Sleep and Quasi-Periodic Patterns During Rest

A Thesis

by

Maya Karkare

Approved by:

Dr. Eric Schumacher, Advisor
School of Psychology
Georgia Institute of Technology

Signature: DocuSigned by: Eric Schumacher 0D1AB3DB597448C... Date: 5/1/2022 | 1:47 PM EDT

Dr. Shella Keilholz
School of Biomedical Engineering
Georgia Institute of Technology, Emory University

Signature: DocuSigned by: Shella Keilholz C17CCC817166491... Date: 5/2/2022 | 8:40 AM EDT

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Introduction

Quasi-Periodic Patterns (QPPs) are important to study because they can be clearly observed in healthy individuals and they contribute to overall functional connectivity (Abbas et al., 2019). In individuals with excessive daytime sleepiness, there is decreased connectivity within the DMN (Ward et al., 2013), which subsequently reduces the anti-correlation between the DMN and the TPN. In patients with sleep disorders like narcolepsy and idiopathic hypersomnia, QPPs may differ in both strength and frequency during resting-state in comparison to healthy controls (Bassil, 2020). Hence, QPP strength may be able to serve as an indicator of neurotypical cognitive functioning. According to this evidence, it is highly likely that sleep quality and time can affect QPPs, even in healthy individuals. Therefore, it is possible that healthy individuals may also present with reduced connectivity in the DMN and reduced anti-correlation of QPPs depending on sleep quality.

Many of the past studies conducted on patients with sleep disorders focus on QPPs obtained from resting-state scans, where subjects focus on a fixation cross while a fMRI scan is performed. Additionally, there is a gap in the research regarding QPPs and healthy participants' sleep prior to their scans. In this preliminary study, I will attempt to establish a relationship between sleep and QPP strength during rest scans.

By studying the QPPs of healthy participants and their sleep patterns, we will hopefully be able to gain insight into how sleep disorders result in abnormal QPPs. This further understanding of how QPPs present in individuals with sleep disorders during different tasks will also help to improve diagnostic tools for sleep disorders. More importantly, this research could lead to the development of more effective treatments for sleep disorders that present with

excessive daytime sleepiness. We hypothesize that sleep quality and time will have a positive correlation with QPP strength.

Literature Review

Quasi-periodic patterns (QPPs) are low-frequency spatiotemporal patterns that occur about every 20 seconds in the human brain (Abbas et al., 2019). This pattern concerns the alternating activity levels of the default mode network (DMN) and the task-positive network (TPN) in the human brain. The DMN is a brain network that is generally active during periods of rest, like when an individual closes their eyes or during visual fixation (Raichle, 2015). This network is composed of the posterior cingulate cortex, the ventral medial prefrontal cortex, and the dorsal medial prefrontal cortex (Raichle, 2015). The TPN is active when an individual is performing a task that requires exogenous attention (Chai et al., 2012). The TPN involves lateral parietal cortex, dorsal premotor regions, supplementary motor areas, bilateral middle temporal gyrus, and the dorsolateral prefrontal cortex (Hu et al., 2017). DMN activity and TPN activity are strongly anti-correlated, meaning that when one network is active, the other network is not as active (Abbas et al., 2019). These activity patterns comprise the QPPs which will be discussed throughout this study.

QPPs can be detected via analysis of functional magnetic resonance imaging (fMRI) blood oxygenation level dependent (BOLD) signals. An increase in BOLD signals in a certain network or part of the brain indicates that there has been an increase in the amount of oxygen to that area of the brain (Gauthier & Fan, 2019). Consequently, an increase in the BOLD signal correlates with an increase in activity in that brain network, whereas a decrease in BOLD activity correlates with a decrease in activity in a certain brain network (Gauthier & Fan, 2019). Although this interpretation of the BOLD signal is widely used to understand fMRI data, it is important to note that this oversimplified model of the BOLD signal remains somewhat controversial.

QPPs are evolutionarily conserved patterns among species with advanced cognitive function, signifying their importance in overall cognitive function. QPPs were originally identified in anesthetized rats (Majeed et al., 2009), but they can be reliably found in other species of animals. The mouse model contains networks analogous to the DMN and TPN, and these networks have been shown to reliably display QPPs (Belloy et al., 2018a). QPPs are also easily observed in mice and other species, including rats (Majeed et al., 2009) and rhesus macaque monkeys (Abbas et al., 2016). Functional connectivity in the DMN and TPN tend to be altered in many neurological disorders, including in attention deficit hyperactivity disorder (ADHD) (Abbas et al., 2019) and Alzheimer's disease (AD) (Karbasfouroushan & Woodward, 2012; Belloy et al., 2018b).

The amount of sleep an individual gets may affect arousal, which may also affect QPPs. Daytime sleepiness reduces connectivity in the DMN (Ward et al., 2013), which, as a result, produces altered connectivity between the DMN and the TPN. A common symptom of sleep disorders such as idiopathic hypersomnia and narcolepsy is excessive daytime sleepiness (Billiard & Dauvilliers, 2001; Morrison & Riha, 2012). A previous undergraduate study concluded that there are small differences in resting state QPP frequency and strength between healthy individuals and individuals with narcolepsy and idiopathic hypersomnia (Bassil, 2020). This study was limited due to small sample size and incomplete analysis, but with more data collection and further analysis, researchers may find stronger evidence of significant differences in the QPPs between healthy individuals and individuals with sleep disorders (Bassil, 2020).

Methods

Participants

Participants were three healthy neurotypical individuals (age range: 20–25, two females) recruited from the Georgia Institute of Technology using the SONA psychology recruiting system. Participants were awarded with credits on the SONA system, upon completion of the study.

Sleep tracking and analysis

Participants' sleep quality and amount of sleep were tracked for three nights prior to their fMRI scan. Sleep was tracked using an activity watch, the ActiGraph wGT3X-BT, that tracks sleep by analyzing movement in three axes (x, y, z). The ActiGraph was set to collect raw data at a frequency of 30 Hz with idle sleep mode disabled for three days prior to the participants' fMRI scan. Participants also filled out a sleep and activity diary, being sure to note times when they took the ActiGraph off and the times that they slept and awoke. Just before the fMRI scan, the ActiGraph was removed, and raw data was downloaded and analyzed using Actilife software which utilizes the Cole Kripke sleep scoring algorithm and then the Tudor-Locke algorithm to determine sleep periods ("*Where can I find documentation for the Sadeh and Cole Kripke algorithms?*"). The Cole Kripke algorithm was used over the Sadeh algorithm due to its sensitivity to detecting sleep periods (Quante et. al, 2018) and due to the age of the participants (Cole et al., 1992).

The Cole Kripke algorithm provides several measures of sleep. Total time in bed was the total time participants were detected to be in bed, whereas total sleep time (TST) was the total number of minutes that the participant was detected to be asleep. Wake after sleep onset (WASO) indicates the total number of minutes that the participant was awake after sleep onset.

Number of awakenings is the number of times that the participant woke after sleep onset and average awakenings is the average number of minutes of each awakening. Sleep efficiency (%) was calculated by dividing TST by total time in bed and multiplied by 100 ("*Where can I find documentation for the Sadeh and Cole Kripke algorithms?*"). Sleep efficiency was used as a measure of sleep quality whereas TST was used as a measure of sleep time.

To determine whether the participants received significantly below average, average, or significantly above average TST and sleep efficiency, significance tests were performed. A one-sample one-tailed t-test for significance was performed for each participant comparing average TST of the participant with the average TST of the average young adult. The average TST for young adults used was 382.51 minutes of TST with a standard deviation of 59.80 minutes (Wilckens et al., 2014). Another one-sample one-tailed t-test for significance was performed for each participant comparing average sleep efficiency of the participant with the average sleep efficiency of the average young adult. The average sleep efficiency of the participants aged 20-30 in the study was 88.60% with a standard deviation of 6.180%. The level of significance was at the 0.05 level. Therefore, p-values below 0.05 were indicated as significant with an asterisk.

fMRI data acquisition

Although the scope of this thesis only involves resting state scans, participants completed three different tasks, including the resting scan, during their fMRI scan. Prior to the fMRI scan, participants practiced each of the working memory tasks and the cognitive control task until they understood the tasks to avoid confusion in the fMRI. During the scan, participants performed four main tasks: a resting state scan, flanker task, and two n-back tasks. Each task was repeated twice so that there were eight blocks in total. Each block was approximately six minutes, and the order of blocks was randomized, but randomized so that the same task did not follow the

previous block's task. Participants remained in the fMRI for approximately 90 minutes. During the resting state scan, participants stared at a fixation cross and were instructed to stay as still as possible. For the working memory tasks, participants determined if the current image matched or did not match the image that was shown either right before (0-back) or two before (2-back) the current image. During the flanker task, participants indicated which way the central arrow in a line of arrows was pointing. The experiment was programmed and ran on E-prime 3.0 software and data was collected at the GT/GSU Center for Advanced Brain Imaging by a Siemens 3T scanner.

fMRI data analysis

First, pre-processing of fMRI data was performed using the fMRIprep pipeline using the default settings (*Processing pipeline details*). Pre-processing is important because it removes noise and increases the signal to noise ratio. Time was corrected during pre-processing as there is a time delay of about two seconds when images of the brain are taken by the Siemens 3T MRI scanner. Motion correction was also performed during preprocessing as subjects tend to shift during the scan, although subjects are reminded to stay as still as possible throughout each block. Lastly, the regions of interest (ROI) filter were applied. Global signal was not extracted during preprocessing. At this point, the data was ready for QPP extraction. QPPs were extracted using the algorithm described in Majeed et. al 2011 using Matlab. After QPP extraction, we attempted to determine QPP strength for each participant, but were unable to do so as the fMRIprep pipline crashed each time this was attempted. In an attempt to yield tangible results, QPP strength was instead averaged amongst the three participants. Sleep data for each participant was analyzed separately in a case study manner as the number of participants was less than 20.

Additional analyses

Due to issues with preprocessing, we were unable to use the C-PAC pipeline that we had originally planned to use. The C-PAC pipeline is ideal for this kind of research because it allows us to remove the global signal. Additionally, time constraints did not allow for individual analysis of each participant's QPP as planned. In future studies, we plan to correct these errors and conduct additional QPP analysis for a more complete study.

Results

Participant 1

In Bed	Out Bed	Efficiency (%)	Total Time in Bed (min)	Total Sleep Time (TST) (min)	Wake After Sleep Onset (WASO)	# of Awakenings	Avg Awakening (min)
11/21/2021 1:09 AM	11/21/2021 11:17 AM	95.23	608	579	29	17	1.71
11/22/2021 1:43 AM	11/22/2021 8:28 AM	86.91	405	352	53	14	3.79
11/22/2021 11:12 PM	11/23/2021 9:25 AM	92.82	613	569	44	20	2.20
	Average	**91.65**	**542**	**500**	**42**	**17**	**2.57**
	Standard Deviation	**4.281**	**119**	**128**	**12**	**3.0**	**1.09**

Table 1. Sleep analysis of participant 1. Sleep efficiencies were calculated using the Cole Kripke algorithm described in the methods section.

Participant 1 had three sleep periods in the three nights before the fMRI scan. The average sleep efficiency of participant 1 was 91.65% with a standard deviation of 4.281%. The total sleep time on average was 500 minutes (8.33 hours) with a standard deviation of 119 minutes (1.98 hours).

Participant 2

In Bed	Out Bed	Efficiency (%)	Total Time in Bed (min)	Total Sleep Time (TST) (min)	Wake After Sleep Onset (WASO)	# of Awakenings	Avg Awakening (min)
1/31/2022 10:46 PM	2/1/2022 7:41 AM	89.53	535	479	56	35	1.60
2/2/2022 1:24 AM	2/2/2022 9:04 AM	88.91	460	409	51	22	2.32
2/3/2022 12:29 AM	2/3/2022 6:52 AM	90.34	383	346	37	26	1.42

Average	**89.59**	**459**	**411**	**48**	**28**	**1.73**
Standard Deviation	**0.7171**	**76.0**	**66.5**	**9.8**	**6.7**	**0.476**

Table 2. Sleep analysis of participant 2. Sleep efficiencies were calculated using the Cole Kripke algorithm described in the methods section.

Participant 2 had three sleep periods in the three nights before the fMRI scan. The average sleep efficiency of participant 2 was 89.60% with a standard deviation of 0.7171%. The total sleep time on average was 411 minutes (6.85 hours) with a standard deviation of 66.5 minutes (1.11 hours).

Participant 3

In Bed	Out Bed	Efficiency (%)	Total Time in Bed (min)	Total Sleep Time (TST) (min)	Wake After Sleep Onset (WASO)	# of Awakenings	Avg Awakening (min)
2/2/2022 4:37 AM	2/2/2022 11:18 AM	91.27	401	366	35	14	2.50
2/3/2022 1:06 AM	2/3/2022 11:08 AM	93.36	602	562	40	17	2.35
2/3/2022 6:00 PM	2/3/2022 9:37 PM	82.03	217	178	39	11	3.55
2/4/2022 4:12 AM	2/4/2022 7:34 AM	93.07	202	188	14	11	1.27
	Average	**89.93**	**356**	**324**	**32**	**13**	**2.42**
	Standard Deviation	**5.349**	**188**	**181**	**12**	**2.9**	**0.933**

Table 3. Sleep analysis of participant 3. Sleep efficiencies were calculated using the Cole Kripke algorithm described in the methods section.

Participant 3 had four sleep periods in the three nights before the fMRI scan. The average sleep efficiency of participant 3 was 89.93% with a standard deviation of 5.349%. The total sleep time on average was 324 minutes (5.40 hours) with a standard deviation of 181 minutes (3.02 hours).

Significance tests: sleep

Participant	t-score	p-value
1	-0.965	0.1694
2	3.702	0.0002*
3	-7.58	0*

Table 4. Calculated t-scores and p-values based on three one-sample one-tailed t-tests conducted for each participant based on TST in comparison to values from Wilckens (2014). p-values below 0.05 were indicated as significant with an asterisk.

In comparison to average TST of adolescents (Wilckens et al., 2014), participant 1 had a t-score of approximately -0.965 and a p-value of 0.1694. Participant 2 had a t-value and p-vale of 3.702 and 0.0002 respectively. Participant 3 had a t-value of -7.58 and a p-value of 0.

Participant	t-score	p-value
1	3.789	0.0002*
2	1.228	0.1122
3	1.651	0.0521

Table 5. Calculated t-scores and p-values based on three one-sample one-tailed t-tests conducted for each participant based on sleep efficiency in comparison to values from Wilckens (2014). p-values below 0.05 were indicated as significant with an asterisk.

In comparison to average sleep efficiency of adolescents (Wilckens et al., 2014), participant 1 had a t-score of 3.789 and a p-value of 0.0002. Participant 2 had a t-score of 1.228 and a p-value of 0.1122. Lastly, participant 3 had a t-score of 1.651 and a p-value of 0.0521.

QPP Results

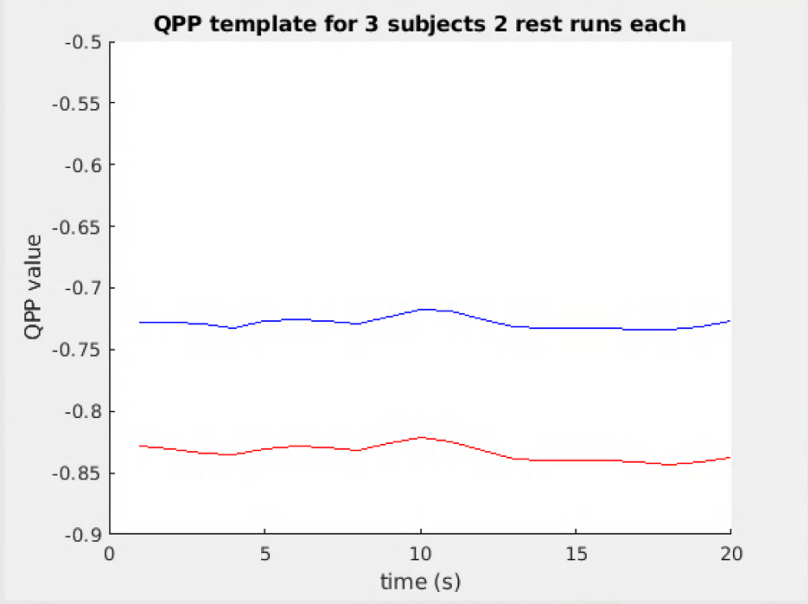

Figure 1. Averaged QPP template for three subjects with two rest runs each. The DMN is in blue, while the TPN is in red.

The QPP value for both the DMN and TPN are relatively flat throughout the time course for the QPP template. The QPP value for the TPN was less than the QPP value for the DMN throughout the length of the QPP template.

Discussion

In a comprehensive study using actigraphy, fifty-nine young adults between the ages of 20 and 30 received an average 382.51 minutes of TST with a standard deviation of 59.80 minutes over the course of one week (Wilckens et al., 2014). This study was the comparison point for our participants' TSTs and sleep efficiency scores. Participant 1 had an average TST of 375 minutes, which was slightly below the average for young adults, but not significantly lower ($t = -0.965$, $p = 0.1694$). Participant 2 had an average TST of 411 minutes which was significantly greater than the average TST for young adults ($t = 3.702$, $p = 0.0002$*). Therefore, on average, participant 2 slept for significantly more time than the average young adult. Participant 3 had an average TST of 324 minutes, which was significantly lower than the average TST for young adults ($t = -7.580$, $p = 0$*). Lastly, participant 3 slept for significantly less time than the average young adult.

The average sleep efficiency of the participants aged 20-30 in the Wilckens 2014 study was 88.60% with a standard deviation of 6.180%. All participants had efficiencies close to this average with respective efficiencies of 91.65%, 89.59%, and 89.93%. All sleep efficiencies were close to 90%, meaning that ninety percent of the time that participants remained in bed they were asleep as calculated by the Cole Kripke algorithm. In comparison to the average sleep efficiency of the Wilckens study, participant 1 had a significantly above average sleep efficiency ($t = 3.789$, $p = 0.0002$*). Participants 2 and 3 did not have significantly above average sleep efficiencies ($t = 1.228$, $p = 0.1122$; $t = 1.651$, $p = 0.0521$).

The resulting QPP template seen in Figure 1 is abnormal and unexpected. Although the QPP template for all three subjects was averaged, giving more timepoints, the normal anti-correlation pattern for QPP was not observed. We expected to see alternating levels of QPP values in the DMN and TPN where DMN QPP values were greater than the TPN values around

5 seconds and the TPN QPP values were greater than the DMN values later in the time course, around 15 seconds. QPPs are more robust with more timepoints; however, our resulting template may point to a greater issue with our preprocessing procedure. Nevertheless, follow up analyses are needed to identify the source of this resulting abnormal QPP. It is possible to identify typical QPPs at the individual level according to other studies (Yousefi et al., 2018), so it may be that these QPPs are a result of an issue with the pattern finding algorithm. Additionally, other studies have shown that QPPs are still present even when the global signal is removed (Chai et al., 2012; Fox et al., 2009). Alternatively, if these abnormal QPPs are an accurate reflection of these subjects' QPPs, it may suggest something unique about this group of subjects. However, given the small sample size of this study, it is premature to speculate on the cause of these errors.

Conclusions

The aim of this study was to establish a relationship between sleep time and quality and QPP strength. Although I have failed in my attempt to establish a relationship between these variables, I have collected data for many more participants, which with time and further appropriate analysis, could provide insight into this relationship. This relationship between sleep and QPP strength is suggested by Bassil 2020. In this study, participants either took a nap prior to their scan or did not take a nap prior. QPP strength of healthy individuals increased when taking a nap prior to their scan, suggesting that perhaps an increase in sleep time prior to a scan may increase QPP strength.

Limitations

The small sample size is a large limitation of this study. We were unable to draw many meaningful conclusions as sample size was not large enough. Additionally, we were required to analyze sleep data in a case study manner and were unable to produce individual QPP strengths, which makes it difficult to be able to generalize results to the population.

Additionally, we were not able to use a pipeline that would extract the global signal in this preliminary study. Therefore, it is likely that the QPP anti-correlation may be stronger than it appears. However, extraction of the global signal is a widely contested issue in fMRI research as it can make some signals appear stronger than they are. In the case of QPPs, there is research supporting the idea that QPPs are not an artifact resulting from the removal of the global signal during preprocessing (Chai et al., 2012). In future iterations of this study, we plan to use a pipeline that will extract the global signal, like C-PAC, to strengthen our QPP anti-correlation.

The current study is an MRI study, which means that the results are solely correlational and not causational. We cannot determine that average amount of sleep or quality causes a

change in QPP strength or frequency, we can only observe the observation and postulate that this is likely. There could be other factors in determining QPP strength and frequency, but we cannot control for them in a correlational study.

Although actigraphy watches are widely used in sleep research, their accuracy is often criticized as time in bed and out of bed does not always match the time that participants indicate that they get in and out of bed. These watches only use movement to detect sleep and wake periods, which are not as accurate as other types of actigraphy watches that consider heart rate and breathing rate. We also saw inaccuracies in our study using the actigraphy watches but attempted to correct for this by using the sleep diaries filled out by participants to correct time in and out of bed.

Further research

With a larger sample size ($n \geq 20$), we would be able to compare results between participants and draw a stronger correlational conclusion. In the future, more participants will be recruited to participate in this study.

Since many studies, including this one, have been conducted on QPPs during resting state, further research should be conducted on QPPs while participants are completing tasks. Some studies have indicated that there are changes in the QPP when an individual is performing a task rather than in a resting state (Abbas et al., 2018). Little is known about the relationship between QPPs and cognition, although QPPs do appear to be related to changes in attention (Abbas et al., 2019). This revelation leads us to question whether the differences observed in the QPP of task-performing individuals as opposed to resting-state individuals is due to arousal, which is closely tied to attention, or to task-related cognitive processing. In future studies, I would recommend that participants perform tasks while arousal is monitored using eye tracking

during the completion of tasks. Either way, further research should be conducted to determine the relationship between QPPs and cognition.

Implications

If the results of the Bassil 2020 study are supported by further analysis of the data from this preliminary study, this could suggest that naps or more sleep could alleviate excessive daytime sleepiness conditions. Moreover, behavioral therapy or medication could be developed to help patients with excessive daytime sleepiness symptoms get more sleep at night or take naps throughout the day without interfering with their daily activities.

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