akiskal, K.,K., Haykal, R.,F., Manning, J.,S., Connor, P.,D. 2005. TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire.J Affect Disord. 85, 3-16.; **7:** Smith, C. S., Reilly, C., Midkiff, K. 1989. Evaluation of three circadianrhythm questionnaires with suggestions for an improved measure of morningness. J. Appl. Psychol. 74,728–738