AN ANALYSIS OF THE COVARIANEC OF TWO ENDOPHENOTYPIC MARKERS FOR DEPRESSION: RESPIRATORY SINUS ARRHYTHMIA AND FRONTAL EEG ASYMMETRY

By

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Abstract:

In this study, I examined how two psychophysiological metrics that have both independently been implicated in depression co-vary with one another within individuals over time: frontal EEG asymmetry and respiratory sinus arrhythmia (RSA). I hypothesized that, within subjects, short epochs of higher RSA, normally indicating low depressive status, would correlate with higher scores on frontal EEG asymmetry, reflecting greater relative left frontal activity like that seen among those with low depressive status. No statistically significant relationship between the two metrics was observed. Future work might investigate whether changes in one system would lead to changes in the other, as only simultaneous changes were examined in the present study.

Introduction:

Frontal EEG Power:

EEG Alpha power, comprising frequencies ranging from 8 – 13 Hz, is typically considered to be inversely related to active cortical processing, since decreases in alpha tend to be observed when cortical systems engage in active processing (Coan & Allen, 2004). This means that in regions where underlying cortical processing is increased, there should be a decrease in the relative strength of alpha frequencies in those regions and vice versa. For this reason, and because alpha is easy to measure in the human electroencephalogram, alpha frequencies are able to be used as an inverse metric for the cortical activity of frontal regions, and there is evidence supporting their role in emotional regulation and other trait measures. Of particular interest is an asymmetry in alpha power over the frontal regions, termed frontal EEG asymmetry, as this variable correlates with various emotional traits and states (Coan & Allen, 2003).

Frontal EEG Asymmetry:

Frontal EEG Asymmetry is a metric that compares the relative alpha power from electrodes over each hemisphere. This is most commonly done by subtracting the natural log of the power of the left hemisphere from the natural log of the power of the right (Allen et al., 2004). This can be done using opposing electrodes on each hemisphere and gives a simple Asymmetry Score centered on 0. Here, Asymmetry Scores greater than 0 would indicate greater alpha power in the right hemisphere whereas scores less than zero would indicate greater alpha power in the left hemisphere. It is important to remember that in the context of these experiments, alpha power is used as an inverse metric of cognitive frontal activity. Therefore, scores greater than 0 indicate greater frontal activity in the left hemisphere, whereas scores less than 0 indicate greater frontal activity in the right hemisphere and for the rest of the paper, "Frontal Activity" will be used to mean cognitive activity and processing rather than Alpha Power itself.

Frontal EEG Asymmetry in Emotion:

Frontal EEG Asymmetry has been studied in many different emotion-related contexts that can be categorized into four groups. 1) Those that examine frontal EEG asymmetry as an individual difference that is related to other traits or trait-like measures; (2) Studies examining frontal EEG asymmetry as an individual difference that can predict state-related emotional changes and responses; (3) Studies examining frontal EEG asymmetry as an individual difference that is related to psychopathology or risk for psychopathology, especially depression and anxiety; and (4) Studies examining state-related change in asymmetry as a function of state changes in emotion (Coan & Allen, 2004). The first 3 types of studies explicitly assume that frontal EEG asymmetry has trait-like properties, whereas the fourth type of study assumes that state-related changes in EEG asymmetry can be elicited and observed. The present study is motivated by the third type of study, examining frontal EEG

asymmetry and its relation to depression in particular, however it will also contain properties of the 4th type of study as well examining the potential changes in frontal EEG asymmetry in relation to another measure: Respiratory Sinus Arrhythmia.

EEG Asymmetry as an endophenotypic marker for Major Depressive Disorder:

Over the past several years, there has been mounting evidence that resting frontal electroencephalographic (EEG) asymmetry can be assessed as an endophenotypic (Gottesman, 2003) marker for Major Depressive Disorder (MDD) (Allen et al., 2004). One of the first studies to identify this link showed a relatively greater right frontal resting activity, or relatively lower left frontal resting activity, correlating with depression (Henriquez, 1990). Greater right frontal activity was associated with higher scores on the Beck Depression Inventory (BDI) in a sample of undergraduate research participants, (BDI is a self-reported inventory and one of the most widely accepted tests for measuring the severity of depression) (Schaffer et al., 1983). Since then, similar results have been found in studies involving seasonal depression (Allen et al., 1993), and among clinically diagnosed participants (Allen et al., 2004a). Additionally, one study in particular, showed that those with greater left frontal activity had more intense positive affects in response to positive stimuli, whereas those with greater right frontal activity had more intense negative affects in response to negative stimuli (Wheeler, 1993). Thus depression-related traits such as reduced motivation and increased withdrawal are associated with frontal EEG asymmetry.

One important note is that these early studies, while showing strong evidence for resting frontal EEG asymmetry as a marker for risk for MDD, used predominantly female samples. A more recent study was conducted to observe sex-specific patterns of frontal brain asymmetry (Stewart et al., 2010). This study was able to distinctly confirm less left frontal activity in both males and females for those who had been diagnosed with MDD at some point in their lifetime (lifetime MDD), regardless of

their current depressive state. This result provides great support for the theory that asymmetry can function as an endophenotype of risk for depression by showing that those who have or have at some point had MDD seem to be differentiated from those with no lifetime MDD by their frontal EEG asymmetry levels. This study also found a correlation between lowered left frontal activity and current depression severity, at least in women.

Cardiac Vagal Control:

One of the key components in controlling heart rate is the vagus nerve. An integrative perspective on the role of the vagus nerve in the control of heart rate is "the Polyvagal Theory" (Porges, 2007). The Polyvagal theory assesses the phylogenetic origins of this vagal cardiac control and attempts to explain the neurophysiological control of the heart as well as how it is related to psychological traits and behavior. It is currently theorized that the nervous system has several distinct pathways that individually impact the heart, each of which phylogenetically evolved sequentially from more basic functions to more complex ones.

Parasympathetic and Sympathetic Control:

There are two sets of neurons that innervate the heart. There are sympathetic motor neurons and parasympathetic vagal motor neurons. The vagal neurons are also split into two categories: myelinated and unmyelinated. The unmyelinated vagal nerves are thought to have phylogenetically evolved first, providing the heart with a tonal slowing resulting in immobilization behaviors. Next in the level of hierarchical specificity is the sympathetic-adrenal system, giving mobilization and active avoidance behaviors under stress. And finally, the greatest precision in control derives from myelinated vagal nerves. These nerves are thought to promote self-soothing and calming traits, facilitating easier social communication. This is thought to be the case because these systems would be able to inhibit the unmyelinated, and more primitive, limbic structures that respond through flight fight, or freeze

behaviors (Porges, 2007). These myelinated nerves provide quick dampening of the heart rate, providing rapid inhibition which can quickly calm an individual to respond appropriately to complex social situations.

Respiratory Sinus Arrhythmia:

One specific metric of this cardiac vagal control is Respiratory Sinus Arrhythmia (RSA), which measures heart rate variability as it is related to respiration. For some time, RSA's relation to respiration was a contentious subject. However, it has now been found that the fibers that produce RSA, which originate in the medullary region, are inherently silent until they are activated by other neural pathways. Additionally, those same medullary structures are involved in the regulation of respiration, giving significant support to the assessment that RSA is indeed dramatically influenced by respiration itself (Wang et al., 2001). Vagal control is most significant during exhalation, slightly depressing the rate, and least significant during inhalation, where the rate slightly increases. This moment to moment fluctuation induced by an individual's respiration is known as RSA with a high beat to beat variability indicating high RSA and low variability indicating low RSA. There are many factors that come together to contribute to RSA, but it is widely agreed that RSA is specifically due to the changes of activity in the myelinated vagus since these nerves are the only ones capable of the rapid instantaneous changes that characterize RSA (Porges, 1995). This subset of nerves have, again, notably been related to social communication and other complex, higher order behaviors, which gives RSA very valuable utility as a metric (Movius & Allen, 2005). It has been implicated in numerous different psychological states and traits, being one of the easiest and least invasive measures of cardiac control.

Respiratory Sinus Arrhythmia as a metric:

Respiratory Sinus Arrhythmia can be calculated in a number of ways, which cause it to more closely or loosely track the variability of the heart rate. The calculation requires first finding the interbeat interval

(IBI) series from the EKG waveform of the participant's heartbeat. The interbeat interval is the number of milliseconds between each beat, and the series shows a rising or falling interval which indicates the beat to beat change in time between heart beats. Some metrics will then take the standard deviation of the interbeat intervals where as others will take the variance of the series (Allen & Chambers, 2007).

RSA and behavioral regulation:

RSA has been studied in a large variety of settings, which have given it a broad range of physiological implications as a predictor of behavioral regulation and traits as well as even more physiological traits as far as low RSA being related to cardiovascular risk, diabetes and obesity (Quilliot, 2001). Most notable and relevant to this study are some which have related RSA to different forms of anxiety, depression, and social regulation.

It has been seen that in general, a high resting level of RSA is a good positive index of emotional regulation, but reliable suppression of RSA is also important for proper regulation. On the other hand, low baseline RSA and unreliable RSA modulation appear to be risk indices for difficulties in social and emotional regulation and in some occasions, associated with psychiatric disorders. Several studies have shown that children with behavioral regulation problems have lower baseline RSA and dampened RSA responses during testing sessions. These studies also showed that children with stable RSA suppression across the preschool period were less emotionally negative and had fewer behavioral problems than other children (Calkins, 2004). In adults, poorer modulation of RSA was associated with greater social anxiety, and greater defensiveness as well as lower behavioral activation sensitivity measured through a number of both experimental and self-reported metrics (Movius & Allen, 2005). High RSA would indicate strong vagal activity, efficiently slowing the heart rate and maintaining good self-regulation. Poor vagal activity would indicate higher levels of arousal with higher risk for anxiety. Similarly, those with a strong

ability to modulate their RSA would have better behavioral regulation as well, being able to attenuate their arousal to their given environment.

Respiratory Sinus Arrhythmia as a marker for depression:

Several studies have observed that RSA is decreased in depression, although the evidence for serving as an endophenotype is not as strong since it may vary by clinical status. Lower RSA has been implicated in depression and seems to be associated with several depressive symptoms. One study showed that depressed individuals who subsequently recovered from depression reacted with a greater RSA withdrawal to a sad video clip than those who did not recover (Rottenberg et al., 2005). Thus RSA responsiveness to emotional situations may be related to the positive effects of the treatment and therefore can be seen as marker for depressive severity. Other studies have more directly shown that RSA patterns have the ability to predict depression symptom severity among adults and adolescents. Perhaps most relevant for the current study is that in clinically depressed adults, low resting RSA is associated with depression (Yaroslavsky, 2014).

The Covariance of Frontal EEG Asymmetry and Respiratory Sinus Arrhythmia:

Both frontal EEG asymmetry and Respiratory Sinus Arrhythmia have been implicated in depression among clinically depressed patients. Both metrics have two relevant characteristics: they appear to identify individuals who may have depression, but also may vary with depression severity. This study was designed to examine covariation over time within individuals for these two metrics. I hypothesize that the two metrics will covary significantly, which would imply a physiological link between these two systems, and suggest that their interaction may be especially important in understanding risk for depression. This study will examine Frontal EEG Asymmetry and RSA recorded from individuals in two resting sessions per day on four separate days within a two-week period of time. Short EEG epochs will be sorted into those associated with RSA higher than the median RSA and RSA

lower than the Median RSA. A comparison of these two categories will test whether EEG asymmetry varies as a function of RSA. I hypothesize that because lower asymmetry scores are associated with depression, as is lower RSA, the epochs categorized by RSA above the median should show statistically higher asymmetry scores than the epochs with RSA below the median. Implications of such a finding would include: 1) that both frontal EEG asymmetry and RSA are moderated by the same pathways or 2) that one could even be a driver for the other.

Methods:

Participants

The Beck Depression Inventory (BDI; Beck, Ward Mendelson Mock, 1961) scores were obtained from either an online survey or pre-testing in an introductory psychology course at the University of Arizona and used to identify prospective participants. The sampling strategy was to recruit subjects with a broad range of depressive symptoms that would include individuals ranging from no symptoms to full clinical severity including extreme low and high scores. Every individual with a BDI score over 20 was invited for screening, with other participants drawn from the ranges of 0-5, 6-10, 11-15, and 16-20 with the objective of capturing the entire range of depressive severity in the sample. A post-baccalaureate project manager initially telephoned prospective participants to identify whether they met exclusionary criteria such as concussion, left handedness, electroshock therapy, use of current psychotropic medications, history of head injury with loss of consciousness > 10 minutes and active suicidal potential necessitating immediate treatment. Participants that passed exclusionary criteria were invited for an intake interview. A strong right handed requirement (greater than 35/39) (Chapman & Chapman, 1987) was required to be accepted as a participant, as brain lateralization may vary as a function of handedness.

A graduate-level trained clinical rater administered the intake interviews on a separate day before any EEG evaluations. During this, participants were screened again on the same exclusion criteria as previously covered in the phone interview, and then further screened using the Structured Clinical Interview for DSM-IV (SCID, First, Spitzer, Gibbon & Williams, 1997) for Axis I psychopathology. If participants met criteria for any current comorbid DSM-IV Axis I disorder other than lifetime MDD or current dysthymia, they were excluded from the study. Inter-rater reliability analysis for a randomly selected 10% of SCIDs demonstrated high inter-rater agreement for past and current MDD diagnoses (Kappa =.91 and .81, respectively). The final sample included 306 participants, with an age range of 17 to 34 years (M-19.1, SE=.01).

EEG Data Collection

Over a 14 day period, on four separate days with no fewer than 24 hours between visits, two resting EEG sessions were recorded on each of the four days. For each session, resting EEG was recorded for one-minute baselines of eyes-closed (C) and eyes-open (O) in one of two counterbalanced orders (COOCOCCO or OCCOCOOC). Intervals of approximately 20 minutes separated sessions within days. A 64-channel NeuroScan Synamps2 amplifier (Charlotte, NC) and acquisition system, utilizing the international 10-20 system for electrode placement were used to collect all EEG data. For ocular artifact rejection, two electrooculogram (EOG) channels (vertical: superior and inferior orbit of the left eye; lateral: outer canthi) were collected. EEG data were acquired with an online reference site immediately posterior to Cz and subsequently re-referenced offline to four different references: 1) average of all EEG leads = AVG, 2) CSD (using algorithms from Kayser & Tenke, 2006 and based on the spherical spine approach summarized by Perrin, Pernier, Bertrand, & Echallier, 1989, 1990), 3) Cz, and 4) averaged ("linked") mastoids = LM. Data for each resting session were digitized continuously at 1000 HZ amplified 2800 times and filtered with 200Hz low pass filter prior to digitization. All impedances were kept under

10K Ohms. Only data from the CSD montage are considered here, as this montage showed the strongest relationship to depression (Stewart et al. 2010).

After collection, epochs with movement and muscle artifacts were removed with visual inspection. Custom scripts in Matlab were used to implement data reduction. Where ocular activity exceeded +/- 75 microvolts in the vertical ocular channel, a blink rejection algorithm rejected data segments. An artifact rejection algorithm excluded segments with large fast deviations in amplitude in any channel (e.g., DC spikes and shifts) that may have eluded visual inspection. Data were segmented into one-minute EEG blocks, and then further separated into 2.048 second epochs with 1.5s overlap between epochs. This overlapping compensated for the use of the Hamming window function's application of minimal weight to the end of each epoch. After windowing, a Fast Fourier Transform (FFT) was performed on all artifact-free epochs. Asymmetry scores for each epoch were calculated by subtracting the natural log of the transformed scores (i.e., ln[Right] – ln[Left]) for each homologous left and right pair of electrodes; e.g., F1 & F2, F3 & F4, F5 & F6, F7 & F8. Higher values on this index reflect relatively lower left frontal alpha power and consequently greater relative left brain activity. Intraclass correlations indicated that these frontal EEG asymmetry scores were highly stable across sessions for each reference montage (AVG range = .71-.77; CSD range = .67-.72; Cz range = .67-.72; LM range = .62-.66). The methods for obtaining the asymmetry scores used in this experiment are the same as those used in Stewart et al., 2010.

RSA Data Collection:

For each participant, during EEG recordings, EKG recordings were also made. Two Ag/AgCl electrodes were attached to the left and right clavicle in a Lead-I formation (Einthoven et all., 1913); a ground was the same as for the EEG, within the cap. Impedances were reduced to less than 20kOhm on all electrodes. EKG signals were amplified 1000 times with a bandpass of .05-100 Hz, then digitized at 1000Hz. In order to calculate the RSA, the EKG recordings were similarly split into one-minute blocks.

Recordings with overpowering noise or ectopic beats that reset the rhythm of the heart-rate were removed through visual inspection of the recordings. Using QRSTool, an IBI (interbeat interval) series, indicating the amount of time (in milliseconds) between each beat, were created for each recording, with each beat being identified by its R-Spike. IBI series were hand corrected for artifacts and then processed by CMETX for measures of heart rate and variability. CMETX converted the IBI series to a time-series sampled at 10HZ. This waveform was used to calculate the RSA, operationalized as the log of the variance of the respiratory-band-passed series (.12-.40 Hz). To create a time series to match to ongoing EEG, a 10-second moving window that shifted by one second provided an estimate of RSA natural log of the variance of the waveform within the window) every one second, centered within the 10-second window. This series was then upsampled to 1000 Hz to match the EEG data so that epochs could be selected based on the RSA values. This was done for all of the EKG recordings, producing RSA values to match with all time-points associated with a matching asymmetry score from the EEG measurements.

Categorizing the data for Analysis:

For each participant, the median RSA was determined for each epoch. The median across epochs then divided epochs based on RSA, creating two blocks, above median RSA, and below median RSA, for each participant. Next, asymmetry scores for each electrode pairing were averaged within each block. A paired-T test was performed to determine whether the asymmetry scores differed significantly between the two blocks: above median RSA and below median RSA.

Results:

After a paired-T test for each of the four electrode pairings (F8-F7, F6-F5, F4-F3, F2-F1), between above median RSA and below median RSA epochs, there was no significant difference in asymmetry scores for any of the pairings ($p>.5$) for all paired-T tests. Figure 1 indicates two boxplots for the asymmetry scores

of F8-F7 for above median RSA and below median RSA epochs across all subjects. This figure is representative of all three other electrode pairing asymmetry scores as well.

Figure 2 indicates an unanticipated finding. Several temporal and parietal electrodes showed significantly higher log-transformed single site alpha power during when RSA was above the median as opposed to below the median. A paired-T test was performed for the log-transformed alpha power of these individual electrodes. Figure 2 indicates electrode T7 averaged across subjects specifically, but the figure is representative of several other parietal and temporal electrodes as well.

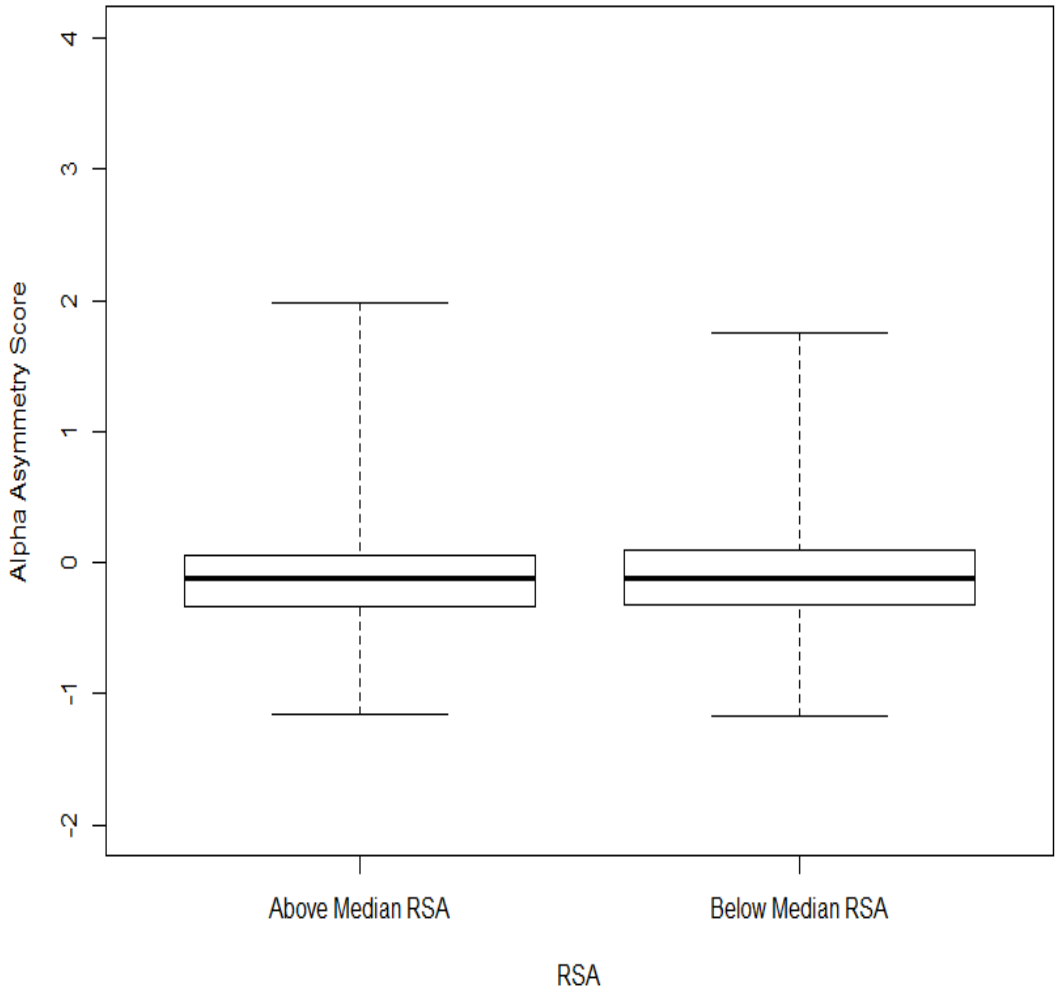

Fig 1. Left) Box-plot of asymmetry scores (F8-F7) for above median RSA averaged across subjects. Right) Box-plot of asymmetry scores for below median RSA epochs averaged across subjects. Whiskers extend to the full range of scores. No significant difference found between the two datasets.

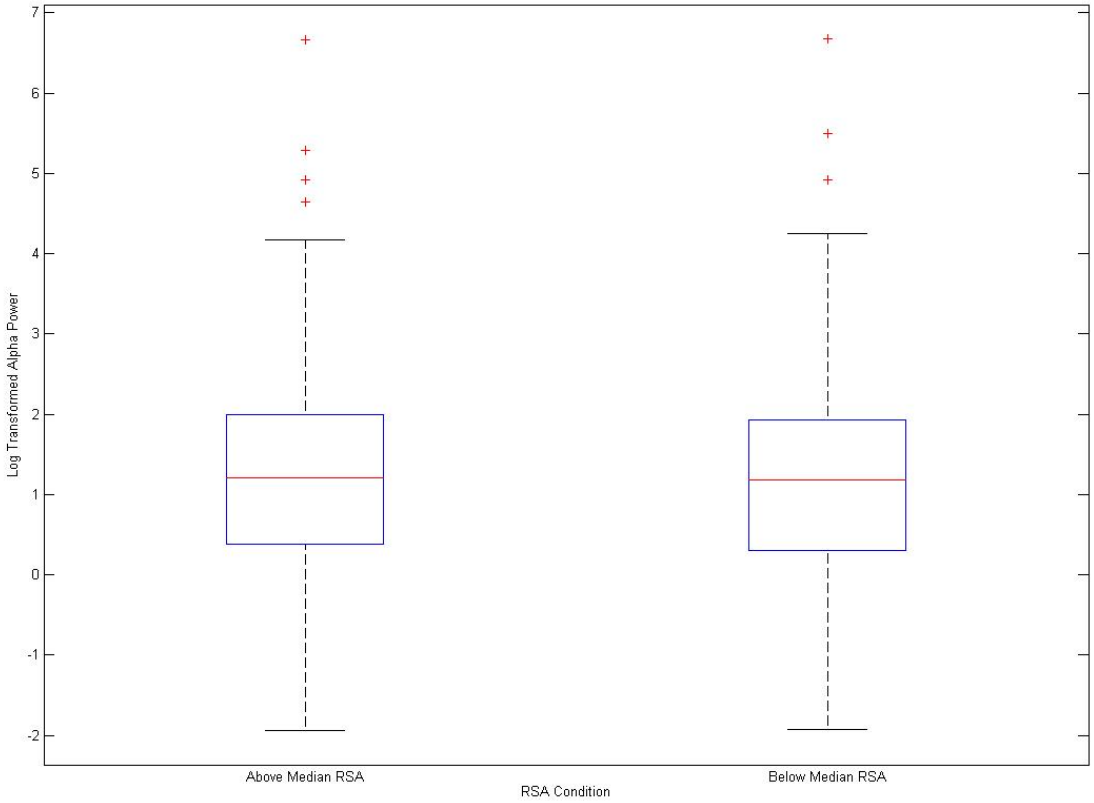

Fig 4. Left) Box-plot log-transformed alpha power for electrode T7 for above median RSA epochs averaged across subjects. Right) Box-plot log-transformed alpha power for electrode T7 for below median RSA epochs averaged across subjects. Whiskers extend to the full range of powers. Differences between datasets are significant (P<.05).

Discussion:

Contrary to prediction, no significant difference emerged in asymmetry scores as a function of whether RSA was above or below each participant's median. This first test was exploratory, and these two systems may in fact be related. I outline several ideas for what could be occurring and how to proceed.

First, it is possible that the two systems are not varying at the same time. There could easily be a short lag between frontal EEG asymmetry and RSA or vice-versa, especially because RSA is a much slower signal than EEG. If these two systems are mediated/modulated by the same system, there is no defined reason why their effects must be exactly simultaneous. I currently predict a short lag between the two, with frontal EEG asymmetry coming first on the order of a few seconds, simply due to temporal precision of EEG. The lab will continue to tweak the timing to understand the role of lag between the two systems and to see if accounting for lag can produce a significant covariance between them.

Second, in the Stewart et al., 2010 paper, Frontal-EEG Asymmetry was linked as an endophenotype for lifetime depression and only significantly associated with current depressive severity in women. With this knowledge, it may be useful to reprocess the data while only using female participants to explore whether the present findings vary by sex. If a significant result could be found, it wouldn't indicate that the two systems are not linked in men, but would indicate that a more complex approach must be implemented to observe their connection.

Finally, if neither of these possibilities supports a relationship, it could mean one of two things. One possibility is that a simple covariance between RSA and frontal EEG asymmetry may not be found and for a relation between the two to be discovered, a more complex approach must be implemented in determining how exactly the two are related. And the other would be that the two could simply be unrelated. The body is very complex and while many systems work in tandem and harmoniously, others may not. Depression is also very multi-faceted and can have a number of contributing factors. Perhaps

RSA and frontal EEG asymmetry work as observations and metrics of different components that are implicated in depression, or different subtypes of depression. In this case, while both would correlate with depression, neither would necessarily have to correlate with the other.

Clearly some connection between brain function and RSA must exist, as RSA is controlled by the vagus nerve and is getting inputs directly from the brain. It seems highly probable that these changes in frontal activity could be directly related to the impulses that get sent down the vagus nerve during every exhale to slow the heart down. Whether these brain systems will be reflected in scalp-recorded EEG remains to be seen.

In assessing the unanticipated results of the temporal and parietal sites that showed higher alpha power during epochs of above median RSA vs Low Median RSA, while these relationships are significant, there has been no prior research on this phenomena. This finding is best treated as preliminary and will await replication. They are however, interesting and potentially valuable data that will be explored in future studies.

The current study failed to support the hypothesis concerning the relationship between frontal EEG asymmetry and RSA. Further investigation, including examining lagged-relationships, may uncover a correlative link between RSA and Frontal EEG asymmetry.

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