Journal of Brain Sciences
2023 Vol. 6, No. 1, pp. 1-15
ISSN(e): 2410-8774
ISSN(p): 2412-3463
DOI: 10.18488/83.v6i1.3582

Constructing a graphical representation of the brain from functional MRI

Mihai Teodor Bica *University of Cambridge, UK.*
Email: mtbica9@gmail.com

Article History
Received: 16 October 2023
Revised: 27 November 2023
Accepted: 13 December 2023
Published: 29 December 2023

Keywords
Connectivity
Depression
FMRI
Major depressive disorder
Mutual information
Neurobiology
Resting state network.

ABSTRACT

This study aims to investigate alterations in brain connectivity, specifically within the Resting State Network (RSN), among adolescents with major depressive disorder (MDD) compared to well-matched healthy controls. Employing functional Magnetic Resonance Imaging (fMRI), the research focuses on using two statistical approaches, namely Pearson Product-Moment Correlation Coefficient (PPMCC) and Mutual Information (MI), to discern changes in connectivity patterns. Resting state fMRI data from 102 adolescents diagnosed with MDD and 34 healthy controls were analyzed. The study utilized PPMCC and MI to assess correlations between different brain regions within the RSN. The investigation scrutinized whether these statistical approaches yield consistent results and explored their efficacy in detecting alterations in brain connectivity associated with depression. While PPMCC analysis revealed no significant differences between any brain regions, MI analysis demonstrated substantial changes in the connectivity of 39 specific brain regions. The study underscores the sensitivity and robustness of the MI technique, establishing it as a more effective method for discerning connectivity variations associated with major depressive disorder. The findings emphasize the importance of selecting appropriate statistical methods in neuroimaging studies. The application of MI in analyzing resting state fMRI data proves to be a valuable tool for identifying nuanced alterations in brain connectivity associated with depression. This insight contributes to refining diagnostic approaches and potentially informs the development of targeted interventions for adolescents with major depressive disorder.

Contribution/Originality: This study is unique in that it compares two statistical methods, PPMCC and MI, for analyzing resting state fMRI data in adolescents with MDD. It demonstrates that MI is a more sensitive and robust technique for detecting alterations in brain connectivity associated with depression, while PPMCC fails to reveal any significant differences. This study provides novel insights into the neural mechanisms of MDD and suggests that MI could be a useful tool for improving diagnosis and treatment.

1. INTRODUCTION

1.1. Magnetic Resonance Imaging in Psychiatry

The use of MRI has become cornerstone in neurology clinics but has until recently failed to translate into psychiatry. This has changed with the development of fMRI, allowing neuroimaging to flourish as a potent research tool in the field. fMRI can provide information about the interface between genotype and phenotype and thus aid in potential drug development and even a personalized diagnosis (Liu et al., 2009). The primary from of fMRI was discovered by Ogawa, Lee, Kay, and Tank (1990). He demonstrated in-vivo changes in the microvasculature of the

brain, when subjects were exposed to a stimulus (flashing lights). fMRI uses blood as a proxy for measuring neuronal activity, this imaging technique being sensitive to the magnetic properties of oxygen-rich blood flow to specific regions (Smith, 2012). By analysing blood oxygen level– dependent (BOLD) signals, it detects changes in activity from deep within the brain and it is rather safe and non-invasive for the patient. The initial paradigm used by Ogawa, task-induced stimulation, was used extensively in many studies in the following 10 years. By using the novel techniques and increasingly sophisticated paradigms, many brain regions have been functionally mapped. The mapping of key functions was important for psychiatry, as many become aberrantly activated in numerous disorders. However, the sensitivity of this technique has arguably approached its limit and not even further improvements in the technology behind fMRI could yield new results.

Functional connectivity between brain regions has been defined as the level of co-activation between anatomically different brain regions in a certain time frame (van den Heuvel, Mandl, Stam, Kahn, & Pol, 2010). Although 25 years have passed since the discovery of fMRI, the paradigms for testing have largely remained the same: primary sensory stimulation and affective/cognitive paradigms (Lopez-Larson et al., 2011). A key paper published by Raichle (2009) encouraged a paradigm shift in functional brain imaging. Essentially, he started questioning the reason for which such a small change in metabolism is observed when a distinct region is activated, since the brain as a whole consumes an enormous amount of resources. This changed the 'localist' approach (region- function correlations) to a global one, looking at the brain as a whole and at the connections within it. This was quite a radical change, because in the previous paradigm, the now fundamental connections had been completely ignored. The theoretical framework was backed up by the development of echo-planar imaging, allowing acquisition of multiple image planes at each second and making observing focal changes easier (Lee, 2012). Therefore, in the emerging field of connectomics, information is being derived from the correlation of resting BOLD time-series, and particularly through its representation as a graph theoretical model. The current narrative is that the global network of the brain has a set of hubs that are highly connected, and that aberrant connectivity of hubs is present in many psychiatric disorders (Wolf et al., 2011).

1.2. Major Depressive Disorder- A Prevalent and Debilitating Disease

Unipolar MDD is the number one psychiatric disorder in the western world and the reports have a shown a steady increase in the number of diagnosed patients of all age groups and nationalities in the past years. Community surveys in 14 countries have estimated that the lifetime prevalence of unipolar MDD is 12% (Kessler et al., 2011). Additionally, it has been ranked as the 11th greatest cause of disability and mortality in the world by the World Health Organisation (Murray et al., 2012). In the United States, major depression is the second most disabling disease with suicide as a result of depression being the eight cause of death (Murray, 2013). What is truly concerning is that current treatment options such as pharmacologic intervention or Cognitive Behavioural Therapy (CBT) are only sometimes effective. As such, the rate of recurrence over two years is greater than 40 percent and after two episodes, the risk of recurrence within five years is approximately 75 percent (Solomon et al., 2000). It is thus becoming increasingly important to have a better understanding of the disease process in order to provide potential treatments at population level. Therefore, with the advent of fMRI and the changes in how brain networks are being looked at, new information about prevalent mental disorders like depression can be derived by looking at resting state fMRI (rs-fMRI) of depressed individuals and matched controls.

1.3. Approach in the Present Study

The brain of each patient was separated in 116 voxels and the activity in these regions was measured over the course of 256 time frames. Now comes the question of how should the intensities of these brain regions be correlated.

The traditional approach to correlating brain regions has been using the Pearson Product-Moment Correlation Coefficient (PPMCC). This statistical approach has not been the golden standard for fMRI studies only, but also in other fields such as gene pairwise relationships (Song, Langfelder, & Horvath, 2012) or EEG (electroencephalogram)

measurements (Bonita et al., 2014). These and other studies have questioned whether using PPMCC is the correct choice, given the fact that it only provides information about linear correlations, which is often not the case in biological systems, especially one as intricate as the human brain. The emergent Mutual Information (MI) approach seems to bypass the limitations of PPMCC and provide sensitive enough correlations, while maintaining robustness and accuracy. Therefore, this statistical tool disregards the concern of whether the association is linear or not, which is a more comprehensive way of looking at changes in connectivity which would have otherwise been ignored. I focused on applying these two techniques and comparing the results for the two groups: depressed and controls.

Since Pearson correlation has been almost exclusively used in mapping correlations, it may well be that a change in this metric would lead to an entirely new view of the connectome. In other words, the present study looks at how dependent our knowledge of the connectome is on the metric that defines its connections.

One novel approach worth mentioning is looking at brain regions from the perspective of graph theory, with nodes representing regions of interest, and edges representing connections between them. The graph can be undirected or directed (weighted/ unweighted) (He & Evans, 2010). Mapping the brain in this way can account for the various properties of the regions and the connections between them and is a significant advance in the emerging field of connectomics. Such rigorous mathematical and computer-based modelling can provide valuable information about changes in the connectivity in the diseased brain. Knowledge of network topology allows us to describe pathological processes and then generate models predictive of how the brain disease is spreading, along with its afferent functional consequences (Fornito & Bullmore, 2015).

2. METHODS

The starting point of the research was accessing the data available on a remote server. The data was obtained from the MR-IMPACT study and consisted of 102 depressed patients and 34 well-matched healthy controls (Hagan et al., 2013). I then constructed an intensity matrix for each patient, with 116 pre-determined voxels across 256 time frames. I thus obtained 102 matrices for depressed patients and 34 matrices for controls. The data had already been pre-processed, in order to remove biases due to head motion and hence increase the BOLD signal: noise ratio and allow for a better interpretation of the data.

Using the new achievements of functional magnetic resonance imaging (fMRI), functional connectivity (FC) can be performed using correlation network statistics on a single individual or on a specific population with certain characteristics. Functional connectivity is defined in terms of correlations or covariance (Friston, Tononi, Reeke Jr, Sporns, & Edelman, 1994). The two ways of assessing functional connectivity that I considered are PPMCC and MI information statistics between time series pairs in specific voxels or regions of interest in which the brain activity was measured.

2.1. Pearson product-moment correlation coefficient

PPMCC has been widely used in sciences as a measure of the linear correlation between two variables. Its development dates back to the late 19th century when it was developed by Karl Pearson based on a related idea introduced by Francis Galton. When applied to a sample PPMCC is usually represented by the letter r and may be referred to as the sample correlation coefficient. A formula for r is easily obtainable by substituting estimates of the covariances and variances based on a sample into the formula for the population correlation coefficient:

$$\rho_{X,Y} = \frac{E(XY) - E(X)E(Y)}{\sqrt{E(X^2) - E(X)^2}\sqrt{E(Y^2) - E(Y)^2}}.$$

Therefore, having 2 data sets containing n values {x1,...xn} and {y1,...yn}, the formula for r is:

$$r = r_{xy} = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2}\sqrt{\sum_{i=1}^{n}(y_i - \bar{y})^2}}$$

Where:

n, x_i, y_i are defined as above;

$\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$ (sample mean);

The above formula for r is the one used by Microsoft Excel function CORREL. Through appropriate programming it can be configured to perform the necessary computations.

2.2. Mutual Information

The mutual information (MI) of two variables is a measure of the variables' mutual dependence. In probability theory mutual information is defined in terms of entropy. The entropy, denoted H(X), quantifies the uncertainty present in the distribution of X (Brown, Pocock, Zhao, & Luján, 2012).

$$H(X) = -\sum_{x \in X} p(x)\, log p(x)$$

Where: lower case x denotes a possible value of X, p(X) is the distribution of X.

The conditional entropy of X given Y is denoted as:

$$H(X|Y) = -\sum_{y \in Y} p(y) \sum_{x \in X} p(x|y) log \;\; p(x \vee Y)$$

Considering the entropy of X given Y, the mutual information between X and Y is defined as the amount of information shared by X and Y. The mathematical formulation is given in the following equation:

$$I(X;Y) = H(X) - H(X|Y) = \sum_{x \in X}\sum_{y \in Y} p(xy)\, log \frac{p(xy)}{p(x)\,p(y)}$$

The computation of all data was performed in the MatLab environment using a toolbox developed by The University of Manchester under the Lesser General Public License (LGPL v3). The MIToolbox provides the implementation of Shannon's Information Theory functions and implementations of Renyi's Entropy and Alpha Divergence.

After the computation of all 136 matrix data (34 controls and 102 depressed patients), two new sets of 136 connection matrices were created, representing the Pearson and MI correlations values between the 116 brain regions. Each obtained matrix is symmetrical. The connection matrices were analyzed in terms of statistical parameters for each type of subjects and analyzed in conjunction.

The formulas used for generating the correlation matrices for PPMCC and MI are:

$$M_p^{Pearson} = \begin{bmatrix} r(In^p_{reg=1}, In^p_{reg=1}) & \cdots & r(In^p_{reg=1}, In^p_{reg=1}) \\ \vdots & \ddots & \vdots \\ r(In^p_{reg=nr}, In^p_{reg=1}) & \cdots & r(In^p_{reg=nr}, In^p_{reg=nr}) \end{bmatrix}$$

$$M_p^{MI} = \begin{bmatrix} I(In^p_{reg=1}, In^p_{reg=1}) & \cdots & I(In^p_{reg=1}, In^p_{reg=1}) \\ \vdots & \ddots & \vdots \\ I(In^p_{reg=nr}, In^p_{reg=1}) & \cdots & I(In^p_{reg=nr}, In^p_{reg=nr}) \end{bmatrix}$$

Where:

p- Subject number in a group (controls/depressed).

n- Total number of subjects in a group (*n*=34 for controls and *n*=102 for depressed).

nr- The total number of analysed regions (116).

r (x,y)- PPMCC between variable x and variable y.

I (x,y)- MI between variable x and variable y.

$In^p_{reg=i}$ – Intensity of activation of region I for subject p.

Both matrices were calculated for both the control group (n=34) and for the depressed group (n=102).

2.3. First Approach

The first step made was to average the values in the correlation matrices obtained with both PPMCC and MI. This essentially yielded two matrices for each statistical approach. By subtracting the values in each matrix slot for controls from the values in each matrix slot for depressed, two further matrices were obtained, termed 'difference matrices' (one for PPMCC and one for MI- obtained correlations). The significance of these differences was then investigated using the Mann-Whitney U test (for data that is not normally distributed).

The average correlation matrices for the two metrics (PPMCC and MI) were obtained as follows:

$$\overline{M}^{Pearson} = \sum_{p=1}^{n} M_p^{Pearson} \cdot \frac{1}{n} \quad \text{and}$$

$$\overline{M}^{MI} = \sum_{p=1}^{n} M_p^{MI} \cdot \frac{1}{n}$$

The formula for generation of the 'difference matrices' for both metrics:

$$\overline{M}_{Dif}^{Pearson} = \overline{M}_{Depressed}^{Pearson} - \overline{M}_{Controls}^{Pearson}$$

$$\overline{M}_{Dif}^{MI} = \overline{M}_{Depressed}^{MI} - \overline{M}_{Controls}^{MI}$$

The correlation power values obtained (in the average matrices) were divided into 4 classes for both PPMCC and MI. For PPMCC-derived data, the absolute values are in the (0, 1) range, meaning that in order to show that two values belong to different classes, the difference between the two has to be at least Δr=0.25. For MI-derived data, the minimum difference (ΔI) was obtained by dividing the range of the values (2.2-0.2=2.0) to 4 similar classes, thus yielding $\Delta I \cong 0.50$. In both cases, the main diagonal of the matrix (the correlations of each regions with itself were neglected). Therefore, the criterion for establishing significant differences from the 'difference matrices' is looking for values greater than 0.25 in the PPMCC matrix and respectively 0.5 in the MI matrix.

2.4. Second Approach

Another approach I considered was averaging all the values in the correlation matrices for PPMCC and MI for each patient, resulting in the creation of two sets of data (depressed and controls). This was followed by analyzing whether they are significant or not, using the Mann-Whitney U test.

The formula used to obtain the average connectivity for each patient taking into account all values (except those on the main diagonal) for both PPMCC ($\overline{cor}_p$) and MI ($\overline{mut}_p$) is:

$$\overline{cor}_p = \frac{2}{nr\,(nr-1)} \sum_{i=2}^{nr} \sum_{j=1}^{i-1} \left| M_p^{Pearson}[i,j] \right|$$

$$\overline{mut}_p = \frac{2}{nr\,(nr-1)} \sum_{i=2}^{nr} \sum_{j=1}^{i-1} M_p^{MI}[i,j]$$

The formula was computed 34 times for the control subjects and 102 times for the depressed subjects. The two vectors shown below for PPMCC were subjected to the Mann-Whitney U test. Similar vectors were obtained for MI.

$$Var_1 = Var_{Controls}^{Pearson} = \left\{ \overline{cor}_1^{Pearson,C}, \overline{cor}_2^{Pearson,C}, \ldots \overline{cor}_{34}^{Pearson,C} \right\}$$
$$Var_2 = Var_{Depressed}^{Pearson} = \left\{ \overline{cor}_1^{Pearson,D}, \overline{cor}_2^{Pearson,D}, \ldots \overline{cor}_{102}^{Pearson,D} \right\}$$

2.5. Third Approach

Finally, I looked at the connectivity of each specific region by averaging all values vertically in the correlation matrix for each patient. I obtained 136 (34 controls and 102 depressed) 1x116 vectors for both correlation techniques. I then incorporated these into two matrices: 34x116 and 102x116. Since the data was not normally distributed, I once again applied the Mann-Whitney U test 116 times for each region, comparing the two sets of data (for controls and depressed). The identical procedure was used in analyzing correlations obtained with both PPMCC and Pearson.

The formula used to generate the vector containing the average value for each region in every subject:

$$V_p^{Pearson} = \left[\sum_{j=1, j\neq i}^{nr} \left| M_p^{Pearson}[i=1, j] \right| \quad \dots \quad \sum_{j=1, j\neq i}^{nr} \left| M_p^{Pearson}[i=nr, j] \right| \right] \frac{1}{nr-1}$$

$$V_p^{MI} = \left[\sum_{j=1, j\neq i}^{nr} M_p^{MI}[i=1, j] \quad \dots \quad \sum_{j=1, j\neq i}^{nr} M_p^{MI}[i=nr, j] \right] \frac{1}{nr-1}$$

The following paragraph addresses the generation of the 116 pairs of vectors subjected to the Mann-Whitney U test. Note that the shown vectors are for PPMCC only, as similar ones were produced for MI.

$$Var_1^{reg} = Var_{Controls,\ reg}^{Pearson} = \left\{ V_{p=1}^{Pearson,C}[reg], \dots V_{p=34}^{Pearson,C}[reg] \right\}$$

$$Var_2^{reg} = Var_{Depressed,\ reg}^{Pearson} = \left\{ V_{p=1}^{Pearson,D}[reg], \dots V_{p=102}^{Pearson,D}[reg] \right\}$$

Applying the Mann-Whitney U test generated 116 p values in the two-tailed test, which were compared with a chosen significance level α=0.05. Regions with a smaller p value than α ($p < \alpha$) will be deemed significantly different from one group to another.

2.6. Mann-Whitney U test

In statistical analysis, the Mann-Whitney U test is a nonparametric test of the null hypothesis that the samples come from the same population (no difference between depressed and control subjects) against an alternative hypothesis (that there are significant differences between depressed and control subjects). In the analysis, a standard significance level α=0.05 was chosen. The usage of a two-tailed test is more rigorous and adequate for the purpose of the study: establishing whether there is a difference between the two groups and between the results obtained through the two metrics (PPMCC and MI). The two-tailed test shows whether there is a significant difference between the two groups at all, without any prior assumption about the direction of this difference (increased/decreased connectivity). What is remarkable about this statistical test is that while it has greater accuracy than the t-test for non- normal distributions, it is just as efficient as the t-test for normal distributions. Therefore, one of the advantages of using the Mann-Whitney U test is that fact that it eliminates the need to check whether the data is normally distributed or not and allows for uniformity when analyzing the data as a whole. The computation of the test was performed in Microsoft Excel, using a free add-in provided by Charles Zaiontz on his website (www.real-statistics.com).

3. RESULTS

3.1. First Approach

Using the appropriate software, correlation matrices were generated for each patient. Averaging these correlation matrices across all the subjects in each group (controls and depressed) yielded two average correlation matrices for PPMCC and MI respectively. Figures 1 and 2 depict average correlation matrices delineating controls (top) and depressed subjects (middle). The matrices were derived using PPMCC for Figure 1 and MI for Figure 2. Corresponding difference matrices are presented at the bottom of each figure.

In this approach, I did not apply any statistical test as this would have required 116*116/2 computations.

A more rigorous way of discerning whether the obtained differences are significant or not is applying the criterion described in Methods, First Approach. No value matches the fixed criterion, therefore no value in one group is significantly different from its pair in the other group. This can also be seen in the 'difference matrices' (in graphical form) for both PPMCC, as well as MI matrices. If such a difference had existed, it would have been at an individual-level and not a population-level, which is not the case.

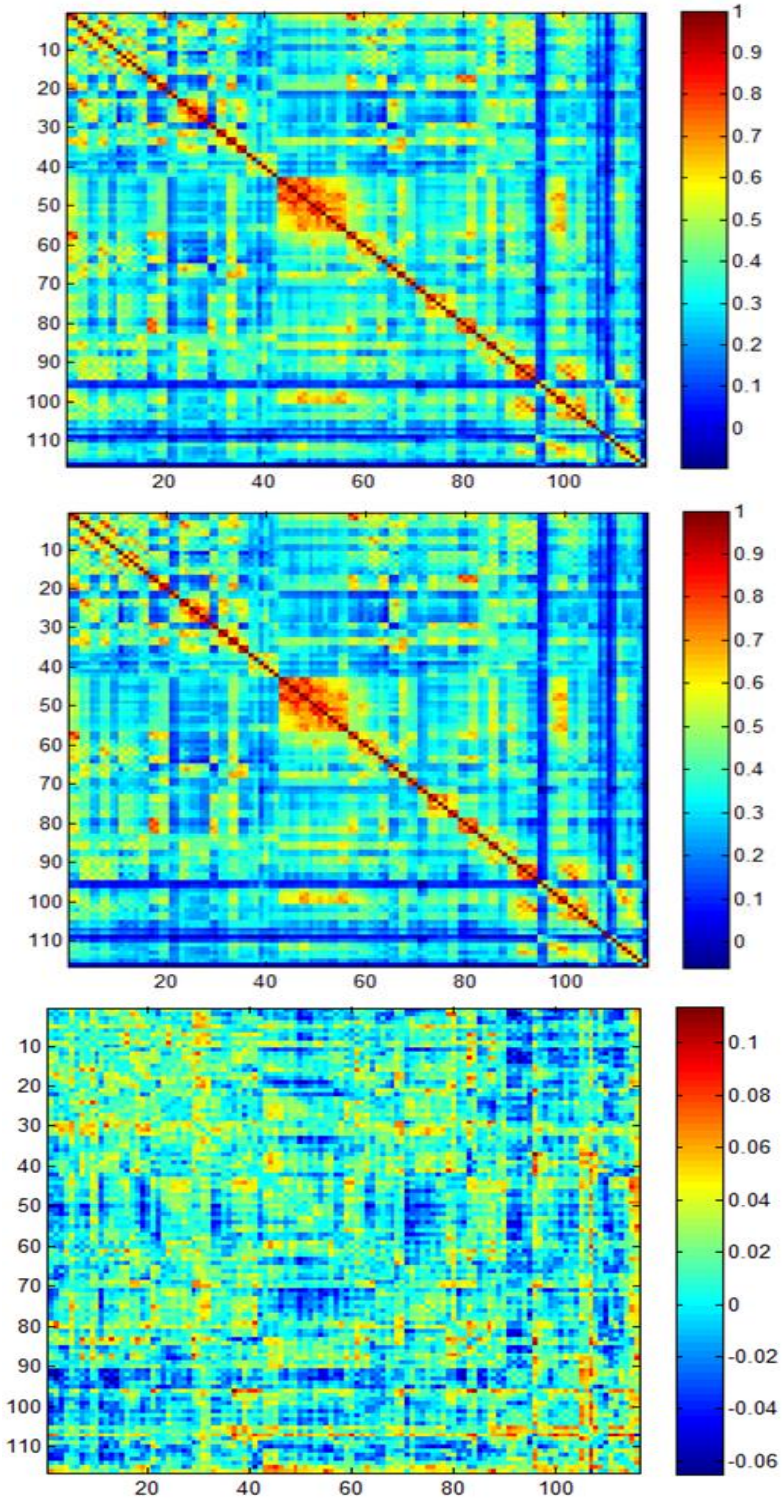


Figure 1. Average correlation matrices for controls (top) and depressed subjects (middle) for data obtained with PPMCC. Difference matrix is shown at the bottom.

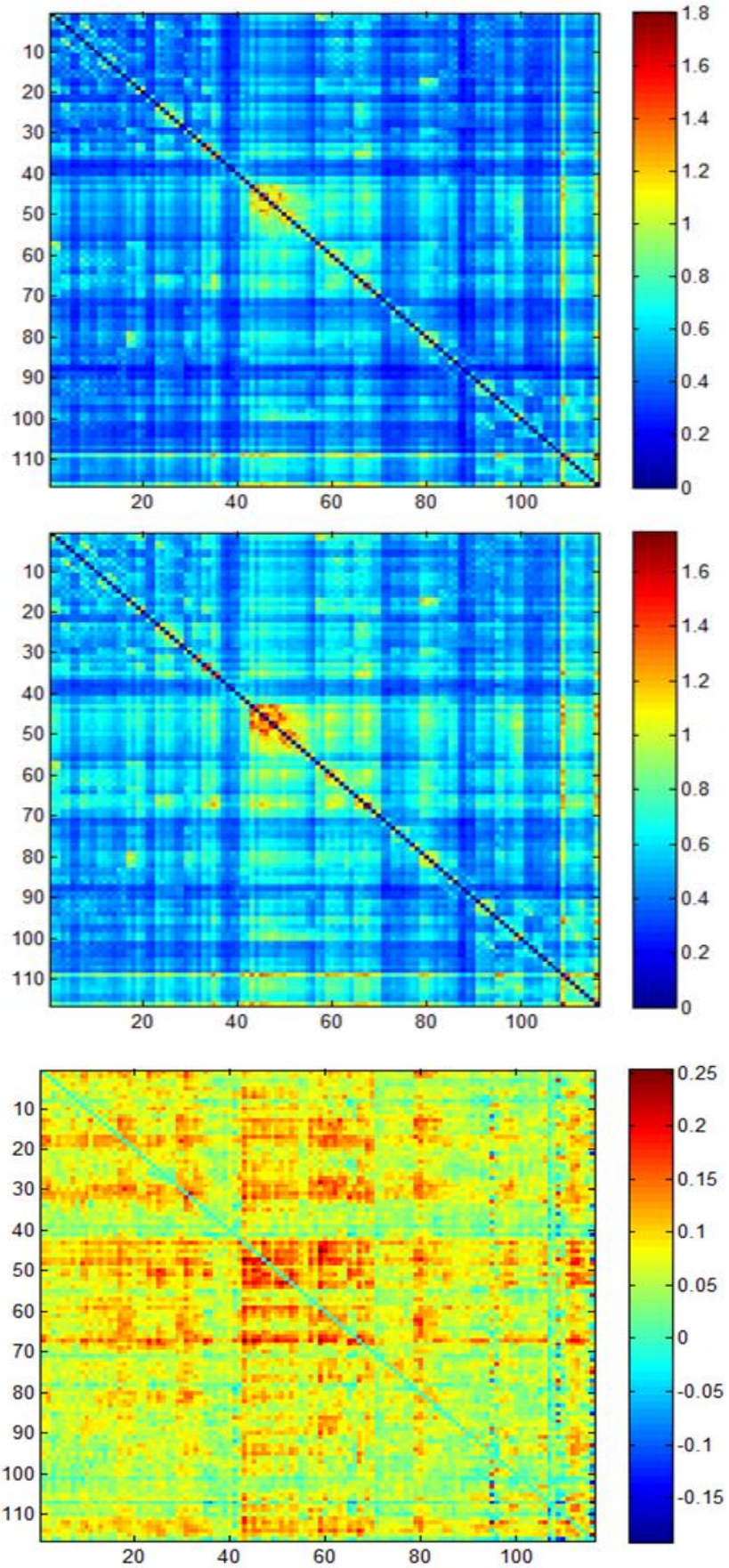


Figure 2. Average correlation matrices for controls (Top) and depressed subjects (Middle) for data obtained with MI. Difference matrix is shown at the bottom.

3.2. Second Approach

Averaging all the values in the correlation matrices for each patient yielded two sets of data, one set containing 34 values for controls and the other 102 values for depressed. Same procedure was applied to the data obtained through MI. The graphs below Figure 3 and 4 show an uneven distribution of the data obtained using PPMCC and MI, therefore further justifying using the Mann-Whitney U test. Additionally, some insight into the distribution of the values is provided. In the two-tailed U test a $p>0.05$ indicated no significant differences between the two sets regardless of the statistical method applied Table 1.

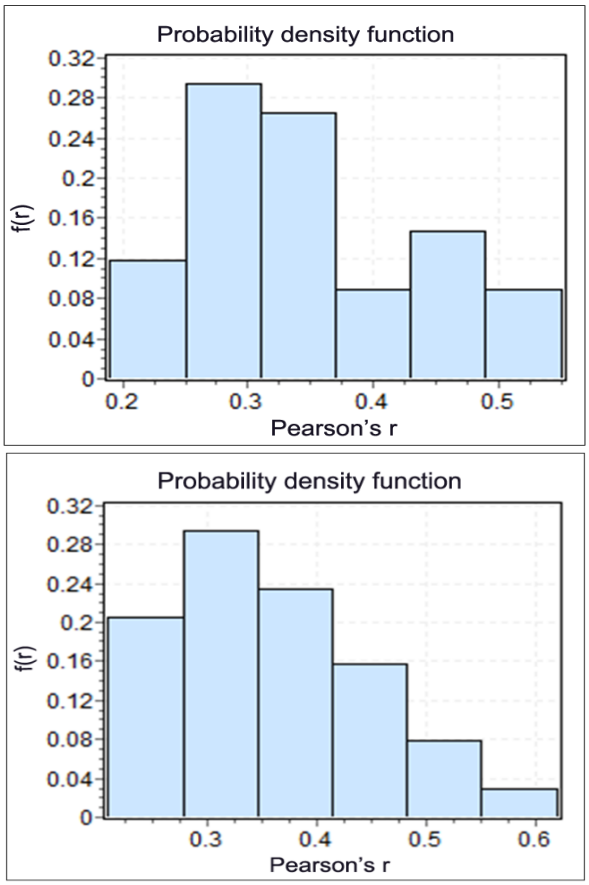
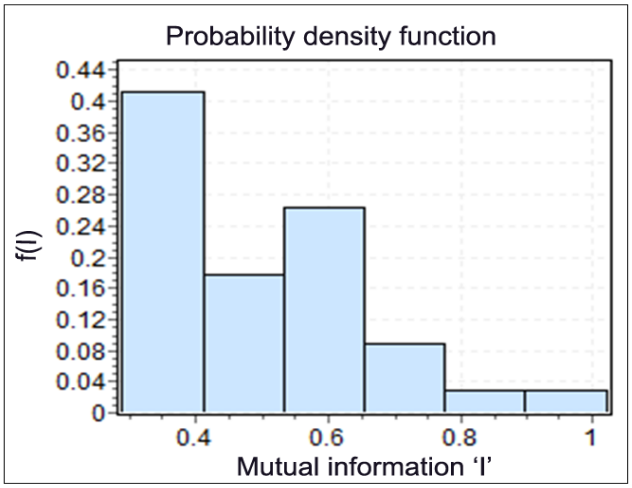


Figure 3. Probability density functions (PMFs) for PPMCC coefficients obtained in the control (Top) and depressed group (Bottom).



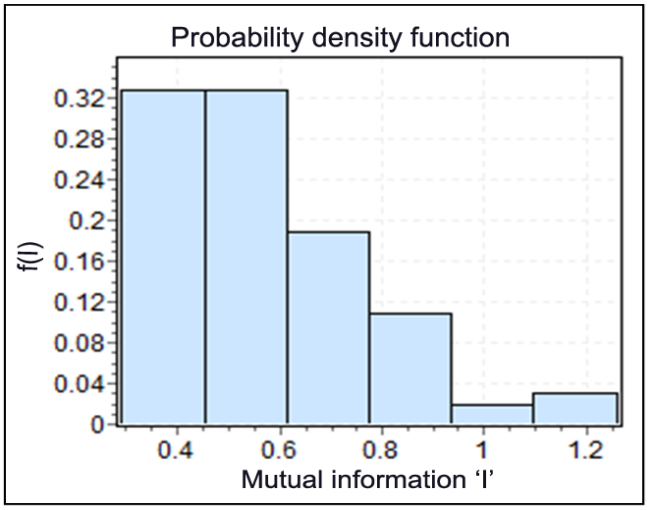


Figure 4. Probability density functions (PMFs) for PPMCC coefficients obtained in the control (Top) and depressed group (Bottom).

The values obtained as a result of the Mann-Whitney U test:

Table 1. Results of the Mann-Whitney U test for PPMCC coefficients (left) and MI coefficients (right). As values are higher than 0.05 for the two-tailed test the null hypothesis is accepted i.e. there is no significant difference between the mean correlation coefficients of the two groups.

Variable	Average Pearson correlation coefficient	Average mutual information dependency
Tail type	Two-tailed	Two-tailed
P-value	0.5473	0.0541
Statistical significance	No	No

3.3. Third Approach

However, when looking at individual brain regions and analyzing differences between them using two sets of data (controls and depressed) different results were obtained, depending on whether PPMCC or MI had been used to process the data. Therefore, when looking at the data obtained through PPMCC, no significant differences were observed between any regions of interest (p>0.05). But when considering the data obtained through MI, 39 regions were found to be significantly different between controls and depressed (p>0.05). In every instance, a higher average correlation value was obtained for the region of the depressed patients relative to the corresponding region of the control patients.

For α=0.05, no regions were shown to be significantly different in the PPMCC obtained data, using the two-tailed test Figure 5.

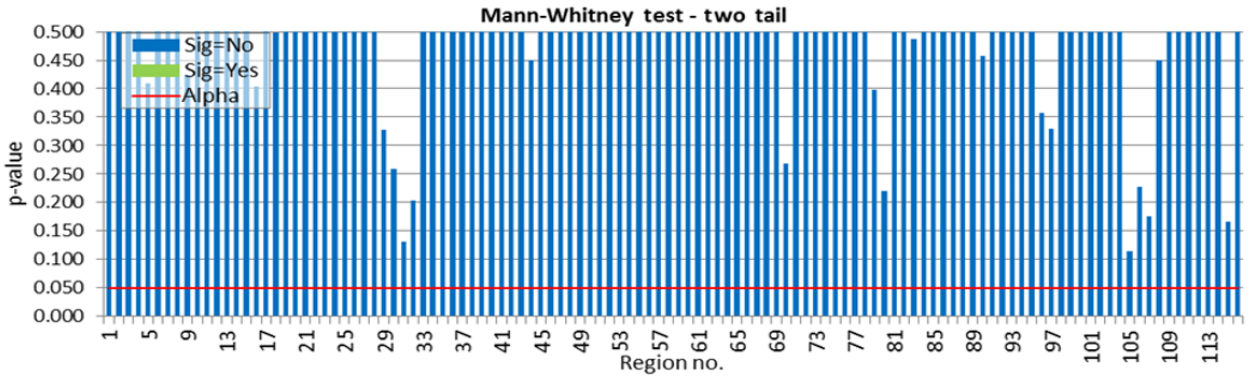


Figure 5. Results of the Mann-Whitney U test (Two-tailed) for data obtained using PPMCC. Blue columns indicate non-significant differences. Green columns indicate significant differences. The red line shows the error level, p=0.05.

Using α=0.05 yielded 39 significantly different regions in the two-tailed test applied to the MI-derived data Figure 6.

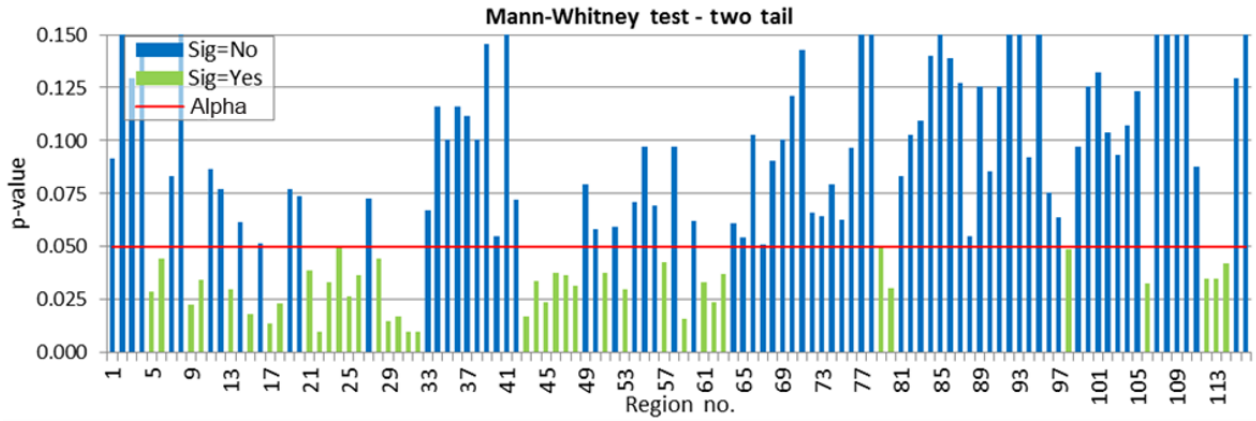


Figure 6. Results of the Mann-Whitney U test (Two-tailed) for data obtained using MI. Blue columns indicate non-significant differences. Green columns indicate significant differences. The red line shows the significance level, p=0.05.

4. DISCUSSION

4.1. First Approach

No significant differences were obtained in the first analysis, where I looked at differences across average correlation matrices. This way of looking at the data however only accounts for how one specific voxel changes its connectivity with respect to another specific voxel. Given the huge individual variability and the multiple ways in which brain regions can connect with each other, a significant variance across the population is therefore expected. One cannot yet pinpoint a very subtle change, such as region 1 having a stronger/weaker connection with region 2 in depressed patients relative to controls. It is too specific and too variable a change to be able to make a reliable distinction between the two groups based on such a minute difference.

$$Cov(X,Y) = E(X,Y) - E(X)E(Y) = \sum_{x,y} p(x,y)xy - \left(\sum_{x} p(x)x\right) * \left(\sum_{y} p(y)y\right)$$

4.2. Second Approach

The second approach of looking at the all the voxels of depressed individuals and comparing them with controls was a bit too ambitious, this time in the opposite direction. Though pinpointing changes in specific connections between voxels (above) was impossible, so was trying to establish whole-brain differences between depressed and controls. Therefore this attempt of trying to look at all the regions at once was unsurprisingly prone to failure. I believe it is unrealistic to assume that changes occur throughout the whole brain in diseased patients. If anything, most of the brain of the depressed patient is normal, with only some differences in connectivity. Looking at all the voxels together may very well annihilate the differences that do exist, as the 'normal connections' compensate for the few with changed activity and this results in an overall inconclusive and non-significant difference. However, even in this approach, the values for MI are much closer to establishing a significant difference between the two groups, being approximately 10 times as lower than those obtained through PPMCC. This hints at the idea that the inter-region connections are non-linear.

4.3. Third Approach

Having gone through these two extremes of too much and too little detail, I eventually settled for the middle ground: looking at changes in the connectivity for each region. This approach does not aim to specifically identify connections between certain regions, nor does it aim to uncover whole-brain differences, it is simply looking at how the 'wiring' of each voxel has changed individually in a diseased patient relative to a control. In the PPMCC- derived

data, no region was identified to be significantly differently connected in diseased patients when using a two-tailed test. However, in the MI-derived data, 39 regions were found to have undergone through significant changes in. The result demonstrates that about one third of the analysed regions of the diseased patients are significantly different than those in healthy controls. In the following paragraphs, I shall address the reasons for which I believe that the two methods yielded such different results, as well as how my findings compare to existing literature.

The fundamental principle of PPMCC (which looks at linear correlations) is covariance ('unstandardized' PPMCC). For two discrete random variables X and Y with pmfs (probability mass functions) p(x), p(y) and joint pmf p(x, y) we have.

$$=> \ Cov\,(X,Y) = \sum_{x,y}[p(x,y) - p(x)\,p(y)]xy$$

The Mutual Information between the two is defined as.

$$I(X,Y) = E(\ln\frac{p(x,y)}{p(x)\,p(y)} = \sum_{x,y} p(x,y)[\ln p(x,y) - \ln p(x)p(y)]$$

When comparing the two, one can observe that each includes a point-wise measure of the distances of the two random variables from independence as it is expressed by the distance between the joint point mass function from the product of the marginal pmfs. The only real way in which the methods differ is that covariance has it as a difference of levels, while I(X, Y) has it as difference of logarithms. How does this translate? In covariance, the measures create a weighted sum of the product of the two random variables, therefore looking at what non-independence does to their product. However, in mutual information, the measure created a weighted sum of their joint probabilities and this shows what non-independence does to their joint probability distribution. So, I(X,Y) reflects an average value of the logarithmic measure of distance from interdependence and Cov(X,Y) reflects the weighted value of the levels-measure of distance from independence, weighted by the product of the two random variables. Therefore, MI is not concerned with whether the association is linear or not, as the covariance may be 0 and the variables could still be stochastically dependent. In order to establish such associations, MI requires knowledge of the probability distributions involved.

As such, using the more sensitive, but robust MI, 39/116 regions were found to be significantly different in depressed patients relative to controls. This rather large proportion of voxels (33%) indicates important changes in the connectivity of the depressed brain. While I did not have the time and resources to identify the specific brain structures that these voxels refer to, the results obtained are in agreement with the existing literature regarding the modified circuitry in depression.

By averaging the correlation values across all depressed patients and comparing them with the values for controls, every significantly different region was shown to have a higher correlation value for the depressed group, indicative of hyperconnectivity within the brain.

In 2011, based on the Miller and Seligman (1975) hopelessness theory, Zhong et al. (2011) explored how brain connectivity might change in individuals diagnosed with cognitive vulnerability and depression. Using fMRI studies, he showed an increase in the left amygdala response and a reduction in the left dorsolateral prefrontal cortex (dlPFC) activation level in individuals with cognitive vulnerability relative to healthy controls. Depressed patients were found to have bilateral enhancements and reductions in the amygdala and dlPFC respectively. This has been proposed to mediate the exaggerated emotional response that might underlie developing depression. Increased corticolimbic connectivity may make patients more prone to rumination- the act of constantly replaying negative thoughts, whereas the reduction in prefrontal cortex connectivity might account for autobiographical memory impairments, a common feature in depression.

Another convincing approach was made by Leuchter, Cook, Hunter, Cai, and Horvath (2012), when he examined resting state functional connectivity using quantitative electroencephalographic coherence- a measure of the degree of association or coupling of frequency spectra between two different time series. Subjects with MDD were found to have higher coherence in all frequency bands. The frontopolar contained the highest number of hub nodes with high

connectivity and particularly, higher beta coherence primarily was seen in connections within and between electrodes overlying the dorsolateral prefrontal cortical (dlPFC) and temporal regions. Thus, using a different method, similar changes have been reported.

Using rs-fMRI and multivariate pattern analysis, another group showed that the majority of the most discriminating functional connections were located within or across the default mode network, affective network, visual cortical areas and cerebellum. This is indicative of the fact that the disease-related resting-state network alterations may result in some of the emotional and cognitive disturbances common in unipolar MDD. Furthermore, the anterior cingulate cortex and the amygdala, along with surrounding regions like the hippocampus and parahippocampal gyrus displayed higher connectivity and may play important roles in the pathophysiology of the disease (Sundermann, lütke Beverborg, & Pfleiderer, 2014).

Changes in the default connectivity network were once again confirmed by Jacobs et al in 2014. The findings are particularly relevant as the group looked at youth diagnosed with MDD relative to matched controls, similar to the present study. The data was obtained using fMRI, followed by voxel-based comparisons of the whole brain. Compared to healthy controls, MDD subjects exhibited hyperconnectivities in both prefrontal cortex and subgenual anterior cingulate cortex. The increased connectivity in the salience networks and default mode networks was related to rumination and sustained attention, factors known to make individuals prone to depression.

Lastly, in 2011 Perrin looked at how ECT alters brain connectivity using fMRI. Although the potency of ECT in treating depression is well recognized, no previous study showed how connectivity is altered following the procedure. Rs-fMRI was performed before and after treatment in patients diagnosed with MDD. The analysis revealed a significant cluster of voxels around the left dlPFC where the average global functional connectivity was majorly decreased following ECT. This reduction was correlated with a significant improvement in depressive symptoms, as judged from the Asberg Depression Rating Scale. This study backs up other findings and supports the idea of hyperconnectivity within the depressed brain.

Therefore, there are abundant studies showing an increase in connectivity in patients with MDD. By using different approaches in patients of different ages, most of the literature agrees with the findings of this study. Although mapping the voxels on the brain was not possible, it is very likely that doing so might point to key area such as the dlPFC, amygdala and cingulate cortex, which have repetitively been shown to exhibit increased connectivity in the depressed brain.

The implication of these findings could provide benefits at a population level. Specific drug targeting to these regions or some form of precisely directed ECT might prove beneficial for the patients, whilst reducing potential side effects. Furthermore, although much progress has been made in understanding depression, the area remains foggy, largely due to individual variability. Studies such as this help shed some light over the problems in understanding a debilitating and prevalent disease. While rs-fMRI is not currently an option in diagnosing due to the cost and time necessary for performing the scans and processing, it might eventually serve as a potential diagnostic tool. With more progress being made, defining certain parameters characteristic of MDD becomes a real possibility. This would allow a precise and personalized diagnosis and treatment with significantly better results.

5. CONCLUSION

Looking at changes in connectivity is clearly the new approach to understanding disease. The paradigm shift from task-induced activation unraveled many unknowns within both the field of neuroimaging and psychiatry. What is yet disputed is whether the metric of choice until recently (PPMCC) impacted our knowledge significantly. Based on my findings, MI was shown to be much more reliable than PPMCC when considering non-linear associations. In this instance, looking at the regions using PPMCC alone would have yielded no significant differences between the two groups, a clear fault, demonstrating how using this metric can be erroneous. The use of MI would increase the chance of reliably detecting non-linear correlations between voxels when analyzing rs-fMRI data. Therefore this

study supports another shift (this time in the metric being used): from using the conventional PPMCC to the more sensitive and robust MI.

Funding: This study received no specific financial support.
Institutional Review Board Statement: Not applicable.
Transparency: The author states that the manuscript is honest, truthful, and transparent, that no key aspects of the investigation have been omitted, and that any differences from the study as planned have been clarified. This study followed all writing ethics.
Competing Interests: The author declares that there are no conflicts of interests regarding the publication of this paper.

REFERENCES

Bonita, J., LCC Ambolode, I., Rosenberg, B., Cellucci, C., Watanabe, T., Rapp, P., & Albano, A. (2014). Time domain measures of inter-channel EEG correlations: A comparison of linear, nonparametric and nonlinear measures. *Cognitive Neurodynamics*, *8*(1), 1-15. https://doi.org/10.1007/s11571-013-9267-8

Brown, G., Pocock, A., Zhao, M.-J., & Luján, M. (2012). Conditional likelihood maximisation: A unifying framework for information theoretic feature selection. *The Journal of Machine Learning Research*, *13*, 27-66.

Fornito, A., & Bullmore, E. T. (2015). Connectomics: A new paradigm for understanding brain disease. *European NeuropsychopharmAcology*, *25*(5), 733-748. https://doi.org/10.1016/j.euroneuro.2014.02.011

Friston, K., Tononi, G., Reeke Jr, G., Sporns, O., & Edelman, G. M. (1994). Value-dependent selection in the brain: Simulation in a synthetic neural model. *Neuroscience*, *59*(2), 229-243. https://doi.org/10.1016/0306-4522(94)90592-4

Hagan, C. C., Graham, J. M., Widmer, B., Holt, R. J., Ooi, C., Van Nieuwenhuizen, A. O., . . . Kelvin, R. (2013). Magnetic resonance imaging of a randomized controlled trial investigating predictors of recovery following psychological treatment in adolescents with moderate to severe unipolar depression: Study protocol for magnetic resonance-improving mood with psychoanalytic and cognitive therapies. *BMC Psychiatry*, *13*(1), 1-12. https://doi.org/10.1186/1471-244x-13-247

He, Y., & Evans, A. (2010). Graph theoretical modeling of brain connectivity. *Current Opinion in Neurology*, *23*(4), 341-350. https://doi.org/10.1097/WCO.0b013e32833aa567

Kessler, R. C., Ormel, J., Petukhova, M., McLaughlin, K. A., Green, J. G., Russo, L. J., . . . Alonso, J. (2011). Development of lifetime comorbidity in the world health organization world mental health surveys. *Archives of General Psychiatry*, *68*(1), 90-100.

Lee, J. H. (2012). Informing brain connectivity with optogenetic functional magnetic resonance imaging. *Neuroimage*, *62*(4), 2244-2249. https://doi.org/10.1016/j.neuroimage.2012.01.116

Leuchter, A., Cook, I., Hunter, A., Cai, C., & Horvath, S. (2012). Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. *PLoS ONE*, *7*(2), e32508.

Liu, J., Pearlson, G., Windemuth, A., Ruano, G., Perrone-Bizzozero, N. I., & Calhoun, V. (2009). Combining fMRI and SNP data to investigate connections between brain function and genetics using parallel ICA. *Human Brain Mapping*, *30*(1), 241-255. https://doi.org/10.1002/hbm.20508

Lopez-Larson, M. P., Bogorodzki, P., Rogowska, J., McGlade, E., King, J. B., Terry, J., & Yurgelun-Todd, D. (2011). Altered prefrontal and insular cortical thickness in adolescent marijuana users. *Behavioural Brain Research*, *220*(1), 164-172.

Miller, W., & Seligman, M. (1975). Depression and learned helplessness in man. *Journal of Abnormal Psychology*, *84*(3), 228-238.

Murray, C. (2013). The state of US health, 1990-2010. *JAMA*, *310*(6), 591-606.

Murray, C. J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., . . . Abdalla, S. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the global burden of disease study 2010. *The Lancet*, *380*(9859), 2197-2223.

Ogawa, S., Lee, T.-M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*, *87*(24), 9868-9872.

Raichle, M. E. (2009). A paradigm shift in functional brain imaging. *Journal of Neuroscience*, *29*(41), 12729-12734. https://doi.org/10.1523/jneurosci.4366-09.2009

Smith, K. (2012). fMRI 2.0: Functional magnetic resonance imaging is growing from showy adolescence into a workhorse of brain imaging. *Nature, 484*(7392), 24-27.

Solomon, D. A., Keller, M. B., Leon, A. C., Mueller, T. I., Lavori, P. W., Shea, M. T., . . . Maser, J. D. (2000). Multiple recurrences of major depressive disorder. *American Journal of Psychiatry, 157*(2), 229-233. https://doi.org/10.1176/appi.ajp.157.2.229

Song, L., Langfelder, P., & Horvath, S. (2012). Comparison of co-expression measures: Mutual information, correlation, and model based indices. *BMC Bioinformatics, 13*(1), 1-21. https://doi.org/10.1186/1471-2105-13-328

Sundermann, B., lütke Beverborg, M. O., & Pfleiderer, B. (2014). *Meta-analysis of resting-state fMRI in depression: Generating spatial hypotheses for potential clinical applications No. e412v1*. Retrieved from PeerJ PrePrints:

van den Heuvel, M. P., Mandl, R. C., Stam, C. J., Kahn, R. S., & Pol, H. E. H. (2010). Aberrant frontal and temporal complex network structure in schizophrenia: A graph theoretical analysis. *Journal of Neuroscience, 30*(47), 15915-15926. https://doi.org/10.1523/jneurosci.2874-10.2010

Wolf, R. C., Sambataro, F., Vasic, N., Schmid, M., Thomann, P. A., Bienentreu, S. D., & Wolf, N. D. (2011). Aberrant connectivity of resting-state networks in borderline personality disorder. *Journal of Psychiatry and Neuroscience, 36*(6), 402-411. https://doi.org/10.3410/f.13335968.14702072

Zhong, N., Liang, P., Qin, Y., Lu, S., Yang, Y., & Li, K. (2011). Neural substrates of data-driven scientific discovery: An fMRI study during performance of number series completion task. *Science China Life Sciences, 54*, 466-473. https://doi.org/10.1007/s11427-011-4166-x