Selective Polysomnographic Findings in REM Sleep Behavior Disorder (RBD) and Parkinson's Disease

20

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Polysomnography (PSG) constitutes the core method for identifying REM sleep behavior disorder (RBD) due to the lack of muscle atonia during REM sleep (REM sleep without muscle atonia—RSWA). Simultaneous documentation with video is central for identifying behavioral, verbal, and minor motor activity during sleep. RBD is related to alpha-synucleinopathies and constitutes a potential risk for conversion into parkinsonism including Parkinson's disease (PD) and dementia with Lewy bodies (DLB), among others [1]. Furthermore RSWA and RBD are strongly associated with hypocretin-deficient narcolepsy [2] (narcolepsy with cataplexy, i.e., type I) and has furthermore been associated with structural brain stem lesions [3–5].

The underlying pathophysiology associated with electrophysiological changes in alpha-synucleinopathies comprises early and progressive involvement of brain stem and midbrain structures including the lower brain stem, pontine, hypothalamus, and thalamic areas consequently. Several sleep abnormalities have been described related to the involvement of these brain structures, and they consist of sleep-wake disturbances; sleep transitions; abnormal sleep structure, such as abnormalities in micro-sleep structure; and abnormal motor control in REM and NREM sleep [6]. Furthermore, impairment of autonomic regulation has been found during NREM and REM sleep as well as in wakefulness [7–10].

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An analysis of changes of electromyographic patterns during PSG of RBD patients is presented in Chap. 31, while Chap. 32 covers the autonomic dysfunction in RBD. In this chapter we primarily focus on other polysomnographic and electrophysiological abnormalities associated with RBD and early stages of synucleinopathy development.

20.1 Electroencephalographic Changes in RBD and PD

Patients with RBD and in particular parkinsonism have shown slowing of the electroencephalographic (EEG) spectra during wake and REM sleep phase. In particular, Fantini et al. were the first to observe that RBD patients during wakefulness are characterized by higher theta power in frontal, temporal, and occipital regions while lower beta power in the occipital region when compared to controls. During REM sleep, RBD patients were characterized by lower beta power in the occipital regions than controls [11]. A recent study by Rodrigues Brazète et al. has shown that during wakefulness, RBD is characterized by slowing in frontal, central, parietal, temporal, and occipital regions and that slowing was enhanced in RBD patients who later developed a synucleinopathy [12]. Iranzo et al. evaluated the spectral changes in RBD patients that later developed mild cognitive impairment (MCI), and they found increased delta and theta activity in the central region compared to the occipital one and also in the right hemisphere compared to the left one [13]. In addition, they observed that these patterns were enhanced in patients who later developed MCI. These results were also confirmed in later studies [14, 15]. Changes related to EEG spectral power during REM sleep in RBD have been used to successfully distinguish RBD from healthy controls with a data-driven machine learning technique reaching sensitivity and specificity of around 90% [16].

NREM sleep seems not to be affected by the same EEG slowing that has been observed in REM sleep and wakefulness. NREM EEG slow-wave features were extracted with an automated algorithm in a study by Latreille et al. [17], and EEG slow-wave density, amplitude, frequency, slope, and duration of positive and negative phases were similar in RBD patients and healthy controls.

The EEG slowing observed in RBD during REM sleep and wakefulness is consistent with the observations performed in the early stages of PD and DLB [18–20]. This phenomenon may be considered as an effect of the pathophysiological changes related to the disease, such as involvement of brain stem and thalamic structures that project to the cortex [21], cortical thinning, and white matter abnormalities [22, 23].

Recently, algorithmic complexity of spectrograms calculated from wakefulness resting EEG in RBD and healthy controls has been investigated by Ruffini et al. [24]. RBD patients that later developed PD and DLB showed decreased complexity of the EEG signals in both low and high frequencies. Another recent study has also shown that during wakefulness, RBD patients are characterized by a loss of delta-band functional connectivity [25].

20.2 Micro- and Macrostructural Sleep Changes in RBD and PD

Concerning microstructural changes observed in PD and RBD, some studies have focused on sleep spindles (SS). Christensen et al. have analyzed SS density and morphology in both manually and automatically identified SS: when the manual annotations were used, there was not any found association between PD disease duration or severity and SS density and morphology [26]. However, when an automated method for SS detection has been employed, it was found that in NREM sleep, RBD and PD patients (with and without RBD) were characterized by a significantly lower density of SS [27]. In another study, O'Reilly et al. confirmed the reduced density of SS in RBD, with the strongest effect in the central and parietal derivations. At the same time, they pointed out that it is important to differentiate between fast and slow SS: for the former, a decreased density is observed, while for the latter, the opposite was shown [28]. These results suggest a possible thalamic dysfunction in early stages of alpha-synucleinopathies. In another study by Latreille et al. [15], it was observed that PD patients who later converted to dementia were characterized by lower SS density and amplitude when compared to the PD patients that remained dementia-free and to controls. Dementia-free PD patients were characterized by intermediate values of SS density values between healthy controls and PD with dementia. In this study, the authors also show EEG-slowing increase in PD that is enhanced in cases of dementia, thus supporting the hypothesis that a general slowing pattern in EEG might be considered as a biomarker for PD dementia, perhaps as a consequence of cholinergic denervation. Sleep spindles are involved in cognitive processing, including memory consolidation [29]; however, currently there are limited studies linking SS, RBD, and alpha-synucleinopathies with cognitive impairment.

Alterations in EOG signals during sleep have been observed. In particular, Christensen et al. used the energy calculated from wavelet decomposition in different frequency bands to differentiate controls and RBD/PD patients achieving sensitivity of 95%, specificity of 70%, and accuracy of 86.7% [30]. In a later study, EOG signals were used in an unsupervised data-driven approach to evaluate eye movements during sleep [31]. It was observed that PD and RBD patients reflect abnormal form and/or timely distribution of eye movements during sleep and that these abnormalities can be used to classify healthy controls versus PD/RBD with sensitivity of 95%, specificity of 80%, and accuracy of 90%. These studies confirm abnormalities in ocular movements that were observed in PD with video-oculography [32].

Alpha-synucleinopathies are characterized not only by micro-sleep abnormalities but also by macro-sleep changes. In a study performed by Arnaldi et al. [33], the authors showed the loss of physiological nocturnal increase in REM sleep duration and the loss of the increase of REM frequency across the night in RBD and PD with RBD patients. These changes suggest alterations in the circadian system in RBD pathophysiology. Generally, studies evaluating alterations in sleep macrostructure encounter difficulties due to the high inter-scorer variability in PSG evaluation [34]

and to the fact that there are several confounding factors in RBD evaluation, such as age [35], periodic leg movements [36, 37], sleep apneas [38], and night-to-night variability [39]. To overcome these problems related to subjective interpretation of PSGs, a data-driven approach based on EEG and EOG signals for sleep staging [40] has been applied to healthy controls, RBD and PD patients in order to identify abnormal patterns in macro-sleep structure. The data-driven method finds "topics" in EOG and EEG signals that correspond to different sleep stages, and for each epoch, the probability of each topic is calculated. In a first study, it has been observed that the altered amount of REM sleep and N3 and the altered ability of maintaining NREM and REM sleep characterize RBD and PD patients; thus, they might be considered biomarkers for PD development [41]. In a later study, wake, REM, NREM stabilities, and REM/NREM transitions were shown to be altered in RBD and PD. These patterns were evident only by applying validated data-driven automatic methods for sleep staging and not when the manual scoring was considered [42]. Figure 20.1 shows the topics for EEG channels, where each color represents the probability of a certain topic stage (i.e., sleep stage). It is possible to notice the increased fragmentation and lower stability in RBD and PD patients compared to the healthy control subject. These macro-sleep abnormalities might be the consequence of the involvement of brain stem areas in the early stages of synucleinopathies [43].

20.3 Evoked Potentials in RBD

The study of evoked potentials (EP) is a useful tool to evaluate the state of the nervous system and therefore offers insights in understanding abnormalities related to sleep diseases [44].

Many patients with PD suffer from pain and have impaired somatosensory function. Hypothetically, pain perception and somatosensory function could be altered already in a preclinical stage of PD. A study has investigated that, and the results showed that RBD and PD patients have abnormal response to pain stimulation using laser stimulation, suggesting that somatosensory impairment might be an early feature in the neurodegenerative process of PD [45]. In another study, de Natale et al. [46] observed higher rate of abnormal vestibular evoked myogenic potentials in RBD patients when compared to controls. Moreover, visual hallucinations are commonly observed in PD. Changes in visual EP have been associated with disease progression of PD and may potentially be modified by dopaminergic treatment suggesting involvement of retinal dopaminergic system and the REM sleep regulatory system [47]. Some studies have also shown altered visual EP and brain stem auditory EP, suggesting that brain stem visual and auditory passageways may be impaired in PD [48, 49]. These observations should be extended also to RBD patients.

A technique that is often used to analyze dysfunction in the brain stem is the electric blink reflex (BR). Alterations of BR have been observed in DLB but not in RBD or parkinsonism [50]. In another study by Peter et al. [51], a case of RBD patient with excessive startle response to visual stimuli was observed, which was probably caused by a pontine lesion and subsequent involvement of the bulbopontine reticular formation.

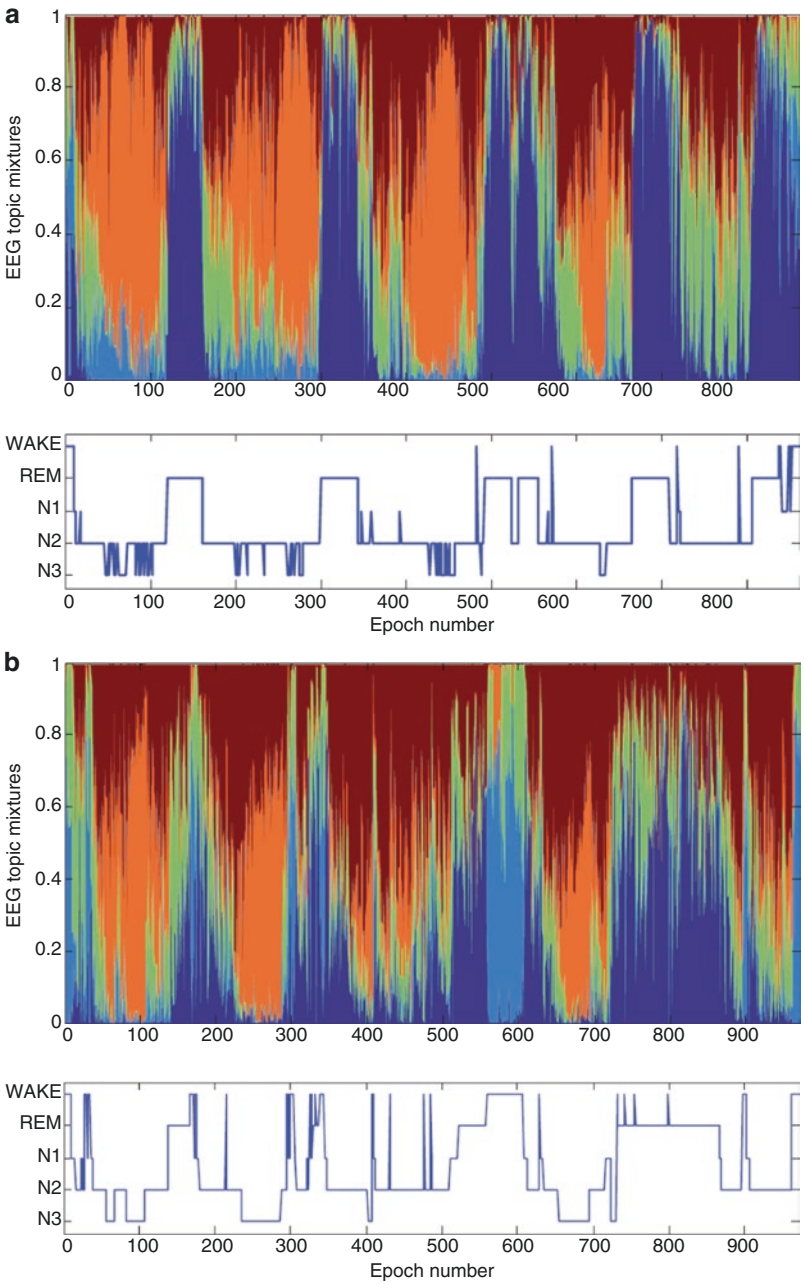

Fig. 20.1 Examples of EEG topic diagrams from a healthy control subject (**a**), an RBD patient (**b**), and a PD (**c**) patient. The figures are stacked percentage column charts, where a sleep epoch is presented as a vertical line possessing a mixture of colors. Each color presents an EEG (dark blue, light blue, green, orange, or red) topic, where the amount of color in each vertical bin presents the probability of the specific topic. The colors are comparable between diagrams. The manually scored hypnograms are provided below the topic diagrams [41]

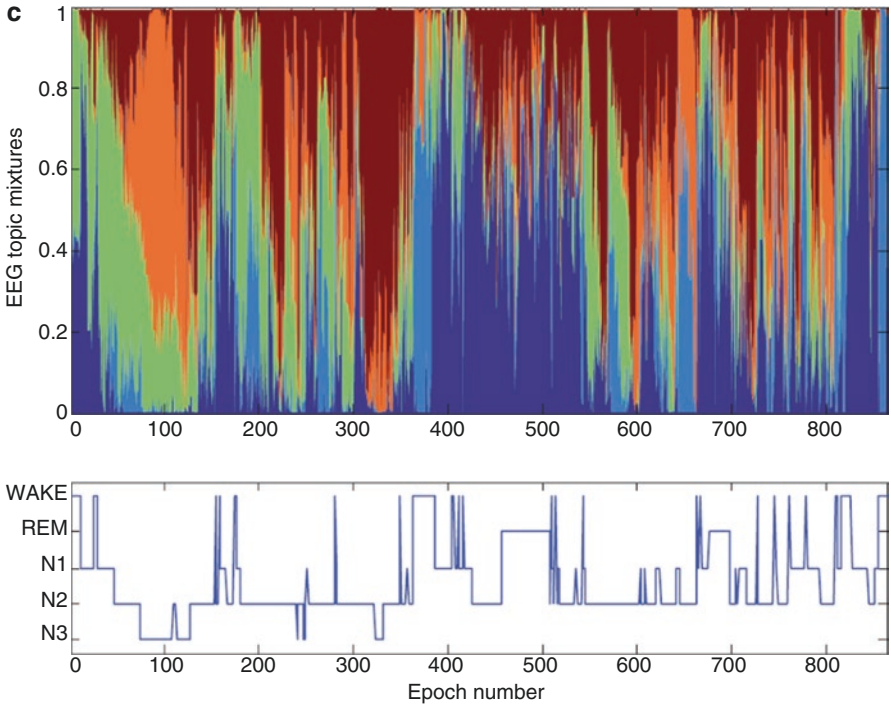

Fig. 20.1 (continued)

20.4 Other Electrophysiological Changes in RBD

Recently, also automated analysis of speech has shown interesting results in RBD/PD identification [52]. In particular, respiration, phonation, articulation, and timing showed abnormalities in RBD and PD patients, suggesting these features as a biomarker for PD development.

Analysis of other electrophysiological signals might offer new insights on RBD, and the integration of mathematical models and machine learning methods will be helpful for future RBD diagnosis and deeper scientific insights.

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