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Editorial

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Can electroencephalography reveal network connectivity alterations in insomnia disorder?

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Sleep–wake transition is orchestrated by a complex interplay between various cortical and subcortical brain areas organized into sleep-promoting and wake-promoting regions [1]. Persistent impairment of the sleep–wake regulatory system results in many sleep disorders, especially insomnia, where individuals have difficulties initiating and maintaining sleep. Given the widespread prevalence of insomnia in the adult population [2], a thorough understanding of the underlying pathophysiological aberrations is pivotal for developing effective treatment strategies.

The transition from acute to chronic insomnia has a complex etiology with several contributing factors. For example, genetic factors and personality traits can predispose an individual to sleep difficulties. With added environmental and psychological stressors, these sleep difficulties can turn into acute insomnia. Eventually, maladaptive behavioral strategies, such as spending prolonged time in bed tossing and turning to fall asleep, and excessive worrying about not getting sufficient sleep can lead to the transition of acute insomnia into a chronic condition [3]. This complex etiology is further complicated by the underlying neurobiological mechanisms of the brain [4]. A review of functional magnetic resonance imaging (fMRI) studies of the brain reported insomnia-related changes in the activation levels of the thalamus and several cortical regions [5]. In addition, positron emission tomography studies found that, when compared to good sleepers, individuals with chronic insomnia have increased global brain metabolism [6] and altered metabolism in brain regions involved in cognition, rumination, and emotion [7]. Given the extensive interaction between different brain regions, an important question is: what goes wrong in the brain at the network level that leads to insomnia?

The human brain is an organ with an extensively interconnected network of subregions specialized in sensory, cognitive, and motor functions. Deficits in one of these regions can end up affecting functions subserved by several other regions, emphasizing the need for a whole-brain approach to understand the neural mechanisms of insomnia. These inter-regional connections, far from being random, are organized into multiple well-defined subnetworks, several of which remain active when humans are simply resting [8]. Functional connectivity studies have revealed insomnia-associated alterations in the connectivity within many of these resting-state networks, including the default-mode network, salience network, dorsal attention network, and fronto-parietal network [9]. For example, hyper-connectivity between the components of the default-mode network has been shown to occur in insomnia [9], however, given the heterogenicity of the studies, additional systematic research is needed to reach a consensus as to the characteristics of the connectivity deficits in insomnia [9, 10]. Nevertheless, current results clearly point towards the benefit of probing network connectivity to understand the neurophysiological changes that drive insomnia.

Alterations in the neurochemical makeup of the brain add another dimension to the pathophysiological changes in insomnia, and in vivo characterization of the distribution of major neurotransmitters—dopamine, serotonin, norepinephrine, GABA, and glutamate—that regulate sleep [1] would shine light on the neural mechanisms of insomnia. However, to date, only some of these neurotransmitters, i.e. GABA and glutamate, have been examined and these assessments have been limited to a handful of studies in insomnia patients [11–15], leading to a preliminary conclusion of elevated glutamate levels close to bedtime [14]. Future studies are required to probe changes in the levels of other neurotransmitters, especially norepinephrine, which has been hypothesized to be involved in insomnia [4] as supported by a recent animal study [16]. While the inherently challenging techniques to measure neurotransmitters mature, a fruitful interim solution would be to use the recently developed cortical maps of the neurotransmitter systems [17, 18] and correlate the locations of insomnia-related changes in the brain with the densities of the neurotransmitter systems at the corresponding locations. Such analyses will give important clues as to which neurotransmitter systems are likely to be altered in insomnia, motivating and guiding further research.

The typical use of fMRI for analysis of the functional connectivity of the brain is well suited for a mechanistic understanding of insomnia. However, fMRI technology is impractical for everyday clinical use. As a more practical alternative, the continued refinement of high-density electroencephalogram (EEG) recordings combined with EEG-source-localization methods that account for artifactual volume conduction [19] has lent itself to EEG-based functional connectivity analyses [20–22].

Leveraging these recent developments, the study by Yu et al. [23] featured in this issue of *Sleep* demonstrates that there is a correlation between resting-state connectivity changes associated with insomnia and the distribution of specific neurotransmitter systems. To this end, the authors recorded EEG signals from patients with chronic insomnia and healthy controls for a period of 5 minutes and estimated the cortical current sources that gave rise to these signals. From these "source-space" data, they computed global brain connectivity, which measures the density of connections of a given cortical region with every other cortical region in the brain. First, they found that the prefrontal and limbic cortical regions exhibit hyper-connectivity in patients with insomnia compared to controls. Second, using a support vector machine classifier, they reported that global brain connectivity can predict whether an individual has insomnia or not. Third, they showed that insomnia-related changes in global brain connectivity occur at brain regions that are frequently associated with cognitive control, hyperactivity, and emotional regulation. Finally, they determined that insomnia-related global brain connectivity changes occur at brain locations where receptors/transporters for dopamine, norepinephrine, and serotonin are found. Through brain networks, this comprehensive analysis elegantly links macroscopic signal changes to microscopic neurotransmitter-system profiles. The methodology clearly shows its potential for clinical use as the time course of insomnia-related brain changes can be tracked in only 5 minutes of EEG recordings.

Although the study focuses mainly on global brain connectivity, it would be of great interest to know how the different subnetworks implicated in insomnia are altered as measured by EEG. Given that rapid-eye-movement sleep is particularly affected in insomnia [24] and that EEG is more practical than fMRI for recording brain activity during sleep, an interesting avenue for future research would be to use EEG to examine how network connectivity changes during rapid-eye-movement sleep. Considering the extensive overlap of the underlying neurobiological and connectivity alterations between insomnia and affective disorders, especially depression [25], further studies would be fruitful to ascertain how specific the study's support vector machine classifier is to insomnia. In addition, future studies should include subcortical structures, such as the thalamus and amygdala, which are strongly implicated in insomnia [26, 27].

Although the short-duration EEG recording used in the study by Yu et al. [23] is a promising aspect for clinical translation, the source-localization method used in their study requires structural MRI of the individual participants. While this requirement is a strength of the study in terms of accurate source localization, this additional step nonetheless adds a bottleneck for clinical translation. Furthermore, applying EEG-based connectivity to the finer scale subcortical structures typically requires a higher resolution MRI (higher magnetic field) [28], adding yet another translational hurdle. Nevertheless, EEG-based connectivity analysis still holds promise, as structural MRI data need to be collected only once for a given participant.

In summary, insomnia remains a widespread public health burden with unmet therapeutic interventions. EEG-based connectivity analyses can be successfully used as a clinically relevant tool for probing and tracking insomnia-related changes during wakefulness and sleep, complementing the advantages of other imaging modalities, such as fMRI and positron emission tomography, which provide more direct localization of neurobiological abnormalities.

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