Cortical functional connectivity inference using MEG

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Abstract—A novel technique to explore functional connectivity using magnetoencephalography (MEG) is presented. Source localization is performed prior to connectivity analysis, allowing identification of the cortical regions involved. This technique controls for point-spread in the minimum norm inverse solution by generating a null distribution with noise data. Data from an auditory attention task reveals that in the alpha-frequency range, cortical activity in the auditory cortices is coherent with frontal eye fields, areas known to be engaged during other attention tasks. Maps generated with this technique allow visualization of inter-areal connectivity to pre-defined regions-of-interest.

Keywords - functional connectivity; magnetoencephalography; auditory attention; coherence; frontal eye fields; auditory cortex

I. INTRODUCTION

Oscillatory synchronization of neuronal activity between cortical areas is thought to provide a crucial role in modulating information transmission between separate neural populations. Recent studies have shown increased synchronization of rhythmic activity across brain areas associated with various cognitive functions, such as conscious perception of stimuli, working memory, and selective attention [1]. While there have been electrode-recording studies in monkeys that explore coordination of oscillations across brain regions [2], most previous functional connectivity studies in humans measured the sluggish hemodynamic responses of fMRI [3], which can only reveal correlations in overall power, rather than coordinated activity in specific oscillation frequencies.

We therefore chose to explore auditory attentional networks using magnetoencephalography (MEG). A majority of past electroencephalography (EEG) and MEG studies have restricted analysis to sensor space, providing limited information about the cortical regions involved in task-related activity. Here, we employed a novel technique for a whole-brain analysis of frequency-specific functional connectivity. We performed distributed-source imaging with cortically constrained minimum norm estimation (MNE) [4] and then looked at the coherence between our seed regions-of-interest (ROIs), namely the left and right auditory cortices, and each source dipole. Specifically, we analyzed synchrony in the alpha-frequency band (8–12 Hz), because it has been implicated in top-down attention [5, 7].

Our approach was similar to that taken in [8]; we generate baseline (null hypothesis) coherence maps with empty-room measurements, which we subtract from the coherence values obtained during task performance. We chose to use coherence instead of the phase-locked value (PLV), as was done in [8], because of its relative robustness to noise [9]. A similar approach was taken in [6], where cortical parcellation was done and the PLV was computed between areas. Our technique allows us to generate coherence maps across the entire cortical surface and functionally define regions-of-interest (ROIs) instead of using anatomical parcellations, enabling us to look for which neural regions are coherent with our ROIs.

A cortical area of particular interest is the frontal eye fields (FEFs), located in the pre-central sulcus. Traditionally, FEF is thought of as controlling eye gaze and visuo-spatial attention; however, recent studies hint that FEF plays a more general role, controlling cross-modal and non-spatial attention [10].

II. METHODS

A. Task

During each trial, two distinct auditory tokens (spoken digits 1–4, approximately 400 ms in duration) were presented simultaneously. Each token was convolved with a head-related transfer function to simulate a source either 30º left or 30º right of midline. The pitch of each token was monotonized and set to 3 semitones above or below 100 Hz (the nominal pitch of the original speech) using Pratt software [11]. In any given trial, the two, presented tokens had different, randomly assigned spatial locations and pitches.

Nine normal-hearing listeners (two females) each performed four runs of roughly 6 minutes duration. Subjects were instructed to maintain visual fixation at a dot in the center of the visual display. Each run consisted of 72 trials. In each trial, subjects were visually cued to attend either one of the spatial locations (left/right) or one of the pitches (low/high) in a randomly intermingled and counter-balanced order. Responses were recorded when subjects pressed a button on a four-button response box with the right hand. To minimize motor artifact, subjects were told to respond only at the end of the trial, when cued by a visual ring (appearing one second after the onset of the auditory mixture).

B. Data Acquisition

MEG data (306 channels - 2 planar gradiometers and 1 magnetometer at each of 102 sites) were recorded at a 600 Hz sampling rate (bandpass 0.1 to 200 Hz) simultaneously with two bipolar electro-oculogram (EOG) electrode pairs measuring horizontal eye movements and blinks. The data were recorded inside a magnetically shielded room using a dc-SQUID Neuromag VectorView system (Elekta-Neuromag). Four head-position indicator coils were placed on the head of the subject to monitor the position and orientation of the head relative to the MEGs sensor array. MRI scans were performed with a 1.5-T Avanto scanner (Siemens Medical Solutions, Erlangen, Germany).
C. Source Imaging

Individualized three-layer boundary element models (BEMs) were constructed for each subject using T1-weighted and two FLASH (flip angle of 5 and 30 degrees) MRI scans. The cortical, inner, and outer skull surfaces were reconstructed using Freesurfer [12]. Source estimation was performed using cortical-surface-constrained, L2-norm-based minimum norm estimation using the MNE software suite [4]. A grid spacing of 7 mm was used for dipole placement, yielding roughly 3000 sources per hemisphere. Dipole orientations were constrained to be normal to the cortical surface. The noise covariance matrix was estimated from data gathered in an empty room at the end of each recording session. We applied the same inverse solution to empty-room measurements to obtain null statistics for the baseline coherence [8].

D. Data Pre-Processing

All raw MEG data were first processed using the signal-space separation (SSS) method [13] to remove biological artifacts and other environmental magnetic sources originating outside the head. In addition, we eliminated the subspace containing the heartbeat artifact using the signal-space projection (SSP) method. Only those trials with correct behavioral responses were included in further processing. Trials were also rejected if there were eye movements or blinks (if the bipolar EOG electrode pairs showed a voltage difference greater than 200 μV), or if the peak-to-peak MEG amplitude exceeded 10 pT in magnetometers or 3 pT/cm in gradiometers. We applied the same SSS projection, SSP projection, and amplitude rejection criteria to the empty-room measurements to establish the associated null statistics for the baseline coherence.

E. ROI Selection

We localized the N100m auditory response to establish our ROI in the auditory cortex. Specifically, after averaging all trials, we plotted the dipole activity using dSPM and thresholded activation at p < 0.05, Bonferroni corrected. We selected an ROI in each hemisphere of each subject based on the largest contiguous cluster of significant activation around Heschl’s gyrus, constrained to have roughly equivalent numbers of sources across listeners. In order to obtain an estimate of the average activation in the ROI that is not corrupted by cancellation of the signal due to point spread across sulcal banks, we picked a reference dipole direction and flipped the polarity of the dipoles within this ROI to align with this chosen reference direction. The mean waveform of all the flipped dipoles gave us the average activation in the ROI.

F. Data Processing

We computed synchrony between the average ROI activation and each vertex on the cortical surface using the coherence metric

\[ C_{xy}(f) = \frac{\sum_{k=1}^{K} X_k(f)Y_k^*(f)}{\sum_{k=1}^{K} X_k(f)\sum_{k=1}^{K} Y_k(f)}, \]

where k = 1, ..., K index the trials, * indicates the complex conjugate and \( X_k(f) \) and \( Y_k(f) \) are the Fourier coefficients for the two source signals \( x(t) \) and \( y(t) \) at each frequency \( f \). Fourier coefficients for 500-ms-long epochs before and after auditory stimulus onset were computed using the multi-taper spectral method with \( W = +/- 4 \) Hz and 3 tapers [14]. We computed the mean coherence of the three frequency bins covering the alpha range (8–12 Hz) for each epoch under consideration. Since coherence is a biased statistic (with the bias depending on the number of trials) [14], we used a randomly selected set of 72 trials from the neural data to match the 72 trials of empty-room measures recorded to ensure that our null model had the same bias and statistical power as the neural measures for each subject. We performed a Fisher z-transform (tanh') on the event-triggered and empty-room coherence values for variance stabilization as in [14].

G. Empty Room Correction and Statistics

We obtained a baseline measure of coherence arising due to the point-spread of the inverse using empty-room measurements gathered at the end of each recording session. We pre-processed the empty room measurements with the same (SSS and SSP) projections and amplitude rejection criteria as the neural data. We then applied the same inverse solution that we used on the data to obtain the projection of MEG sensor noise onto the cortical surface. We computed the coherence for the empty room using the same procedure; specifically, we used the same ROIs defined for the neural data and used the Fisher z-transform, just as before. These transformed empty-room coherence values were subtracted from the transformed neural coherence values at each vertex to produce coherence difference maps.

Coherence difference maps were morphed onto an average cortical surface (fsaverage in the FreeSurfer software suite) [15]; one-tailed, paired t-tests were then performed at each dipole. False discovery rates of statistical thresholds were controlled at 0.10 [16]. One-tailed paired t-tests were used to reveal the network that is significantly more synchronous with the auditory cortex than expected by chance.

III. RESULTS

To illustrate the necessity for our empty-room baseline correction procedure, we computed the average coherence map (with Fisher z-transformed coherence values) in one of the conditions from each subject’s left auditory cortex ROI, with and without correction (Fig. 1).
Figure 1. Mean alpha coherence maps (morphed onto an average brain) relative to individually defined left-hemisphere auditory cortex ROIs. The coherence is the mean taken over the three frequency bins in the 8–12 Hz frequency range. Results are shown for the 500-ms-long epochs after the auditory stimulus onset in the “attend pitch” trials. (a) Fisher z-transformed (tanh-1) coherence values of the trials and (b) Coherence values in (a) after subtracting coherence values obtained from empty room measurements. The same processing was done on the empty room data as on the neural data and the same inverse solution was used to control for artifacts from the point-spread of the inverse.

Without correction, large spurious coherence is seen over much of the ipsilateral hemisphere and portions of the contralateral hemisphere. With correction, spurious coherence that arises due to the point-spread in the minimum norm inverse is removed. An additional benefit of our empty-room correction is that it accounts for the bias in the coherence metric, which depends on the number of trials used in the computation.

Corrected coherence maps for space and pitch trials were indistinguishable, so we only present the maps for space trials here. Fig. 2 shows the statistical maps of alpha coherence with auditory cortex seeds for the 500-ms-long epoch after auditory stimulus onset. Coherence around Heschl’s gyrus (around auditory cortex) is significant in the left and right hemispheres. This makes sense, given that the auditory cortices receive a common sensory drive and respond with the onset event-related field (ERF) response, yielding coherence between these ROIs in this condition. Interestingly, we also found coherence between our seed ROIs and the FEFs, which are located in the pre-central sulcus, the inferior and superior portions of which are outlined in Fig. 2. These ROIs were obtained from the Freesurfer anatomical parcellation [12]. Note that the left FEF shows clusters of activity coherent with both the left and right auditory cortical seeds, whereas the right FEF does not show significant coherence with the left auditory seed. The tendency for ipsilateral synchrony to be stronger than contralateral synchrony has been reported previously [6].

A similar asymmetry was found with the FEFs for the preparatory period (500 ms prior to auditory stimulus onset; see Fig. 3). There is little significant cross-hemispheric auditory cortex activation in these epochs. Although a past study found inter-hemispheric auditory synchronization in the resting-state, this analysis used much longer epochs, yielding more power in the statistical analysis [8].
To quantify asymmetry in synchronization in the FEFs, we computed the average (empty-room corrected) coherence for each subject in each epoch and trial type (Fig. 4). The right auditory to left FEF coherence was stronger than the left auditory to right FEF coherence in epochs before the auditory stimulus onset for both pitch and space (one-tailed paired t-test, p < 0.05), but not after.

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Figure 4. Bar graph showing the mean coherence over the pre-central sulcus anatomical ROIs taken over all subjects in all epochs and conditions. Error bars represent one standard error of the mean. * – Statistically significant difference (one-tailed paired t-test, p < 0.05).

IV. DISCUSSION

A technique to explore frequency-specific functional connectivity from any pre-defined ROI to the whole cortical surface is described. Sources were localized using cortically constrained minimum norm estimation. Recordings from an empty room generated a null distribution against which coherence measures were compared, allowing us to correct for spurious coherence due to the point-spread of the inverse function. Applied to activity in the alpha band during an auditory attention task, the approach reveals a hemispheric asymmetry in contralateral coherence between FEF and auditory cortex. Specifically, ipsilateral auditory cortex-FEF synchronization is always present; however, even though left FEF is coherent with right auditory cortex, right FEF is not coherent with left auditory cortex.