Chapter 49

Neuroimaging of sleep-related epilepsies

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Introduction

Epilepsy is a brain disorder characterized by recurrent and unpredictable interruptions of normal brain function. Epileptic seizures result from abnormal paroxysmal brain activity and accompany the clinical manifestations [1]. Although the seizures are unpredictable, some regularity can be discovered in the epilepsy population. For example, some patients have seizures only in their sleep and sleep deprivation can trigger seizures.

The occurrence of seizures during sleep has been noted since antiquity. In 1885, Gowers reported that seizures occurred exclusively at night in one-fifth of patients [2]. Some recent reviews demonstrate that nearly one-third of all patients with epilepsy report a tendency to have seizures during sleep except their diurnal seizures [3, 4]. Nocturnal seizures are considered as a distinct subset of epilepsy, and include Rolandic epilepsy or benign epilepsy with centrotemporal spikes (BECTS), nocturnal frontal lobe epilepsy (NFLE), encephalopathy related to electrical status epilepticus during sleep (ESES), continuous spikes and waves during slow sleep etc. Extensive research reveals that sleep and epilepsy have a complicated interrelationship. Some patients report a higher rate of sleep problems, disturbed daytime behavior, poor-quality sleep, and anxieties about sleeping. Nocturnal seizures disrupt sleep structure, with consequent effects on daytime functioning of patients. On the contrary, the distinct states of sleep (i.e., non-rapid eye movement [NREM] sleep and rapid eye movement [REM] sleep) can influence epileptiform discharges on different levels. Recently, various advanced neuroimaging approaches have been adopted in epilepsy studies. In this chapter, we will focus on the application of neuroimaging approaches in sleep-related epilepsy, to help further understand the pathophysiological investigation of sleep and epilepsy.

These neuroimaging approaches, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), may provide not only a static representation of the patient, such as the structural imaging, but a highly dynamic or evolving entity related to the pathophysiology of illness or treatment interventions. On the other hand, the network of the interconnected brain regions is another issue of hot debate. The findings describe epilepsy on the overall view of brain, and challenge the concept of "localization-related" epilepsy. Furthermore, the brain connectivity may facilitate discovering the cognitive deficits in epilepsy.

Electroencephalography (EEG)

EEG is the most useful diagnostic procedure for epilepsy, and the most general method to diagnose and manage the epileptiform discharges. Likewise, EEG is also the essential element for investigation of the sleep structure. The interictal epileptiform discharge remains the hallmark of epilepsy, vividly demonstrating cortical hyperexcitability and hypersynchrony, and is present in the "normal" interictal state. The presence of an interictal spike helps to confirm a clinical diagnosis of epilepsy, aids in defining the epilepsy syndrome, provides information that assists in planning drug management, and helps to assess candidacy for epilepsy surgery.

In clinical practice, nocturnal seizures are rarely witnessed, and therefore a complete description is often lacking. The video-EEG is a powerful tool to determine when nocturnal seizures occur. Direct observation of epileptic events with video-EEG monitoring provides the ideal method of assessing the episodes. An early study using video-EEG recordings in 100 patients with NFLE showed that NFLE comprises a spectrum of distinct phenomena, different in intensity but representing a continuum of the same epileptic condition. And these clinical characterizations may contribute to understanding the pathogenic mechanisms and different clinical outcomes [5]. The video-EEG polysomnography combines video-EEG monitoring with standard polysomnographic recording, thus providing not only information to permit an accurate determination of sleep stage, but also more epileptic behavioral and discharge information. The approaches based on EEG play a critical role in discovering the relationship between sleep and epileptiform discharges.

Many authors have noted that generalized spike-wave discharges increase during sleep in humans as well as experimental animals [6]. The generalized epileptiform activity is wavelike in nature and may build up as oscillations, which are manifestations of the corticothalamic system. This system is also the main structure responsible for generating sleep oscillations. It comprises the cortical neurons, dorsal thalamic nuclei, and reticular nucleus of the thalamus. The slow oscillations (sleep spindles) in NREM have been found to be intimately associated with the formation of generalized spike-wave discharges. A recent review of the rat model of absence epilepsy suggests that the sleep spindles and the spike-wave discharges are considered as autonomous EEG phenomena and accompanied by different neuronal

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processes and require different neurotransmitters [7]. However, the precise mechanism between the sleep and epileptic discharges is unclear.

Sleep may induce clinical seizures and interictal epileptiform discharges. Sleep activates both focal and generalized spikes in about one-third of all patients [6]. The occurrence of nocturnal seizures is influenced by sleep stage. These are most frequent in stage 2 NREM sleep, followed by stage 1 and stage 3 and 4 NREM sleep, and then REM sleep [6]. The common view of the influence of sleep on epileptiform discharge includes that NREM sleep activates interictal discharges and REM sleep inhibits interictal discharges. Shinnar et al. found that some patients had spike discharges that were only seen during sleep in 347 children with epilepsy [8]. Obtaining an EEG with adequate sleep improves the chances of detecting such discharges. Sleep may alter the morphology of epileptiform discharges. For example, Frost et al. found that compared with wakefulness, spikes seen in NREM sleep were of higher amplitude, longer duration, and less sharp, whereas spikes in REM sleep were of lower amplitude, shorter duration, and increased sharpness [9]. The typical 3 Hz per second spike and slow-wave complexes of children with absence epilepsy are replaced by either single spike-wave discharges or polyspike and wave configuration during sleep. On the other hand, sleep deprivation may increase cerebral irritability, which may result in epileptiform activity [10]. In clinical EEG practice, sleep deprivation becomes established as an activating method to elicit epileptiform activity.

Impairments of cognitive function are frequently reported in patients with epilepsy. Accumulated evidence indicates that specific sleep stages are involved in memory formation and cognitive performances [3]. For example, NREM may enhance and consolidate declarative memories, and REM sleep preferentially supports procedural and emotional memories. Memory disruption has been demonstrated in the patients with nocturnal seizures, even in the benign form of epilepsy, such as BECTS. By using questionnaires, memory and phonological awareness difficulties are found in patients with BECTS [11]. Event-related potentials (ERP) were used to investigate cognitive function, and the smallest mismatch negativity to speech stimuli were found in individual patients with atypical BECTS and learning difficulties [12]. The other EEG character, the slope of slow-wave during sleep, which is directly related to the degree of synchrony of the firing of cortical neurons [13], may be used to evaluate the cognitive impairment reduced by the epileptiform discharge during sleep. Bolsterli et al. found a significant difference of the slope of slow waves from the first to the last hour of sleep between the patients with ESES and the healthy controls, and speculated that the change in ESES may be associated with the cognitive regressions [14]. Although EEG is considered as the most useful diagnostic tool for epilepsy, it also is valuable to assess cognitive function in sleep-related epilepsy.

Simultaneous EEG and fMRI (EEG/fMRI)

Simultaneous EEG and fMRI scanning opens an opportunity to uncover the regions of the brain showing changes in the fMRI signal in response to epileptic spikes seen in the EEG [15]. It may localize abnormal neuronal activity at the origin of epileptiform discharges. Using simultaneous EEG and fMRI to study the human spontaneous NREM sleep, Kaufmann et al. described a specific pattern of decreased brain activity during sleep and suggested that this pattern must be synchronized for establishing and maintaining sleep [16].

EEG and fMRI are complementary imaging techniques, due to their respective strengths and weaknesses in terms of spatial and temporal resolution. Therefore, integrating EEG and fMRI may provide a combined imaging technique with a high level of dynamic temporal information and high spatial resolution [17]. There are three main methods to realize the fusion between EEG and fMRI. One proposed method is an "EEG-informed fMRI" algorithm, which requires the precise onset information of events or blocks such as the onset of epileptiform discharges and details of the actual hemodynamic response function (HRF). An alternative method, the "feature fusion" approach uses independent component analysis (ICA) to simultaneously analyze electromagnetic and hemodynamic data. A spatial pattern derived from fMRI can then be associated with a temporal waveform of EEG according to a common feature. The third approach is to use a statistical parametric map (SPM) obtained from fMRI to improve EEG source estimation. In this approach, SPM information can be used either to constrain the spatial locations of the likely sources of EEG, or to initially seed dipoles within the active regions found in the SPM for further dipole fittings. In addition, we proposed a new method for examining temporally coherent networks (TCNs) using scalp EEG in conjunction with data obtained by fMRI. In this approach, termed NEtwork based SOurce Imaging (NESOI), multiple TCNs derived from fMRI with ICA are used as the covariance priors of the EEG source reconstruction using parametric empirical Bayesian [18].

The potential of combined EEG and fMRI as a tool to explore mechanisms of epileptiform spike and seizure generation has been reviewed elsewhere [15]. One of the earliest studies to report on nocturnal seizures was based on spike triggered fMRI data in a girl with BECTS [19]. The finding showed that the fMRI activation in the ipsilateral face region of the somatosensory cortex in response to the epileptiform activity was consistent with facial sensorimotor involvement of BECTS seizures [19]. Recently, Masterton et al. reported similar localization with activation in association with centro-temporal spikes in BECTS by using EEG/fMRI [20]. A more recent study explored whether sleep-specific activity (sleep spindles, K-complexes, and vertex sharp waves) increase the sensitivity of EEG/fMRI of interictal epileptiform discharges in 11 patients with mono-focal epilepsy during sleep [21]. When considering the sleep-specific activity in SPM, it was possible to increase the statistical significance of the activated voxels inside the expected source of the interictal epileptiform discharge [21]. The sensitivity of EEG/fMRI increases by using the modified model; however, the findings implicate a complex relationship between sleep activity and epileptiform discharges.

Functional MRI (fMRI)

Functional MRI, which takes advantage of the observation that both blood flow and the ratio of oxy- to deoxyhemoglobin

increase with neural activation (dynamic time course on each voxel), is another powerful and non-invasive tool to detect brain function. The main application of fMRI in epilepsy is the detection of cognitive function changes in patients, such as language and memory. Memory is considered to closely associate with the slow oscillations during sleep, i.e., memory consolidation. The epileptiform discharges interfere with the process, for example the nocturnal seizures, or directly relate with the structure related to memory, i.e., hippocampal in temporal lobe epilepsy (TLE).

The impairment of language, memory, or motor function after epileptic surgery, particularly memory impairment in temporal lobe resection, is a topic of great interest. Functional MRI could be used to determine the extent of these functions, and then give a prediction of the likely changes following surgery. In candidates for epilepsy surgery, the Wada test was used to determine language and memory dominance before fMRI. In the Wada test (intracarotid amobarbital test), the portions of one hemisphere supplied by the anterior circulation are transiently anesthetized using a bolus of short-acting amobarbital, allowing the contralateral hemisphere to be assessed independently [22]. The non-invasive fMRI is considered as a method to displace the Wada test. However, the Wada test provides more direct information about language and memory functions. The diagnostic value of fMRI and the Wada test seems to be rather complementary. Killgore et al. reported that the method of combined fMRI and the Wada test improved prediction of postoperative seizure control compared with either procedure alone [23].

In previous studies, task-related or resting state fMRI was commonly used to detect memory function in TLE patients. A lesion of the hippocampus, which is considered as a main structure related to memory function, may explain the abnormal findings in fMRI. Memory fMRI studies in mesial TLE have typically shown reduced activity in mesial TLE on the side of seizure onset [24]. Richardson et al. used event-related verbal encoding task fMRI to study memory function outcome after surgery in ten TLE patients with left hippocampal sclerosis [25]. Results revealed that fMRI provided the strongest independent predictor for evaluating memory outcome of surgery, and implicated the fMRI data in the high positive predictive value for memory decline individually [25]. Language fMRI is another application for patients with epilepsy. The language task may be relatively simpler than memory. Typically, participants will perform a task related to language in the fMRI scanner, such as a verb generation task, in which the participants are asked to generate an appropriate verb or noun as a response to the target displaying on the screen. In general, language function has left lateralization in normal subjects. However, using language fMRI, patients with left mesial TLE showed less left lateralization than other left-onset focal epilepsy patients [26] and also showed weaker functional connectivity between language network regions than normal individuals [27]. Abnormal lateralization of language function to the right in left mesial TLE patients correlated with the frequency of epileptiform discharges [28] and may correlate with mixed or left handedness [29].

Structural MRI

Structural MRI is widely adopted in clinical practice to detect lesions in brain and diagnose illness with MRI signs. Abnormalities in brain, including hippocampal sclerosis, malformation of cortical development, focal cortical dysplasia, tumors, brain trauma, etc., are associated with epilepsy. On the other hand, some patients with epilepsy are characterized by absence of structural, inflammatory, or metabolic brain lesions, and are designated “idiopathic.” By using high-resolution T1 imaging or diffusion MRI, more and more reports have demonstrated the MRI abnormalities in patients with “idiopathic” or “benign” epilepsy such as BECTS and idiopathic generalized epilepsy [30]. Although, these structural abnormalities are also found in some patients with sleep-related epilepsy, i.e. BECTS and ESES, no specific structural change was found in the sleep-related epilepsy.

Even if structural MRI is unnecessary in BECTS, it is often performed before a specific diagnosis has been reached. Gelisse et al. reported that structural neuroimaging was abnormal in 14.8% of patients with BECTS in large samples (98 cases) [31]. In another group case (25 cases) study, Boxerman et al., found that at least one abnormality was detected in 52% of BECTS patients by using brain structural MRI, suggesting that the routine brain MRI abnormalities were common in BECTS [32]. Recently, Sarkis et al. found that the prevalence of abnormalities in BECTS is 27% [33]. Additionally, hippocampal abnormalities were also found on the MRIs in BECTS, and they were almost ipsilateral to the main EEG findings [34]. Thus, it may be of interest to consider the function of an abnormal hippocampus in epileptogenesis, and especially its relation to epilepsy arising from the Sylvian cortex. A more recent study explored serial changes in frontal and prefrontal lobe volumes using three-dimensional MRI in patients with BECTS [35]. The findings suggest that longer active seizure periods, such as frequent spike waves coupled with the occurrence of frequent seizures in patients with BECTS, may be associated with prefrontal lobe growth disturbance, which relates to neuropsychological problems [35]. Although the prevalence and location of brain lesion in BECTS is variable in different studies, these abnormalities are non-specific for BECTS, and rarely Rolandic in location. The relationship between the lesion in the brain and the centro-temporal spikes requires additional study.

Diffusion tensor imaging (DTI), which quantifies the diffusion of water and characterizes the degree and direction of anisotropy, is another powerful tool of structural MRI. In epilepsy, DTI has been used to localize the epileptic foci and white matter tracts. Diffusion abnormalities have been found to lateralize in mesial TLE [36] and refractory partial epilepsy [37]; hence DTI may provide limited independent information beyond these more conventional measures. DTI data can be used to infer the presence, direction, and integrity of white matter tracts in the brain. Using DTI to tract white matter, we found that structural connectivity was significantly decreased between the posterior cingulate cortex/precuneus and bilateral medial temporal lobes in TLE patients [38]. Recently, Wang et al. used DTI to investigate the diffusion property in frontal lobe epilepsy, as characterized by brief, recurring seizures that

arose in the frontal lobes of the brain while the patient was sleeping. Decreased fractional anisotropy (FA) was found in the frontal lobes and thalamus in patients with frontal lobe epilepsy compared with controls. The abnormalities in the frontal lobe white matter and the thalamus are considered to contribute to cognitive impairment in patients with frontal lobe epilepsy [39].

Brain networks

Human brain function is thought to rely on two principles of functional specialization and integration. Functional integration is implemented by the complex and reciprocal neural networks in the brain. Brain networks have been depicted in terms of functional connectivity by EEG, magnetoencephalography (MEG), and fMRI, and in terms of structural connectivity by DTI and morphological studies. The analysis of functional and structural connectivity networks provides new avenues for assessing complex network properties of healthy and diseased brain. Indeed, altered brain network topology has been shown in several psychiatric and neurological diseases.

For more than a decade, fMRI has been applied in the field of neuroscience to help us understand the brain network. Using correlation analysis, Biswal et al. first reported the correlated connectivity pattern of the spontaneous blood oxygen level-dependent (BOLD) signal in the motor system [40]. Since then, several analysis tools, such as independent component analysis, cluster analysis, etc., have been applied to fMRI data. Up to now, it has been suggested that at least 10 to 12 resting state functional networks (RSNs) can be detected from the brain cortex in fMRI. The fMRI data sets resulting from the task-related design or resting state are used to construct the brain network. Assessing functional connectivity in brain networks may allow for identification of more fundamental abnormalities underlying disease. Using resting state fMRI, Bettus et al. studied basal functional connectivity within the temporal lobes in eight patients with mesial TLE. The findings demonstrated decreased basal functional connectivity within epileptogenic networks but increased concomitant contralateral connectivity, possibly reflecting compensatory mechanisms [41]. This was the first resting state fMRI study to investigate the functional connectivity in epileptogenic networks in epilepsy [41]. Waites et al. evaluated the language functional network in TLE on the language task-related and resting state fMRI data, and found reduced connectivity seen at the language area in left TLE. These findings may reflect a disturbance of the language network during resting state in patients, which may be related to subtle language difficulties in the patient population [27]. Recently, using resting state fMRI on 18 mesial TLE patients, we built a functional brain network within 90 cortical and subcortical nodes. The findings suggested altered small-world properties in patients, along with a smaller degree of connectivity, smaller absolute clustering coefficients, and shorter absolute path length [42]. Recent network analyses have revealed that several distributed brain networks are involved in the genesis and manifestation of idiopathic generalized epilepsy based on the fMRI [43, 44].

An extension of functional connectivity, called functional network connectivity (FNC), has been developed. FNC is powerful in characterizing distributed changes in the brain by examining the interactions among different RSNs. Jafri and his colleagues conducted FNC analysis in schizophrenia, and found significant differences between patients and controls, suggesting deficiencies in cortical processing in patients [45]. Recently, in order to investigate the functional connectivity inter- and intra-RSNs in patients with partial epileptic seizures, we selected eight RSNs and conducted a systematical RSN analysis in a cohort of partial epilepsy patients and healthy controls. By dividing the eight RSNs into three subsystems, we found that intra-system connections were preserved for all the three subsystems, while the lost connections were confined to intersystem connections (Figure 49.1). These findings, in which the intra-system connections were preserved for all the three subsystems while the lost connections were confined to intersystem connections in patients with partial epilepsy, might suggest that decreased resting state functional connectivity and disconnection of FNC are two remarkable characteristics of partial epilepsy [46]. In our preliminary study, we also assessed the FNC among 10 RSNs in patients with BECTS with nocturnal seizures, 10 patients with BECTS (8 right, 2 left), and 12 controls. Then ten RSNs were selected to estimate the FNC in two subjects, among which some networks were related to primary perceptional function, including the lateral part of the visual network, the medial part of the visual network, the occipital visual network, the auditory network, and the sensorimotor network, while others were higher level cognition networks, including the self-referential network, default mode network, dorsal attention network, and ventral attention network. The basal ganglia network appeared to be an important intermediary for modulation between sensory and higher level cognitive processing. The hierarchical disconnections of FNC (between the perceptional level and cognitive level) were found in BECTS (Figure 49.2). The selective impairment of FNC had an important functional and theoretical implication in that it was unsuitable to understand the partial epilepsy only from a global or local view.

The brain network can be constructed on the structural MRI data. He et al. investigated large-scale anatomical connection patterns of the human cerebral cortex using cortical thickness measurements from MRI [47]. A recent study has derived whole-brain networks from volumetric data and obtained network measures (cortical thinning characteristic) in patients with TLE [48]. The network features were used to classify a given MRI scan into TLE or normal, and additional summary statistics related to the extent and spread of the disease were obtained. The proposed network approach improved classification accuracy (control and TLE) from 78% for non-network classifiers to 93% [48]. Meanwhile, the white matter tractography resulting from DTI was also used to describe the edge of the network. Hagmann et al. non-invasively mapped white matter pathways within and across cortical hemispheres in individual human participants and identified the core within the cortex with spatial and topological centrality [49]. Zhang et al. used the resting state fMRI signal correlations and DTI tractography to generate functional and structural connectivity networks in 26 idiopathic generalized epilepsy patients with tonic-clonic seizures [50]. Results showed that the patients

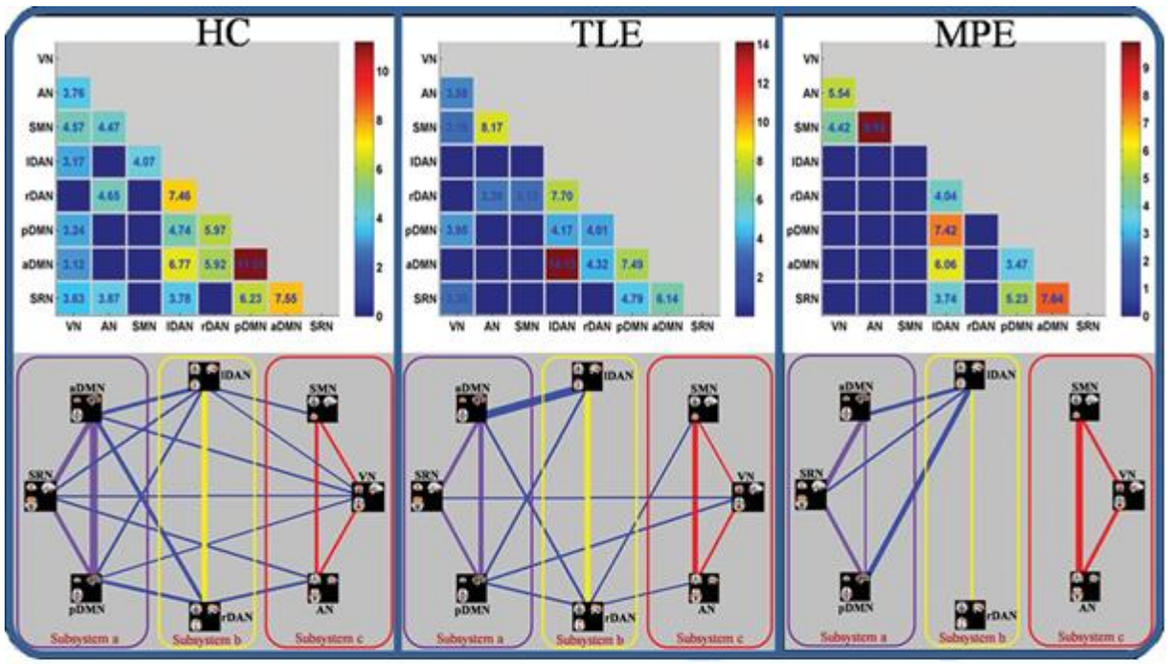

Figure 49.1 Correlation matrices representing results of FNC analysis for healthy control (HC, left), temporal lobe epilepsy (TLE, middle), and mixture partial epilepsy (MPE, right). Eight RSNs were identified by ICA, and used to assess the FNC in the three groups. Significant connections ($P < 0.05$ FDR-corrected) were marked by corresponding T values at upper of the figure. The network map was showed at the bottom of the figure. Three subsystems: (a) these RSNs (in the purple rectangle) related to information integration and modulation including the posterior part of the default mode network (pDMN), the anterior part of the default mode network (aDMN), and the self-referential network (SRN); (b) these RSNs (in the yellow rectangle) related to higher level cognition including the left dorsal attention network (lDAN) and right dorsal attention network (rDAN); (c) these RSNs (in the red rectangle) related to primary perceptional function including the sensorimotor network (SMN), visual network (VN), and auditory network (AN). The intensity of the temporal dependency between RSNs was indicated by the thickness of the corresponding line.

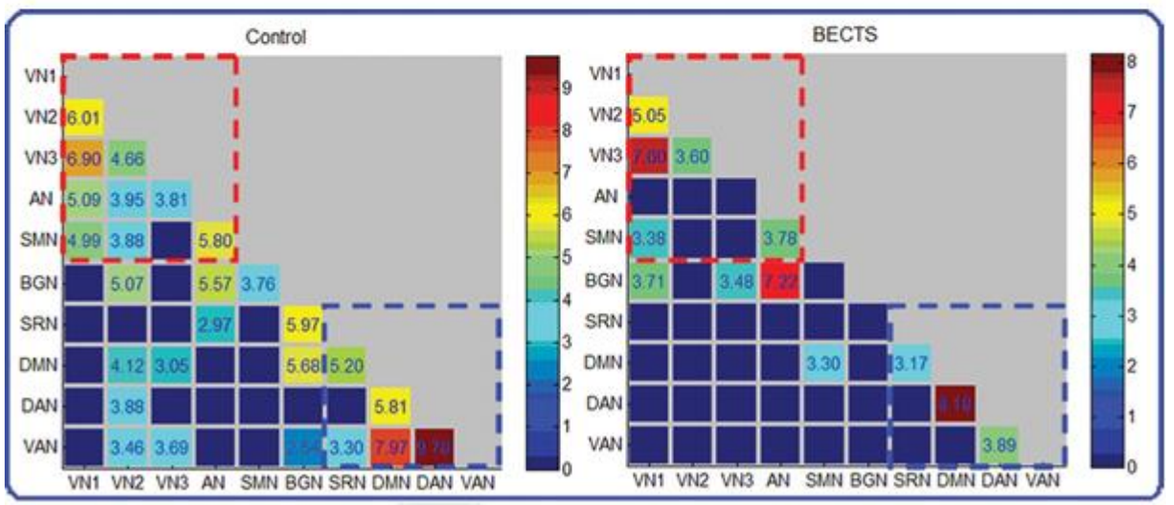

Figure 49.2 FNC (functional network connectivity) analysis for 12 controls (left) and 10 BECTS (right). Significant connections ($p < 0.05$ FDR-corrected) were marked by corresponding T-values (color bars). The networks (in the red dotted rectangle) related to primary function included the lateral part of the visual network (VN1), the medial part of the visual network (VN2), the occipital visual network (VN3), the auditory network (AN), and the sensorimotor network (SMN). The networks (in the blue dotted rectangle) related to higher level cognition included the self-referential network (SRN), default mode network (DMN), dorsal attention network (DAN), and ventral attention network (VAN). The basal ganglia network (BGN) was suggested as an important intermediary for modulation between sensory and higher level cognitive processing.

lost optimal topological organization in both functional and structural connectivity networks, and the degree of coupling between functional and structural connectivity networks was decreased [50].

Conclusion

Currently, neuroimaging research on epilepsy is vigorous and thriving, along with an eagerness to adopt new methods. However, there are relatively few studies focused on

sleep and epilepsy, specifically. Obviously, the relationship between sleep and epilepsy is a complicated one. This complexity mainly lies in two aspects: one is the ambiguous electrobiological mechanism between the sleep activity and generalized epileptiform discharges, such as the relationship between spindle and generalized spike wave discharge; the other is the complex relationship between the nocturnal seizures and sleep structure. Simultaneous EEG and fMRI, and brain network approaches along with data acquisition during sleep in patients with epilepsy will be powerful means to evaluate these complicated relationships in the future.

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