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MINI REVIEW

Relationship between circadian rhythm and brain cognitive functions

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Abstract Circadian rhythms are considered a masterstroke of natural selection, which gradually increase the adaptability of species to the Earth's rotation. Importantly, the nervous system plays a key role in allowing organisms to maintain circadian rhythmicity. Circadian rhythms affect multiple aspects of cognitive functions (mainly via arousal), particularly those needed for effort-intensive cognitive tasks, which require considerable top-down executive control. These include inhibitory control, working memory, task switching, and psychomotor vigilance. This mini review highlights the recent advances in cognitive functioning in the optical and multimodal neuroimaging fields; it discusses the processing of brain cognitive functions during the circadian rhythm phase and the effects of the circadian rhythm on the cognitive component of the brain and the brain circuit supporting cognition.

Keywords circadian rhythm, cognition, optical neuroimaging, multimodal neuroimaging

1 Introduction

For thousands of years, living organisms have evolved in synchrony with the day–night cycle [1]. Most species, from single-celled organisms to humans, individually have an internal circadian clock that modulates critical function phases, such as sleep, metabolism, hormone levels, core body temperature, behavior, and cognitive function. The eminent chronobiology scholar, Jeffrey Hall, and his colleagues won the Nobel Prize in Physiology or Medicine in 2017 in recognition of their meaningful discoveries concerning the mechanisms that control diurnal rhythms at the molecular level [2]. This phenomenon had been documented several hundred years before. However, circadian rhythms have been described for hundreds of years. For example, in the 18th century, Jean Jacques, an astronomer, recorded that the leaves of mimosa plants opened during the day and closed at night [3]. Moreover, numerous studies have inspected, classified, and recognized the essence of the biological clock, elucidating that not only physiologic functions but also the brain cognitive functions are regulated by the inner circadian rhythm [4,5]. In particular, these studies also demonstrated that the circadian rhythm has a significant influence on cognitive performance, which peaks during the day and drops at night [6]. Recently, Walker et al. [7] reported that circadian disruption may not be the sole cause of mood disorders; however, it may elicit or exacerbate symptoms in individuals with a predisposition to mental disorders. However, individual differences, such as gender, age, IQ, and educational, and cultural background, might affect the relationship between the circadian rhythm and cognitive functions [8–11]. More importantly, the relationship in the metabolic fluctuation phase between the brain and circadian rhythms in our body systems is still unclear. Most of the cells in the body have circadian molecular clocks, e.g., the gut. Eating late and operating cellphones at night, for example, are known to disrupt the circadian rhythm [12,13]. Moreover, recent studies have shown that the sleep quality in specific populations (e.g., surgical nurses) is related to the CLOCK genes [14].

Recently, neuroimaging technologies, such as functional near-infrared spectroscopy (fNIRS), and other multimodal techniques, such as functional magnetic resonance imaging (fMRI), diffuse optical tomography (DOT), and an electroencephalogram (EEG), have been employed to determine the effect of circadian rhythms on brain cognitive functions [1,2].

fNIRS is an optical, non-invasive neuroimaging technology that can measure the changes in the concentration

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of oxyhemoglobin and deoxyhemoglobin in the brain tissue after neuron activation [15]. This is accomplished by irradiating the head with near-IR light (650–950 nm) and accessing the brain tissue via the relative biological tissue transparency. With the development and use of multi-channel and wearable devices for cognitive experiments, fNIRS has enabled important progress in the understanding of the functional brain activities and higher cognitive functions in adults and infants. The fMRI technique is a category of imaging methods that use strong magnetic fields developed for displaying time-varying alterations and metabolism changes, common in the increase or decrease in blood oxygenation during the performance of an experimental task [16]. DOT is an imaging approach that uses near-IR light to illuminate the structure of the soft tissue. The most valuable and common application of this technique is for the detection of tumors in the breast and brain [17]. As an electrophysiological monitoring method, the EEG is widely used to record the electrical activity of the brain, which results from ionic currents within the neurons of the brain. EEG is a non-invasive monitoring method for recording the electrical activity of the brain; the process mostly involves attaching electrodes to the scalp. The EEG records evoked potentials (EP), which includes the averaged EEG activity time-locked to presenting auditory, somatosensory, or visual stimuli. Moreover, the event-related potentials (ERPs) refer to the averaged EEG responses that are time-locked to more complex processing of stimuli [18].

The focus of this mini review is to summarize the recent advances in the investigation of the relationship between brain cognitive functions and the circadian rhythm using neuroimaging techniques. First, the cognitive process of attention during the circadian rhythm phase will be introduced and highlighted. Following this, the influence of the diurnal rhythm on cognitive functions, including working memory, cognitive flexibility, and switching, will be demonstrated. Most importantly, the future of research perspectives and the neural implications of the circadian rhythm will be stated clearly in the final section.

Two main electronic databases: PubMed and Web of Science, were inspected to extract studies published in the English language; the studies were in areas related to the relationship between the circadian rhythm and brain cognitive functions. Notably, there were no time limitations on the publication since no meta-analysis of the studies on the circadian rhythm and the brain cognitive functions had been conducted. A search strategy was established for each database with a combination of free text and controlled MeSH keywords. Moreover, additional psychological web-based databases and specialized journals, such as PsycINFO and Google search for gray literature, were exploited. Furthermore, the reference lists of the studies retrieved from the database were screened for relevant studies. The three research steps were conducted without time limitations. The search keywords included "circadian rhythm", "neuroimaging", "brain", "cognitive functions", and "cognitive task". The selected articles are listed in Table S1, see Electronic Supplementary Material.

2 Relationship between circadian rhythm and brain cognitive functions

2.1 Attention

Attention refers to the function that allocates limited cognitive processing resources to the environment [19]. Attention can also be categorized into selective alertness, phasic alertness, tonic attention, and vigilance in accordance with each function [20]. Selective attention is a function that filters the stimulus of perceptions from the environment, which keeps us focusing on the pertinent information. Phasic alertness refers to the function that prepares for a specific incoming event under the exception. Tonic alertness reflects the general level of alertness and the basic activation of the cognitive system of an individual. Finally, vigilance is the ability to continue focusing on one object for a relatively long period. Studies in forced desynchronization and sleep deprivation have suggested that circadian effects and time awake alterations may impact tonic alertness [21], phasic alertness, and selective attention [12]. Nevertheless, studies related to sustained attention are controversial, since the circadian rhythmicity and awake time changes can be observed in some studies [22], but not in others [23].

The activation state of attention depends on the activity of the cerebral cortices. Notably, tonic alertness is influenced by the reticular activating system, which regulates the general activation level of the entire forebrain [24], while the frontal and the parietal cortex are interpreted as the core components of the system supporting phasic alertness [25]. Unlike tonic alertness and phasic alertness, selective attention is recognized as following a top-down pathway in the cortex, and it correlates with the prefrontal and parietal control regions [26–28].

Valdez et al. [29] investigated the circadian variations of selective alertness, phasic attention, and tonic alertness, concluding that these processes suffer a performance hit from 4:00 AM to 7:00 AM. Another research proposed by Pablo concluded that tonic alertness might peak in the morning (around 10:00 AM–12:00 AM) and decrease immediately after that [6]. Riley [30] found that the attention span of an individual may increase to a peak between 9:00 AM and 11:00 AM and subsequently decrease progressively. Moreover, the peak time of selective attention is recognized to be around midday [6,31]. Nicholls et al. [32] explored the diurnal variations in the visuospatial attention and the limited effect of circadian variation. However, not all researchers support the idea that circadian variation can be modulated by attention [33].

There is empirical evidence suggesting that cognitive functions are closely related to the body temperature, which is recognized as an important indicator of the metabolic rhythm. Primarily, the body temperature may increase during the day and decrease in the evening [1]. The close relationship between the body core temperature and cognitive performance has also been confirmed by other researchers [34–36]. Additionally, researchers discovered more factors that may impact the changes in the attention function caused by the circadian rhythm, such as chronotype (the behavioral manifestation of the underlying circadian rhythms of myriad physical processes) [31] and task difficulty [37].

Studies based on the manipulation of the desynchronization of the circadian rhythm of participants while researchers separate the subject's inherent circadian rhythm demonstrated that the ability to sustain attention might weaken, followed by lowered activation of the corresponding cortex, as well as the neural networks that are affected by sleep deprivation. For example, the Stroop tasks related to prefrontal cortex functions have been found to be affected by one night of sleep deprivation [38–40]. Therefore, it was observed that tonic alertness, selective attention, sustained attention, and vigilance are sensitive to sleep deprivation, which might result in the impairment of the attention function [41–43]. Moreover, sleep deprivation affected the visual search task, which required the attention function [44]. Recent neuroimaging studies using fMRI techniques have found that the activation of the prefrontal cortex and the parietal cortex is highly hindered by sleep deprivation, and this has implications for cognitive processes driven by these regions [45,46]. Furthermore, the neural network of attention is affected by sleep deprivation. Tomasi et al. [47] observed that the thalamic hyperactivation was inversely correlated with the activation of the parietal cortex after sleep deprivation during a visuospatial attention task, highlighting that the attentional networks were potentially impaired. Moreover, the sleep-deprived participant had lower accuracy in the task. Chee et al. [48] explored the endogenous attention function under sleep deprivation and suggested the decrease in the frontal-parietal top-down control concerning attention and the extrastriate visual cortex process. De Havas et al. [49] proposed that significant selection may decrease in the default mode network for functional connectivity after sleep deprivation (see Fig. 1). Muto et al. [50] examined the sustained attention task related to 42 h of sleep deprivation and found that the subcortical areas regulated by the circadian rhythms, which are followed by the melatonin profile and the cortical responses, were influenced by the circadian rhythms in a different phase.

2.2 Working memory

Working memory is an essential component of the cognitive system that holds and stores extracted information. It can be divided into long-term memory and short-term memory, depending on the length of the memory to be stored [51]. A long-term memory may be longer than one day, while a short-term memory can vary from a few seconds to a few hours. There is also strong evidence of the important role of short-term memory in advanced cognitive processes, such as reasoning, language comprehension, learning, and problem solving. Studies in the cognition field affirm that the working memory is the most appropriate name considering function because short-term and long-term memories are distinguished by time length

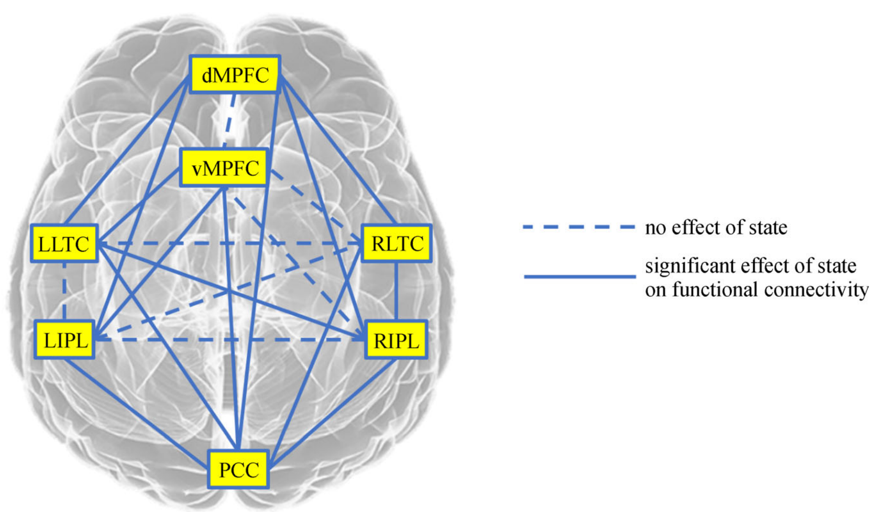

Fig. 1 Effect of state on Default Mode Network functional connectivity. The extensive functional connectivity decreased after sleep deprivation (adapted from Ref. [49]). dMPFC: dorsomedial prefrontal cortex, vMPFC: ventromedial frontal cortex, RLTC: right lateral temporal cortex, RIPL: right inferior parietal lobe, PCC: posterior cingulate cortex, LIPL: left inferior parietal lobe, and LLTC: left lateral temporal cortex

[52]. From a cognitive perspective, the role of the working memory is to hold and manipulate the information in the mind for further processing. Regarding neural mechanisms, neuroimaging studies have demonstrated that tasks involving the working memory are highly connected to the prefrontal cortex activation [53,54]. Furthermore, studies have shown that damage or lesion in the prefrontal cortex may cause a decrease in the working memory performance [55].

According to Gerstner and Yin [56], the regulation of memory formation by the circadian rhythms and effects of the day–time cycle is phylogenetically preserved in many species and is also associated with the cycling levels of melatonin, independent of the changes in the behavioral conditions, such as wakefulness and sleepiness. A recent study by Domagalik et al. on sustained attention and the visuospatial working memory in circadian rhythmicity revealed that the reduction of blue light exposure led to a significant decrease in performance. In other words, the reaction time was slow when the exposure to blue light was reduced [57].

Previous studies based on the working memory declared that the capacity of working memory tasks usually reaches the peak at noon [23,58], which correlates with the metabolic activity in the brain, thus promoting the changes in the capacity of the working memory. These relevant findings confirm the close relationship between the working memory and temperature, which is considered as an indicator of the metabolic activity [36]. The working memory ability appears to improve when the temperature reaches the peak and weaken when the temperature decreases in the circadian rhythm fluctuation according to the desynchrony protocol. Vedhara et al. [59] reported the level of salivary cortisol as another important indicator of the circadian rhythmicity and its association with the working memory. Therefore, it is important to emphasize that the circadian rhythm also affects the results of the working memory measurement since it requires a relatively long testing period [60].

Although the fluctuation of the working memory capacity during the day and at night is not always the same under different situations, the individual differences between the participant groups and the difference in the tasks applied have a significant influence on the changes in the working memory capacity. First, we must identify two different groups related to the circadian rhythm: "morningness" and "eveningness," according to the different activity peaks during the day. Second, the different ages of the group possibly contributed to the impact of the circadian rhythm on the working memory.

Studies have shown that children reach their peak of cognitive functions in the morning, while adults achieve their best performance in a similar task at night [61]. Rowe et al. [62] suggested that the age differences in the visual working memory span are determined by the time of the test and the interference of other factors. Furthermore, studies have shown that the working memory load is related to the fluctuation of the working memory capacity during the day. Folkard [63] found that the performance of an easy working memory load task is correlated with the temperature change; however, this phenomenon disappears if the working memory load increases considerably. Many factors can exert influence, including the decision process [64], which may determine the change in the curve of circadian rhythmicity. Nevertheless, we certainly must consider the metabolic activity as the fundamental base of the circadian rhythm. Interestingly, a variable number of studies have found ambiguous results for the changes in cognitive functions during the day and at night. Further, these results did not lead to an accurate conclusion under a different group of participants or with different tasks. The application of precise technologies that can reflect the cortex activity and the collaborative cortex may be an advantageous approach for inspecting those previous cases. The activity of the prefrontal cortex is considered a reflection of the working memory process, and it could be combined with traditional protocol in future studies.

Neuroimaging studies related to the circadian rhythm and the working memory are considered as the relatively common studies associated with sleep deprivation and circadian rhythm desynchronization. For instance, the healthy participants were asked to follow a sleep-deprivation protocol, which was manipulated by the researcher. Chee and Choo [65] found that the anterior medial frontal and posterior cingulate regions in young healthy subjects are deactivated after sleep deprivation (see Fig. 2). Moreover, the left frontal lobe is activated when the working memory is exhausted after sleep deprivation. The results of the sleep deprivation study involving young healthy subjects were similar to those of previous studies, displaying that the activation of the left anterior cingulate cortex was suppressed. Concurrently, the activation of the left and right middle occipital gyrus is strengthened during a working memory task after sleep deprivation. The interaction effect between the working memory load and sleep deprivation has been also observed in the left inferior frontal and right middle frontal gyrus, as well as the right insula [66]. Mu et al. [67] found that both groups, i.e., the sleep-deprivation group and the resting group, exhibited significantly reduced whole brain activation, compared with the baseline. Chee et al. [68] affirmed that not only the superior parietal regions but also the left thalamus experience a reduction in task-related activation after sleep deprivation during a working memory task. Lim's findings [69] also indicated that the bilateral parietal regions experience deactivation after sleep deprivation. Despite the fMRI studies, Honma et al. [70] conducted an experiment using fNIRS and concluded that the activity of the right prefrontal cortex indicates an attempt to resist sleepiness during a working memory task in a sleep-deprivation situation.

In recent studies related to circadian rhythm disorders,

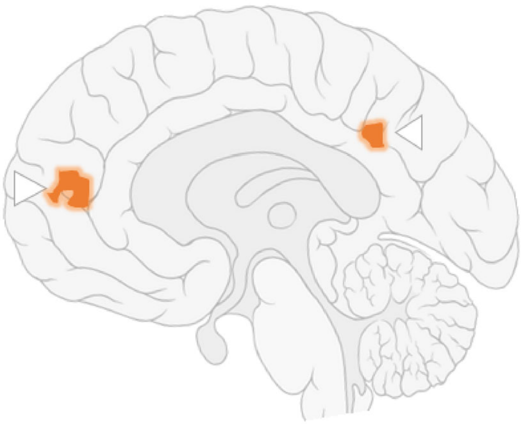

Fig. 2 Reduced task-related deactivation in the anterior medial frontal and posterior cingulate regions after sleep deprivation. Region of interest from which the extent of deactivation was determined. Reproduced from Ref. [65]

patients diagnosed with mental impairments were recruited to have their cortical activation analyzed by neuroimaging methods. McKenna and Eyler, after reviewing the literature on bipolar disorder and its deficits in the prefrontal cortex, found that sleep and circadian rhythms may be involved in this system, potentially suggesting that the ability of the working memory was impaired [71]. The findings of Thomas et al. [72] suggest that the working memory might be affected by obstructive sleep-disordered breathing, and the reason for the weakening of the working memory competency is related to the loss of function in the dorsolateral prefrontal cortex. McKenna et al. [73] examined the association between the circadian rhythm and euthymic bipolar disorder desynchrony using fMRI approaches. The results indicated that the circadian rhythm variable was significantly associated with the degree of deficit in the dorsolateral prefrontal cortex and supramarginal gyri. Drummond et al. [74] explored the working memory ability in patients with primary insomnia and compared them with those of a healthy control group. Subsequently, it was confirmed that the task-related working memory regions were deactivated in the primary insomnia patients, and the effect of the modulation of the right dorsolateral prefrontal cortex activation was reduced as the task difficulty increased.

2.3 Cognitive conflicts and inhibition

Cognitive conflict refers to the function that manages contradiction and restrains irrelevant information from the working memory, and it is indispensable for the cognitive system of humans. A pragmatic example is the Stroop task, where the name of a random color (e.g., purple) is printed against an inconsistent different color (e.g., the word "PURPLE" colored in red). It would be undoubtedly more difficult to distinguish, rather than if it were written in the same color (e.g., the word "PURPLE" colored in purple) [75].

The equivalent brain regions of these cognitive functions have been shown to have a deep relationship with the fluctuation of the circadian rhythm. A current study on high-order cognitive functions demonstrated that the inhibition ability decreases in the early evening, compared to the constant routine protocol [76]. The inhibition ability may reach the peak in the afternoon, while the lowest point is observed in the early morning, according to the *Sustained Attention to Response Test* [77]. Furthermore, the study concludes that the aspect related to the active control appears to be more sensitive to the circadian rhythm than the automatic aspects of cognitive functions. Nevertheless, this study could not separate the effect of the homeostatic pressure from the increase in the waking time. Harrison et al. [78] applied a forced desynchronization protocol to divide the circadian rhythm and the homeostatic pressure. All the subjects were instructed to have 28 h per "day" in this experiment. Consequently, the results showed the significant effect of the waking period without the circadian effect on the performance of the inhibition task. Bratzke et al. [79] evaluated the impact of sleep deprivation and the circadian effect on the inhibition ability using the Stroop and Simon task. Although the interference effect remained unaffected across 40 h under the wakefulness status, the study proposed that the circadian rhythm might not be affected by the inhibition ability. Finally, Sagaspe et al. [39] did not find meaningful discrepancies in the effect of day and night changes on the inhibition ability utilizing a Stroop task.

The frontal cortex is considered as the corresponding brain region for cognitive conflicts and inhibition [78]. Lately, Schmidt et al. [80] assessed the influence of the circadian rhythm and the chronotype on the conflict processing ability, including the corresponding cerebral activity in a constant routine protocol. The hemodynamic responses of the evening chronotype precipitates remain constant or increase in the subjective morning. In contrast, the morning chorotype reduces in the morning categories under the same situation. The relationship between sleep pressure and the circadian process is confounded, and their impact on the cognitive process is not easily distinguished. This is because the relationship between them is complex, and they may affect each other. Consequently, new protocols, tools, and techniques to study the current topics are undeniably required to achieve accurate results.

2.4 Cognitive flexibility and switching

Cognitive flexibility is the mental ability to adjust or adapt to the changes in environmental requirements [81]. In neuroimaging studies, the ability of cognitive flexibility and switching is commonly associated with the prefrontal cortex [82].

There are only a few studies related to the influence of the circadian rhythms on cognitive flexibility. In one of these studies [83], the time-of-day protocol and the constant routine protocol were used to measure the ability of task switching [83–85]. As a result, it was verified that the participants performed poorly in the cognitive flexibility task in the morning. Bratzke et al. [79] led an investigation into the effects of circadian rhythm and sleep loss on the switching task efficiency. This study revealed that the switching task competence is influenced by sleep stress and circadian rhythms. Ramírez et al. [86] suggested that flexibility is modulated by sustained attention, which may be affected by the circadian rhythms. Recently, the cognitive flexibility of shift workers who had to work at night showed a reduction in the earlier circadian phase. It is important to accentuate that cognitive inhibition and flexibility are essential for problem solving and creativity.

2.5 Cognitive association and creativity

For Mednick [87], creative thinking is "a form of associating elements into new combinations that either meet specific requirements or are, in some way, useful. The more mutually remote the elements of the new combination, the more creative the process or solution." Thus, the association ability is the fundamental base of creativity. A neuroimaging research using a word-pair associate task demonstrated that the hippocampal activity (see Fig. 3) mediates the circadian rhythms and associative memory process [88]. However, the studies on creativity indicated that creativity itself does not relate to the circadian tendency of the association ability. May [89] examined the association processes, where each participant was instructed to find an answer word (SPACE) linked to given three associated cue words (e.g., SHIP OUTER CRAWL), and the results showed that the patterns of impaired versus preserved performance over the day are consistent with an inhibitory-deficit account of synchrony effects, which would be disrupted at the best time for the essential cognitive functions. This previous study, as well as other investigations, such as the one conducted by Wieth and Zacks [90], confirmed that the participants would solve the problem of insight efficiently when testing at a non-optimal time.

Overall, following the studies listed above, it is possible to establish that even advanced cognitive functions combine effects and their differential roles in cognitive processes, including fundamental cognitive components, such as attention and working memory, and this could have different effects on the circadian rhythm of advanced cognitive functions.

3 General discussion

In this review, we summarized many studies concerning the relationship between the circadian rhythm and cognitive functions. These studies were divided into subcategories, such as attention, working memory, and higher-order functions, according to the order of cognitive processing. Generally, the circadian rhythm influences the cognitive functions; however, the results of previous studies are still inconsistent. From a neuroimaging perspective, the corresponding regions are related to the diurnal activity of cognitive performance. Additionally, the brain network connection is modulated by the circadian rhythm.

There are different activity curves on the cognitive functions including attention, working memory, and the higher-order cognitive functions, since the peaks related to the performance of different cognitive functions are distributed differently throughout the day. This suggests that attention and working memory have slightly similar regulations. According to the previous studies listed above, the participants had their best performance in attention and working memory in the afternoon, while the worst performance was observed in the early morning. Further,

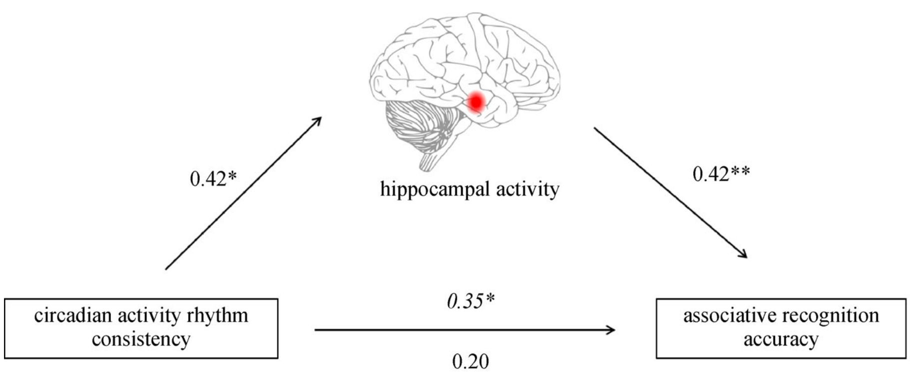

Fig. 3 Mediation model demonstrates that the relationship between circadian activity rhythm consistency and associative recognition accuracy was mediated by hippocampal activity. Standardized beta values are included on the model paths in black. The gray value on the path represents the standardized beta value before the hippocampal activity was included in the model. The scatterplots show paths A and B, which illustrate the relationships between hippocampal activity, circadian activity rhythm consistency, and associative recognition accuracy. *$p < 0.05$, **$p < 0.01$. Adapted from Ref. [88]

the higher-order cognitive functions are not consistent with regulation, such as inhibition and creativity. On the contrary, with the attention and the working memory, the ability of inhibition and creativity might be stronger in the subjective morning rather than in the subjective afternoon. Therefore, this phenomenon might be explained by the inhibition-based model [91]. Inhibitory processes, in the case of the filter of the working memory, act by restraining the input of the irrelevant information and inhibiting excessive responses that might waste the cognitive resources according to this model. Therefore, the critical clues for the higher-order functions equivalent to inhibition, creativity, or problem solving need more integration since it appears to be unrelated to current tasks. It is also because the basic and advanced cognitive tasks may be affected by the circadian rhythm. This hypothesis may explain why there are no effects or weak effects in some studies concerned with the effects of circadian rhythms on the higher-order functions. Thus, some clues for solving advanced cognitive function tasks will be suppressed by the currently active working memory. Just as Aristotle discovered the method of weighing the crown when taking a bath or discovered the benzene ring while Kekune was taking a nap, the circadian rhythm performance of advanced cognitive tasks and basic cognitive tasks do not always maintain the same trend.

Another possible hypothesis suggests that higher-order cognitive functions are more sensitive to individual differences, such as chorotype and aging, due to the involvement of more neural networks. In recent years, more studies on higher-order cognitive functions have reflected the collaborative working system among the brain regions [88]. Consequently, the higher-order cognitive functions may be sensitive to individual differences due to the interaction effect and accumulative effect among the basic functions. To verify this hypothesis, more neuroimaging studies need to be conducted in the future.

In summary, the previous studies based on the relationship between the circadian rhythm and cognitive functions have proven that the circadian rhythm affects the cognitive functions. However, substantial bases are lacking, implying that more studies are required to evaluate the neural network connection using neuroimaging technologies (e.g., fMRI, EEG, PET, and fNIRS), which will revitalize the field [92,93]. Many neuroimaging researches are focused on sleep deprivation or the comparison between healthy populations and patients; this suggests that the sleep-deprivation protocol plays an essential role in the process of discovering the effect of the circadian rhythm on cognitive functions. However, a few researches have focused on the constant routine protocol in a healthy control population. For that reason, studies in this area should receive more attention in the future.

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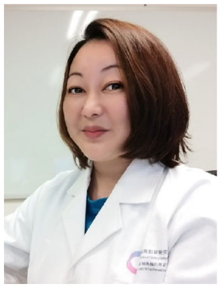

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