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Review

Multimodal neuroimaging investigations of alterations to consciousness: The relationship between absence epilepsy and sleep

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ABSTRACT

The link between epilepsy and sleep is well established on many levels. The focus of the current review is on recent neuroimaging investigations into the alterations of consciousness that are observed during absence seizures and the descent into sleep. Functional neuroimaging provides simultaneous cortical and subcortical recording of activity throughout the brain, allowing a detailed definition and characterization of large-scale brain networks and the interactions between them. This has led to the identification of a set of regions which collectively form the consciousness system, which includes contributions from the default mode network (DMN), ascending arousal systems, and the thalamus. Electrophysiological and neuroimaging investigations have also clearly demonstrated the importance of thalamocortical and corticothalamic networks in the evolution of sleep and absence epilepsy, two phenomena in which the subject experiences an alteration to the conscious state and a disconnection from external input. However, the precise relationship between the consciousness system, thalamocortical networks, and consciousness itself remains to be clarified. One of the fundamental challenges is to understand how distributed brain networks coordinate their activity in order to maintain and implement complex behaviors such as consciousness and how modifications to this network activity lead to alterations in consciousness. By taking into account not only the level of activation of individual brain regions but also their connectivity within specific networks and the activity and connectivity of other relevant networks, a more specific quantification of brain states can be achieved. This, in turn, may provide a more fundamental understanding of the alterations to consciousness experienced in sleep and epilepsy.

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1. Introduction

There is a long history of basic and clinical research indicating a bidirectional link between many aspects of epilepsy and sleep (for reviews, see [1–4]). In this review, we will briefly recapitulate some of these links before focussing on recent neuroimaging investigations that relate to the alterations of consciousness and awareness that are observed during epileptic seizures and the descent into sleep. We will concentrate on absence seizures as perhaps the most obvious example of a modification to the conscious state in epilepsy. Absence seizures affect the level and the contents of consciousness [5], although they are not accompanied by complex experiential phenomena and are characterized by abrupt cessation of responsiveness associated with staring. They may also be accompanied by myoclonic movements, atonia, or automatisms. Electrophysiologically, they demonstrate spike–wave discharges (SWD) with durations of around 10 s and abrupt onset and offset. Shorter bursts of SWD do not result in the overt loss of awareness that is observed in absence seizures, although the reason for this is not clear, given that they are presumably generated by the same networks.

While in vitro and in vivo electrophysiology studies allied with clinical studies are able to identify and characterize the basic links between sleep and epilepsy, they are less well suited to addressing the questions of how and why consciousness is altered. To investigate whether similar mechanisms are involved in the alterations to consciousness experienced in normal sleep and absence seizures, whole-brain functional recordings are needed which can provide a system-level characterization of the neural substrates underpinning such complex behaviors. The major neuroimaging techniques of functional MRI (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) have all been extensively used to delineate the regions involved in the maintenance of the conscious state in patients with epilepsy and in sleeping subjects. A consistent picture generally emerges of a network of cortical and subcortical regions which comprise a 'consciousness system' [6,7]. Cortically, this involves the default mode network (DMN) and other regions such as the lateral frontal association cortices, with subcortical structures including the thalamus, hypothalamus, basal forebrain, and regions in the

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upper brainstem which are involved in arousal. How these distributed regions, which consist of contributions from several specific networks, interact to maintain the conscious state is an unresolved question. In particular, the relationship between the DMN and the thalamocortical (TC) and corticothalamic (CT) networks that generate the paroxysmal discharges of sleep and generalized epilepsy is not clear. In the following, we will review the evidence from functional neuroimaging that there are shared mechanisms responsible for the alterations to consciousness observed in sleep and absence seizures, with particular attention paid to the relationship between TC interactions and the DMN. Firstly, however, we will briefly discuss some of the electrophysiological links between epilepsy and sleep. Epilepsy is inherently an electrophysiological disorder, and there are a number of indications that specific electrophysiological markers of epileptogenicity are linked with the neurobiological processes underlying sleep.

2. Electrophysiological links between epilepsy and sleep

One example of the link between sleep and epilepsy that has a long history and has received a considerable amount of attention is the hypothesis that the TC networks that generate sleep spindles are pathologically utilized to generate SWD (see [8–10] for reviews). Sleep spindles are one of the defining characteristics of non rapid-eye movement stage 2 sleep (N2, [11]) and are generated by reciprocal connections and interplay between the cortex, thalamic reticular nucleus (TRN), and TC neurons located in the dorsal thalamic nuclei. They originate in the thalamus as a result of hyperpolarization of TC neurons mediated by γ-aminobutyric acid (GABA), released through the firing of TRN neurons. Thalamocortical neurons, through low threshold calcium currents, experience a postinhibitory rebound, causing excitatory input into the TRN neurons. It is this cyclic alternation that results in rhythmic sleep spindles, which are then transferred to the cortex through TC neurons and become evident on scalp EEG [12–15]. Abnormal overexpression of these low threshold calcium currents has been implicated in the generation of SWD in rodent studies [16–18]. The relative importance of the thalamus and cortex in the generation of SWD is an ongoing debate [10], with the recent evidence pointing towards an initiating site in the cortex [19], rather than the thalamic origin of sleep spindles. Differences in time–frequency characteristics have also highlighted a less-than-straightforward relationship between sleep spindles and SWD (for a review, see [20]).

It is not only in absence seizures that the electrophysiological markers of epileptogenicity have been associated with sleep. Recently, it has been suggested that high frequency oscillations (HFO) represent one of the most specific markers of the epileptogenic zone in focal epilepsies, particularly in the fast ripple (>250 Hz) range [21,22]. At lower frequencies, ripples (>80 Hz) are considered to be one of the mechanisms of memory consolidation, whereby hippocampal traces acquired during wakefulness are transferred for long-term storage to the cortex [23]. Hippocampal ripples are temporally coincident with cortical sleep spindles [24], supporting the view that sleep spindles are an important part of the memory consolidation process [25]. The rate of occurrence of ripples and pathological fast ripples is strongly dependent on sleep stage, peaking in non-REM (NREM) sleep and minimal in both wakefulness and REM sleep [26]. This link between sleep stage and manifestations of epilepsy is also seen for interictal epileptiform discharges as well as overt seizures [2–4,27]. Seizures also tend to become more likely following sleep deprivation, potentially because of changes in cortical excitability that occur with prolonged wakefulness [28].

These observations, as well as others which are reviewed in detail elsewhere [1–4], cement the concept of a strong link between various types of epilepsy and sleep. In some cases, such as the link between spindles and SWD, hypotheses are very specific, and the putative neurobiological mechanisms are well developed. In other cases, the observed relationship may be more related to the profound changes in the electrophysiological and neuromodulatory environments that occur during sleep, which consequently affect epileptogenic processes. Clearly, continued efforts are needed to clarify how and why epileptogenic processes are facilitated by sleep. However, with regard to the question of alterations to consciousness, functional neuroimaging has the advantage that it records the activity and interactions of regions distributed throughout the brain, allowing them to be linked with overt behaviors. This has facilitated some important observations regarding the disruptions to consciousness experienced in sleep and seizures.

3. Neuroimaging of alterations to consciousness in absence epilepsy and sleep

There is a reasonable body of work which has examined the cortical and subcortical regions involved in SWD and absence seizures. From a practical point of view, this activity is amenable to investigation with functional magnetic resonance imaging (fMRI) since it does not necessarily result in motor activity which would have safety implications and degrade data quality. This has led to the application of EEG-fMRI in several studies, and reduced activity in the nodes of the DMN and increased thalamic activity, with less consistent alterations elsewhere in cortical and subcortical regions [29–40], have been consistently observed. The DMN includes the precuneus, posterior cingulate cortex, and bilateral inferior parietal and medial prefrontal cortices [41]. It is one of a series of resting state networks (RSNs) that can be reliably extracted from neuroimaging data which have become an increasingly important method of investigating the brain's functional architecture [42]. Activity in the DMN increases when the subject is not engaged in cognitively demanding activity [41,43], and it was originally identified as a set of regions which were consistently deactivated across a range of tasks [44]. It is considered to be particularly important for intrinsic thought processing and representing one's self in relation to the external environment [5].

Reduced DMN activity during SWD would imply a cessation of the self-monitoring that occurs during normal consciousness in the absence of an overt task and could be considered to be consistent with the observed clinical correlates of SWD. Besides reduced DMN activity during SWD, disruptions to the DMN have also been observed in patients with focal epilepsy, suggesting an inherent ability of epileptic activity to disrupt ongoing brain processes including the DMN and consciousness system [6,45]. However, bearing in mind that the DMN routinely deactivates during normal sensory and cognitive processing without leading to the loss of consciousness observed in absence seizures, it is perhaps not completely clear how to interpret the deactivation seen during SWD. Even in the simpler case of task responses, the interpretation of reductions in hemodynamic activity is still a matter of ongoing debate within the neuroimaging community, and it has been suggested that the physiological origin of negative responses may be dependent on task type and brain region [46]. This suggests that some caution is needed when considering the interpretation of deactivations in networks of ongoing brain activity in response to internally generated, pathological paroxysmal discharges.

Alterations to DMN activity have also been implicated in the alterations to consciousness that are seen in the descent into sleep, often in terms of the connectivity between regions, which will be discussed below. When considering the regions activated or deactivated by sleep spindles, which have been more widely studied than K-complexes or vertex sharp waves and which are of particular relevance to the foregoing discussion, it is notable that they are not immediately comparable to those linked with SWD, and deactivation of the DMN is not observed [47–49]. While this would not preclude the same networks being involved in the generation of the two types of activity, it would require a more complex interpretation of the relationship between electrophysiology and hemodynamic neuroimaging. For example, if the same TC circuit is driven by very different modes of neuronal firing, it is conceivable that the downstream expression of that activity on the cortex, as well as the regional metabolic demands that drive hemodynamic