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THEORETICAL REVIEW

The microstructure of REM sleep: Why phasic and tonic?

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SUMMARY

Rapid eye movement (REM) sleep is a peculiar neural state that occupies 20–25% of nighttime sleep in healthy human adults and seems to play critical roles in a variety of functions spanning from basic physiological mechanisms to complex cognitive processes. REM sleep exhibits a plethora of transient neurophysiological features, such as eye movements, muscle twitches, and changes in autonomic activity, however, despite its heterogeneous nature, it is usually conceptualized as a homogeneous sleep state. We propose here that differentiating and exploring the fine microstructure of REM sleep, especially its phasic and tonic constituents would provide a novel framework to examine the mechanisms and putative functions of REM sleep. In this review, we show that phasic and tonic REM periods are remarkably different neural states with respect to environmental alertness, spontaneous and evoked cortical activity, information processing, and seem to contribute differently to the dysfunctions of REM sleep in several neurological and psychiatric disorders. We highlight that a distinctive view on phasic and tonic REM microstates would facilitate the understanding of the mechanisms and functions of REM sleep in healthy and pathological conditions.

Introduction: Rapid eye movement sleep (REM) sleep is not a homogeneous state

REM or paradoxical sleep is a fundamental sleep state, especially in terrestrial mammals [1] and birds [2]. The distinguishing electroencephalographic (EEG) features of REM sleep are low amplitude, mixed-frequency waves that, when contrasted with non-REM (NREM) sleep, resemble wakefulness. In addition, REM sleep is characterized by skeletal muscle atonia due to brainstem-mediated inhibition of alpha motor neurons, as well as the burst-like occurrence of saccadic eye movements and peripheral muscle twitches [3]. REM sleep has also been most dominantly associated with dreaming experiences, although dreams can occur during other stages of sleep as well [4]. REM sleep occupies around 20% of nighttime sleep in healthy human adults, and even more in newborns and infants, before NREM sleep becomes the dominant sleep state [3]. The large amount of REM sleep, particularly in mammals, who undergo substantial development from birth, led to the hypothesis that REM sleep is critical for brain maturation [5]. Indeed, empirical data indicates that REM-related muscle twitches contribute to the development of the sensorimotor system [6,7]. In addition, REM sleep functions putatively encompass a wide range of neural and cognitive phenomena from basic mechanisms such as the regulation of brain temperature [8], modulation of receptor sensitivity [9], and synaptic plasticity [10], to more complex processes such as procedural [11] and declarative [12] learning, emotional memory processing [13,14], or the development of consciousness [15].

Although our knowledge regarding the complex neural circuitry that orchestrate REM sleep increased substantially in the last decade [16,17], the functions and precise mechanisms of this intriguing neural state remain rather elusive more than 65 y after its scientific discovery [18,19], urging researchers to adopt new approaches. We propose here that exploring the fine microstructure of paradoxical sleep is a promising way to provide new insights

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Abbreviations

BOLD	blood oxygen level dependent
EEG	electroencephalography
ERP	event related potential
fMRI	functional magnetic resonance imaging
HFO	high frequency oscillations
MD	major depression
PGO	ponto-geniculo-occipital
PTSD	post-traumatic stress disorder
RBD	REM sleep behavior disorder
SOZ	seizure onset zone
TMR	targeted memory reactivation
WPLI	weighted phase lag index

Glossary of terms

Microarousals	short-lasting events during sleep that involve wake-like electroencephalographic (alpha and beta) activity, and occasionally, increases in muscle tone and autonomic activity (e.g., heart rate)
K-complex	Typical large amplitude, low frequency (1–2 Hz) waveform of stage 2 sleep that can be elicited by external stimulation, but may also occur spontaneously. It has important roles in sleep regulation and information processing during NREM sleep
Slow oscillations	Bursts of low frequency (<1 Hz), large amplitude EEG waves that occur predominantly during deep sleep and reflect the coordinated activity of neural ensembles consisting of an alternation of active periods (Up states) and silent periods (Down states)
Sleep spindles	Bursts of electroencephalographic oscillatory activity arising from thalamocortical oscillations during stage 2 and slow wave sleep in a frequency range between 9 and 16 Hz and a duration of approximately 0.5–1 s. They are involved in many functions including sensory gating, synaptic plasticity, and memory consolidation
PGO waves	Ponto-geniculo-occipital waves are electric potential that can be recorded from the pons, the lateral geniculate and the occipital cortex. PGO waves were first described in cats, but have analogs in other mammals, including humans. PGO waves are prominent in REM, especially, phasic REM sleep
Sawtooth waves	Characteristic 2–4 Hz rhythmic oscillations during REM sleep that have a triangular shape and maximal amplitude at frontocentral locations
ERPs	Event related potentials reflect electroencephalographic activity time-locked to a specific sensory, cognitive or motor event. ERPs are extracted by averaging multiple trials of EEG oscillations time-locked to a specific input
TMR	Targeted memory reactivation is a paradigm that aims to selectively facilitate the consolidation of specific memories during sleep. In TMR studies researchers presenting stimuli during sleep that were associated to specific memory elements in a learning phase before falling asleep
Neural synchronization	Here we refer to long-range neural synchronization that is a statistical property reflecting the temporally correlated activity of distant neural ensembles in different oscillatory properties (e.g., phase, amplitude)
α-synucleinopathy	Neurodegenerative disease exhibiting the excessive accumulation of aggregates of alpha-synuclein protein in neurons, nerve fibers or glial cells
Homeostatic sleep drive	The homeostatic pressure to fall asleep and to enter into deep NREM sleep. The homeostatic sleep drive is increasing after prolonged wakefulness following a logarithmic function
Forced desynchronization protocol	A technique in chronobiological research that induces a misalignment between the homeostatic sleep drive and the circadian rhythm and is achieved by depriving participants from the signals of time (e.g., changes in daylight) as well as by manipulating the timing of sleep and wake periods

into the understanding of this peculiar sleep state. This approach has already been successfully applied in the study of NREM sleep, eventually disclosing a wealth of valuable information, far beyond the appearance and distribution of discrete sleep states (i.e., sleep architecture). The identification of short lasting cortical events such as *microarousals*, *K-complexes, slow oscillations*, and *sleep spindles* does not simply provide a more accurate description of the constituents of NREM sleep [20,21], but examining the characteristics (e.g., morphology, density, topography, or frequency) of these transient EEG activities led to remarkable findings regarding their roles in cognitive functioning in healthy and pathological conditions [22–25]. We believe that similar advances can be made by examining the microstructure of REM sleep.

Whereas the heterogeneity of NREM microstates is now well established, REM sleep remains commonly treated as a homogeneous state characterized by desynchronized EEG, rapid eye movements and muscle atonia. However, recent studies seem to challenge a view of REM sleep as a uniformly desynchronized state [26,27]. Moreover, it has been known for a long time that REM sleep is characterized by the alternation of two microstates, namely the phasic and tonic REM periods (Fig. 1.). Although the need for the distinction between these microstates was first proposed by Moruzzi in 1963 [28], studies, especially human research focusing on the mechanisms and putative functions of REM sleep scarcely examine phasic and tonic phases as different neural states. Consequently, overlooking the multidimensional nature of REM sleep makes the integration of research data difficult, eventually contributing to inconsistent findings. In this review we highlight empirical findings indicating that phasic and tonic periods are markedly different brain states with respect to spontaneous and evoked cortical activity, information processing, and mental experiences. Furthermore, we emphasize the relevance of REM

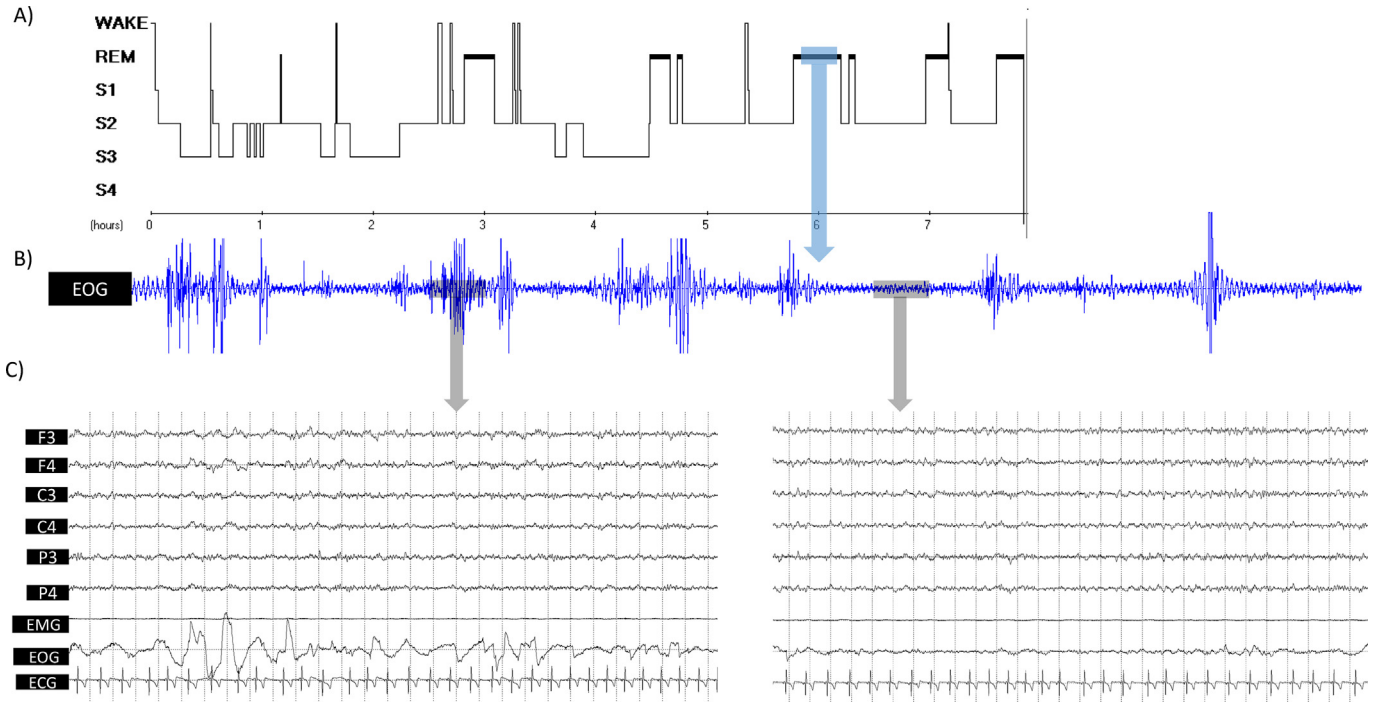

Fig. 1. Phasic and tonic REM microstates. A) The hypnogram of a healthy human participant. REM sleep cycles reappear 4–5 times a night and last approximately 20 min.. B) A 15-min long REM sleep segment of EOG activity. Periods with rapid eye movements (phasic REM) as reflected by bursts of increased EOG amplitudes, and periods without eye movements (tonic REM) as reflected by reduced EOG amplitudes alternate within the REM segment. C) A 30 s long period of phasic (on the left) and tonic (on the right) REM sleep. The time series represent frontal (F3, F4), central (C3, C4) and parietal (P3, P4) EEG, and electromyographic (EMG), electrooculographic (EOG), and electrocardiographic (ECG) activity.

microstates in the study of sleep-related disorders, and raise open questions that have broader implications for future studies aimed at investigating the mechanisms and functions of REM sleep.

Environmental alertness versus internally focused processing

The phasic periods of REM sleep are characterized by bursts of eye movements linked to so-called ponto-geniculo-occipital *(PGO) waves* [29], contractions of the middle ear muscles, myoclonic twitches of skeletal muscles, *sawtooth waves*, as well as irregularities in respiratory and cardiac activity [30]. Tonic REM sleep, in contrast, consists of the longer and apparently more quiescent segments in between periods of phasic activity. Although phasic periods are considered as more activated states compared to tonic REM sleep, the reverse seems to be the case with respect to environmental alertness. Indeed, studies delivering acoustic stimulation during sleep showed that behavioral responsiveness [31] (e.g., estimated by the speed at which a button is pressed in response to the acoustic stimulation) is higher, and the arousal threshold [32] lower during tonic periods in contrast to phasic ones. Also, processing of external stimuli, which is often quantified by event related potentials (ERPs) elicited by acoustic stimulation during different sleep stages including REM sleep [33], also seems to differ between REM sleep microstates. The few studies that examined ERPs in phasic and tonic microstates converge in showing reduced external processing during phasic periods, whereas evoked responses are to some extent preserved during tonic periods [34–36]. Notably, two evoked potential peaks are clearly visible 200 and 400 ms after deviant stimuli (e.g., an infrequent tone embedded in frequent ones) during tonic REM sleep [34,35], while changes in auditory inputs are not followed by prominent ERPs in the phasic states. In a subsequent experiment from the same group [36], participants were instructed to attend to the deviant tone during one of the two experimental nights. Under this condition, the later P400 component in response to deviant tones was even more pronounced during the tonic state, suggesting that higher attentional control improves external processing in tonic periods. In sharp contrast however, the instruction to attend to the target stimuli did not modify the evoked responses in the phasic periods. These findings indicate that at least in the auditory domain, the processing of external information is largely reduced in phasic, but partially reinstated during tonic REM sleep (see Fig. 2).

Phasic REM periods seem somewhat incompatible with sensory stimulation, as the latter inhibits rapid eye movements and facilitates the transition to the tonic state [37]. Therefore, the analysis of phasic microstates by functional magnetic resonance imaging (fMRI) is extremely difficult due to the noise and vibrations produced by the MR environment [38]. In spite of these challenges, Wehrle and colleagues [39] succeeded to analyze brain reactivity to acoustic stimulation during REM sleep. Although in most cases acoustic stimulation suppressed phasic REM activity (and shifted sleep to tonic REM), three participants remained in the phasic microstate during the stimulation period, allowing preliminary comparisons of brain activity between wakefulness, phasic REM, and tonic REM sleep. In line with the findings of ERP studies, cortical reactivity was largely reduced during phasic, but preserved to some extent in tonic periods as compared with cortical responses during wakefulness (Fig. 2). In sum, during phasic periods, external information processing appears to be attenuated, and cortical activity to be detached from the surrounding environment, in contrast to tonic REM sleep in which alertness and environmental processing are partially maintained, thus resembling a wake-like state.

What is the mind focused on during the phasic state if disconnected from the external environment? A possible answer is that the brain engages in intrinsically generated cognitive processes

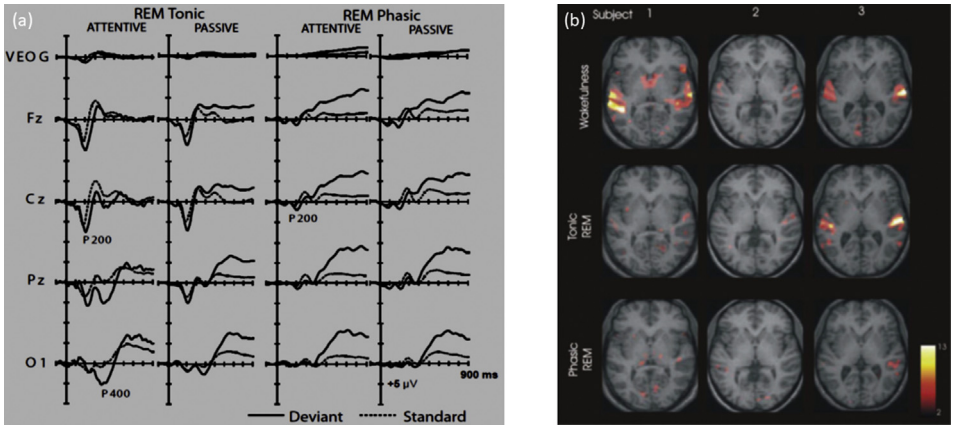

Fig. 2. External information processing during phasic and tonic REM periods. (a) Evoked potentials (P200 and P400) in response to acoustic stimuli are more pronounced in tonic than phasic REM sleep, and deviant tones elicit an even larger P400 response during tonic REM sleep in posterior sites when participants are instructed to attend to the stimuli, whereas no such late responses are seen in phasic periods regardless of the instructions [36]. (b) Blood oxygen level dependent (BOLD) responses to acoustic stimulations during wakefulness, tonic and phasic REM sleep in three participants. Activity in the auditory cortex increased upon stimulation in wakefulness, and was present to some extent in tonic but not phasic state periods [39]. Reproduced with permission from [36,39], Oxford University Press and John Wiley and Sons, respectively.

during phasic periods, in particular in sensorimotor activity that underlies intense dream experiences. In line with this notion, early studies linked intense dream experiences to bursts of eye movements (i.e., phasic REM periods) [40], and individuals awakened from phasic REM periods reported more movement, self-participation and less thought-like material compared to when awakened from tonic states [41]. Though the reliability of these early findings is admittedly disputable, a more recent study showed that suppressing REMs by acoustic stimulation not only facilitated the transition to tonic REM sleep, but decreased the rate of visual imagery reports collected after awakening [37]. Beyond subjective reports, recent studies that analyzed cortical activity in epileptic patients implanted with intracranial electrodes confirmed intense sensorimotor activity during phasic REM sleep, reminiscent of waking experiences. More specifically, ERPs and single-unit activity time-locked to REMs in the Medial Temporal Lobe (MTL) as measured by depth electrodes, showed striking similarities to the responses elicited by the presentation of images during wakefulness [42]. Another study using intracerebral electrodes showed that oscillatory activity in the motor cortex during the phasic state is similar to the pattern seen in wakefulness during an executed voluntary movement, while tonic states resemble relaxed wakefulness [43].

To sum up, studies examining the effects of auditory stimulation on REM microstates confirm the heterogeneity of REM sleep, and suggest that tonic periods are intermediate states between phasic REM sleep and wakefulness with respect to external information processing. Whether this restored environmental alertness is restricted to simple tasks such as auditory discrimination or enables more complex processing, possibly even learning [44] is still unexplored and remains a generally controversial issue in sleep research.

REM and learning: a controversial topic

In the last decade, NREM sleep has been given the prominent role in learning and memory consolidation processes, whereas REM sleep was deemed less consistent (for a review see Ref. [45]). Still, we have clear evidence for the spontaneous replay of learning-related neuronal patterns during REM sleep both in rodents [46] and humans [11,47]. In rodents, decreasing firing rates and increased synchrony in hippocampal CA1 during the course of sleep are correlated with the power of theta oscillations during REM episodes, furthering a role for REM sleep in sleep-related neuronal plasticity [48]. Human Targeted Memory Reactivation (TMR) studies also support complementary roles for NREM and REM sleep; successful integration of new words into existing knowledge following repeated presentation of learned words during NREM sleep was actually predicted by the time spent in REM sleep [49]. Furthermore, pontine wave activity was found causally linked to memory consolidation in rodents [50,51], suggesting a specific role for the phasic component of REM sleep.

In addition, recent studies investigated hypnopedia, i.e., the ability of the sleeping brain to learn *de novo* information. In line with studies demonstrating the conditioning of lick suppression responses in rats during NREM and REM sleep [52], humans were able to learn novel paired tone-odor associations during both sleep stages. However, only associations learned during NREM sleep were transferred to subsequent wakefulness [53], suggesting that even if an elementary form of learning (i.e., conditioning) took place during REM sleep, it was not consolidated enough to be transferred in another state of vigilance. Why these associations created during REM sleep are not preserved remains to be investigated. At variance, formation of perceptual acoustic memories was found possible during REM and light NREM sleep, and transferrable to wakefulness, whereas learning was suppressed when exposure took place during slow wave sleep [44]. Noticeably, learning in REM sleep was primarily driven by tonic REM in this latter study. Nonetheless, learning and processing capabilities during sleep appear limited to elementary mechanisms. Indeed, although partial auditory event-related potential mismatch responses were observed during REM and NREM sleep, higher-order prediction errors completely vanished [54]. Likewise, despite the preservation of basic auditory processing, learning auditory statistical regularities [55] or high-level speech parsing [56] were abolished during both REM [56] and NREM sleep [55,56]. Systematically investigating the respective roles of tonic and phasic REM sub-states and their interaction with other states of vigilance to achieve efficient information and memory processing is a promising approach to be developed.

Spontaneous oscillatory activity during phasic and tonic microstates

Sleep EEG analysis is an easily applicable and efficient procedure to examine spontaneous cortical oscillations in different states of

vigilance in healthy and impaired sleep as well as to characterize subtle fluctuations in arousal and the profoundness of sleep [57]. Studies focusing on the extent of frequency-specific power in REM microstates reported a relative increase in alpha and beta frequency band power during tonic states [58–60], particularly over the high-alpha and beta (12–30 Hz) frequency ranges [60,61] (Fig. 3/a). This pattern of oscillatory activity was also evidenced by intracranial recordings with electrodes located in the orbitofrontal [62] and motor [43] cortex of epileptic patients.

These oscillations in tonic REM sleep converge with the abovementioned findings suggesting increased environmental alertness in the tonic state. Indeed, high alpha and beta power measured in resting wakefulness is associated with a neural network that maintains alertness and facilitates the processing of external stimuli [63]. Alternatively, decreased high alpha and beta oscillations during the phasic state (that in fact bears strong resemblance to oscillatory activity during executed and imagined movements) might reflect sensorimotor activity (i.e., related to dreamt movements during phasic REM sleep). On the other hand, alpha and beta band activity reappearing during the tonic state is analogous to the pattern observed in relaxed wakefulness [43,61] (Fig. 3/b). On a related note, alpha and beta band power was assumed to maintain the current sensorimotor set and to enable a sustained state at the expense of voluntary (or imagined) movements [64]. These interpretations are not in the least conflicting, as environmental alertness during tonic periods may require the suppression of motor and visual imagery in order to efficiently anticipate, process and react to external stimulation.

Although the neural networks underlying increased high alpha and beta power during the tonic state remain largely unexplored, a recent investigation provided some preliminary insights into the neural sources of these oscillations [61]. In this high-density EEG study, associative areas (e.g., the supramarginal gyrus, the inferior parietal and inferior frontal lobules, and the superior frontal gyrus) and regions critical in auditory processing were identified as sources of relatively increased alpha and beta activity during tonic REM sleep. These potential sources point to the involvement of neural structures which during wakefulness support the higher-order cognitive functions (e.g., attention) required for monitoring the external environment. In addition, sensorimotor areas were identified as sources of high alpha and beta power [61], in line with the assumption that these oscillations reflect the suppression of sensorimotor imagery in tonic REM sleep, similarly to the sustained state of relaxed wakefulness [43]. In addition, a study that analyzed large-scale *neural synchronization* in REM microstates showed that phase synchronization of alpha and beta frequencies is relatively increased during tonic periods, and resemble the pattern of resting wakefulness [65]. More specifically, long-range neural synchronization (i.e., phase synchrony across distant electrode pairs) in tonic REM sleep exhibited intermediate values with respect to the alpha range between phasic REM sleep and resting wakefulness, and did not differ in the case of the beta range (15–25 Hz) from wakefulness (Fig. 3/c).

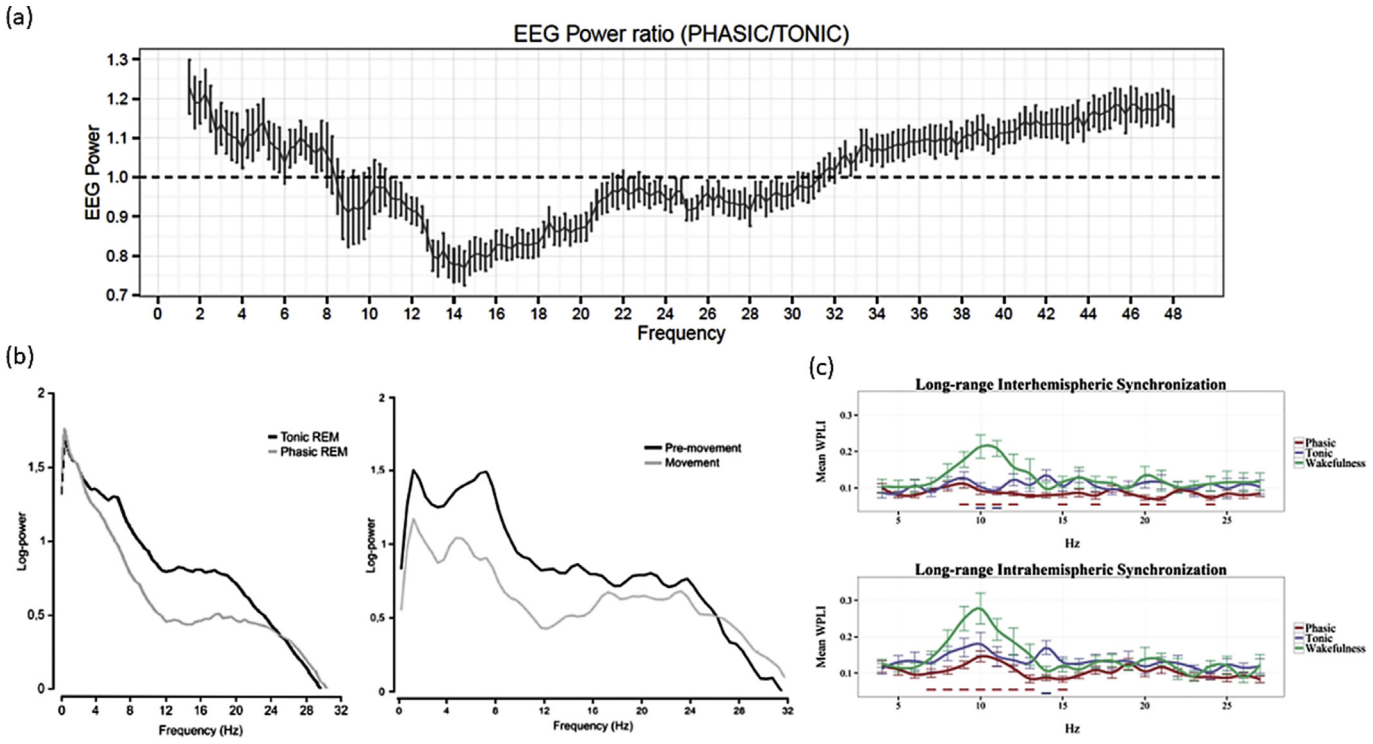

Fig. 3. Spontaneous cortical oscillations in phasic and tonic microstates. (a) Phasic vs Tonic spectral power ratio averaged across scalp electrodes and phasic and tonic trials. Values above the dashed line indicate relatively higher spectral power in phasic periods, whereas values below the dashed line indicate higher power in tonic periods in the specific frequency bins. The graph is based on night-time sleep EEG data of 20 healthy, young adults, and suggests that phasic and tonic REM phases are clearly distinguishable by consensus-based frequency boundaries. Phasic REM periods are characterized by the predominance of slow (delta–theta range between 2 and 8 Hz) and high (gamma range above 32 Hz) frequency activity, whereas (high) alpha and beta power between 12 and 30 Hz is enhanced during tonic periods [60]. (b) Averaged power spectra in the motor cortex during tonic and phasic REM sleep (left), and during and before the onset of a voluntary leg movement (right). Power spectra in the motor cortex during phasic REM exhibits reduced alpha and beta power, similar to the pattern observed during voluntary movements, while oscillatory activity during tonic REM periods bears resemblance to relaxed wakefulness [43]. (c) Large-scale interhemispheric and intrahemispheric EEG synchronization as quantified by the weighted phase lag index (WPLI) in phasic and tonic REM sleep, and resting wakefulness. Tonic REM periods exhibit intermediate values with respect to neural synchronization in the alpha frequency range, especially in the case of intrahemispheric electrode pairs, and was not significantly different from wakefulness with respect to WPLI values in the beta range. Red dashed lines highlight significant differences between phasic REM periods and wakefulness, blue dashed lines mark significant differences between tonic REM periods and wakefulness.Reproduced with permission from [43,60] John Wiley and Sons, and [65] Oxford University Press. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The other consistent finding with respect to spectral power in REM microstates is the relative increase in high frequency activity comprising the gamma (30–50 Hz) frequency range. Enhanced gamma power in phasic REM periods was reported by scalp EEG [59–61,66] as well as intracerebral studies, the latter arguing against a mere effect of muscular artifacts caused by eye movements [67,68]. The increase in gamma power is assumed to reflect intense sensorimotor, emotional and cognitive processes that individuals experience in the form of vivid dreams [61,67,68]. Source localization of phasic gamma power supports this assumption to some extent: neural generators were identified in fronto-limbic regions including the ventromedial prefrontal and anterior cingulate cortex, and in regions that play a key role in perceptual processes (e.g., superior temporal, lingual and fusiform gyrus), especially in the perception of emotional stimuli [61]. These sources appear to overlap with the findings of neuroimaging studies that examined the neural correlates of REMs and highlighted the activity of a fronto-limbic network following REMs [39,69,70]. Furthermore, a recent study showed increased gamma power after REMs in the human amygdala [68], providing further support for the activity of emotion-related networks linked to phasic REM.

The third frequency range that differentiates REM microstates is within the delta and theta bands, exhibiting increased power particularly between 2 and 4 Hz during phasic REM periods [60,61,71]. These oscillations that resemble so-called sawtooth waves are prominent at fronto-central derivations, associated with increases in gamma power [71], and highly synchronized over the scalp [61]. Low frequency oscillations in NREM are known to emerge from widely distributed thalamo-cortical and cortico-cortical neural ensembles and to reflect the rhythmic alternation of hyperpolarized and depolarized states [72]. Slower oscillations are not restricted to NREM, but also appear in REM sleep [26]. As this is especially true in conditions of high sleep pressure [73], widely synchronized low frequency oscillations might facilitate disconnection from the external environment. On the other hand, low frequency oscillations might reflect PGO waves and, coupled with gamma oscillations, may activate the cortex [71]. Whether such low-frequency activity during phasic periods facilitate disconnection from the external environment, or rather, are the cortical analogs of PGO waves is a matter for future research.

As an intermediate conclusion, findings regarding spontaneous cortical oscillations further strengthen the fact that phasic and tonic REM periods are markedly different neural sub-states within REM sleep. Future studies investigating the roles of frequency-specific activities on different cognitive processes should take into consideration that power spectra and phase synchrony are remarkably different across REM microstates.

The reprocessing of salient memories

A prevailing view posits that REM sleep is intimately linked to the processing of emotionally and motivationally salient information [14,74]. These assumptions are supported by different lines of evidence including neuroimaging studies of REM sleep [70,75], investigations on sleep-related memory consolidation in animals and humans [76], as well as clinical findings linking emotional disorders and REM sleep disturbances [77]. Although REM sleep does not seem to be the exclusive element in supporting such cognitive functions [78], empirical studies suggest that the phasic REM period emerges as a key player in this regard.

First, limbic and parahippocampal regions, known to support emotional memory processing and to exhibit increased activity during REM sleep [70,75], are specifically coupled to REMs (i.e., phasic periods) [29,39,69] (Fig. 4). In addition, an intracranial study showed transient activation (i.e., increased gamma power) in the amygdala following the onset of REMs (Fig. 4/a) [68]. Regarding animal studies, the beneficial influence of REM sleep on emotional (usually fear-and/or avoidance-related) memories were associated with theta oscillations [79,80] and pontine waves [13,50], both being prominent features of phasic periods [81,82]. On a related note, theta oscillations during REM sleep were shown to modulate the firing rates and neural synchrony of hippocampal CA1 neurons during NREM sleep, indicating an interplay between REM and NREM sleep, as well as a critical role for REM theta power in neuronal plasticity [48]. Human studies also pointed to the putative roles of REM density (reflecting the number of rapid eye movements per minute of REM sleep [83]) and REM theta power [84–86] in emotional memory consolidation. Nonetheless, it must be acknowledged that the functional and phenomenological similarity (i.e., the frequency boundaries) of REM theta waves across humans and rodents is still a matter of debate [87,88].

Other theories suggest that phasic REM sleep has its own specific role in dreaming and emotion regulation processes during sleep [77]. Early theories of dreaming describe two alternating processes during REM sleep: (re)activation and integration [89]. Reactivation consists of the activation of vivid (emotionally relevant) mental pictures, and is related to PGO waves and REMs, thereby connecting this process to phasic REM sleep. More recent hypotheses describe a similar process and relate it directly to the reprocessing of emotional memories during sleep [14,77]. In these theories, (strongly negative) emotional memories are triggered during the activation phase and subsequently contextualized and integrated with existing memories. Through this process, the content of the memory is consolidated, while the emotional arousal associated with the event is attenuated. At the neural level this mechanism is proposed to involve increased limbic and paralimbic activity to facilitate the reactivation of emotional memories, which might again point toward a role for phasic REM in particular [14,77] in emotional (re)processing.

These theories in turn suggest that in between (phasic) REMs, quiet periods (i.e., tonic REM periods) facilitate the integration/contextualization of reactivated emotional memories, but there is currently no direct empirical evidence to support this notion. Still, several studies found higher activity in widespread multimodal and higher order brain areas which would be suitable for such a function during REM sleep when activity is not time-locked to REMs [90–92]. Especially intriguing is the study by Chow and colleagues [90], who found rhythmic, anti-correlated fluctuations (associated in time with phasic events during REM sleep) between two major brain systems: unimodal sensorimotor and subcortical areas, and higher-order, multimodal regions. While these findings do not provide any direct proof, they are consistent with the hypothesis that alternating phasic and tonic periods during REM sleep could facilitate the reprocessing and integration/contextualization of salient, emotional memories. In any case, putative links between emotional processing and phasic REM sleep in particular should encourage researchers to take into consideration the heterogeneity of REM sleep when examining the cognitive and affective functions of REM sleep. Likewise, a deeper look into phasic and tonic REM periods with respect to cortical, autonomic (e.g., heart rate, skin conductance, respiration) and motor activity would benefit the investigation of sleep disturbances in psychiatric disorders.

For instance, increased REM sleep density was reported in patients with post-traumatic stress disorder (PTSD) and major depression (MD) [93,94], indicating a relatively higher percentage of phasic REM sleep in these populations. Disturbed sleep is among the core symptoms of PTSD and MD and the targeted treatment of sleep quality in these disorders was proven to exert a beneficial effect on daytime symptoms [95,96]. In case of PTSD, impaired REM sleep was hypothesized to be the hallmark of the disorder [97],

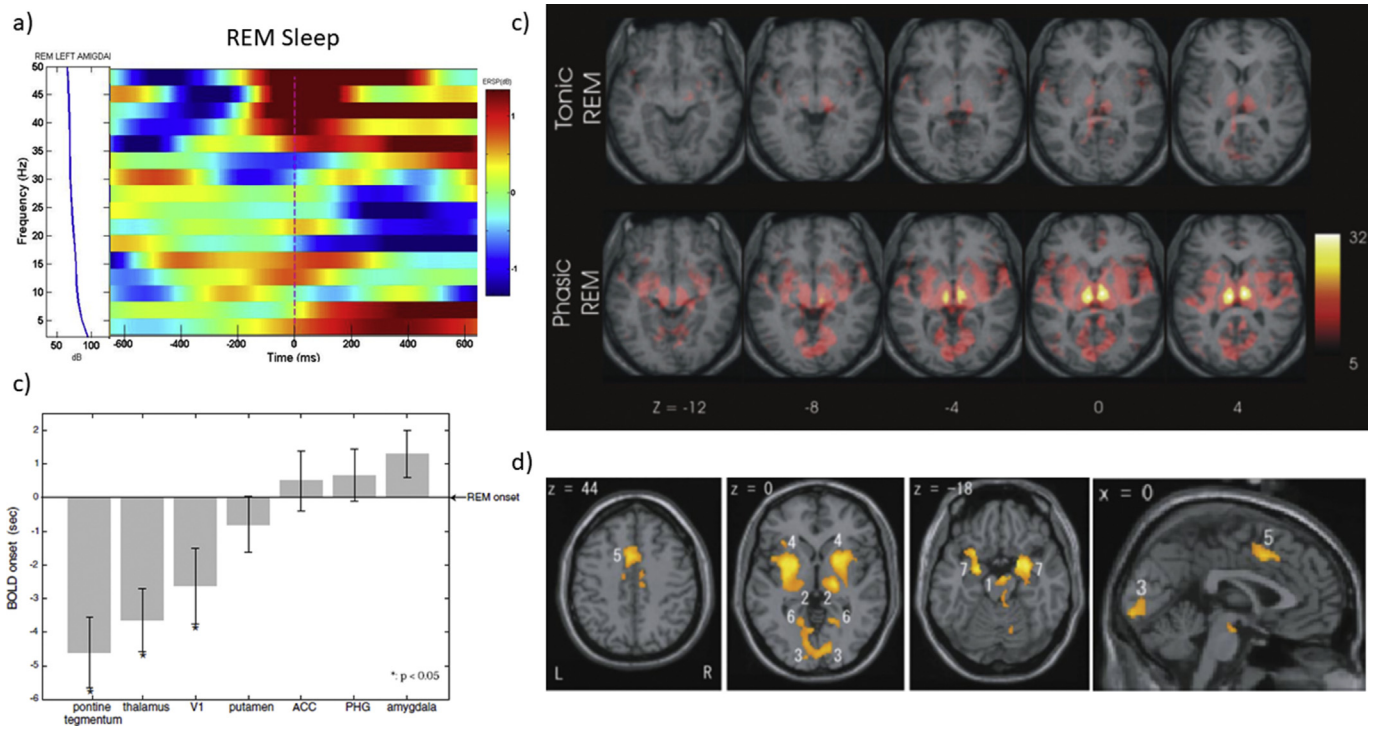

Fig. 4. Emotional network activity during phasic REM periods. (a) Increased gamma frequency activity following REMs (phasic activity) measured from intracranial recordings placed at the left amygdala [68]. (b) Thalamocortical activity in phasic tonic REM periods as seen using fMRI [39]. During phasic microstates strong interregional correlations with thalamic BOLD response emerged in the putamen, brainstem, occipital lobe, superior and middle temporal gyrus, amygdala, insula, anterior and posterior cingulate gyrus, parahippocampal gyrus, and in the middle and inferior frontal gyrus. (c–d) Event-related fMRI responses time locked to eye movements in REM sleep [69]. (c) Regional activity preceding (negative values in the y-axes) and accompanying (positive values in the y-axes) the onset of REMs. (d) Brain activity coupled to REMs. 1: pontine tegmentum, 2: ventroposterior thalamus, 3: primary visual cortex, 4: putamen, 5: cingulate cortex, 6: parahippocampal gyrus, and 7: amygdala. Reproduced with permission from [39,68] John Wiley and Sons, [68], and under Creative Commons license [69].

albeit sleep disruption is clearly not limited to the REM phase [98]. Considering the proposed role of REM sleep microstates in emotion regulation and memory as discussed above, this imbalance between tonic and phasic REM could be directly related to the affective and cognitive symptoms of these disorders. A recent study showed that REM interruptions (as reflected by state changes, arousals, or awakenings) predicted sustained amygdalar activity (i.e., impaired overnight emotional adaptation) in response to previously presented distressing stimuli [99]. REM interruptions observed in PTSD [98,100] (and hence the microarchitecture of REM sleep) might be linked to preserved emotional reactivity to stressors that are associated with recent or early adverse life events.

Increased REM sleep density (along with shortened REM latency) is considered as a trait or vulnerability marker of depression that seems to precede the clinical symptoms and persist even after symptomatic remission [101]. Moreover, increased REM sleep density before treatment predicted poor outcomes and relapse, whereas REM sleep density was reported to be normalized with successful treatment of depression (see [102] for a comprehensive review). The link between depression and REM sleep is also exemplified by the fact that almost all antidepressants increase the latency and suppress the amount of REM sleep [103], albeit some antidepressants (e.g., trimipramine) do not influence REM sleep while showing an antidepressant effect [102]. Theoretical models explaining the role of abnormal REM sleep in depression cover a variety of hypothesis such as neurochemical imbalance, impaired sleep homeostasis, circadian dysregulation, or dysfunctional memory processing, but empirical evidence supporting these theories is usually scarce and indirect [14,102]. Studying REM sleep microstates in more detail in these populations might thus provide new hints for the functional implications of REM sleep abnormalities, and clarify their role in the pathology of these (and possibly other) psychiatric disorders.

Clinical relevance of REM microstates

REM sleep behavior disorder

REM sleep behavior disorder (RBD) is a parasomnia characterized by the occurrence of vivid, frequently frightening dreams, accompanied by simple or complex motor behaviors during REM sleep, mirroring the content of patients' dreams ("enacted dreams") [104,105]. RBD is now recognized as a precocious manifestation of an *α-synucleinopathy*. In RBD patients, the physiological muscle atonia of REM sleep is replaced by an excess of muscle tone and/or phasic muscle twitching. The origin of the complex behaviors manifesting during RBD episodes and the role of cortical and subcortical structures is still a matter of debate [106,107]. However, what is evident from clinical studies is that violent behaviors in RBD patients occur most frequently during phasic REM sleep than during tonic REM sleep [108] suggesting a distinct level of activation of the sensory-motor system during these two REM sleep substates. Evidence in support of this hypothesis derives from intracerebral electrophysiological studies in epileptic patients showing a pattern of electroencephalographic activation of the motor cortex during phasic REM sleep similar to the one observed during voluntary movements in wakefulness [43]. Moreover, spectral power measures and indices of functional connectivity reveal more pronounced differences across phasic and tonic REM periods in RBD patients compared to controls, indicating abnormal motor cortex activity in RBD during phasic REM sleep [109]. Studying the activity and excitability of the sensory-motor system during phasic

and tonic REM sleep in RBD patients may shed lights on the pathophysiological mechanisms at the basis of motor dyscontrol in this disorder.

Epilepsy

It is well known that NREM and REM sleep exert opposite effects on seizures and interictal epileptic activity in epilepsy patients. In particular, the thalamocortical oscillations operating during NREM sleep may favor seizure occurrence and the activation and spread of interictal epileptic discharges [110,111]. Contrarily, seizures during REM sleep are notably rare and in addition the production of interictal epileptic activity is strongly reduced during this sleep state [112]. Such an inhibitory effect of epileptic activity has been interpreted as the result of the depolarization of the thalamocortical neurons leading to a blockage of the thalamocortical oscillations [112]. However, more recently it has been shown that this inhibitory effect on epileptic activity is mostly exerted by phasic REM sleep, which markedly suppresses the occurrence and propagation of both interictal spikes and pathological high frequency oscillations (HFO) [113,114]. On the other end, the effect of tonic REM sleep is not significantly different from that of NREM sleep. The inhibitory effect on epileptic activity seems to be an intrinsic feature of phasic REM sleep, independent from the time of REM sleep occurrence during nocturnal sleep, the epileptic syndrome, the location of epileptic activity within the brain and the pathological substrate [113]. Experimental studies suggest that the suppressing effect of REM sleep on epileptic activity could be related to the production of acetylcholine, which is particularly raised during phasic REM sleep [115]. A better comprehension of the underlying mechanism of the protecting influence of phasic REM sleep on epileptic activity might have important value for potential therapeutic approaches.

The paradoxical nature of phasic and tonic REM

The pioneer of sleep research Michael Jouvet [19] named the REM sleep state “paradoxical” because brain activity resembled wakefulness but the person or animal was in a sleeping state. This “paradoxical” denomination for the REM sleep stage also holds for phasic and tonic microstates. On the one hand, phasic periods are highly activated states with respect to cortical [39,69], mental [40,42] and autonomic activity [116] and resemble active wakefulness. The duration of phasic REM sleep (i.e., REM density) increases towards the end of the night, suggesting that the appearance of phasic periods is facilitated with decreasing homeostatic sleep pressure [117]. Accordingly, sleep deprivation reduces REM density during the recovery night by suppressing the late night increase of phasic periods [117]. REM density is also to some extent modulated by circadian factors, especially in periods of low sleep pressure as revealed by a study applying a *forced desynchronization protocol*. This study showed maximal REM density when low sleep pressure coincided with the wake maintenance zone, a period when the circadian drive produces a strong alerting effect [118].

In spite of this state of heightened activity however, the brain is strongly disconnected from the external environment during phasic REM. As discussed above, environmental alertness is largely reduced, and a thalamocortical network including limbic and parahippocampal regions provides functionally isolated, intrinsic activity during phasic microstates [39,69]. The combination of intense cortical activity and sensory disconnection is also accentuated by the coexistence of widely synchronized slow frequency oscillations and high-frequency (gamma) activity [61,71]. Whereas the former indicates a deeper sleep stage facilitating the stability of sleep and the attenuation of sensory processing, the latter is indicative of intense activity of localized cortical networks [119,120]. In contrast, tonic states are apparently more quiescent periods with regard to autonomic and cortical activity, but on the other hand seem to be closer to wakefulness (as compared to phasic periods) with respect to environmental alertness and arousal.

From an evolutionary point of view, being disconnected from the external environment for longer periods can be seen as not adaptive, as it exposes the organism to potential threats. Therefore, tonic REM periods interspersed between more vulnerable phasic states might counteract the risks of environmental disconnection. Tonic periods might thus provide a transient alerting mechanism and reinstate external processing after periods of sensory disconnection. Such episodes would be especially required in conditions of higher sleep pressure when the arousability of the organism is generally lower (e.g., in the beginning of the night or during recovery sleep after sleep deprivation), or in the case of sleep in an inconvenient (e.g., noisy, uncomfortable) environment, a notion which several studies support [38,39]. On the other hand, higher demands of internally focused processing are expected to enhance phasic REM periods. Accordingly, animal studies and experiments with humans indicate an increase in phasic REM activity following intensive learning periods [50,121,122].

We propose here that the dynamic interplay between phasic and tonic periods might support the integrity of the biological functions of REM sleep by preserving the stability of REM periods. Imbalance between REM microstates seems to be present in different sleep disorders For instance, patients with insomnia disorder characterized by increased environmental alertness might exhibit a shift towards tonic states. Although no data is available regarding REM microstates in insomnia, the instability of REM sleep (i.e., more awakenings during REM sleep) was consistently reported in insomnia disorder [123,124]. Moreover, insomnia patients reported to feel as if they were awake before being awakened from tonic REM sleep, indicating abnormally increased environmental processing especially during tonic, but not during phasic REM [125].

Conclusions, open questions and future directions

Sensory disconnection and at the same time arousability are considered to be opposing but essentially complementary functions of sleep [126]. The rhythmic alternation between stable sleep periods that promote the restorative functions of sleep (e.g., off-line memory consolidation) and more fragile epochs when susceptibility to external stimulation is higher is well described in the case of NREM sleep [126,127]. Here we propose that these antagonistic processes of sleep are reflected by the alternation of phasic and tonic microstates during REM sleep. In this framework, phasic states are considered an “off-line” mode promoting sleep stability and internal processing, and tonic periods an “on-line” mode facilitating environmental alertness and responsiveness to external inputs. We may speculate that beyond the regulation of sleep and arousability, the dynamic alternation of phasic and tonic REM periods has been enriched with additional functions facilitating learning, memory, and affect regulation through processes of exaptation and secondary adaptation (especially, in species with highly developed central nervous system). Nevertheless, several questions remain unanswered and warrant future research that take the heterogeneity of REM microstates into consideration.

Studies that investigate the role of REM sleep in cognitive processes should examine the differential association of phasic and tonic REM activity with behavioral or physiological measures, such as post-sleep changes in task performance and neural response patterns. In addition, examining the contribution of REM

microstates to memory processes in studies using Targeted Memory Reactivation might provide new insights into the mechanisms of sleep-related memory function. Such analyses could be undertaken by reanalyzing previously collected datasets involving TMR. As regarding information processing during REM sleep, studies applying acoustic stimulation are consistent in showing enhanced external processing during tonic REM periods [34,35,44]; however, future studies should corroborate these findings and verify whether increased environmental alertness is limited to the auditory domain or if it extends to other modalities.

Although the appearance of phasic periods within REM segments was observed to follow a rhythmic pattern occurring at a periodicity of about 2 min [128], the temporal aspects of REM microstates are far from being established. Rapid eye movement density increases progressively over the night for successive REM phases [129], is reduced after sleep deprivation [130], and increased after periods of extended wakefulness [131], but the significance of these changes is still not clear. For instance, is the proportion of phasic and tonic REM microstates related to the microarchitecture of NREM phases, sleep quality, or information processing during sleep (e.g., memory consolidation)? Or does the proportion of REM microstates exhibit trait-like stability that can be linked to endophenotypes of pathological conditions [93,132]?

Another open question is whether the differences between phasic and tonic microstates are influenced by age. Unfortunately, the published studies that examined EEG activity in REM microstates involved small samples of relatively narrow age ranges. Nevertheless, two studies indicate that differences across REM microstates in regard to spectral power are also present in children [60] and even in newborns [133]. As REM sleep plays a prominent role in brain maturation during ontogenesis [6,10], a special focus on the micro-architecture of REM sleep in relation to development and aging should be addressed in future research. Furthermore, does the proportion and distribution of REM microstates vary across the lifespan, or in function of pathological aging? On a related note, clinical studies that examine pathological conditions characterized by abnormal REM sleep might also benefit from a more detailed perspective taking into account the heterogeneity of REM sleep. Finally, the examination of neural activity in phasic and tonic REM microstates should not be limited to humans. For instance, a study in mice reported remarkable differences across phasic and tonic REM states with respect to theta and gamma oscillations in the parietal cortex of the animals [134]. Exploring the distribution of, and neural (i.e., frequency-specific) activity during phasic and tonic REM periods in species exhibiting peculiar forms of sleep due to environmental constraints [8], or in species outside the mammalian order [2,135] could shed more light on the functions and evolutionary origins of REM sleep [136,137].

Research agenda

- To examine the role of phasic and tonic REM in memory consolidation and affect regulation
- To examine the nature of REM microstates in pathological conditions featuring abnormal REM sleep (PTSD, Depression, Insomnia, etc.)
- Explore REM microstates in different species
- Investigate the influence of development and aging on phasic and tonic EEG activity
- To examine information-processing during tonic REM in modalities other than the auditory domain

Practice points

- Phasic and tonic REM sleep are different neural states with respect to spontaneous and evoked cortical activity.
- Environmental alertness is largely reduced during phasic REM, but is reinstated to some extent during tonic REM.
- The alternation of phasic and tonic REM periods may facilitate sleep regulation and information processing during REM sleep.
- The in-depth study of REM sleep microstructure may provide novel insights into the pathophysiology of sleep disorders.

Conflicts of interest

The authors report no conflicts of interest.

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