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CLINICAL REVIEW

REM sleep dysregulation in depression: State of the art[d]

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SUMMARY

Disturbances of sleep are typical for most depressed patients and belong to the core symptoms of the disorder. Since the 1960s polysomnographic sleep research has demonstrated that besides disturbances of sleep continuity, depression is associated with altered sleep architecture, i.e., a decrease in slow wave sleep (SWS) production and disturbed rapid eye movement (REM) sleep regulation. Shortened REM latency (i.e., the interval between sleep onset and the occurrence of the first REM period), increased REM sleep duration and increased REM density (i.e., the frequency of rapid eye movements per REM period) have been considered as biological markers of depression which might predict relapse and recurrence. High risk studies including healthy relatives of patients with depression demonstrate that REM sleep alterations may precede the clinical expression of depression and may thus be useful in identifying subjects at high risk for the illness. Several models have been developed to explain REM sleep abnormalities in depression, like the cholinergic–aminergic imbalance model or chronobiologically inspired theories, which are reviewed in this overview. Moreover, REM sleep alterations have been recently considered not only as biological "scars" but as true endophenotypes of depression. This review discusses the genetic, neurochemical and neurobiological factors that have been implicated to play a role in the complex relationships between REM sleep and depression. We hypothesize on the one hand that REM sleep dysregulation in depression may be linked to a genetic predisposition/vulnerability to develop the illness; on the other hand it is conceivable that REM sleep disinhibition in itself is a part of a maladaptive stress reaction with increased allostatic load. We also discuss whether the REM sleep changes in depression may contribute themselves to the development of central symptoms of depression such as cognitive distortions including negative self-esteem and the overnight consolidation of negatively toned emotional memories.

Introduction

Depression as a clinical disorder is a common condition[1–3] and has become increasingly prevalent in Western industrialized countries,[4] with a point-prevalence of ca. 5% and estimates of lifetime-prevalence ranging up to 20% of the general population. Depression has severe consequences and is associated with increased rates of disability, morbidity and mortality.[4] Symptoms of depression include depressed mood, loss of interest and fatigue/tiredness, cognitive dysfunction, i.e., negative view of the self, negative ruminations, loss of appetite and libido, suicidality and sleep problems. Disturbed sleep is reported by up to 90% of depressed subjects[5] and might be involved, at least partially, in the onset and course of depression[4] and in the response to treatment.[4,6] Patients suffering from depression complain of sleep disruptions mainly consistent with symptoms of insomnia (i.e., prolonged sleep latency, frequent nocturnal awakenings and early morning awakening), which are part of the core complaints of depression.[4,7–12] Sleep disturbances in depression have interested many researchers and for many decades sleep research has been a major pillar of neurobiological investigations into its cause, onset and course. Since the 1960s polysomnographic sleep research has demonstrated that besides disturbances of sleep continuity[7–11] a typical constellation of sleep-electroencephalography (EEG) architecture changes is present in depression.[12–16] The most reliable EEG sleep changes include a decrease in rapid eye movement (REM) latency (REM latency = interval between sleep onset and the occurrence of the first REM sleep period), an increase in total REM

[d] In memory of Professor Mario Guazzelli.

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sleep time and REM density (i.e., the frequency of rapid eye movements per REM period), and diminished slow wave sleep (SWS) production.[12–16] REM sleep alterations, especially shortened REM sleep latency, might have prodromal[4,13,17,18] and residual properties[4,13,18] with respect to depressive episodes. REM sleep alterations in fact often persist beyond the clinical episode and thus are supposed to increase the vulnerability to relapse or recurrence and in general may have a negative effect on treatment response.[4,6] High risk studies investigating hitherto unafflicted relatives of patients with depression demonstrated that particularly REM density changes are already present before the onset of the disorder and may predict its development.[19–22]

The phenomenology of sleep alterations in depression will be reviewed in more detail in the next chapter, followed by an overview concerning the impact of antidepressant medication on sleep (see below). REM sleep alterations, especially shortened REM sleep latency, have been interpreted as biological markers for depression and even been assumed to be of differential diagnostic value for the classification of depressive disorders.[23–27] Some theoretical models to explain REM sleep abnormalities in depression hypothesize a key role of these sleep phenomena for the etiology/pathophysiology of depression, while others interpret REM sleep changes as mere consequences of the neurobiological processes underlying depressive disorders. Doubtlessly, genetic factors might be involved in the development of REM sleep changes in depression, which are mediated by complex neurobiological processes involving among others noradrenergic, serotoninergic, cholinergic and orexinergic neurotransmitter systems. Presently, REM sleep alterations are not only seen as state markers or biological "scars", but even as vulnerability markers or "true" endophenotypes of depression.[16,28–30] A review of presently discussed models will be given below followed by a critical discussion of these concepts. At present, none of the established models sufficiently explain the whole range of sleep abnormalities in depression.[4,16,31] A novel pathophysiological concept of depression, to be outlined in this review, therefore proposes that a dysfunction of neural plasticity might represent a final common pathway underlying the biological and clinical characteristics of the disorder. Interestingly, changes in neurogenesis have been implicated in the pathophysiology of depression, but also in stress-related REM sleep hyperactivation or disinhibition.[32–34] New concepts in depression are reviewed and then we propose a model of the role of REM sleep dysregulation in depression based on the literature taken into consideration.

This paper aims at reviewing data and hypotheses about the complex relationship between REM sleep dysregulation and depression, starting with a brief historical perspective from the first polysomnographic studies in the 1960s to the present situation. This approach will encompass data from different strands of research including psychopathology, experimental and clinical psychology, genetics, electro-, neuro- and psychophysiology, molecular biology and neuroimaging.

REM sleep dysregulation in depression

Phenomenology

Sleep-EEG changes in patients with depression consist of impaired sleep continuity, i.e., prolonged sleep latency, increased number of intermittent awakenings, early morning awakening, reduced slow wave sleep and disinhibition of REM sleep (encompassing shortened REM latency or even sleep onset REM periods, prolonged first REM period, increased amounts of REM sleep and elevated REM density particularly during the first REM period)[12,13,15,16,35–37] (see Fig. 1). It has been demonstrated that many of these sleep parameters are affected by factors such as age, gender and illness severity. REM Latency for example becomes progressively shorter with middle age in depressed individuals.[38,39] Sleep efficiency and SWS also show an age-related decline, while REM density does not vary with age.[38] The amounts of nonREM sleep have been correlated with gender differences,[14,40] while both nonREM sleep disturbances[41] and REM sleep dysregulations have been shown to be positively correlated with illness severity.[42,43] An increasing frequency of REM sleep alterations occurs with illness duration,[44] whereas the amount of SWS did not differ between recurring episodes.[45] From a historical perspective, the initial sleep-EEG studies in depression aimed to confirm the diagnostic classification of depressive disorders into the "endogenous"/"primary" versus the "neurotic"/"secondary" forms.[23–25] Shortened REM latency was postulated to be a biological marker for the "endogenous/primary" subtype. As empirical data in the end were unable to confirm these diagnostic distinctions (see for example[46]) and with the publication of the Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV), subsequent sleep-EEG studies now focus mainly on major depression.[36] The REM sleep specificity hypothesis for subtypes of depression was further challenged by observations of comparable sleep changes in other psychiatric disorders.[47–49] Nevertheless, almost all of the empirical studies in the field pointed toward the conclusion that the observed alterations of REM sleep in depression are more than mere epiphenomena of the disorder.[30] In subsequent research, the main focus turned toward the question whether REM sleep abnormalities are "state" or "trait" markers of the disorder. Several studies have shown that depression-like polysomnographic changes are not state-dependent and persist during remission. Giles et al.[19] found the persistence of shortened REM latency during remission to be associated with an increased risk of relapse and longitudinal studies have shown REM sleep latency to be stable within depressed individuals over time regardless of clinical state.[21,50] Recurrent depressed subjects present REM sleep disturbances before the onset of the treatment and after symptomatic remission independently of treatment method.[44] Increased REM density has been associated with a negative treatment outcome in patients

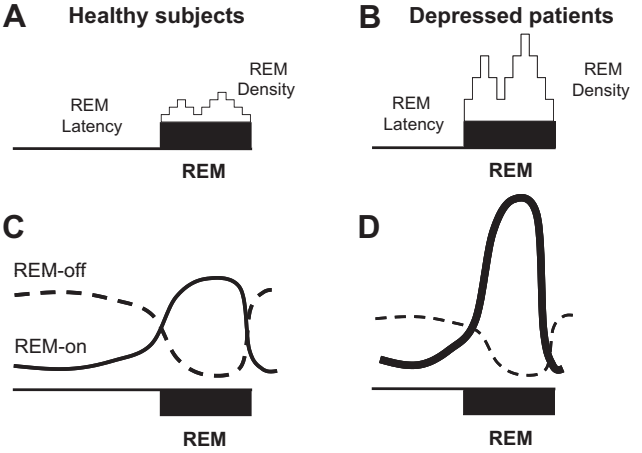

Fig. 1. Schematic representation of changes in rapid eye movement (REM) latency and density and related neuronal activity in depressive illness. A) REM latency (black line) and REM density (white area) in normal subjects. B) REM latency (black line) and REM density (white area) in depressed patients. To note the shortening of the REM latency and increased REM density in depressed patients compared to normal subjects. C) Schematic representation of the temporal dynamics of neuronal activity triggering REM sleep (REM-on cholinergic activity, thin black line) and inhibiting REM sleep (REM-off aminergic activity; dashed line) according to the classical neural model of McCarley.[161] D) Schematic representation of absolute or relative cholinergic overdrive (thick black line) underlying REM sleep changes (panel B) in depressed patients according to the cholinergic hypothesis of Janowsky et al.[67] and McCarley.[161]

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with major depression independently of treatment method.[6] A set of sleep-EEG variables, such as REM latency, REM density and sleep efficiency (if in the normal range), were predictive for a positive response to psychotherapy.[51,52] REM density before treatment was higher in patients who did not respond to psychotherapy, whereas a decrease in REM density after psychotherapy was the most robust correlate of remission.[53] These findings, taken together, suggest a "trait" or "vulnerability" characteristic of at least some of the polysomnographic REM sleep alterations in patients with depression, though some interindividual variability has to be taken into account. A recent meta-analysis of the polysomnographic literature on depression[16] demonstrated convincingly that REM latency and REM density discriminated depressed sleep from unafflicted sleepers with the greatest statistical effect size; with respect to within subject comparisons from the depressed to the remitted state only REM density remained totally unchanged. A critical caveat needs to be mentioned here: changes of REM sleep do not occur in every subject suffering from depression – probably between 50 and 70% of subjects afflicted with major depression are estimated to display these changes.[5] The psychobiological mechanisms through which an alteration of REM sleep would lead to the onset of depression and contribute to its maintenance are not yet fully understood. As described in later paragraphs, REM sleep per se might be important for the regulation of cognitive and emotional processes, which might suggest different pathways as to how and why changes of REM sleep might be involved in the pathogenesis of depression.[54] Interestingly, REM sleep alterations do not seem to be strictly specific for depression,[47] but might play a role also in other psychiatric disorders by affecting the normal functioning of the cognitive and the affective systems, as recently suggested in the transdiagnostic hypothesis for sleep disturbance (e.g.,[55]). Thus, the understanding of the role of REM sleep dysregulation for depression may also shed light on other psychopathological conditions. The next chapter will review the impact of antidepressant medication on sleep, especially REM sleep, as this type of investigation had a strong impact on theories about the interplay between depression and REM sleep changes.

Effects of antidepressants on sleep, especially REM sleep

Antidepressant drugs exert an effect on sleep architecture which varies over time and generally tend to ameliorate the sleep impairments of depression. Almost all antidepressants inhibit REM sleep,[13,56–59] thus delaying the onset and reducing the amount of REM sleep (see Fig. 2). The suppression of REM sleep occurs with classic tricyclic antidepressants (TCA, e.g., amitriptyline), tetracyclic drugs (i.e., mianserine), most of the selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine, monoamine-oxidase inhibitor (MAOI, e.g., phenelzine) and the mixed serotonin/norepinephrine re-uptake inhibitor (SNRI) venlafaxine (overview: Riemann et al.[5]). The REM sleep suppressing effects of tricyclic antidepressants are dose-related and consist of a drastic reduction in the overall amount of REM sleep, followed by REM sleep rebound after abrupt drug discontinuation, a phenomenon which has been described for all antidepressant substances which possess an initial strong REM sleep suppression. This REM sleep rebound may be related to a rebound increase in cholinergic neurotransmission, especially in those substances (mainly TCAs) having a strong anticholinergic effect.

REM sleep suppression following the administration of the older, irreversible MAOI phenelzine is profound, with a total suppression of REM sleep during the first week of treatment. An important recent finding is that the REM sleep suppression by phenelzine can be reversed by rapid tryptophan depletion, implying that its REM sleep effects are mediated via increased serotonin function.[60] The reversible MAOI moclobemide, interestingly, does not have these remarkable REM sleep suppressing effects: in some studies it turned out to be only a mild REM sleep suppressing agent; in one study it even increased the amount of REM sleep, but nevertheless a rebound increase of REM sleep during drug discontinuation was observed.[57] Similarly, the REM sleep suppressing effects described with all SSRIs and also with the mixed serotonin/norepinephrine re-uptake inhibitor venlafaxine are dose-related and consist of a strong reduction in the overall amount of REM sleep during the whole night, including a delay of the first REM period. REM sleep suppression after SSRIs administration is probably mediated via an increase of serotoninergic tone. Considering other antidepressants, mianserin only modestly suppresses REM sleep[61]; mirtazapine also blocks α2-adrenoceptors and therefore increases synaptic norepinephrine, thus only modestly increasing REM latency.[62] Trazodone has a slight suppressing effect of REM sleep, while nefazodone does not display such an effect. Some antidepressants may even impair physiological sleep regulation and sleep continuity.[63] A few studies suggested that not all antidepressants are accompanied by REM sleep suppression,[5,56] especially trimipramine.[64]

Fig. 2 graphically summarizes the effects of antidepressants on REM sleep (duration and latency). The literature on the REM sleep suppressing effects of most antidepressants formed the basis of the hypothesis by Vogel et al.[65,66] that an excess of REM sleep might be involved in the etiology and pathophysiology of depression (see below) and that therefore REM sleep suppression maybe considered a "condition sine qua non" of any kind of effective antidepressive therapy. The evidence about nefazodone, trazodone and trimipramine, however, casts serious doubt on this postulate. Furthermore, the clinically proven effectiveness of several forms of psychotherapy like interpersonal therapy (IPT) or cognitive behavioral therapy (CBT) (which do not suppress REM sleep), at least for mild to medium severe depression, weakens the central assumption of this model. The knowledge about the impact of antidepressants on REM sleep also emphasizes an important methodological issue – polysomnographic research in depressed patients must carefully rule out the influence of previous drug treatment: thus wash-out intervals of at least one week (better two weeks) prior to polysomnography are considered necessary to gain REM sleep data independent of drug treatment and rebound phenomena.

Pathophysiological models/concepts and REM sleep dysregulation in depression

This chapter will review theories and models which were suggested to explain the underlying mechanisms leading to a dysregulation of REM sleep in depressive disorders. As the relevant publications span over a time period of more than 40 y, it is not surprising that the theories differ largely in the way they are elaborated and in basic neurobiological knowledge about the regulation of REM sleep. Furthermore, these theories can be roughly divided into those viewing the observed changes in REM sleep as a consequence or reflection of some basic underlying mechanism involved in the pathogenesis of depression like for example the cholinergic–aminergic hypothesis and other models ascribing a more independent role for REM sleep dysregulation in the etiology/pathophysiology of depression like for example the REM sleep deprivation/ontogeny model.

The cholinergic–aminergic imbalance hypothesis of affective disorders

The original paper on the cholinergic–aminergic imbalance hypothesis model of depression was published 40 y ago.[67] This

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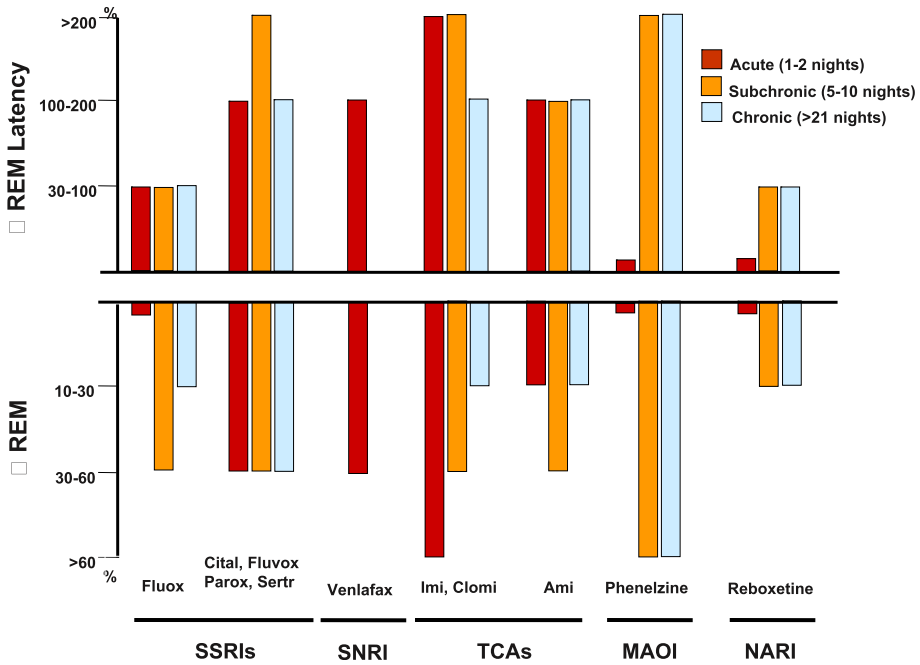

Fig. 2. Effects of the various classes of antidepressants on rapid eye movement (REM) sleep Fluox: floxetine; Cital: citalopram; Fluvox: fluvoxamine; Parox: paroxetine; Sertr: sertraline; Venlafax: venlafaxine; Imi: imipramine; Clomi: clomipramine; Ami: amitriptiline; SSRIs: selective serotonin re-uptake inhibitors; SNRI: serotonin–norepinephrine re-uptake inhibitors; TCAs: tricyclic antidepressants; MAOI: monoamine-oxidase inhibitors; NARI: noradrenaline re-uptake inhibitors. From Argyropoulos and Wilson[58] modified.

hypothesis is based on observations that organophosphate poisoning, which leads to a profound inhibition of acetylcholinesterase and therefore elevates acetylcholine levels throughout the brain and body, provokes depression-like symptoms in humans.[68] The hypothesis, at the time it was published, was seen as an extension and improvement over the classical monoamine deficiency theory,[69] which had primarily postulated that depression is causally linked to a decreased production of central nervous serotonin, noradrenalin and dopamine. Introducing an (im-) balance model between different neurotransmitters seemed to overcome some caveats of the monamine hypothesis and also appealed as more adequate from a neurobiological point of view. There are several lines of evidence to support the involvement of central cholinergic neurotransmission in the regulation of mood, REM sleep and the pathophysiology of affective disorders. Cholinomimetics, probably via muscarinic receptors, induce depression-like symptoms such as anhedonia and anergia in healthy volunteers.[70–73] Supersensitive responses of several parameters to an acute cholinergic challenge were described in affective disorders, including: a) increased anergia and anhedonia and full-blown depression, even in the euthymic interval[74,75]; b) increased secretion of adrenocorticotropic hormone (ACTH), cortisol and endorphin[73,75]; c) dramatic shortening of REM sleep latency.[76–82] Thus, both spontaneous hypercortisolism and reduced REM sleep latency frequently observed in depression could be provoked through an overactivity of central nervous cholinergic neurotransmission.

Independently from the work in depression, the temporal dynamics of the neuronal activity triggering REM sleep (REM-on cholinergic activity) and inhibiting REM sleep (REM-off aminergic activity) were described in cats, and later in humans.[34,83] These data, published at approximately the same time as the cholinergic–aminergic imbalance hypothesis, indicated that cholinergic neurons in the brainstem are mainly responsible for triggering and maintaining REM sleep, whereas noradrenergic and serotonergic neurons, mainly in the locus coeruleus and the dorsal raphe, were identified as REM-off neurons being mainly active during nonREM sleep ("reciprocal interaction model of nonREM/REM sleep regulation"). These animal data thus confirmed that a disinhibition of REM sleep might result from an altered balance between cholinergic and aminergic neurotransmission at brainstem level. In the meantime, the specificity of the pronounced REM sleep response (i.e., a further shortening of REM latency and an increase of REM density with some cholinomimetics = CRIT: cholinergic REM induction test) for affective disorders has been questioned[84] and there is an ongoing debate whether the response of the REM sleep system to a cholinergic stimulus is a trait,[81,82] as opposed to a state marker of depression.[78,79] Important in that context are findings revealing that healthy relatives of depressed patients show a more pronounced REM sleep response to a cholinergic stimulus than a normal population – furthermore, in a longitudinal design those subjects with an exaggerated REM sleep response in the high risk sample had a higher probability to develop depressive illness during an observation period of 10 y.[85,86] The described observations in humans and data from animal studies[87] strongly suggest that a hypersensitivity of central nervous cholinergic neurotransmission is involved in the pathophysiology of depression. Consequently, anticholinergic drugs were investigated as potential treatments for depression. Some recent studies show significant antidepressant responses to the antimuscarinic compound scopolamine in depressed patients,[88–91] however not unequivocally.[92,93] The dose dependency of scopolamine's effect across different studies and the lack of antidepressant effects with other anticholinergic drugs suggest that a specific muscarinic receptor subtype might be relevant to the potential antidepressant property of anticholinergics.[93]

The cholinergic–aminergic imbalance hypothesis of affective disorders, as formulated initially, still seems to have its merits and its relationships to basic neurobiological knowledge about REM sleep regulation is convincing with respect to REM sleep changes in depression. Unfortunately, experimental work in humans testing the impact of cholinomimetics on sleep is expensive and time consuming – this may be one reason why the exciting results of an

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increased sensitivity of the REM sleep system to a cholinergic stimulus even in healthy first-degree relatives of depressed patients[85,86] has not been tried to be replicated by now. This finding is among the very few empirical hints proving that a given biological abnormality (following a cholinergic challenge) is present long before the onset of the index disorder. Thus, it would be worthwhile to think of developing a simpler and easier version to perform the cholinergic REM induction test in order to stimulate further experimental work in this field.

The two-process model of sleep–wake regulation and the "S-deficiency" hypothesis

Borbely[94] proposed a general model of sleep–wake regulation based on the assumption that sleep is dependent on two processes: a homeostatic process "S" and a circadian process "C". According to this model, the interaction between the homeostatic sleep drive and a circadian process determines sleep propensity. This model also attempts to explain REM and nonREM sleep dysregulation in depression. Borbely[94] assumed a deficiency of process "S" in patients with depression as reflected by the observed reduction in SWS during nighttime sleep in depression. The authors hypothesized that as a consequence of reduced SWS, particularly during the first phase of nonREM sleep, REM sleep may occur earlier. The model also postulates that measures of phasic REM activity are inversely related to process "S", suggesting that process "S" can be regarded as exerting an inhibitory influence on phasic REM activity. In contrast, Knowles et al.[95] suggested that REM sleep is strongly influenced by circadian processes and its own intrinsic homeostatic properties, while process "S" might play only a relatively minor role in its regulation.[96] The antidepressant effect of sleep deprivation was attributed to the increased level of process "S", attained by prolonging wakefulness, according to this model.[97] With respect to explaining the paradoxical effects of sleep deprivation on depressed mood it needs to be mentioned, that indeed, sleep deprivation leads to an increase of SWS following the procedure; however, after the first night of sleep after sleep deprivation these positive effects usually disappear.[5]

Conflicting evidence to this model came from several studies which did not confirm a reduction of SWS in depressed patients.[38–40] As above mentioned, a recent meta-analysis of polysomnographic studies of patients with depression[16] revealed that differences in effect size between depressed patients and healthy sleepers were far greater for REM latency and REM density compared to SWS, suggesting an independence of REM sleep findings from SWS regulation. Insofar, the main tenet of the two-process model in its application to explain REM sleep changes, i.e., a reduction of SWS of depressed sleep, is seriously challenged by the empirical evidence.

Circadian rhythm abnormalities and REM sleep dysregulation: the "phase-advance" hypothesis

In 1975 Papoušek[98] integrated rhythm disturbances in mood disorders within a framework of circadian rhythm regulation: a phase advance of circadian rhythms was proposed to account for the abnormalities of REM sleep in depression. Later on, it has been hypothesized that in depression the rhythm of the central pacemaker driving REM sleep, temperature and cortisol, was abnormally advanced relative to the rhythm of the "weak" oscillator that controls sleep onset.[99–102] Findings indicative of advanced circadian phase such as early morning awakenings, shortened REM latency in patients with depression compared to non-depressed subjects were thought to confirm these assumptions.[103,104] The finding that advancing main sleep episodes in depressed patients to the afternoon, thereby reducing the mismatch between sleep onset and REM onset, was associated with improvements in mood also supported this hypothesis.[99] This initial pilot study of an experimental phase advance was followed by other studies documenting the antidepressant effect of this intervention.[105] Wehr and Goodwin[100] reviewed nearly 20 studies and confirmed that phase position of depressed patients was advanced one or more hours. Despite these data later on controlled studies have failed to show consistent alteration of circadian rhythms in depression.[106–109] A major problem of this type of research is the fact that in order to gain insight into biological rhythms the relevant variables have to be studied repeatedly over long periods of time, at least 24 h. Taking blood samples every 30 min from a depressed patient or measuring rectal temperature over 24 h is extremely difficult in a clinical population. Furthermore, if this type of research is not conducted in special research facilities, lots of confounding influences need to be taken into account (pre-determined sleep–wake routines in hospitals, timing of meals, light exposure, etc.). With respect to depressed patients, it was also unconceivable to subject them to a research protocol in a time-isolation unit (e.g., so-called bunker experiments[110]). State of the art experimental protocols use a constant routine design.[111] Complex interaction of sleep–wake cycle and circadian phase modulates mood in healthy subjects, which lasts between one and half and two days. However, also this procedure is considered to be too strenuous for clinically depressed patients. Recent progress in molecular genetics has offered new research avenues in this field by investigating clock genes being implicated in delayed or advanced sleep-phase syndrome[112] and circadian sleep abnormalities in depression.[113] Polymorphisms in the circadian rhythms genes, CLOCK, BMAL1, Period 3 (Per 3) and TIMELESS, have been associated with an increased susceptibility to mood disorders. Single nucleotide polymorphisms and haplotypes in several circadian genes have been observed among those displaying certain circadian phenotypes, including impaired mood in the evening, insomnia in mania and early, middle or late insomnia in depression.[114] The 3111T/C CLOCK gene polymorphism might even account for the circadian sleep dysregulation in depression.[113] Despite the many interesting and promising findings, the molecular and genetic underpinnings of this hypothesis are still largely unknown.

Basal sleep–wake regulation and REM sleep abnormalities: the hypocretin hypothesis

Orexin (also known as hypocretin) is a hypothalamic neuropeptide that contributes to stabilize the transition from wake to sleep and vice versa.[115] Studies indicate that sleep–wake switching and vice versa depends on the interaction of cell groups that cause arousal with other nuclei that induce sleep, a mechanism called "flip–flop switch".[116] This switch may help to produce distinct transitions between discrete behavioral states, but it is not necessarily stable. The orexinergic neurons in the lateral hypothalamus may help stabilize this system by exciting arousal regions during wakefulness, preventing unwanted transitions between wakefulness and sleep. The importance of this stabilizing role is apparent in narcolepsy, in which an absence or dysfunction of the orexin neurons causes numerous, unintended transitions in and out of sleep and allows fragments of REM sleep to intrude into wakefulness or to initiate sleep with REM sleep.[117] This phenomenon of starting sleep with REM sleep has been named SOREM (=sleep onset REM period) and can also be observed, though less frequently, in depressed patients. The shortening of REM latency in depression typically refers to a change of REM latency from on average 70–90 min characterizing healthy sleep to mean values of 50–60 min in depressed patients. Accordingly, it has been

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suggested that understanding the pathways that underlie the regulation of sleep and wakefulness may provide important insights into how cognitive and emotional systems interact with basic homeostatic and circadian drives for sleep.[117] In fact, major targets of orexin-containing fibers include the locus coeruleus and the raphe nucleus, areas that play important roles in the regulation of mood and sleep.[118] Because of the observed REM sleep alterations, especially shortened REM sleep latency, it has been suggested that there might be a reduction in orexin secretion in depression.[118] A defect in the lateral hypothalamus, including the orexin neurons, has been described in an animal model of depression.[119] During the past 10 y since the discovery of orexin, the list of their physiologic implications has been growing, from their primary roles in the sleep–wake cycle and feeding to the control of stress, and mental disorders such as panic, anxiety, and depression.[119] This diverse set of functions is consistent with the localization of orexin neurons in the lateral hypothalamus, a major integrating center of sensory inputs and emotional processes, and their widespread excitatory projections throughout the brain. Animal models of depression have been used to test this hypothesis.[120–122]

In animal models, prenatal stress has been shown to induce reduced latency to the onset of REM sleep, a prolongation of the first REM episode, and diminished SWS.[123] Because of the link between stress, sleep and depression,[124,125] it has been investigated in animal models whether there is a reduction in orexin levels during stress in depression. Utilizing unpredictable chronic mild stress, it was demonstrated that the involvement of orexinergic neurons of the dorsomedial and perifornical hypothalamus may contribute to the pathophysiology of depressive disorders.[125,126] Summarizing these results, growing evidence from animal studies indicates that a dysfunction of the orexin system might be involved in the pathophysiology of major depression and REM sleep alterations.

REM sleep deprivation/ontogeny model

Vogel et al.[65] suggested that an excess production of REM sleep might be involved causally in the etiology and pathophysiology of depression. Consistently, Vogel and his colleagues demonstrated that selective REM sleep deprivation by awakenings over a period of 2–3 wk exerts an antidepressant effect comparable to antidepressant drugs in depressed patients.[65,127] Unfortunately, these early studies on REM sleep deprivation's positive effect on mood were never replicated independently.[128] Another line of evidence supporting the hypothesis by Vogel was that most of the effective antidepressant drugs suppress REM sleep,[66] however, with some notable exceptions. Vogel and colleagues went so far to hypothesize that REM sleep suppression is a "conditio sine qua non" of the basic underlying mechanism of antidepressant action.[65,129] Some authors even speculated about a "depressiogenic" property of sleep in depression.[130] Recently, Vogel et al.[131] revisited this idea based on studies ascribing an important rule for brain maturation to REM sleep. This line of thinking assumes that the ontogeny of REM sleep in humans (with very high amounts of REM sleep prenatally, after birth and in the first year of life) is indicative of a developmental process that may be altered in humans predisposed to endogenous depression, and may account for the life-long REM sleep abnormalities observed in the disorder. In detail, the REM sleep – ontogeny hypothesis proposes that alterations in REM sleep provide an endogenous source of activation, possibly critical for structural maturation of the central nervous system which might lead to depression in later life.[131] This proposal led to a series of experiments looking at the role of REM sleep in brain development.

During the central nervous system (CNS) maturational processes in the late prenatal and neonatal periods, a large percentage of time is spent in REM sleep (up to 50% of all sleep in the first two weeks of life), characterized by endogenous, intense, generalized neuronal firing in most areas of the brain. The intensity of phasic neuronal activity during REM sleep is high in early development and diminishes as brain maturation is completed.[132] Roffwarg and coworkers were the first to propose that the primary purpose of REM sleep was to act as an "inducer" of CNS development in the fetus and the neonate.[133] Based on the early myelination of the sensory processing areas in the CNS, they further suggested that REM sleep serves to provide endogenous stimulation to these areas. Fetal movements that are anticipatory in nature (breathing, sucking, swallowing, yawns, stretches and eye movements) primarily seem to occur during REM sleep. Studies of REM sleep deprivation in animal models have provided consistent support for the role of REM sleep in brain maturation, as a suppression of REM sleep was capable of disrupting the aforementioned maturational processes.[134,135] Recent studies indicate that mechanisms of synaptic plasticity, which are important for brain development, remain susceptible to the effects of REM sleep deprivation in the adolescent rat.[135] The role of REM sleep for CNS development is further illustrated by studies indicating long-lasting behavioral changes due to REM sleep deprivation in the early development of rats.[136–138] Moreover, REM sleep deprived animals have a reduced brain size and display increased hyperactivity, anxiety, attention and learning difficulties and increased voluntary alcohol consumption. While environmental enrichment has been shown to enhance cortical maturation, this effect is abolished in rats having undergone prior REM sleep deprivation.[136] Vogel et al.[131] described that adult rats subjected to an animal model mimicking endogenous depression had the same distinctive REM sleep characteristics as healthy neonatal rats (i.e., displayed high amounts of REM sleep). The similarity suggests that an underdeveloped, relatively weak REM sleep inhibitory process may account for the REM sleep abnormalities of depression. Thus, Vogel et al.[131] hypothesized that the ontogeny of REM sleep suggests a developmental process that may be altered in humans predisposed to endogenous depression, and may account for the (life-long) REM sleep abnormalities of the disorder. Despite these intriguing findings the hypothesis of a role of REM sleep for CNS development needs to be more intensively studied in animal models of depression.

Interestingly, evidence from research into insomnia delivers additional data for the hypothesis that REM sleep deprivation processes might be involved in the origin of REM sleep abnormalities. Riemann et al.[139] recently speculated about REM sleep instability as a new pathway for insomnia and depression. Polysomnographic studies have shown that primary insomnia is characterized by a decreased percentage of REM sleep and increased EEG arousals during REM sleep.[140] Based on this observation, the "REM instability" hypothesis was advanced[139]: modest REM sleep reduction and fragmentation increases arousals and awakenings in patients with chronic insomnia and is associated with the experience of stress. Consistently, enhanced arousal during REM sleep might be partly perceived and memorized as wake and could result in the experience of disrupted and non-restorative sleep. With respect to the relationship with depression, this hypothesis suggests[139] that the chronic fragmentation of REM sleep in insomnia might interfere with basal processes of emotion regulation and with the underlying network functioning in a limbic and paralimbic system. With persistence of the insomnia, at some point a REM sleep rebound (as evidenced by shortened REM latency and increased REM density) might occur, which would facilitate the development of a depressive episode.

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This kind of reasoning is supported by a recent meta-analysis demonstrating that insomnia is an early and independent risk factor for the development of depression.[141] Summarizing, this line of thinking brings together ontogenetic data from REM sleep regulation, which clearly revealed high amounts of this sleep stage in early developmental periods in mammals, with REM sleep abnormalities observed in adult depression and evidence from insomnia research. It thus offers intriguing hypotheses, however, in its original version linked mainly to the subtype of endogenous depression, for which strong genetic influences are assumed.[28,29] In human psychopathology, the concept of endogenous depression has been criticized on many grounds as lacking validity.[5,40,76,77] As mentioned before, REM sleep abnormalities are not restricted to a specific subtype of depression; furthermore, serious doubts have been raised about the central postulate of Vogel that REM sleep suppression is a necessary prerequisite of any kind of antidepressive treatment and his original data showing that experimental REM sleep deprivation by awakenings acts as antidepressive were never successfully replicated. Insofar, weaknesses of the original theory seem to balance its merits. A new aspect to the idea of REM sleep deprivation being at the core of REM sleep disinhibition comes from insomnia research.[139,141]

Neuroimaging studies and REM sleep

Studies of depressed patients with neuroimaging methods document increased global cerebral metabolism during the first nonREM sleep period (=REM latency). Patterns of relative regional cerebral glucose metabolism changes from presleep wakefulness to nonREM sleep differ in health subjects and depressed patients. Specifically, the transition from wakefulness to nonREM sleep seems characterized by the relative persistence of elevated metabolic activity in frontoparietal regions and thalamus in depressed patients compared with healthy subjects.[142,143] These findings suggest that abnormal thalamocortical network function may underlie sleep abnormalities and complaints of non-restorative sleep in depressed patients. These findings provide further support for the hyperarousal hypothesis of some types of major depressive disorders.[142,143] Abnormal patterns of cerebral metabolism during nonREM sleep in depressed patients showed decreased relative frontal and abnormal limbic metabolic activity and striatal metabolism in association with posterior cortical increases, leading to the assumption of a hypofrontality pattern in depression.[142,143] Instead, from waking to REM sleep, an activation in the anterior paralimbic structures has been observed. Additionally, an activation in bilateral dorsolateral prefrontal, left premotor, primary sensorimotor, and left parietal cortices, as well as in the midbrain reticular formation, has been described.[144,146] On this basis it has been hypothesized that altered function of limbic/anterior paralimbic and prefrontal circuits in depression is accentuated during the REM sleep state and that this may be related to affective dysregulation.[144,146] The investigation of functional neuroanatomical correlates of sleep in depressed patients evidenced that REM density positively correlates with regional metabolic rate bilaterally. REM density appears to negatively correlate with relative regional cerebral metabolic rate in areas corresponding bilaterally to lateral occipital cortex, cuneus, temporal cortices and parahippocampal gyrus.[144–146] It has been hypothesized that since temporal and occipital cortices showed hypermetabolism during REM sleep in depressed patients compared with healthy controls, REM density might be an indirect correlate of metabolic activity in these areas.[145]

It has been hypothesized that since temporal and occipital cortices showed hypermetabolism during REM sleep in depressed patients compared with healthy controls, REM density might be an indirect correlate of metabolic activity in these areas.[145] Recently McNamara et al.[54] suggested that one mechanism that does directly reflect the pathophysiologic pattern of hyperactive paralimbic/ventromedial prefrontal cortex (vmPFC) and hypoactive dorsomedial prefrontal cortex (dPFC) in mood disorders might be "REM-hyperactivation or -disinhibition" driven. This neurometabolic activation/hypoactivation exactly characterizes, normal REM-related brain activation/deactivation patterns throughout the sleep cycle.[147–149] Several times per night, REM sleep selectively and intensively activates paralimbic/vmPFC systems and down-regulates dPFC systems.[150,151] This pattern of vmPFC overactivation and dPFC hypoactivation naturally occurs only in REM sleep.[54]

Taken as a whole, these findings indicate that the neuronal processes underlying sleep differ between brain regions in depression and that REM sleep dysregulations might be an indirect correlate of temporal and occipital cortices showing hypermetabolism in depressed patients. The hypothesis of McNamara et al.[54] which suggests that one mechanism that does directly reflect the pathophysiologic pattern of vmPFC hyperactivation/dPFC hypoactivation in mood disorders might be "REM-hyperactivation or -disinhibition" driven needs further investigation.

Stress, brain plasticity and REM sleep: the "allostatic load" hypothesis

The stress system represents an essential alarm system that is activated by internal and environmental stimuli, such as lack of information, loss of control, unpredictability or psychosocial overload. The stress system is subject to allostasis, i.e., by the adaptive response of the organism to stressful agents that comprehends systemic and behavioral changes essential to the development of the optimal individual homeostatic capability. These adaptive changes are produced by (neuro-)chemical mediators, such as catecholamines, glucocorticoids and cytokines that act on specific receptors localized in different organs.[152] Besides the physiological role of stress, stress "overload" is one of the most important causes of disease in western countries. Chronic stress leads to receptor desensitization and tissue damage, generating a state termed "allostatic load".[32–34] The latter has been proven to have far-reaching consequences, such as insomnia, depression and cardiovascular diseases.[153–155] In this respect, the study of bi-directional interactions between sleep and stress represents a crucial research field for preclinical medicine. Chronic sleep disruption can be regarded as both a stress result and a physiological stressor per se, since it impairs brain functions; it increases sympathetic tone, blood pressure and evening cortisol levels, and it raises blood levels of pro-inflammatory cytokines, insulin and glucose.[155] Experimental studies in rats have shown that chronic sleep curtailment gradually leads to neurobiological and neuroendocrine changes similar to those found in depression.[156] Preclinical studies demonstrate that chronically disrupted and restricted sleep can interfere also with hippocampal neurogenesis[157,158] and it may contribute to depression and other stress-related mental disorders.[124] The mechanisms by which sleep loss affects different aspects of adult neurogenesis are unknown. It has been proposed that adverse effects of sleep disruption may be mediated by the stress system and glucocorticoids.[37,155] A number of studies clearly show that prolonged sleep loss can inhibit hippocampal neurogenesis independent of adrenal stress hormones. These effects of sleep loss may endanger hippocampal integrity, thereby leading to cognitive dysfunction and contributing to the development of mood disorders.[124] Exposure to chronic stress causes alterations in REM sleep,[159] such as an increase of a) the duration of the first REM period, b) the density of eye movements, and c) an increase of the total REM sleep duration. In 1997, from a study on the effects of

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chronic stress on sleep in rats,[160] the authors stated that changes in REM sleep included increases in the duration of and transitions into REM sleep and a reduced latency to the onset of the first REM period. The authors hypothesized that these sleep abnormalities, in particular the decrease in REM latency, are consistent with those reported in depression. The REM sleep changes seem essential to link sleep both with stress and psychopathology. As mentioned above, short REM latency and increased REM density seem to be sustained by a central cholinergic hyperactivity, either absolute or relative.[67,161] Recent evidence indicates that pontine cholinergic REM-on cells are tonically activated during sleep by neuronal groups belonging to the amygdaloid complex.[162] This structure, which during wakefulness plays a key role in the modulation of emotional responses, such as fear, anxiety or stress, is overactivated in wakefulness[163] and in the sleep of depressed patients.[145] The hyperactivation of the amygdaloid complex and REM sleep alterations, sustained by HPA axis activation, thus seem to contribute to some depressive symptoms, such as insomnia, negative emotional memory consolidation and depressive mood.

The "allostatic load" hypothesis allows us to establish a connection between genetic polymorphisms and environment or stressful situations, and REM sleep alterations supposedly mark the transition between eu-stress and di-stress. In particular the role of REM sleep in emotional memory consolidation could explain the reinforcement of negative stimuli even unconsciously. On the other hand some subjects react to stress without an involvement of HPA axis, and thus the theory does not apply to this kind of population. For this kind of population the depressive outcome could be sustained by completely different mechanisms.

REM sleep dysregulation – an endophenotype for depression?

The psychological and neurobiological mechanisms underlying the onset and the maintenance of depression are assumed to be multifactorial with a proposed polygenic component; hence researchers are looking for markers which are characteristic of depression and provide complementary information about their distal genetic roots.[29,30] One of the most frequent approaches searches for so-called "endophenotypes",[165,166,198] which can be markers on a "… neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological …" level.[167] Endophenotypes are thought to represent a bridge between the involved genes and overt, measurable behavioral abnormalities[167]; as such they also represent relatively elementary functional phenomena of any behavior and are encountered in mental disorders where they should help to identify responsible gene(s).[28,29]

Recently, the REM sleep disinhibition of depression was suggested as a good candidate for an endophenotype for depression.[28–30] According to Tsuang,[168] endophenotypes should fulfill the following specific criteria: a) the marker must be specifically associated with the illness in the general population; b) state-independent stability over time, observable also in partial or complete remission; c) heritability, associated with genetic variance; d) familial association should segregate with illness within families; e) co-segregation should be observed at a higher rate among unaffected family members compared with the general population.

REM sleep dysregulation in depression indeed shows state-independent stability over time, observable also in partial or complete remission (especially REM density). In many patients, changes in REM sleep persist despite full clinical remission and seem to be associated with an increased relapse risk.[169] REM sleep dysregulation in depression shows heritability, associated with genetic variance. High risk studies in relatives supported the existence of a genetic influence on depression, sleep and its regulation. Sleep studies in relatives of depressed subjects, including healthy monozygotic and dizygotic twin pairs, found a greater concordance of sleep patterns among monozygotic twins than dizygotic twins.[170] Giles et al.[20,21] investigated the polysomnographic parameters in first-degree relatives of unipolar patients, classifying these probands according to the presence or absence of a reduced REM latency in the index patient. In the "short REM latency" group, they found sleep-EEG alterations similar to those of depressed patients regardless of a personal history of depression. Moreover, psychiatric illness prevalence, especially depression, was very high among relatives with reduced REM latency and it was almost three times greater than for those with normal REM latency.[21] In a subsequent investigation[22] parents and probands of unipolar depressed patients were evaluated for their lifetime history of psychiatric disorders and for their sleep-EEG profile. Shortened REM latency was found to be familial and to be associated with an increased risk of major depression beyond the "normal" familial risk. Sitaram and Gillin[81] applied the cholinergic REM induction test to a sample of depressed patients and their relatives and observed a much faster induction of REM sleep in relatives with a lifetime diagnosis of depression compared to relatives without such a diagnosis. Summarizing, though not unequivocal, the bulk of the evidence points out that altered REM sleep parameters, especially increased REM density, may constitute an endophenotype for depression.[171]

Genes that are discussed to be involved in the pathogenesis of depression include cholinergic receptor genes, which are also involved in REM regulation,[172] circadian clock genes,[173] which might be important because of the strong circadian modulation of REM sleep propensity, and genes involved in the orexinergic system (a neuropeptide which is also involved in REM sleep regulation). Regarding the latter, the human leukocyte antigen (HLA) DQ6, allele form DQB1*0602, and genes for the hypocretin receptors are particularly interesting because they might be involved in REM sleep dysregulation in depression and stress.[174] Moreover, basic research targets sleep's underlying genetics in general,[175,176] implying that the cyclic adenosine monophosphate-response element binding protein gene (i.e., CREB1 gene), is involved in REM sleep regulation, memory consolidation, and major depression.[177] Though the identification of vulnerability genes for depression is still an open field, endophenotypes, such as REM sleep changes, can decisively help in the search by reducing the phenotypic heterogeneity of major depression.

Role of REM sleep dysregulation for the genesis of depressive symptoms – a synopsis

Though REM sleep changes in depression have been known for decades, their role in the pathogenesis of depressive symptoms has never been adequately clarified.[12,13,35] Main symptoms of depression are: depressed mood, emotional imbalance, cognitive dysfunctions and distortions, diminished abilities in attention and concentration, cognitive impairments including learning and long-term memory, and deficits in working memory, short-term memory, and selective attention.[8,178] Intentional and mnemonic biases toward processing of mood-congruent information and memories are also reliable and relatively specific findings for depression.[8,179,180]

Sleep has been implicated in both the encoding and the consolidation of memory.[181] Without adequate sleep, hippocampal function becomes markedly altered, resulting in a decreased ability for storing new experiences.[181] An influential hypothesis postulated the importance of nonREM and REM sleep for both declarative and procedural memories.[182–184] It was hypothesized that REM sleep dysregulation in depression might negatively impact on the neurocognitive features of the disorder having a role in both

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depressive cognitive distortions and dysfunctions.[54] Moreover, insomnia and REM sleep dysregulation in depression might have a key role in the emotional brain processing of depressed patients.[181,185–187] Both areas will be reviewed in detail below.

Cognitive distortion/dysfunction and REM sleep

In 1986, Giles et al.[188] showed a correlation between REM sleep alterations in depression and some clinical features of depressive symptoms. Consistently, among so-called "endogenous" depressive symptoms, anhedonia, unreactive mood and appetite loss were reported to be related to short REM latency in depressed patients.[188] The additional finding that both selective REM sleep deprivation and total sleep deprivation provide immediate, though only temporary, relief for some patients with mood disorders,[189–191] supported the claim that REM sleep does indeed play a role in the genesis of at least some clinical symptoms in depression. A role of REM sleep in overnight regulation of negative mood has been suggested recently.[192,193] REM sleep related indices, such as REM density, have been strongly correlated with neurocognitive distortions in depression such as autoaggression, suicidal ideation, rumination and difficulties in concentration.[188,190,192] More recently, McNamara and colleagues[54] explored the possibility that REM sleep physiology might differentially impact the neurocognitive symptoms of depression including executive cognitive dysfunction and distorted evaluative appraisals of self, unpleasant dream content and biased emotional memory processing. McNamara et al.[54] hypothesized that REM sleep physiology significantly contributes to the production of these cognitive distortions in depressed patients. The authors found a significant reduction in positive ratings and a significant increase in negative ratings of the self after awakenings from REM sleep but not nonREM sleep in depressed/anxious persons, thus demonstrating an impact of REM sleep on the cognitive appraisal of the self-concept. Moreover the dream-self was rated as negative relative to both a significant other and daytime-self after REM sleep awakenings. These are important clinical findings as both REM sleep related indices and poor self-concept predict mood dysfunction and suicidal ideation and attempts.[192] The authors also found a greater production of emotionally negative memories after REM sleep awakenings. Negative memories were retrieved more quickly after REM sleep awakenings vs. nonREM sleep awakenings or wake conditions. Dreams from REM sleep contained greater amounts of negative emotion and aggression than did nonREM sleep dreams. These results suggest that REM sleep in itself may significantly contribute/reinforce cognitive distortions typical for mood disorder.

Emotion regulation and REM sleep

Despite substantial research focusing on the interaction between sleep and cognition the impact of sleep dysregulation on affective and emotional regulation has received only limited attention. Nevertheless, a number of recent studies offer an emerging understanding for the critical role of sleep in regulating emotional brain function.[187] Sleep might play an important role in both affective reactivity[187,194] and emotional information processing.[181] Insomnia, which is a common feature of depression, is associated with altered subjectively reported emotional reactivity.[187] Impairments in emotional responses objectively measured have also been found, although available data are still too few up to now[187] and the exact nature of this impairment is still controversial. Both conditions of sleep loss and deprivation continue to be associated with maladaptive emotional regulation, leading to exaggerated neural and behavioral reactivity to negative, aversive experiences. Sleep loss is shown to amplify negative emotional consequences of disruptive daytime events while blunting the positive benefit associated with rewarding activities.[195] Sleep deprivation is commonly associated with increased subjective reports of irritability[194] and determines an amplified hyperlimbic reaction by the human amygdala in response to negative emotional stimuli.[196] Furthermore, a loss of functional connectivity with the medial prefrontal cortex in the sleep deprivation condition implies a failure of top-down inhibition by the prefrontal lobe.[196] Recently, it was hypothesized that sleep deprivation not only is associated with enhanced reactivity toward negative stimuli, but indicates a bi-directional nature of affective imbalance, associated with amplified reward-relevant reactivity toward pleasure-evoking stimuli. Such findings may offer a neural foundation on which to consider interactions between sleep loss and emotional reactivity in mood disorders.[197] Nevertheless, it appears that a night of sleep may "reset" the correct affective brain reactivity to next-day emotional challenges by maintaining functional integrity of the medial prefrontal cortex–amygdala circuit and thus govern appropriate behavioral repertoires.[198] Recently, a benefit of REM sleep in decreasing next-day brain reactivity to recent waking emotional experiences[199] was suggested. Suppression of central adrenergic neurotransmitters during REM coupled with activation in amygdala–hippocampal networks that encode salient events, is proposed to re-process and depotentiate previous affective experiences, decreasing their emotional intensity. REM sleep physiology seems associated with an overnight dissipation of amygdala activity in response to previous emotional experiences, altering functional connectivity and reducing next-day subjective emotionality.[199] In contrast, the failure of such mechanisms during REM sleep has been described in depressive disorders contributing to exaggerated amygdala reactivity, affective reactivity and emotion imbalance of depression. Sleep is also involved in the processing of emotional information.[181] There is a wealth of evidence demonstrating that memory processing is modulated by emotion.[200,201] Moreover, aspects of REM and nonREM sleep neurobiology have been implicated in the facilitation of various types of memory consolidation.[202,203] REM sleep seems to be specifically involved in emotional memory and appears to facilitate the consolidation of memories with negative valence.[204,205] To date numerous investigations have begun to test a selective REM-dependent hypothesis of affective human memory consolidation based on the consideration that both sleep and emotion modulate processes of memory consolidation.[204,206] The actual model of sleep-dependent emotional memory processing is the "sleep to forget and sleep to remember" hypothesis.[207] When formed, a newly encoded "emotional–memory" is created in a milieu of high adrenergic tone, it results in an associated affective "blanket." With multiple iterations of sleep, particularly REM sleep, memory, contained within that affective experience strengthens overnight(s), resulting in improved memory for that event, the autonomic tone "enveloped" around the memory becomes gradually ameliorated, leading to emotional forgetting. The neuroanatomical, neurophysiological and neurochemical conditions of REM sleep might offer a unique biological state in which to achieve both a balanced neural potentiation of the informational core of emotional experiences, the memory, and also depotentiate and ultimately ameliorate the autonomic arousing load originally acquired at the time of learning, the emotion.[207,208] Neurochemically, levels of limbic and forebrain acetylcholine (ACh) are markedly elevated during REM sleep.[209] Considering the known importance of ACh in the long-term consolidation of emotional learning,[201] the pro-cholinergic REM sleep state may result in a selective facilitation of affective memories, similar to that reported using experimental manipulations of ACh.[210] Thus, one of the most intriguing hypotheses of emotional brain processing is the "REM sleep hypothesis of

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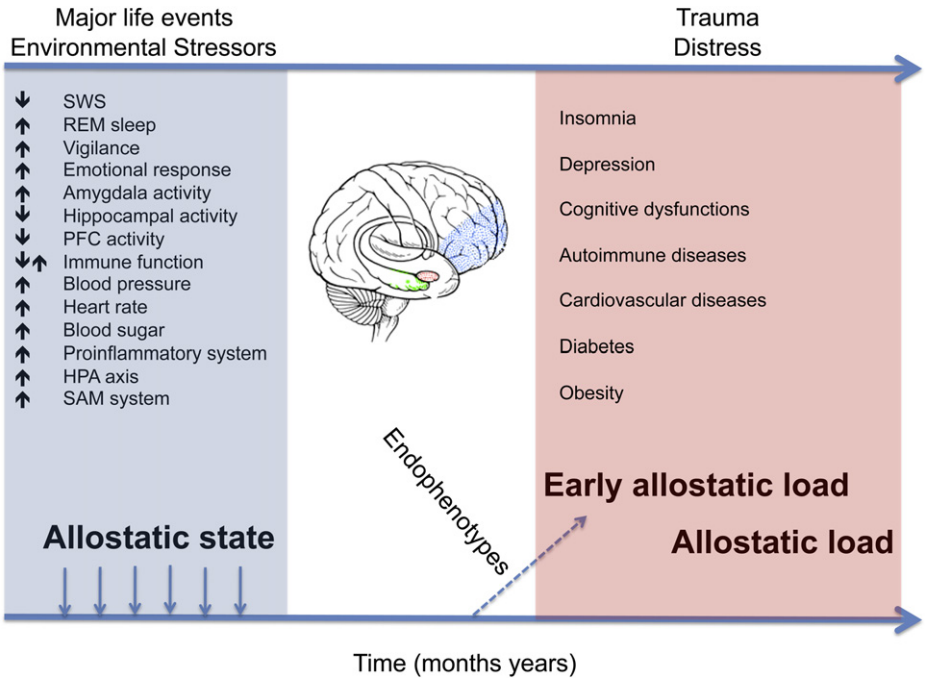

Fig. 3. Brain as core structure of the effect of allostatic state and allostatic load. Major life events and environmental stressors modulate the regional brain response to stressors (allostatic state), in particular of hippocampus (green), the first higher brain centre target of stress hormones, amygdala (red) and prefrontal cortex (PFC, blue). If this response holds for a long time (months or years) it can induce the so-called allostatic load which in turn influences the susceptibility to insomnia, depression, cardiovascular disease, diabetes, and so on. This connection can occur earlier in the life only when chronic stress response is amplified by specific endophenotypes. On the left side (blue) the classical stress response, while on the right side the pathological effect of the allostatic load. SWS: slow wave sleep; HPA axis: hypothalamic–pituitary–adrenal axis; REM: rapid eye movement; SAM system: sympatho–adreno–medullary system. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

emotional memory processing" that ascribes to REM sleep the crucial role in the affective modulation of human brain function. This model predicts that a pathological increase in REM, as seen in depression,[13,14] may disproportionately amplify the strength of negative memories, so much that it would create a perceived autobiographical history dominated by an excess of negative memories.

Conclusions

Strong links exist between the dysregulations of REM sleep and the course of major depressive disorders, as the presence of these abnormalities seems to increase the risk of onset, recurrence, relapse and even impacts on treatment response regardless of treatment method applied. REM sleep disinhibition not only seems to qualify for a vulnerability and trait-marker for depression, but even is a likely candidate for a "true" endophenotype. Several hypotheses were suggested to explain the underlying neurobiology of REM sleep changes. Doubtlessly, knowledge from basic sleep research about the processes involved in nonREM–REM patterning has been extremely fruitful for psychopathological research, as evidenced by the emphasis on cholinergic or orexinergic mechanisms being involved in sleep regulation and mood disorders. A key role for REM sleep has been emphasized in regulating affective reactivity and emotional information processing in depression. Neurometabolic alterations in depression might even be considered to be driven or at least reinforced by "REM sleep hyperactivation". This relation is mediated by complex neurobiological modifications that involve noradrenergic, serotoninergic, cholinergic, orexinergic systems and the stress system. Stress-related REM sleep hyperactivation/disinhibition could affect adult neurogenesis and thus might endanger hippocampal integrity, thereby contributing to the development of mood disorders through allostatic load.

A genetic influence on REM sleep changes in depression is likely: genes that may be related to both depression and REM sleep regulation include cholinergic receptor genes, circadian clock genes and orexinergic mechanisms. We propose a model (Fig. 3) in which REM sleep dysregulation in depression may be related to the individual response to stress acknowledging a genetic vulnerability factor. The brain is the key organ to perceive and process stressful stimuli and to react to them, thus determining the physiological, behavioral and psychological responses to stressors. Brain regions such as the hippocampus, amygdala, and prefrontal cortex respond to acute and chronic stress by undergoing structural remodeling (i.e., brain plasticity), which in turn alters behavioral and physiological, and emotional responses.[32–34] If the process is maladaptive, allostatic load can affect vulnerability to brain-dependent and stress-related mental conditions contributing to the development of mood disorders.[32–34,164] It is assumed that REM sleep alterations not only reflect maladaptive coping with stress but are also involved in maintaining these processes.

Practice points

1) REM sleep dysregulation seems to constitute a trait or vulnerability marker of depression, by increasing the risk of onset, recurrence, and relapse and modify treatment response regardless of treatment method applied. REM sleep alterations do not seem to be strictly specific for depression, but might play a role also in other psychiatric disorders.
2) REM sleep alterations significantly contribute to the production of cognitive distortions and dysfunctions, through the effect on memory functions. Additionally, a key role of REM sleep has been shown for affective reactivity and emotional information processing: a REM sleep hypothesis of emotional memory processing has

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been proposed. REM sleep dysregulation might also contribute to neurometabolic alterations in depression that seem "REM-hyperactivation or disinhibition" driven.

3) REM alterations in depression seem mediated by complex neurobiological modifications that involve noradrenergic, serotoninergic, cholinergic, hypocretinergic systems and stress system which can affect adult neurogenesis and brain plasticity. Moreover, increase of stress hormones might affect adult neurogenesis and it may endanger hippocampal integrity, thereby contributing to the development of mood disorders (allostatic load). A key role of REM sleep alterations in the pathogenesis of depression has been indicated within the defect of brain maturation hypothesis. In this case a defect in the ontogeny of REM sleep might endanger hippocampal integrity, contributing to the development of mood disorders.
4) REM sleep changes in depression might be under a genetic control: genes that may be related to depression include cholinergic receptor genes that are involved in REM regulation, circadian clock genes and REM sleep regulation by hypocretin that are involved in REM sleep dysregulation, depression and stress. In the search of new "vulnerability markers" or "endophenotypes" for depression, changes during the REM sleep period have been considered of potential interest.
5) REM sleep dysregulation in depression may be related to the individual response to stress acknowledging a genetic vulnerability factor. The brain is the key organ to perceive and process stressful stimuli and to react to them, thus determining the physiological, behavioral and psychological responses to stressors. Brain regions such as the hippocampus, amygdala, and prefrontal cortex respond to acute and chronic stress by undergoing structural remodeling (i.e., brain plasticity), which in turn alters behavioral and physiological, and emotional responses. If the process is maladaptive, allostatic load can affect vulnerability to brain-dependent and stress-related mental conditions contributing to the development of mood disorders.

Research agenda

1) The contributing role of REM sleep in the establishment of depressive symptomathology, by facilitating cognitive dysfunctions/distortions and altering emotional processes should be more deeply evaluated. Longitudinal studies, both observational and interventional, to describe the sequences are necessary.
2) Studies should take into account the role of genetical, neurochemical and neurobiological factors in the relationship between REM sleep and depression. Especially, the role of the hypocretin system in the relationship between sleep, stress and depression seems to be relevant.
3) The role of REM sleep in conditions strictly associated with depression, such as insomnia, should be better understood as it could be relevant to understand psychiatric consequences.

Conflicts of interest

All authors report no financial or other relationships relevant to the subject of this article.

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