Review Article

Sleep and Cognition in Schizophrenia

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Abstract

Background and Objective: Schizophrenia (SCZ) affects both genders with similar rates. It usually appears in the second to the third decades of one's life. Schizophrenia is marked by a wide spectrum of symptoms, which functionally impair patients. The symptoms are categorized as positive, negative, or cognitive deficits. Among them, cognitive disturbance is highly valued. However, the relationship between sleep and cognition in patients with schizophrenia has been less widely considered. In this study, we aimed to review the relationship between sleep and cognition in patients with schizophrenia.

Materials and Methods: We considered selected key words (e.g. Cognition, Schizophrenia, and Sleep), and searched the online databases at the first step with defined time window of 2010 to the present; while at the second step, the incomplete knowledge was completed from 1990 to 2010. Among them, articles related to our research objectives were selected for further review.

Results: Cognitive functions including memory, attention, reasoning, decision-making, and many other elements are tightly related to quality of sleep. Moreover, sleep deficit exacerbate the symptoms of schizophrenia. It is known that cognitive function is dependent on certain activities in brain that occur during sleep. A body of research has indicated that the slow wave sleep, rapid eye movement (REM) sleep, K-complex, and also sleep spindle are at least partly explained by these functions.

Conclusion: In the light of these findings, study of brain activity via electroencephalogram (EEG) during sleep is a reasonable objective method for assessment of sleep-related cognitive markers in patients with schizophrenia.

Keywords: Cognition; Schizophrenia; Sleep

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Introduction

As a syndrome with broad symptoms, schizophrenia (SCZ) is mainly diagnosed by delusion, hallucination, disorganized speech and behavior, and behavioral disturbances (1), most of which are related to cognitive dysfunctions.

Cognition is simply defined as an intellectual or mental process whereby an organism obtains knowledge (2). Attention, concentration, memory, intelligence, judgment, executive functions, and social cognition are among the major cognitive functions (3). Those afflicted with SCZ appear to have problems in variety of domains, such as working memory, language function, and executive function, episodic memory, processing speed, attention, inhibition, and sensory processing (4-6). Dorsolateral prefrontal cortex (Dl-PFC), the major region for cognitive function, interacts with other areas specially thalamus, basal ganglia (striatum and other nucleuses), and temporal and parietal cortex (7-9). DL-PFC in combination with the dysfunctions of excitatory or inhibitory neurotransmitters plays a key role in developing SCZ (10). Major research findings on cognitive dysfunction in SCZ are based on the evaluation of wakefulness (3, 5, 6, 9-15). These cognitive symptoms will persist even in the remission peri-

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od (14). They have been also seen in relatives of patients with SCZ. In the case of cognitive disturbance, one is seriously faced with a high risk of developing SCZ (13, 16).

Regarding the important role of sleep in cognition and importance of cognitive disturbances in patients with SCZ, in present study, we reviewed the related studies.

Materials and Methods

We considered the key words including Cognition, Schizophrenia, Sleep, K-complex, Sleep Spindle, and Ripple wave; and searched the online databases at the first step with defined time window of 2010 to the present; while at the second step, the incomplete knowledge was completed from 1990 to 2010. Articles related to our study objective goal were selected consequently.

Results

We put extracted findings in the best matched clusters including cognitive assessment instruments during wakefulness, memory and sleep, cognitive cues during sleep, structures of sleep in SCZ, cognition in SCZ, sleep spindle and cognition, and sleep spindle -thalamocortical pathway-cognition and SCZ.

Discussion

Cognitive assessment instruments: There is a myriad of measures of cognition in patients with SCZ such as Weksler Memory Scale III (WMS-III), Spatial Span Working Memory Test, the Brief Assessment of Cognition in SCZ (BACS) Battery, MATRICS Consensus Cognitive Battery (MCCB), index scores of category fluency, trail making A, digital sequence, Hopkins Verbal Learning Test (HVLT), mazes, Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) motor skills, Tower of London (ToL), and mirror tracing (3, 13, 15, 17). A number of the above tests are also used to assess intelligence. However, cognitive assessment tools simply evaluate the reaction time or more complex problem-solving tasks (18). Similar to the mirror tracing, which is a visual motor task to measure visual integration, hand-eye coordination and learning of a new early cognitive intervention could be used to prevent disabling symptoms of SCZ (19).

Cognition and sleep: Cognitive functioning during wakefulness is mainly related to brain activity during sleep, while it seems that there is a bidirectional association between sleep and cognition (20-23). The electroencephalogram (EEG) during sleep has variable indices with aging. It also varies between individuals, and is largely consistent within them. EEG not only depends largely on genetic basis, but it also depends on cognitive tasks (18). Data, flow from neocortex to hipocampal-enthorineal loop during wakefulness, are riding on theta and again to cortex throw non-rapid eye movement (NREM) via sharp ripples and spindle. They prefer to be more processed in REM and consolidated (24).

Memory and sleep: Beside the memory consolidation role, sleep plays an erasing role for some information stored in brain (25). The relationship between memory and sleep in at least slow wave sleep (SWS) in episodic memory is age-related; a stronger correlation is observed among younger adults compared to elderly (26). It seems that the age-related decrease in prefrontal atrophy and activity leads to less SWS, and is accompanied by an impaired long-term memory and cognitive function among elderly (26, 27). Due to the effect of SWS on extracting rules from many experiences, it proves more effectiveness during the early years of life in the memory (28).

In spite of the relationship between explicit visuospatial information, memory consolidation, and SWS, the explicit verbal recall is related to both SWS and REM sleep (29).

Memories that are linked to tasks that involve hypocampus are mainly the declarative type of memory. Recalling such memories is closely related to first half night NREM and SWS (30). Non-declarative types of memory are highly related to the second half of sleep in which REM sleep is prominent to a lesser degree than NREM (31). Entorhinal cortex has a key effect on passing new information to the CA3 region of hypocampus during wakefulness. This flow of information will occur in a reversed direction from the hippocampus to neocortex to shape the long-term memory. In particular, the sharp wave-ripples (SWRs) pattern activity, characterized as a sharp wave, especially in CA3 followed by 140-200 Hz in CA1 hippocampal regions, is transferred via the entorhinal cortex to the neocortex (32-34).

Furthermore, SWR complexes seem to be temporally coupled with sleep spindles. This coupling has been suggested to provide information transfer mechanism from the hippocampus to cortex, and make the long-term memory (35). Due to the effect of SWRs on episodic memory and its procedure, it has been considered as a cognitive biomarker (34). As described above, sleep spindle indirectly reflects SWRs activities. Sleep spindle is highly correlated with intelligence. It also induces synaptic changes in the long-term memory in neocortex (34).

The overnight verbal memory retention excluding the newly-learned faces is highly associated with the number of sleep spindles (36). Furthermore, the fast sleep spindle is correlated with the sleep-dependent visuomotor performance. “The thalamocortical network underlying fast-spindle generation may contribute to or reflect plasticity during sleep” (37). Broadly speaking, thalamocortical neuronal circuits generate slow oscillations. However, waxing and waning spindles facilitate cortical plasticity. Fast and brief hippocampal ripple oscillations correlate with reactivation of neurons that are recruited in prior wakefulness (38).

Cognition in SCZ: Patients with SCZ typically have learning, recalling, and recognizing problems in their memory. The key clinical co-factors of these impairments are earlier age of onset, more negative symptoms, and greater anticholinergic medication dosage (39). Patients with SCZ suffer from impairment in all cognitive domains including memory (40). These cognitive impairments add to the symptoms and function of the patient. Verbal memory predicts all measures of community outcomes; vigilance predicts social outcomes; executive function predicts work and daily activities (41). Furthermore, as the most consistent cognitive finding in SCZ, verbal memory showed to be associated with all types of functional outcomes (42). Therefore, some researches have explored the cognitive rehabilitation therapy in patients with SCZ (43, 44).

The cognitive rehabilitation training significantly reduces SCZ relapse rate. It prolongs the patients’ time without relapse, and improves the time stored for employment (45). Positive symptoms and memory deficits in SCZ are linked to dysfunctional hippocampal hyperactivity (46). Furthermore, it seems that thalamus and cortex communicate to generate sleep spindle and memory consolidation (47, 48). Dysfunction of thalamocortical connection (especially prefrontal cortex) in patients with SCZ is previously confirmed (49, 50). At the neuronal and receptor levels, an investigation of mice showed that Ca(V) 3.3 calcium channel is the major sleep spindle pacemaker in thalamus (51). Calcium channel is encoded by the SCZ risk gene CACNA1I that is abundantly expressed in the thalamic spindle generator, and has an important role in spindle activity (52).

Macrostructures of sleep in SCZ: In the short run, disturbed sleep showed by objective and subjective measures could predict functional impairment and psychotic symptoms in SCZ. Sleep fragmentation and decreased sleep efficiency predict auditory hallucinations in the next day. Moreover, increased sleep fragmentation recorded by objective measures and decreased sleep quality reported by patients predict paranoia and delusions of control. However, increased objective sleep fragmentation and reduced subjective sleep quality predicted a greater paranoia and delusions of control (53). In this study, patients with SCZ had misperceptions of sleep. Polysomnography also showed a marked decrease in stages 3, 4, and REM. It also revealed an increase in stage N1 of sleep. These authors reported that at least 35% of patients with SCZ overestimate their sleep time. This overestimation was mainly explained by negative and cognitive symptoms in these patients. Moreover, antipsychotic drugs may play a role in disturbing time perception in them (54).

Microstructure of sleep in SCZ: Anomaly in REM sleep is reported in patients with SCZ. Such an anomaly is present in expected atonia during REM sleep, which suggests a common neuronal control mechanisms between SCZ and REM sleep. Moreover, sleep stage shift is significantly higher in patients with SCZ than the control group (270 vs. 226). In general, instability of sleep is much higher in patients with SCZ (55).

Sleep spindle -thalamocortical pathway- cognition and SCZ: Sleep spindle is a type of sleep oscillation, which originates from the thalamus, and is correlated to memory consolidation. Memory dysfunction is a cognitive dysfunction in SCZ, and has shown to affect SCZ symptoms. This impairment is represented by reduced sleep spindle in patients with SCZ (56, 57). This is in line with other findings attested to the thalamocortical dysfunction in SCZ (38, 49, 50). Thalamic reticular nucleus has been implicated in attention because information coming from the environment goes to the cortex, and is modulated in this site. Symptoms such as impairment of attention are a sort of cognitive impairment in SCZ. Hallucination induced by the sensory gating problem (58, 59) as well as sleep spindle deficits can predict reduced cognitive performance. This reduction points to a thalamus reticular nucleus - medial dorsal thalamus- prefrontal cortex circuit deficit in SCZ (60).

Retrotrapezoid nucleus (RTN) is a gamma-aminobutyric acid (GABAergic) complex which integrates information. It selects relevant information, and puts away distracters during activity or resting situations; it integrates information during consciousness, cognition, emotion, and thought. When thalamic lateral inhibition is disrupted, the disruption may be involved in lack of coordinated activity between regions of brain; the situation which can be observed in psychiatric diseases such as SCZ. New generation of antipsychotics (serotonin-dopamine antagonists) such as clozapine target dopamine receptors GABAergic neurons in RTN, and especially D4 receptors. Dopamine antagonists selectively suppress GABA-A receptors (61).

Decrease in sleep spindle number, amplitude duration, and integrated spindle activity are common findings among patients with SCZ (62). Furthermore, integrated spindle activity showed to have an effect size corresponding to 93.0% or 90.2% differentiation of SCZ from the control or depression group (62). Clozapine used to treat patients with SCZ showed to improve the markers related to sleep spindle amplitude and frequencies (63).

In a cognitive task, which used ToL and mirror tracing, sleep EEG, spindle activity, and K-complexes were analyzed. In this study, performance improved in ToL and mirror tracing. When the participants had more solved ToL tasks, there was an increase in the density of K-complexes. K-complexes in this study were contributed to new information uptake. Furthermore, this study indicated that K-complexes might have links to executive function; thus deficits of them may be an important feature in SCZ (17).

Conclusion

In general, sleep microstructures such as the amount of SWS, sleep instability index, REM without rapid eye movement, NREM with rapid eye movement, or REM without atonia, and K-complex density reflect brain cortical, thalamic, hippocampal, or other pathways important in vigilance in patients with SCZ. Memory types or executive function showed to have change. The unique and most investigated microstructure is sleep spindle. Reduced sleep spindle is the most frequent finding in these patients, which is related to memory consolidation and attention. It reflects thalamocortical perfect function or dysfunction. Thalamus is the gate of sensory information flow to the cortex and integrates information. Thalamocortical dysfunction in SCZ has been reported from several studies. Thalamocorrtical dysfunction presents itself in polysomnography by reducing and changing the frequency of sleep spindles.

Consequently, sleep spindle is a biomarker which can be used for diagnosing and monitoring the response to cognitive rehabilitation and medical treatment sub-typing, and assessing the functionality of patients with SCZ.

There is a need for more sleep research in microstructures and task-dependent sleep in patients with SCZ.

Conflict of Interests

Authors have no conflict of interests.

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