# Methods

## Data Collection

This study utilizes control and schizophrenia patient data from the Function Biomedical Informatics Research Network (FBIRN) preprocessed according to the description given in (Du et al. 2020). To summarize, the statistical parametric mapping package (SPM12, <http://www.fil.ion.ucl.ac.uk/spm/>) was used to correct for subject head motion, 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 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 (HC).

## Estimation of the Functional Networks

Spatial functional networks were estimated using NeuroMark’s adaptive independent component analysis (adaptive-ICA) (Du et al. 2020), which extends group information-guided independent component analysis (GIG-ICA) (Du and Fan 2013) to map known fMRI network templates to novel subject data. This requires balancing two at times 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. To achieve this goal, Du and Fan take a leaf from expectation-maximization: given two competing objectives, they develop two competing objective functions and design an algorithm which maximizes each in turn until a solution is achieved. This allows adaptive-ICA to capture subject-unique characteristics while maintaining comparability of subject-specific functional networks across datasets. It should be noted that this method also allows the capture of both the internal structure of brain functional connectivity networks and the extent of inter-network connectivity via both static and sliding-window functional connectivity estimates.

## Estimation of the Functional Network Connectivity (FNC)

Once the subject-level functional networks and their time series have been established, connectivity measures can be estimated with the same methods as utilized in analyses which use atlas-based parcellation. More specifically, the pairwise Pearson correlation establishes the static functional network connectivity (sFNC), which measures of the average similarity between time series across the length of the scan. Other measures of time series or statistical similarity may be used; for instance, mutual information has been proposed as an alternative due to its sensitivity to nonlinear interactions. However, Pearson correlation remains the dominant method for estimating functional connectivity, and this study continues in that tradition.

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. Several methods have been proposed to circumvent this problem, the two most notable being sliding time windows (Hutchison et al. 2013; Allen et al. 2014; Sakoğlu et al. 2010) and coherence (Fries 2005; Glerean et al. 2012; Cabral et al. 2017; Deco, Cruzat Grand, and Kringelbach 2019). The present study uses the sliding window approach. As the name suggests, this method uses a tapered window which is often generated by convolving a rectangular window with a Gaussian function. This window slides 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 concatenated into an array ( being the number of ICNs and the number of time series windows).

Before estimating the functional network (FN) connectivity, Du *et*. *al*. chose to remove noise sources from each FN’s subject-level time series. Removal of noise sources involves 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 in order 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 sFNC matrices were computed via Pearson correlation. dFNC arrays were computed using the sliding-window method and Pearson correlation. The sliding-window analysis used a rectangular window with a length of 40 time steps convolved with a normal distribution of zero mean and a standard deviation of (Du et al. 2020).

## Number of Components

For most clustering or source separation algorithms, users must specify the number of elements for the algorithm to find. This poses a problem in neuroimaging analysis, as the number of elements is seldom known in advance. The number of recurrent connectivity states which the human brain expresses remains a topic of research in the community. As such, researchers cannot know *a priori* which number to input into their separation algorithm. It is common to circumvent this problem by testing several numbers of recurrent states, usually within the range of four to eight (Rashid et al. 2014; Abrol et al. 2017; Fu et al. 2018; 2019; Du, Fu, and Calhoun 2018) and applying a validity index to determine the optimal number. Although data-driven, this method requires running the separation algorithm many times, which adds time and computational cost.

This study proposes two methods to identify the number of connectivity states in the dFNC array. The first method is a variant of the above; potential component counts will be tested and compared via three common comparison metrics, namely the silhouette score, the Calinski-Harabasz score, and the Davies-Bouldin score. The second applies a method from random matrix theory to find this parameter directly from the data. Given an matrix with statistically independent rows (e.g. the phase time series of uncoupled noisy oscillators), the eigenvalues of its autocorrelation matrix follow the Marčenko-Pastur distribution (Marčenko and Pastur 1967). Most importantly, these eigenvalues must remain within the bounds of this distribution:

where is the standard deviation of and . Should an eigenvalue surpass this upper boundary, a statistical dependence between rows of the matrix —that is, a recurrent community in the matrix—must exist. Further, the number of eigenvalues which surpass this upper limit corresponds precisely to the number of recurrent communities in the matrix. This method has been detailed in theory (Peyrache et al. 2009; 2010) and validated in spiking neurons (Lopes-dos-Santos et al. 2011; Lopes-dos-Santos, Ribeiro, and Tort 2013), but has only recently appeared in the context of fMRI (Blair et al. 2022).

## Temporal components

This study represents an attempt to quantify the dynamics of the recurrent connectivity states hypothesized to exist in the human brain, as captured by fMRI imaging. To quantify their dynamics, the relevant connectivity states must be captured. Both clustering and source separation algorithms may be used to achieve this goal, dependent on how these states are hypothesized to manifest in time-resolved fMRI images. A nonlinear clustering algorithm, such as *k*-means, may be appropriate if each time-resolved fMRI “snapshot” primarily consists of a single state . If, on the other hand, each time-resolved snapshot contains a mixture of states , a blind source separation algorithm may be more applicable.

Our analysis presumes that each time-resolved fMRI image consists of a linear mixture of underlying “source” connectivity states with statistically unrelated time courses . As such, we select a linear source separation algorithm which maximizes the statistical independence of each predicted source, i.e. independent component analysis (ICA). In addition to its theoretical aptitude for the task, ICA has been proven to minimize the statistical dependencies between sources in neuroimaging data (Calhoun et al. 2013) and to isolate functionally meaningful communities in spike train data (Lopes-dos-Santos, Ribeiro, and Tort 2013). It is thus a natural choice for the problem of isolating the source states in a linearly mixed signal.

Most ICA algorithms are intended to process two-dimensional data arrays, with one dimension representing input variables and the second representing time. For instance, the time series of functional networks should produce a data array of , with being the number of samples taken over the course of recording. A dFNC array, on the other hand, has three dimensions: , which standard ICA algorithms cannot process. Researchers typically circumvent this by converting the upper triangle of each sample dFNC array to a vector:

[insert illustrative image here]

Repeating this process across all samples converts the data array from to , which can be fed into any standard ICA algorithm. We initially used the fastICA algorithm (Hyvärinen 1999; Hyvärinen and Oja 2000), but later applied InfoMax (Bell and Sejnowski 1995; J. P. Nadal and Parga 1997; J.-P. Nadal and Parga 1999) to remain consistent with previous work.

## Entropy analysis

To estimate each state’s subject-level rate of entropy production, we used a Kozachenko-Leonenko entropy estimator (Delattre and Fournier, 2017; Kozachenko and Leonenko, 1987; Shannon, 1949; Singh et al., 2003). This produces an array of entropy values for each group, with being the number of substates and the number of subjects per group. Since substates’ temporal independence ensures that their Shannon entropies are unrelated, one can estimate the joint entropy of all components as the sum of individual substates’ Shannon entropy (Cover and Thomas 2006):

Thus, by summing the Shannon entropies of each subject’s substates, one can estimate each subject’s total entropy.

## Comparison Tests

We utilize both a difference-of-means permutation test (Krol 2021) and the Kolmogorov-Smirnov two-sample test to search for differences between groups. Student’s *t*-test was also employed if the Jarque-Bara test indicated normally distributed data. Multiple-comparison correction consists of the false-discovery rate (Benjamini and Hochberg 1995).

## Regresison Analysis

To correct for possible confounds in the data, a multiple linear regression is employed alongside standard hypothesis tests. This regression separately models the effects of site, age, gender, and diagnosis on subject-level joint and component entropies. Additional regression analyses examine the effects of clinical (PANSS positive and negative) and cognitive (CMINDS composite) scores on subject entropy distributions, again while correcting for site, age, and gender effects. As cognitive scores are shown to be highly correlated (Figure []), it was decided to examine only the most general cognitive score to avoid effect cross-contamination.