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Cross-Frequency rs-fMRI Network Connectivity Patterns Manifest Differently for Schizophrenia Patients and Healthy Controls

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Abstract

Patterns of resting state fMRI functional network connectivity in schizophrenia patients have been shown to differ markedly from that of healthy controls. While some studies have explored connectivity within fixed frequency bands, the question of network phase synchrony across disparate frequency bands, or *cross-frequency connectivity*, has remained surprisingly underexplored. Computational modeling at the neuronal scale however has long acknowledged the existence of coupled fast and slow subsystems. Here we present preliminary evidence that cross-frequency coupling exists at the network level, that it patterns in meaningful ways over functional domains, and that this patterning differs between the healthy population and individuals with diagnosed schizophrenia.

Index Terms

Neuroimaging; fMRI; brain networks; time-frequency analysis; network connectivity; schizophrenia

I. Introduction

Functional network connectivity (FNC), i.e., connectivity among brain networks, is a longstanding and continuing focus of much resting state fMRI (rs-fMRI) research. Pearson correlation between network timecourses is the predominant metric by which inter-network connectivity is assessed. Among other limitations as vehicle through which to estimate network connectivity, Pearson correlation will fail to identify phase-synchronized time series oscillating at different frequencies, and we do not yet have reason to believe that network-pairs “communicate” or couple only within extremely well-matched spectral regimes. At the neural level, for example, phase synchrony is still utilized as a central indicator of coupling strength [1, 2] even though different cell types are known to have different natural rates of firing [3]. The activation patterns captured by fMRI are at a much coarser spatial and

temporal scale than multi-electrode neuronal recordings. It seems possible however that the neuronal scale simply offers a more tractable window into a more generic phenomenon in which units of the brain influence or couple to each other through frequency-blind phase-entrainment. Moreover, if this kind of coupling is present at the scale of fMRI functional networks, it may provide a substrate upon which disease exerts discernible effects. There is already an extensive literature pointing to widespread reduction in broad-band correlation-based fMRI resting-state network connectivity strength among schizophrenia patients [4–8], among other broad-band correlational disturbances. Newer research is also indicating diminished plasticity and adaptability in the time-varying (dynamic) whole-brain connectome of those with the illness [9–11]. Several previous studies from more time-resolved brain recording modalities (EEG and MEG) [12, 13] have supported a potential role for cross-frequency coupling (at supra-neural scales) in distinguishing healthy populations from the severely mentally ill. Using a simple, intuitive approach, we demonstrate the existence of cross-frequency coupling between resting state functional networks, and also find that patterns of cross-frequency network connectivity differ significantly between schizophrenia patients and controls.

II. Methods

A. Participants, Preprocessing and Network Preprocessing

Preprocessing and network identification follows protocols from detailed in [9] that we shall simply outline here. Resting state functional magnetic resonance imaging data (160 volumes of echo planar imaging BOLD fMRI, TR = 2 sec.) was collected from 163 healthy controls (HC) (117 males, 46 females; mean age 36.9) and 151 age and gender matched patients with schizophrenia (SZ) (114 males, 37 females; mean age 37.8) during eyes closed condition at 7 different sites across United States. After standard preprocessing, the fMRI data from all subjects was decomposed using group ICA into 100 maximally spatially independent spatial maps (<http://mialab.mrn.org/software>) of which 47 were identified as functionally meaningful resting state networks (RSNs). The RSNs fell into seven broad categories: sub-cortical (SC), auditory (AUD), visual (VIS), sensorimotor (SM), cognitive control (CC), default mode network (DMN) and cerebellar (CB). Subject specific spatial maps and timecourses were obtained from the group level spatial maps via spatio-temporal regression. The timecourses were detrended, despiked and subjected to additional postprocessing steps detailed in [9]. The auditory, visual and sensorimotor (AVSM) networks tend to behave very coherently and are sometimes referred to as one category in the text that follows.

B. Time-Frequency Domain Transformation of Network Timecourses

We are investigating cross-frequency network coupling both in a time-varying context, using Matlab's continuous wavelet transform with the complex Morlet wavelet. In this area we follow the protocols of [14]. All raw power spectra are normalized to have maximum of 1 (ie., divided by their maximum value). The complex Morlet wavelet transform centered at 20 equally spaced frequencies in [0.01,0.25] Hz produces temporally indexed network spectra of length $\ell = 20$ for each timepoint $t = 1, \dots, 160$.

C. Cross-Frequency Network Connectivity: Phase Synchrony Between Frequencies with High Spectral Power

Our analysis starts with a function $\Phi_{i,j}(v, w): \mathbb{C}^{2\ell} \rightarrow [-1, 1]$ that for every network pair $(i, j) \in \{1, \dots, N\}^2$ is applied at each frequency pair $(v, w) \in \{1, \dots, \ell\}^2$ of the length ℓ complex spectra of each network-pair's timecourses, where Φ is designed to peak at the frequency pair (v, w) at which timecourses of networks i and j exhibit maximal evidence of both high spectral power and high phase synchrony. The main requirement for Φ is that it increase monotonically in (1) the power at frequency v of network i , (2) the power at frequency w of network j and (3) the cosine of the phase difference between frequencies v, w of networks i, j . In this work we specify $\Phi_{i,j}$ as follows:

$$\Phi_{i,j}(v, w) = \frac{P_i(v) + P_j(w)}{2} \cos(|\theta_i(v) - \theta_j(w)|)$$

where $P_i(v)$, $\theta_i(v)$ and $P_j(w)$, $\theta_j(w)$ are the power and phase of network i at frequency v and of network j at frequency w respectively. In this framework, networks i and j are coupled with

- Cross-frequency *connectivity strength* $\hat{\Phi}_{i,j} \equiv \max_{v,w} \Phi_{i,j}(v, w)$
 - Cross-frequency *connectivity power* $\hat{P}_{i,j} \equiv \frac{P_i(\hat{v}) + P_j(\hat{w})}{2}$
 - Frequency *disparity* $\Delta_{i,j}^f \equiv |\hat{v} - \hat{w}|$
 - Phase *disparity* $\Delta_{i,j}^\theta \equiv \arccos(\cos(|\theta_i(\hat{v}) - \theta_j(\hat{w})|)) \in [0, \pi]$
 - Spectral *disparity* $d_{i,j}^P \equiv \sqrt{\sum_{u=1}^{20} (\vec{P}_i(u) - \vec{P}_j(u))^2}$
- where $(\hat{v}, \hat{w}) = \{(v, w) \mid \Phi_{i,j}(v, w) = \hat{\Phi}_{i,j}\}$.

D. Clustering and Statistical Modeling

Results are presented both with respect to clustered multivariate measurements presented in Section C, and also in global terms. Each of the four measurements is computed separately for the 314 subjects at 160 timepoints, so for every measure, there are a total of 50,240 observations, each the 1081-dimensional upper triangular portion of a 47×47 symmetric matrix with constant diagonal. Clustering each collection of 50,240 upper-triangular matrix observations associated with each measure was performed using Matlab's kmeans function with the correlation distance, 5 clusters, 500 iterates and 150 replicates following [11]. Unless otherwise indicated, our reported schizophrenia effects are regression coefficients on the diagnosis variable from a multiple regression on age, gender and schizophrenia diagnosis. Significant effects are those that survive false discovery rate (FDR) correction for multiple comparisons at the $\alpha = 0.05$ level. The binary diagnosis variable codes schizophrenia patients with '1' and controls with '0'. Thus, displayed positive schizophrenia effects (red shades in matrix images) indicate that the dependent variable is, after correcting for any confounding linear effects of age and gender, significantly higher in patients. Negative schizophrenia effects (blue shades in matrix images) indicate a dependent variable

that is significantly higher in controls. The displayed population means are averages of all observations of the specified measure, i.e., means taken over all timepoints on which the measurement is taken for all subjects (both patients and controls) in the study.

III. Results

A. Cross-Frequency Connectivity: Global Patterns and Schizophrenia Effects

Very broadly speaking we find that mean cross-frequency connectivity strength $\hat{\Phi}$ is high where standard correlation-based FNC is high/positive and lower where correlation-based FNC is low/negative (Figure 1, (left) Figure 2 (top left)). Moreover, mean $\hat{P}$ is high where mean $\hat{\Phi}$ is high, and mean θ , mean f are high where mean $\hat{\Phi}$ is low, all as one might expect given how $\hat{\Phi}$ is computed and the fact that more disparate frequencies are more likely to include one with lower spectral power (Figure 2 (top row)). The univariate effect of schizophrenia on the cross-frequency measures (Figure 2 (bottom row)) echoes the way that schizophrenia affects correlation-based connectivity (Figure 1 (right)) but the patterns are stronger, more directionally uniform and include more functional domains. Particularly noticeable are the strong, homogeneous effect patterns between AVSM and CC networks, and between AVSM and DMN networks, functional domains whose connectivity has been shown to be disrupted in the severely mentally ill.

B. Network Spectra: Global Patterns and Schizophrenia Effects

The fMRI signal tends to be concentrated at lower frequencies and network timecourse Z-scored spectra show the expected pattern of diminishing power as frequency increases (Figure 3, top left). In AVSM networks schizophrenia uniformly raises spectral power in middle-band frequencies and suppresses power in low and high-band frequencies. Conversely, Schizophrenia has amplifying effects on low-frequency SC network power and suppresses some middle-band frequencies. The effect of schizophrenia on other networks is more mixed (Figure 3, bottom left). We also observe that the overall normalized spectrum of SC networks differs notably from all other networks (Figure 3, top right). Visual and SM networks are the most spectrally similar. Schizophrenia increases the spectral dissimilarity among AVSM networks, and also increases the spectral dissimilarity between AVSM networks and other networks (Figure 3, bottom right).

C. Cross-Frequency Connectivity: Clustering of Patterns, Occupancy Rates and Schizophrenia Effects

We find that clustering the 50,240 observations of each cross-frequency connectivity measure (Figures 4, 5, 6 and 7) reveals distinctive patterns of cross-frequency coupling behavior that are obscured in the global mean, i.e., the mean over all timepoint observations of the measure for all subjects. The summary patterns obtained by clustering time-varying observations of our four measures of cross-frequency connectivity exhibit greater divergence from their global means (Figure 2, top row) than do the cluster centroids of conventional correlation-based windowed FNCs (Figure 8) from their global means (Figure 1, left). The modular structure of the windowed FNC global mean: uniformly high intra-domain correlations; evident anti-correlation between SC and AVSM networks and between DMN and CC networks etc. are mirrored in the global means of cross-frequency connectivity

measures, often in fact sharpened or amplified in the cross-frequency setting. Moreover, schizophrenia effects on the time-averaged cross-frequency connectivity measures (Figure 2, bottom row) pattern in ways that are similar to schizophrenia effect patterns on time-averaged correlation-based FNC (Figure 1, right). details are provided in figure captions, but broadly speaking patients occupy cross-frequency connectivity clusters whose centroids are patterned less like standard correlation-based FNCs than do controls.

IV. Discussion

The various ways that brain networks communicate with each other is an important and continuing topic of investigation. It seems quite possible that different kinds of information are being communicated simultaneously at different spatiotemporal scales and along different signal parameters. We take a straightforward approach to investigating the existence of cross-frequency synchronization among fMRI resting state networks and find evidence that networks are communicating via phase synchronization across disparate frequencies, that this form of communication patterns plausibly over known functional domains and that schizophrenia affects many properties of cross-frequency network connectivity.

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Figure 1.

Network connectivity measured using windowed network timecourse correlations for the same dataset [9]: population means (left); SZ effects (right). Strong mutual coherence among and between AVSM networks is evident; other modular domains are also fairly internally coherent; SC-AVSM and DMN-AVSM weakly negatively correlated; SZ affects the intra-AVSM block very negatively, and also affects the SC-AVSM connections positively.

Figure 2.

Cross-frequency network connectivity strength, phase disparity, power and frequency disparity: population means (top row) and univariate cell-wise SZ effects (bottom row). These connectivity and effect patterns echo those in Figure 1 above, but the SZ effects in CC-to-AVSM and DMN-to-AVSM cross-frequency connections are much stronger and more directionally uniform. Generally networks that are strongly positively correlated in Figure 1 have large $\hat{\Phi}$ and $\hat{P}$, and small $\Delta\theta$ and Δf . Conversely, those that are more negatively correlated in Figure 1 have relatively low $\hat{\Phi}$ and $\hat{P}$, and larger $\Delta\theta$ and Δf . Although the displayed cell-wise means over 50,240 observations necessarily will blur out many interesting and replicable patterns, even the mean of $\hat{\Phi}$ and $\Delta\theta$ provide evidence of more phase-synchrony in AVSM-to-CC, AVSM-to-DMN, SC-to-CC, SC-to-DMN and CC-to-DMN networks than is evident in Figure 1. From Δf however, it becomes clear that this synchrony is often occurring between relatively disparate frequencies.

Figure 3.

(Column 1) Individual network timecourse spectra (Z-scored): population means (top); SZ effects (bottom); (Column 2) Distance between network-pair spectra, each normalized to have max 1: population means (top); SZ effects (bottom). SZ uniformly raises AVSM network spectral power in middle-band frequencies, suppresses AVSM power in low and high-band frequencies. SZ has a different effect pattern for SC networks, and some CC, DMN, CB networks. The overall normalized spectrum of SC networks differs notably (top right) from all other networks. Visual and SM networks are most spectrally similar. SZ amplifies spectral dissimilarity within AVSM and between AVSM and other networks (bottom right).

$\hat{\Phi}$ Kmeans Cluster Centroids

Figure 4.

Centroids of the five cross-frequency connectivity strength clusters with overall occupancy rates and SZ effects on occupancy rate (when significant) shown below x-axes; centroids of clusters significantly more occupied by either patients or controls are indicated as such; those without significant SZ effects on occupancy rate are designated as “shared”. These clusters represent replicable patterns of cross-frequency connectivity, many of which are obscured in the global mean (Figure 2, top left) which is plotted on a significantly different color scale so green shades in the global mean correspond to blue shades in this figure, while green shades in this figure correspond to light red shades in the global mean. Patients occupy a state with low SM-to-other, high intra-SC/AUD/VIS and a state with low AUD-to-other, low DMN-to-other, low CB-to-other, low intra-VIS and high intra-CC cross-frequency connectivity strength significantly more often than do controls.

Figure 5.

Centroids of the five phase-disparity clusters with overall occupancy rates and SZ effects on occupancy rate (when significant) shown below x-axes; centroids of clusters significantly more occupied by either patients or controls are indicated as such; those without significant SZ effects on occupancy rate are designated as “shared”. The two states significantly more occupied by controls exhibit small θ in network-pairs that have high mean correlation in the standard FNC (Figure 1). The shared and patient-dominated states have higher or more mixed intra-VIS/SM θ and one of the SZ-dominated states has broad high θ between AVSM networks and the higher cortices of CC, DMN, CB in a pattern not evident either in global means of Figure 2 or the standard FNCs of Figure 1.

Δ^f Kmeans Cluster Centroids **Figure 6.**

Centroids of the five frequency-disparity clusters with overall occupancy rates and SZ effects on occupancy rate (when significant) shown below x-axes; centroids of clusters significantly more occupied by either patients or controls are indicated as such; those without significant SZ effects on occupancy rate are designated as “shared”. The two states significantly more occupied by SZs have an inverse correspondence with the SZ-dominated $\hat{\Phi}$ states (Figure 4, bottom), as do the first displayed states for controls. High frequency disparities in the SZ states thus seem likely to contain cases where at least one of the frequencies has relatively low power, which would serve to suppress corresponding values of $\hat{\Phi}$. Controls are also significantly more likely to occupy a Δ^f cluster whose centroid, displayed third, features very small inter-network frequency disparities nearly globally, with the exception of five networks that show persistent frequency disparities with all others.

L^2 Distance Between Normalized Network Timecourse Spectra: Kmeans Cluster Centroids

Figure 7.

Centroids of the five spectral disparity clusters with overall occupancy rates and significance of the SZ effect on occupancy rate shown below x-axes; no clusters have significant SZ effects on occupancy rate, so centroids all are designated as “shared”. The absence of SZ or HC-specific patterns of network spectral similarity is evidence that the cross-frequency analysis captures information not available from simply comparing power in matched frequencies between the networks.

Standard Correlation-Based Windowed FNC Kmeans Cluster Centroids

Figure 8.

Centroids of the five windowed correlation-based FNC clusters, with overall occupancy rate in parentheses above the corresponding centroid and significant SZ effects on occupancy rate displayed in the lower right inset bar plot. The hypo-connected States 1 and 3 (red boxes) in which DMN and other networks are anti-correlated are more occupied by patients; the three remaining modularized states (green box) are more occupied by controls. All states have patterns discernible in the global mean (Figure 1) while this is not as true for states associated with the cross-frequency connectivity measures (Figures 3, 4, 5, 6, 7) relative to their own respective global means (Figure 2).