Quasi-Periodic Patterns of Resting-State Brain Activity in Individuals with Idiopathic Hypersomnia and Narcolepsy

by

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A Thesis

Submitted to the Georgia Tech Research Option

Georgia Institute of Technology

In Partial Fulfilment of the Requirement

For the Research Option

April 2020

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ACKNOWLEDGEMENTS

I would like to thank my faculty mentor, Dr. Shella Keilholz, for being a continuous source of support and encouragement throughout my undergraduate career. From my thesis research, to the coordination of neuroscience hackathons, to conferences on science communication, she has been an inspiring and dedicated mentor throughout my undergraduate research experience.

I am also incredibly thankful for the whole Keilholz Lab for fostering a collaborative, welcoming, and inclusive research environment. I would not have been able to accomplish any of my research projects without their constant dedication to helping others learn and succeed.

Thank you to Dr. Eric Schumacher, who was on my reading committee and was a source of support and feedback for this project as well.

Additionally, I would like to thank Dr. Lynn-Marie Trotti for providing the opportunity and funding to conduct this collaborative research.

Lastly, I would like to thank every ambassador that is a part of the Undergraduate Research Ambassadors for showing me that research is much more than an individual project; research is collaborative, interdisciplinary, communicative, inclusive, and something that has grown to be one of my biggest passions.

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ABSTRACT

The brain's overall organization of its networks is often studied through its functional connectivity, defined as the spatiotemporal dependency of neuronal activity in anatomically separated regions. Altered functional connectivity in cortical networks, such as the default mode and task positive networks, is often associated with neurological disorders and can be studied and measured through resting-state functional MRI (rs-fMRI). This study compares dynamic changes in functional connectivity between individuals with idiopathic hypersomnia, narcolepsy, and typically functioning controls. This comparison is conducted through the investigation of the quasi-periodic pattern (QPP), a low-frequency spatiotemporal pattern in the brain linked to infra-slow activity. This study showed that this spatiotemporal pattern of focus, the QPP, differed in strength, frequency, and spatial distribution between the three subject groups. These findings represent preliminary differences that can be expanded upon through further analyses, including additional functional connectivity analyses, QPP regression, and statistical testing. It can be concluded that quasi-periodic patterns provide insight into the mechanisms behind spatiotemporal pattern differences seen in individuals with sleep disorders. Further analysis of these patterns could help expand current knowledge of connectivity differences in individuals with neurological disorders, as well as allow for development of effective diagnoses.

INTRODUCTION

Idiopathic hypersomnia (IH) is a hypersomnolence disorder of the central nervous system that presents itself through excessive daytime sleepiness (EDS). EDS is diagnosed when affected individuals experience substantial fatigue and episodes of an irrepressible need to sleep, even with more than seven hours of sleep at night (Sateia, 2014). Specifically, symptoms of idiopathic hypersomnia include long unrefreshing naps, prolonged night-time sleep, and awakening with sleep drunkenness (Billiard et al., 2001). As idiopathic hypersomnia is a relatively newer condition with an unknown cause, its features are ill-defined and often overlap with other sleep disorders. In these cases, IH is most often compared to narcolepsy. However, a significant difference between these conditions is that narcolepsy specifies that diagnosed individuals most likely have premature onset of rapid eye movement (REM) sleep and cataplexy (an uncontrollable muscle weakness or paralysis) (Aldrich, 1992). By definition, premature onset of REM sleep and cataplexy are *not* prevalent in individuals with idiopathic hypersomnia. To observe the lack of these symptoms in IH, abnormal REM sleep is observed through an electroencephalogram (EEG) test by analyzing waveform features of the EEG signal, and cataplexy is usually seen through the individual's mobility capabilities.

Since idiopathic hypersomnia was added to the International Classification of Diseases (ICD-10), its diagnosis code, symptoms, and biomolecular mechanisms have been discovered and properly defined. Prior studies have shown that IH has distinctly different neurochemistry and behavioral correlates than narcolepsy, which manifest through decreased hypocretin-1 levels. (Mignot et al., 2002; Kanbayashi et al., 2002; Dauviliers et al., 2003). In addition, IH is correlated with significantly higher activity of GABA-ergic receptors in cerebrospinal fluid than control individuals (Trotti, 2017), which is not seen in patients with narcolepsy.

Since these two disorders are neurobiologically distinct, a distinction in neural connectivity and functional brain networks is predicted to be seen as well. Neural connectivity can be studied through observing anatomical connectivity, which is the way neurons are structured and connected, or through functional connectivity, which is defined as the correlative relationship between spatially separated regions. Previous research has shown that neural connectivity differences between individuals with idiopathic hypersomnia and control subjects are mostly due to altered functional connectivity, instead of due to structural differences or anatomical abnormalities (Trotti & Bliwise, 2017). This indicates that connectivity abnormalities in individuals with idiopathic hypersomnia are largely focused in functional connectivity differences, which have not been previously explained through literature. Therefore, the whole-brain connectivity mechanism for idiopathic hypersomnia is largely unknown.

Neuroimaging, specifically functional MRI (fMRI), can serve as a useful tool to observe these functional connectivity differences and their contribution to overall neural connectivity and healthy brain function. fMRI measures connectivity in the brain through the blood-oxygen-level-dependent (BOLD) signal, which is a correlate of underlying neural activity (Biswal et al., 1995). Therefore, the fMRI BOLD signal can be used to analyze spatiotemporal patterns relevant to the neural connectivity of idiopathic hypersomnia.

This study focuses on the quasi-periodic pattern (QPP), a reliably observable low-frequency pattern in the brain that captures the strong anti-correlation between the default mode network (DMN) and the task-positive network (TPN). (Majeed et al., 2009; Majeed et al., 2011; Thompson et al., 2014; Belloy et al., 2018; Yousefi et al., 2018; Abbas et al., 2018). The QPP represents an aspect of typical cognitive functioning, which can often be affected by sleep abnormalities. Specifically, increasing daytime sleepiness was shown to be correlated with

reduced DMN connectivity (Ward et al., 2013). In addition, sleep deprivation affects intrinsic functional connectivity, exemplified through reduced DMN connectivity, as well as a reduced anticorrelation between the DMN and its anti-correlated network, the TPN.

To further observe fundamental connectivity differences seen in idiopathic hypersomnia, this study examines how IH affects spatiotemporal patterns in the DMN and TPN, specifically through the contribution of the QPP to functional connectivity using resting-state functional MRI. Examining how QPPs contribute to functional connectivity differences in IH would further the understanding of dynamic neural processes involved in the etiology of idiopathic hypersomnia, as well as clarify the connectivity distinctions between IH and narcolepsy. In this study, comparisons are made between three groups: individuals with idiopathic hypersomnia, individuals with narcolepsy, and typically-functioning controls. Scans were acquired from the Emory Brain Health Center's Sleep Center, collecting 9 scans from controls, 14 scans from subjects with idiopathic hypersomnia, and 9 scans from subjects with narcolepsy. To analyze the fMRI scans, we applied a pattern-finding algorithm to search for the QPPs in each group, then differentiated between the spatiotemporal patterns that were observed. Afterwards, we compared the average QPPs from each group in analyzing their strength, frequency, and spatial distributions.

We predict that the analysis will show differences in the QPP between healthy controls and those with sleep disorders, as well as differences between individuals with idiopathic hypersomnia and individuals with narcolepsy. This study was set to be completed by the spring of 2020, however unusual circumstances have left some additional analyses and statistical tests to be incomplete.

METHODS

Data acquisition

Resting-state fMRI scans were acquired from the Emory Brain Health Center, using a SIEMENS PRISMA 3T scanner. Scans were collected from 9 typically-functioning healthy controls, 14 individuals with idiopathic hypersomnia, and 9 individuals with narcolepsy. Images were taken from the scanner in an interleaved manner and slices had a cortical thickness of 7mm. All subjects participated in two scanning sessions, one day including a nap before the scan and one day not including any naps any all. Therefore, there are two sets of anatomical and functional scans for each subject, reflecting the nap and no-nap days. These naps lasted for 30 minutes and took place right before the scanning of the subjects. All participants had been removed from any psycho-stimulant medication for at least 48 hours prior to the scanning session. For individuals that had more than one functional scan, only the first functional scan was used in the study to create uniformity in subject data. In addition, subjects that did not have both the nap and no-nap day scans were omitted from the study for the sake of experimental consistency. In the end, the healthy control (HC) group contained 9 neurotypical individuals (age range #–#, $\mu = \# \pm \#$; M = # , F = #), the idiopathic hypersomnia (IH) group contained 14 individuals with idiopathic hypersomnia (age range #–#, $\mu = \# \pm \#$; M = # , F = #), and the narcolepsy (NC) group contained 9 individuals with narcolepsy (age range #–#, $\mu = \# \pm \#$; M = # , F = #).

Preprocessing

The preprocessing pipeline used in this study was The Configurable Pipeline for the Analysis of Connectomes (C-PAC), a configurable, open-source, Nipype-based, automated preprocessing pipeline for resting-state fMRI data (Craddock et al., 2013). C-PAC uses certain image preprocessing tools to run its automated pipeline, including FMRIB Software Library (FSL) version 5.0 (Woolrich et al. 2009, Smith et al., 2004, Graham et al., 2016) and the Analysis of Functional NeuroImages (AFNI) software (Cox, R. W., 1996).

The following steps refer to preprocessing conducted through the configurable C-PAC pipeline. Preprocessing on anatomical scans, also referred to as T1 images, was conducted first. Anatomical preprocessing included N4 bias field correction (using AFNI's ANTS), a method to correct for non-uniformity in low-frequency intensity in MRI data. Anatomical scans were also skull-stripped to delineate the boundary between the skull and the brain (using AFNI's 3dSkullStrip). Anatomical scans were then registered to the 2mm Montreal Neurological Institute (MNI) brain atlas, through both a linear registration (using FSL's FLIRT) and non-linear registration (using FSL's FNIRT). Anatomical registration is conducted to register the brain image to a standard space, allowing for inter-subject comparisons and generalization of results to the group.

Functional scans, also referred to as EPI sequences, also went through a number of preprocessing steps. First, slice time correction was conducted on the functional scans using the pipeline's default tool. Slice time correction accounts for the scanner collected adjacent parts of the brain at different time points within a certain repetition time (TR) and is essential to preprocessing functional data. The standard pipeline then proceeds to complete distortion correction (using FSL's BET), functional masking (using AFNI's 3dAutoMask), motion

correction (using AFNI's 3dvolreg), and nuisance signal regression using the default pipeline methods. The pipeline also offers the option of extracting the average timeseries of certain ROIs using a user-determined ROI mask. For this study, we used the Brainnetome atlas to acquire average ROI timecourses for 246 cortical regions (Fan et al., 2016). Temporal filtering was conducted with a bandpass temporal filter between 0.01Hz and 0.1Hz and global signal regression was completed using the pipeline's PyPEER tool. Global signal regression effectively removes artifacts driven by motion and respiration, also discarding globally distributed neural information that is often regarded as noise.

All parameters for these preprocessing tools were set to their default settings and the rest of anatomical and functional preprocessing followed the standard C-PAC pipeline.

Acquisition of QPPs

A pre-established spatiotemporal finding algorithm, described in Majeed et al., 2011, was applied to the functional timeseries for each group to search for repeating patterns. The algorithm was run on each of the group functional timeseries 60 times with randomly generated starting timepoints. This algorithm creates two outputs: a representative QPP template for the group and a correlation vector for when that QPP most strongly occurred through the scan. The group's representative QPP template was acquired by choosing the trial with the maximum correlation to the average QPP. The correlation timecourse was then created by correlating that representative QPP to each timepoint of the functional scan, outputting a correlation vector.

The strength and frequency of the acquired QPPs were then compared between the groups through analysis of the QPP correlation vector. The QPP correlation vector local maxima

were considered peaks if they have a maximum value larger than the arbitrary threshold value of 0.2 (Figure 1). QPP strength for a certain group was defined as the average height of the peaks in the correlation vector for the duration of one iteration of the QPP. Additionally, QPP frequency for a certain group was defined by the number of peaks during one iteration of the QPP. Frequency was measured in peaks per second, with peaks defined as any local maxima with a correlation greater than 0.2. These QPP measures have been similarly defined through previous literature (Abbas et al., 2019). Additionally, histograms of the correlation vector itself were created for the three groups and compared. Finally, the spatial aspects of the QPP were compared between groups through a visual comparison of the 2D arrays of the patterns. This 2D array displayed the QPP through seven functional networks of interest: visual, somato-motor, dorsal attention, ventral attention, limbic, fronto-parietal, and default mode network.

Additional analyses

There were a few additional analyses that would have been conducted for this study; however, unusual circumstances in the spring 2020 semester did not allow for these analyses and statistical testing to be completed. These circumstances mostly included the project's time constraints and issues with image preprocessing. Further analyses would have included acquiring timecourses of the default mode network (DMN) and task-positive network (TPN), analyzing functional connectivity across all ROIs before and after QPP regression, and conducting statistical tests on group differences.

DMN and TPN timecourses would have been acquired across the healthy control (HC), idiopathic hypersomnia (IH), and narcolepsy (NC) groups using a data-driven approach. For each group, the average BOLD signal would be calculated from each functional timeseries, measuring

the mean timecourse of the signal in the posterior cingulate cortex (PCC), a region heavily involved in the DMN. The PCC timecourse would then be correlated with every voxel in the brain using a Pearson correlation. To acquire these individual voxels, the Brainnetome atlas would be used to segment the brain into distinct regions of interest (ROIs) (Fan et al., 2016). The 10% most correlated voxels with the PCC would be labeled as the DMN, and the 10% most anti-correlated voxels with the PCC would be labeled as the TPN (Fox et al., 2005). This process would allow us to then establish distinct cortical locations, or regions of interest (ROIs), for each network to be able to look at total DMN and TPN signal over time.

Additionally, functional connectivity analyses would have been conducted for each of the groups, before and after QPP regression. This analysis would have used the Brainnetome atlas as the template for the functional connectivity matrices, creating connectivity matrices before and after QPP regression from the neural signal. We would have then compared these connectivity matrices to analyze the effect of regression on the overall neural connectivity of distinct ROIs. Multiple comparisons correction would be performed using the false detection rate method used in Benjamini and Hochberg (1995).

RESULTS

Comparing QPP Correlative Strength

For the "No Nap" scanning day, the HC QPP (strength $\mu = 0.248 \pm 0.049$) had significantly less correlative strength than both the IH QPP (strength $\mu = 0.308 \pm 0.016$) and the NC QPP (strength $\mu = 0.320$) (Table 1).

For the "Nap" scanning day, the HC QPP's strength (strength $\mu = 0.281 \pm 0.014$) was similar to the IH QPP (strength $\mu = 0.284 \pm 0.067$); however, both the HC QPP and the IH QPP both had significantly less strength than the NC QPP (strength $\mu = 0.405 \pm 0.061$) (Table 1).

For within-group comparisons, none of the groups showed significant change in the QPP's correlative strength in comparing the group's "no nap" sessions with their "nap" sessions (Table 1).

Comparing QPP Frequencies

For the "No Nap" scanning day, frequencies were calculated for the HC QPP (frequency $\nu = 0.074$), the IH QPP (frequency $\nu = 0.024$) and the NC QPP (frequency $\nu = 0.019$) (Table 1).

For the "Nap" scanning day, frequencies were calculated for the HC QPP (frequency $\nu = 0.037$), the IH QPP (frequency $\nu = 0.048$), and the NC QPP (frequency $\nu = 0.037$) (Table 1).

A paired *t*-test was run on the "nap" and "no nap" groups, and there were no statistically significant differences in any group between frequencies calculated from the "nap" session and the frequencies calculated in the "no nap" session.

QPP STRENGTHS & FREQUENCIES // NAP & NO NAP GROUPS

QPP STRENGTH	NO NAP SESSION	NAP SESSION
Healthy controls (HC)	0.248 ± 0.049	0.281 ± 0.014
Idiopathic hypersomnia (IH)	0.308 ± 0.016	0.284 ± 0.067
Narcolepsy (NC)	0.320 *	0.405 ± 0.061
QPP FREQUENCY	NO NAP SESSION	NAP SESSION
Healthy controls (HC)	0.074	0.037
Idiopathic hypersomnia (IH)	0.024	0.048
Narcolepsy (NC)	0.019	0.037

Table 1. QPP strengths and frequencies from the QPP correlation timecourses of each group. Shown are the strengths and frequencies of the QPP over time in each group. There is a significant difference in correlative strengths between the "Nap" and "No Nap" scanning sessions. There were no significant differences in frequencies between the groups or the sessions. A star symbol in the table (*) indicates that there was only one data point, which means that standard deviation could not be calculated.

Comparing QPP Correlation Timecourses

The QPP correlation timecourses themselves also showed slight differences between groups, illustrated through vectors of the QPP correlation timecourses (Figure 1) as well as histograms of those timecourses (Figure 2).

Visually, the only major difference seen through the QPP correlation timecourse vectors was the absence of QPP correlation in the narcolepsy (NC) group after the "nap" session (Figure 1).

Other group comparisons were completed through visual comparison of the QPP correlation timecourse historgrams (Figure 2). These histograms show a significant increase in QPP correlative strength for the idiopathic hypersomnia (IH) group, with QPP correlative strength throughout the scan being higher than both the HC and NC groups (Figure 2).

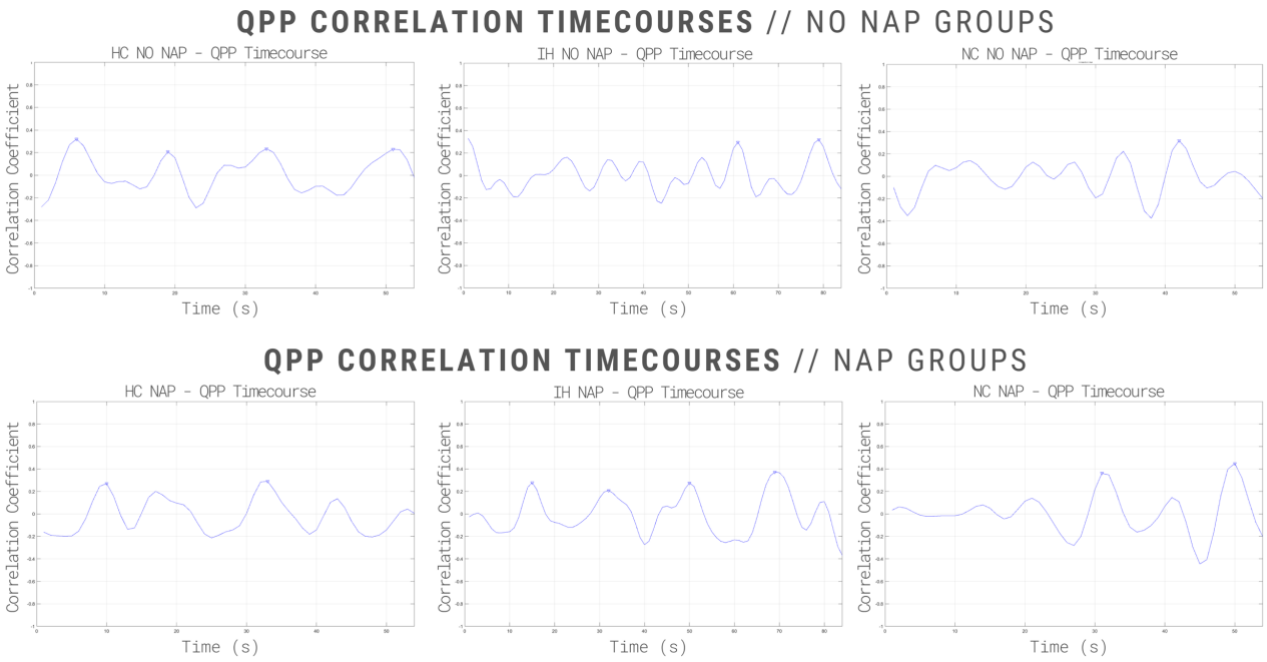

Figure 1. QPP correlation timecourses in the "Nap" and "No Nap" scanning sessions. Shown are the correlation timecourses over time throughout the course of the representative QPP for each group. Arrows are drawn on the peaks that passed the threshold of 0.2.

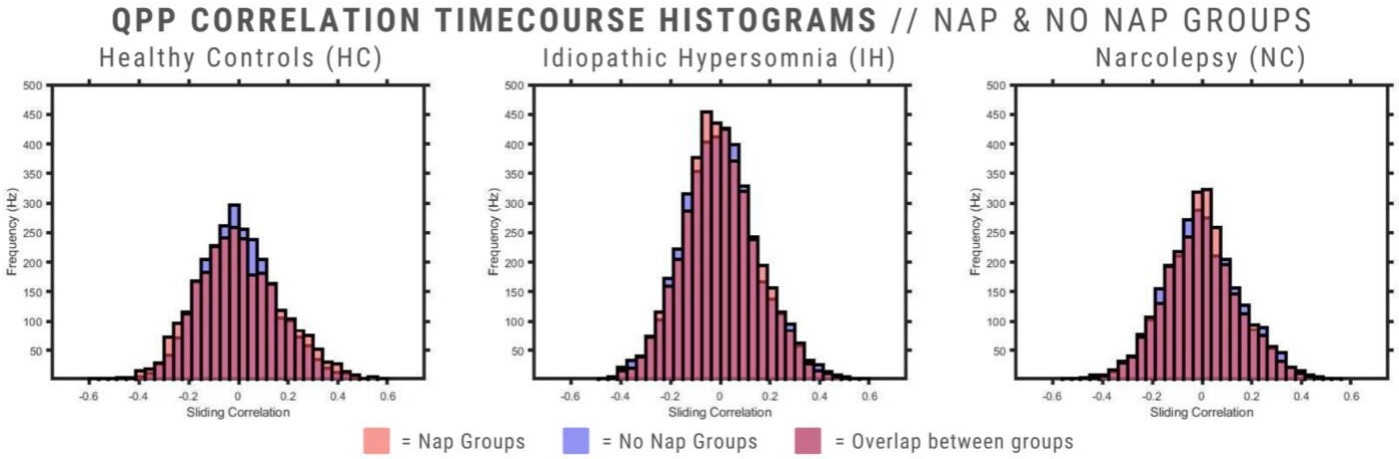

Figure 2. QPP correlation timecourse histograms. Shown are the histograms of the correlation timecourse values for the representative QPP for each group. A visual comparison of these graphs indicates that there is an increase in QPP correlation in the idiopathic hypersomnia (IH) group.

Comparing QPP Spatial Distribution

There were a few key differences that we speculated from visual comparisons of the 2D QPP arrays, including differences between the "nap" and "no nap" session for the IH group, as well as visual abnormalities in the NC group (Figure 3).

When comparing the "nap" and "no nap" sessions from individuals with idiopathic hypersomnia, the QPP correlation for certain regions are reversed (Figure 3). During the "no nap" sessions, individuals with idiopathic hypersomnia have high to low QPP correlations in the somato-motor, dorsal attention, and limbic areas over the course of the pattern, but low to high QPP correlations in the default mode and visual areas. However, this is reversed for the "nap" sessions, with these individuals showing the reverse effect on QPP correlation in those same areas.

Additionally, a visual comparison of these QPP arrays reveals differences between the healthy controls and the individuals with narcolepsy (Figure 3). The QPP correlations in the seven networks of interest have an irregular pattern, both in the “nap” and “no nap” sessions.

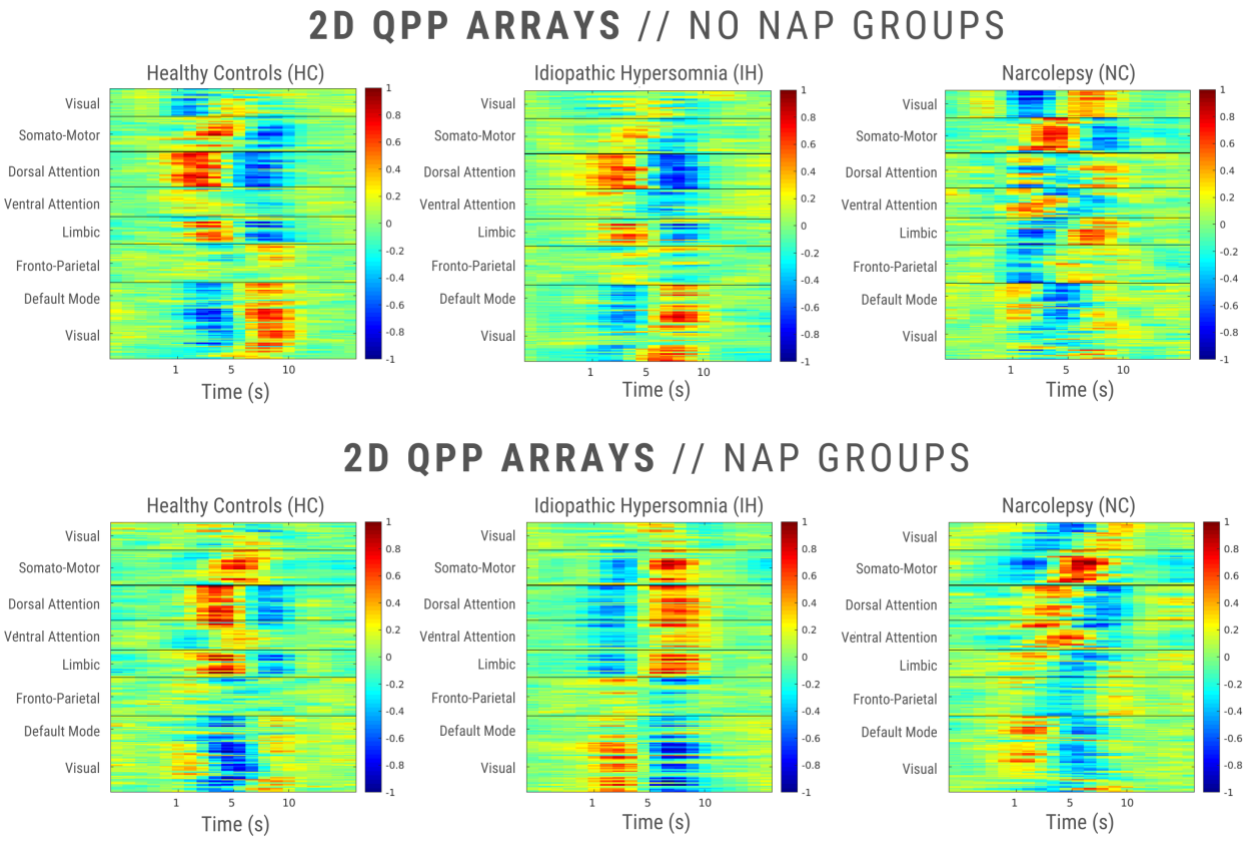

Figure 3. 2D QPP spatial arrays of correlative values. Shown are the 2D QPP spatial arrays of the correlative values for the representative QPP of each group. Redder colors indicate a more positive correlation value, and bluer colors indicate a more negative correlation values. QPP correlation measures are split between seven distinct neural networks: visual, somato-motor, dorsal attention, ventral attention, limbic, fronto-parietal, and default mode network.

DISCUSSION

This study focused on the dynamics of BOLD fluctuations through the quasi-periodic pattern (QPP) to identify core differences in functional connectivity and spatiotemporal patterns between idiopathic hypersomnia and narcolepsy, as well as compare these two sleep conditions to typically-functioning controls. Prior studies have illustrated the prevalence and importance of QPPs for healthy brain function and in certain psychological disorders; however, until now, there has not been an investigation of QPPs in the context of atypical sleep patterns and conditions. We hypothesized a relationship between atypical QPPs in the groups with sleep disorders, compared to healthy controls. Specifically, we also hypothesized a difference in the QPP's prevalence and spatial contributions between idiopathic hypersomnia and narcolepsy, due to the already existing neurobiological and chemical differences in the two sleep disorders.

Through the speculated results, there has been some differences between individuals with sleeping disorders and healthy controls. However, there have also been apparent differences in how spatiotemporal patterns contribute differently to idiopathic hypersomnia and to narcolepsy, especially through the 2D QPP arrays and histograms of the QPP correlation timecourses. If these differences were further analyzed through additional statistical testing and functional connectivity analyses, they might lead to more robust differences between these two disorders in their neural connectivity and etiology.

Though this study was not able to be completed, it provides the infrastructure for the next steps in analyzing quasi-periodic patterns in individuals with sleep disorders. Due to additional unforeseen time constraints, additional processing analyses on the collected data were not able to be completed and the outcomes of the study are consequently inconclusive. Therefore,

deductions related to the differences in idiopathic hypersomnia and narcolepsy are isolated to analyzing the strength, frequency, and spatial contribution of the QPP.

Future implications

Since idiopathic hypersomnia is a relatively new sleep condition, the results from this study heavily weigh in on the explanation of distinct differences in whole-brain spatiotemporal patterns that define the disorder as unique from other sleep conditions. This preliminary work sets the backbone for further analyses on functional connectivity and quasi-periodic patterns in individuals with sleep disorders.

Therefore, if this study had been carried to completion, it could contribute to diagnoses efforts for IH, as well as create the distinction between idiopathic hypersomnia and narcolepsy. This would help in avoid unnecessary pharmaceutical prescriptions, in addition to lowering rates of misdiagnosis. Future studies could further this research by analyzing additional regions of interest, regressing different spatiotemporal patterns, or conducting more analyses on the QPP pattern itself.

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