Effect of chronotype on the length and cycle times of REM and NREM sleep

Grant Proposal

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Abstract

Sleep consists of different phases, including Rapid Eye Movement (REM) and Non-Rapid Eye Movement (NREM). REM sleep involves random, rapid movement of the eyes and the presence of dreams. In contrast, the latter stage–particularly the N3 phase of NREM–involves the body relaxing its movements and healing tissues. Previous studies have analyzed many parameters of sleep and how they affect its cycles. However, studies related to chronotype–the body's natural preferences for sleep and wake times–have yet to be thoroughly explored. Thus, this project proposes a study on how an individual's chronotype can affect the length of their sleep cycles, as well as other disruptions throughout the night that are indicative of a decreasing sleep quality. By using the Munich Chronotype Questionnaire (MCTQ) to evaluate an individual's chronotype and then using an electroencephalogram (EEG) to record electrical activity during sleep, a connection can be made between an individual's chronotype and their length of sleep phases. The results of this process hope to elucidate further research into how different circadian parameters can contribute to the onset of sleep and neurological disorders.

Effect of chronotype on the length and cycle times of REM and NREM sleep

Different phases of sleep serve different purposes; there are between four and six sleep cycles that occur every night in a healthy individual (Suni & Singh, 2023). The two main stages of sleep are REM (Rapid Eye Movement) and NREM (Non-Rapid Eye Movement), each serving a different purpose. NREM sleep can be divided into three stages: N1, N2 and N3. The N1 stage is only part of the first sleep cycle, as it transitions between an individual's wakefulness and sleep; N2 and N3 are part of each subsequent cycle (Suni & Singh, 2023).

Both NREM and REM sleep have important functions that they carry out. NREM sleep is believed to be a time of rest and healing, where metabolism increases and heart pressure drops. Additionally, skills in declarative memory are consolidated. Declarative memory relates to the ability to recall information, such as facts learned, throughout the day (Liu et al., 2023). In addition, different stages of sleep can be characterized by different brain waves, which can be measured by an electroencephalogram (EEG). N3 sleep, also known as deep sleep, is characterized by the slow delta-waves that are produced by the brain, while alpha and beta-waves are more commonly found at the beginning of N2 and REM sleep (Hussain et al., 2022). Recent evidence has also shown that NREM sleep is crucial in neuronal survival. As NREM sleep helps to protect neurons against cell death, it can play an important role in delaying the onset of such diseases marked by neuronal cell death. Once neurons undergo apoptosis, the damage done is irreversible and can lead to the onset of neurodegenerative diseases such as Alzheimer's Disease, resulting in loss of memory and other mental functions (Liu et al., 2023).

REM sleep is where brain activity increases. Most muscles are temporarily paralyzed in a process called atonia, with the exception of the eyes and the muscles that control breathing (Suni & Singh, 2021). This phase of sleep gets its name from the quick eye movements that occur.

Additionally, REM sleep is well-known for the presence of dreams, which is supported by the increase in brain activity (Behzad & Behzad, 2021).

Chronotype as a Circadian Parameter

Circadian rhythms encompass a variety of changes that follow a 24-hour cycle, including alertness, appetite, and body temperature. One of the most well-known circadian rhythms is the sleep-wake cycle. An important parameter of the circadian rhythm is chronotype, which determines an individual's preference for wakefulness and sleep. According to the Munich Chronotype Questionnaire (MCTQ), there are seven possible chronotypes, ranging from extreme early to extreme late, although they are usually condensed into three: morning, normal, and evening (Harfmann, 2020). People with earlier chronotypes are often described as "early larks," while those with later chronotypes are called "night owls". An individual with a morning chronotype will prefer sleeping and waking at an earlier time, achieving peak performance and productivity early in the morning. On the contrary, an individual with an evening chronotype will prefer staying up later and waking up later, achieving peak performance and productivity later at night. The intermediate chronotype does not have a preference for morning or evening activity. Typically, people with morning chronotypes wake up 2-3 hours earlier compared to people with evening-types (Zou et al., 2022). However, there is little information on how chronotypes can affect the number of sleep cycles or the percentage of each stage of NREM sleep, which would play a role in understanding chronotype as a risk factor for changes in sleep quality, as well as sleep disorders that manifest in different stages of sleep.

Factors That Affect Chronotype

While chronotypes have a genetic basis, it is possible for an individual's chronotype to change as they age; chronotype is not constant throughout one's lifespan. The morning chronotype is more common among babies and older adults, while the evening chronotype is more common among adolescents and young adults ages 25-34 (Zou et al., 2022). This is a result of both genetics and zeitgebers (“time-giver” in German)–environmental time cues that entrain an individual’s biological rhythms every day. The most predominant zeitgeber is naturally occurring sunlight, but social zeitgebers have become more significant due to the use of alarm clocks and artificial light (Zou et al., 2022). Due to the presence of other exogenous factors such as school, shift work, and caffeine, there can be misalignments between sleep times and the preferences of the biological clock in different individuals. This misalignment is known as social jet lag (SJL), which quantifies disruption of the circadian rhythm as the difference between the midpoint of sleep time between weekdays and weekends (Harfmann et al., 2020). Interestingly, a study conducted by Harfmann et al. in 2020 resulted in greater subjective sleep quality reported by individuals with a later chronotype. The higher reported quality was presumably because of their high social jet lag, leading to higher sleep satisfaction when they were not woken up due to work. Additionally, older adults with evening chronotypes were found to have an increased number of nighttime disruptions, leading to more restless sleep (Sauers et al., 2023).

Chronotype and Diseases

Previous research has shown that the chronotype of an individual can increase the risk for certain diseases. For example, in a Mendelian randomization study conducted by Yuan et al. (2023), people with evening chronotypes were shown to have a greater risk for six different types of cancers, including stomach, liver, and colorectal cancer. Additionally, due to slight alterations in brain structure including regional gray matter density between chronotypes, there is an association with psychiatric disorders such as major depressive disorder (MDD) and bipolar disorder (BD) (Zou et al., 2022). It has also been linked to eating disorders and neurodegenerative diseases like schizophrenia, but the exact pathological reasons behind this association have yet to be determined (Zou et al., 2022).

Section II: Specific Aims

This proposal's objective is to delineate the importance of chronotypes and how they could contribute to differences in key parameters of sleep cycles. In the long term, this project will assist in understanding different circadian parameters that measure certain qualities of sleep, and provide further insight into the development of sleep-related disorders. The work proposed here will provide a solid foundation for further evaluation of sleep parameters and how they are affected by different attributes in individuals.

Specific Aim 1: Implement the Munich Chronotype Questionnaire (MCTQ) to assess the chronotype of different individuals; analyses from later phases of this experiment can help to establish connections between chronotype and certain sleep parameters.

Specific Aim 2: Regulate and rule out confounding factors that could interfere with the activity shown by the recordings. Then, use an EEG to record data for one night of sleep in individuals with different chronotypes.

Specific Aim 3: Integrate knowledge of different brain waves to characterize the different phases of sleep from the EEG recordings; in doing so, the length and start time of each phase of sleep can be obtained and statistically analyzed.

The expected outcome of this work would show that a later chronotype in adolescents is correlated with more disruptions throughout the night and less time spent in REM sleep. Through a better understanding of how sleep cycles and phases are affected, sleep-related disorders that result in alterations of certain phases can be further investigated with other circadian parameters.

Section III: Project Goals and Methodology

This study focuses on the role that an individual's chronotype plays in measures of objective sleep quality, including the length of sleep phases and cycles, as well as any disturbances that may occur during sleep. In adolescents, evening chronotypes are presumably more common; however, early start times for school can lead to sleep deprivation and disruption of sleep cycles. Thus, it is important to examine the effect that circadian parameters can have on individuals, especially during a time when they are required to wake up at certain times due to constraints such as school and other activities in the morning.

Specific Aim #1

Determining the chronotype of an individual is vital for this study, as it allows for comparisons and analysis of data between different chronotypes. For this study, the chronotype of an individual will be assessed using the Munich Chronotype Questionnaire (MCTQ). Previous questionnaires like the Morningness-Eveningness Questionnaire by Horne and Östberg in 1976 (MEQ), as well as its reduced version by Adan and Almirall in 1991 (rMEQ), have been used to evaluate an individual's chronotype. However, the measures of the MEQ were considered to be too subjective, and it ignores the difference in wake times between weekdays and weekends, making it less reliable in accurately determining chronotype (Danielsson et al.,

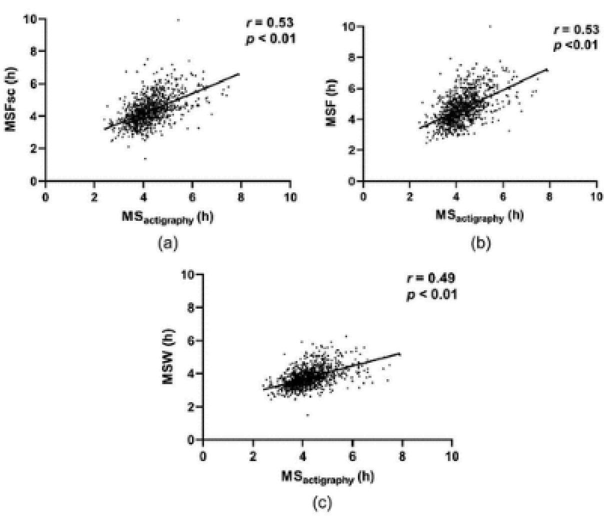

Figure 1: Three different parameters of the MCTQ were measured and compared to the results of an actigraphy. The mid-sleep point corrected for sleep debt on weekdays (MSFsc), the mid-sleep point on free days (MSF), and the mid-sleep point on workdays (MSW) were all significantly correlated with the mid-sleep point calculated from an actigraphy. Figure from Wang et al., 2023.

2019). The MCTQ was originally developed by Roenneberg et al. in 2003 and has been widely used to effectively determine an individual's chronotype ever since. Unlike the MEQ, it can gather information about sleep and activity times for work and free days separately; this is crucial because there are more constraints on how late someone can sleep or wake up on work days. These constraints may lead to the use of an alarm clock in the morning, which could be a confounding factor. As the objective measures for assessing chronotype are time-consuming and expensive, the MCTQ is a subjective measure that is reliable and practical. As shown by a study by Wang et al. in 2023, the results of an actigraphy–a noninvasive method of measuring activity–were positively and significantly correlated with three MCTQ parameters (Figure 1). These results help to confirm the validity of the MCTQ and its usefulness in ascertaining an individual's chronotype using the different parameters. The overall outcome of this aim is to establish participants with early, intermediate, and late chronotypes, with its knowledge contributing to discovering how the chronotype of adolescents can affect the different phases of sleep. However, the possibility of confounding factors in sleep times is expected. Thus, it is important that the participants who answer the MCTQ do not exhibit sleep disorders and do not consume caffeine before going to bed. When consumed within six hours prior to bedtime, caffeine can reduce sleep by more than an hour (Drake et al., 2013).

Specific Aim #2

Once an individual's chronotype is determined, the tracking of sleep cycles can be achieved. An EEG will track the electrical signals from their brain for one night of sleep. EEGs are reliable and noninvasive tools for diagnosing conditions like sleep disorders and are also used to record brain activity during sleep (Harfmann et al., 2020). For this test, electrodes will be attached to the scalp of the participant, which will take signals from different areas and lobes in the brain. A gel will be used to help pick up and conduct the electrical signals from the scalp. The overall outcome of this aim is to obtain the raw data, which will be needed to determine the start time and length of sleep cycles; additionally, any disturbances to sleep could be identified.

Specific Aim #3

Different types of waves have different frequencies. Delta waves, a characteristic of N3 sleep, have a frequency from 0.5 to 4.0 Hz. In order of increasing frequency, delta waves are followed by theta waves, alpha waves, beta waves, and at 30.0 to 44.0 Hz, gamma waves (Hussain et al., 2022). By analyzing the frequency of the waves that the EEG records, different time periods can be classified into different phases of sleep. A study by Hussain et al. in 2022 showed the relative mean power of EEG waves in different parts of the brain during each phase of sleep (Figure 2).

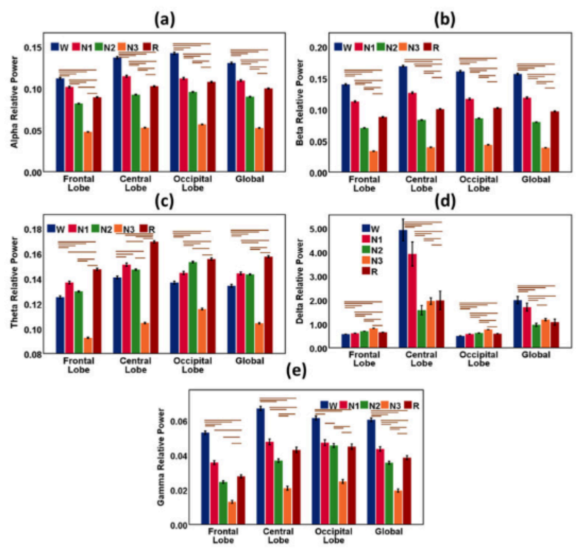

Figure 2: Relative mean power of the waves during different phases of sleep (wake, three stages of NREM, and REM), measured by the EEG in three different parts of the brain. Alpha, beta, and gamma relative power decreased as the body transitioned into N3 deep sleep, and increased again in REM sleep. Theta relative power decreased in N3, while delta relative power increased from N2 to N3. Figure from Hussain et al., 2022.

Higher-frequency bands like alpha and beta decrease in power leading up to N3 sleep and then rise again in REM, while delta bands increase in N3. These results are consistent with previous findings and help to solidify the role that waves obtained from EEG recordings can help in identifying sleep stages. These recordings can further be analyzed to find the length and start time of each phase, as well as disturbances in sleep that occur. This knowledge can be used to characterize parts of the EEG recording into different stages of sleep.

Section IV: Resources/Equipment

The OpenBCI GUI can record the data collected by the EEG, which will be helpful for viewing physiological data. Additionally, it can be streamed to other applications and tools, which could be implemented to further analyze data. Either saltwater or conductive gel can be used in tandem with the electrodes on an EEG, as they both will help with amplifying the electrical activity from the brain. For sleep, the conductive gel will be used, as saltwater may not last for the entire duration of sleep, and it is not at all optimal for participants to wake up in the middle of the night and reapply the material. The gel being used is the OpenBCI Electrode Cap Gel, which will help with low impedance and therefore, better quality in EEG measurements.

Section V: Ethical Considerations

This study aims to investigate the effect of an individual's chronotype on their length and cycle times of the different phases of sleep. As an EEG will be used to detect electrical activity and waves from different parts of the brain, this study will involve humans. The EEG requires saltwater or conductive gel to enhance the electrical connection between the device and the scalp to obtain its findings. However, participants only need to apply the conductor to their scalp; neither of the aforementioned substances will be used to harm them. Additionally, the EEG does not produce any sensation for the wearer and is not at risk for shocking the wearer. During EEG tests, patients with epilepsy may experience seizures. Consequently, people who take part in this study will be confirmed to not have any disorders that could cause seizures during testing, so that there is no risk for injury when using the device. Data from each patient will be de-identified and encrypted to ensure privacy and security of the recordings.

Section VI: Timeline

<table>
<tr><th>August</th><th>September</th><th>October</th><th>November</th><th>December</th><th>January</th><th>February</th></tr>
<tr><td colspan="4">Preliminary research
Start exploring methodology</td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td colspan="2">Acquiring materials
EEG, corresponding software, and MCTQ</td><td colspan="2">Acquiring participants
Evaluating chronotype of each participant</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="3">Conducting EEG tests</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td colspan="2">Data analysis + conclusions</td></tr>
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