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Review

Do sleep abnormalities and misaligned sleep/circadian rhythm patterns represent early clinical characteristics for developing psychosis in high risk populations?

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ABSTRACT

Sleep architecture changes, such as slow-wave sleep (SWS) percentage variations and reductions in latency and density of rapid eye movement (REM), are found in most patients with schizophrenia and are considered to be an important part of the pathophysiology of the disorder. In addition to these sleep parameters changes, disruptions in sleep homeostasis and the sleep/circadian rhythm also occur in these patients. Sleep/circadian rhythm abnormalities negatively affect neocortical plasticity and cognition and often precede the diagnosis of the illness. Thus, it has been suggested that the sleep/circadian rhythm might be involved in the pathophysiology of psychosis.

Recent advances in the identification of individuals at a high risk for developing schizophrenia allow us to investigate several neurobiological processes involved in the development of psychosis. In this article, we review the current evidence of the effects of sleep parameter abnormalities, disruptions in sleep homeostasis and misalignments of sleep circadian rhythm on the early stages of schizophrenia. In addition, we discuss the preliminary evidence of sleep and circadian rhythm abnormalities during the prodromal stages of psychosis and propose that these abnormalities can be explored as potential predictors, as an adjunct to clinical diagnosis, of developing a psychotic disorder in at risk populations.

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1. Introduction

Schizophrenia is a prevalent and potentially severe psychotic disorder and includes a broad range of symptoms, such as hallucinations, delusions, blunted affect and lack of volition (Kessler et al., 1994; Saha et al., 2005). Schizophrenia usually begins during the transition to adulthood, impairs one's productive potential and reduces life expectancy by 15 years (Saraceno, 2002; Bell et al.,

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2009). Although there have been important breakthroughs in the development of pharmacological agents, only a minority of patients return to premorbid levels of functioning (Bell et al., 2009).

Considering the enormous impact of schizophrenia on a person's health, schizophrenia prevention is an urgent and unfulfilled need in the field of psychiatry. In the last 15 years, a large body of evidence has documented the existence of a prodromal period for the majority of individuals with schizophrenia, which exists prior to the first psychotic episode and varies in duration and in the expression of symptoms (Brietzke et al., 2011; Yung et al., 2003). The detection of schizophrenic individuals during the prodromal period could potentially allow for early intervention, with the objective of preventing its emergence; delaying the onset; and reducing the clinical, neurocognitive, and functional consequences of psychosis (Phillips et al., 2002).

Current evidence indicates that schizophrenia results from an interaction of genetic and environmental factors that leads to brain changes and occurs simultaneously with the maturation of the central nervous system (CNS) (neurodevelopment) (Andreasen, 2010). Therefore, the prodromal period may reveal abnormalities in the developmental trajectory. However, examining this period alone is insufficient for characterizing a well-defined illness (Correll et al., 2010; Yung et al., 1998). Thus, exploring the neurobiology of prodromal stages may offer new and potentially reliable predictors of the transition to a well-characterized mental disorder (Brenner et al., 2010).

Among the various neurobiological abnormalities found in schizophrenia, the sleep circadian rhythm disorders and others sleep disorders are prevalent in individuals with this condition (Cohrs, 2008) and tend to become more severe before acute episodes (Poulin et al., 2010; Tandon et al., 1992).

In this article, we review the current evidence of sleep parameter abnormalities, disruptions in sleep homeostasis and sleep circadian rhythm misalignment on the early stages of schizophrenia. In addition, we propose that these abnormalities, as adjuncts to a clinical diagnosis, can potentially be explored as possible predictors of developing a psychotic disorder in at risk populations.

2. From the prodromal stage to psychosis: the evolution of schizophrenia

During the last decade, there has been growing interest in the early stages of schizophrenia, especially the prodromal stage, because of increasing evidence that a period of low-grade symptoms may precede the onset of psychosis (Brietzke et al., 2011; Phillips et al., 2002; Yung et al., 2003, 2008). Because the concept "prodromal" implies a necessary disease evolution, it has only been valid for retrospective studies. Prospective observations of individuals who may or may not present a transition to psychosis allow patients' mental states to be designated as "at risk", "clinical high risk" or "Ultra High Risk".

Although the operationalization of criteria for identifying these individuals remains under debate, the Ultra High Risk (UHR) criteria are the most widely used (Brietzke et al., 2011; Correll et al., 2010). According to the UHR criteria, individuals between the ages of 14 and 25 years who present with one or more of the following characteristics can be considered part of the interest group: (1) attenuated psychotic symptoms, namely, sub-threshold or attenuated positive psychotic symptoms during the past year; (2) brief, limited and intermittent psychotic symptoms, namely, episodes of psychotic symptoms that last no more than 1 week and that abate on their own; or (3) trait and state risk factors, namely, a schizotypal personality disorder or having a first-degree relative with a psychotic disorder and a significant decrease in functioning during the previous year (Amminger et al., 2006; Yung et al., 2004, 2008).

Several neurobiological abnormalities were also found in individuals in the UHR category. These abnormalities included structural changes, such as reductions in gray matter in the prefrontal cortex (Fusar-Poli et al., 2011a,b), and functional alterations, such as decreased activation of the anterior cingulate gyrus (Fusar-Poli et al., 2011a,b). There is also evidence of cognitive impairment in UHR individuals, including deficits in working memory (Wood et al., 2003), processing speed measures (digit symbol coding, Trail Making Test-B, and Stroop Color-Naming), verbal working memory measures, verbal memory and learning, and verbal fluency (Pukrop and Klosterkotter, 2010).

Although descriptions of structural, functional and cognitive changes have been growing in the literature, several topics of investigation, such as peripheral biomarkers, neurophysiology and sleep disturbances, remain underexplored (Kauer-Sant'Anna et al., 2009; Mansur et al., 2011; Yung and Nelson, 2011). Schizophrenia has been associated with abnormalities in these parameters, which should be the focus of research in at risk individuals. In the next section, we will focus on sleep and sleep circadian rhythm abnormalities that are found in the clinical stages of schizophrenia, which could be explored in the at risk individuals.

3. Normal sleep, sleep regulation, and sleep circadian rhythm

Normal sleep in humans is divided into two phases: REM sleep (Rapid Eye Movement) and NREM sleep (Non-REM). NREM sleep is further divided into the N1, N2 and N3 stages, according to the depth of the sleep (Kryger et al., 2010). In a normal young adult, these phases alternate cyclically approximately every 70–110 min (Aserinsky, 1969; Aserinsky and Kleitman, 1953). Each REM-NREM sequence defines one cycle, which is repeated approximately 4 to 6 times during the night, depending on the total sleep time. In general, humans fall asleep by entering non-REM sleep (N1 stage). This stage represents the transition from wakefulness to the onset of sleep and lasts only a few minutes. Furthermore, the N1 stage is associated with a low arousal threshold. Then, sleep advances to N2, then to N3 (also called slow-wave sleep [SWS], delta sleep or deep sleep) and finally to REM sleep. In general, REM sleep constitutes 20–25% of an individual's total sleep time, and NREM sleep constitutes approximately 75–80% of the total sleep time. The greatest amount of sleep time (45–55%) is spent in the N2 stage. Moreover, NREM sleep predominates the first half of the night, while REM sleep episodes are more common during the second half of the night (see Kryger et al., 2010; Aserinsky, 1969).

Each state has specific electroencephalographic (EEG) patterns. Non-REM sleep stages are characterized by low neuronal activity, which is represented by synchronized waves, alpha rhythms and occasional vertex acute waves (N1 stage); sleep spindles; K complexes (N2 stage); and high amplitude delta waves that reach at least 75 μV (N3 stage) during at least 20% of each epoch. The metabolic rate and brain temperature are at their lowest point during NREM stages. Moreover, sympathetic outflow decreases, and the heart rate and blood pressure decline. On the contrary, parasympathetic activity increases. The EEG patterns of REM sleep and wakefulness are similar. Brain temperature and metabolic rate rise due to the overall increase in neural activity during this phase. REM sleep is characterized by unsynchronized waves, sawtooth waves, rapid eye movements, and a strong reduction in almost all skeletal muscle tone, as monitored by electromyography. In addition, most of the dreams that one remembers occur during REM sleep. Homeostatic mechanisms are diminished: respiration is less responsive to changes in blood CO_2 and O_2 pressure, and heat and cold stimulations present low or no response. As a

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