Controllability Of Brain Networks Using Targeted Stimulation

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Abstract

Selective stimulation of brain areas can aid in understanding the connectivity, effect and function of the corresponding brain areas. This can lead to a better understanding of neurological disorders and to develop treatments for them. For our research, a non-linear model of brain dynamics was chosen and the effect of local stimulation of brain region was observed. Brain regions are clustered together in a set of 90 nodes according to AAL Atlas parcellation scheme and a weighted adjacency matrix was obtained. Network control theory(NCT) was deployed to study regional stimulation and to validate the findings with a non-linear model. We concluded that NCT can successfully be used for predictions of regional stimulation and it's effect on other brain regions. The procedure is repeated for 9 different subjects, it was observed that the dynamics and NCT measures and their correlations vary between subjects.

1. Introduction

Targeted stimulation of brain areas have exceedingly proven useful in understanding, detecting and treating brain diseases such as Schizophrenia, Alzheimer's and Parkinson's disease etc. It can also be helpful in diagnosing the damaged brain areas due to an accident or trauma and associating it with the resulting behaviour of the subject.

The challenge that exists in selective stimulation of brain areas is the parameter required for stimulation and the optimal resulting state which is targeted for clinical use. Since the understanding of how the stimulation of a particular brain area affects the targeted region locally is important, it also of importance to understand the global spread of the stimulation through the connected brain regions. The imaging techniques deployed to capture the brain states during stimulation needs a computational model for depicting the resulting effect of the stimulation on cortical and sub-cortical brain regions connected to the stimulated region. The model should be biologically accurate in describing how the affect spreads through the connected regions. It is also important that the computational model is fairly flexible to the changing parameters which can capture the variability of the brain states resulting from the difference in activity of different subjects.

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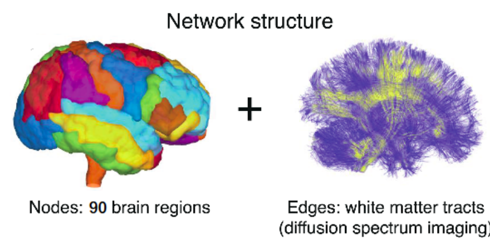

Figure 1. **Mapping of the brain into nodes** Muldoon et al. 2016

We use network control theory(Gu et al., 2015) to model and predict the effect of stimulation of a brain region and how it affects the the whole network. The use of network control theory in studying complex and biological systems turned out to be revolutionary for the field of automated control. Control of a network is defined as the net effect on the entire network if the a node is interacted with locally, in a sense how the local effect on the node steers the whole system on a defined trajectory. Network Control Theory also outlines how the stimulation or activity captured by the functional effect is limited or enhanced due to the structural connectivity of the brain regions(node). We measure the modal controllability(Gu et al., 2015) which identifies the brain areas which can move the system to difficult to reach states and average controllablity(Gu et al., 2015), which identifies the brain areas which can move the system in many different states, for each node in order to estimate the performance of our linear model of the form **(Eqn 1)**:

$$\dot{x} = Ax + Bu \tag{1}$$

We attempted to model the dynamics of the brain regions using a non-linear computational model based on structural connectivity data. We bring the system close to bifurcation point at low point and observe the effect of adding control to a single node at a time and observe the change in the dynamics of the system. We measure the effect of change in dynamics of the system with Functional Effect which measures how the global functional activity across brain regions is modulated by region-specific stimulation and System Energy which represents the average energy of the system when control to a particular node is applied at a time, treating input to the nodes as discrete signals. We also studied the correlations between the network control parameters to the non-linear dynamics. And how these parameters vary between the subjects.

2. Related Work

Our research is based on the work previously done by (Muldoon et al., 2016). They examine the regional simulation of the brain dynamics using Wilson Cowan Oscillator and calculate the functional effect for each node. Their work provides the idea of using Network Control Theory to approximate the network dynamics during the regional stimulation. They show that structural connectivity constrains the effect of regional stimulation. The work also examines the variability of the measures between 8 patients with 83 cortical and sub-cortical nodes summarized in a weighted adjacency matrix and shows the though the results are highly reproducible for each subject, they vary a lot between subjects. (Kostova et al., 2004) provides the detailed analysis of FritzHugh Nagumo(FH-N) model for modelling non-linear dynamics.

3. Methodology

3.1. Structural Connectivity

Structural connectivity is defined as the anatomical connection strength between different areas of the brain, which also encapsulates the properties related to the node's effectiveness. In our study we used the structural connectivity of nine healthy human subjects and compared a network with the average structural connectivity and the networks with structural connectivity of each individual subject. It is important to visualize the connectivity of the brain regions before the stimulation to identify the nodes with the the most structural connectivity in order to understand and categorize the nodes which are most effective or least effective under stimulation(**Fig. 2**). The degree distribution(**Fig. 3**) of the network was obtained using the network adjacency matrix and it was observed that most of the nodes in the network have less degree which corresponds to low structural connectivity. The structural connectivity matrix is normalized so that the largest Eigenvalue is 1.

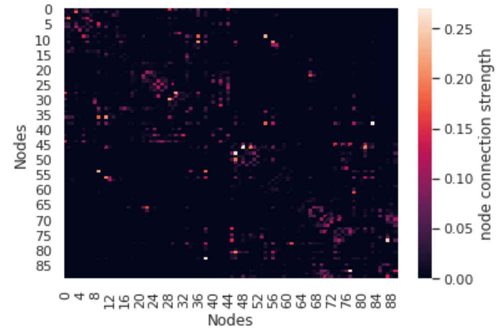

Figure 2. **Structural Connectivity of a subject**. The upper left quadrant represents the left hemisphere and lower right quadrant represents right hemisphere.

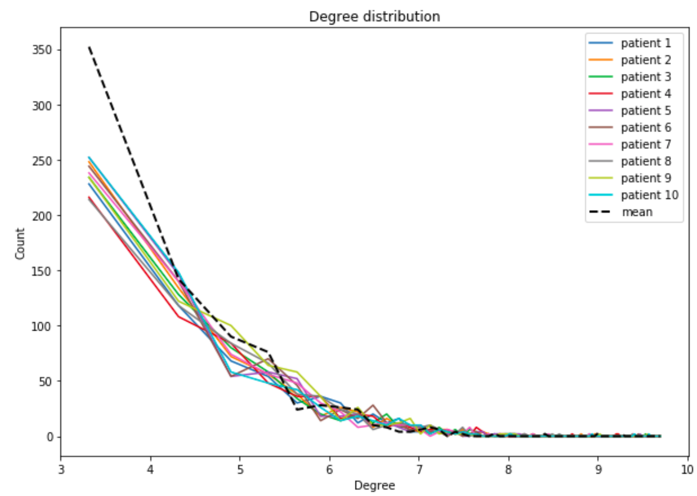

Figure 3. **Degree distribution of the connectivity matrix.** Each line corresponds to one subject, with the black line corresponding to the mean.

3.2. FritzHugh-Nagumo model

The dynamics of the system was modelled using FH-N (Kostova et al., 2004) model as follows:

$$\frac{dx}{dt} = \epsilon g(x) - w + I, \tag{2}$$

$$\frac{dw}{dt} = x - aw, \tag{3}$$

Where $g(x) = x(x - \lambda)(1 - x)$, $0 < \lambda < 1$ and a,$\epsilon > 0$. For mathematical convenience we choose $\epsilon g(x) = -\alpha x^3 + \beta x^2 - \gamma x$ and $x - aw = (x + \delta - \epsilon w)/\tau$, i.e, we get:

$$\frac{dx}{dt} = -\alpha x^3 + \beta x^2 - \gamma x - w + I \tag{4}$$

$$\frac{dw}{dt} = \frac{x + \delta - \epsilon w}{\tau} \tag{5}$$

With initial values of parameters as $\alpha = 3.0$, $\beta = 4.0$, $\gamma = -1.5$, $\delta = 0.0$, $\epsilon = 0.5$, $\tau = 20.0$.
Full network equation was obtained by using FH-N for each node and also adding coupling(K) and noise as follows:

$$\frac{dx_i}{dt} = (-\alpha x_i^3 + \beta x_i^2 + \gamma x_i - w + I + \tag{6}$$
$$K * SC_{ij} * x_j(t - c * DM_{ij}) + \sigma * noise)$$

$$\frac{dw_i}{dt} = \left(\frac{x_i - \delta - \epsilon w_i}{\tau}\right) \tag{7}$$

Where 'i' represents the index of the node ($i \in (0, 89)$), K is the global coupling strength, SC_{ij} is the ij_{th} element of the network adjacency matrix, u_j is the input from j_{th} node, c is the transmission speed and σ is variance of the additive noise. We ignore the noise and delay in our implementation. Hence, $c, \sigma = 0$.

3.3. Simulation

To study the non-linear dynamics brain network, we prepared a simulation for the evolution of the dynamics based on FH-N and using our weighted adjacency matrix. We plotted the time series with the scale of activity for each node which is sensitive to each the input and coupling parameter. We run the simulation for 30000ms, i.e ($t = \in (0, 30000)$). It helped us to visualize how the system is transitioning from low state into the limit cycle.
To initialize the simulation at (t=0), we use the end values from an initial run of the simulation with K = 0 and I = 0.6.

3.4. Average Controllability

To obtain the Average controllability, we employ a simplified noise-free linear discrete-time and time-invariant network model:

$$x(t+1) = Ax(t) + B_\kappa u_\kappa(t) \tag{8}$$

where x describes the state of brain regions over time, **A** is a normalized structural connectivity matrix. The input matrix B_κ identifies the control points, and u_κ denotes the control strategy. From the set of control nodes κ, we obtain the controllability Gramian W_κ being invertible. (Muldoon et al., 2016)

$$W_\kappa = \sum_{\tau=0}^{\infty} A^\tau B_\kappa B_\kappa^T A^\tau \tag{9}$$

We take Trace(W_κ) as the measure of average controllability.

3.5. Modal Controllability

Modal controllability is computed by the Eigen value matrilx $V = [v_{ij}]$ of the network adjacecny matrix **A**. We define Modal Controllability (Muldoon et al., 2016) to be:

$$\phi_i = \sum_{j=1}^{N} (1 - \lambda_j^2(\mathbf{A})) v_{ij}^2 \tag{10}$$

4. Network Dynamics

We studied the the effect of stimulation on each node and the network control dynamics using a non-linear model. We used the weighted adjacency matrix with 90 nodes for 9 subjects for brain structure.

4.1. Single Node

The regional mean-field dynamics of the single node is modelled using FritzHugh Nagumo(FH-N) (Kostova et al., 2004) oscillator. **(Eqn 4 and 5)**. An important feature of the FH-N oscillators is that it can exhibit three states. It depends upon the kind amount of input provided to the node. When low external current is applied, the system stays in a state called low fixed point which is a relaxed state. For intermediate level of input current, the oscillator is shifts into a limit cycle, and if the amount of input is increased further, the system settles to a high fixed point**(Fig. 7)**. The nodes receive inputs from other nodes depending upon the coupling parameter(K) which scales the adjacency matrix, therefore the connection strength of all pairs of nodes.

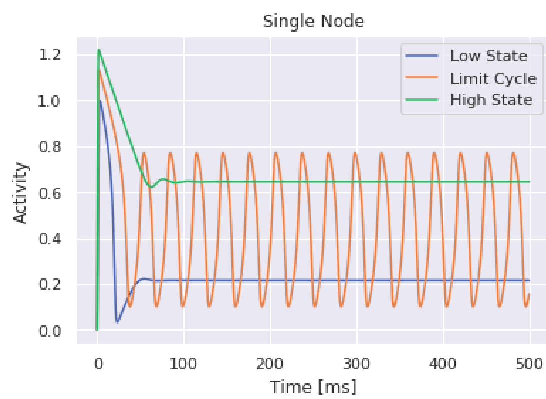

Figure 4. **Dynamics of single node.** It represents the example dynamics for the three states(low fixed point, limit cycle and High fixed point) of an uncoupled FH-N oscillator **(Eqn 2)**. The evolution of the states corresponding to the input currents are as follows: I=0.6 (Blue curve), I=1 (Orange curve), I=1.4(Green curve)

4.2. Network

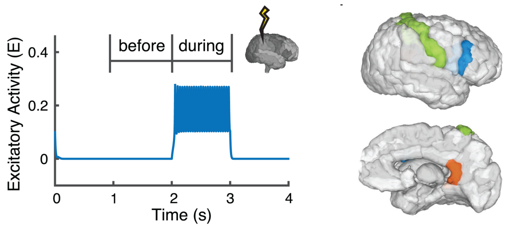

Figure 5. **Node activity before and during the stimulation** Muldoon et al. 2016

The bifurcation point at which the system jumps into the limit cycle was obtained for each subject(**Fig. 6**), by keeping the current constant(I=0) and varying the coupling coefficient. The system was adjusted very close to the bifurcation point and the behaviour of the system is observed when control is applied to single node with two measures (**Eqn 6 and 7**). Namely, Energy and Functional effect(see methods).

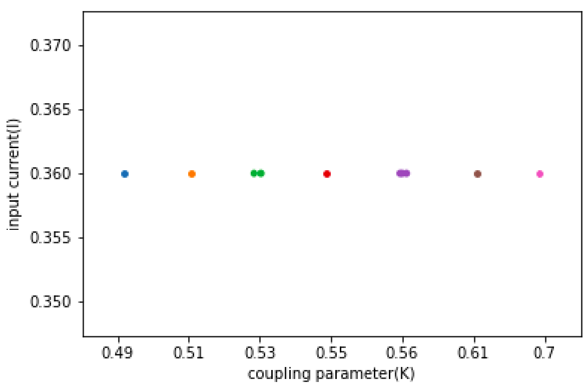

Figure 6. **Variation of bifurcation point between subjects**

4.3. Functional Effect

We assess the pairwise change in brain states by subtracting the correlation values obtained in with-stimulation and without-stimulation windows for each stimulated node. We then measure the average change in functional brain states, called the functional effect for the respective stimulated node, as the absolute value of this difference averaged over all region pairs. (**Eqn. 11** (Muldoon et al., 2016) In other words, it the the effect on global activity of the network by regional stimulation of a particular node.

$$Fs = \{x(n)\} = \| \, \mathrm{Corr}(x(n,t_1)) - \mathrm{Corr}(x(n,t_2)) \| \tag{11}$$

For all n $(n \in (0,89))$ with $t_1 \in (5000, 14999)$ and $t_2 \in (16000, 30000)$.

Greater functional effect means greater effect of stimulation on brain states of the network. We found out that the functional effect is directly depends upon the structural connectivity(i.e degree) of the node **(Fig 8)**. The nodes with high connectivity have high functional effect and vice-versa.

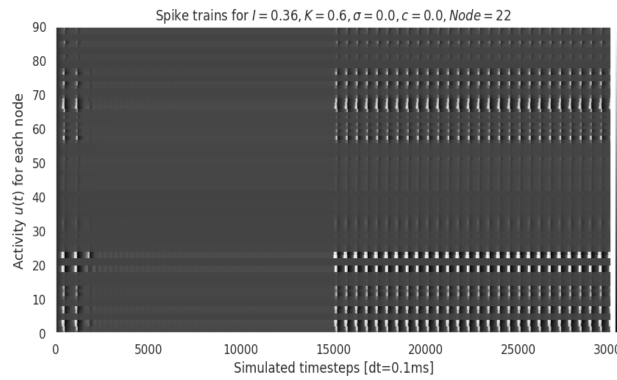

Figure 7. **Simulation window of the network dynamics in limit cycle(right) when node 22 is stimulated and before stimulation at bifurcation point(left).**

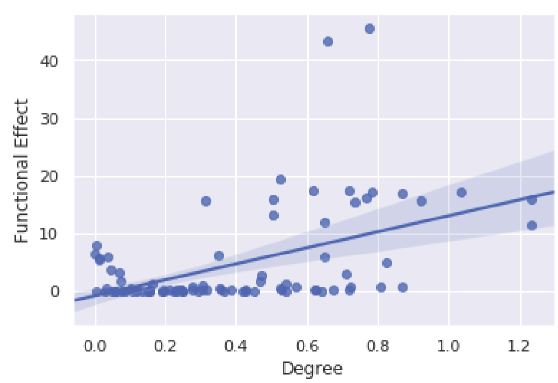

Figure 8. **Functional effect vs Degree regression plot.**

4.4. Energy

Each input to the node is treated as discrete signal in time. The energy of the system under stimulation is calculated when input is applied to a single node and the values are squared and summed over time for each node. Then the values of each node is summed to acquire the energy of the system.

$$Es = \{x(n)\} = \left\| \sum_{n=1}^{90} \left(\frac{\sum_{t=4999}^{30000} |x(n,t)|^2}{30000 - 4999} \right) \right\| \tag{12}$$

It was observed that nodes with high degree exhibit a high energy(**Fig. 10**).

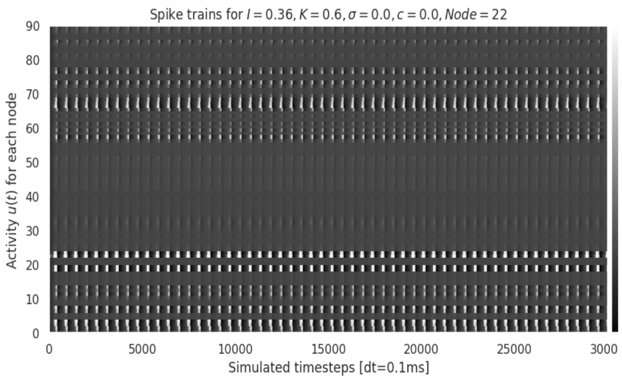

Figure 9. **Simulation window of the network dynamics in limit cycle when node 22 is stimulated.**

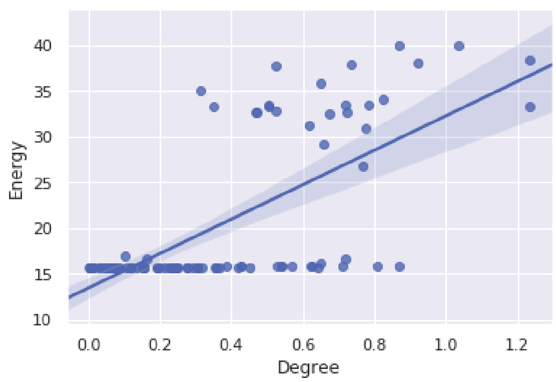

Figure 10. **Energy vs Degree regression plot.**

5. Linear Control Measures

For examining the effect of regional stimulation in the structural network, we deploy linear network control theory and quantified controllabitily measures based on the structural connectivity using the network adjacency matrix. We were successful in encapsulating the simplified version of non-linear computational model for brain dynamics using our linearised approach of network control theory. We obtain two different types of regional controllability measures (Wu-Yan et al., 2018), average controllability and modal controllability respectively.

5.1. Average Controllability

Average controllability of a network equals the average input energy from a set of control nodes and over all possible target states (Muldoon et al., 2016). Regions with high average controllability are, on average, most influential in the control of network dynamics over all nearby target states with least energy. We found out that the region with high degree have high average controllability **(Fig. 11)** and in turn have high functional effect and energy. Which demonstrates that our linear model successfully encapsulates the behaviour of non-linear dynamics of brain states.

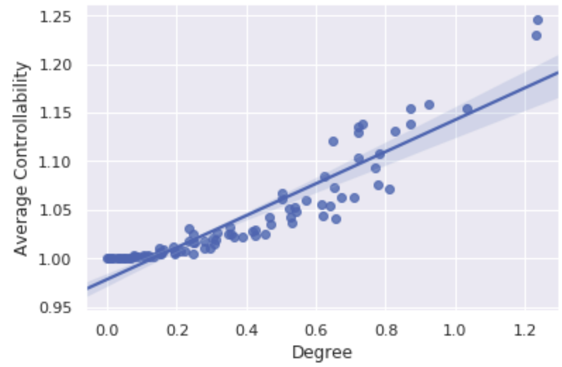

Figure 11. **Average Controllability vs Degree regression plot.**

5.2. Modal Controllability

Modal controllability refers to the ability of a node to control each evolutionary mode of a dynamical network (Hamdan & Nayfeh, 1989), and can be used to identify states that are difficult to control from a set of control nodes.(Muldoon et al., 2016) The nodes with high modal controllablilty can place the system in difficult to reach states but requires high energy input. We observed that nodes with high degree have low modal controllability **(Fig. 12)** and show low functional effect and low energy.

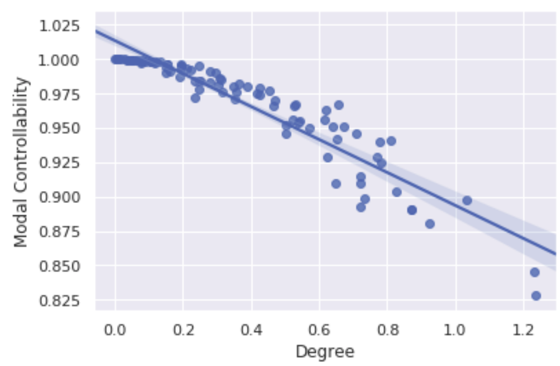

Figure 12. **Modal Controllability vs Degree regression plot.**

6. Network Measures and Correlations

We characterized different aspect of the network using various network measures(Rubinov & Sporns, 2010) such as Degree, Closness Centrallity, Betweenness Centrality and Triangles. We prepared a correlation matrix between network measures, (Linear Control Theory) LCT measures and network dynamics measures **(Fig. 13)**. We observe a strong positive correlation between energy, functional effect and average controllability but a negative correlation between modal controllabiliy. Also, network measures, though correlate well among themselves, do not show a strong correlation with non-linear dynamics measures but show a strong positive and negative correlation with average controllability and modal controllability respectively.

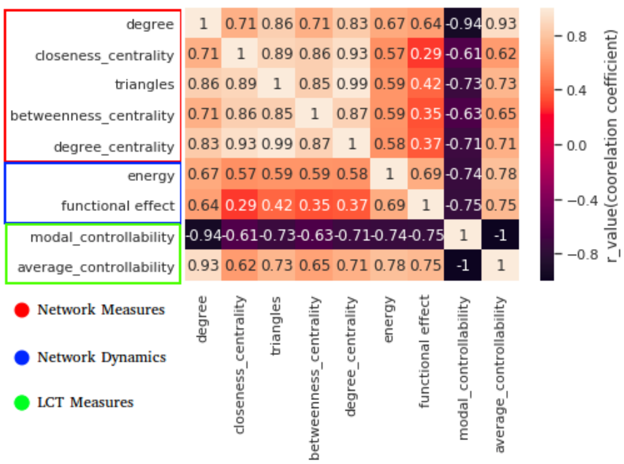

Figure 13. **Correlation matrix between network measures, LCT measures and dynamics measures.**

6.1. Measures Variability Between Subjects

We also investigated the variability of these measures between 9 different subjects. It was found that the measures show a lot of variability between subjects. It is interesting to see that the network dynamics vary a lot between the subjects compared to LCT measures **(Fig. 14)**.

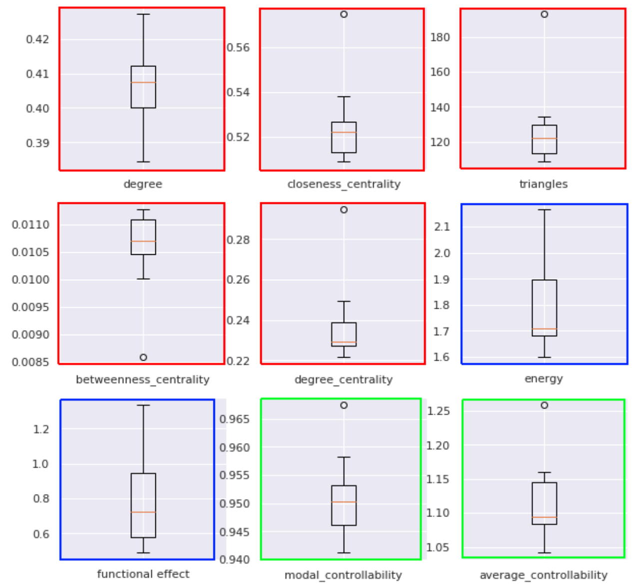

Figure 14. **Variability of network measures between subjects.**

6.2. Correlation Variability Between Subjects

We observed a stark variability of the correlation of LCT and Dynamics measures between the subjects**(Fig. 15)**. Which indicates that the dynamics and LCT measures correlate differently for each subject and though the subjects sometimes indicate similarity of correlation, it might be misleading to assume the degree of dependence of measures on each other.

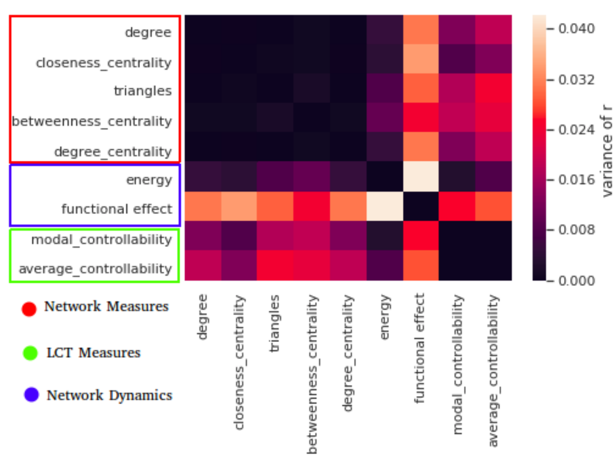

Figure 15. **Variability of measures between subjects.**

7. Concluding Remarks

It is observable that linear model can successfully approximate the regional controllability i.e non-linear control dynamics. It is observable that nodes with high average controllability correlates postiviely with the structural connectivity and have high functional effect and energy. Which means they controlling these nodes can effect the states of the entire network more than any other nodes. The nodes with high modal controllability have low functional effect and energy. It is also observed that the LCT measures, network dynamics and network control measures vary between subjects. Though the scale of variability is larger with measures of non-linear dynamics than the LCT measures. The correlations between the linear and non-linear measures vary between the subjects, therefore, it is advised to not generalize the correlation between these two types of measures. Every subject needs its due diligence.

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