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Research Report

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Time-Resolved Phase-Amplitude Coupling (PAC) in the Brain's Resting-State Network using Magnetoencephalography (MEG)

ABSTRACT

The resting state networks (RSNs) in the brain can be investigated non-invasively using magnetoencephalography (MEG). The underlying network connectivity is revealed through cross-frequency phase-amplitude coupling (PAC) in which the amplitude of high-frequency oscillations is coupled to and modulated by the phase of slower oscillatory activity. In the present work, a new measure for assessing PAC in a time-resolved manner is explored to better capture the dynamic fluctuation of coupling intensity. The measure is applied to resting-state recordings in healthy subjects from the open MEG archive (OMEGA). The preliminary findings presented here draw insight to the technical aspects of this technique and offer future direction for examining long-range communication in the brain, specifically in RSNs.

Introduction

Cross-frequency coupling (CFC) occurs in neural oscillatory activity and is suggested to be involved in facilitating long-range communication, information transfer, learning, and memory (Canolty & Knight, 2010). Ongoing neural oscillations interact with one another across spatial and temporal scales, reflecting dynamic changes in cortical excitability (Fries, 2005). One of the most well recognized forms of CFC is phase amplitude coupling (PAC) in which the amplitude of a high (nested) frequency is modulated by the phase of a slower (nesting) frequency (Tort et al., 2010). The phase in the nesting oscillation at which the amplitude of the nested signal is consistently at a maximum is described as the coupling phase. This type of coupling has long been demonstrated in hippocampus studies involving theta/gamma nesting (Bragin et al., 1995), in the neocortex (Canolty et al., 2006), and in different cognitive tasks such as attentional selection and memory (Schroeder & Lakatos, 2009; Tort et al., 2010). Additionally, PAC has been observed across a variety of species: rats (Sirota et al., 2008), monkeys (Lakatos et al., 2005), humans (Canolty et al., 2006; Cohen, 2008; Voytek et al., 2010) and across many frequency bands (Lakatos et al., 2005). Most importantly, recent findings using magnetoencephalography (MEG) have highlighted that synchronized PAC is occurring during resting-state activity and could be facilitating communication between different brain regions (Florin & Baillet, 2015).

Time-Resolved Phase-Amplitude Coupling

There are different methods for measuring PAC, each one being preferential in addressing the experimental question at hand and with its own limitations. Generally speaking, most techniques extract an average value across a large temporal scale and neglect to account for dynamic changes in ongoing neural activity. Apart from event-related phase-amplitude coupling (ERPAC), which accounts for the temporal evolution but only for event-related datasets (Voytek et al., 2013), a new method called dynamic phase-amplitude coupling (DPAC) is proposed (Samiee & Baillet, in prep) for studying the dynamics of coupling. This new metric is used to study time-resolved cross-frequency coupling and is able to be applied to study spontaneous rhythmic brain activity in the resting state.

Resting-State Networks (RSNs)

Cross-frequency PAC has recently been speculated as being an underlying mechanism to long-range neural communication between brain structures in the resting state networks (RSNs) (Florin & Baillet, 2015). Past functional MRI studies of human resting state have shown coactivation of time-series between different brain regions that suggest functional connectivity (Lowe et al., 2000). It is these regions that demonstrate correlated activity at rest which comprise different RSNs. Namely, there was found to be a high correlation between the left and right primary motor areas in resting recordings (Biswal et al., 1995), primary visual network regions, attentional networks, as well as other cognitive networks (Van den Heuvel et al., 2008a). One of the most prominent RSNs is the default mode network (DMN) which is said to be active during internal cognitive events such as taking on the perspective of others, future envisioning, and self-referential processing, generally in the absence of goal-directed or attention-demanding tasks (Raich et al., 2001). The interconnected brain regions that comprise the DMN are the medial prefrontal cortex (mPFC), the lateral temporal cortex, the medial temporal lobe (MTL), the posterior cingulate cortex/retrosplenial cortex, inferior parietal lobe (IPL), as well as the hippocampal formation (HF) (Buckner et al., 2008).

Magnetoencephalography (MEG)

Using MEG, which has millisecond temporal resolution, the functional connectivity of the RSNs can be studied directly, unlike fMRI which depends on an indirect measure of neural activity (haemodynamic signal) and has a poor temporal resolution. In a previous study, Florin and Baillet (2015) were able to extract RSNs using a signal model, called megPAC, that measured PAC in the ongoing neural activity at rest. They then proposed the synchronized gating hypothesis which theorizes that the synchrony of phase between the slow (nesting) oscillations is the principal mechanism for "opening the gate" for long-range communication, allowing for the coherence of the amplitude of high frequency bursts (Florin & Baillet, 2015). Thus, by using the new DPAC metric to study intrinsic connectivity in RSNs, it is possible to better examine the dynamics of PAC fluctuations and confirm the similarities between RSNs found in fMRI studies.

Methods

Subjects

The resting-state MEG data and T1-weighted anatomical MRI data from the open MEG archive (OMEGA) was collected for 2 subjects (Niso et al., 2016) to be examined to present preliminary findings. The subjects were both healthy, right-handed, and provided consent for use of their data. In the future for group analysis, more subject data will be used.

MEG Data Acquisition

Prior to recording, it was verified that subjects did not contain any metal on or in them that could contaminate the data. Next, registration of scalp points was performed from properly positioned head coils and electrodes were placed on the subject's chest as well as on one eye in order to measure electrocardiac activity (ECG) and eye blink (EOG). The resting-state MEG data was recorded from subjects in seated position eyes-open using a 275 channel CTF MEG system for a minimum of a 5 minute duration at a sampling rate of 2400Hz. There were also 2 minutes of empty-room data recorded to control for sensor and environmental noise.

Anatomy and Data Preprocessing

The MEG data was pre-processed and analyzed using the open-source software Brainstorm (Tadel 2011). The cortical surface models were extracted using Freesurfer (Dale et al., 1999). Data from the sensors was then projected onto the cortex models created by Brainstorm. Next, the power line DC offset and harmonics were accounted for (at 60, 120, 180Hz) and removed from the raw data. Further, contaminating artifacts such as heartbeats, eye-blinks, and head movement beyond a 5mm threshold were removed.

Source Estimation and Regions of Interest

A head model was created using the overlapping spheres model available in Brainstorm. After the noise covariance matrix was obtained from the noise recordings, the sources were computed using minimum norm imaging and a constrained source model. A PAC atlas was created with 8 user-defined seed regions of interest (ROIs) in the left visual (LV), right visual (RV), left motor (LMot), right motor (RMot), left auditory (LA), right auditory (RA), posterior cingulate cortex (PCC), and medial prefrontal cortex (PFC) regions (See Figure 1).

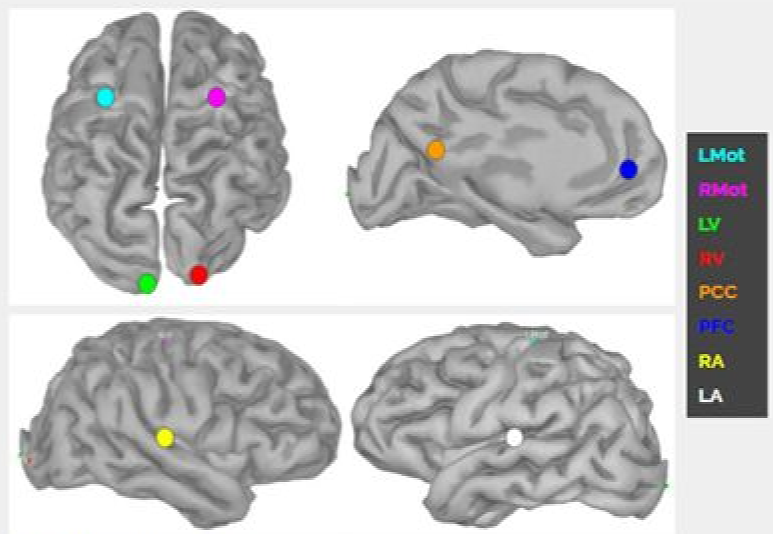

Figure 1: Seed locations

Dynamic Phase Amplitude Coupling (DPAC) Analysis

The DPAC metric was computed across each source time series of 298 seconds in each subject. This method extracts the low frequency from the power spectrum of the high frequency envelope that is responsible for modulating the amplitude of the nested signal (Samiee & Baillet, in prep). The mean vector length algorithm is then applied to measure the coupling intensity between the phase of the lower frequency (nesting signal) and the amplitude of the high frequency (nested signal). The parameters were set to 2-12Hz for the nesting low frequency band, 80-150Hz for the nested high frequency band and a time window of 149 seconds. As mentioned, the data length should be twice the duration of the sliding time window or longer to obtain a minimum of 3 points in the time domain in the outputted map (Samiee, 2015). A semi-comodulogram is then computed for each DPAC map to visualize the cross-frequency coupling in the frequency domain. The PAC parameters for a point in the map that has maximum coupling intensity are then saved to be used for the generation of the megPAC signal.

megPAC Signal Model

The signal model used was an extension of Florin & Baillet (2015) megPAC signal model using the direct PAC measure. First, a Hilbert transform was applied for both the low nesting frequency signal (Flow) and the high nested frequency signal (Fhigh) to find the instantaneous phase and amplitude (magnitude) values respectively. The Hilbert transform used a band-passed signal in the range of Flow+/-0.5Hz for the nesting signal and Fhigh+/-2Hz for the nested signal. Using the measured phasePAC value (the coupling phase of the slow oscillation), the time points at which coupling occurred (tpac) were obtained and the gamma amplitude of the source signal (in the range of [Fhigh - 2 Hz, Fhigh + 2 Hz]) was extracted for each time occurrence. These data points were then linearly interpolated using the interp1 function in Matlab. This process was repeated for each of the 8 sources and the resulting megPAC signals were concatenated in a file to be generated in Brainstorm. The resulting megPAC signals were downsampled to 10Hz and then low-pass filtered at 0.1Hz to create filtered megPAC signals to be used for connectivity analysis.

Correlation in RSNs

The connectivity analysis included finding pairwise correlation coefficients between the different pairs of time-series at the specified sources. An array of correlation values [N x N] was created for each subject.

Preliminary Results

The resting-state pipeline to extract the megPAC signal produced 8 separate plots for each source as seen in Figure 2, which presents the filtered results for a single subject. Each generation of megPAC signal depended on the parameters that the DPAC method optimally selected from the semi-comodulogram: the nesting frequency (Flow), the nested frequency (Fhigh), the coupling phase (phasePAC), and the coupling intensity (maxPAC). As mentioned, these values were extracted for a 149 second time window at the point with maximum coupling intensity in the semi-comodulogram map.

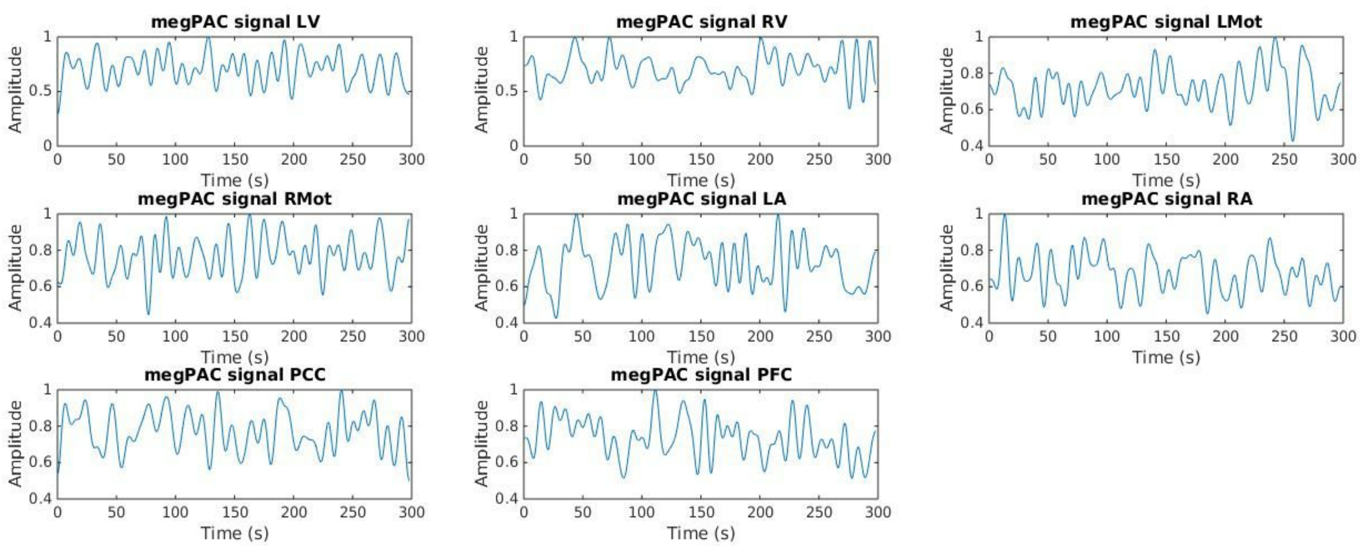

Figure 2: Filtered megPAC signals for all sources

A connectivity matrix was then produced from computing the correlation between all pairs of the 8 filtered megPAC time-series, as seen in Figure 3. Table 1a shows the highest correlation values found between different sources, with the highest correlation coefficient being between RMot and RV (c = 0.3093). The corresponding DPAC estimates for the optimal parameters for RMot were: [Flow = 2.20Hz, Fhigh = 102.11Hz, phasePAC = 230.35°, maxPAC = 0.0225] and for RV were: [Flow = 2.20Hz, Fhigh = 127.89Hz, phasePAC = 5.35°, and maxPAC = 0.0078]. The second highest correlation was found between the PFC and LMot (c = 0.2343) which had DPAC estimates of [Flow = 2.20Hz, Fhigh = 146.21Hz, phasePAC = 301.20̂, maxPAC = 0.0070] and [Flow = 2.82Hz, Fhigh = 83.68Hz, phasePAC = 192.52̂, maxPAC = 0.0109] respectively.

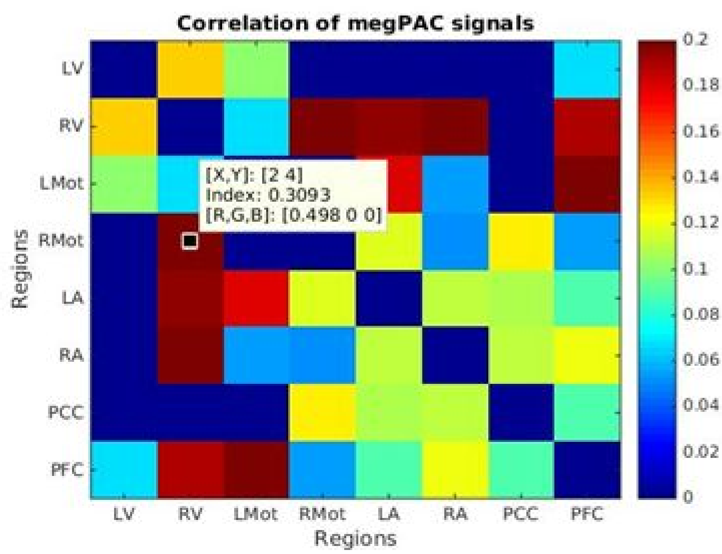

Table 1a: Highest Correlation

RMot & RV	0.3093
PFC & LMot	0.2343
RA & RV	0.2043
LA & RV	0.1961
PFC & RV	0.1887
LA & LMot	0.1804

Table 1b: Expected Networks

RV & LV	0.1325
LA & RA	0.1098
PCC & PFC	0.0877
LMot & RMot	0.00

Figure 3: Connectivity matrix between megPAC time-series

In Table 1b, the correlations between the regions that were expected to show relatively high connectivity in the resting state are shown. Of these expected highly connected regions, the highest correlation was found to be between the RV and LV (c = 0.1325) with DPAC estimates of RV mentioned above and for LV being Flow = 2.20Hz, Fhigh = 131.58Hz, phasePAC = 338.11̂, and maxPAC = 0.0124. Note that in this analysis, there was found to be a correlation of 0.00 between LMot and RMot, contrary to what has previously been observed in resting-state in fMRI studies (Biswal et al., 1995).

Discussion

This seed-based analysis approach using an extension of the megPAC model is a promising way to investigate the dynamic coupling across large spatial and temporal scales. The preliminary findings for 1 subject were based on a few select sources (only 8) to demonstrate the application of the resting-state pipeline in extracting the megPAC signals. The megPAC signal model is an excellent way to represent cross-frequency time-resolved PAC as it captures the temporal aspects (phase information) of the slow oscillation (nesting) frequency and plots the corresponding amplitude values of the high gamma nested frequency at those coupling instances. In this sense, both the phase and amplitude information are being integrated into the signal model. The resulting megPAC signals after filtering, as shown in Figure 2, allow for the visualization of ongoing PAC dynamics at the sources in the regions of interest, in this case in the LV, RV, LMot, RMot, LA, RA, PCC, PFC.

For analyzing the connectivity between different brain regions, it is possible to examine the similarity between different megPAC time-series. In figure 3, a connectivity matrix for all possible pairs of sources is shown. Generally speaking, the higher the correlation between a pair of sources, the greater the likelihood that these two brain regions share similar low-frequency-phase and gamma amplitude (Florin & Baillet, 2015). In this analysis, RV was shown to be highly connected to RMot, to RA, to LA, as well as to PFC, and LMot was highly connected to PFC and to LA, which is shown in Table 1a. Table 1b examines the connectivity of brain regions that were expected to have higher correlation as they are part of different resting-state networks such as the default mode, auditory, and visual networks. Of these predicted connections, the correlation between the RV and LV of the visual resting-state network was the highest (c = 0.1325) and the second highest being between the LA and RA of the auditory resting-state network (c = 0.1098). In the resting-state analysis using the original megPAC model done by Florin & Baillet (2015), there was high pairwise correlation between regions in the DMN. As presented in the results of Table 2b, the PCC and PFC, which are regions from the DMN, showed a modest correlation of c = 0.0877 relative to other source pairs. In fact, the PFC megPAC signal had a higher correlation to that of LMot (c = 0.2343) and to RV (c= 0.1887). One possibility for a weaker correlation coefficient between regions corresponding to the DMN could be that MEG has a lower sensitivity to medial cortical surfaces (Florin & Baillet, 2015) and of course that only one subject was used for which the preliminary findings are presented. As well, apart from only one subject being used, only 8 seed locations were chosen from a user-defined atlas. In the future, many cortical source locations from the region of interest must be used and the DPAC estimates should be averaged to have a better sense of the coupling characteristics in that region. This could certainly be the reason for seeing a 0.00 correlation between the left and right primary motor regions, along with not using an established anatomical atlas to select the seeds.

Moving forward, the analysis requires a group of subjects to reveal similarity of PAC dynamics in the resting-state networks. There have been promising results that PAC serves as an underlying mechanism for the emergence of RSNs as networks based on the megPAC signal model have shown overlap with fMRI RSNs such as the DMN, the dorsal attention network with the sensorimotor network (DAN/SMN), visual network, and the right fronto-parietal network (Florin & Baillet, 2015). It is important that MEG continue to be used for studying the hierarchy of functional connections in the resting-state with methods such as DPAC, which is time-resolved and can reveal fluctuations of optimal PAC down to exact coupling phase and millisecond time. An advantage of using the DPAC metric instead of direct PAC for constructing the megPAC signal in this analysis is that the bursting of high gamma frequency (when there is higher amplitude of Fhigh) was able to be found for the exact preferential coupling phase (phasePAC) in the slow nesting frequency (Flow) for the specified time sample. In the past, the bursts of Fhigh were always examined at either the peak or the trough in the Flow, as proposed by Canolty et al., (2006). If the coupling phase of the slow oscillation is able to be determined precisely, the dynamics captured by the megPAC signal can improve. This is especially crucial when considering the synchronized gating (SG) hypothesis, as put forth by Florin and Baillet (2015) which emphasizes that there must be a synchronization of phase in the slow oscillation to have coherence between the Fhigh bursts and that this allows for communication across brain regions.

To summarize, it is plausible that communication between brain regions, particularly in the RSNs, is facilitated by PAC between the delta to alpha range (2-12Hz) and the high gamma range (80-150Hz). The extended megPAC signal model that represents the dynamical PAC characteristics in different brain regions can be applied to extract RSNs where long-range information processing is said to be taking place. Eventually, this form of resting-state analysis can help to identify connectivity patterns in individuals with existing neurological or psychiatric conditions compared to the healthy brain in which underlying mechanisms of neural communication would be identified and marked.

Supplementary Material

There was a significant amount of time spent validating the DPAC methods as its use is relatively new and exploratory. Seeing as how the DPAC methods are not available for public distribution as of yet, it was necessary to ensure that they were producing the correct results. Many PAC simulations at source level were run to identify whether the DPAC estimates were reliable and accurate. In the simulations, a methodical approach was taken to check for the measurement of coupling intensity, coupling phase, Flow, and Fhigh on the DPAC estimates as well as for seeing their effects on the megPAC signal model and correlation. Additionally, DPAC estimation tests were performed on real subject resting-state data to determine whether the bursting of high gamma frequency was being accurately represented in the megPAC signal model, in which the amplitude is plotted at the coupling phase time occurrences. All of this validation and testing can be found in the supplementary material.

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