The brain cortex is a heart-brake

Elisabetta Patron, Ph.D.[a], Rocco Mennella, Ph.D.[b], Simone Messerotti Benvenuti, Ph.D,[a] Julian F. Thayer, Ph.D.[c]

[a] *Department of General Psychology, University of Padua, Padua, Italy.*

[b] *Laboratoire de neurosciences cognitives, Département d'études cognitives, École normale supérieure, INSERM, PSL Research University, Paris, France.*

[c] *Department of Psychology, The Ohio State University, Columbus, OH, United States.*

Correspondence:

Elisabetta Patron, Ph.D., Department of General Psychology, University of Padua, Via Venezia, 8, I-35131 - Padua. Tel.: +39 049-8276957; Fax: +39 049-8276600, E-mail: elisabetta.patron@unipd.it

Abstract

Prefrontal brain regions have been proposed to modulate vagally mediated heart rate variability (HRV) through their action on subcortical structures. This study aimed at investigating the beat-to-beat causal influence of the brain cortex over the heart through a high temporal resolution estimation of brain-heart coupling. Electrocardiogram (ECG) and electroencephalogram (EEG) from 32 scalp positions were recorded at rest for five minutes in 38 participants. To assess beat-to-beat cortical control on vagal activity, the longest and shortest inter-beat intervals (IBIs) were identified for each participant. Then, the EEG activity was time-locked to R waves in the ECG signal and analyzed using a time-frequency approach. Logistic regression models were applied to predict the trial-by-trial occurrence of long and short IBIs from cardiac-related EEG activity. Delta power reduction over prefrontal areas preceding the R-wave increased the probability for a long IBI to occur, as compared to a short one. Moreover, reduced prefrontal delta power preceding the R wave was correlated to higher cardiac vagal control, as reflected by the High Frequency (HF) power of HRV calculated on the whole recording time. The present results support the hypothesis that phasic activation/deactivation of prefrontal areas modulates vagal control of heart rate at rest.

Keywords

Cardiac vagal control; Delta activity; EEG; Heart rate variability; Prefrontal cortex

Introduction

Heart rate (HR) is directly controlled by the synchronous activity of the sympathetic and parasympathetic (vagal) branches of the Autonomic Nervous System (ANS). While sympathetic postganglionic fibres innervate the sinoatrial and atrioventricular nodes, most of the parasympathetic preganglionic fibres reside in the nucleus ambiguous (NA) and in the motor nucleus of the vagus. On one hand, sympathetic activation increases both HR and ventricular contractility in response to external and/or internal stimulation (Glick and Braunwald, 1965). On the other hand, parasympathetic activation predominantly slows down HR in resting conditions, by inhibiting the natural firing rate of the sinoatrial node cells (Robinson et al., 1966). Importantly, the general balance between sympathetic and parasympathetic nervous system effects on the heart is responsible for the Heart Rate Variability (HRV), which is the physiological variation in time intervals between heartbeats. Accordingly, there is large evidence showing that a high HRV represents an important index of an effective sympathovagal balance (Bootsma et al., 1994) and, therefore, of cardiac health (Thayer et al., 2010).

However, several authors proposed that HRV, and in particular the vagally mediated part of HRV as reflected by the high frequency power (HF-HRV), ought to be considered as more than a mere index of cardiac health (Beauchaine and Thayer, 2015). Such a claim is supported by the evidence that high HF-HRV is associated with positive affect (Geisler et al., 2010; Patron et al., 2012), adequate emotional regulation (Patron et al., 2013), and high cognitive performance (Hansen et al., 2004, 2003; Luft et al., 2009; Scrimin et al., 2017), whereas reduced HF-HRV has been linked to many psychopathological symptoms, including anxiety (Chalmers et al., 2014), depression (Kemp et al., 2010), and trait hostility (Sloan et al., 1994). In light of these findings, HRV has been proposed to serve as a peripheral index of the integrity of cortical (prefrontal) networks that support goal-directed behaviour, executive functions, affect regulation, and other high-order brain functions (Benarroch and Bennaroch, 1993; Thayer et al., 2009; Thayer and Lane, 2009).

Consistent with this hypothesis, prefrontal areas involved in cognitive and affective regulation, such as the medial prefrontal cortex (mPFC) and ventromedial prefrontal cortex (vmPFC), have been shown to directly modulate the parasympathetic branch of the ANS (Ongur and Price, 2000; Ter Horst and Postema, 1997). This cortical control over ANS responses is thought to be possible given that the mPFC and vmPFC, along with the insular cortex and anterior cingulate cortex, form an interconnected network with core regulatory subcortical nuclei, one of the most important being the amygdala. In general, the activation of the central nucleus of the amygdala (CeA) leads to increased HR and reduced HRV by three routes: 1) inhibition of the nucleus of the solitary tract (NTS), which, in turn, leads to inhibition of vagal neurons in the dorsal motor nucleus (DVN) and in the NA, the main vagal connections with the sinoatrial node; 2) disinhibition of tonically active neurons in the caudal ventrolateral medulla (CVLM), which, in turn, leads to activation of tonically active sympathoexcitatory neurons in the rostral ventrolateral medulla (RVLM); 3) direct sympathoexcitatory connections with the RVLM (Matthews et al., 2004; Thayer and Lane, 2000; Wong et al., 2007). By downregulating amygdala activity, activation of PFC leads to longer inter-beat intervals (IBIs), that is, slower HR (Balaban and Thayer, 2001; Matthews et al., 2004; Thayer and Lane, 2000; Wong et al., 2007). Notably, increased PFC tonic activity is associated with higher parasympathetic than sympathetic cardiac influence; on the contrary, decreased PFC tonic activity leads to lower parasympathetic than sympathetic inputs on the heart (Lane et al., 2009; Ruiz Vargas et al., 2016).

Several functional Magnetic Resonance Imaging (fMRI) studies provided support for this model reporting positive correlations between the activation in prefrontal and subcortical areas and HF-HRV during cognitive (Critchley et al., 2003; Gianaros et al., 2004; Gillie et al., 2014; Nugent et al., 2011) and emotional (Lane et al., 2009; O'Connor et al., 2007) tasks, and volitional exercise (Shoemaker et al., 2015). These findings are in line with the view that a common network involving (prefrontal) cortical and subcortical areas is activated when vagal autonomic modulation is needed,

such as during cognitive and emotional tasks. However, although neuroimaging studies conducted so far have provided valuable information on cortical and subcortical structures involved in HRV modulation, they did not examine fast variations (in terms of milliseconds) in the brain control over the heart due to poor temporal resolution. Indeed, in the majority of the studies, both HRV and neural indexes are calculated over several seconds or minutes and represent a single steady-state measurement. These are important limitations if one considers that parasympathetic control over the heart is rapid (< 1 sec; Nunan et al., 2010; Smith, 1974), and cortical areas implicated in parasympathetic modulation are more likely to be involved in moment-by-moment rather than long-lasting cardiac adjustments.

EEG could overcome temporal limitations of other brain imaging techniques but, to date, only a few studies have investigated EEG correlates of autonomic control. Among these, Mueller and colleagues investigated brain-heart coupling during tasks involving feedback to task performance. Intriguingly, they found that feedback-evoked modifications in frontocentral EEG activity predicted subsequent cardiac modulations (Mueller et al., 2010; Panitz et al., 2013). Slow wave bands, particularly frontal theta and delta power, have been associated with cardiac vagal control (Kubota et al., 2001; Liou et al., 2014). However, those results derived from simple correlation analyses between EEG and ECG signals conducted over long-lasting recordings (typically 1 to 5 minutes), thus providing only a "static" picture of brain-heart coupling. The few studies examining EEG correlates of fast variations in the cardiac rhythm found that increases in EEG slow wave activity were associated with higher sympathetic activity on the heart in preterm infants (Pfurtscheller et al., 2008) and in children with temporal lobe epilepsy (Piper et al., 2014). To our knowledge, only one recent study applied a time-frequency approach on EEG data to investigate moment-by-moment electrocortical correlates of cardiac activity during daytime sleep (i.e., nap; Naji et al., 2017). Specifically, Naji et al. calculated changes in slow wave EEG (i.e., delta band) time-locked to heart rate bursts (i.e., two standard

deviations [*SDs*] below the mean of all IBIs). Results showed that increases in low-frequency oscillations (including delta activity) precede successive bursts of increased HR (shorter IBIs). Intriguingly, the coupling between central and autonomic activity during sleep has been reported to improve learning in a non-declarative memory task, suggesting that an efficient cortical control of the cardiac sympathovagal balance is associated with improved cognitive functioning (Naji et al., 2017).

In addition, even though brain-heart coupling has been consistently reported, the majority of fMRI and EEG studies in this field mainly relied on a correlational method. However, correlation limits the possibility of examining the direction of the brain-heart coupling. In fact, it has to be noted that bottom-up influences from the heart to the brain have been reported as well. For instance, increased cardiac vagal control (as measured by HF-HRV) can modulate the activity of higher level integrative neural networks through baroreflex activity (Grossman and Taylor, 2007; Porges, 2007). A novel method to investigate top-down control of beat-to-beat variability exerted by brain cortex is to compare very long and very short heartbeats in terms of the EEG activity that precedes them. Indeed, long beats in the resting condition indicate increased vagal control on the heart (see for instance the NN50 index of HRV; Malik et al., 1996), as compared to short ones, which, in turn, reflect reduced cardiac vagal control. Given that brain cortex modulation of cardiac vagal tone occurs in a short time range (Nunan et al., 2010; Smith, 1974), a difference could be expected in the EEG activity preceding long (high vagal control) and short (low vagal control) heartbeats, especially over prefrontal areas as suggested by the Neurovisceral Integration Model (Thayer and Lane, 2009, 2000).

In light of these considerations, the present study investigated the role of brain oscillations as recorded by scalp EEG in controlling beat-to-beat variability at rest through a high temporal precision approach. It was hypothesized that a reduction in EEG oscillations in the low-frequency range (i.e., delta and theta bands) over prefrontal areas preceding, and time-locked to, the following heartbeat would be predictive of increased beat-to-beat vagal control on the heart, as indexed by the occurrence

of long IBIs. Since reduced slow wave EEG activity preceding long vs. short IBIs would reflect greater phasic vagal control over the heart, it was also hypothesized that average prefrontal slow wave activity would be negatively correlated with tonic vagal control as calculated with frequency-domain analysis (i.e., HF-HRV calculated over the whole recording period). Therefore, individuals with a greater reduction in prefrontal slow wave activity occurring prior to longer IBIs were expected to show greater tonic vagal control.

Method

Participants

Forty-three healthy undergraduates (31 females; mean age: 22.95 ± 2.14 years; mean education: 16.37 ± 1.30 years) from the University of Padua volunteered for the study. All participants were righthanded and had normal or corrected-to-normal vision. Data from five participants were excluded for artefacts in the electrophysiological data. Thus, the final sample consisted of 38 individuals medically healthy and free of medication. The study was approved by the ethics committee of the University of Padua and all volunteers gave written consent prior to participation. The study was conducted in accordance with the Declaration of Helsinki.

Procedure

Upon arrival at the laboratory, participants received general information about the experiment, and read and signed an informed consent. Then, each participant was seated in a comfortable armchair in a sound-attenuated, dimly-lit room, and sensors were attached. An elastic cap embedded with 32 EEG electrodes was applied and ECG electrodes were attached; then, each participant completed a five-minute resting-state recording. Participants were instructed to stay still and to keep their gaze on a central fixation cross during the electrophysiological recording in order to minimize eye movements.

Electrophysiological data recording and processing

ECG

Ag/AgCl surface electrodes were positioned on the participant's chest in a modified lead II configuration to register the ECG. The raw signal was amplified with a gain of 150, bandpass filtered (0.3–100 Hz) and digitized at 500 Hz (16 bit A/D converter; resolution 0.559 μV/LSB). Time-series of IBIs were obtained applying a digital trigger to the R-waves. The signal was visually inspected and a piecewise cubic spline interpolation method, which generates missing or corrupted values into IBIs series, was applied for artefact correction. Then, using Kubios HRV Analysis Software 2.2 (The Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland), fast Fourier spectral analysis was applied on the IBIs series to compute frequency domain indexes, in particular: 1) HRV total power in ms^2, reflecting the variance of all IBIs (Malik et al., 1996); 2) HF-HRV power (0.15–0.40 Hz) in ms^2, which primarily reflects cardiac parasympathetic tone (Malik et al., 1996). Frequency domain indexes were logarithmically transformed to normalize their distribution.

EEG

The EEG signal was collected using an elastic cap with tin electrodes (Electro-cap International, Inc.) from 32 scalp positions (i.e., Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, T3, C3, CZ, C4, T4, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8, O1, Oz, O2 and A2 [right mastoid]), referenced online to A1 (left mastoid). Both vertical and horizontal electrooculograms (EOGs) were recorded using a bipolar montage to monitor eye-movements and eye-blinks. The electrode pairs were placed at the supra- and suborbit of the right eye and at the external canthi of the eyes, respectively. The EEG signal was bandpass filtered online (EEG filter = 0.1-70 Hz), digitized at 500 Hz (16 bit AD converter, accuracy 0.034 μV/bit). Offline the EEG was re-referenced to a linked mastoids montage,

corrected for eyeblink artefacts using a regression-based algorithm (Scan 4.1 software), and low-pass filtered at 30 Hz. Filtering and further EEG processing were run in Brainstorm (Tadel et al., 2011).

As an index of beat-to-beat parasympathetic vagal influence on the sinoatrial node, the longest IBIs were identified for each participant, assuming that in the resting condition sympathetic activation is at its minimum and that variations in HR are mainly driven by vagal firing over the sinoatrial node (Robinson et al., 1966). First, outliers in the IBIs series (IBIs exceeding ±3 *SDs* from the individual average) were detected and excluded from the following computations. Long IBIs were defined as the intervals equal to or above the 85th percentile of each participant's distribution, intervals equal to or below the 15th percentile were defined as short IBIs. The threshold choices represent a compromise between obtaining a sufficient number of EEG epochs time-locked to R-waves to perform statistical analyses and ensuring separation between long and short IBIs. At the group level, average long IBIs significantly differed from short IBIs (M_{long} = 0.85 ms, SD_{long} = 0.11 ms*;* M_{short} = 0.69 ms, SD_{short} = 0.09 ms; $t(37) = -20.30$, $p < .001$, 95% $CI_{Long\ -Short}$ = {-0.17 -0.14}; see also Figure 1a). To further control that the distributions of long and short IBIs were uniform throughout the five-minute recording session (and not clustered at the beginning and/or at the end of the recording as a possible consequence of modifications in arousal state during the recording), frequency distributions were plotted. As shown in Figure 1b, the two categories of IBIs are evenly distributed over the entire 300 sec.

The EEG signal was then epoch time-locked to the R-waves corresponding to long and short IBIs with a -2000 ms to +2000 ms interval to prevent potential boundary effects in the time-frequency decomposition. Artefact rejection procedures included the automatic rejection of epochs in which the signal exceeded ±70 µV amplitude and visual inspection of the remaining epochs for residual artefacts. Then, Morlet wavelet transformation on individual trials was applied for each 1 Hz frequency bin between 1 and 30 Hz, using a mother wavelet at 1 Hz with 3 seconds time-resolution (as calculated by

the Full Width at Half Maximum; FWHM). Time-frequency decompositions were then averaged for each participant and condition (short and long IBIs).

All electrophysiological signals were amplified with Neuroscan Synamps (El Paso, TX, USA), and stored on to a Pentium IV computer. All electrode impedances were kept below 5 kΩ.

Statistical analysis

Following a method proposed in recent EEG studies (El Zein et al., 2015), we performed single-trial general linear regression models (GLM) to analyze the data. A logistic model was applied, where EEG power at each electrode, frequency and time point, before and after stimulus onset (from 1240 ms before to 1240 ms after stimulus onset, after cutting out the extremes of the epoch contaminated by the edge effect), was introduced as a trial-per-trial predictor of heartbeat length (see Equation 1).

$$beat\ length(1\ =\ long;\ 0\ =\ short) \sim ln(EEG\ power)$$

The resulting parameter estimates of the regression, reported in arbitrary units, were measured per participant. The time course of the parameter estimates describes the log-odds of the probability of having a long vs. short heartbeat for each unit increment in EEG power. Positive values indicate that an increment in EEG power predicts an increment of the probability of having a long vs. short heartbeat in that trial.

All regression-based analyses of the EEG data were performed independently for each participant. Then, analyses at the group level were employed to test the significance of the observed effects across participants. Namely, standard parametric tests against zero were run, controlling for the type I error rate arising from multiple comparisons across electrodes, frequencies and time points through non-parametric cluster-level statistics (Maris and Oostenveld, 2007). The pairing between the experimental condition and zero was shuffled pseudo-randomly 1000 times, and the maximal cluster-level statistics (the sum of t-values across contiguously significant electrodes, frequencies and time

points at a threshold level of 0.005) were extracted for each shuffle to compute a "null" distribution of effect size across the whole-time window. The proportion of clusters in the null distribution whose statistics exceeded the one obtained for each significant cluster in the original (non-shuffled) data was computed, resulting in its cluster-corrected p-value.

To further confirm that the parameter estimates of the regression reflected parasympathetic control over the sinoatrial node, Pearson correlations were computed between the parameter estimates for each participant in the significant cluster frequencies at each time point, and the average individuals' cardiac parameters calculated over 5 minutes (i.e., IBIs, total lnHRV, and lnHF).

Results

Cluster-based EEG analysis highlighted the presence of a significant negative frontal cluster (p_{corr} = 0.01), ranging from -1240 to -260 ms and relative to the 2 to 3 Hz (i.e., delta) frequency range (Figure 2). This result indicates that for this specific cluster of electrodes (i.e., Fp1, Fp2, F3, FZ, F4, F8, FC3, FCZ, FC4, FT8, CZ), frequencies and time points, the parameter estimates of the logistic regression were significantly lower than zero, indicating that as delta power decreases the probability of a subsequent long heartbeat to occur increases, compared to the probability of a short one.

As depicted in Figure 3, regression parameter estimates in the delta range revealed a negative association with both lnHF and total lnHRV values, which was largest at frontal electrodes during the time period preceding the heartbeat. In other words, at the single subject level, the greater the decrease in frontal delta preceding long relative to short heartbeats, the higher the HF power and total HRV power over the whole period. Interestingly, this correlation pattern did not emerge for IBIs, strengthening the specificity of the association between prefrontal delta power and vagally mediated HRV.

Discussion

The main aim of the present study was to evaluate the possibility of predicting beat-to-beat cardiac vagal activation from EEG activity using a high temporal precision approach. The results showed that higher cardiac vagal control, as indexed by longer IBIs, was preceded by a reduction in delta activity over prefrontal and frontocentral areas. Consistent with this finding, the measure of brain-heart coupling was specifically associated with lnHF power, which is a well-established parameter reflecting vagally mediated HRV. In contrast, average IBIs, which is influenced by both parasympathetic and sympathetic ANS branches, did not correlate with prefrontal and frontocentral delta activity.

Since reductions in delta activity over anterior scalp sites have been associated with higher cortical activity over prefrontal brain regions (Kilner et al., 2005), it could be proposed that increased prefrontal activity triggers high cardiac vagal control. In this fashion, the waxing and waning of the prefrontal cortex activity, as reflected in delta oscillations, seems to act as a dynamic brake on the cardiac rhythm. Consistent with this interpretation, slow wave oscillations (including both delta and theta band activity) have been associated with autonomic control and long-range communication/modulation between brain areas (Knyazev, 2012). More specifically, delta band activity has been proposed to be crucial for the synchronization of brain activity with autonomic functions, such as heartbeat and breathing (Knyazev, 2012). Accordingly, it has been recently shown that increases in EEG slow oscillations predict bursts of increased HR (Naji et al., 2017), thus supporting the hypothesis of delta activity as an EEG indicator of brain-heart coupling. In addition, the present findings are in line with those of previous fMRI studies reporting that increased frontal activity is associated with higher vagal control over the heart (Gillie et al., 2014; Lane et al., 2009; Ruiz Vargas et al., 2016; Shoemaker et al., 2015).

The present results are also consistent with previous findings reporting a positive association between tonic cardiac vagal control (as indexed by HF-HRV) and phasic HR response to emotional stimuli (Ruiz-Padial et al., 2017; Thayer et al., 2000). This has important implications for better understanding cortical processes underlying the relation between tonic HRV measures and phasic vagal control of the heart. Greater phasic vagally mediated response has been suggested to index the integrity of neuroregulatory processes involved in organism-environment regulation, and tonic HRV can be an indicator of flexible responsiveness to environmental demands (Goldberger, 1991). Therefore, these findings are interesting from a clinical perspective. A wide range of psychopathological syndromes has been linked to both central and peripheral alterations. Indeed, reduced activity in PFC, particularly vmPFC and dorsolateral PFC (DLPFC), and decreased HF-HRV have been reported in individuals with psychopathology, including depression (Rottenberg et al., 2007, 2005), anxiety (Åhs et al., 2009; Hastings et al., 2008; Kemp et al., 2014) and schizophrenia (Clamor et al., 2016). Consistent with these findings, a disruption in top-down PFC control mediated by an increased activation in the ventral portion of the anterior cingulate cortex (vACC) has been proposed to characterize individuals with psychopathology and, more intriguingly, to confer vulnerability to psychopathology (Beauchaine and Thayer, 2015). Given that increased slow wave EEG activity at rest has been reported in depression (Bjørk et al., 2008; Gatt et al., 2008; Korb et al., 2008), anxiety disorders (Gauthier et al., 2009; Velikova et al., 2010) and schizophrenia (Alfimova and Uvarova, 2003; Bates et al., 2009; Boutros et al., 2008), it can be speculated that the reduced integrity in the brain-heart network may be reflected by disrupted delta-HRV coupling in individuals with psychopathology. Clearly, future studies are warranted to test whether individuals with psychopathology, particularly those suffering from anxiety and depressive disorders, are characterized by abnormal delta-HRV coupling.

The present study is, to our knowledge, the first to evaluate beat-to-beat EEG correlates of resting heart rate modulation. The GLM approach applied here allowed an accurate estimation of the

probability of increased vagal control on the heart (i.e., the occurrence of a long heartbeat) from each electrode, time-point and frequency, providing a powerful trial-by-trial measure of the causal impact of brain activity on the heart rhythm. Combined with a cluster-based approach for multiple comparison correction, this method allowed a rigorous and conservative data-driven approach, which did not require any a-priori assumption on the scalp sites, frequencies and time points implied in the EEG-ECG coupling.

The current findings ought to be interpreted in light of some limitations. First, the sample is only representative of a young and healthy population, limiting the generalizability of the results. Second, the possibility of an influence of ECG artefacts on the results cannot be completely ruled out. Nevertheless, the ICA procedure run to identify this artefact over the EEG signal was ineffective, since the artefact was hardly visible in the majority of the participants. Therefore, no correction was applied in order to avoid the risk of removing meaningful physiological EEG signal. It has to be noted that the typical frequency range of ECG artefact (~15-35 Hz; Jiang et al., 2007) is clearly separate from the frequency range reported in this study (2-3 Hz). Thus, the findings reported in delta activity are unlikely to be explained by ECG artifacts. Future studies should better control for this possible confound by using recording techniques that allow clear identification of ECG artifacts, such as magnetoencephalography (MEG). Finally, MEG or high-density EEG studies may help clarify the neural generators of frontal delta activity preceding heartbeats. This would be a critical step toward a more detailed comparison with findings obtained by fMRI studies, which reported specific cortical regions (e.g., the vmPFC) to be associated with vagal control on the heart.

In conclusion, the present findings support the hypothesis that phasic activation/deactivation of prefrontal areas modulates vagal control of heart rate at rest, in line with the assumptions made by the Neurovisceral Integration Model. Specifically, the utilization of a high temporal resolution approach revealed that a reduction in delta activity over the prefrontal areas, presumably indicating prefrontal

activation, predicted an immediate increase in vagal control on the sinoatrial node. Future studies on beat-to-beat brain-heart coupling disruption could shed light on the risks for psychopathology and help provide more specific treatment.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Figure 1. Panel a. Plot of means for short IBIs and long IBIs for each participant. **Panel b.** Distributions of short (red area) and long (blue area) IBIs throughout the five-minute recording session.

Figure 2. **Panel a.** Mean of t-values over frequency and time in the significant cluster. **Panel b.** Average of beta values in the significant cluster (time 0 corresponds to the R-wave). The blue square represents significance in time and frequency. The negative beta values displayed in the square indicate that a decrease in delta activity preceding the heartbeat increases the log odds of having a long vs. short heartbeat. A decrease in delta activity is associated with higher probability of the following IBI to be a long one, indicating higher vagal control. **Panel c.** Odds ratios in the delta band over time (blue line represents the mean, orange line represents the median, blue shade represents 95% interval of confidence).

Figure 3. Correlations between regression parameter estimate in the delta range at time points before and after each heartbeat (0 corresponds to the occurrence of the R wave) and HRV parameters (lnHF; lnHRV, and IBIs). lnHF: natural logarithm of High-Frequency power spectrum; lnHRV: natural logarithm of the total power of Heart Rate Variability; IBIs: Inter-Beat Intervals.

References

Åhs, F., Sollers, J.J., Furmark, T., Fredrikson, M., Thayer, J.F., 2009. High-frequency heart rate variability and cortico-striatal activity in men and women with social phobia. Neuroimage 47, 815–820. doi:10.1016/j.neuroimage.2009.05.091

Alfimova, M., Uvarova, L., 2003. Cognitive peculiarities in relatives of schizophrenic and schizoaffective patients: heritability and resting EEG-correlates. Int. J. Psychophysiol. 49, 201–16. doi:10.1016/S0167-8760(03)00133-8

Balaban, C.D., Thayer, J.F., 2001. Neurological bases for balance ± anxiety links. J. Anxiety Disord. 15, 53–79.

Bates, A.T., Kiehl, K.A., Laurens, K.R., Liddle, P.F., 2009. Low-frequency EEG oscillations associated with information processing in schizophrenia. Schizophr. Res. 115, 222–230. doi:10.1016/j.schres.2009.09.036

Beauchaine, T.P., Thayer, J.F., 2015. Heart rate variability as a transdiagnostic biomarker of psychopathology. Int. J. Psychophysiol. 98, 338–350. doi:10.1016/j.ijpsycho.2015.08.004

Benarroch, E.E., Bennaroch, E.E., 1993. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin. Proc. 68, 988–1001. doi:10.1016/S0025-6196(12)62272-1

Bjørk, M.H., Sand, T., Bråthen, G., Linaker, O.M., Morken, G., Nilsen, B.M., Vaaler, A.E., 2008. Quantitative EEG findings in patients with acute, brief depression combined with other fluctuating psychiatric symptoms: a controlled study from an acute psychiatric department. BMC Psychiatry 8, 89. doi:10.1186/1471-244X-8-89

Bootsma, M., Swenne, C.A., Van Bolhuis, H.H., Chang, P.C., Cats, V.M., Bruschke, A. V., 1994. Heart rate and heart rate variability as indexes of sympathovagal balance. Am. J. Physiol. Circ. Physiol. 266, H1565–H1571. doi:10.1152/ajpheart.1994.266.4.H1565

Boutros, N.N., Arfken, C., Galderisi, S., Warrick, J., Pratt, G., Iacono, W., 2008. The status of spectral EEG abnormality as a diagnostic test for schizophrenia. Schizophr. Res. 99, 225–37. doi:10.1016/j.schres.2007.11.020

Chalmers, J.A., Quintana, D.S., Abbott, M.J.-A., Kemp, A.H., 2014. Anxiety Disorders are Associated with Reduced Heart Rate Variability: A Meta-Analysis. Front. psychiatry 5, 80. doi:10.3389/fpsyt.2014.00080

Clamor, A., Lincoln, T.M., Thayer, J.F., Koenig, J., 2016. Resting vagal activity in schizophrenia: Meta-analysis of heart rate variability as a potential endophenotype. Br. J. Psychiatry 208, 9–16. doi:10.1192/bjp.bp.114.160762

Critchley, H.D., Mathias, C.J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B., Cipolotti, L., Shallice, T., Dolan, R.J., 2003. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain 126, 2139–2152. doi:10.1093/brain/awg216

El Zein, M., Wyart, V., Grèzes, J., 2015. Anxiety dissociates the adaptive functions of sensory and motor response enhancements to social threats. Elife 4, 1–22. doi:10.7554/eLife.10274.001

Gatt, J.M., Kuan, S.A., Dobson-Stone, C., Paul, R.H., Joffe, R.T., Kemp, A.H., Gordon, E., Schofield, P.R., Williams, L.M., 2008. Association between BDNF Val66Met polymorphism and trait depression is mediated via resting EEG alpha band activity. Biol. Psychol. 79, 275–284. doi:10.1016/j.biopsycho.2008.07.004

Gauthier, A., Chevrette, T., Bouvier, H., Godbout, R., 2009. Evening vs. morning wake EEG activity in adolescents with anxiety disorders. J. Anxiety Disord. 23, 112–117. doi:10.1016/j.janxdis.2008.04.005

Geisler, F.C.M., Vennewald, N., Kubiak, T., Weber, H., 2010. The impact of heart rate variability on subjective well-being is mediated by emotion regulation. Pers. Individ. Dif. 49, 723–728. doi:10.1016/J.PAID.2010.06.015

Gianaros, P.J., Van Der Veen, F.M., Jennings, J.R., 2004. Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: Implications for the cortical and subcortical regulation of cardiac autonomic activity. Psychophysiology 41, 521–30. doi:10.1111/1469-8986.2004.00179.x

Gillie, B.L., Vasey, M.W., Thayer, J.F., 2014. Heart rate variability predicts control over memory retrieval. Psychol. Sci. 25, 458–65. doi:10.1177/0956797613508789

Glick, G., Braunwald, E., 1965. Relative roles of the sympathetic and parasympathetic nervous systems in the reflex control of heart rate. Circ. Res. 16, 363–75.

Goldberger, A.L., 1991. Is the normal heartbeat chaotic or homeostatic? Physiology 6, 87–91.

Grossman, P., Taylor, E.E.W.E., 2007. Toward understanding respiratory sinus arrhythmia: relations to cardiac vagal tone, evolution and biobehavioral functions. Biol. Psychol. 74, 263–85. doi:10.1016/j.biopsycho.2005.11.014

Hansen, A.L., Johnsen, B.H., Sollers, J.J., Stenvik, K., Thayer, J.F., 2004. Heart rate variability and its relation to prefrontal cognitive function: the effects of training and detraining. Eur. J. Appl. Physiol. 93, 263–272. doi:10.1007/s00421-004-1208-0

Hansen, A.L., Johnsen, B.H., Thayer, J.F., 2003. Vagal influence on working memory and attention. Int. J. Psychophysiol. 48, 263–274. doi:10.1016/S0167-8760(03)00073-4

Hastings, P.D., Sullivan, C., McShane, K.E., Coplan, R.J., Utendale, W.T., Vyncke, J.D., 2008. Parental Socialization, Vagal Regulation, and Preschoolers' Anxious Difficulties: Direct Mothers and Moderated Fathers. Child Dev. 79, 45–64. doi:10.1111/j.1467-8624.2007.01110.x

Jiang, J.-A., Chao, C.-F., Chiu, M.-J., Lee, R.-G., Tseng, C.-L., Lin, R., 2007. An automatic analysis method for detecting and eliminating ECG artifacts in EEG. Comput. Biol. Med. 37, 1660–1671. doi:10.1016/j.compbiomed.2007.03.007

Kemp, A.H., Brunoni, A.R., Santos, I.S., Nunes, M.A., Dantas, E.M., Carvalho de Figueiredo, R.,

Pereira, A.C., Ribeiro, A.L.P., Mill, J.G., Andreão, R. V, Thayer, J.F., Benseñor, I.M., Lotufo, P.A., 2014. Effects of Depression, Anxiety, Comorbidity, and Antidepressants on Resting-State Heart Rate and Its Variability: An ELSA-Brasil Cohort Baseline Study. Am. J. Psychiatry 171, 1328–1334. doi:10.1176/appi.ajp.2014.13121605

Kemp, A.H., Quintana, D.S., Gray, M.A., Felmingham, K.L., Brown, K., Gatt, J.M., 2010. Impact of Depression and Antidepressant Treatment on Heart Rate Variability: A Review and Meta-Analysis. Biol. Psychiatry 67, 1067–1074. doi:10.1016/j.biopsych.2009.12.012

Kilner, J.M., Mattout, J., Henson, R., Friston, K.J., 2005. Hemodynamic correlates of EEG: A heuristic.

Knyazev, G.G., 2012. EEG delta oscillations as a correlate of basic homeostatic and motivational processes. Neurosci. Biobehav. Rev. 36, 677–695. doi:10.1016/j.neubiorev.2011.10.002

Korb, A.S., Cook, I.A., Hunter, A.M., Leuchter, A.F., 2008. Brain Electrical Source Differences between Depressed Subjects and Healthy Controls. Brain Topogr. 21, 138–146. doi:10.1007/s10548-008-0070-5

Kubota, Y., Sato, W., Toichi, M., Murai, T., Okada, T., Hayashi, A., Sengoku, A., 2001. Frontal midline theta rhythm is correlated with cardiac autonomic activities during the performance of an attention demanding meditation procedure. Cogn. Brain Res. 11, 281–287. doi:10.1016/S0926-6410(00)00086-0

Lane, R., MCrae, K., Reiman, E., Chen, K., Ahern, G., Thayer, J.F., 2009. Neural correlates of heart rate variability during emotion. Neuroimage 44, 213–222. doi:10.1016/j.neuroimage.2008.07.056

Liou, L.-M., Ruge, D., Kuo, M.-C., Tsai, J.-C., Lin, C.-W., Wu, M.-N., Hsu, C.-Y., Lai, C.-L., 2014. Functional connectivity between parietal cortex and the cardiac autonomic system in uremics. Kaohsiung J. Med. Sci. 30, 125–32. doi:10.1016/j.kjms.2013.11.001

Luft, C.D.B., Takase, E., Darby, D., 2009. Heart rate variability and cognitive function: Effects of physical effort. Biol. Psychol. 82, 186–191. doi:10.1016/j.biopsycho.2009.07.007

Malik, M., Bigger, J.T., Camm, A.J., Kleiger, R.E., Malliani, A., Moss, A.J., Schwartz, P.J., 1996. Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. Eur. Heart J. 17, 354–381. doi:10.1161/01.CIR.93.5.1043

Maris, E., Oostenveld, R., 2007. Nonparametric statistical testing of EEG- and MEG-data. J. Neurosci. Methods 164, 177–190. doi:10.1016/j.jneumeth.2007.03.024

Matthews, S.C., Paulus, M.P., Simmons, A.N., Nelesen, R.A., Dimsdale, J.E., 2004. Functional subdivisions within anterior cingulate cortex and their relationship to autonomic nervous system function. Neuroimage 22, 1151–6. doi:10.1016/j.neuroimage.2004.03.005

Mueller, E.M., Stemmler, G., Wacker, J., 2010. Single-trial electroencephalogram predicts cardiac acceleration: a time-lagged P-correlation approach for studying neurovisceral connectivity. Neuroscience 166, 491–500. doi:10.1016/j.neuroscience.2009.12.051

Naji, M., Krishnan, G., McDevitt, E.A., Bazhenov, M., Mednick, S.C., 2017. Coupling of autonomic and central events during sleep boosts declarative memory consolidation. bioRxiv 195586.

Nugent, A.C., Bain, E.E., Thayer, J.F., Sollers, J.J., Drevets, W.C., 2011. Heart rate variability during motor and cognitive tasks in females with major depressive disorder. Psychiatry Res. 191, 1–8. doi:10.1016/j.pscychresns.2010.08.013

Nunan, D., Sandercock, G.R.H., Brodie, D.A., 2010. A Quantitative Systematic Review of Normal Values for Short-Term Heart Rate Variability in Healthy Adults. Pacing Clin. Electrophysiol. 33, 1407–1417. doi:10.1111/j.1540-8159.2010.02841.x

O'Connor, M.F., Gündel, H., McRae, K., Lane, R.D., 2007. Baseline vagal tone predicts BOLD response during elicitation of grief. Neuropsychopharmacology 32, 2184–2189. doi:10.1038/sj.npp.1301342

Ongur, D., Price, J.L., 2000. The Organization of Networks within the Orbital and Medial Prefrontal Cortex of Rats, Monkeys and Humans. Cereb. Cortex 10, 206–219. doi:10.1093/cercor/10.3.206

Panitz, C., Wacker, J., Stemmler, G., Mueller, E.M., 2013. Brain–heart coupling at the P300 latency is linked to anterior cingulate cortex and insula—A cardio-electroencephalographic covariance tracing study. Biol. Psychol. 94, 185–191. doi:10.1016/j.biopsycho.2013.05.017

Patron, E., Messerotti Benvenuti, S., Favretto, G., Gasparotto, R., Palomba, D., 2013. Depression and reduced heart rate variability after cardiac surgery: The mediating role of emotion regulation. Auton. Neurosci. 180, 53–58. doi:10.1016/j.autneu.2013.11.004

Patron, E., Messerotti Benvenuti, S., Favretto, G., Valfrè, C., Bonfà, C., Gasparotto, R., Palomba, D., 2012. Association between depression and heart rate variability in patients after cardiac surgery: A pilot study. J. Psychosom. Res. 73. doi:10.1016/j.jpsychores.2012.04.013

Pfurtscheller, K., Bauernfeind, G., Müller-Putz, G.R., Urlesberger, B., Müller, W., Pfurtscheller, G., 2008. Correlation between EEG burst-to-burst intervals and HR acceleration in preterm infants. Neurosci. Lett. 437, 103–6. doi:10.1016/j.neulet.2008.03.079

Piper, D., Schiecke, K., Leistritz, L., Pester, B., Benninger, F., Feucht, M., Ungureanu, M., Strungaru, R., Witte, H., 2014. Synchronization analysis between heart rate variability and EEG activity before, during, and after epileptic seizure. Biomed. Eng. / Biomed. Tech. 59, 343–55. doi:10.1515/bmt-2013-0139

Porges, S.W.S.W., 2007. The polyvagal perspective. Biol. Psychol. 74, 116–43. doi:10.1016/j.biopsycho.2006.06.009

Robinson, B.F., Epstein, S.E., Beiser, G.D., Braunwald, E., 1966. Control of heart rate by the autonomic nervous system. Studies in man on the interrelation between baroreceptor mechanisms and exercise. Circ. Res. 19, 400–11.

Rottenberg, J., Chambers, A.S., Allen, J.J.B., Manber, R., 2007. Cardiac vagal control in the severity and course of depression: The importance of symptomatic heterogeneity. J. Affect. Disord. 103, 173–179. doi:10.1016/j.jad.2007.01.028

Rottenberg, J., Salomon, K., Gross, J.J., Gotlib, I.H., 2005. Vagal withdrawal to a sad film predicts subsequent recovery from depression. Psychophysiology 42, 277–281. doi:10.1111/j.1469-8986.2005.00289.x

Ruiz-Padial, E., Mendoza Medialdea, M.T., Reyes Del Paso, G., Thayer, J.F., 2017. Individual Differences in Attentional Capture by Pictures of Fear and Disgust as Indexed by Cardiac Responses. J. Psychophysiol. 1–11. doi:10.1027/0269-8803/a000198

Ruiz Vargas, E., Sörös, P., Shoemaker, J.K., Hachinski, V., 2016. Human cerebral circuitry related to cardiac control: A neuroimaging meta-analysis. Ann. Neurol. 79, 709–716. doi:10.1002/ana.24642

Scrimin, S., Patron, E., Florit, E., Palomba, D., Mason, L., 2017. The role of cardiac vagal tone and inhibitory control in pre-schoolers' listening comprehension. Dev. Psychobiol. 59, 970–975. doi:10.1002/dev.21576

Shoemaker, J.K., Norton, K.N., Baker, J., Luchyshyn, T., 2015. Forebrain organization for autonomic cardiovascular control. Auton. Neurosci. 188, 5–9. doi:10.1016/j.autneu.2014.10.022

Sloan, R.P., Shapiro, P.A., Bigger, J.T., Bagiella, E., Steinman, R.C., Gorman, J.M., 1994. Cardiac autonomic control and hostility in healthy subjects. Am. J. Cardiol. 74, 298–300.

Smith, O.A., 1974. Reflex and central mechanisms involved in the control of the heart and circulation. Annu. Rev. Physiol. 36, 93–123.

Tadel, F., Baillet, S., Mosher, J.C., Pantazis, D., Leahy, R.M., 2011. Brainstorm: A user-friendly application for MEG/EEG analysis. Comput. Intell. Neurosci. 2011. doi:10.1155/2011/879716

Ter Horst, G.J., Postema, F., 1997. Forebrain parasympathetic control of heart activity: retrograde transneuronal viral labeling in rats. Am. J. Physiol. Circ. Physiol. 273, H2926–H2930. doi:10.1152/ajpheart.1997.273.6.H2926

Thayer, J.F., Friedman, B.H., Borkovec, T.D., Johnsen, B.H., Molina, S., 2000. Phasic heart period reactions to cued threat and nonthreat stimuli in generalized anxiety disorder. Psychophysiology

37, 361–368. doi:10.1111/1469-8986.3730361

Thayer, J.F., Hansen, A.L., Saus-Rose, E., Johnsen, B.H., 2009. Heart rate variability, prefrontal neural function, and cognitive performance: The neurovisceral integration perspective on self-regulation, adaptation, and health. Ann. Behav. Med. 37, 141–153. doi:10.1007/s12160-009-9101-z

Thayer, J.F., Lane, R.D., 2000. A model of neurovisceral integration in emotion regulation and dysregulation. J. Affect. Disord. 61, 201–16.

Thayer, J.F., Lane, R.D., 2009. Neuroscience and Biobehavioral Reviews Claude Bernard and the heart – brain connection : Further elaboration of a model of neurovisceral integration. Neurosci. Biobehav. Rev. 33, 81–88. doi:10.1016/j.neubiorev.2008.08.004

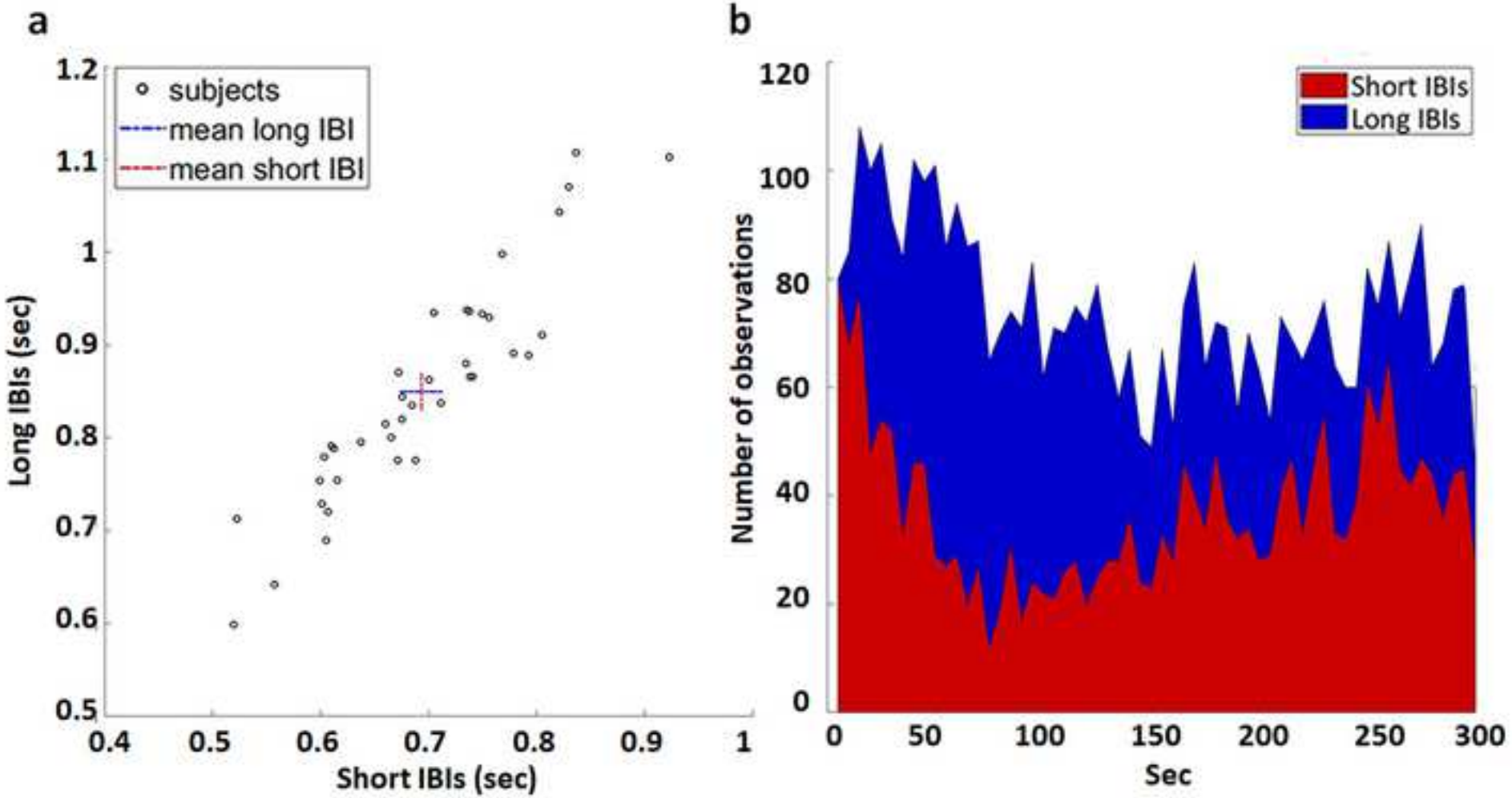
Thayer, J.F., Yamamoto, S.S., Brosschot, J.F., 2010. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int. J. Cardiol. 141, 122–31. doi:10.1016/j.ijcard.2009.09.543

Velikova, S., Locatelli, M., Insacco, C., Smeraldi, E., Comi, G., Leocani, L., 2010. Dysfunctional brain circuitry in obsessive–compulsive disorder: Source and coherence analysis of EEG rhythms. Neuroimage 49, 977–983. doi:10.1016/j.neuroimage.2009.08.015

Wong, S.W., Massé, N., Kimmerly, D.S., Menon, R.S., Shoemaker, J.K., 2007. Ventral medial prefrontal cortex and cardiovagal control in conscious humans. Neuroimage 35, 698–708. doi:10.1016/j.neuroimage.2006.12.027

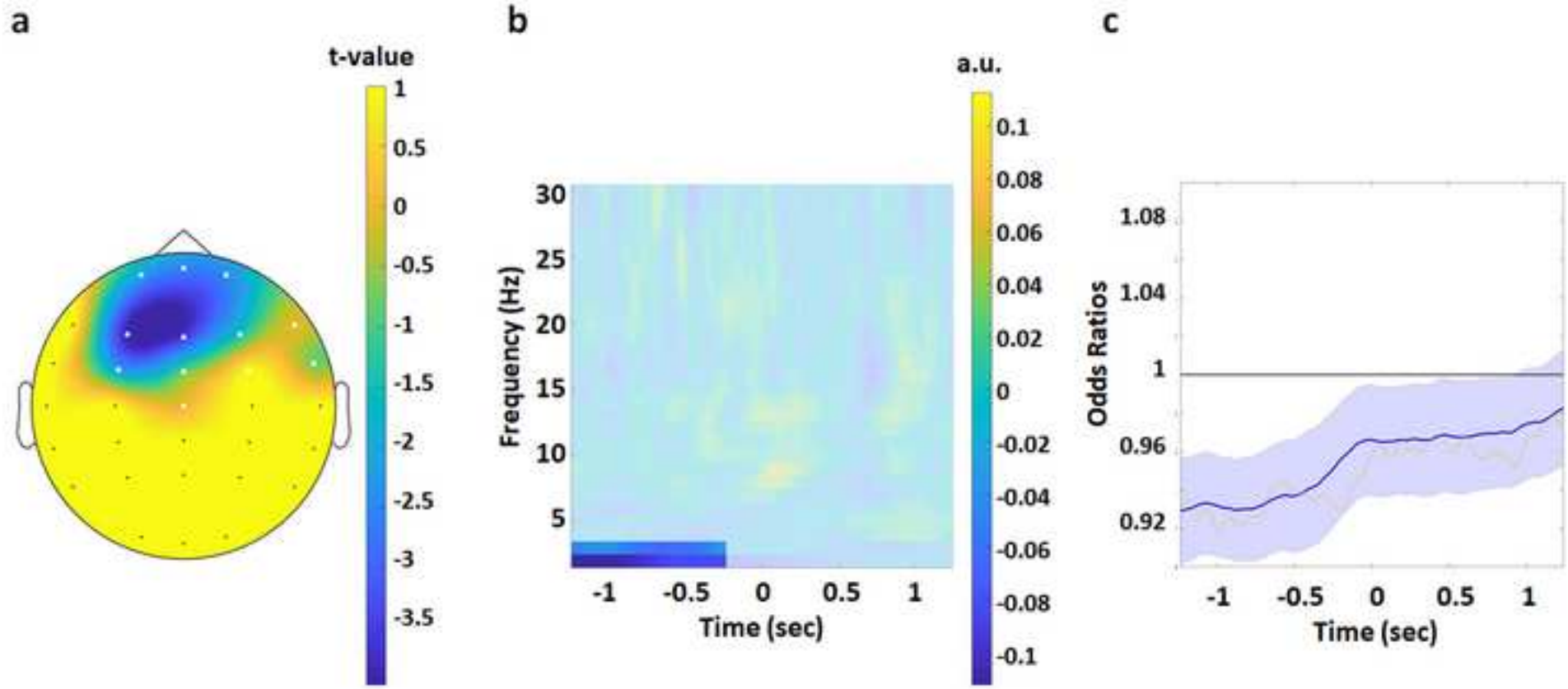
9. Figure 1

Click here to download high resolution image



9. Figure 2

Click here to download high resolution image



9. Figure 3

Click here to download high resolution image