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Sliding window study of brain connectivity dynamics based on Energy Landscape analysis

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ABSTRACT

Computational neuroscience models can be used to understand neural dynamics in the brain and these dynamics change as the physiological and other conditions like aging. One such approach we have used in this work is Energy Landscape analysis based on resting-state fMRI data. The dataset consists of 70 subjects with normal cognitive function, of which 23 are young adults and 47 are old adults. In this analysis, disconnectivity graphs and activity patterns are generated and using connectivity statistics among seven prominent brain networks. To study brain dynamic behaviors, we perform sliding window studies on the dataset and observe local minima of each window evolving in time. By varying the window shift from multiple seconds to 1 second, we can obtain statistics and evaluate the speed and activity pattern holding time of individual and group subjects. We found that older subjects can hold the brain states for a longer time but then jump to other dominated brain state local minima with a large hamming distance, whereas young subjects change dominated local minima more frequently but with a small hamming distance of 1 or 2. In fact, when averaged over the full time course, old subjects have more stable brain states local minima compared to young subjects. For both young and old subjects, the default mode network (DMN) and visual network (VIS) are coupled but for young subjects the two networks are on and off together and strongly correlated. For old subjects, there is an extra dominated brain state local minimum that the DMN and attention network (ATN) are correlated and anti-correlated with (VIS) and sensory-motor networks (SMN). This state may suggest old subjects are more capable of focusing on brain internal models and not getting influenced by external visual and sensory factors than young subjects.

Keywords: Energy landscape, disconnectivity graph, activity patterns, sliding window.

1. INTRODUCTION

In the last few decades, a lot of neuroimaging studies has gathered evidence which supports the phenomenon of spontaneous brain activity during the resting state is not random and cannot be averaged out in statistical analysis^{1,2,3}. During the resting state the brain shows consistent spatial activity patterns called as resting-state networks (RSN's)^{2,3}. In this study we are concentrating on 7 major RSN's which are default mode network (DMN), frontal parietal network (FPN), salience network (SAN), attention network (ATN), sensorimotor network (SMN), visual (VIS) and auditory network (AUD). We have a dataset consisting of old and young subjects and in this study, we are concentrating on identifying differences between the dynamics of old and young brains by doing the inter-network analysis among the 7 RSN's. The dataset we have used in this study is a resting state fMRI data of 70 subjects with normal cognitive function, of which 23 are young adults and 47 are old adults, fMRI provides information on the neural dynamics in the brain with reasonable spatial resolution in a non-invasive manner. To study the dynamics of the brain, we have further processed the fMRI data using sliding window analysis. Here, energy landscape analysis was done on this sliding window data and the results were analyzed to identify the differences between the young and the old brains.

2. MATERIALS AND METHODS

In this energy landscape method, multivariate time-series data at a specified region of interest (ROI) is extracted from the fMRI data. Pairwise maximum entropy model (MEM) explains large-scale brain activity patterns and gives much richer information about the interactions in the resting state networks^{4,5}. Pairwise MEM is applied, the energy values at each activity state is computed using MEM model. After that, Dijkstra-like method is applied on the energy values to plot the disconnectivity graph and the activity pattern^{4,5}. In general the approach can be summed up as: Importing the data,

binarizing it, calculating the energy values using the MEM model, finding local minimums, performing Dijkstra-like algorithm to obtain disconnectivity graph, and plotting the activity pattern.

2.1 Maximum Entropy Model

The fMRI signals at the ROIs, result in a multivariate time series. The number of ROIs is denoted by N . Then, the binarization is performed at each time point (i.e., in each image volume) for the fMRI signal and each ROI by thresholding the signal. A sequence of binarized signals representing the brain activity for ROI i ($i = 1, \dots, N$), is obtained $\{\sigma_i(1), \dots, \sigma_i(t_{max})\}$, where t_{max} is the length of the data, $\sigma_i(t) = 1$ ($t = 1, \dots, t_{max}$) indicates that the i th ROI is active at time t , and $\sigma_i(t) = -1$ indicates that the ROI is inactive. The threshold is arbitrary, and is set to the time average of $\sigma_i(t)$, for each i . The activity pattern of the entire network at time t is given by an N -dimensional vector $\sigma \equiv (\sigma_1, \dots, \sigma_N) \in \{-1, 1\}^N$, where t is suppressed. There are 2^N possible activity patterns in total. It has been previously shown that the pairwise MEM with binarized signals predicted anatomical connectivity of the brain better than other functional connectivity methods that are based on non-binarized continuous fMRI signals and that ternary as opposed to binary quantization did not help to improve the results^{4,5}. The relative frequency, $P_{empirical}(\sigma)$ is with which each activity pattern is visited, the Boltzmann distribution is fit to $P_{empirical}(\sigma)$ and is given by

$$P(\sigma|h, J) = \frac{\exp[-E(\sigma|h, J)]}{\sum_{\sigma'} \exp[-E(\sigma'|h, J)]} \quad (1)$$

where,

$$E(\sigma|h, J) = - \sum_{i=1}^N h_i \sigma_i - \frac{1}{2} \sum_{i=1}^N \sum_{\substack{j=1 \\ j \neq i}}^N J_{ij} \sigma_i \sigma_j \quad (2)$$

is the energy, $h = \{h_i\}$ and $J = \{J_{ij}\}$ ($i, j = (1, \dots, N)$) are the parameters of the model. We assume $J_{ij} = J_{ji}$ and $J_{ii} = 0$ ($i, j = 1, \dots, N$). The equation (1) implies that an activity pattern with high energy value does not mean that it is frequently visited and vice versa. Values of h_i and J_{ij} represent the baseline activity at the i th ROI and the interaction between the i th and j th ROIs, respectively^{4,5}. The equation (2) implies that, if h_i is large, the energy is smaller with $\sigma_i = 1$ than with $\sigma_i = -1$, such that the i th ROI tends to be active.

The principle of maximum entropy implies the selection of h and J such that $\langle \sigma_i \rangle_{empirical} = \langle \sigma_i \rangle_{model}$ and $\langle \sigma_i \sigma_j \rangle_{empirical} = \langle \sigma_i \sigma_j \rangle_{model}$ ($i, j = 1, \dots, N$), where empirical and model represent the expected value with respect to the empirical distribution and the model distribution, respectively. By maximizing the entropy of the distribution under these constraints, the Boltzmann distribution is given by equation (1). Some of the algorithms for fitting h and J are likelihood maximization, Pseudo-likelihood maximization and Minimum probability flow⁴. In this study we are using the likelihood maximization.

For MEM model, its parameters are calculated as:

$$(h, J) = \arg \max \mathcal{L}(h, J),$$

where $\mathcal{L}(h, J)$ is the likelihood given by

$$\mathcal{L}(h, J) = \prod_{t=1}^{t_{max}} P(\sigma(t)|h, J)$$

2.2 Dataset

We did the energy landscape analysis on the resting state fMRI data of normal aging 70 participants with normal cognitive function⁶. Exclusion criteria were major CNS trauma, previous brain surgery, or prior documented history of stroke that resulted in lasting sequelae, active neurological dysfunction, or the use of antipsychotic and/or antiepileptic medications with known neurological side effects. The young adult group had 23 participants (aged 18–38 years, 11 male and 12 female). The old adult group included 47 participants (aged 65–90 years, 22 male and 25 female). All subjects have

completed and signed a consent form, which was approved by the Institutional Review Boards at Virginia Tech and the Wake Forest University School of Medicine. fMRI data was collected on a GE 1.5 T scanner with an eight-channel head coil. T1-weighted and rs-fMR images were collected for each subject⁷.

The fMRI data of the 70 subjects was of 180 seconds long and the signals selected from the available 90 regions were in accordance with the AAL atlas and for this study only the seven large networks have been considered, namely: DMN, FPN, ATN, SAN, SMN, AUD and VIS. These seven regions are responsible for the proper functioning of the cognitive functions. In order to obtain the individual network results the whole data set has been considered with no exceptions.

2.3 Sliding Window Algorithm

The sliding window algorithm, as the name suggests is a method where a window is formed over some part of the data and it is slid over the rest of the data to capture different portions. The two parameters for this algorithm are window size and shift size, the window size data is formed and is slid over the whole dataset with a specific shift size. We have played around with few window sizes and shift sizes and we have used 90 seconds of window size and 4 seconds shift size initially in this case we have 24 sliding windows data, and the rest of the analysis was done with 50 seconds of window size and 4 seconds of shift size which ends up with 34 sliding windows data.

The sliding window algorithm was applied on each subject's data and saved each sliding window data, applied the energy landscape analysis method for these sliding windows data for each subject. That means we get 24 different activity patterns and disconnectivity graphs for the sliding window data with window size 90 seconds and shift size 4 seconds whereas 34 different activity patterns and disconnectivity graphs for the window size 50 seconds and shift size 4 seconds.

3 RESULTS

In this study we have used the sliding window algorithm to get the dynamics of the brain activity from the fMRI time course data of 70 subjects consisting of 23 old and 47 young subjects.

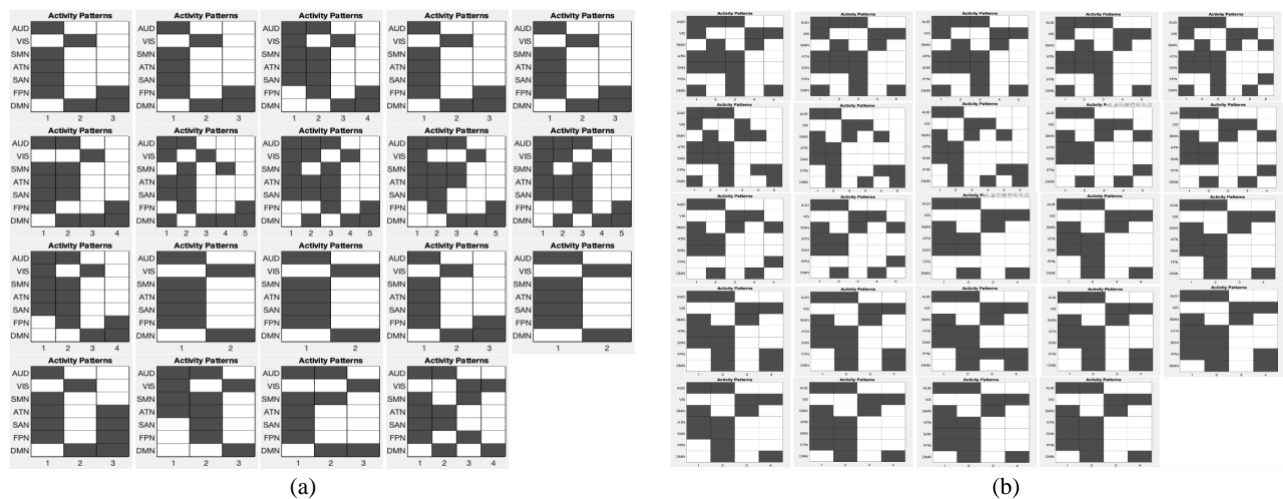


Figure 1. Activity maps for window size 90 seconds and different shift sizes. (a) in this case the window size is 90 and shift size is 5 seconds (b) in this case the window size is 90 and shift size is 1 seconds

As we vary the shift size from various seconds to 1 second, we have observed that the change in the activity pattern between the sliding windows was slow compared to when the shift size was higher. Figure 1 shows the activity patterns for two different subjects with different shift sizes, we can see from figure 1a that the change in the activity patterns is prominent when compared to the one in figure 1b who's shift size is 1 second and the activity pattern in this case tends to change very slowly between the sliding windows.

We found that older subjects can hold the brain states for a longer time but then jump to other dominated brain state local minima with a large hamming distance, whereas young subjects change dominated local minima more frequently but with a small hamming distance of 1 or 2. In fact, when averaged over the full time course, old subjects have more stable brain

states local minima compared to young subjects. Stable brain states here refer to the case where a particular state has its anti-correlated state present in the activity pattern. For example, in figure 2, the local minima 1 and 2 form a stable pair, since the networks VIS and DMN are both getting on and off together representing a stable brain state.

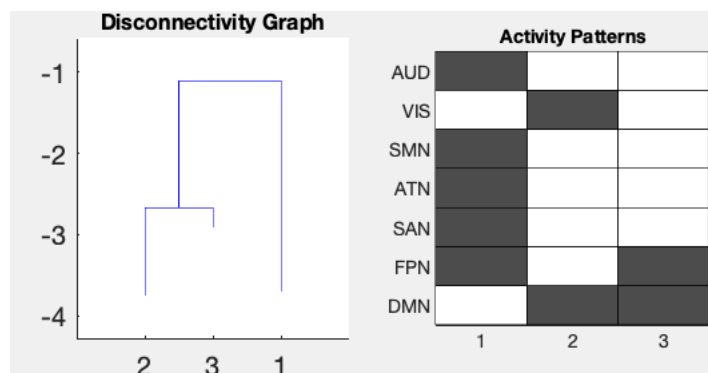


Figure 2. Activity pattern and disconnectivity graph, showing stable pair of states.

So, the averaged results of old subjects have more stable local minima pairs in the activity pattern when compared to young subjects.

For both young and old subjects, the DMN and VIS network are coupled but for young subjects the two networks turn on and off together showing strong correlation. For old subjects, there is an extra dominated brain state local minimum that the DMN and ATN are correlated and anti-correlated with VIS and SMN, we can see this behavior in figure 3. This state may suggest old subjects are more capable of focusing on brain internal models and not getting influenced by external visual and sensory factors than young subjects.

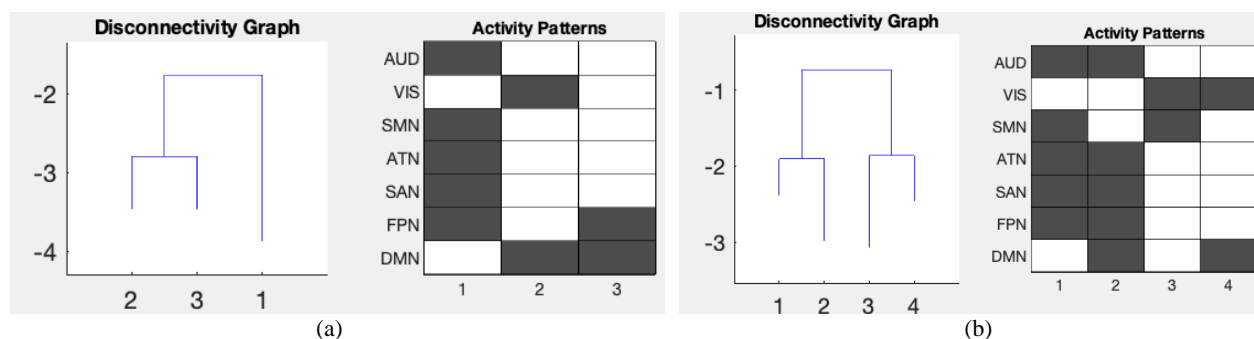


Figure 3. (a) Disconnectivity graph and activity pattern for the young brain, (b) Disconnectivity graph and activity pattern for the old brain

To get better understanding of how the states energies are changing over the sliding windows, we did some analysis on the data we got for the activity pattern and disconnectivity graph from the energy landscape code. So, here we are considering 7 RSN's, which means there are a total of 2^7 (128) possible states. Not all states appear in the sliding window results there will be states that are repeating over the sliding window results. For example, with a window size of 50 seconds and shift size of 4 seconds we will get a total of 34 sliding windows for a data of 180 seconds long. For each subject we will get different number of states that appear in all the sliding window results, we have listed all the states that are appearing in the sliding window results and their corresponding energy values and plotted them. One such plot is shown in figure 4. The plot in figure 4 is of an old subject, for which the sliding window analysis was done using 90 seconds of window size and 4 seconds of shift size, which will give us 24 sliding windows in total. As we can see in the plot there are 21 states out of 128 states that appear in the 24 sliding windows for this subject. We have taken the energy of each state and plotted it over the sliding windows, and not all states appear in all the sliding windows so for the states that are not present in that particular sliding window we took the energy of that state as zero. The data1 to data21 we see in the plot refer to the brain states.

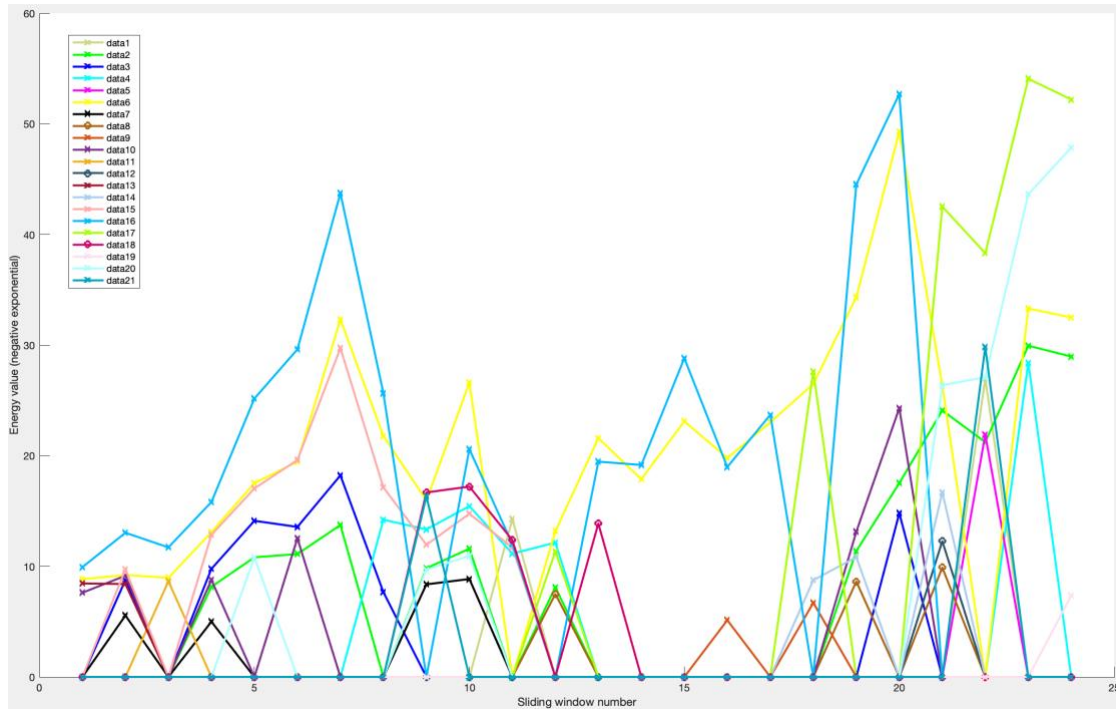


Figure 4. Plot showing the energy of each state changing for each sliding window.

Each of the state above has its own definition which is shown in table 1. We can see what each of the data point represented in the plot above has a corresponding definition give in table 1. Here we have used 0's and 1's to make it easy to understand where 0 means on and 1 means off, so we can see which of the brain networks are working together.

DMN	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1
FPN	0	0	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0	1	1	1
SAN	0	0	1	0	0	0	0	0	1	1	1	0	1	1	1	1	1	0	1	1
ATN	0	1	0	0	0	0	1	1	1	0	0	1	1	0	0	1	1	1	1	0
SMN	0	1	0	0	0	0	0	1	1	0	0	1	1	0	1	1	1	1	1	0
VIS	1	1	0	0	1	1	1	1	1	0	0	1	1	0	0	0	0	1	1	0
AUD	1	1	1	0	0	1	0	0	1	0	1	1	1	1	0	1	1	0	0	0
StateNo	3	15	17	32	34	35	42	46	47	48	49	63	79	81	85	92	93	95	110	112
data	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20

Table 1: Brain state definition for the plot shown in figure 4.

The “state No” in table 1 refers to state number, which we have assigned so that it will be easy to uniquely identify the state based on its pattern. If we consider each state’s definition (which networks are on and off together) as a binary sequence, the state number is nothing but decimal conversion of this binary number starting from DMN’s value as msb (most significant bit) and AUD networks value as lsb (least significant).

It is kind of hard to see which states are working together and which are not from the plot in figure 4. To get a better representation of the plot, we have first calculated the correlation coefficient matrix of each state’s energy data over the sliding windows and plotted a heatmap of that correlation matrix which is giving a better representation of the data more accurately. The correlation coefficient can be calculated using the formula,

$$\rho(A, B) = \frac{1}{N-1} \sum \left(\frac{A_i - \mu_A}{\sigma_A} \right) \left(\frac{B_i - \mu_B}{\sigma_B} \right)$$

where A and B are two samples whose correlation is being calculated, μ_A and σ_A are the mean and standard deviation of sample A, respectively, and μ_B and σ_B are the mean and standard deviation of sample B.

So, as we can see from the formula that correlation coefficient is calculated for two samples in our case it is the energy values of two states over all the sliding windows. The correlation coefficient values range between 1 and -1, 1 means highly correlated (both samples increase and decrease at the same time) samples and -1 means highly uncorrelated (one sample increases as the other decreases and vice versa) samples.

Figure 5 shows the heatmap of the correlation coefficient matrix for the data in the plot in figure 4. Here the correlation coefficient is calculated between each pair of state's energy values and hence we see a matrix and the diagonal of the matrix has all 1's because the diagonal values refer to the correlation between each sample by itself.

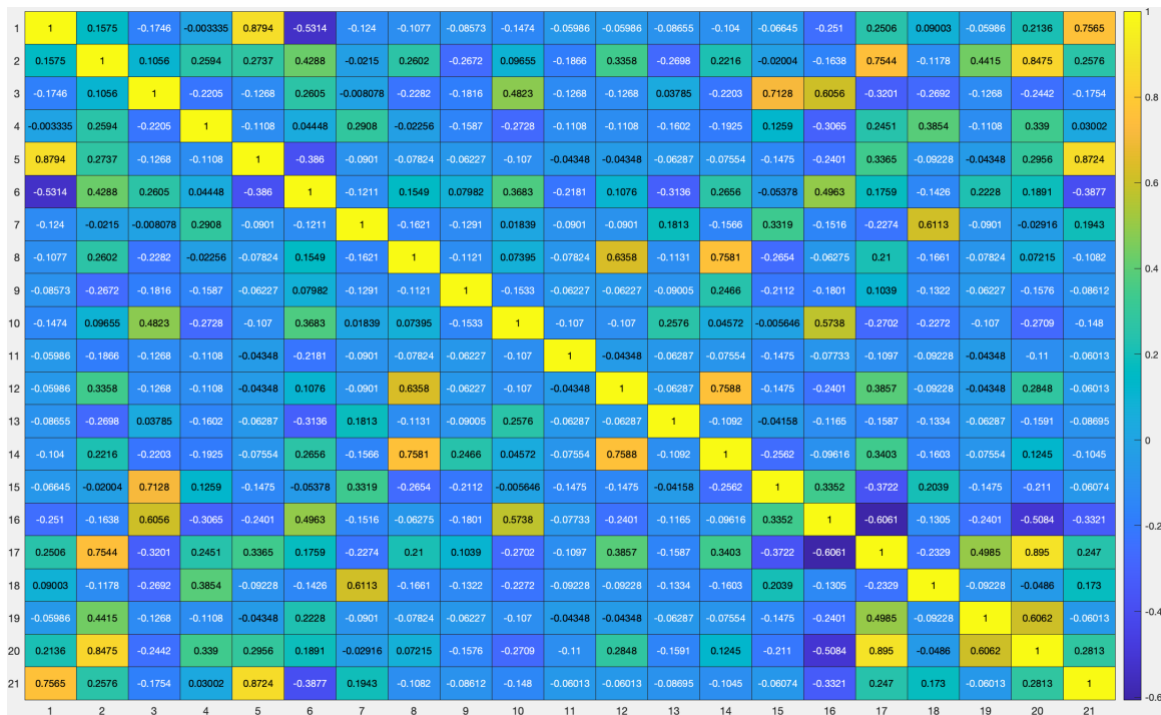


Figure 5. Heatmap of the correlation matrix of the data plotted in figure 4

From the above heatmap we can see that the states 17 and 20 are highly correlated, similarly there are other states like 5 and 21, 1 and 5 which are also correlated too. It is hard to determine this from the temporal plot shown in the figure 4.

We are further working on optimizing this heatmap and the data used to generate it to make more meaningful results from the approach. More details are explained in the future work section.

4 CONCLUSION AND FUTURE WORK

In this study, we used the energy landscape analysis to identify brain connectivity biomarkers that can tell the differences between young and the old brains. We have identified a few brain connectivity states that can distinguish the old subject's brain from young subject. To understand the mechanisms of these connectivity differences, we focused our study on the temporal behavior of brain connectivity by applying sliding window techniques to analyze energy landscape dynamics. With this approach, we obtained data which shows how the energies of all the states are changing over the course of sliding windows. To better understand the correlation between the states, we have generated a correlation matrix among all the states and displayed that as a heat map. Here correlation means which states energies are changing synchronously, like energies increasing and decreasing together over the sliding windows. The heat map will help to pick up states that are highly correlated and highly uncorrelated. But the drawback in this approach is we are only able to see the correlation between two states. For cases where there are more than two states that are correlated, further processing of the data may be required in the future.

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