Local Cortical Activations During REM Sleep and Implications for RBD

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29.1 Introduction

REM sleep can be considered as a state of high cerebral and low physical activation. Indeed, subjects awakened from REM sleep may report florid and vivid story-like dreams [1]; in our dreams we move and act with different and complex motor behaviors, but actually we are completely motionless. Indeed, despite generalized postural muscle atonia, REM sleep is characterized by the presence of different markers of brain activation: EEG activity shows a "wake-like" pattern, brain metabolism increases in different cortical regions, and behaviorally signs of activations, such as rapid ocular movements and muscular twitches, appear.

However, from an electrophysiological point of view, there is a paucity of studies analyzing directly the activity of the human motor cortex during REM sleep. Animal models and clinical observations in patients with REM sleep behavior disorder (RBD) suggest a possible activation of the motor cortex during REM sleep. In particular, in RBD, muscle atonia is lost, and patients are deemed to enact their dreams with coordinated and often violent motor behaviors. As mentioned in Chaps. 40 and 44, the core circuits required for generating REM sleep are contained within the brainstem, with the involvement of other midbrain and forebrain circuits for their modulation. However, considering that during RBD, movements are often highly

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elaborated, resembling voluntary movements during wakefulness, it has been hypothesized that also the motor cortex could be involved in driving movement during RBD [2]. This theory is confirmed by the observation that pyramidal tract neurons, which mediate voluntary limb movement, are highly active during both wakefulness and REM sleep [3].

From a similar point of view, a clinical and video-polysomnography (vPSG) investigation of RBD in Parkinson's disease postulated that the restored motor control during REM sleep in this group of patients originates from the motor cortex and that the inputs generated follow the pyramidal tract, bypassing the basal ganglia [4].

REM sleep can be subdivided into two different sub-states, characterized by functionally different neuronal circuits and different responsiveness to external stimuli: phasic REM sleep (REM sleep with bursts of rapid ocular movements, REMs) and tonic REM sleep (REM sleep without REMs) [5, 6]. Compared to tonic REM sleep, phasic REM sleep is associated with activation in the right lateral geniculate body, the posterior hypothalamus, and the occipital cortex as demonstrated in earlier positron emission tomography (PET) studies [7]. A more recent functional MRI study with simultaneous PSG recordings while applying acoustic stimulation showed that within REM sleep a widespread thalamocortical synchronized activity is selectively enhanced during phasic REM sleep when compared with a predominantly tonic REM sleep background [8]. In addition, the authors observed a strongest decrease in brain reactivity to acoustic stimulation during phasic REM sleep periods, whereas processing of acoustic stimulation was preserved during tonic REM sleep as compared with wakefulness. These data seem to suggest that phasic REM sleep acts as a functionally isolated and closed intrinsic loop [8].

Evidence from clinical studies has shown that complex motor-behavioral episodes in RBD were significantly more likely to occur during phasic REM sleep than during tonic REM sleep [9, 10], suggesting a different level of activation of the motor cortex during these two REM sleep sub-states.

29.2 Activation of the Motor Cortex During REM Sleep

Previous studies, conducted with intracerebral electrodes, have shown that during NREM sleep, the motor cortex exhibits frequent activations (lasting from 5 to more than 60 s) characterized by an abrupt interruption of the sleep electroencephalographic (EEG) slow wave pattern and by the appearance of a wake-like EEG high-frequency pattern (alpha and/or beta rhythm). These local activations in the motor cortex could occur in absence of any movements and were paralleled by a concomitant increase of slow waves in the dorsolateral prefrontal cortex (dlPFc) and scalp EEG recordings [11, 12].

In recent work, De Carli et al. [13] evaluated the activity of the motor cortex during physiologic REM sleep. Particularly on the basis of the above-described clinical observations derived from RBD, the authors hypothesized that the electrophysiological activity of the motor cortex during phasic REM sleep could be similar to that occurring during voluntary movements. In order to verify this hypothesis, the activity of the motor cortex and the dlPFc in seven patients with drug-resistant epilepsy

undergoing presurgical evaluation with stereotactically implanted intracerebral electrodes (stereo-EEG, SEEG) was analyzed. The unequivocal localization of contacts pairs within the motor cortex (in particular within the paracentral lobule, leg motor area) and dlPFc was confirmed by post-implantation magnetic resonance imaging, intracerebral electrical stimulation, and evoked motor potentials [14]. DlPFc was selected as a "control" anatomical region because in a previous SEEG study, this brain structure showed a physiological and progressive decay of slow wave activity across NREM sleep cycles comparable to scalp sleep EEG dynamics [11]. Mean SEEG power spectrum of the motor cortex and dlPFc during phasic and tonic REM sleep as well as in voluntary movement during wakefulness was compared.

As shown in Fig. 29.1, during tonic REM sleep, motor cortex showed an alpha-like oscillatory activity (mu rhythm), which disappeared during phasic REM sleep, characterized by a desynchronized pattern. The results of this visual analysis were confirmed by the log-transformed power spectra of the relevant motor cortex EEG signals, showing a decrease of power in a large frequency band up to 25 Hz, with a slight increase of power above 25 Hz during phasic REM sleep.

Post hoc comparisons showed that only the motor cortex presented higher mean frequency spectral values during phasic REM sleep than during tonic REM sleep, while the difference was not significant in dlPFc (motor cortex phasic, 20.45 ± 0.73 Hz, vs. motor cortex tonic, 17.78 ± 0.47 Hz, $p < 0.002$; dlPFc phasic, 19.5 ± 60.40 Hz, vs. dlPFc tonic, 19.08 ± 0.46 Hz, NS; mean standard error).

In order to evaluate if the activation of the motor cortex could be directly related to the occurrence of REMs, mean frequency values associated with the 8-second intervals preceding and following the onset of REMs were analyzed, and no significant difference was found (motor cortex pre, 19.98 ± 0.86 Hz; motor cortex post, 20.89 ± 1.08 Hz; paired *t* test = 1.58, d*f* = 6, NS; mean standard error) (Fig. 29.2).

This suggests that the activation of the motor cortex is not related to REMs per se, but seems to reflect a widespread involvement of the motor system during this specific REM sleep sub-state (i.e., phasic REM sleep). This observation could also justify the occurrence of sporadic and brief RBD episodes unrelated to concomitant REMs.

In order to evaluate possible similarities between the EEG activity of the motor cortex during REM sleep and wakefulness, electrophysiological data were also acquired during the day following nocturnal sleep recordings. During the waking sessions, while patients were lying on their back in a resting condition (with closed eyes), they were requested to raise the leg corresponding to the motor area investigated with intracerebral electrodes. In Fig. 29.3, an EEG trace example of the activity of the motor cortex at rest and during voluntary leg movements in a single subject is represented. A predominance of a clear mu rhythm (8–12 Hz) characterizes the premovement epoch and disappears at movement onset, followed by a predominance of higher-frequency beta activity. Mean EEG spectra in the motor cortex showed a decrease of power in a large frequency band up to 25 Hz and with a slight increase of power above 25 Hz during leg movement. Mean frequency was significantly affected by the experimental condition (before or after movement onset, $p < 0.001$) and was not significantly different between regions (motor cortex vs. dlPFc, $F_{1,6} = 0.41$, NS), but the region-condition interaction was significant

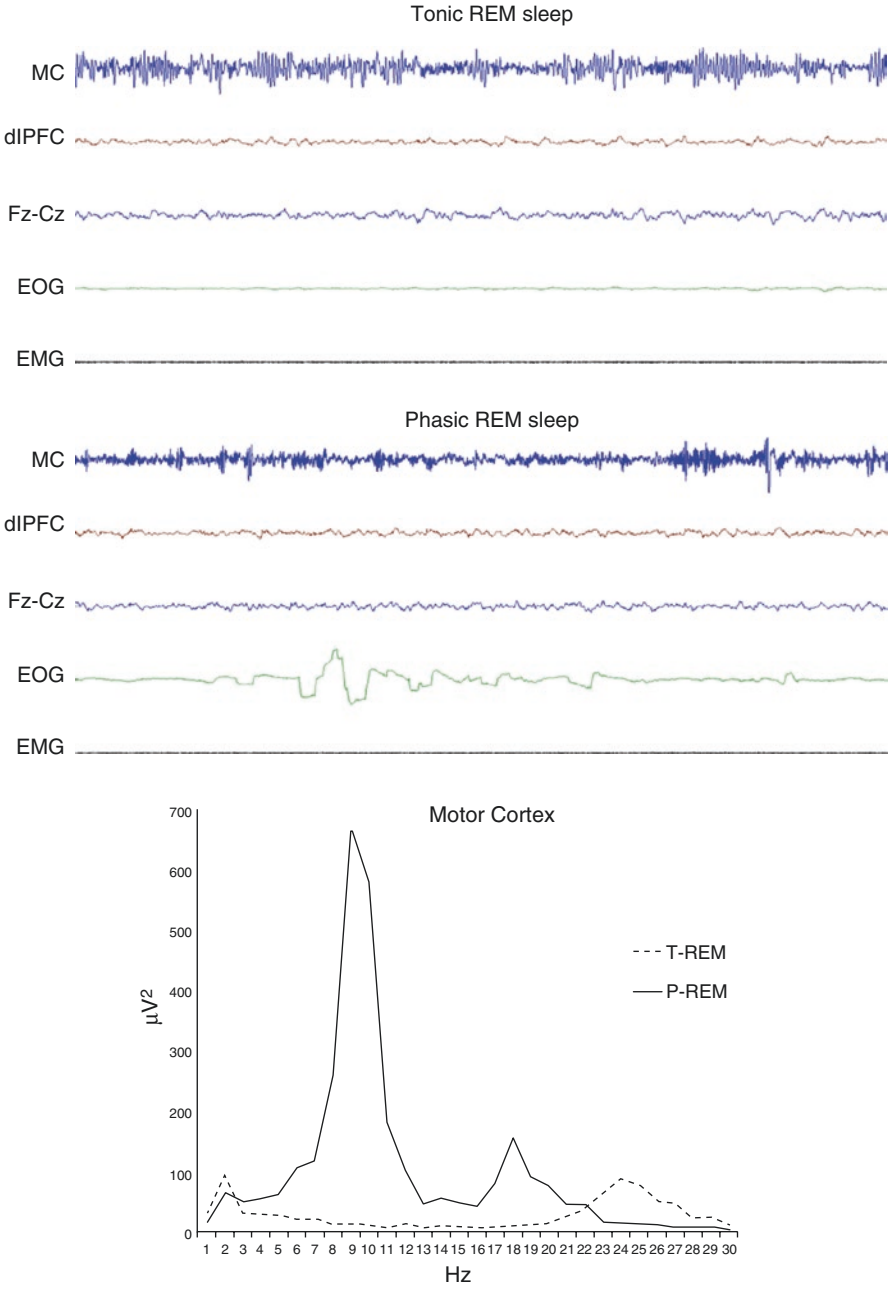

Fig. 29.1 Example of tonic and phasic rapid eye movement (REM) 30-second epochs. Each epoch shows three electroencephalographic (EEG) derivations (*MC* motor cortex, *dlPFC* dorsolateral prefrontal cortex, *FZ-CZ* scalp EEG), one electrooculographic (Eog) trace, and one chin electromyographic (Emg) trace. In the bottom part absolute values of motor cortex EEG spectra during tonic and phasic REM sleep are shown

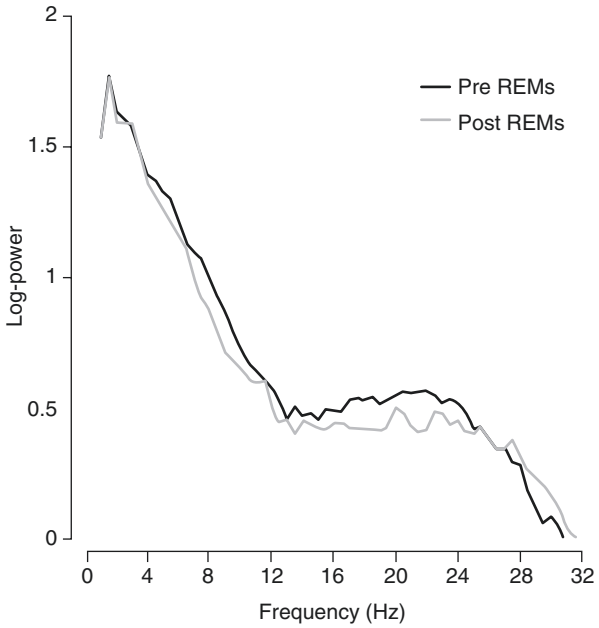

Fig. 29.2 Mean log-transformed power EEG spectra of motor cortex associated with the 8-second intervals preceding and following the onset of rapid eye movements (REMs)

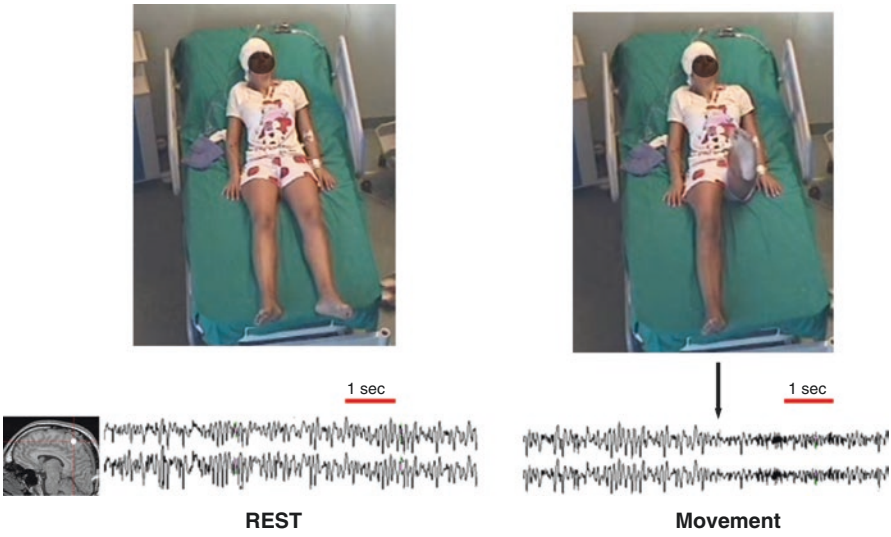

Fig. 29.3 Example of electroencephalographic (EEG) activity in the motor cortex (paracentral lobule; white circle in the sagittal magnetic resonance image) during rest and voluntary limb movement (arrow)

($F_{1,6}$ = 40.62, $p < 0.001$). Post hoc comparisons demonstrated that only the motor cortex presented significant changes between conditions (motor cortex after movement, 20.81 ± 0.87 Hz, vs. motor cortex before movement, 17.96 ± 0.81 Hz, $p < 0.001$; dlPFc after movement, 19.18 ± 0.78 Hz, vs. dlPFc before movement, 18.57 ± 0.55 Hz, NS; mean standard error). It's worth underlining that similar EEG frequency values and changes were observed in the motor cortex during wakefulness (before and after movement) and during phasic and tonic REM sleep. In particular, motor cortex showed a similar increase of the mean EEG frequency during phasic REM sleep and active wakefulness compared to tonic REM sleep and resting state, respectively (Table 29.1). These data suggest that during phasic REM sleep and active wakefulness, the motor cortex exhibits a similar pattern of activation.

Previous studies have already showed that the sensory-motor cortex of relaxed humans exhibits rhythmic activities around 10 and 20 Hz and such activity is suppressed during movement [15–17]. Intracerebral recording confirms these data, showing that this behavior seems to be specific to the primary cortex, and not involving other associative areas, such as the dlPFc. Analogously, in 2007 Miller et al. [18], using electrocorticography, quantified changes in electrocorticographic signals associated with motor movement in a group of epileptic patients with subdural electrode arrays placed for identification of seizure foci. They observed a spatially broad decrease in power in a low-frequency band (8–32 Hz), including the disappearance of the peak in the "mu rhythm" spectral frequency, and a spatially more focal increase in power in a broad high-frequency band (up to 100 Hz) during movement compared with rest. Moreover, they found that this high-frequency change seems to be particularly specific to the Rolandic cortex.

More recently, the same group demonstrated that this "activation" of the motor cortex is a phenomenon not only related to the movement but that can also be observed in other conditions, such as motor imagery [19]. In particular, they measured electrocorticographic cortical surface potentials during overt action and kinesthetic imagery of the same movement. As already described in MEG- and EEG-based imagery studies [20, 21], they found a similar pattern of desynchronization of the primary motor areas between movement and imagery [19].

Dreams characterized by actions seem to be more frequently reported by patients after an awakening from phasic REM sleep than from tonic REM sleep [22]; our observations seem to represent the electrophysiological background of these findings. It can be hypothesized that during dreamed movements the motor cortex can be activated, as observed during active wakefulness or during motor imagery. A

Table 29.1 Mean frequency spectral values of the motor cortex during rest, movement, tonic, and phasic REM sleep

Rest	*Tonic REM sleep*
17.96 ± 0.81 Hz	17.87±0.47 Hz
Movement	*Phasic REM sleep*
20.81 ± 0.87 Hz	20.45 ± 0.73 Hz

Notice a similar increase of the mean EEG frequency during phasic REM sleep and active wakefulness compared to tonic REM sleep and resting state, respectively

fMRI and near-infrared spectroscopy study in lucid dreamers seems to confirm this interpretation [23]. In lucid dreams, the subject is aware of the dreaming state and capable of performing predefined actions. By combining brain imaging with polysomnography, Dresler et al. [23] observed that a predefined motor task performed during dreaming elicits neuronal activation in the sensorimotor cortex that largely overlaps with the activation observed during motor execution or during motor imagery.

Elevated motor cortical activity associated with REM sleep has been already described in electrophysiological animal studies. In particular, using an autonomous, implantable recording system, Jackson et al. [24] examined the relationships between the firing of motor cortex cells and forearm muscle activity in the macaque monkey during active wakefulness and natural sleep. They found that during the night, motor cortex cells often exhibited regular periods of high firing rate, corresponding to periods of desynchronized EEG possibly related to REM episodes. Indeed, the highest firing rates were comparable to daytime values, but associated with complete atonia, characteristic of REM sleep. A more recent study conducted in freely behaving mice measured spectral properties and cross-frequency coupling of left parietal cortex activity during wakefulness and during the two REM sleep sub-states [25]. They found higher spectral frequencies and larger band power in phasic REM sleep compared to tonic REM sleep and wakefulness, suggesting similarities between phasic REM sleep and active waking.

In conclusion, SEEG findings in humans seem to confirm a similar pattern of activation of motor cortex in phasic REM sleep and active wakefulness as observed in animal studies. However, although SEEG offers a unique opportunity to investigate simultaneously the activity of different cortical and subcortical structures along the entire vigilance spectrum, going from active wakefulness to REM sleep and deep NREM sleep, this invasive technique does not allow the exploration of the entire brain structures in a single patient. SEEG data show a desynchronization of the EEG activity during active wakefulness and phasic REM sleep only in the motor cortex and not in the dlPFc. It can be hypothesized that this activation is a specific pattern belonging to primary brain areas and not to the associative ones. This hypothesis seems to be supported by functional studies demonstrating that during REM sleep, several brain regions (subserving important executive and attentional functions during wake) are significantly hypoactive when compared to wakefulness (i.e., the dlPFc, the orbitofrontal cortex, the posterior cingulate gyrus, and the precuneus) [26, 27].

29.3 Activation of the Limbic System During REM Sleep

Recent studies investigated the activity of other human brain structures during REM sleep, such as the limbic or the visual system. In particular, several studies have already shown that the human amygdala is activated selectively during REM sleep with respect to wakefulness and NREM sleep [28, 29]. More recent functional neuroimaging studies seem to demonstrate that the amygdala activation during this

sleep stage is related to the occurrence of REMs. Indeed, magnetoencephalographic current density in the amygdala increases several milliseconds before the onset of REMs in REM sleep [30]. More recently, simultaneous EEG and functional magnetic resonance imaging recordings found an increased amygdala activation in a close time relation to the REMs of REM sleep [8, 31]. In 2016, Corsi-Cabrera et al. [32] employed SEEG recording to analyze, with higher temporal and spatial resolutions, the activity of the amygdala during spontaneous sleep in four epileptic patients with depth electrodes implanted in the temporal lobes. They observed a transient activation of the amygdala time-locked to the onset of REMs during REM sleep, but not during waking eye movements. In particular, absolute power in the 44–48 Hz band increased significantly in the 250-ms time window after eye movement onset during REM sleep. The increase in gamma activity in the absence of known external visual input seems to suggest a transient amygdala activation related to an endogenous excitatory signal time-locked to REMs. This observation seems to be in line with electrophysiological studies in rats showing that REMs are time-locked to ponto-geniculo-occipital (PGO) waves, generated at the pontine level [33], and propagating not only to visual areas but also to other thalamic nuclei, the neocortex [34] and the amygdala [35]. From an electrophysiological point of view, transient activation of the amygdala during phasic REM sleep seems to suggest its central role for a further limbic-paralimbic network activation during this sleep sub-state. Finally, these findings suggest a participation of the amygdala in the emotional content of dreams, as well as for the reactivation and consolidation of emotional memories during REM sleep [32, 36, 37].

29.4 Activation of the Visual System During REM Sleep

Early positron emission tomography (PET) studies found that during REM sleep, activation within the temporo-occipital regions showed some functional dissociation: extrastriate visual cortices (particularly within the ventral processing stream) activation correlated with an unexpected striate cortex (primary visual cortex) deactivation during REM sleep [38]. For these authors, opposite interactions between low- and high-level visual areas during REM sleep might indicate that internal visual information is processed within a closed system (extrastriate areas and paralimbic projections, among others) dissociated from interactions with the environment (via striate cortex and prefrontal cortex, both deactivated during REM sleep; [38]). These early PET results are also consistent with the observation that patients with cortical blindness (after primary visual cortex or perichiasmatic lesions) report that they still dream with visual images [39].

More recently, some research has focused upon phasic activities of visual cortex temporally related to REMs during REM sleep. Peigneux et al. [7] showed a high positive correlation between REM density and visual cortex activities. By means of simultaneous fMRI and PSG recording during REM sleep, and event-related analysis time-locked to the occurrence of REMs, Miyauchi et al. [31] found an activation of the pontine tegmentum, ventroposterior thalamus, and primary visual cortex

before the onset of REMs. Due to the low temporal resolution of these neuroimaging techniques (PET and fMRI), some authors employed EEG/MEG recording to analyze the temporal relationship between REMs and brain activities, finding significant activities in the visual cortex before [30] or after [40] the REMs.

A more recent work employed intracerebral EEG recordings to establish the relation between the activity in visual-mnemonic regions and the REMS of REM sleep and to compare such modulations with those occurring during waking vision [41]. To this end, they examined the intracranial EEG and single-unit activities in the medial temporal lobe and neocortex surrounding REMs during sleep and wakefulness and during controlled visual stimulation in drug-resistant epileptic patients. They observed that REMs during sleep were associated with transient biphasic modulations of spiking activity in the mid temporal lobe, related to evoked potentials in depth EEG signals. In particular, individual neurons exhibit reduced firing rates before REMs, as well as transient increases in firing rate immediately after REMs, similar to activity patterns observed upon image presentation during fixation without eye movements. The authors assumed that these evoked potentials time-locked to REMs during REM sleep could be closely related to PGO potentials. Indeed, although PGO waves have been observed in cats, recent studies have already described similar phenomena in humans [7, 30, 31]. Moreover, initially PGO waves were believed to occur exclusively during sleep, but subsequent evidence suggested that they are analogous to visual evoked potentials [42]. The more convincing interpretation of these results seems to be that REMs during REM sleep transiently increase cortical excitability: the decreased activity before REMs may prepare the ground for subsequent processing by increasing sensitivity to inputs and amplifying responses, thus enhancing the signal-to-noise ratio. One of the main limitations of this study consists in the absence of electrodes examining directly the activity of the visual primary cortex.

Finally, a very recent work investigated the neural correlates of dreaming by performing serial awakenings of subjects recorded throughout the night with high-density EEG [43]. In both NREM and REM sleep, reports of dream experience were associated with local decreases in low-frequency activity in posterior cortical regions. Moreover, they found that specific contents of a subject's REM sleep dream—such as thoughts, perceptions, faces, places, movement, and speech—were associated with increased high-frequency EEG activity in specific cortical areas, which corresponded closely to those engaged during waking perception of the same contents.

29.5 Implications for RBD

Motor output and dream enactment are acknowledged as core distinctive features of RBD [44]. Yet, despite these hallmarks of RBD, neuropathophysiology of such dream-enactment events remains unclear. In this framework, investigating the cortical control of the motor and visual/emotional systems during REM sleep is expected to help clarify the cortical contributions to RBD clinical manifestations.

Motor activation in RBD manifests in the form of increased tonic and phasic muscle activity, exaggerated myoclonic twitching, limb movements (purposeful or aimless, violent or calm, rapid or slow), and complex motor-behavioral manifestations during REM sleep [9, 10, 45, 46]. The actual role of brainstem and cortical networks in generating movements and dream enactment has been discussed. In particular, some evidence suggests that the brainstem per se can play a crucial role in generating not only muscular twitches but also more complex movements, including defensive and aggressive behaviors [47]. On the contrary, complex elaborate movements reflecting socially learned behaviors were suggested to correspond to motor cortex activation [45]. Interestingly, the electrical stimulation of cingulate gyrus is reported to trigger movements similar to those commonly seen in RBD episodes [48].

Based on current possible interpretations of the potential brainstem role in movement generation in RBD, a dichotomous conceptualization can be formulated:

1. A bottom-up (brainstem-centric) hypothesis, identifying the brainstem as the main site responsible for generating movements (including complex behaviors). Accordingly, the brainstem would be the source of the pathological movements, while sensory feedback inputs to cortical networks would affect dream mentation [47].
2. A top-down (cortico-centric) hypothesis, postulating that cortical networks are the main site responsible for motor output related to dream mentation [45], with a permissive involvement of the brainstem.

Neuroimaging studies have revealed different patterns of activations during RBD episodes. In particular, by means of single-photon emission computed tomography (SPECT) and PSG recording, a selectively increased perfusion of the supplementary motor area was observed during a RBD episode [49]. Using the same technique in four patients with different RBD etiologies [50], all the RBD episodes were characterized by activations in the bilateral premotor areas, the interhemispheric cleft, the periaqueductal area, the dorsal and ventral pons, and the anterior lobe of the cerebellum. Moreover, this study also showed that the neural activity generating movements during RBD bypasses the basal ganglia, a mechanism that is shared by RBD patients with different etiologies. In line with this observation, complex, non-stereotyped motor manifestations during RBD episodes are observed in Parkinson's disease-affected subjects, suggesting that RBD motor activity could be generated by the motor cortex bypassing the basal ganglia, as a fundamental phenomenon in RBD, irrespective of the clinical subtype of RBD (idiopathic, secondary to Parkinson's disease, narcolepsy, etc.) [4].

In conclusion, the above-described findings in RBD patients and the occurrence of more complex RBD episodes during phasic REM sleep, together with the observation of activations of the motor, visual, and limbic systems during physiologic phasic REM sleep, seem to indicate a high level of sensory-motor drive during RBD episodes.

29.6 What Do These Data Add to the Interpretation of Motor Dyscontrol in RBD?

RBD patients show quite a wide variety of motor-behavioral manifestations. These range from simple, primitive movements to more complex movements (gestures, actions) occurring in isolation or in the context of what appears to be, in most cases, the enactment of a dream. Though RBD is primarily characterized by violent behaviors, nonviolent behaviors also occur, as well as facial and verbal mimicry not related to anger or aggression. This variability of the motor patterns may be an indication that different parts of the central motor system are involved in the genesis of movements in RBD. The observation that local activations and variations in cortical background rhythms occur in REM sleep argue in favor of a role of the cortical motor areas in the genesis of RBD manifestations.

However, it does not necessarily mean that cortical networks play the main role in RBD. Indeed, it can be hypothesized in an articulated model that takes into account both cortical networks and brainstem motor regulators, that these different components of the motor system are dynamically engaged to varying extents, resulting in a spectrum of muscular twitching, simple movements, complex movements, and aggressive and violent behaviors emerging as dream-enacting behaviors.

Future research agenda using stereo-EEG recordings, focusing on local cortical activity during phasic and tonic REM sleep, may include:

- Study of muscle activity (twitches, jerks, and more complex movements) synchronously with corresponding neural sensory and motor cortices
- Simultaneous analysis (when possible) of data from premotor, SMA, and primary motor cortices
- Analysis of data from visual regions specialized for different functions: dorsal and ventral stream

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