Type of the Paper (Article, Review, Communication, etc.)

Title

Firstname Lastname 1, Firstname Lastname 2 and Firstname Lastname 2,\*

|  |
| --- |
| **Citation:** To be added by editorial staff during production.  Academic Editor: Firstname Lastname  Received: date  Revised: date  Accepted: date  Published: date    **Copyright:** © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/). |

1 Affiliation 1; e-mail@e-mail.com

2 Affiliation 2; e-mail@e-mail.com

**\*** Correspondence: e-mail@e-mail.com; Tel.: (optional; include country code; if there are multiple corresponding authors, add author initials)

**Abstract:** A single paragraph of about 200 words maximum. For research articles, abstracts should give a pertinent overview of the work. We strongly encourage authors to use the following style of structured abstracts, but without headings: (1) Background: Place the question addressed in a broad context and highlight the purpose of the study; (2) Methods: briefly describe the main methods or treatments applied; (3) Results: summarize the article’s main findings; (4) Conclusions: indicate the main conclusions or interpretations. The abstract should be an objective representation of the article and it must not contain results that are not presented and substantiated in the main text and should not exaggerate the main conclusions.

**Keywords:** keyword 1; keyword 2; keyword 3 (List three to ten pertinent keywords specific to the article yet reasonably common within the subject discipline.)

1. Introduction

2. Materials and Methods

2.1. Data Collection

This study utilizes control and schizophrenia patient data from the Function Biomedical Informatics Research Network (FBIRN) repository [34], preprocessed according to the description given in [35]. To summarize, a statistical parametric mapping package ([SPM12](http://www.fil.ion.ucl.ac.uk/spm/)) was used to correct for subject head motion and slice timing differences, to warp subject anatomy to the Montreal Neurological Institute (MNI) echo planar imaging (EPI) template space, to resample the collected data to mm3 isotropic voxels, and to smooth the resampled fMRI images with a Gaussian kernel with a full width at half maximum (FWHM) of mm. Subjects with head motion greater than were excluded from the study, as were subjects whose full brains could not be normalized due to incomplete imaging data. These criteria led to a final dataset of 151 schizophrenia (SZ) patients and 160 healthy controls (HCs).

2.2. Estimation of the Spatial Functional Networks

Spatial functional networks were estimated using NeuroMark’s adaptive independent component analysis (adaptive ICA) [35], which extends spatially constrained independent component analysis [36,37] to map known fMRI network templates to novel subject data. This requires balancing two competing goals: to maximize the spatial independence of networks in each subject and to ensure that the network maps in each subject correspond to known group-level templates. Here, we use the multi-objective optimized ICA with reference (MOO-ICAR) approach, which maximizes two competing objective functions in turn until a solution is achieved. This allows adaptive ICA to capture subject-unique characteristics while maintaining comparable functional networks across datasets. It should be noted that this method allows us to capture both the internal structure of brain functional connectivity networks and the extent of inter-network connectivity via static and sliding-window functional connectivity estimates.

2.3. Estimation of the Functional Network Connectivity

Before estimating the functional network connectivity (FNC), Du et al. [35] chose to remove noise sources from each functional network’s subject-level time series. The removal of noise sources involved four steps: first, the removal of linear, quadratic, and cubic trends in the data; second, multiple regressions of the six realignment parameters and their temporal derivatives to control for in-scanner motion; third, de-spiking to remove outliers; and fourth, band-pass filtration to select for signals in the 0.01–0.15 Hz frequency bands. Once these steps were completed, subject-level static functional network connectivity (sFNC) was computed via Pearson correlation. Other measures of statistical similarity could have been used; for instance, mutual information has been proposed due to its sensitivity to nonlinear interactions [38,39]. However, Pearson correlation’s simplicity, interpretability, and ease of computation means it remains the dominant method for estimating functional connectivity.

While the static FNC provides valuable information on the extent of inter-network communication, its poor time resolution makes it unable to capture the dynamics of this communication. The two most notable methods proposed to circumvent this problem are the sliding time window approach [25,27,40] and coherence-based connectivity [41–43], [44]. The present study uses the sliding window approach. As the name suggests, this method slides a window over the time series of each ICN in small steps, thus segmenting the total time series into many short, overlapping time series. The functional network connectivity of each time series window is computed in the same way as for static FNC, and the resulting connectivity matrices are concatenated into an array ( being the number of functional networks and the number of time series windows). This study convolved a normal distribution with a mean of zero and a standard deviation of three with a rectangle 40-times-to-repetition (TRs) long [35] to generate its selection window.

2.4. Estimation of the Dynamic Mode Decomposition

The authors’ goal is to identify spatial modes which recur at specific frequencies in the functional network connectivity. To achieve this, they employ dynamic mode decomposition, a novel

3. Results

3.1. Initial Estimates of the Modes

The selected patient’s dynamic mode decomposition (DMD) displays sixty-eight (68) unique finite frequencies in addition to the constant component of frequency zero (0). Each frequency is associated with a spatial connectivity mode (map) and spatial phase mode (map). It was initially hypothesized that modes would display clear modular structure similar to those displayed in static FNC or the recurrent states of previous studies. This has not proven to be the case, however. Mode structure will be discussed here. It must be borne in mind that two spatial modes affiliate with each nonzero frequency, with the second mode’s imaginary part having its sign reversed. As each

3.1.1. (Constant)

The constant spatial mode , perhaps unsurprisingly, displays consistent structure. Weak intra-domain modular connectivity is visible along the diagonal, although it is not universal. Several sensorimotor networks display only weak relationships with other sensorimotor networks, and the cognitive control domain displays two distinct components with a notable break between them. Intra-domain connectivity is strongest and most consistent in the cerebellum, with auditory and subcortical networks close behind. As for inter-domain connectivity, the cerebellum strongly anticorrelates with subcortical and auditory networks, but positively interacts with most of the visual and default-mode systems. Nine out of seventeen cognitive control networks strongly interact with subcortical and auditory systems, with these nine also forming the main intra-domain module, maintaining modest positive correlation with default-mode networks, and weakly anticorrelated to most visual networks. Being a constant mode, phases are universally zero.

3.1.2.

The slowest spatial mode also displays consistent structure with visible, though hardly universal, intra-domain modularity along the diagonal. Auditory, subcortical, visual, and cerebellar networks all display highly consistent intra-domain correlation, with subcortical and auditory networks also consistently correlating with one another. Visual, sensorimotor, and cerebellar networks tend towards inter-domain correlation, although this is not as consistent as the auditory-subcortical block. Auditory and subcortical networks also tend to co-activate with cognitive control and default-mode networks, although this is not universal. Network 51 is the most prominent exception, as it strongly anticorrelates with the subcortical-auditory block and, correspondingly, correlates relatively well with cerebellar networks. Overall, this mode is dominated by a division between subcortical-auditory and sensorimotor-visual-cerebellar blocks, with cognitive control and default-mode networks tending to co-activate with the subcortical-auditory networks. No correlations in this network reach the magnitudes observed in the constant mode.

3.1.3.

Modular structure begins to break down in the spatial mode of . Strong correlations are notably fewer, with the most prominent being networks 15-69, 15-70, 15-17, 17-13, and 83-[45,21,58,3]. Network 72 also strongly correlates with all cerebellar networks. Blocks of anti-correlation are more visible, with much of cognitive control anticorrelated with subcortical and auditory networks. This is not universal, however, with networks 49, 38, and 83 all showing weak but consistent correlation with auditory and subcortical networks. Subcortical and auditory networks, for their part, weakly correlate with cerebellar networks, while focal anticorrelations include 94-[79,54,11], 96-79, 15-[8,18620,93], 72-[98,99,45,21,58,3], and 62-[98,99,45,21,58,3,9].

3.1.4.

Modular decay continues in the mode of . The subcortical-auditory block no longer appears, nor do these domains consistently correlate with any other. Networks 93, 48, and 4 correlate with the subcortical and auditory networks, while networks 9, 66, 81, and 96 tend to anticorrelate with them. No other consistent pattern is apparent with respect to the subcortex or auditory networks. Interestingly, both cerebellar and cognitive control domains tend to anticorrelate with themselves, with the exceptions of networks 48, 37, and 67. Default mode networks generally anticorrelate with cognitive control but correlate with cerebellar networks, while visual networks tend to co-activate with cognitive control. No consistent pattern appears in sensorimotor networks. Generally, the mode associated with shows a breakdown of modular structure compared to slower frequencies.

At , co-activation dominates the spatial mode even as intra-domain modularity continues to decline. Subcortical, auditory, and sensorimotor domains all show a strong tendency to co-activate, along with the upper half of the cognitive control circuits. Default mode networks generally anticorrelate with this block, but this is not universal. Only the cerebellum shows consistent intra-domain correlation, with block-diagonal structure almost entirely absent from the center of the connectivity matrix. It is also notable that the strongest anticorrelations tend to cluster, while major correlations form a constellation of relatively isolated points across the matrix.

Limited modularity returns at , with subcortical, auditory, and cerebellar networks displaying consistent intra-domain correlation while visual and cognitive control networks show partial intra-domain correlation. Intra-domain correlation is quite limited in sensorimotor and default-mode domains, however. Default-mode networks tend to co-activate with subcortical, auditory, and some cognitive control networks, but generally anticorrelate with cerebellum. The cognitive control landscape is quite fractured, however, with the last six networks showing no obvious relation to the remainder of the domain. Sensorimotor domain is similarly fractured, although network 66 appears to have the strongest correlations of this mode with networks 89 and 37.

No modular domain structure is evident at , which is dominated by modest positive correlation across most connections. Anti-correlation is concentrated in the lower right corner of the connectivity matrix, although potential clusters are broken up by constellations of correlated connections. Few domain-level trends are evident, with perhaps the most notable being the default-mode domain’s weak correlation with subcortical and auditory domains. Networks 67 and 38 also appear to anticorrelate with most other networks while co-activating with one another at this frequency. Other such network pairs appear as well: networks 8 and 20, 81 and 37, 38 and 83, 17 and 51, and 4 and 7. The author can offer no speculation as to the purposes of these pairs.

The connectivity mode of does not display modularity *per se*, but structure does reappear. Sensorimotor networks correlate with most of the sudatory and subcortical domains, although only one sensorimotor network consistently co-activates within its own domain. Network 72 strongly co-activates with networks 11 and 80, but aside from these does not meaningfully interact with sensorimotor networks. Visual networks generally anticorrelate with one another and have only scattered strong connections with sensorimotor or cognitive control networks. Cognitive control shows weak intra-domain modularity in its upper 13 networks, as well as some links to the sensorimotor domain. Network 77 of the visual domain notably correlates strongly with the first third of the cognitive control domain. Networks 72, 93, and 51 display high variability in connection strength despite not forming part of a discernable module; network 51 also forms a strong pair with 17, 23 and 94, with another pair occurring at 4 and 7. Network 77 of the visual domain notably correlates strongly with the first third of the cognitive control domain.

Network 77’s correlation with the cognitive control domain notably reverses in mode . The auditory domain and the first five networks of the sensorimotor domain tend to co-activate with the cerebellar networks, but further domain-level structure is not immediately apparent. Networks 66 and 89 appear to co-activate most regularly, while networks 2 and 9 anti-correlate most strongly. However, the scale of correlation coefficients at this frequency is less than a third that of the mode at .

Domain-level interactions are restricted to default-mode-cerebellar and auditory-subcortical linkages at . Within domains, co-activation is the exception rather than the rule, although auditory networks and networks 55, 63, 79, 61, and 70 appear to interact to some extent. Anti-correlation blocks form around network 79 in the cognitive control and default-mode domains, and network 83 displays considerable variance in its interactions with other cognitive control networks. Beyond this, however, consistent themes are difficult to identify. Perhaps the most notable trend is the final dissolution of the cerebellar domain, whose intra-domain interactions, having weakened as frequencies rose, now appear to be almost zero.

At , a slight modular structure returns between the subcortical and auditory domains. The first eleven networks of the cognitive control domain also co-activate with this subcortical-auditory block. However, correlation coefficients at this frequency are generally quite low, with none reaching beyond 0.12. The first thirteen cognitive control networks weakly interact, but this is the only real indication of intra-domain interaction. The cerebellar domain, stable at lower frequencies, appears to have split into two opposing blocks in this frequency. Notably, network 83 continues to strongly influence the default-mode networks.

is the highest frequency which the present analysis can resolve, and it sees a slight return of modular structure. Auditory and sensorimotor networks tend to co-activate, with both domains also showing strong intra-domain interactions. The first thirteen cognitive control networks also weakly interact amongst each other, although this is probably a consequence of the strong interactions between nine cognitive control networks and networks 27, 80, and 72 of the sensorimotor block. Networks 12 and 77 of the visual domain also show strong interactions with the cognitive control network, but these are outliers in the visual domain. The nine most active cognitive control networks, as well as subcortical networks and default-mode networks, appear to influence or be influenced by the cerebellar networks at this frequency, even more than fellow cerebellar networks are.

3.1.4. Summary

As frequencies increase, the imaginary part of the signal grows in relation to the real part. This is most visible in the range of , as the amplitude of both real and imaginary components decays rapidly at higher frequencies.

One domain-level feature consistent across frequencies is the splitting of the cognitive control domain. While he upper two-thirds of this domain generally form a coherent module, such structure is rarely evident in the lower third. These networks seem to fracture without any domain-level organization, and indeed seldom form a coherent block with any other domain.

3.2. Initial Estimates of the Phases

3.2. Mean Squared Error of the Samples

The mean squared error (MSE) per reconstructed sample (time point) is universally quite small , a fact reflected in the excellent visual agreement between original and reconstructed sFNC. However, the time-resolve MSE contains a quasiperiodic peaks-and-valleys structure that resembles a periodic function. The period is irregular, with gaps between peaks separated by anywhere from 15 to 31 time points. It may be a linear combination of functions with different frequencies, which could also explain why the last error “peak” has a gap of two samples in its center.

4. Next Steps

4.1. Study-Level Modes and their Spectra

An obvious next step in the present study is to extract DMD modes from all subjects in the FBIRN dataset and search for notable differences in power spectra between groups. This may show whether the disorders contained in the FBIRN data affect the dynamic evolution of dFNC. It may also be worth comparing spectra to clinical or behavioral scores to determine whether any frequencies have clear behavioral effects. This second analysis may need to account for interaction effects.