Is the insula linked to sleep? A systematic review and narrative synthesis

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GRAPHICAL ABSTRACT

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ABSTRACT

Background: Sleep is critical to human beings in a surprisingly diverse set of ways, and there is, thus, continual investigation into the mechanisms of sleep. Although current studies have confirmed that multiple brain regions are involved in the regulation of both sleep and wakefulness, the association between certain important brain regions such as the insula and sleep is still unclear.

Objective: The purpose of this study was to systematically review studies on the insula and sleep and to discuss the relationship between the insula and sleep.

Methods: We searched the PubMed and Web of Science Core Collection (WoSCC) for articles on sleep and the insula. The time span was from inception to June 30, 2022. The search results were then narratively summarized.

Results: A total of 939 studies were identified in the PubMed and WoSCC of which 115 studies were included in the narrative synthesis. These 115 studies can be roughly divided into 41 studies on insomnia, 39 on sleep deprivation, 33 on sleep-related experiments examining the insula, and 2 studies using basic experiments.

Conclusion: The combined findings of many sleep-related studies have confirmed a close link between the insula and sleep loss, including insomnia, sleep deprivation, sleep-related disorders, and more. Although these results do not directly confirm that the insula is involved in sleep, an overall analysis of the results indicates that the insula may be a potential key brain region involved in sleep.
1. Introduction

Sleep is essential for the maintenance of normal body activities and functions and accounts for approximately one-third of our lives. Adequate sleep regulates the body systems and affects a variety of physiological functions, such as body temperature, blood pressure, heart rate, respiration, and hormone secretion [1, 2, 3, 4]. However, sleep-related health problems have gradually increased in recent years [5, 6]. Numerous studies have shown that short-term sleep loss can affect cognitive and emotional performance, and long-term sleep loss is associated with neurodegeneration [7, 8, 9, 10]. In addition, sleep-related health problems have also gradually evolved into serious social public health problems [11, 12].

Given the importance of sleep to the body, sleep mechanisms have been intensively investigated. Sleep has been shown to involve many regions and nuclei in the brain, including subcortical nuclei such as the hypothalamus, brainstem, and basal forebrain, as well as the prefrontal cortex, motor cortex, anterior cingulate cortex (ACC), and primary visual cortex [13, 14, 15, 16, 17, 18]. However, these findings have raised new questions, such as why so many nuclei as well as the cerebral cortex are involved in the maintenance of sleep or wakefulness while the detailed mechanisms underlying sleep and wakefulness are incompletely understood. Additional questions are whether, in view of the importance of sleep, the brain requires multiple switches to induce sleep, and whether other as yet undiscovered regions of the brain are involved in the control of sleep and wakefulness.

The insula has a unique anatomical location in the brain deep within the Sylvian fissure, inferior to the frontal lobe, medial to the temporal lobe, and anterior to the parietal lobe [19]. As described above, sleep has different effects on the brain, affecting both systemic and autonomic physiology, and sleep loss can lead to cognitive impairment, emotional disturbances, and hyperalgesia, among other adverse effects. The insula also participates in emotion, pain, and cognitive and autonomic functions, suggesting an overlap between the role of sleep and the function of the insula. This invites the question of whether there is an intrinsic link between the insula and sleep.

In recent years, thanks to the development of imaging, electroencephalography (EEG), and other technologies, the role of the insula in relation to sleep has received more attention. The aim of the present study was to review the published research on the association between the insula and sleep to better understand the relationship between the two and provide a reference for future studies.

2. Methods

2.1. Literature search

Data were retrieved from the PubMed and WoSCC, an extended version of the Science Citation Index, using advanced search strategies. The following search terms were entered in the topic field: (“insula” OR “insular”) AND (“sleep” OR “sleepiness” OR “sleep deprivation” OR “insomnia” OR “sleep disorder” OR “parasomnias”). The time span was from inception to June 30, 2022 (Figure 1).

2.2. Inclusion and exclusion criteria

Our objective was to investigate the role of the insula in sleep. Therefore, the criteria included all articles involving the insula and sleep or sleep-related disorders. We excluded articles that were not written in English. In addition, the article type was limited to original articles, and reviews, meeting abstracts, editorial material, early access, proceedings proceedings
Insomnia is a recognized health problem in modern society that can lead to physiological dysfunction, emotional disorders such as anxiety and depression, cognitive impairment, and increased risk of cardiovascular, nervous system, and multisystem diseases [29, 30]. Interestingly, the range of health problems caused by insomnia closely resembles the documented functions of the insula, suggesting the possibility of a connection between the two.

Regional homogeneity (ReHo), amplitude of low-frequency fluctuation (ALFF), and fractional amplitude of low-frequency fluctuations (fALFF) are commonly used metrics for analyzing fMRI data and represent spontaneous neural activity. Interestingly, abnormalities in the insula have been observed. Wang et al. observed patients with primary insomnia by rs-fMRI and found that the ReHo value of the left insula was increased and that this increased ReHo value was positively correlated with the patients’ self-reported anxiety scores [24]. In a study of patients with major depressive disorder who complained of insomnia, Liu et al. found that the ALFF was increased in the right anterior insula and that the increased ALFF value in the insula was correlated with sleep disturbance scores [22]. Chen et al. used fMRI/EEG to record the Blood Oxygen Level-Dependent (BOLD) signal and EEG gamma frequency power in 17 female insomniacs; the results suggested that the insula, as a key node of a salient network, was involved in hyperarousal in patients with insomnia [31]. These results suggest another thought. Since the subjects of these studies were all insomnia patients, it might be possible that the change in spontaneous neural activity in the insula itself leads to insomnia, or vice versa, or the related complications of insomnia such as anxiety, in turn leading to alterations in the spontaneous neural activity of the insula, which regulates emotion.

FC is an fMRI indicator that can study the interactions between different brain regions and is also often used to study the underlying neural circuitry associated with insomnia. Several recent studies of patients with insomnia have found abnormal FC between the insula and other brain regions [32, 33, 34, 35]. Unfortunately, these studies did not use the insula as the region of interest. To investigate neural mechanisms underlying insomnia, Li et al. selected the right anterior insula as the region of interest to analyze the directional FC of the insula in patients with primary insomnia (PI), revealing abnormalities in the directional FC between the right anterior insula and multiple brain regions, and that effective connectivity between the right anterior insula and the left posterior central gyrus was associated with insomnia severity [26]. In another rs-fMRI study of patients with PI, Li et al. observed that abnormal voxel-wise functional connectivity strength (FCS) in the right anterior insula cortex and left middle frontal gyrus are potential neural markers of PI [36]. These results all indicate that there are FC abnormalities between the insula and other brain regions in PI patients, suggesting that sleep loss in PI patients leads to abnormal FC in the insula and other brain regions, or vice versa.

### Table 1. Changes in spontaneous neural activity in the insula shown in recent sleep-related studies.

| fMRI Metrics | Study | Subjects | Changes in the insula |
|--------------|-------|----------|----------------------|
| ALFF         | Chen et al. [20] | Healthy female with SD 24h | Increased ALFF in left insula |
|              | Ji et al. [21] | Children with OSA | Increased ALFF in the right insula |
|              | Liu et al. [22] | patients with insomnia complaints in MDD | Increased ALFF in the right anterior insula |
| fALFF        | Wu et al. [23] | sleep disturbance in individuals with MDD | Increased fALFF in the right anterior insula |
| ReHo         | Wang et al. [24] | patients with primary insomnia | Increased ReHo in the left insula |
| fMRI: functional magnetic resonance imaging; ALFF: amplitude of low-frequency fluctuation (ALFF); fALFF: fractional amplitude of low-frequency fluctuations; ReHo: Regional homogeneity; SD: sleep deprivation; OSA: obstructive sleep apnea; MDD: major depressive disorder. |
et al. [27] Levichkina [28] Chen et al. [26] Primary sleep quality in college-age volunteers [42]. A similar study of sleep found that changes in the GMV in the right insula were associated with the insular cortex was associated with poor sleep quality [41]. Yin et al. of 37 states [40].

4.3. Sleep-related experiments examining the insula

Various sleep studies have reported changes in the insula. In a study of 37 firefighters, Park et al. found that reduced cerebral blood flow in the insular cortex was associated with poor sleep quality [41]. Yin et al. found that changes in the GMV in the right insula were associated with sleep quality in college-age volunteers [42]. A similar study of sleep quality in young volunteers by Guadagni et al. revealed that BOLD signals in the left insula were increased in individuals who subjectively reported better sleep quality [43]. Although these studies have confirmed that the imaging changes observed in the insula are related to sleep quality, several studies have questioned whether the insula is involved in the physiological process of sleep. Falgás et al. found that changes in the insular GMV were related to the severity of sleep loss in a comparison of insomnia and non-insomnia groups; however, no differences were seen when the volumes were compared [44]. Coincidentally, van den Heuvel et al. found that maternal stress during pregnancy can alter fetal

Table 2. Sleep-related studies focusing on the insula.

| Study | Subjects | Methods | Results |
|-------|----------|---------|---------|
| Qi et al. [25] | Healthy volunteers (TSD 36 h) | Utilizing fMRI | The FC between the insula and other brain regions is significantly altered after TSD. |
| Li et al. [26] | Primary insomnia patients | Utilizing fMRI | Abnormal efficient connections exist in the right anterior insula in patients with primary insomnia. |
| Levichkina et al. [27] | Cat | Electrodes for electrical stimulation and recording | Insula has a dual role in sleep and wakefulness |
| Chen et al. [28] | Rat | Record with sleep monitor | The anterior insula is involved in regulating sleep and wakefulness |

TSD: total sleep deprivation; FC: functional connectivity; fMRI: functional magnetic resonance imaging.

4.4. Research on insula participation in sleep in basic experiments

Basic experiments investigating the involvement of the insula in sleep are rare. Chen et al. reported that rats with lesions of the anterior insula showed increased REM sleep and non-REM sleep time, together with a reduced duration of sustained wakefulness [28]. Levichkina et al. reported efficient afferent and efferent connectivity patterns in the insular cortex during the transition from wakefulness to sleep by studying neuronal responses in the cat insular cortex following electrical stimulation of the gut wall during wakefulness and natural sleep. The observed changes demonstrated the dual function of the insula in sleep and wakefulness [27]. From these two basic experiments, it can be concluded that the role of the insula in sleep is complex, which may be because the insula is considered an important information transfer station in the brain.
4.5. Open questions and outlook

The studies described above point to a close relationship between the insula and sleep. Nevertheless, these findings do not directly demonstrate a relationship between the insula and sleep. At the same time, these results invite the consideration of several key open questions. First, it is clearly recognized that lack of sleep can lead to impairment of both emotion and cognition, and the insula is known to be a key brain area for emotion and cognition. However, the subjects used in these studies were not in a state of normal sleep and wakefulness but a state of sleep loss. This raises the question of whether the observed changes in the imaging data and other aspects of the insula were caused by complications arising from sleep loss or whether the changes in the insula were caused by sleep loss itself.

Several techniques have recently been developed to enable whole-brain multimodal studies. In human studies, direct evidence can be obtained using Stereo-Electroencephalographic (SEEG) for direct intervention in the insula to understand its impact on sleep. At the same time, the circuits between the insula and key brain regions known to be involved in sleep, such as the brainstem and hypothalamus, can also be explored to study the role of the insula in sleep. These new technologies may enable a breakthrough in the question of the involvement of the insula in sleep.

5. Conclusion

Overall, the combined findings of many sleep-related studies have confirmed a close link between the insula and sleep loss, including insomnia, sleep deprivation, sleep-related disorders, and more. Although these results do not directly confirm that the insula is involved in sleep, they suggest that the insula may be a potential key brain region involved in sleep.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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