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## The effect of acute sleep deprivation on the activity of attention supporting brain areas

## ABSTRACT

More than 30% of adults suffer from sleep deprivation (SD). SD has adverse effects on cognitive functions such as attention. In psychology, attention is defined as the concentration of awareness on some events to exclude other stimuli. It has a very important role in regulating the human behavior. Although several studies have investigated the alteration in activity of different attention supporting brain regions following SD, however, these effects are not still fully addressed. Considering the significance of attention in learning and directing the human behavior and regarding the high prevalence of SD, here we review the consequences of acute SD on activity and connectivity of different regions involved in the attention processing by focusing on neuroimaging studies.

**Keywords:** Sleep deprivation, Attention, Brain networks, Functional connectivity, Neuroimaging

## Abbreviation list

SD:sleep deprivation; NREM: non-rapid eye movement; REM: rapid eye movement; fMRI: functional magnetic resonance imaging; FPN: frontoparietal attention network; DMN: default mode network; ACC: anterior cingulate cortex; EEG: electroencephalography; NBM: nucleus basalis of meynert

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## Introduction

Sleep is one of the important physiological events playing a crucial role in maintaining the physical and mental health [1]. Sleep is characterized by a remarkable decrease in consciousness and a significant reduction in responding to sensory stimuli, which can be quickly reversed [2]. Sleep associated with complex alteration in is physiology of different systems and affects almost all physical and mental functions [3, 2]. During sleep, the organism body take actions necessary to maintain brain function and body health [3]. Neurogenesis and synaptogenesis occur during different stages of sleep. Sleep also plays an important role in removing the harmful substances accumulated surrounding brain neurons during the wakefulness. In fact, the production and flow of cerebrospinal fluid increases dramatically during sleep and somehow washes and removes toxic substances such as beta amyloid from brain tissue. In addition, sleep plays a key role in regulating emotions and maintaining mental balance. Having sustained and effective cognitive functions including learning, consolidating new memories, attention, language, reasoning, creativity and decision making is dependent on sleep.

The brain neuronal activity undergoes remarkable changes during both non-rapid eye movement (NREM) and rapid eye movement (REM) stages of sleep (Box 1). Thus, sleep is expected to play an important role in brain-related functions [4]. Normally, healthy adults need 7-9 hours and elderly individuals require 8-9 hours of night sleep [1]. Missing even one hour from normal sleep duration causes sleep deprivation (SD), which is the most common type of sleep complaint [5]. SD implies a reduction in both normal duration or quality of sleep [5]. If sleep deficiency lasts for one or two days, it is considered as acute SD and if it encompasses a long period of time, it is regarded as chronic SD [5]. The severity of SD can vary across individuals [5]. The prevalence of acute SD is more than 30% and the prevalence of chronic SD is estimated to be 6-10% worldwide [5, 6].

Multiple factors can cause or contribute to SD including severe life stress, illness, psychological or physical injuries, as well as environmental parameters such as sound, light, and low or high ambient temperature [7]. People with SD undergo impairment of cognitive functions so that they exhibit reduced performance in analytical and logical reasoning. They also need more time for responding to environmental stimuli and show a weak performance in tasks engaging sustained attention [4]. SD leads to enhancement of sleep pressure and weakens the executive function of the individuals. Then, SD exposes the people at risk when they are doing their everyday activities that require high attention, such as driving [8]. The neurological alterations underlying SD consequences are of interest of many researchers. Various studies have attempted to address the changes in activity or connectivity of the relevant neuronal substrates. By focusing on the neuroimaging studies, here we review how the brain networks underlying sustained attention are affected by acute SD in human.

## Box1. Sleep stages

Nocturnal sleep consists of several cycles repeating sequentially, and each cycle consists of a maximum of four stages [65]. In a typical night, a person goes through four to six sleep cycles [65]. Duration of sleep cycles is variable, however each cycle lasts about 90 minutes on average [65].

Characteristics of sleep cycles changes over time from sleep onset [66]. The first sleep cycle is often the shortest ranging from 70 to 100 minutes, while subsequent cycles last 90 to 120 minutes [65, 67]. Additionally, sleep cycles can vary from person to person and from night to night based on a range of factors such as age, recent sleep patterns and taking a medication [65].

In general, sleep consists of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep stages [65, 66]. NREM sleep includes 3 phases comprising N1, N2 and N3, and REM sleep has only one stage [65]. These stages are determined based on the analysis of brain activity during sleep that reveals distinct EEG patterns and characterize each period [66]. During stage 1 of NREM sleep, consciousness is reduced but not completely lost [65]. This stage is actually considered as the stage of transition from waking to real sleep [65]. It is easy to awake a person in this phase [66]. In the recording of EEG signals, the power of alpha waves (8-12 Hz) decreases while the power of theta (4 to 8 Hz) enhances [65].

Second phase of NREM sleep is actually the first stage of real sleep as the consciousness is completely lost at the onset of this phase. During this stage, body temperature falls, muscles relax, breathing slows, heart rate decreases and eye movement stops [65]. Stage 2 of NREM sleep last 10 to 25 minutes in the first sleep cycle, but it become longer in later cycles. In this phase, delta (0.5 to 4 Hz) and theta (4 to 8 Hz) waves are dominant pattern of the recorded signal [65]. Furthermore, two distinct patterns of waves are manifested which referred as sleep spindles and k-complex waves [66] (Fig 1). Sleep spindles (10–15 Hz) are transient oscillatory cortical activity arises from local thalamocortical events that periodically alters neuronal activity in grey matter of neocortex. K-complex are short negative high-voltage signal with more than 100  $\mu$ V in amplitude and are followed by a slower positive deflection around 350 to 550 ms (Fig 1). They often precede a bursts of sleep spindles. sleep spindles and k-complex are considered as hallmarks of stage 2 of NREM sleep.

The third stage of sleep is known as deep sleep because it is more difficult to awake a person from this phase [65]. Muscle tone, heart and breathing rate continue to decrease further [65] and delta waves constitute the dominant pattern in EEG [65]. Even though brain activity is reduced, there is evidence that deep sleep supports thinking, creativity and memory [65]. The most time of deep sleep is spent in the first half of the night. In the first sleep cycles, stage N3 typically lasts 20 to 40 minutes [65]. As sleep continues, these stage becomes shorter, and instead, REM sleep becomes longer [65].

After the 3<sup>rd</sup> stage of NREM sleep, REM sleep appears [65]. During the REM sleep, brain activity increases and approaches to what observed during wakefu.lness [65, 68]. In this stage, muscle tone is temporarily lost in almost the entire body except for the respiratory muscles, pupil sphincter and the muscles that are responsible for eye movement [65]. The eyes show apparent quick movements so that they are easy to be recognized even with closed eyelids [65, 68]. This is the reason that this stage is referred as REM [65]. It is believed that REM sleep is essential for maintaining cognitive functions like some forms of memory such as emotional memory, learning and creativity [65]. REM sleep is characterized by vivid dreams which is explained by the significant increase in brain cortical activity [68]. As already implied, the duration of REM sleep may last only a few minutes, the later ones can last up to an hour [65]. On average, the REM stage accounts for about 25% of sleep duration in adults [65].



Fig 1. Sleep pattern in a healthy person during 8 hours of night sleep. An example of a hypnogram is shown on the left and a schematic diagram of the EEG pattern in different stages of sleep is shown on the right

### Effects of acute SD on attention

Attention is the ability to actively process specific information in the environment while excluding other details (Box 2). It is one of the basic cognitive processes which is considered as the basis of the learning processes and plays a very important role in decision-making, motor execution and behavior [9]. Being conscious and alert is the primary condition for having normal attention [9].

SD, which is associated with weak consciousness and low vigilance, impairs attention. A number of studies have indicated that attention deficits persist even when awareness is restored with stimulants such as caffeine following SD, suggesting that SD has a complex effect on attention impairment rather than simply reducing the vigilance [10–12].

Despite the inter-individual variations observed in SD-mediated attention impairment, generally, performance of sleep-deprived persons in attentional tasks decreases in a dose-dependent manner with increasing duration of wakefulness and therefore with rising the sleep pressure [13– 15]. During these tasks, the attention is completely disrupted for short periods of time known as microsleep [16, 13, 14]. In other words, attention becomes very unstable and irregular [16] and causes the performance of people to vary in attention tasks [17]. Therefore, the severity of attention impairment can be predicted with regard to the cumulative duration of wakefulness in both acute and chronic SD [14].

## **Box2. What is attention?**

Attention is one of the topics widely discussed in psychology and cognitive neuroscience, and is considered as one of the main research fields in education, psychology and neuroscience [69]. William James in the 19<sup>th</sup> century defined attention as follows: "the taking possession by the mind in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. It implies withdrawal from some things in order to deal effectively with others" [69].

According to John Ratey (2001), attention is more than only paying attention to incoming stimuli [69]. "It involves a number of processes including filtering out perceptions, balancing multiple perceptions and attaching emotional significance to these perceptions" [69]. Attention is believed to be the basis of learning, acts as the leader of our brain and determines how neural resources are engaged [69].

In general, there are two types of attention including passive or involuntary attention and active or voluntary attention [69]. In passive attention, a strong and sudden stimulus attracts the attention [69].

Voluntary attention is exactly what its name implies and is divided into 5 different types including focused, sustained, alternating, divided and selective attention [69].

- 1) Focused attention: It is a type of attention that includes a basic reaction to various environmental stimuli such as auditory, visual or tactile. For instance turning the head after hearing a sound [70].
- 2) Sustained attention: It is considered as the ability to focus on a specific stimulus or information for a continuous period of time without being distracted.

For example, playing a computer game needs sustained attention [71, 72].

- 3) Alternating attention: It is the ability of mental flexibility to shift attention from one activity to another such as cooking the food [73].
- 4) Divided attention: It is the ability of an individual to carry out more than one activity or task at the same time, like talking on the phone while surfing the web [74].
- 5) Selective attention: It implies to focusing on one activity, external stimulus or a certain information among several activities, stimuli or information [75]. for example, listening to a friend at a crowded party [75, 72, 76].

Posner and Rafal (1987) proposed a model that can be used for analyzing the circadian changes of attention [77]. This model was later elaborated further by Cohen (1993) [77]. According to this model, attention can be defined with four components including phasic alertness, tonic alertness, selective attention and vigilance [77]. Alertness is an organism capability to respond to the environmental stimuli [77]. Tonic alertness is the basic capacity of an organism for responding to stimuli during the day and phasic alertness is defined as the ability to respond to a stimulus after a warning signal [77]. Selective attention is the capacity to respond to a specific stimulus and ignore distractors [77]. Vigilance is the capacity of an organism to focus on a task and preserve this activity over time [77]

Total SD for 24 hours reduces components of attention including tonic alertness, selective attention, and sustained attention, while the effects of total SD on phasic alertness are observed only after periods of SD longer than 24 hours (periods of 48 hours or more) [78]

# Effect on lateral frontoparietal attention network

Functional magnetic resonance imaging (fMRI) studies have revealed that SD reduces the neuronal activity in lateral frontoparietal attention network (FPN) related regions including dorsolateral prefrontal cortex and intraparietal sulcus in attention tasks [18–25]. In addition, SD decreases activity in the extrastriate visual cortex and also diminishes functional connectivity of this area with both dorsolateral prefrontal cortex and intraparietal sulcus during the visual attention task [18–20]. The behavioral consequences of these alteration in attention tasks are observed as losing the attention to a particular stimulus in the visual field or as a disruption in the top-down allocation of attentional resources, such as looking at the target location where the visual

stimulus is expected to emerge [26, 18, 27]. In addition to focusing attention at a particular moment (selective attention), SD also diminishes the capacity of attention maintenance over time (sustained attention; box 2) [16].

### Effect on thalamus

The coordinate activity of cortical neurons is regulated to a large extent by thalamus. It is a diencephalon brain region that has extensive connections with the different areas of cerebral cortex and possesses both sensory and motor functions. In addition, it also plays an important role in cognitive processes including attention, consciousness and sleep-wake transitions [26, 27].

The thalamocortical functional connectivity significantly reduces following SD, which leads to a decreased vigilance level [28]. The thalamus has been suggested to be considered as an interacting hub in the SD-affected network [17]. It is noteworthy that the pattern of alteration in thalamus activity is not uniform among different individuals following SD [17]. While some studies have observed an increased activity in this area [29, 30, 25, 21], others have reported intermittent periods of decreased activity subsequent to SD [19, 21]. Considering the role of thalamus in arousal and regarding the attention instability following SD, reporting such contradictory results are not surprising [17].

### Effect on default mode network

Study on the sleep deprived human brain also indicated that the default mode network (DMN) is also sensitive to SD [31]. The DMN comprises a network of interacting brain regions that are more active during awake resting state when the mind is not focused on anything in outside. By contrary, the DMN activity consistently reduces when an individual focuses on something in external or internal worlds. This network is also called medial frontoparietal network and includes the medial prefrontal cortex, posterior cingulate cortex and angular gyrus [32]. Several studies have suggested that instability in the functional connectivity within DMN also participate in the attention impairment following SD [22, 25, 33]. In addition, it has been observed that the reduction in the activity of this network does not occur following SD when the person needs to concentrate in an attention task [17].

Normally, there is a pivotal inhibitory relationship between FPN and DMN activity [17, 34]. In the resting state, when the person does not concentrate on anything in the outside, DMN activity is high and FPN activity is low [34]. The opposite change happens during a sustained attention [34, 17]. This reciprocal inhibitory association is required for establishment of the sustained and effective attention. The thalamus, which sends projections to both networks, participates in setting up the inhibitory interplay between these two networks [35]. When a person has adequate night sleep, thalamus receives continuous inputs from the ascending arousal pathways and causes establishment of effective reciprocal inhibition of the FPN and DMN [35, 36]. Following acute SD, the activity of ascending arousal inputs to the thalamus becomes erratic and irregular, and then, inhibitory pivotal relationship between DMN and FPN activity alter into an unstable state [36, 17]. This causes the increased activity in FPN does not reach the normal level in an attention task. Moreover, the activity of this network also shows intermittent reductions due to the general increase in DMN activity following the SD. As a consequence, performance of attention and working memory weakens and becomes even unstable [17]. This disturbance is worsened with a decrease and improves with an increase in thalamic activity [17].

## Effect on salience network

The salience network, which is also regarded as one of the major brain networks, is also vulnerable to SD [37, 17]. It is more active than other networks in many complex cognitive functions such as attention, and hence, it is also called attention network [37]. This network comprise the anterior insula, dorsoanterior cingulate cortex, inferior parietal cortex, right parietal temporal junction and lateral prefrontal cortex [37].

It has been shown that the activity of frontoinsular areas of this network are impaired in attention tasks following acute SD [38-40]. In fact, the insula itself is considered as a core hub in the attention network and also plays an important role in decision making, sensory processing and salience detection [41-43, 35]. Neuroimaging studies has reported that activity, gray matter volume and blood flow in the insula increase following SD [44]. This increment may reflect upregulated bottom-up modulation of cortical attention networks that maintain attention [45]. In addition, SD results in a decreased functional connectivity between the insula and several regions of executive control network including some areas of temporal lobe (such as the inferior temporal gyrus, middle temporal gyrus and fusiform gyrus), the superior parietal

lobule, certain regions in prefrontal cortex (comprising orbital gyrus, dorsolateral superior frontal gyrus, middle frontal gyrus and medial prefrontal cortex) and anterior cingulate cortex (ACC) [45]. All of these areas are involved in attentional processes, and to some extent, the decrease in the functional connectivity of the insula with them may account for the attention impairment following SD [45].

As already pointed out, the reciprocal inhibitory connectivity between DMN and FPN becomes irregular and unstable following SD [17]. Although the cause of such disturbance is not known yet, however, considering that salience network controls the switch between DMN and FPN activity, the abnormal activity of salience network may explain this instable connectivity following SD.

ACC is the frontal part of the cingulate cortex and is involved in some higher-level functions, such as attention allocation [46]. Neuroimaging studies have reported a decrease in ACC activity during attention tasks after an acute SD [47]. An electroencephalography (EEG) study has demonstrated that SD disrupts the functional connectivity between ACC and posterior cingulate cortex [46]. However, the functional connectivity of the ACC with some cortical and subcortical areas including the frontoparietal, putamen and anterior insula has been observed to increase following one night of SD [48].

## Effect on nucleus basalis of meynert

Another brain area involved in attention is the nucleus basalis of meynert (NBM), which is located in the substantia innominate of the basal forebrain. This area contains mostly cholinergic neurons projecting to various parts of the brain [49]. The NBM is involved in multiple functions, especially supporting wakefulness and maintaining visuospatial attention [47]. Activity of cholinergic neurons in the NBM has been shown to support supramodal attention by modulating activity in the FPN [50].

High concentrations of adenosine in extracellular space, which occur during prolonged wakefulness, has been shown to suppress the activity of basal forebrain cholinergic neurons [51]. It indicates that NBM activity is sensitive to SD due to impaired sleep homeostasis [47]. In a recent study, Jing Qi et al. (2021) has shown that 36 hours of total SD reduces functional connectivity of the left NBM with superior parietal lobule while it enhances the functional connectivity of the right NBM with thalamus and also with the middle and anterior parts of the cingulate cortex [47]. Reduction of activity in cholinergic projections to superior parietal lobule is associated with impaired performance of verbal episodic memory and visuospatial attention in Parkinson's disease [52]. Therefore, the disruption of the connectivity between NBM and superior parietal lobule may also participate in memory and attention disturbances after total SD [47]. Enhanced functional connectivity of the NBM with thalamus confirms the recruitment of arousal networks by brain to maintain vigilance and cognitive abilities following SD [47]. Furthermore, increased functional connectivity between NBM and ACC reflects a synergistic effect in regulating the attention in sleep-deprived states [47].

## Effect on hypothalamus

Another brain area that has been shown to be sensitive to SD is hypothalamus [35]. It is a heterogeneous subcortical region located below the thalamus and has numerous nuclei. It has extensive connections with the brainstem, thalamus, limbic areas, basal ganglia and cerebral cortex, and plays a crucial role in regulating sleep wakefulness, temperature, glucose and metabolism, body fluid balance and ingestion [53]. In addition, it also participates in regulating attention because some important nuclei of the arousal system are located within the hypothalamus [54].

SD is also associated with alterations in hypothalamus activity that can be followed as an impairment in the function of hypothalamuspituitary-adrenal axis [55]. It has been observed that cortisol release from adrenal gland in response to stressful factors decreases flowing SD [55]. Fifel et al. (2018) have reported alteration in neural activity of different rat hypothalamus subregions including paraventricular nucleus, lateral hypothalamus, mammillary bodies and arcuate nucleus after a SD [56]. Schmidt et al. (2009) found that with increased homeostatic sleep pressure, the hypothalamic suprachiasmatic area activity during a sustained attention task decreases [57]. This nucleus plays a central role in controlling the body's circadian rhythms and regulating sleep and wakefulness [58]. A functional connectivity decreased between hypothalamus and middle frontal gyrus following acute SD has also been reported [35]. As discussed before, the prefrontal cortex is involved in a wide range of cognitive processes including top-down attention control [59]. The middle frontal gyrus is a key hub that mediates the interaction between dorsal and ventral attention networks and contributes to the integration of neural circuits associated with attention [60]. Therefore, it has been suggested that the hypothalamus acts as a key controller in the regulation of attention networks, such that the disturbance of hypothalamic circuits activity can lead to attention deficit [35].

In the recent study conducted by Jing Qi et al. (2021), 36 hours of total SD caused a change in the functional connectivity of the hypothalamus with the brain regions involved in attention control as enhancement of the connectivity with thalamus, ACC, insula and right amygdala and a decreased connectivity with middle frontal gyrus [35]. The role of the thalamus, insula and ACC in controlling the attention has already implied. Amygdala participate also in attention modulation, as it has a strong connection with the sensory networks and indirect connections with the attention and arousal network [61-64].

The increase in the functional connectivity of the hypothalamus with the mentioned areas again demonstrate that the brain organizes more attentional resources to meet the requirements of cognitive performance under increased sleep pressure [35]. However, redistribution of attentional resources is not sufficient to counteract the negative effects of SD [35].

### Conclusion

According to what reviewed above, acute SD causes a complex set of changes in the activity and connectivity of different brain areas which participate in processing or modulating the attention. While the functional connectivity between some of these areas reduces, the activity and functional connectivity between others enhances. The brain seems to recruit various

resources to maintain vigilance and attention following an SD. However, these compensatory solutions are not sufficient and then, the sustained attention impairs and becomes even unstable. Of course, it should be noted that attention does not decrease to the same extent in all people following SD, and inter-individual differences are usually observed. It demonstrates that the activity of brain attention networks may be affected differently in each individual following SD. Another noteworthy point is that most of SD consequences on SD reviewed above are related to fMRI studies. Despite the high spatial resolution, this method has a low time resolution for examining the alteration in activity or connectivity of different brain areas, while momentary fluctuations in the activity or connectivity of these regions in a small timescale significant. Therefore, repeating the are experiments using high temporal resolution supplementary methods, such as EEG, are required.

The last point is that our current knowledge about the effect of chronic SD on human brain is still largely unknown, because most studies have focused on effects of acute SD. Also, there is no comprehensive understanding of how human brain networks may recover from acute and chronic SD and more studies should be carried out to address this issue.

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### **Conflict of interest**

The authors declare that they have no conflicts of interest.

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