Title: Structural Balance of Resting-State Brain Network in Attention Deficit Hyperactivity Disorder

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To appear in: **Basic and Clinical Neuroscience**

Received date: 2023/09/03

Revised date: 2024/01/13

Accepted date: 2024/01/21

Please cite this article as:

Ruzbeh Fakhari, R., Moradi, A., Ebrahimpour, R., Khosrowabadi, R. (In Press). Structural Balance of Resting-State Brain Network in Attention Deficit Hyperactivity Disorder. Basic and Clinical Neuroscience. Just Accepted publication Jul. 10, 2024. Doi: http://dx.doi.org/10.32598/bcn.2024.276.3

DOI: http://dx.doi.org/10.32598/bcn.2024.276.3

Abstract:

Study of brain functional network in attention deficit hyperactivity disorder (ADHD) has provided useful information about the hyper/hypo connectivity between distinct brain regions. Nevertheless, impact of negative links (anti synchronies) and their topology on the stability of the network still requires to be well understood. In this study, we hypothesized that effect of dysconnectivities and antisynchronies should mainly be local and may not influence the overall stability and flexibility of the network in ADHD. Therefore, differences between brain functional organization of ADHD individuals were compared to a typically developed group using the structural balance theory. Our results did not show any significant differences in the balance energy of the resting-state network between healthy individuals and three subtypes of the ADHD. However, a negative correlation was found between behavioral measures of the ADHD and balance energy; highlighting that the higher disorder index may push the network to a less flexible (more balanced) state. We hope these findings could enhance our understanding on the systemic mechanism behind the ADHD.

Keywords: Attention deficit hyperactivity disorder, Functional brain network, Resting-state fMRI, Structur-al balance theory

Introduction:

Attention Deficit Hyperactivity Disorder (ADHD) is a developmental neurological disorder and its main features are difficulty in regulating attention and controlling impulsive movements and hyperactivity [1-3]. ADHD generally develops in childhood; however, it may be diagnosed later in life. The disorder lasts until adolescence and adulthood and affects various aspects of a person's life such as success in education and work, personal relationships, health and financial issues. We have three types of ADHD: hyperactive, Inattentive, and a combination of both.

In recent years, functional network studies of hyperactive attention deficit patients obtained from functional magnetic resonance imaging have shown that these patients are hyperconnected at inter-network levels, such as dorsal and ventral attention network, salience network, and default mode networks. There have also been changes within these networks and also shown how these changes can be related to patients' behavioral symptoms [4-6]. Although many studies have been conducted with the network approach in ADHD [7-11], it seems that more efforts should be made with new tools based on the collective behavior of connections to better understand the systemic behavior of brain regions in this disorder.

According to the above-mentioned approach, it is very important to study the features that represent complexity in the brain network [12-14]. One of these features is the organization of network components. Structural balance is another achievement of network science that is inspired by interpersonal social relationships [15-16]. Brain network researchers traditionally study the dual relationships of nodes and use them to describe the collective behavior of the brain network. While in structural balance, the three relations of nodes are considered. The important point is that the relationship of two nodes in a network does not depend solely on them and is strongly influenced by other relationships. There are generally four modes for a triadic relationship [17-18]: Your friend's friend is your friend. The enemy of your enemy is your friend. The enemy of your enemy is your enemy. Your friend's friend is your enemy. The first and the second triads are called the balance triad, and the third and fourth ones are called the unbalance triad. Unbalanced triads are in an unstable state and must be balanced and returned to a stable state by changing one or two relationships [19]. The number of triadic relations we can have in an N-node network is a combination of 3 of N. The higher the balance triads of a network compared to its unbalanced triads, the closer that network is to the overall balance. The lowest possible energy is when all three are unbalanced and the highest possible energy occurs when all three are unbalanced [18].

In recent years, our research colleagues have tried to use this theory and its features to study brain networks (Figure 1) [20-22]. In the conceptualizations, the synchrony and anti-synchrony between the temporal activities of the brain regions determines the sign of the links of the signed network of the brain. It has been shown that the brain network is in a meta-stable state close to absolute stability and ready for phase transition to another mode [20]. A meta-stable state is a temporary and unstable condition in which a system exists for a considerable period before transitioning to other states. Despite its instability, the system remains in the meta-stable state until it is disturbed by an external force or event. In addition, a prospective study of balance energy for brain networks can provide us with useful information about the dynamics, flexibility, and changeability of the brain network that can itself be associated with the symptoms and deficits of mental disorders.

We hypothesized that effect of dysconnectivities and antisynchronies should mainly be local and may not influence the overall stability and flexibility of the network in ADHD, so in this study, we intend to study the structural balance of functional brain networks as a global effect in ADHD. So we compare the balance energy of functional brain networks of healthy people with three subtypes of ADHD. We also examine the relationship between the behavioral characteristics of the indicators associated with this disorder and balance energy. Because previous studies have emphasized structural balance changes over a lifetime [21], we compare the relationship between age and balance energy between healthy and sick people.

Method

Participants

The participants of this study were selected from the ADHD200 project [23] which is a consortium consisting of a large number of universities. We used all available subjects. In this study, there had 947 healthy and ADHD people. ADHD patients were divided into three groups: hyperactive, inattentive, and combined. The age of the participants ranges from 7 to 21, and includes both male and female.

Brain activity time series

We used data from ADHD Preprocessed [24]. The existing images are preprocessed by the Athena pipeline [25] that use FSL (The FMRIB Software Library) [26] and AFNI (Analysis of Functional NeuroImages) [27], that includes skull-stripping, segmentation into CSF, WM, and GM, and normalization to MNI standard space for structural images and slice timing correction, deobliquing, motion correction, co-registration to native space, normalizing to MNI standard space, temporal band-pass filtering, and spatial smoothing for functional images in addition to extracting brain activity time-series based on the three atlases of AAL (Automated Anatomical Atlas), CC200 (Craddock 200), and CC400 (Craddock 400) [25, 28]. These atlases include 116, 192, and 392 brain regions, respectively. Each time-series correspond to a region, which represents the activity of that area over time. We should mention that global signal has not been removed. In addition, AAL is an anatomical parcellation atlas in spite of CC200 and CC400 which were developed based on brain function, we used them to increase the reliability of the results.

Signed Networks

For each participant, we developed a continuity matrix whose values represent the temporal correlation of the time series related to the two regions of the brain. We calculated this property for each subjects and each pair of regions to full matrices. Then we considered signs of correlations to provide a signed network for each subject. Thus, if the correlation value is positive, the corresponding link becomes positive, and if the correlation value turns negative, the corresponding network link becomes negative. Thus, we developed a signed network for each parcellation and each subject.

Balancing energy

In 2009, Marvel et al. formulated balance energy in the context of physics [18], So if we set the friendship between two nodes to +1 and the enmity between the two nodes to -1, the energy of a triad will be as follows:

$$U_{ijk} = -S_{ij}\, S_{ik}\, S_{ik}$$

Where the value of Sij corresponds to the friendship and enmity between nodes i and j. The product of these three factors is equal to +1 in the balanced triad and equal to -1 in the unbalanced triad. Because in physics, steady state that do not need to change have less energy, and balanced triads do not need to change, we multiplied this product by a negative. Thus, the energy of a triple balance is -1 and the energy of an unbalanced triple is +1.

In this context, Marvel et al. stated the structural balance energy as the average of the energy of all triads:

$$U = -\frac{1}{\binom{3}{n}} \sum_{\substack{i,j,k \\ i\neq j\neq k}} S_{ij} S_{ik}\, S_{ik}$$

In this formula, the sum is based on the energy of the triads, n is the number of network nodes and $\binom{3}{n}$ is the combination of 3 of n as the number of triads in the network. The network balance energy ranges between -1 and +1. If all three triads are balanced, the energy is equal to -1.

Tendency to Make Hub (TMH)

TMH is a global hubness measure introduced by Saberi et.al. [20] . It matter in structural balance investigation since they showed increasing global hubness of signed links is correlated to decreasing balance energy. TMH is defined as follow:

$$TMH = \frac{\sum_{i=1}^{N} D_i^2}{\sum_{i=1}^{N} D_i}$$

where D_i is degree of i th node.

Statistical analysis

In multi-group comparisons of balance energies, we first checked the normality of the distribution with the Shapiro-Wilcoxon test. Since these distributions were not normal (Figure S1), we resorted to nonparametric statistics and Kruskal-Wallis test (Figure 2). We also used the Dunn's post-hoc test for post hoc comparisons and Pearson's correlation test to examine the relationships between continuous behavioral variables and balance energies (Figure 3). Also we used ANOVA test to compare TMH between group of subjects since TMH distributions were normal. To compare the relationship between age and balance energy between healthy and patient people, we used ANCOVA test in which age was a covariate and group was the dependent variable (Figure 4). We also used ANOVA for comparison of each connection between 4 groups of subjects (Figure 6).

We also used R software and "ggplot2" package to analysis the data and provide graphic information [29-30].

Results:

Between group comparison of the balance energies

We calculated the balance energy of the functional networks, which represent the structural balance, and compared them between the healthy controls and groups of ADHD disorders. The patients were divided into three groups: Combined, Hyperactive, Inattentive. Figure 2 shows the intergroup comparison of three patient groups and one healthy group for three different brain parcellations of AAL, CC200, and CC400. Since balance energies had not normal distributions (p-value of Shapiro-Wilk test < 0.001) (Figure S1), We chose nonparametric statistics for multi-group comparisons and used the Kruskal-Wallis test. As Figure 2 shows, there is no significant difference between the balance energies of the different groups.

Between group comparison of negative TMHs

We obtained TMH of negative subnetworks for each subject and its parcellation altases. ANOVA test showed significant differences between TMH of different types of subjects(AAL: P-value = 0.00508, CC200: Pvalue = 0.0142, CC400: P-value = 0.0105) (Figure 3). Also post-hoc tests indicate Hyperactive group has significantly lower TMH compared to other groups.

Relationship between behavioral metrics and balance energy

We examined the linear relationship between the three behavioral variables that are important for ADHD, including ADHD Index, Hyperactivity, and Inattention, with the network balance energy for the three brain parcellations. As Figure 4 shows, the ADHD Index has a significant linear relationship with the balance energy in the AAL atlas (R = -0.16, P-value = 8.52e-4), although no significant relationship was found in the other atlases. Examining the relationship between Hyperactivity and balance energies, a significant linear relationship is observed for AAL and CC200 atlases (AAL: R = -0.16, P-value = 3.64e-4; CC200: R = -0.08, P-value = 0.06). Also, the study of the relationship between the Inattention and balance energy shows a significant relationship for AAL and CC200 atlases (AAL: R = -0.16, P-value = 3.89e-4; CC200: R = -0.09, P-value = 0.03).

Relationship between age and balance energy

In previous studies, it has been observed that the number of imbalanced triads changes over a lifspan [21]. Therefore, we examined whether the relationship between age and energy balance is different between healthy and patient groups or not? Therefore, we grouped all three patient subtypes and compared them with healthy individuals. Figure 5 shows a correlation comparison, with ANCOVA test results showing a slight difference between patients and healthy individuals in the brain parcellations of AAL (F = 2.805, P-value = 0.094).

Between-group connectivity differences

As we showed there is no significant differences between balance energies of different groups, considering balance energy is a global network measure, we decided to check functional links those are the main local measures. So we compared connectivity patterns of patients and healthy subjects to check any significant differences in the level of connections. Figure 6 shows a huge numbers of connections have significant difference between healthy and 3 subtypes groups for all three parcellations.

Discussion:

Results showed that the balance energy of the functional networks of the brain of the patient and healthy groups was not different. Although Hyperactive patients have significantly lower hubnees in their negative subnetworks. There was also a negative correlation between behavioral measures associated with ADHD and brain balance energy in some brain parcellations. The linear relationship between age and balance energy also had a weak difference between healthy and patient people, which is not very significant but cannot be ignored.

Numerous studies have been performed on the networks of ADHD, in many of which researchers have shown that there are differences in the local and global properties of the brain network of healthy people with ADHD disorders [5, 10]. The networks that have been studied before in this field were binary networks that had or did not have a connection. However, in this study, we examined the signed brain network to provide the readers with information on the structure of structural balance and network stability, which was a new approach and no difference was found in terms of balance.

"The whole is greater than the sum of the parts"; an expression attributed to Aristotle which is one of the main concepts of complex systems. It tell us thers is some features in the system that express in the collection of elements. Based on our results, although healthy and AHDH connectivty pattern are not the same (Figure 6) but the connections form a global topology with the same balance energy. It means that exploration of local measures is so important to clear the mechanism of ADHD.

The study of structural balance in the brain network is a new research theme that has recently been considered by researchers and its capacities have been revealed. In one of the studies, it has been shown that the gathering of functional signed connections around nodes lead the brain to lower energy and greater stability [20]. The structural balance of the brain also changes over a lifespan [21]. And in other study, pattern of frustrations (imbalanced triads) as the source of conflictual brain link arrangements were identified [22]. The significance negative links topology on the balance of functional networks were investigated during pleasant and unpleasant stimuli [31]. Recently, structural balance in Obsessive-Compulsive Disorder (OCD) were explored, with a particular emphasis on the role of positive and negative link arrangements [32].

Examining the structural balance in disorders can be particularly interesting because it provides us with information about the quality of the organization of connections and can reveal the mechanism of brain disorders. Our research is in the line of previous researches and tries to explore the finding in ADHD that its mechanism is not well-know.

As we know, patients with ADHD have poor cognitive control, for example, they have relatively poor ability to pay attention and control inhibition [3]. On the one hand, we have shown that as the disease score increases, the energy balance decreases, and the network stability increases. Increasing stability and decreasing energy is proportional to decreasing flexibility because the system loses its flexibility at low energy and cannot easily switch between different states easily.

Therefore, the findings of this study can help to better identify the brain mechanism of the disorder at the network level. As you can see in Figure 3, the correlations are significant in some cases, but not in others. Therefore, developing and modifying the method of checking the balance, strengthening the information obtained from the brain and improving the methods of determining the level of behavioral symptoms may also lead to more accurate and powerful results.

A recent study showed that structural balance changes over the age groups [21]. In this study, according to the age of the participants, we could focus only on the lower age groups, and tried to examine the linear relationship between the age of the participants and their brain balance energy in a continuous analysis. In the two atlases, there was a relative difference in this relationship between healthy and patient people. The results suggest that further studies are needed in this case as well.

Studies on brain networks show that the results obtained in some cases were selected under the influence of the Atlas [33-34]. Therefore, it is important to see whether the results are independent of the type of parcellation. An important point that we tried to observe in this study was to review the results with different atlases. Because we wanted to compare the reproducibility of the results using other atlases. The findings of this study showed that the results obtained from the AAL atlas show relatively stronger differences and relationships. These results are relatively weak at CC200 and CC400 atlases, but in most cases are unavoidable. Therefore, it can be said that the results obtained in the network balance study are almost independent of the atlas, but the type of atlas selected affects their quality, which seems to be a legitimate argument in its own right.

All in all, it can be concluded that the structural balance of functional brain networks is not significantly different between healthy individuals and ADHD patients, although the greatest behavioral symptoms of these patients cause the more balanced brain networks. Combining these two pieces of finding, it may be concluded that the mechanisms needed to study the systemic features of the brain still need to be developed so that we can provide a better explanation, just as the behavioral mechanisms of this disorder need to be develop.

Conclusion

Based on the results of this study, it is suggested that further research be done on the effects of ADHD on the structural balance of the brain, and that the variables in the analysis should be modified to achieve more valid results. Significant differences of TMH values indicate that more topological investiagations can obtaine further information on the balance related mechanism of ADHD. We propose investiagtion of local balance-based measures to unreveal ADHD mechanims in the level of network. In addition, this approach can be studied in other diseases and also these studies can be done on the brain images in the task and examine the structural balance of patients' brains during activity.

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Figures

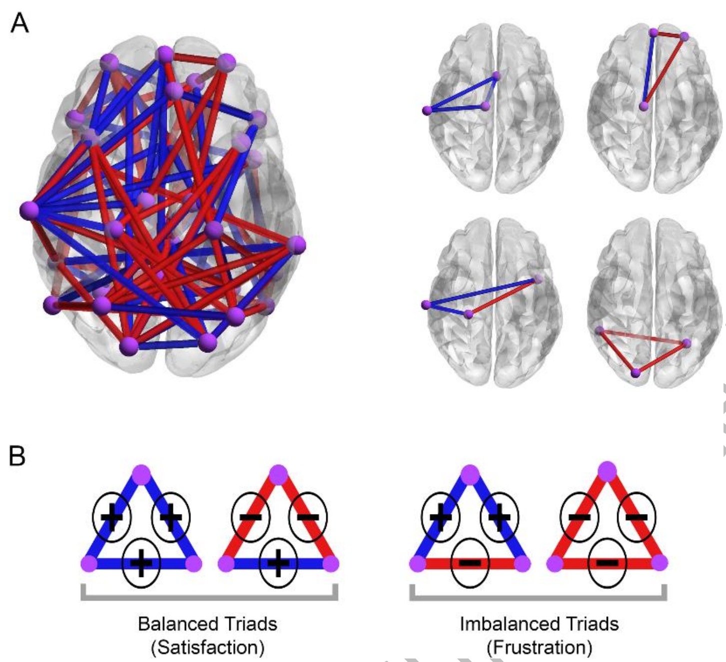

Figure 1: **(a)** Brain signed network. Positive and negative links are discriminated by blue and red colors. **(b)** Four types of closed triadic relations. (Abbreviation; R: correlation *c*oefficient). Reproduced with permission from Saberi et al., 2021 [21].

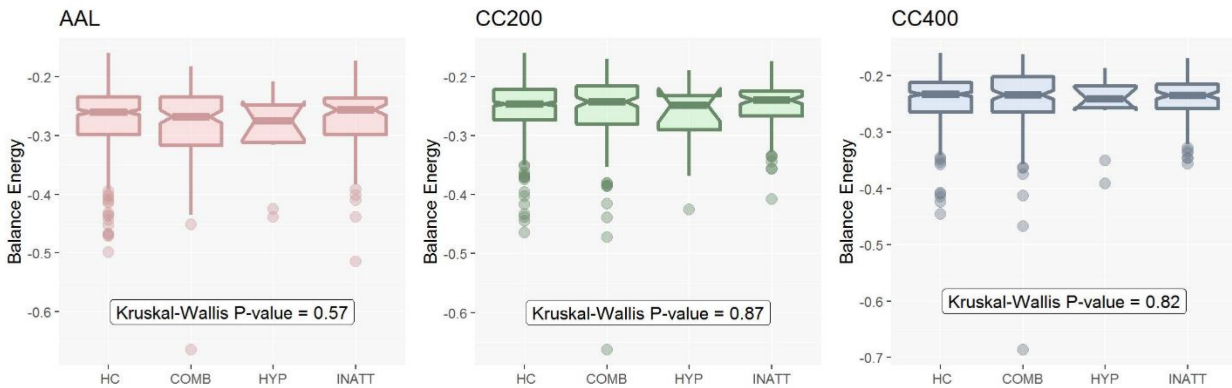

Figure 2: Comparison of balance energies for different brain parcellations. The horizontal lines of the boxes represent the medium, and the notches set the 95% confidence interval for the medium. Spherical dots represent outlier points. P-values of nonparametric multi-group comparisons are reported at the bottom of each subfigure. HC: Healthy Control; COMB: Combined; HYP: Hyperactive; INATT: Inattentive.

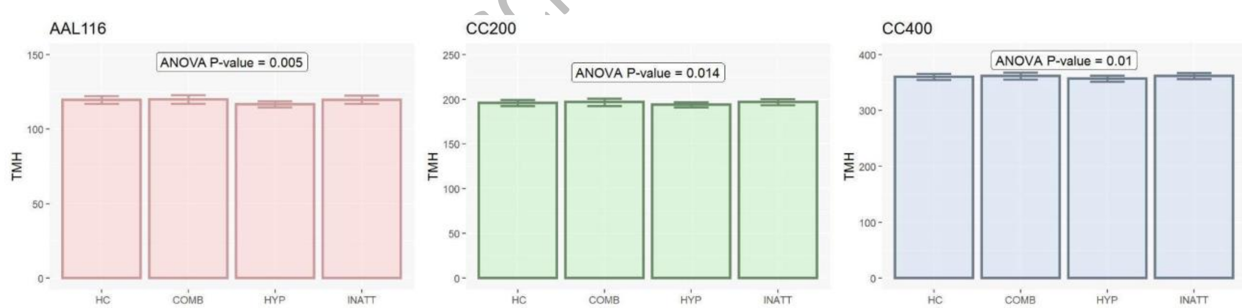

Figure 3: Comparison of negative TMHs. Box heights show the mean values and error bars denote standard errors. ANOVA p-vlaue is reported for each atlas separately. HC: Healthy Control; COMB: Combined; HYP: Hyperactive; INATT: Inattentive; TMH: Tendency to Make Hub.

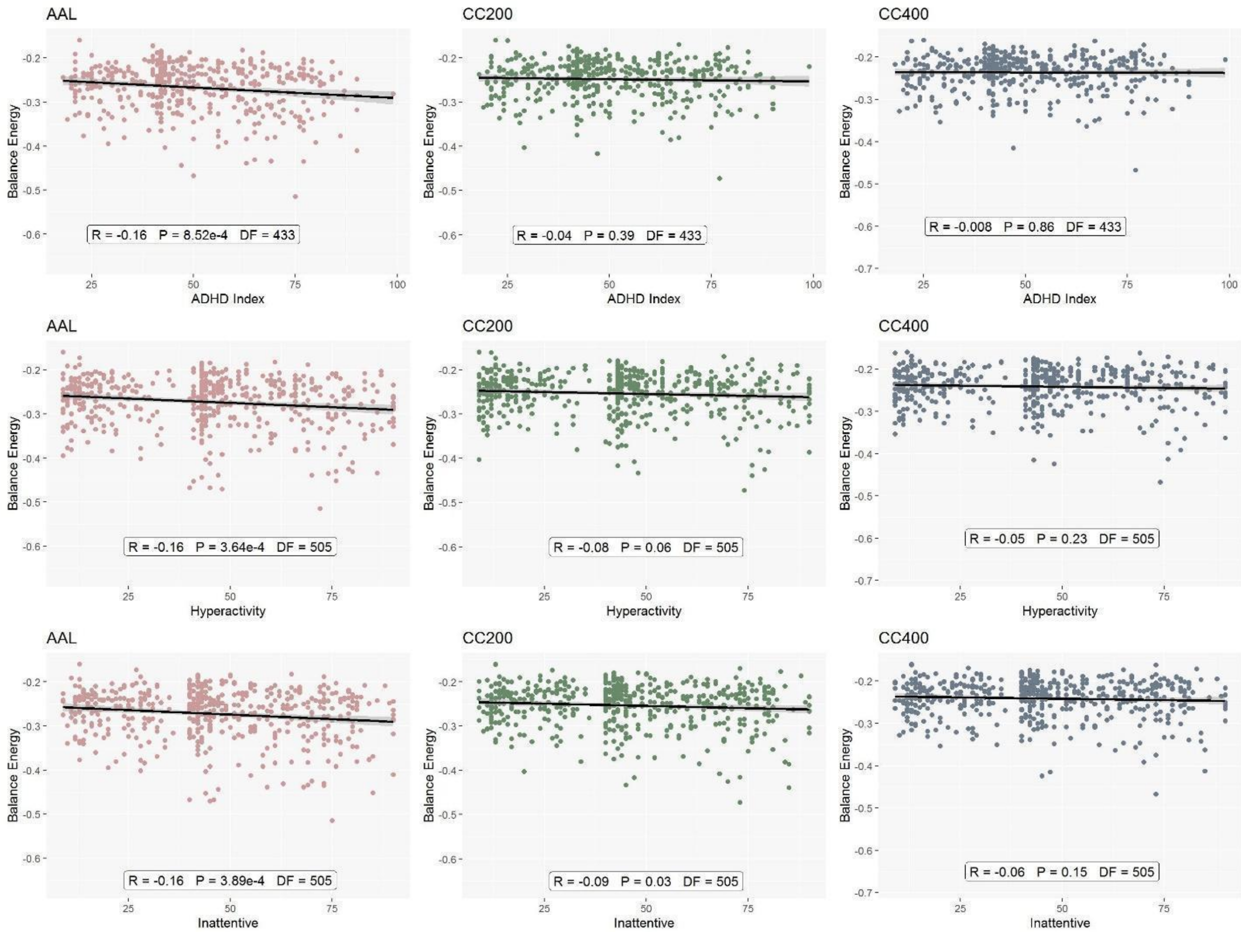

Figure 4: Correlation analysis between behavioral measures of ADHD and balance energy. The points are related to the subjects. The black lines show the fitted linear relationship to the points. The values of the correlation coefficients and its significance are shown in the box below each subfigure (Abbreviation; R: correlation coefficient, P: p-value, DF: degree of freedom)

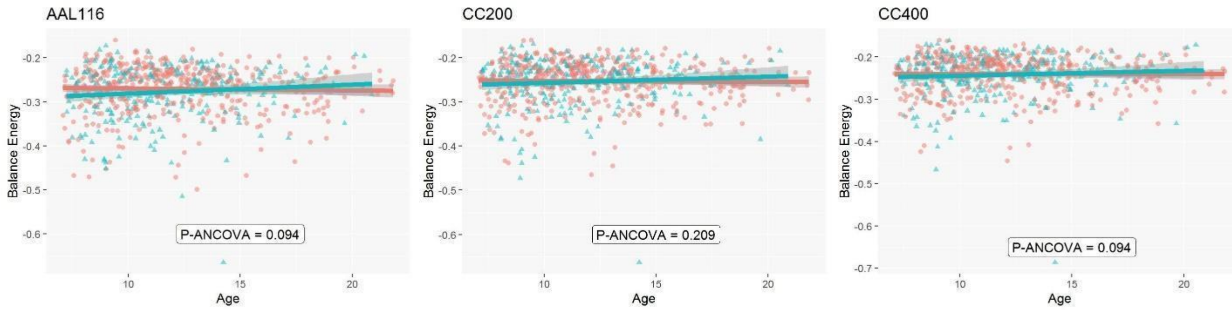

Figure 5: Comparison of the relationship between age and balance energy in healthy and patient individuals. The points are related to the subjects. The red dots are for healthy people and the blue dots are for patients. The colored lines show the fitted linear relationship to the points. The P-value values of the ANCOVA test, which show the quality of the comparison, are reported below each subgraph.

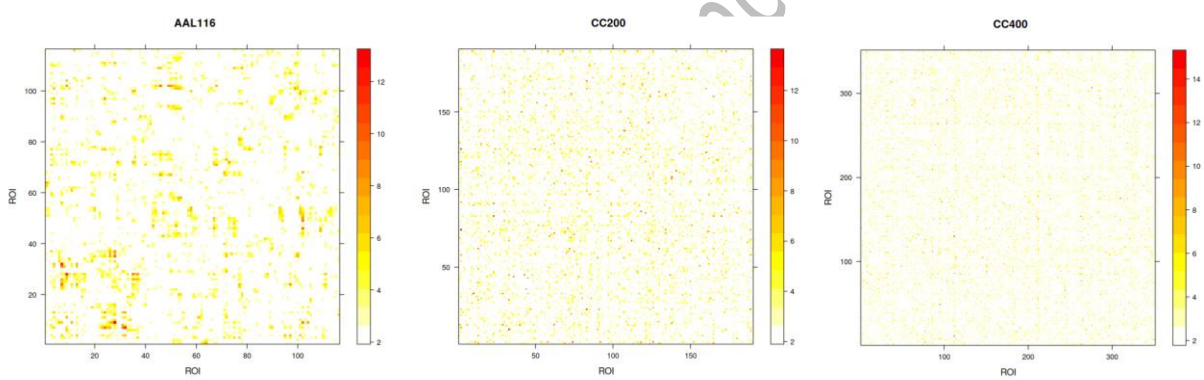

Figure 6: Comparison between connectivity patterns of healthy and ADHD groups. Non-white cells are those connections with significant differences between 4 groups of subjects based on ANOVA test. Color bars denote F-values of multiple group comparisons. ROI: Region of Interest.