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Pattern Discovery of ADHD Disorder Using Graph Theory on Task-Free fMRI Data

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***Abstract*— Study of neural correlates of ADHD could potentially help us to develop an automated diagnosis system. In 2011, a rich and heterogeneous neuroimaging dataset was provided by the ADHD-200 consortium to be used for this purpose. Considering the fact that the brain functional connectome in ADHD subjects is altered compared to healthy controls; we hypothesized that local and global parameters of functional connectome extracted using graph theory from task free fMRI data could give us a good tool to identify ADHD subjects from healthy controls.**

***Keywords*— Attention deficit hyperactivity disorder; Task free fMRI; Functional connectivity; Graph theory; Classification**

I. INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a prevalent and persistent neurodevelopmental disorder, characterized by excessive behavioral inattention and disorganization or hyperactivity-impulsivity (American Psychiatric Association, 2013 [1]). The disorder is frequently associated with several comorbid disorders, functional impairment and poor long-term outcomes (Dopheide and Pliszka, 2009[2]; Rommelse et al., 2009). However, despite substantial progress in understanding the related brain systems, small effect sizes and variability of associations with neurobiological correlates limit clinical utility.

The search for structural or functional neural correlates of ADHD, and consequently for potential biomarkers of the disorder, is crucial in the pursuit of its prevention, early detection and more effective treatment (Cuthbert and Insel, 2013 [3]; Insel, Cuthbert, Garvey & et al, 2010[4]). For this purpose, machine learning techniques can be applied on resting-state functional neuroimaging data (Linden, 2012[5]).

Graph theoretical analysis is a promising approach to investigate brain structural and functional networks (Rubinovand and Sporns, 2010[6]). Descriptors derived from graph theory are measurements quantifying different characteristics of the network organization. When applied to task-free fMRI data, graph measures may be used to enhance our understanding about functional network dynamics (Damoiseaux, Rombouts, Barkhof & et al, 2006 [7]). Resting state networks (RSN) are characterized by consistent correlations with the spontaneous fluctuations of the BOLD signal among certain brain regions. Among several RSNs identified by fMRI analysis, specifically sensory-motor, fronto-parietal, salience and default mode networks (DMN) have been implicated in ADHD pathophysiology (de La Fuente, Xia, Branch and Li, 2013[8]). Studies have introduced abnormal interactions within distinct RSNs as a key factor contributing to various neuropsychiatric disorders. The abnormalities have been particularly reported in the DMN (Buckner, Andrews-Hanna, and Schacter, 2008[9]).

Neuroimaging data analysis based on graph theory has recently been applied to categorize atypical neurodevelopment processes. Investigations performed by Lynall et al. [10] and Fornito et al. [11] demonstrated suitability of graph-based approach when they evaluated networks of patients with schizophrenia. In addition, application of graph theory has been very successful in the study of ADHD. Wang et al. [12] described differences in small-world measures in children with ADHD when compared to typical development (TD) controls. Fair et al. [13] have identified neural substrates associated to control networks that may contribute to the high heterogeneity of ADHD, using the community detection method. More recently, Tomasi and Volkow [14] have used a data-driven graph theory approach to investigate functional connectivity between a large sample of ADHD children and TD controls. Higher connectivity was found in reward-motivation regions such as ventral striatum and orbitofrontal cortex. In contrast, lower functional connectivity was found in regions of dorsal attention such as superior parietal cortex and unexpected functional attributes of precuneus were observed comparing neuroimaging data of ADHDs with typically developed controls.

In this study, we investigated changes in local and global parameters of the brain functional network due to ADHD using graph theoretical approach. We hypothesized that ADHD individuals could be distinguished from TPDs based on these measures. The findings may help us to pave the way towards an automatic screening method.

II. METHODOLOGY AND EXPERIMENTAL DESIGN

ADHD is a psychiatric disorder characterized by impulsiveness, inattention, and hyperactivity. This condition affects about 5% of children and adolescents worldwide (Polanczyk et al., 2007[15]).Data

analyzed in this paper came from the ADHD-200 dataset, comprising data from 973 participants (for more details, see ADHD-200-Webpage). Children with ADHD were recruited through the New York University Child Study Center (NYU). We enrolled 28 children with ADHD.
Automated ADHD diagnosis protocols were tested on data from the ADHD-200 Global Competition dataset.

III. PARTICIPANTS

Our Training Data set included 58participants. In this study, we included 28 ADHDs (21male, 7 ± 12 years old, 18 right hand) and 30 healthy controls (15 male, 7 ± 12 years old, 18 right hand) from the ADHD-200 dataset specially form dataset provided by the NYU. The ADHD-200 dataset also included other non-imaging data including gender, age, Handedness, verbal IQ, Performance IQ and Full IQ. Further details about this dataset can be obtained at the ADHD-200 consortium website.
The cognitive measures including verbal IQ (HC=112±16.04, ADHD=110.10±11.09), performance IQ (HC=105.63±15.01, ADHD=105.35±14.16), Full score IQ (HC=110.33±15.33, ADHD=108.60± 13.04.
As shown in Table1, the selected groups were not significantly different in terms of age, gender, handedness, verbal IQ and performance IQ.
On the other hand, ADHD measures including Index, Inattentive, Hyper/Impulsive scores exhibited highly significant differences between the groups.

Table 1. Characterization of control (n=30) and ADHD (n=28) populations

	ADHD	Control	Statistics	
	(Mean±SD), Range		P-value	T-Value
Gender	21 male	15 male	0.051	-1.9939
Age	(9.63±1.40), (7-12)	(9.57±1.38),), (7-12)	0.8708	-1.633
Handedness	18 right hand	18 right hand	0.4029	-0.8428
ADHD Index	(73.17±9.39), (58-86)	(43.86±4.22), (40-57)	0.3188*10(-22)	-0.149649
Inattentive	(70.39±8.35), (56-90)	(43.93±4.47), (40-58)	8.193*10(-21)	-0.14653
Hyper/Impulsive	(74.17±11.03), (54-90)	(46.31±6.67), (41-66)	4.155*10(-16)	-0.113254
Verbal IQ	(110.10±11.89),(82-141)	(112.7±16.04), (85-143)	0.5045	0.6718
Performance IQ	(105.35± 14.16),(79-129)	(105.633±15.01),(72-136)	0.9448	0.0695
Full IQ	(108.60± 13.04),(78-133)	(110.33±15.33),(80-142)	0.6583	0.4446

IV. NEUROPSYCHOLOGICAL MEASUREMENTS

A. *Imaging acquisition*

All images were collected using 3T Siemens system (SIEMENS MAGNETOM Allegra syngo MR 2004A). Each participant underwent a T1-weighted structural MRI(Scan Time: 8:07) and a task-free fMRI scan(Scan Time: 6:00). High-resolution T1-weighted structural MRI was acquired using magnetization prepared rapid gradient echo sequence (MPRAGE) (continuous sagittal slices, TR/TE/TI = 2530 / 3.25 / 1100 ms, flip angle = 7˚, isotropic voxel size = 1.3×1.0×1.3 mm3). A 6-min task-free fMRI were acquired using a single-shot EPI sequence (TR/TE = 2000/15 ms, flip angle = 90˚, voxel size = 3.0×3.0×4.0 mm3, Bandwidth= 3906 Hz/Pixel), During acquisition, participants were asked simply to remain still, close their eyes, think of nothing systematically.

B. *Tf-fMRI preprocessing*

Data pre-processing was carried out using both analysis of functional neuroimaging (AFNI) (http://afni.nimh.nih.gov/afni/) (Di Martino et al, 2008)[16],(Shehzad et al., 2009)[17],and fMRIB software library (FSL) (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library,www.fmrib.ox.ac.uk) (Smith SM et al. 2004)[18] (Woolrich MW et al. 2009) [19] (Jenkinson M et al. 2012)[20].
Seven different preprocessing strategies have been evaluated. However, for all the preprocessing strategies, these data underwent a few established preprocessing steps. Initially, the first 3 images where removed to avoid T1 effects, despiked, slice-time corrected,3d motion corrected, nuisance regression with motion parameters, registered to MNI152 (using the T1 structural image). Registration to MNI space was visually inspected for each subject. Spatial smoothing was not performed in order to not extend blood oxygen level dependency (BOLD) signal between different regions of interest (nodes). Additionally, motion parameters, as well as the average BOLD signal of cerebro spinal fluid (CSF), white matter (WM) and whole brain where extracted for subsequent use.

C. *Brain anatomical parcellation*

To measure the functional connectivity among regions, the brain was first parcellated into 126 anatomical regions of interest, including 114 cortical regions derived from the 17 functionally parcellated networks (Yeo BT et al. 2011[21]) and 12 subcortical regions from automatic anatomical labeling (AAL) template (Tzourio-Mazoyer N et al. 2002 [22]). This parcellation scheme is referred to as ROI 126. Considering different anatomical parcellation may lead

to different result in brain network analysis (Zalesky A et al. 2010[23]), we also defined the brain nodes using the AAL template which is composed of 116 cortical and subcortical regions.

D. Brain connectivity Networks

A network is a collection of nodes and edges, where nodes indicate basic elements within the system of interest and edges indicate the associations among those elements. An accurate method for defining the most essential elements of a network (i.e., nodes and edges) is vital for a network (i.e., nodes and edges) is vital for network construction. Specifically, for brain networks, they can be described at different spatial levels, such as microscale, mesoscale, and macroscale or large-scale (Sporns et al., 2005[24]). Given technical limitations and computational demand, most current studies focus on the macroscale or large-scale brain networks. In this review, we will also concentrate on the macroscale brain networks.

E. Graph theoretical approaches

Graph theory is the natural framework for the exact mathematical representation of complex networks. Formally, a complex network can be represented as a graph by G(*N, K*), with *N* denoting the number of nodes and K the number of edges in graph G.

1) Nodal and global graph ,measures

We use the Brain Connectivity Toolbox in Matlab (http://www.brain-connectivity-toolbox.net)(Rubinov and Sporns,2010[25]) to compute weighted global and nodal graph theoretical metrics.
Global metrics were clustering coefficient (CC) and local efficiency, which measure the degree to which neighbors of a node are connected to each other; characteristic path length (CPL), which represents the average number of edges needed to get from any node in the network to any other node in the network; global efficiency, which is similar to the inverse of CPL but can be computed for networks that are not fully connected, normalized CC and CPL (gamma and lambda), which are calculated as a ratio of CC or CPL to the average CC or CPL.
Degree is a straight and intuitive way to quantify nodes centrality, and it is defined as the number of edges connected to a particular node. The closeness centrality is the average distance between a given node and all other nodes of the network. Betweenness quantifies the influence of a node and is defined as the number of shortest paths passing through it.

2) Small-World

The small-world (Watts and Strogatz, 1998[26]) is an important model to characterize the organization principles that govern a remark- able variety of social, economic, and biological complex networks. A small-world network can be described by high local clustering, characterized by a high clustering coefficient, Cp, and low minimum path length between any pair of nodes, characterized by a low characteristic path length, Lp.

3) Network effiiency

Efficiency is a more biologically relevant metric to describe brain networks from the perspective of information flow, which can deal with the disconnected graphs, nonsparse graphs or both (Latora and Marchiori, 2001[27]; Bassett and Bullmore, 2006[28]).

4) Nodal centrality

Nodal centrality quantifies how important a node is within a network. Several different metrics exist for measuring nodal centrality, such as degree centrality, nodal efficiency (Achard and Bullmore, 2007[29]), closeness centrality (Freeman, 1979[30]), and betweenness centrality (Freeman, 1977[31]).

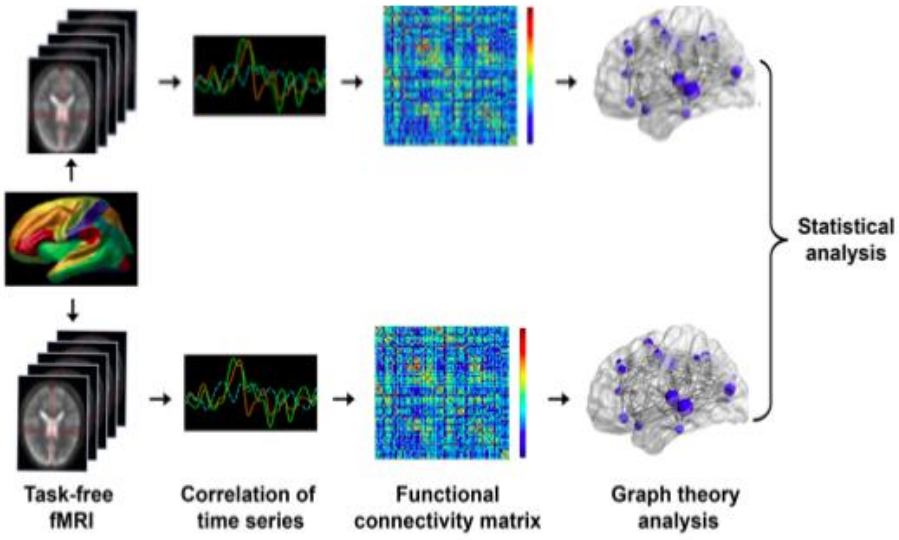

Fig1 . Schematic of study design

F. Statistical analysis

1) Network thresholding

A matching strategy such as using the same cost threshold should be decided prior to statistical analyses between groups of subjects (Bernhardt BC et al. 2011[32]; Zhang Z et al. 2011[33]).
The integral of measures at the selected range were then calculated as summary metrics for comparing the nodal measurements (Gong G et al. 2009[34]). Finally, to examine the effects of brain anatomical parcellation methods on topological properties, all analyses were repeated using AAL116 ROIs and results or both global and nodal properties were presented in supplementary materials.

2) Group differences in network global metrics

To examine the group difference of global and local efficiency of functional connectome, we employed a general linear model (GLM) with age and handedness as covariates of nuisance to test whether there is significant difference between groups ($p<0.05$). The GLM was applied on both integrated global metrics and a range of network cost.

3) Pattern recognition

Pattern recognition methods based on machine learning techniques have shown to be a promising approach to the analysis of neuroimaging data[35]. Support vector machine (SVM)[36] and k nearest neighbor rule (KNN) are two of the most frequently used methods in this field, given their robust properties when dealing with high dimensional multivariate data in addition to providing predictions for each individual case. In other words, given a set of features (e.g., brain measurements) and a label (e.g., healthy and patient), SVMs are used to learn a function, which maps the set of features to their respective labels within a training dataset. Thus, given a new set of features produced from an unseen observation, SVMs are able to provide a predicted label for this novel observation.
Graph theory descriptors can be used as predictor variables (i.e. features) in a machine-learning framework. Merging graph theoretical approaches and machine learning techniques might provide a better-adjusted way to scrutinize the impairment of RSNs in ADHD as well as mapping predictions to a single individual case.

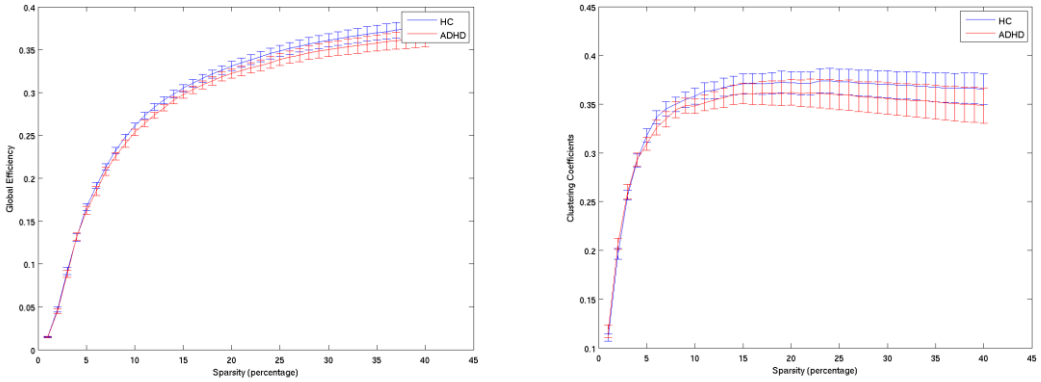

Fig 2. Group differences in brain network global metrics

G. Results

1) Group differences in network global metrics

Comparison between ADHD and HC group revealed no significant difference in global characteristic of functional connectome.
The ADHD group showed lower global efficiency and lower global clustering coefficient. in comparison to other group. However, between-group differences were not statistically significant ($p>0.05$). The same comparison was performed for AAL 116 parcellation scheme that the same results were observed.(Fig 2.)

2) Group fifferences in brain network nodal metrics

In terms of nodal metrics of functional connectome of ROI 126 parcellation scheme, the ADHD compared to HC had incresed Closeness in the ParaHippocampal gyrus _L (PHG-L), Cerebelum_9_L (CER-9-L), Cerebelum_9_R (CER-9-R) and decreased Betweenness in the Inferior Parietal_R (SP-R), ParaHippocampal gyrus _L (PHG-L), Pallidum_L (PAL-L), Cerebelum_4_5_R (CER-4-5-R), Paracentral_Lobule_R (PCL-R) and decreased in the Calcarine_L (CAL-L), Calcarine_R (CAL-R), Lingual gyrus_R (LING-R), Supplementaly Motor Area _L, (SMA-L) Heschl gyrus _L (HES-L), Heschl gyrus_R (HES-R) , decresed Degree Centrality ParaHippocampal gyrus _L (PHG-L), Superior Temporal Pole_L (STP-L), Cerebelum_4_5_R (CER-4-5-R), and increased Degree Centrality in Calcarine_L(CAL-L), Calcarine_R (CAL-R), and reduced clustering-coefficient in the Calcarine_L(CAL-L), Calcarine_R (CAL-R),, Lingual gyrus_R (LING-R), Supplementaly Motor Area_Left, (SMA-L) Heschl gyrus _L (HES-L), Heschl gyrus _R (HES-R) (uncorrected $p<0.05$) (Fig 3,Table 2).

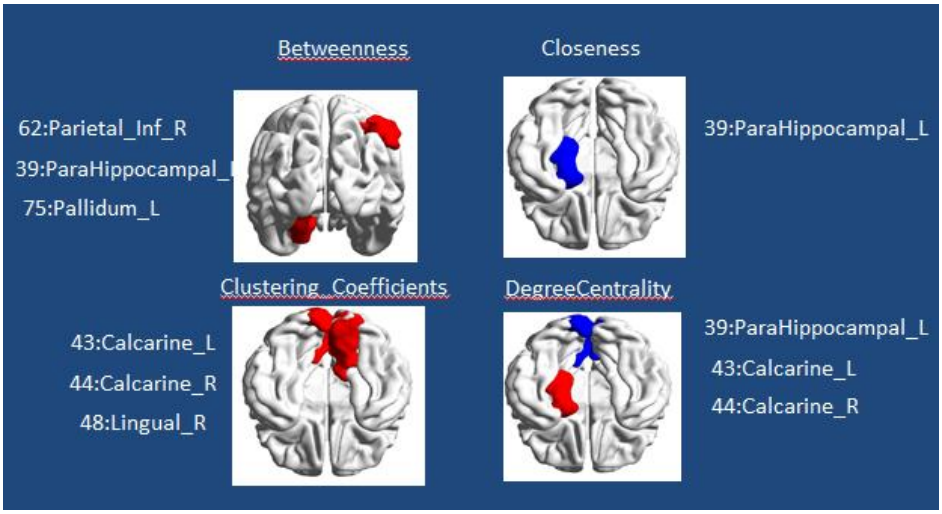

Fig3 . Group differences in brain network nodal metrics

Table2. Group differences in brain network nodal metrics

Graph Measure	Region	P-value	T-value
Closeness	Left ParaHippocampal	0.023192*	2.338
	Left Cerebelum_9	0.028297	2.2756
	Right Cerebelum_9	0.050979	2.0172
Betweenness	Right Inferior Parietal	0.003359*	-3.0714
	Left ParaHippocampal	0.003963*	-3.0128
	Left Palladium	0.007688*	-2.7711
	Right Cerebellum (4,5)	0.027273	-2.2704
	Right Paracentral Lobule	0.048424	-2.0202
Clustering Coefficients	Left Calcarine gyrus	0.00551*	-2.894
	Right Calcarine gyrus	0.007835*	-2.764
	Right Lingual	0.014442*	-2.5292
	Left Superior motor area	0.030245	-2.2266
	Left Heschl	0.039881	-2.1068
	Right Heschl	0.042302	-2.0808
	Left Lingual	0.055522	-1.9578
Degree Centrality	Left ParaHippocampal	0.003585*	-3.0484
	Left Calcarine gyrus	0.006728*	2.8207
	Right Calcarine gyrus	0.009629*	2.6862
	Left superior Temporal pole	0.027721	-2.2636
	Right Cerebelum_4_5	0.028489	-2.252
Nodal Efficiency	ns	ns	ns

*: pval<0.05, FDR corrected; ns: not significant

3) Evaluating classification performance

Comparing the value of different classifiers requires a measure capable of representing the utility of one classifier over another. One natural measure is the accuracy which quantifies the probability that the classifier will make a correct prediction of ADHD vs. TDC. However, under differing practical scenarios, it may be more important to be confident that the classifier provides a correct diagnosis of ADHD positive (high true positive rate) or that the classifier provides confidence in ruling out an ADHD positive diagnosis (low false positive rate).

Table 3. Classification Result

Classifier	Closeness	Betweenness	Clustering Coefficients	Degree Centrality	Nodal efficiency
KNN	0.7606	0.6424	0.5348	**0.7742**	0.4121
SVM	0.4136	0.6712	0.5314	**0.7227**	0.6045

H. Discussion and conclusion

In general, there was no significant difference between the control group and ADHD in terms of global measures. This finding is inconsistent with some of the previous studies (Mostofsky, 2006 [37]; Ricardo Sato, 2013 [38]) which partly lies on heterogeneity of the ADHD (Wåhlstedt et al., 2009)[39].
Nevertheless, our results showed that nodal metrics such as centrality of the regions (closeness, betweenness and degree) as well as their local connectivity (clustering coefficients) present significant difference between two groups. These results are in line with other studies reports that have used different techniques [40,41]. The results may represent a possible neural basis for some of the motor and intentional deficits commonly found in ADHD.
We observed alteration in terms of centrality of the cerebellum (increase of closeness at Left and right Cerebelum-9 , decreased betweenness and degree centrality at Right Cerebelum-4-5 in ADHD group. The cerebellum is often described as a structure involved in motor coordination and numerous cognitive and behavioral functions which are disrupted in ADHD. For example, patients with cerebellar lesions or atrophy have been found to show deficits in ability to shift their attention, with visuospatial processing, and with planning (Akshoomoff & Courchesne, 1994 [42]; Golla, 2005 [43]). Neuroimaging studies on patients with cerebellar damage have also indicated involvement of cerebellum in temporal information processing, working memory and executive functioning abilities (Ivry et al, 2002 [44]; Schmahmann, 2004 [45]). In a classic study on the neural correlates of motor and non-motor cerebellar function (Allen, Buxton, Wong, and Courchesn,1997 [46]) demonstrated differential activation within the cerebellum for visual attention and motor performance in healthy participants. This double dissociation suggested the cerebellum contains distinct regions for attention that are independent of motor movement regions. The findings are somehow in line with our results which indicate there are different types of alteration within the cerebellum region in course of ADHD.
In addition, functionality of the left parahippocampal gyrus shows increase in terms of closeness and decrease in terms of betweenness and degree centrality in ADHD individuals. The parahippocampal gyrus is a grey matter cortical region of the temporal lobe. There is evidence for structural (Kobel et al., 2010[47]) and functional (Shafritz et al., 2004; Tamm et al., 2004 [48]) abnormalities in the temporal lobe in ADHD. Kobel et al. [49] found that boys with ADHD showed smaller gray matter volumes and decreased magnetization transfer imaging values in the temporal lobe. They speculated that the temporal lobe might play a key role in the etiology of ADHD. During the divided attention task, adolescents with ADHD show significantly less activation in the middle temporal gyrus than TPDs and only the left middle temporal lobe activation was correlated with accuracy on the visual selective tasks (Shafritz et al., 2004 [50]).
Moreover, several neuroimaging studies have shown decreased gray matter volume or thickness in left parahippocampal gyrus (Carmona et al, 2005 [51]; Abernethy et al, 2002[52]).
Our result showed that centrality of the right parietal region is also decreased in ADHD individuals. These finding are consistent with studies of ADHD that report abnormal patterns of activation in parietal regions (Dickstein et al, 2006 [53]) during working memory, (Burgess et al, 2010) [54] attentional (Schneider et al, 2010 [55]) or response inhibition tasks (Dillo et al, 2010 [56]). Decreased betweenness in the parietal regions is consistant with several fMRI studies that show aberrant activity in the attention system in ADHD (Tamm et al., 2006 [57]; Cao et al., 2008 [58]). Previously, Cao et al. ([59]) showed that activation of the left inferior parietal lobe decreased in ADHD during an alerting task as well as during a Go / No Go task reported. Children with developmental coordination disorder (DCD) exhibit increased connectivity between the left middle frontal and inferior parietal cortices and reduced connectivity between the right striatum and parietal cortex (Querne et al., 2008[60]). These findings suggest that functional connections between the striatum and parietal cortex, areas that integrate sensory information in motor responses, are altered in children with DCD.
A few studies have been conducted on the function of left palladium. The palladium is a structure within the basal ganglia. In ADHD patients, reductions in volume have been observed in terms of total cerebral volume specifically at prefrontal cortex, basal ganglia, dorsal anterior cingulate cortex, corpus callosum and cerebellum (Emond et al, 2009 [61]). Compensatory networks including basal ganglia, insula and cerebellum have been implicated for relative lower cognitive load tasks in ADHD patients (Castellanos et al, 2002 [62]). DTI studies have also revealed developmental changes in cortical white matter pathways in prefrontal regions and in pathways surrounding the basal ganglia and cerebellum in patients with ADHD, which presumably reflect decreasing myelination of axons. It is believed that these changes cause a decrease in speed of neuronal communication (D'Agati et al, 2010[63]).
The right paracentral lobule includes portions of the frontal and parietal lobes. Neurons in this regions are concerned with motor and sensory innervations of the contralateral lower extremity that contribute to regulation of physiological functions such as defecation and micturition (Totowa, 2003)[64]. Based on our findings, centrality of this region (betweenness) is decreased more significantly observed within fronto-striatal and fronto-parietal circuits (Steven et al, 2006)[65].
The results obtained in other brain regions are consistent with the findings of yassin and colleague[66]. They studied differences in brain function at rest between children and adolescents diagnosed with and without ADHD by using data acquired by single-photon emission computerized tomography (SPECT).

Their results showed significant differences for the angular gyrus, calcarine fissure, caudate nucleus, cerebellum, cuneus gyrus, frontal lobe, fusiform gyrus, Heschl's gyrus, lingual gyrus, occipital lobe, paracentral lobule, parahippocampal area, parietal lobe, post central gyrus, precuneus, rolandic operculum, supplementary motor area, supramarginal gyrus, and temporal lobe (yassin et al, 2014)[67]. In our study, frontal and temporal lobes were found to have the highest number of areas that were significantly different between the two groups. Temporal lobe has the most number of areas with significant differences between ADHDs and TPDs.

The results of this study suggest multiple brain regions are associated in ADHD, particularly the areas of the frontal and temporal lobes. This indicates the functional abilities of the frontal and temporal lobes are implicated in children and adolescents with ADHD which may account for their difficulties in motor control, problem solving and self-regulation difficulties. However, other brain areas were involved as well indicating while there is heavy frontal and temporal involvements; it is not restricted to these areas.

Overall, lower functional activity in children with ADHD (Hamilton et al., 2008[68]; Pavuluri et al., 2009[69]) is typically interpreted as evidence of disruption in motor and attentional circuits. On the other hand, higher functional activity is also considered as deficit in neuronal branching (Li et al., 2011; Silk et al., 2009[70]). Nevertheless, ADHD individuals show a delayed cortical maturation which may associate with different developmental trajectories in adolescence and beyond (Shaw et al, 2009[71]). The grey matter peaks are shifted by about 3 years in ADHDs compared to TPDs (Shaw et al, 2006 [72]). The delay is most prominent in prefrontal regions which are important for control of cognitive processes including attention and motor planning (Shaw et al, 2007)[73]. These finding could provide an insight into the pathophysiological mechanisms of ADHD from a network analysis perspective.

REFERENCES

[1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Association, Arlington, 2013; VA.

[2] Dopheide, J.A., Pliszka, S.R., (2009). Attention-deficit-hyperactivity disorder: an update. Pharmacotherapy 29 (6), 656–679.

[3] Cuthbert. B. N. and Insel, T. R. Toward the future of psychiatric diagnosis: the seven pillars of RDoC, BMC Medicine. 2013; 11. 1, 126.

[4] Insel, T. Cuthbert, B. Garvey . M. et al. Research Domain Criteria (RDoC): toward a new classification framework for research on mental disorders," American Journal of Psychiatry. 2010; 167.7.748–751.

[5] Linden, D. E. J. The challenges and promise of neuroimaging in psychiatry," Neuron. 2012; 73,.1.8–22.

[6] Rubinovand, O. M .Sporns. Complex network measures of brain connectivity: Uses and interpretations, NeuroImage, 2010; 52, 3, 1059–1069.

[7] Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof. F. & et al,. Consistent resting-state networks across healthy subjects, Proceedings of the National Academy of Sciences of the United States of America, 2006; 103, 37, 13848–13853.

[8] De La Fuente, A., Xia. S., Branch, C. and Li, X. A review of attention-deficit/hyperactivity disorder from the perspective of brain networks, Frontiers in Human Neuroscience, 2013; 7, 192.

[9] Buckner, R. L., Andrews-Hanna, J. R., and Schacter, D. L. The brain's default network: anatomy, function, and relevance to disease, Annals of the New York Academy of Sciences, 2008; 1124, 1–38.

[10] Lynall, M.E., Bassett, D.S., Kerwin, R., McKenna, P.J., Kitzbichler, M., et al. Functional connectivity and brain networks in schizophrenia. Journal Neuroscience. 2010; 30, 9477–9487.

[11] Fornito, A., Zalesky, A., Pantelis, C., Bullmore, E.T. Schizophrenia, neuroimaging and connectomics. Neuroimage, 2012; 62, 2296–2314.

[12] Wang, L., Zhu, C., He, Y., Zang, Y., Cao, Q., & et al. Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Hum. Brain Mapp. 2009; 30, 638–649.

[13] Fair, D.A., Dosenbach, N.U., Church, J.A., Cohen, A.L., Brahmbhatt, S. Development of distinct control networks through segregation and integration. Proceedings of the National Academy of Sciences U. S. A. 2007; 104, 13507–13512.

[14] Tomasi, D., Volkow, N.D. Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. Biological Psychiatry. 2012; 71, 443–450.

[15] Polanczyk G, De Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry 2007; 164: 942-8.

[16] Di Martino A, Scheres A, Margulies DS, Kelly AM, Uddin LQ, Shehzad Z, Biswal B, Walters JR, Castellanos FX, Milham MP., Functional connectivity of human striatum: a resting state FMRI study, Cereb Cortex. 2008 Dec;18(12):2735-47. doi: 10.1093/cercor/bhn041. Epub 2008 Apr 9.

[17] Shehzad Z, Kelly AM, Reiss PT, Gee DG, Gotimer K, Uddin LQ, Lee SH, Margulies DS, Roy AK, Biswal BB, Petkova E, Castellanos FX, Milham MP (2009) The resting brain: unconstrained yet reliable. Cereb Cortex 19: 2209 –2229

[18] Smith SM1, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J,Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM,Advances in functional and structural MR image analysis and implementation as FSL, Neuroimage. 2004;23 Suppl 1:S208-19.

[19] Woolrich MW1, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, Beckmann C, Jenkinson M, Smith SM, Bayesian analysis of neuroimaging data in FSL, Neuroimage. 2009 Mar;45(1 Suppl):S173-86,doi:10.1016/j.neuroimage.2008.10.055. Epub 2008 Nov 13.
[20] Jenkinson M., Beckmann CF., Behrens TEJ., Woolrich MW., Smith SM,FSL, Neuroimage, 15/08/2012,voloum 62,pages 782 - 790
[21] Yeo BT1, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zöllei L, Polimeni JR, Fischl B, Liu H, Buckner RL, The organization of the human cerebral cortex estimated by intrinsic functional connectivity, J Neurophysiol. 2011 Sep;106(3):1125-65. doi: 10.1152/jn.00338.2011. Epub 2011 Jun 8.
[22] Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain,Tzourio-Mazoyer N1, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M, Neuroimage. 2002 Jan;15(1):273-89.
[23] Zalesky A1, Fornito A, Bullmore ET, Network-based statistic: identifying differences in brain networks, Neuroimage. 2010 Dec;53(4):1197-207. doi: 10.1016/j.neuroimage.2010.06.041. Epub 2010 Jun 25
[24] Olaf Sporns,* Giulio Tononi, and Rolf Kötter, The Human Connectome: A Structural Description of the Human Brain, PLoS Comput Biol. 2005 Sep; 1(4): e42.Published online 2005 Sep 30. doi: 10.1371/journal.pcbi.0010042
[25] Rubinov M1, Sporns O, Complex network measures of brain connectivity: uses and interpretations, Neuroimage. 2010 Sep;52(3):1059-69. doi: 10.1016/j.neuroimage.2009.10.003. Epub 2009 Oct 9.
[26] Duncan J. Watts & Steven H. Strogatz, Collective dynamics of 'small-world' networks, Nature 393, 440-442 (4 June 1998) | doi:10.1038/30918; Received 27 November 1997; Accepted 6 April 1998.
[27] Latora V1, Marchiori M, Efficient behavior of small-world networks, Phys Rev Lett. 2001 Nov 5;87(19):198701. Epub 2001 Oct 17.
[28] Bassett DS1, Bullmore E, Small-world brain networks, Neuroscientist. 2006 Dec;12(6):512-23.
[29] Achard S, Bullmore E, Efficiency and cost of economical brain functional networks, PLoS Comput Biol. 2007 Feb 2;3(2):e17.
[30] Freeman, Linton C., Centrality in Social Networks Conceptual Clarification, Social Networks, 1 (1978/79) 215-239 @Elsevier Sequoia S.A., Lausanne - Printed in the Netherlands
[31] Linton C. Freeman, A Set of Measures of Centrality Based on Betweenness, ociometry, Vol. 40, No. 1. (March 1977), pp. 35-41 Key: citeulike:1025135
[32] Bernasconi A., Bernasconi N., Bernhardt B. C., Schrader D. (2011). Advances in MRI for 'cryptogenic' epilepsies. Nat. Rev. Neurol. 7, 99–108. 10.1038/nrneurol.2010.199 PubMed
[33] Zhang Z, et al. (2011) A packing mechanism for nucleosome organization reconstituted across a eukaryotic genome. Science332(6032):977-80
[34] Gong Y, et al. (2009) An atlas of chaperone-protein interactions in Saccharomyces cerevisiae: implications to protein folding pathways in the cell.Mol Syst Biol 5:275
[35] S. Klöppel, A. Abdulkadir, C. R. Jack Jr., N. Koutsouleris, J. Mourão-Miranda, and P. Vemuri, "Diagnostic neuroimaging across diseases," NeuroImage, vol. 61, no. 2, pp. 457–463, 2012. View at Publisher · View at Google Scholar · View at Scopus.
[36] V. N. Vapnik, The Statistical Learning Theory, Springer, 1998.
[37] Mostofsky SH, Rimrodt SL, Schafer JGB, et al. Atypical motor and sensory cortex activation in attention deficit/hyperactivity disorder: A functional magnetic resonance imaging study of simple sequential finger tapping. Biol. Psychiatry. 2006; 59(1):48–56. [PubMed: 16139806]
[38] Ricardo Sato J., Yasumasa Takahashi D., Brauer Massirer K, Queiroz Hoexter M, Fujita A, Measuring network's entropy in ADHD: A new approach to investigate neuropsychiatric disorders. NeuroImage, 2013; 77, 44–51
[39] Wåhlstedt, C., Thorell, L.B., Bohlin, G. Heterogeneity in ADHD: Neuropsy- chological pathways, comorbidity, and symptom domains. Journal of Abnormal Child Psychology. 2009; 37 (4), 551–564.
[40] Xiaolong Peng ,Pan Lin,Tongsheng Zhang ,Jue Wang, Extreme Learning Machine-Based Classification of ADHD Using Brain Structural MRI Data",Plos ONE, 2013
[41] Yosefi Mehdi,EbrahimZadeh A.,Khazaei A.,Babaeian A., "resting state fmri analysis using pso algorithm to diagnose adhd disease", journal of soft coputing and inormation technology(iscit) 2012,volume 1,number 3; page(s)53 to 66.
[42] Akshoomoff NA, Courchesne E. ERP evidence for a shifting attention deficit in patients with damage to the cerebellum. Journal of Cognitive Neuroscience. 1994; 6(4):388–399.
[43] Golla H, Thier P, Haarmeier T. Disturbed overt but normal covert shifts of attention in adult cerebellar patients. Brain. 2005; 128:1525–1535. [PubMed: 15872017].
[44] Ivry RB, Spencer RM, Zelaznik HN, Diedrichsen J. The cerebellum and event timing. Annal of the New York Academy of Science. 2002; 978:302–317.
[45] Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. Journal of Neuropsychiatry and Clinical Neuroscience. 2004; 16:367–378.
[46] Allen G, Buxton RB, Wong EC, Courchesne E. Attentional Activation of the Cerebellum Independent of Motor Involvement. Science. 1997; 275(28):1940–1943. [PubMed: 9072973].

[47] Kobel, M., Bechtel, N., Specht, K., Klarhöfer, M., Weber, P., Scheffler, K., Opwis, K., Penner, I.K. Structural and functional imaging approaches in attention deficit/hyperactivity disorder: does the temporal lobe play a key role? Psychiatry Research: Neuroimaging. 2010; 183, 230–236.
[48] Shafritz, K.M., Marchione, K.E., Gore, J.C., Shaywitz, S.E., Shaywitz, B.A. The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. The American Journal of Psychiatry. 2004; 161, 1990–1997.
[49] Kobel, M., Bechtel, N., Specht, K., Klarhöfer, M., Weber, P., Scheffler, K., Opwis, K., Penner, I.K. Structural and functional imaging approaches in attention deficit/hyperactivity disorder: does the temporal lobe play a key role? Psychiatry Research: Neuroimaging. 2010; 183, 230–236.
[50] Shafritz, K.M., Marchione, K.E., Gore, J.C., Shaywitz, S.E., Shaywitz, B.A. The effects of methylphenidate on neural systems of attention in attention deficit hyperactivity disorder. The American Journal of Psychiatry. 2004; 161, 1990–1997.
[51] Carmona, S., Vilarroya, O., Bielsa. A., Tr`emols. V., Soliva J.C., Tom`as. J., Raheb. C., Gispert. J.D., Batlle. S., Bulbena A. Global and regional gray matter reductions in ADHD: A voxel-based morphometric study. Neuroscience Letters 389 ,2005; 88–93.
[52] Abernethy. L.J., Palaniappan. M., Cooke. R.W., Quantitative magnetic resonance imaging of the brain in survivors of very low birth weight, Arch. Dis. Child. 87 2002; 279–283.
[53] Dickstein SG, Bannon K, Castellanos FX, Milham MP. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J Child Psychol Psychiatry. 2006; 47(10):1051– 1062. [PubMed: 17073984]
[54] Burgess GC, Depue BE, Ruzic L, Willcutt EG, Du YP, Banich MT. Attentional control activation relates to working memory in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2010; 67(7):632–640. [PubMed: 20060961]
[55] Schneider MF, Krick CM, Retz W, Hengesch G, Retz-Junginger P, Reith W, Rosler M. Impairment of fronto-striatal and parietal cerebral networks correlates with attention deficit hyperactivity disorder (ADHD) psychopathology in adults - a functional magnetic resonance imaging (fMRI) study. Psychiatry Res. 2010; 183(1):75–84. [PubMed: 20558047]
[56] Dillo W, Goke A, Prox-Vagedes V, Szycik GR, Roy M, Donnerstag F, Emrich HM, Ohlmeier MD. Neuronal correlates of ADHD in adults with evidence for compensation strategies--a functional MRI study with a Go/No-Go paradigm. Ger Med Sci. 2010; 8:Doc09. [PubMed: 20421953]
[57] Tamm L, Menon V, Reiss AL. Parietal attentional system aberrations during target detection in adolescents with attention deficit hyperactivity disorder: event-related fMRI evidence. Am J Psychiatry. 2006; 163:1033–1043. CrossRef Medline
[58] Cao Q, Zang Y, Zhu C, Cao X, Sun L, Zhou X, Wang Y. Alerting deficits in children with attention deficit/hyperactivity disorder: eventrelated fMRI evidence. Brain Res, 2008; 1219:159 –168. CrossRef Medline
[59] Cao Q, Zang Y, Zhu C, Cao X, Sun L, Zhou X, Wang Y. Alerting deficits in children with attention deficit/hyperactivity disorder: eventrelated fMRI evidence. Brain Res, 2008; 1219:159 –168. CrossRef Medline
[60] Querne, L., Berquin, P., Vernier-Hauvette, M.P., Fall, S., Deltour, L., Meyer, M.E. et al. Dysfunction of the attentional brain network in children with developmental Coordination disorder: A fMRI study. Brain Research 1244, 89–102. http://dx.doi. org/10.1016/j.brainres.2008.07.066 , 18718456.
[61] Emond V, Joyal C, Poissant H: [Structural and functional neuroanatomy of attention-deficit hyperactivity disorder (ADHD)]. Encephale 2009; 35:107-114.
[62] Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL, Walter JM, et al: Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 2002; 288:1740-1748.
[63] D'Agati E, Casarelli L, Pitzianti MB, Pasini A: Overflow movements and white matter abnormalities in ADHD. Prog Neuropsychopharmacol Biol Psychiatry. 2010; 34:441-445.
[64] Totowa, NJ: Neuroscience in medicine. Humana Press. 2003. p. 348. ISBN 1-58829-016-6
[65] Steven G. Dickstein, Katie Bannon, F. Xavier Castellanos, Michael P. Milham. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. Journal of Child Psychology and Psychiatry 47:10. 2006; pp 1051–1062.
[66] Yassin. S., Spengler. K., Amen. D., Willeumier. K., Taylor. D., Golden. C. Differences in SPECT Perfusion in Children and Adolescents with ADHD. Archives of Clinical Neuropsychology.2014; 29(6). 541-542.
[67] Yassin. S., Spengler. K., Amen. D., Willeumier. K., Taylor. D., Golden. C. Differences in SPECT Perfusion in Children and Adolescents with ADHD. Archives of Clinical Neuropsychology.2014; 29(6). 541-542.
[68] Hamilton, L.S., Levitt, J.G., O'Neill, J., Alger, J.R., Luders, E., Phillips, O.R., Caplan, R., Toga, A.W., McCracken, J., Narr, K. Reduced white matter integrity in attention-deficit hyperactivity disorder. NeuroReport . 2008; 19 (17), 1705–1708.
[69] Pavuluri, M.N., Yang, S., Kamineni, K., Passarotti, A.M., Srinivasan, G., Harral, E.M., Sweeney, J.A., Zhou, X.J. Diffusion tensor imaging study of white matter fiber tracts in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. BPS. 2009; 65 (7), 586–593.

[70] Silk, T.J., Vance, A., Rinehart, N., Bradshaw, J.L., Cunnington, R. White-matter abnormalities in attention deficit hyperactivity disorder: A diffusion

tensor Imaging study. Human Brain Mapping. 2009; 30 (9), 2757–2765.
[71] Shaw P, Rabin C: New insights into attention-deficit/hyperactivity disorder using structural neuroimaging. Curr Psychiatry Rep 2009; 11:393-398.
[72] Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A, Giedd J, Castellanos FX, Rapoport J: Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/ hyperactivity disorder. Arch Gen Psychiatry 2006; 63:540-549.
[73] Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL: Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci USA 2007, 104:19649-19654.