Broad Effects of Arousal on Quasi-Periodic Patterns of Brain Activity

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Abstract

Quasi Periodic Patterns (QPPs) are recurring patterns of brain activity found in brain imaging data that last approximately 20 seconds and occur at no regular interval. In this experiment, researchers aim to establish a link between the level of mental arousal and the strength and frequency of QPPs. It was thought that increased levels of arousal would result in an increase in the strength and frequency of QPPs. To test this, subjects from three different contrasting experimental groups conducted tasks while in a functional magnetic resonance imaging (fMRI) scanner: (1) young subjects vs. old subjects, (2) task-engaged vs. resting-state, and (3) sleep disorder vs. no disorder. QPPs were regressed from the fMRI scans using an extensive processing and analysis pipeline. It was generally found that increased arousal levels led to an increase in the incidence and strength of QPPs. Increased arousal is present in young subjects, task-engaged subjects, and subjects without sleeping disorders. These results open the door for future experiments to quantify the link between arousal and QPPs. Establishing a link between these two can be vital to future research involving therapeutic devices, diagnostic tools, and even human-computer interfaces.

Introduction

Everyday there is a bombardment of information to our senses that we selectively attend to so that we can determine the most important information. We are often required to switch between different types of tasks as we go throughout the day. For example, at work we may need to remember the names of our coworkers, which would utilize long term memory. On the other hand, we may need to quickly switch to understanding the requests and wants of a customer at

work, which would involve working memory. These switches between tasks manifest themselves as actual switches of activity between different regions of interest in the brain. Since arousal affects how we attend to immediate stimuli, it is reasonable to think that different levels of arousal would affect the strength and frequency of these switches in the brain, which can be seen in fluctuations of classic measures of brain activity.

Throughout a day we are subject to many different levels of arousal. We may be exceptionally slow and tired right after we wake up and it may take some time to reach a higher level of arousal. On the other hand, in the early afternoon we may be at our most alert and best prepared to respond to stimuli. On top of the known effects of consciousness on arousal, brain matter is known to decrease with age (Morrison 1997), so it is reasonable to assume that age affects arousal, and therefore the power of task switches. When a switching of tasks occurs, the brain switches activity from the Default Mode Network (DMN), a network known to be active when the subject is at rest and not engaged with the external environment, to the Task Positive Network (TPN) (Abbas 2018), a network known to be active when the subject is aroused and actively engaged in some task. The neural circuitry underlying this task-switching control mechanism was unknown until recent research revealed the dynamics behind it (Majeed 2009).

In 2009, Majeed used an anesthetized rat model to show the spatiotemporal dynamics that underlie task switches. The researchers found that there was a specific recurring pattern of brain activity that occurred along with the task switch seen in the blood oxygen level dependent (BOLD) signal, a classic measure of neural activation. The patterns in activation occurred in both the normal awake rats and the anesthetized rats. The pattern was not consistently detectable and occurred at inconsistent intervals. This led them to name these patterns Quasi Periodic Patterns (QPP) because of their lack of a consistent period. The introduction of QPPs was a big step

because it challenged researchers to understand the reason that these patterns occurred. These patterns were very similar to other functional networks within the rat, leading researchers to believe that QPPs must be connected to some known neural processes. In 2011, Majeed continued their research and expanded their findings to humans. The same protocol and pattern finding algorithm that was used on the mice was adapted to humans to prove that QPPs exist in humans as well. While this data was useful in confirming the existence of QPPs in humans, it did not look any further or distinguish the differences between QPPs in resting state or task-engaged individuals.

To build on Majeed's research and QPP discovery, researchers investigated the differences in QPPs between resting state and task performing subjects (Abbas 2018). Abbas and researchers used a 20-second window to look for QPPs, as it was experimentally found that QPPs last approximately 20 seconds (Abbas 2018). They found that the QPPs occurred with both greater strength and frequency in the task performing scans compared to the resting state scans. This was a substantial finding because it firmly linked task engagement with QPP modulation. These findings opened the door for other QPP experiments to more generally test what else may modulate these patterns. While these findings were important, there were still some more issues to address in regards to experimental design.

The study by Abbas et al. in 2018 used both short and long term memory paradigms to engage the subject in a task but failed to distinguish between the two in terms of their QPPs. Researchers used both a 0-back and 2-back task to create a different setting than the resting state scan. A 0-back task is a basic task designed to utilize the subject's long term memory. The subject is presented with a target image before a block of stimuli and must indicate whenever the target image appears during the experimental block. A 2-back task is a task that is slightly more

complicated task that is designed to utilize the subject's working memory. Instead of a target image, the subject is supposed to indicate whether the current image is a match to the image that was presented two stimuli ago. This requires the subject to continuously update the image to match in their working memory. It is necessary to elaborate on this research to see whether or not QPPs are affected by the presence or type of memory task, or arousal in general.

This work aims to study the effects of varying states of arousal on the strength and frequency of QPPs of brain activity. There will be three ways that arousal is modified: through varying working and short term memory tasks, through sleep status, and through age. The memory tasks will consist of a 0-back task, a 2-back task, and a flanker task. The flanker task relies less on memory than the 0-back and 2-back tasks but requires the subject to indicate the direction the middle arrow in a set of five arrows is pointing. These tasks are different enough in nature that they may elicit different patterns from one another. The sleep status will be changed according to whether or not the subject takes a 2-hour nap immediately preceding the scan. All subjects participated in two separate scans, one after no nap has taken place, and another on a separate day immediately following a nap in a controlled setting. The age factor split the subjects into two population groups: young and old. The young group consists of college-age students around the age of 21, whereas the old group consists people over the age of 60. It is hypothesized that the QPPs will occur with greater strength and frequency in the conditions that represent elevated arousal.

The conditions that would theoretically represent elevated arousal would occur in the working memory task in the first group because of the increased demands of working memory on attention. The no-nap group in the second group would have higher arousal because of the known effects of immediately exiting sleep on arousal. The young group in the third group

would have higher arousal because of the effects of aging on cognition and general arousal. These three groups can be used to more broadly describe the link between arousal and spatiotemporal patterns of brain activity. If a link between arousal and QPPs can be established, then QPPs can be used to detect changes in arousal or neural function before one is even aware of these changes.

QPPs and their effects on cognition have potential to be a useful tool to the world outside of the cognitive neuroscience community. How we think about and process information is important because it can be used to design better products, software, and therapeutics. The goal of these devices should be to integrate information taken from QPPs and the subject to make everything not only more efficient but also more user friendly. Theoretically, if we could sync up the patterns of brain activation with patterns of stimuli from devices then we could expand this design to other areas of life, so everything is in sync with us. The information from QPPs can be vital to future human-computer interfaces and can expand the current uses of such robotics. Further down the road, QPPs could also be used as a diagnostic tool that can quantify levels of arousal that simple behavioral measures can't. The use of QPPs in the medical field is not far off and only requires further research to get a simple quantification of the signal for diagnostic use.

Literature Review

As technology improves and the number of devices we constantly attend to increases, so do the demands on our brain and the neural networks underlying attention. Attending to multiple things at once, or multitasking, is an essential part of day to day life. Multitasking requires us to switch back and forth between multiple stimuli and is therefore highly dependent on our level of arousal. It is important that we understand the mechanisms behind this task switching in the brain

and what affects this so we can better multitask in the future. The default mode network-task positive network switch is a vital neural mechanism underlying task switching. The current research aims to establish a link between patterns of brain activity, QPPs, and arousal via three separate modulations of arousal.

Majeed et al. examined the spatiotemporal dynamics of low frequency fluctuations in brain activity in the rat brain using the detection of functional networks via functional Magnetic Resonance Imaging (fMRI) (Majeed 2009). fMRI is an important tool in the field because its' constant perturbation and recording of brain responses allows for a measurable blood oxygen level dependent (BOLD) signal (Mitra 1997). The BOLD signal is indicative of brain activation because brain areas that are more metabolically active will require more oxygen and this effect can be seen using the BOLD signal. Researchers found that low frequency fluctuations (LFF) in the BOLD signal in areas known to be strongly anatomically connected were correlated even in the absence of any task or stimulus. These fluctuations came from the same areas that the task-related responses came from leading researchers to believe that the correlated fluctuations actually reflect deeper correlations in neural activity. Previous research has also established that attention modulates the BOLD signal fluctuations in the visual cortex (Watanabe 2011). The BOLD signal is classically used as an indicator of brain activation due to its correlation with mental processes like attention.

The link between attention and arousal is well established so the interactions between the BOLD signal fluctuations, arousal, and brain activity are important to look into. Researchers proposed that these fluctuations reflect the functional connectivity of the brain, which is the idea that certain brain regions are anatomically connected because of their similar function (Cordes 2000). These fluctuations lasted approximately 25 seconds in Majeed's experiments but did not

occur with regular frequency, leading to their naming as Quasi Periodic Patterns (QPPs). The discovery of these patterns in the rat brain was important because they were never before observed and continue to puzzle researchers today. More research needed to be done based on these experiments to see if QPPs exist in the human brain.

In 2011, Majeed returned with more research on QPPs but this time with human subjects. Majeed was looking to replicate the findings of the rat study, that there is a clear coordination between these patterns and known functional networks. Researchers found an alternation of activity between the "default-mode network" (DMN) and the "task-positive network" (TPN) in humans (Majeed 2011). The default mode network was discovered several years earlier and found to be active when individuals are out of focus from their external environment, or when they are just at rest (Buckner 2008). Previous research has also shown that the DMN and TPN networks are anti-correlated in normal resting state human fMRI data. Majeed looked further into these networks and used knowledge of QPPs in rats to run his experiments to find them in humans. These experiments by Majeed were very important because they were the first ones to explore QPPs in humans and associate BOLD signals with these patterns. While QPPs were found to also exist in humans, it was not known what causes them to occur or what could affect their activity.

To expand on Majeed's research earlier in the decade, Abbas et al. investigated what modulates these QPPs in humans. The researchers aimed to explore the links between one's state of activity and the corresponding responses in QPPs or lack thereof. Abbas et al. did this by comparing the QPPs that were found in both resting state and task-performing scans (Abbas 2018). The subject performed both 0-back and 2-back memory tasks to simulate the task positive condition. The researchers found that there was a difference within the same subject between

their resting state and task performing scans. The QPPs in the task performing scans were stronger and occurred with greater frequency than the resting state QPPs. These findings were significant because they showed the coordination of the QPPs with the DMN-TPN network. The anti-correlation between these networks seen as the QPP occurs has become a standard visual illustration for the QPP. While QPPs may be modulated by memory tasks, my current research aims to more broadly establish a link between arousal levels and QPPs.

Methodology

Participants in my experiment will undergo a series of memory recall tasks when in the presence of a functional magnetic resonance imaging (fMRI) scanner. fMRI perturbs hydrogen ions found in water throughout the brain and measures their responses to get the blood oxygen level dependent (BOLD) signal. Unlike a traditional magnetic resonance imaging (MRI) machine, the fMRI machine has the capability to detect changes over time, making it a perfect tool to measure the BOLD signal. Participants will be in the scanner for approximately 90 minutes as they complete a series of memory tasks. The subjects will have two 4-button boxes to make responses while they are in the scanner. The participants will participate in a resting state scan, a flanker task scan, and two variations of n-back memory tasks. There are two blocks of each task, and one block for the resting state scan meaning the experiment lasts a total of 7 blocks. The flanker task is one that requires the subject to indicate the direction of the middle arrow of a set of five arrows. The arrows outside of the middle one may be pointing in opposite directions so it is important for the subject to only focus on the middle arrow and indicate its direction. The two variations of the n-back memory tasks are the 0-back and 2-back tasks. In the 0-back task the subject will be presented with a target image at the beginning of each task block

and they are instructed to make a positive response whenever the target image appears. The 2-back task requires the subject to indicate whether the stimulus image 2 positions back matches the current image. The 2-back image will change every time the subject advances to the next image so the subject will need to remember 3 total images: the current one, the previous one, and the 2-back image. During the resting state blocks, participants are instructed to stare at a fixation cross in the middle of the display screen and stay as still and relaxed as possible; there are no stimuli to pay attention to, just the fixation cross. Examples of the three types of memory tasks the participants will be asked to do are shown at the end of this section. Stimuli are presented by and the experiment is run via E-Prime 3.0 software and the data is collected using Siemen's 3T trio MR software.

Analysis of the data requires several pre-processing and processing steps before brain activation can be determined from the data. The pre-processing pipeline used to prepare the data for processing was the Configurable Pipeline for Analysis of Connectomes (C-PAC), an open-source pre-processing pipeline used for the analysis of resting-state fMRI data using elements of both the FMRIB Software Library (FSL) and the Analysis of Functional NeuroImages (AFNI) toolkit. (Remove listing of 14 steps) We must first begin by pre-processing the anatomical brain scans, or T1 scans. This step would entail first organizing the data so that it is accepted by the C-PAC pipeline. The steps vital to the pre-processing of anatomical scans are N4 bias field correction, skull stripping, and registration to the Montreal Neurological Institute (MNI) brain atlas using both linear and non-linear registration methods from FSL (FLIRT and FNIRT). The anatomical images must first be cropped, re-sized, and re-oriented so that they are all the same size and can be handled by the pipeline. Once all scans are the same size they are segmented into white matter, grey matter, and CSF and other non-brain structures. Once the skull is stripped

away the functional scan is then registered using FSL's FLIRT (for linear transformation) and FNIRT (non-linear transformation) to the Montreal Neurological Institute (MNI) brain atlas.

Next, it is imperative to pre-process the functional scans and these steps would entail slice time correction, distortion correction, functional masking, motion correction, nuisance signal regression, temporal filtering, and global signal regression. Due to the time that it takes for one full image of the brain to be taken (~2 seconds), the scans must be lined up in a process called slice time correction. Subjects also generally move around throughout the course of the scan, so motion correction needs to be done to ensure alignment of the entire 4D time series. The next step would be to functionally register the data the pre-processed T1 scans so the functional data can be stretched to fit the standard atlas. The global signal is always present and has the potential to affect results and data, so it is best practice to regress out the global signal. Temporal filtering is done as well to ensure that there are no extreme frequencies in either direction affecting the overall spread of the data. Lastly, the data is z-scored so that all scans can be compared accurately across the same axes.

The conjunction of the anatomical and functional registration steps in the C-PAC pipeline will extract the average time-course over the ROI mask that was applied via the brainnetome atlas. Once all data has been appropriately pre-processed via the C-PAC pipeline, it is ready for further processing and the extraction of the actual QPP. The QPPs are regressed using a pre-established algorithm described in further detail in Majeed et. al., 2011. The QPP-finding algorithm was run on each timeseries a total of 60 times with a randomly generated starting point. The QPP-finding algorithm produces two important outputs: (1) The representative QPP, and (2) The correlation vector for when that QPP appeared in the scan. The representative QPP was selected as the one with the maximum correlation to the average QPP. The resulting QPP

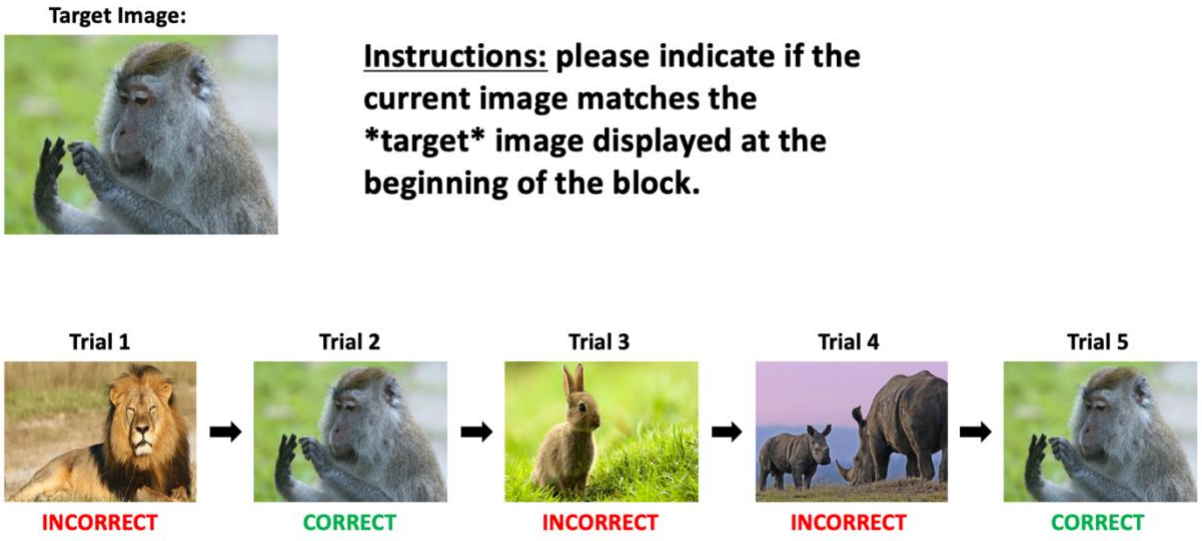
strengths and frequencies were obtained by examining the peaks of each scan, peaks are defined as any local maxima with a correlation of 0.2. The QPP frequencies were calculated by estimating the number of peaks per second. Once QPP strengths and frequencies were calculated, descriptive statistics were obtained, namely mean and standard deviation for each experimental group. Mean and standard deviation are appropriate statistical descriptors as the temporal filtering step of pre-processing removed any noise that may be considered an outlier and skew the mean to one direction. Additionally, histograms of the normalized correlation vectors were obtained for each experimental group and compared within the experimental condition group.

Flanker Task Example:

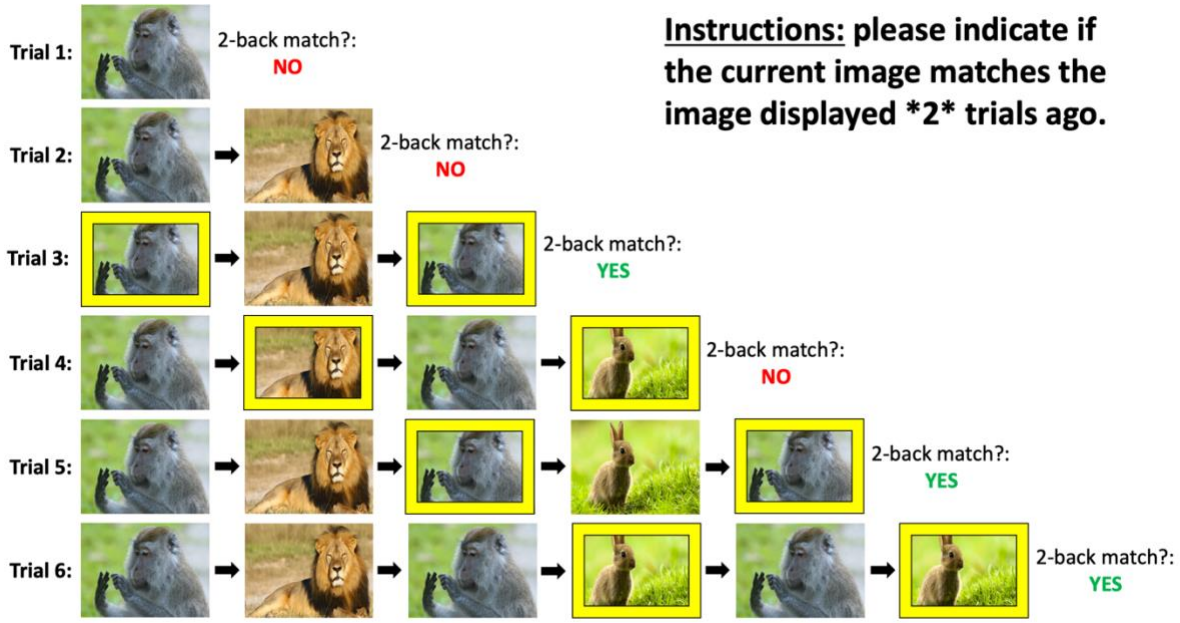
> > > > > (Right)
> > < > > (Left)
< < < < < (Left)
< < > < < (Right)

Instructions: please indicate the direction of the *MIDDLE* arrow in the sequence

0-Back Task Example:



2-Back Task Example:



Results

The QPP strength, defined earlier as the average heigh of peaks in the correlation vector, was compared across the three different sleep conditions (HC vs IH vs NC). The results of the paired t-test between the no-nap groups showed that the HC group (0.248 +/- 0.049) did in fact have a significantly lower strength than the IH (0.308 +/- 0.016) and NC groups (0.320). On the other hand, when examining the nap groups, the HC (0.281 +/- 0.014) and IH (0.284 +/- 0.067) groups were comparable, but both were significantly less than the NC group (0.405 +/- 0.061). When comparing the means within experimental groups (nap vs no-nap) no significant differences were found between the conditions.

Average QPP Strength

Condition	No-Nap	Nap
Healthy Control	0.248 +/- 0.049	0.281 +/- 0.014
Idiopathic Hypersomnia	0.308 +/- 0.016	0.284 +/- 0.067
Narcolepsy	0.320*	0.405 +/- 0.061

QPP frequencies were then calculated using the methods described above and compared within group using a paired t-test. The HC no-nap group (0.074) showed nearly double the frequency of the nap group (0.037), but the t-test showed these groups to not be significantly different. On the other hand, the IH nap group (0.048) had nearly double the frequency of the no-nap group (0.024) but again these two groups were not found to be statistically different. The trend continues to the NC group, showing nearly double the peaks in the NC nap group (0.037) when compared to the NO no-nap group (0.019), but across all subjects these differences were not found to be statistically significant. While there are no statistically significant differences, it

is still useful to acknowledge the trend in the data. In both the IH and NC nap groups there is greater frequency, contrasted against the HC group where the effect is the opposite.

Average QPP Frequency

Condition	No-Nap	Nap
Healthy Control	0.074	0.037
Idiopathic Hypersomnia	0.024	0.048
Narcolepsy	0.019	0.037

Discussion

Due to time constraints and unforeseen circumstances surrounding the analysis of this data over the past 2 semesters, completed analysis on the data could not be fully performed as was originally desired. Additionally, there were several unforeseen roadblocks when pre-processing the data that required a complete change in the selection of the pre-processing pipeline. The data is initially evaluated using statistical comparisons of means, but further analyses were intended for this project. Despite the hiccups in pre-processing and along the way, initial analyses based on the means and visual comparisons of the QPP correlation distributions can give some information on the sleep subjects data. Unfortunately, further analyses were not performed on the task-based data or age-stratified data, however we expect these results to continue trends set forth by Abbas et. al. in 2018 - an increase in both the strength and frequencies of QPPs in the task-engaged groups when compared with the resting state groups. We also expect this trend to continue with analysis of the data concerning the groups divided into old (60 years+) and young subjects (college-age). We expect the young group of patients to represent those with elevated arousal, so we expect to see higher QPP strengths and frequencies

when looking at the correlations to the ideal QPP in this group when compared with the more elderly subjects. This effect should also continue in the long-task data, with the task-engaged individuals showing both greater QPP strength and frequency when compared with resting state. Furthermore, we anticipate the 2-back task to show the highest number of QPPs among the tasks due to its more complex nature when compared with the other tasks.

These results should lead the way for further experiments that solidify the link between QPPs and arousal. While these are promising results, more research needs to be done to replicate these experiments and other possible variations. An established link between QPPs and arousal is important, yet little is still known about QPPs. The future direction of this research should include a way to use the QPP to quantify arousal, and even explore other possibilities of mental processes linked to QPPs. The quantification of arousal can lead to its use as a diagnostic tool for a wide array of neurological disorders dealing with arousal. The establishment of this link means that QPPs can be used to quantify arousal when it is a symptom and not a cause in disorders like major depressive disorder, schizophrenia, bipolar disorder, and others. Quantification of arousal can also make future work with human-computer interfaces easier. The hope is that we can determine when people are best primed to respond to stimuli and use this information to better design software and interfaces for human use. To summarize, the link between QPPs and arousal found in this experiment serves as a solid base and should be used as a base for future research quantifying this link to expand into other fields.

Figures

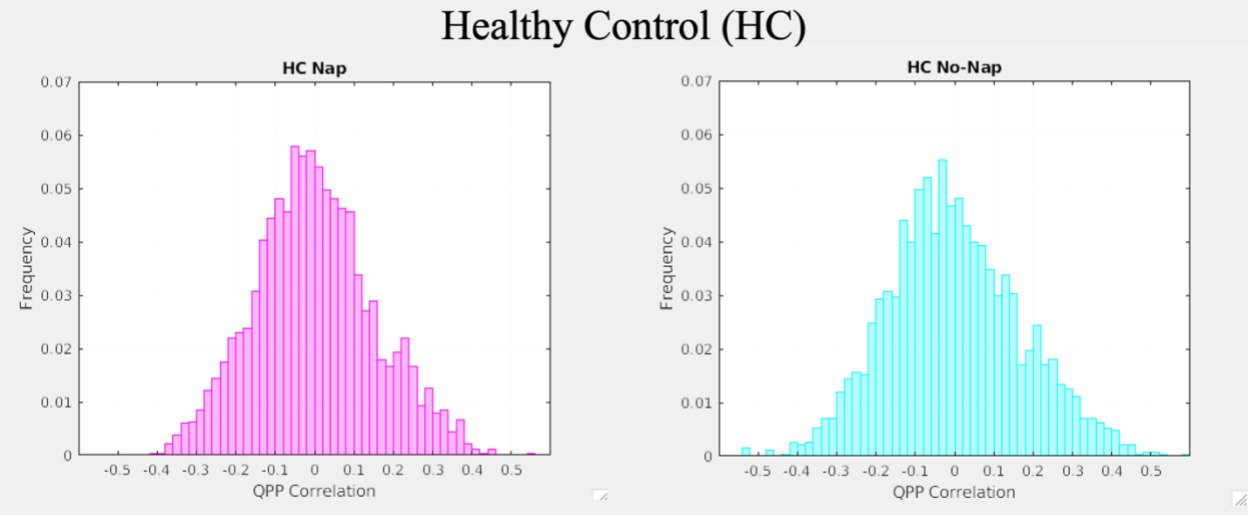


Figure 1. Healthy Control Normalized QPP Correlation Histograms. Shown above is a histogram of the QPP correlations for the no-nap and nap conditions for the healthy control experimental condition. The data is aggregated across all ROIs and correlated to the ideal QPP, as discussed earlier. The QPPs were first normalized so that they can be compared and correlated more easily across ROIs and experimental conditions.

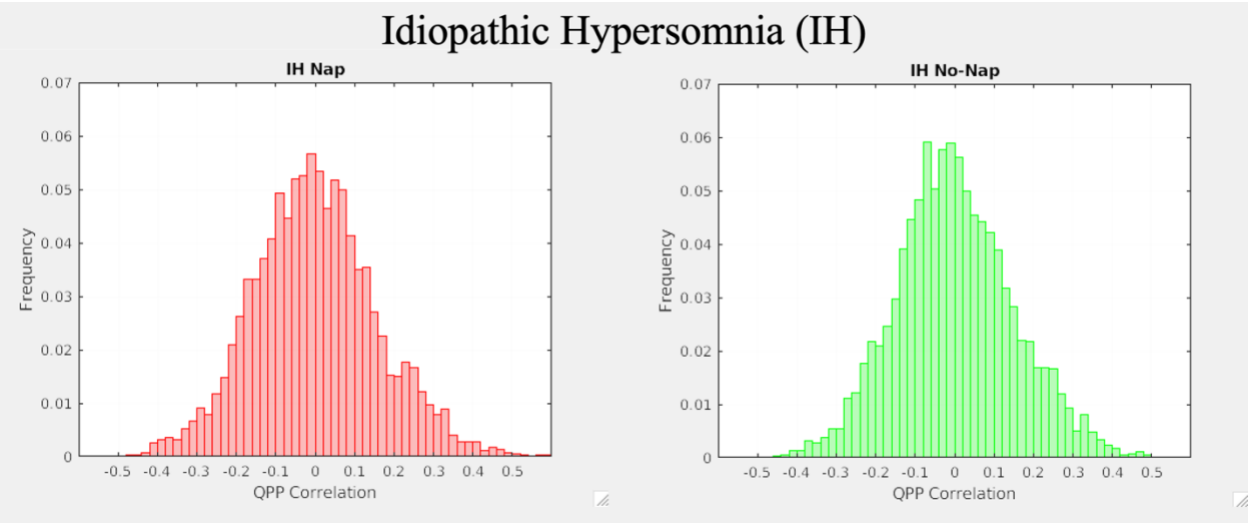


Figure 2. Idiopathic Hypersomnia Normalized QPP Correlation Histograms. Shown above is a histogram of the QPP correlations for the no-nap and nap conditions for the idiopathic

hypersomnia experimental condition. The data is aggregated across all ROIs and correlated to the ideal QPP, as discussed earlier. The QPPs were first normalized so that they can be compared and correlated more easily across ROIs and experimental conditions.

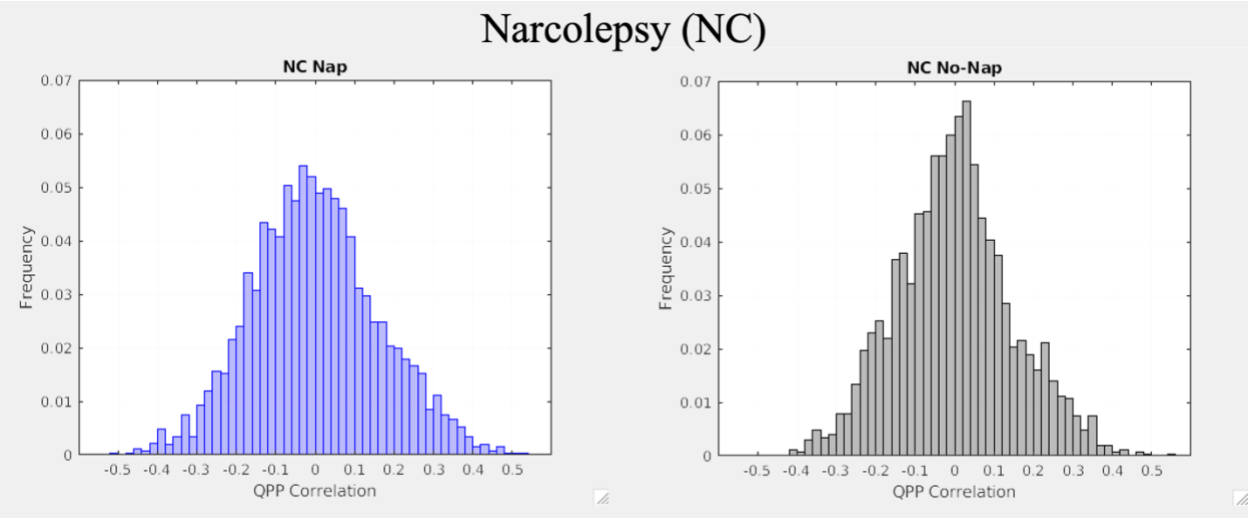


Figure 3. Narcolepsy Normalized QPP Correlation Histograms. Shown above is a histogram of the QPP correlations for the no-nap and nap conditions for the narcolepsy experimental condition. The data is aggregated across all ROIs and correlated to the ideal QPP, as discussed earlier. The QPPs were first normalized so that they can be compared and correlated more easily across ROIs and experimental conditions.

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