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Research Article

An fMRI study on betweenness Centrality in Brain Networks of Teenagers with Inhaled Substance Abuse Disorder

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Abstract

A first approach study on the effects on resting state functional brain networks of Inhaled Substance Abuse Disorder (ISAD) during adolescence is presented. The ISAD group had lower IQ scores, higher affective problems and anxiety. On the network analysis, it was found that longer paths were used in information transfer in the ISAD group, which is correlated to the lower IQ found. Betweenness centrality had higher values in the ISAD population across regions of different subnetworks.

Abbrevations: FMRI: Functional Magnetic Resonance Imaging; ISAD: Inhaled Substance Abuse Disorder; IQ: Intelligence Quotient; CPL: characteristic path length; BC: Betweenness Centrality; DSM: Diagnostic and Statistical Manual of Mental Disorders.

Introduction

The use of imaging connectomics, based on graph theory, in research regarding neurodevelopment has made some characterizations of normal adaptive, and maladaptive behavior. It is interesting to study the development of the brain under different environmental conditions due to the radical developmental and changes in structure and function of the brain undergoes during this period [1,2]. Brain networks, as a graph theoretical model, consist of a collection of nodes interconnected by edges. Nodes represent regions of the brain and edges are thresholder statistical measures of structural or functional connectivity between regions. This information is summarized in the network's connectivity matrix. The arrangement of this matrix defines the topology of the network. These brain network models share principles of complex systems suchlike high clustering (like regular lattices), short path length between any two nodes in the network (like random graphs); which constitute a small-world architecture. Other characteristic organizational principles present in brain networks are high modularity and high resilience to random attacks, high degree hubs, rich-clubs, high global efficiency.

These are traits that account both for the biological cost minimization and a maximization of topological value [3]. These traits strongly influence the dynamic properties of the network such as information transfer and processing. For example, studies have reported how there is an inverse linear correlation between intelligence and the topological parameter path length [4]. The study of resting state networks in adolescents has given valuable information on the maturation processes of coordinated brain activity. Previous studies have shown that the configuration of these networks can be altered during development due to neuropsychiatric disorders such as ADHD or cannabis use [5]. Nonetheless, few studies have been carried out on the negative impact of drug abuse during adolescence on brain development and cognitive function in inhaled substance abuse disorder. Inhalants are the second most commonly abused substance by middle and high school students (7^{th}-12^{th} grades) in Mexico City.

Many consumers continue their use into adulthood. Conversely, in high-income countries, these drugs are associated with an experimental phase in adolescents. In the past, inhaled substance abuse (ISA) was more widespread among more vulnerable groups, such as homeless. However, the use of inhalants currently increasing among students living with their families. ISA can adversely affect intellectual and behavioral functioning because these substances are neurotoxic to myelin and thus impede cognitive and psychosocial development and brain structures. Previous studies in adults with ISAD have reported white matter damage [6] and others have compared the scores of intelligence tests with and without white matter damage. The performance of ISA subjects with and without white matter damage was shown to be noticeably below controls. In some subtests the performance of those with white matter changes were even lower [7].

Materials and Methods

Patients

A population of 57 teenagers, (30 ISAD), age range:13-17years. ISAD participants were recruited by contacting a Juvenile Integration Center in Mexico City. The Institutional Review Board at the Hospital Infantil de México Federico Gómez approved the study protocol. Informed consent was obtained from parents or guardians.

Behavioral measures of interest

A comprehensive neuropsychological test battery was administered on the day of or within a few days of brain scanning. The cognitive ability measures included were the Wechsler Scale of Intelligence, subjects over age 16 were given the Mexican version of the Wechsler Adult Intelligence Scale (WAIS), 4th ed; subjects under age 16, the Mexican version of the Wechsler Intelligence Scale for Children (WISC), 4th ed. Additionally, three achievement subtests and eleven cognitive subsets from the Woodcock-Muñoz Psycho-Educational Battery-III (WM-III) were administered. These measures are intended for use with children within the age range of the participants in the current study. Standardized scores were used for all analyses.

Image acquisition and processing

Data acquisition: The resting-state functional magnetic resonance images (eyes open, fixated on a cross) were acquired in a Siemens Magnetom Skyra 3T scanner 64-channel head coil. Multiband rs-fMRI (TR/TE/Flip Angle=720ms/29s/44°, 48 slices, multiband accelerate factor=8, matrix=82×82, FOV=268mm, voxel size= 3×3×3 mm^3, scan duration 6 min i.e. 500 vol) was performed. Additionally, a high resolution T1-weighted anatomical image 3DMPRAGE (TR/TE=2200ms/2.45ms, voxel size=1mm^3, iPAT=2) was acquired.

Preprocessing: Image processing was carried out using FEAT (FMRIB's Software Library in FSLv5.0.9). The first 3 volumes were removed to allow signal stabilization; MCFLIRT was used for motion correction; slice timing correction; brain extraction; a 6 DOF non-linear registration to the structural image and MNI space. Average time series from 5mm spheres centered at the coordinate given by the Power atlas [8] were extracted. A six-level wavelet decomposition by applying the maximal overlap discrete wavelet transform [9] to each of the 264 regions' time series. The estimation of the pairwise inter-regional correlations between wavelet coefficients at each scale resulted in a set of six correlation matrices for each subject. The focus was on scale 4 because for resting state data corresponds to the frequency range of interest below 0.1Hz [10], in this case of 0.043--0.087Hz.

Graph construction

Wavelet correlation matrices in scale 4 were binarized through a cumulative thresholding procedure in order to study the connectivity patterns of the network. This procedure sets a fixed number of edges and a threshold is used to preserve this fixed number of edges. A set of 15 thresholds were used to vary connectivity density, 2-30% of the edges were preserved in each case.

Topological network measures

Characteristic path length and betweenness centrality were calculated for this study using the brain Graph 2.6.0 [11] package for R. The characteristic path length (CPL) is a measure or integration of a network, that is it indicates how easily information flows through the network. It is the mean distance between all pairs of nodes of the network. The distance is the lowest number of edges to connect one node to another. A network with a low CPL indicates that it is an efficient network in which two given nodes are likely to be linked by few edges.

$$L = \frac{1}{N(N-1)} \sum_{i,j \in N i \neq j} d_{ij}$$

Betweenness centrality [12] (BC) quantifies the number of times that a node acts as a bridge along the shortest path between two other nodes, that is, how much is a brain region involved in the flow of information across the brain network. In a binary undirected network, the BC of a node i is defined as the proportion of shortest paths between nodes j and h that pass through i:

$$b_i = \frac{2}{(N-1)(N-2)} \sum_{j \neq h \neq i} \frac{n_{hj}(i)}{n_{hj}}$$

where $n_{hj}(i)$ is the number of shortest paths between h and j that pass through i, n_{hj} is the number of all shortest paths between h and j, and $(N-1)(N-2)/2$ is the number of node pairs that do not include node i.

Results and Discussion

This work explores the functional connectivity topological measures of a resting state functional brain network of two populations of adolescents, one is the ISAD group and the second is the control group. As observed in table 1, there were statistically significant differences between groups. The ISAD group showed increased affective problems and anxiety, and a lower IQ. Consistent with previous studies [4,13]. IQ and path length were inversely correlated. Figure 1 shows how the ISAD population (blue) clusters around the lower values of IQ and the higher values of the characteristic path length. As previously explained in literature, short path length is a characteristic of efficient information processing. The higher values of CPL indicate there is a disadvantage in information processing in the ISAD group. This suggests that global integration of information between regions of the brain is less efficient than in the control group. This may be due to changes in the structural organization of the brain [14]. Such changes should be looked into through a structural connectivity analysis.

Table 1: Demographics of Inhaled Substance Abuse Disorder (ISAD) and Control Groups.

	ISAD (n=30)	Control(n=27)	p-value
Age, Years	15.23 ± 1.36	15.07 ± 1.41	0.71
Sex, Male	24	19	0.157
Education, Years	8.10 ± 1.12	9.90 ± 1.42	0
IQ	81.67 ± 8.71	108.33 ± 12.53	0.001
DSM, Affective Problems	72.23 ± 12.46	60.15 ± 12.51	0.001
DSM, Anxiety	66.87 ± 8.90	60.00 ± 8.01	0.003

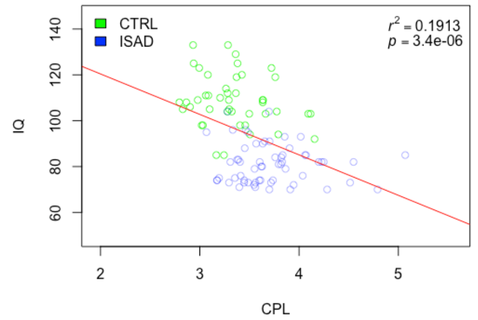

Figure 1: IQ vs CPL. The control is group (in green) has higher values of IQ and lower values of CPL while the ISAD group has lower IQ scores and higher CPL.

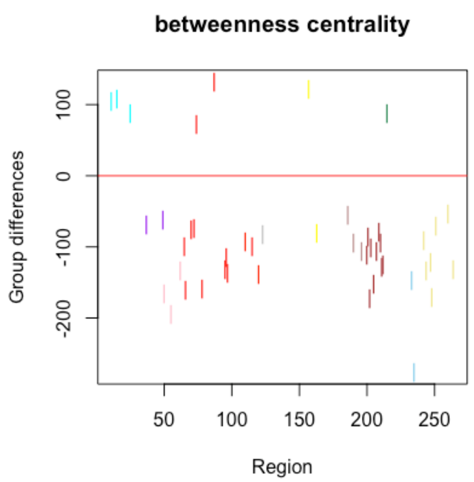

Figure 2: The plot shows the betweenness centrality (BC) in the control group minus the BC of the ISAD group.

Betweenness centrality measures the importance of a node in the process of information transfer. Higher values of betweenness centrality indicate that for information to reach one set of regions to another a middle region *i* will be passed many times, that means that this middle region *i* plays an important role in information flow. Figure 2 shows that for the 16% connectivity density (similar results were observed for the other densities) the BC values of the ISAD group are higher than for the control group. This indicates that there are many nodes that are highly used during information transfer. The network is strengthening several paths instead of favoring a few. This results in a less globally integrated network and is consistent with the higher CPL also found.

Conclusion

In this work a first characterization of the functional connectivity network of an ISAD population in contrast to a control group was done through the use of the network parameters of CPL and BC. It was found that longer paths were used in information transfer in the ISAD group, which is correlated to a lower IQ. Betweenness centrality was found to have higher values in the ISAD population, in regions from different subnetworks in general. This might be an indicator that the structural organization of the network, which underlies functional connectivity networks, is altered. Further analysis on the specific regions that are altered and whether they are linked to the observed increase in anxiety and affective problems should be explored. The generalized greater values of the BC may be an adaptation of the network in order for it not to lose function at the cost of a less efficient information transfer.

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