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Sleep EEG as a Tool for Exploring Mechanisms of Schizophrenia

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ABSTRACT

Despite the extensive neuroimaging research investigating the neurodevelopmental mechanisms of schizophrenia, to date we have a limited understanding about how schizophrenia develops. Feinberg's (1982) popular neurodevelopmental model proposes that excessive synaptic pruning during adolescence as indexed by the loss of delta brain-wave activity (EEG) in non-rapid eye movement (NREM) sleep may underlie the pathophysiology to schizophrenia. Several studies have shown that the amplitude and incidence of delta wave EEG are disrupted in stage 3 sleep in schizophrenia. However, little research has investigated sleep EEG in adolescents who are at high risk for transitioning into psychosis. The current paper reviews recent longitudinal findings documenting the normal rate of delta EEG changes over the childhood and adolescent periods and proposes a sleep EEG study that can help inform how schizophrenia develops in adolescence.

Introduction

Schizophrenia is an idiopathic mental condition that affects people regardless of gender or lifestyle, and it is prevalent among young adolescents and adults (Saha et al. 2005). Symptoms of schizophrenia are commonly divided into positive and negative. Positive symptoms refer to the existence of content-related thought disturbances, ego disturbances, and perceptual disturbances, whereas negative symptoms include anhedonia, social withdrawal, and cognitive and motor deficits such as blunted facial expressions and gestures (McCutcheon et al., 2020). In addition to these symptoms, sleep abnormalities, although not part of the clinical symptoms required for diagnosis, have been reported in schizophrenia since the earliest description of the disorder and are commonly observed in patients with schizophrenia in the clinical setting (Ferrarelli, 2021; Kraepelin, 1919, as cited in Manoach & Stickgold, 2015). Although scientists have been able to uncover symptoms of schizophrenia, to date the cause of the disorder remains unknown (Insel, 2010).

The predominant model of how schizophrenia develops is the "neurodevelopmental model," which posits that clinical symptoms of schizophrenia emerge due to aberrations in neurodevelopmental processes that begin before the onset of those clinical symptoms (Rapoport et al., 2005). In this model, schizophrenia is thought to be associated with maldevelopment during the prenatal, perinatal, and adolescent periods of human development (Folsom & Fatemi, 2009; Keshavan, 1999). Perturbations occurring in the early stages of brain development as well as during the adolescent period when the brain undergrounds programmed elimination of synapses or synaptic pruning combine to produce the symptoms associated with schizophrenia (Kevanshan, 1999). An extensive body of work has used neuroimaging methods to examine whether neurodevelopmental abnormalities during the adolescence period underlie the transition to schizophrenia. One area of research that has been informative are sleep EEG studies which use electroencephalogram (EEG) to objectively measure sleep characteristics and disturbances in schizophrenia (Cox & Fell, 2020). This procedure involves placing EEG electrodes on participants' scalps while they sleep to detect small electrical potentials produced by the brain (Feinberg & Campbell, 2010).

As mentioned above, sleep disturbances are often thought to be connected with schizophrenia and an abundance of research suggests that sleep disturbance is tied to the pathophysiology of schizophrenia. For example, Benson (2008) notes that serious sleep disturbances are associated with psychotic worsening and often precede relapse. Moreover, negative symptoms and cognitive dysfunctions are often associated with common sleep dysfunctions seen in schizophrenia. When drug therapeutic efforts are made to help patients with schizophrenia, both sleep quality and psychiatric symptoms improve (Kantrowitz et al., 2010). Retrospective studies also show that patients with psychotic disorders and their family members report general sleep problems as one of the earliest signs of psychiatric illness, present in the period immediately preceding transition into psychosis (e.g., Hambrecht et al., 1994; Heinrichs & Carpenter, 1985). These findings all converge on the notion that sleep disturbances may occur before transitioning into psychosis. Indeed, a recent review argues that sleep dysfunction across a broad range of factors may precede psychosis onset because studies have shown that they are present in at-risk populations or in patients with schizophrenia prior to psychosis onset (Lunsford-Avery & Mittal, 2013). However, little research has focused on sleep disturbances in individuals at high-risk for schizophrenia. The current paper sheds light on this topic by reviewing recent advances in the sleep EEG literature that can help illuminate the pathogenesis of schizophrenia.

Sleep EEG Studies and Schizophrenia

Sleep comprises two states – rapid eye movement (REM) and non-REM (NREM)– that alternate cyclically across a sleep episode. The first set of rules published by Rechtschaffen and Kales (1968) proposed to divide NREM into four distinct stages 1, 2, 3, and 4. This was updated by the American Academy of Sleep Medicine in 2007 so that sleep stages 3 and 4 were merged into stage N3 (Iber et al., 2007). Stage N1 is characterized by low-voltage EEG waves in the theta frequency range (4-7 Hz). Stage N2 is defined by the presence of rapid activity “sleep spindles” and intermittently spiking “K-complexes”. Sleep spindles refer to bursts of 12-14 Hz waves predominant over central scalp electrodes and lasting between 0.5 and 2s (Rechtschaffen & Kales, 1968 as cited in Combrisson et al., 2017). K-complexes are defined as sharp negative waves followed by a positive component, prominent over frontal scalp electrodes and lasting more than 0.5 s (Combrisson et al., 2017). Stage N3 is characterized by the presence of slow waves (SWS, or delta waves) that have high-amplitude (>75 μV) and low-frequency (<3 Hz) oscillations. According to the guidelines, N3 sleep is defined by the presence of 20% or more slow waves in a given period of time. Finally, REM sleep is characterized by rapid eye movements that are detected on electrodes placed near the eyes. The sleep cycle begins with NREM (N1) and progresses through deeper NREM stages (N2 and N3) in approximately 80 to 100 minutes. Subsequently, the first episode of REM sleep occurs as the final stage of the sleep cycle (Carskadon & Dement, 2011) (see Figure 1).

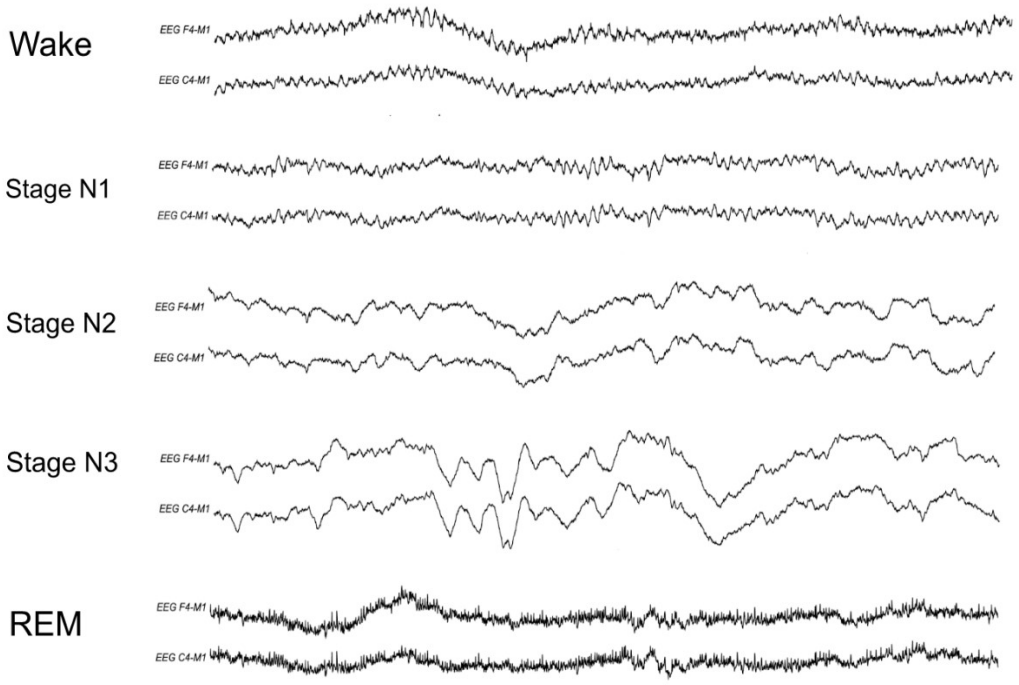

Figure 1. Ten-second EEG traces over right frontal and central electrode sites from a participant accessed from the open Haaglanden Medisch Centrum sleep staging database (Alvarez-Estevez & Rijsman, 2022). As noted by Feinberg and Campbell (2010), waking EEG is characterized by high-frequency low amplitude waves. Stages 1-3 comprise NREM sleep and are a continuum of increasing slow wave activity. REM sleep EEG is similar to that of waking and shows high-frequency low amplitude waves.

This paper focuses on sleep EEG studies that have investigated dysfunction in NREM stage N3 sleep comprising SWS or delta activity. Abnormalities in this stage are prominent features in schizophrenia populations, and studies with genetic high-risk and ultra-high-risk individuals suggest the occurrence of abnormal SWS prior to the onset of psychosis (Lunsford-Avery & Mittal, 2013). Moreover, an important neurodevelopmental model proposed by Feinberg (1982) posits that abnormalities in the normal rate of decline in SWS/delta activity over adolescence may underlie the pathophysiology of schizophrenia. I expand on these points below and propose a study with individuals at high-risk for schizophrenia to investigate the potential role of sleep dysfunction in the pathogenesis of schizophrenia.

There is a long history of studies investigating sleep disturbances in schizophrenia. Following the discovery of REM sleep by Aserinsky and Kleitman (1953), Dement and Kleitmen (1957) discovered a low voltage, fast EEG with accompanying rapid eye movements which correlated with the subjective experience of dreaming. Early studies sought to investigate this phenomenon in schizophrenia patients. Dement (1955) for example, reported that both "control" and schizophrenia patients showed a relationship between eye movements during REM and incidence of dreaming. The interest in REM sleep and dreams in schizophrenia seemingly originated from the notion that dreams and hallucinations may have a common underlying neural source (Caldwell & Domino, 1967). However, early studies did not find any consistent abnormalities or intrusions that could differentiate schizophrenic patients from non-schizophrenic participants (Feinberg et al., 1964; 1965; Benson, 2008).

Shortly thereafter studies focused on abnormalities in stage 3 and 4 NREM sleep in schizophrenia. For example, Caldwell and Domino (1967) revealed that 40% of 25 unmedicated schizophrenia patients did not show any visually scored stage 4 sleep and exhibited a significantly reduced amount of stage 3 sleep as compared to 10 medical school control participants. This finding has been well replicated in both acute and chronic schizophrenia patients

(reviewed in Feinberg & Hiatt, 1978). Developments in the 1970s and 1980s of computer algorithms allowed researchers to directly measure the brain waveforms and identify the incidence and amplitude of EEG delta (0-3 Hz) frequencies of non-REM sleep. For instance, Hiatt, Floyd, Katz, and Feinberg (1985) provided a computer analysis to show that the characteristics of delta waves in 5 schizophrenia patients – amplitude, frequency, and rate of production – all deviated significantly from those of a control group. Studies using computer methods to score sleep have confirmed the loss of delta EEG in schizophrenics relative to non-psychiatric controls (Keshavan et al., 1998), however, there are inconsistencies in the literature (for a recent review see Castelnovo et al., 2018).

Delta Wave Findings and the pathogenesis of Schizophrenia

The implications of these findings for understanding the pathophysiology of schizophrenia can be understood in the context of Feinberg's neurodevelopmental framework (Keshavan & Tandon, 1993). Feinberg (1982) proposed a model of schizophrenia that accounts for the loss of delta EEG over adolescence. He noted two observations: one was that schizophrenia had a high incidence in adolescence, and the second was that the adolescence stage of development is associated with the substantial reorganization of brain structure and function. There is an initial increase of synaptic density in infancy followed by a subsequent decrease of cortical synaptic density through adolescence (Huttenlocher, 1979). EEG data similarly shows a decline in the amplitude of delta waves characterizing NREM sleep over the adolescent years (10-14 years of age) (Feinberg et al., 1977). Putting together these two observations, Feinberg proposed that schizophrenia may develop during the second decade of life during adolescence because of a fault in the normal maturational process of synaptic elimination scheduled for this stage of development. Less synchronous delta EEG activity (and associated SWS deficits) would reflect excess synaptic pruning.

Although the direct causes of schizophrenia are uncertain, scientists have predicted that schizophrenia is strongly correlated with the excessive pruning of synapses (Jaaro-Peled & Sawa, 2020). During the stage of infancy, neurons connect with one another, and those connections, in other words, synapses, continuously increase in number. Then, there exists an excess number of synapses. However, as people enter adolescence, there is a significant amount of decrease in synapses due to the body's elimination of any unnecessary connections. In the case of schizophrenia patients, their synapses prune away in a much-accelerated way, and reduction occurs in even the necessary connections. Thus, there is an insufficient number of synapses to carry out normal signal processing (Johnson & Stevens, 2018).

Recently, longitudinal studies by Feinberg and colleagues have investigated delta wave changes over the course of childhood and adolescence. In these studies, undergraduate technicians are trained to use non-invasive portable EEG recorders in participants' homes. Participants were children volunteers who were clinically normal and performing at grade level or better in school. Technicians attached metal electrodes with glue and tape to record children's brain waves and eye movements. Thin wires attached to the metal electrodes connected to the EEG machine recorded children's brain waves continuously throughout the night. Using this methodology, Feinberg and Campbell (2013) reported that delta power, reflecting delta wave incidence and amplitude, increased from about age 6 to 8 years and then gradually declined. By age 10 years delta power did not differ significantly from its level at age 6. In another study, Feinberg and Campbell (2010) reported a rapid decline in NREM delta power across ages 12-16.5 years, with analysis revealing that the most rapid period of delta power decline was observed at 13.32 years of age.

These findings establish the expected rate of decline in delta power normally seen during late childhood and early adolescence. They also provide the empirical basis for future research to investigate whether disruptions in the rate of decline occur during adolescence in individuals who later develop schizophrenia. To date, however, there have been a limited number of studies that use sleep EEG in high-risk individuals. In one such study, Keshavan, Diwadkar, Montrose, Stanley, and Pettegrew (2004) observed the number of delta waves in high-risk youth aged 6 to 25 years who never had a diagnosis of a psychotic disorder but were relatives of schizophrenia patients and therefore had a high genetic risk of schizophrenia. Their analysis of visually scored delta wave counts (or incidence) per minute revealed deficits in a small sample of high-risk adolescents (n = 9) as compared to controls (n = 10). In addition, they

found that older high-risk participants showed steeper declines in delta waves, suggesting that adolescents at risk for psychotic disorders may possess an accelerated rate of decline in delta wave reduction during adolescence. The finding of decreased delta wave incidence in non-psychotic high-risk participants suggests that these changes may underlie predisposition to the illness and supports the model of enhanced synaptic pruning mechanism in schizophrenia as proposed by Feinberg (1982).

Although informative, this study had a number of limitations that could be addressed with future research. First, the study had a low sample size, limiting the generalizability of the findings. Second, the researchers used visual scoring of delta wave counts but there exist more advanced computer analysis techniques to score sleep EEG. Visual sleep scoring is subject to both inter and intra-rater variability (Combrisson et al., 2017). More modern techniques use algorithms to automatically score sleep stages and have the advantage of being fast, reproducible, and generally good agreement with visual scoring (Combrisson et al., 2017). For example, Feinberg and colleagues (2010) use computer analysis with the fast Fourier transformation (FFT) to measure both the incidence and the amplitude of delta waves in the frequency range of 1-4 Hz. An important direction for future research is therefore to recruit a larger sample of high-risk individuals and record sleep EEG waves longitudinally during the adolescent years. Following Keshavan et al. (2014), researchers could recruit high-risk individuals, defined as those who had never had a diagnosis of a psychotic disorder, and had at least one first- or second-degree relative with schizophrenia or schizoaffective disorder. FFT analyses could focus on measuring the rate of NREM delta power decline in high-risk individuals as compared to control individuals with no family history of schizophrenia. If evidence for an enhanced decline in delta wave amplitude and incidence during NREM in youth who are at high risk for schizophrenia is found, then this would lend support to Feinberg's hypothesis that perhaps an increased rate of synaptic pruning may precipitate the onset of schizophrenia.

Implications for Treatment Interventions

Although an understudied area, EEG sleep studies with individuals at high-risk can inform the neurobiology of schizophrenia and inform researchers about potential biomarkers of schizophrenia. In a recent paper, Ferrareli (2021) reviewed the literature and argued that sleep abnormalities that are consistently seen in schizophrenia, especially those related to spindles and slow-wave alterations, should be assessed as biomarkers for schizophrenia. A biomarker is a "defining characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention" (Califf, 2018). In this regard, reduced delta wave EEG could offer a window into the neurobiological dysfunctions that may underlie the pathophysiology and clinical manifestations of schizophrenia (Thibaut et al., 2015). Future studies using a larger sample of control group and individuals at high-risk for schizophrenia are needed to establish whether amplified delta wave reduction may be a diagnostic biomarker for schizophrenia.

Limitations and Conclusions

A major limitation of the current review is that it only focused on the adolescent period of human development. It is well known that other risk factors may contribute to schizophrenia earlier in life. For example, research has shown that prenatal risk factors including maternal to fetal infections or malnourishment of pregnant mother are associated with schizophrenia, as disorderly neurodevelopment of infant can affect body movement and cognitive skills (McCutcheon et al., 2020). Moreover, as risk of developing schizophrenia involves both environmental and genetic factors, developmental period may vary among individual patients, requiring further studies to look at multiple periods of development.

To conclude, sleep EEG in individuals with individuals at high risk for schizophrenia is an understudied area of research (Lundsford & Mittal, 2013). This paper reviewed recent longitudinal findings that characterize the

expected rate of decline in SWS or delta activity during N3 sleep in adolescence (Feinberg & Campbell, 2010; 2013). Future research investigating N3 sleep characteristics in individuals at high risk can inform people about patterns of sleep EEG that may predict the transition to schizophrenia in adolescence (Lundsford & Mittal, 2013). Such research can help inform the neurobiological mechanisms that predict the transition to schizophrenia.

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