The Distinctly Altered Functional Connectivity Density In Alcohol Use Disorder With- And Without- Cognitive Impairment

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Abstract

Background: Alcohol use disorders (AUD) is one of the most common substance use disorders, contributing to both behavioral and cognitive impairments in AUD patients. Recent neuroimaging studies point that AUD is a typical disorder featured by altered functional connectivity. However, the details about how largescale functional coordination remains unknown.

Methods: Here, we adopted a newly proposed method named functional connectivity density (FCD) to depict altered largescale functional coordination in AUD. We applied resting state functional MRI (rs-fMRI) towards subjects to obtain their FCD, including global FCD (gFCD), local FCD (lFCD) and long-range FCD (lrFCD). 61 AUD patients and 29 healthy controls (HC) were recruited, and the AUD patients were further divided into alcohol-related cognitive impairment group (ARCI, n=11) and non-cognitive impairment group (AUD-NCI, n=50). All subjects were asked to stay stationary during the scan in order to calculate the resting-state gFCD, lFCD and lrFCD values, and further to investigate the abnormal connectivity alterations among AUD-NCI, ARCI and HC.

Results: Compared to HC, both AUD groups exhibited significantly altered gFCD in left inferior occipital lobe, left calcarine, altered lFCD in right lingual and altered lrFCD in VMPFC. It is notable that gFCD of ARCI group was found to be significantly deviated from AUD-NCI and HC in left medial frontal gyrus, which change probably contributed by the impairment in cognition. In addition, no significant differences in gFCD were found between ARCI and HC in left parahippocampal, while ARCI and HC were profoundly deviated from AUD-NCI, possibly reflecting a compensation of cognition impairment. Further analysis showed that within AUD patients, gFCD values in left medial frontal gyrus is negatively correlated with MMSE scores, while lFCD values in left inferior occipital lobe positively related with ADS scores.

Conclusions: In conclusion, AUD patients exhibited significantly altered functional connectivity patterns mainly in several left hemisphere brain regions, while AUD patients with or without cognitive impairment also demonstrated an intergroup FCD differences which correlated with symptom severity, with AUD cognitive impairment patients would suffer less severe alcohol dependence. This difference in symptom severity probably served as a compensation for cognitive impairment, suggesting a difference in pathological pathways. These findings assisted future AUD studies by providing insight for possible pathological mechanisms.

1. Introduction

Alcohol use disorders (AUD) is progressive chronic disease, and it is considered as a major public health problem in the world. With heightened reactivity to alcohol-associated stimuli being hallmarks of AUD [1], AUD patients are suffered from compulsive alcohol drinking and even impaired cognitive functions [2]. During the past few decades, many researchers have applied functional magnetic resonance image(fMRI) to assess the functional connectivity strength, which represents the temporal association of

spontaneous brain activity alterations within two selected brain regions [3], with an altered pattern in functional connectivity was considered to be associated with impaired brain functions.

Many efforts have been devoted into the exploration of functional connectivity, and significantly altered functional connectivity pattern in AUD patients were found by many researchers. For example, Han et al. have reported in a resting state fMRI study that alcohol addicts showed a wide range of abnormal functional connections including the frontal lobe, anterior cingulate gyrus, bilateral insula, thalamus, precuneus, left caudate nucleus, some temporal and occipital lobes [4]. Compared with the healthy control (HC), AUD group decreased in the right anterior cuneiform lobe and left cerebellar peduncle II area, but increased in the left posterior cingulate gyrus, right middle temporal gyrus, right superior temporal gyrus and right anterior cuneiform lobe area, indicating an abnormal default mode network function (DMN) [5], where was later found to have increased functional connectivity in AUD patients[6]. In addition, AUD patients also exhibited enhanced functional connections in orbitofrontal cortex network, left executive control network, amygdala striatum network, executive control network and visual input network, possibly severed as a neural compensation [7]. In contrast, the functional connectivity of basal ganglia network and primary visual network were significantly reduced in alcohol-addicted patients, and the functional connectivity intensity of executive control network was negatively correlated with the degree of alcohol abuse [8]. However, most of the previous studies that investigating the abnormal pattern in AUD's functional connectivity focused on hypothesis-drive methods based on region of interest (ROI) or independent component analysis (ICA), which only explored limited specific networks seed. Therefore, the complete picture of largescale functional coordination remains unclear.

Recently, resting state functional connectivity density (rsFCD) was proposed to provide a comprehensive analytical method for brain's "scale-free" networks by comparing differences in functional connectivity between the whole brain and the given voxel in a high spatial resolution. During the past few years, FCD mapping has proven to be instructive in diagnosing and providing supplementary evidences for symptom improvement of several psychiatric disorders such as depression and schizophrenia [6, 9, 10], and there were also studies investigating smoking and internet addiction had applied FCD to demonstrate the link between the aberrance in brain functional connectivity and addictive behaviors [11, 12]. Although several FCD researches were conducted on AUD, these studies focused on the early diagnose and assessment [13, 14] instead of probing into the correlation of pathological changes in functional connectivity with the development of AUD.

Since previous mechanistic AUD studies mostly utilized seed-based strategies which are highly depended on the prior selection, the functional connectivity analysis was limited to $\sim 10^2$ surrounded the seed regions [15]. However, as an alternative voxel-wise data-driven method, FCD are capable of identifying functional hubs of human brain and then set them as seeds instead of prior selection, hence are able to measure the functional connections in a "whole brain" range [16]. A higher FCD values of a region indicates a tighter and larger connection with other brain voxels, suggesting the importance of this specific brain region during information processing. In addition, FCD mapping are able to measure local FCD values as well as global FCD values, giving more details in the functional connections of a specific

brain region. Therefore, FCD could provide information about the crucial network hubs when brain undergoes pathological changes in functional and structural, thus is instructive for revealing the correlation between altered FCD values and the pathological mechanisms of AUD.

In the current study, we applied rs-fMRI to compare the functional connectivity alterations in AUD patients using FCD mapping, and investigated its association with symptom severity. 61 AUD patients and 29 matched healthy controls were recruited, with AUD being divided into alcohol-related cognitive impairment (ARCI, $n = 11$) or AUD with non-cognitive impairment group (AUD-NCI, $n = 50$) groups.

2. Materials And Methods

2.1 Sample

This present study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University and complied with the declaration of Helsinki, as revised in 2008, and all participants provided informed written consent before completing the survey.

Individuals with AUD were recruited from a variety of sources including inpatient ward, internet posting, and advertisements. The control participants were volunteers from the local communities.

Inclusion criteria were: (1) meeting the DSM-5 criteria for AUD, based on the clinical assessment of principal investigator; (2) drinking on average more than 14 units of alcohol per week, according to the U.K. Chief Medical Officers[17]. (3) Clinical Institute Withdrawal Assessment-advanced Revised (CIWA-Ar) <9 ; (4) could understand and consent to study procedures.

Primary exclusion criteria for both AUD and healthy controls (HCs) were: (1) having history of addictive, psychiatric, neurological, or physical disorder that could influence brain morphology; (2) having contraindications for magnetic resonance imaging (MRI); (3) reported currently taking centrally active medications.

Demographic and clinical data are shown in Table 1. The sample consisted of 29 HCs, and 61 patients with AUD. We measured cognitive impairment using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). All participants ranged in age from 18 to 65. The HCs were screened using the Structured Clinical Interview (SCID)-non-patient edition[18], and the HCs were confirmed not to have any present or previous mental health problems. All AUD patients were screened using the Alcohol Dependence Scale (ADS), Clinical Institute Withdrawal Assessment-advanced Revised (CIWA-Ar), Visual Analog Scale (VAS), Obsessive Compulsive Drinking Scale (OCDS), Generalized Anxiety Disorder (GAD-7), Patient Health Questionnaire (PHQ-9), Pittsburgh Sleep Quality Index (PSQI).

AUD patients recruited for our study were further divided into alcohol-related cognitive impairment group (ARCI) ($MMSE < 24$ and $MOCA < 26$) and non-cognitive impairment group (AUD-NCI) ($MMSE \geq 24$ and $MOCA \geq 26$) by testing MMSE and MOCA scales[19, 20].

2.2 Neuroimaging Data Acquisition

All MRI images were obtained in SIEMENS 3.0T scanner (MAGNETOM Prisma, SIEMENS, Germany) with a 16-channel head coil at the First Affiliated Hospital of Zhengzhou University. All subjects were requested to keep their eyes closed, and foam padding and earplugs were used to control participants' head movements. At the end of scanning, subjects were also asked if they had fallen asleep during scanning. the rs-fMRI data were obtained using the following parameters: TR =1000ms, TE=30 ms, field of view 220*220 mm², slice thickness 2.2 mm, slice gap 0.4 mm, flip angle 70°, and voxel size 2.0×2.0×2.2 mm³, with 52 slices and 400 dynamics. The slices aligned along the AC-PC line were acquired with a total scan time of 360s.

2.3 Data preprocessing

Functional images were preprocessed following the pipeline of Data Processing Assistant for Resting-State fMRI package (<http://www.restfmri.net>). Main steps included removal of the first 10 volumes, slice timing correction, realignment. Subjects would be excluded if the translational and rotational displacement exceeded 3.0 mm or 3.0°. Images were resampled to 3 mm³ and normalized to the standard EPI template. Smoothing with 6 mm³ full-width at half maximum Gaussian kernel, detrend, filtered with band-pass (0.01-0.1 Hz) and regression of nuisance covariates including Friston 24 motion parameters [21], white matter signal and cerebrospinal fluid signal. Finally, to further excluded the effect of head motion, scrubbing with cubic spline interpolation was used [22]. The 'bad' points were identified with a threshold of frame displacement larger than 0.5 mm as well as one-forward and two-back neighbors [22].

2.4 Calculation of functional connectivity density

As done in the previous study, local, long-range and global FCD maps were calculated [15]. The global FCD of a voxel was defined the number of significant functional connections between it with other voxels in the gray matter. The local FCD was defined as the size of continuous cluster of spatially connected voxels that were significantly correlated with a give voxel [23]. The long-range FCD was obtained by global FCD minus local FCD [23]. A functional connection (Pearson's correlation) was considered significant of its p-value < 0.05 (Bonferroni corrected for voxels across gray matter). FCD maps were further were transformed to z scores by subtracting the mean value and divided by the standard deviation across gray matter voxels in the brain[24].

2.5 Statistical analysis

One-way ANOVA was used to compare (global, local or long-range) FCD maps among the three groups respectively. In this procedure, age and mean FD were included as covariates. Results reported in this study were corrected for multiple comparison (voxel-wise p < 0.001, cluster-level p < 0.05; Gaussian random field (GRF) corrected). Then, we extracted mean FCD values presenting significant difference

among three groups by averaging each peak coordinate with spherical radius of 6 mm. The mean FCD values were compared with each pair of groups by using two-tailed two-sample t-test.

2.6 Association with symptom severity

To investigate the correlation between altered FCD values and symptom severity. Pearson correlations between these altered FCD values (extracted before) and scores of clinical scales were calculated.

3. Results

3.1 Clinical demographics

The clinical demographics of subjects were included in Table 1. The three groups presented no significant difference in age. The details could be seen in Table 1.

Table 1. Demographics of subjects.

	AUD-NCI (n=50)	ARCI (n = 11)	HC (n = 29)	p
Age (year),	46.88 ± 8.95	49.45 ± 7.95	46.44 ± 10.83	0.6700 ^b
ADS	13.62 ± 6.8	11.18 ± 8.75	-	<0.001 ^a
CIWA-Ar	8.42 ± 6.76	4.82 ± 4.49	-	<0.001 ^a
OCDS	14.94 ± 8.67	13.09 ± 7.82	-	<0.001 ^a
VAS	2.16 ± 2.46	2.45 ± 2.77	-	<0.001 ^a
MoCA	27.52 ± 1.39	18.64 ± 3.53	-	<0.001 ^a
PSQI	6.44 ± 3.10	5.36 ± 4.32	-	<0.001 ^a
GAD-7	4.48 ± 4.53	3.73 ± 6.36	-	<0.001 ^a
PHQ-9	5.92 ± 5.22	5.90 ± 7.97	-	<0.001 ^a
MMSE	27.40 ± 1.70	19.91 ± 3.02	-	<0.001 ^a

^a two sample t test; ^b one-way ANOVA; ADS, Alcohol Dependence Scale; CIWA-Ar, Clinical Institute Withdrawal Assessment-advanced Revised; OCDS, Obsessive Compulsive Drinking Scale; VAS, Visual Analog Scale; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index; GAD-7, Generalized Anxiety Disorder; PHQ-9, Patient Health Questionnaire; MMSE, Mini-Mental State Examination.

3.2 Altered FCD in AUD

The three groups presented significant difference in FCD maps (voxel-wise $p < 0.001$, cluster-level $p < 0.05$; GRF corrected). Specially, main effect of global FCD was located in brain regions including left medial frontal gyrus, left parahippocampa gyrus, left inferior occipital lobe and left calcarine (Figure 1). As for local FCD, these three groups exhibited significant difference in brain regions such left parahippocampa gyrus and left lingual (Figure 1). In addition, left medial frontal gyrus presented differences in long-range FCD among these three groups.

Table 2. ANOAV results of FCD.

FCD	Clusters	Voxels	Including regions	Peak MNI (x, y, z)	F
Global	1	59	Medial frontal gyrus	0,66,-6	20.60
	2	54	Left inferior occipital lobe	-21,-87,-3	11.32
	3	43	Left calcarine	-18,-66,3	10.27
			Left parahippocampa gyrus		
Local	1	56	Left parahippocampa gyrus	-21,-51,0	13.20
			Left lingual		
			Left calcarine		
	2	52	Right lingual	12,-69,-3	12.38
Long-range	1	73	Left medial frontal gyrus	0,63,-6	18.86
			Left superior frontal gyrus		
	2	37	VMPFC	6,45,-24	11.64

To further determine the details about FCD aberrance. We extracted the mean FCD values by averaging Z scores of each peak coordinate with spherical radius of 6 mm. Then we compared them between pair of groups by using two-tailed two-sample t-test. The peak MNI coordinates and the results were summarized in Table 3 and Figure 2.

Table 3. Post hoc analysis results. The “*” meant the difference was significant ($p < 0.05$).

FCD	Regions	MNI (x,y,z)	T(AUD-NCI vs. ARCI)	T(AUD-NCI vs. HC)	T(ARCI vs. HC)
Global	Medial frontal gyrus	0,66,-6	-4.34*	-0.74	2.88*
	Left inferior occipital lobe	-21,-87,-3	0.71	-3.68*	-3.11*
	Calcarine	0,-75,6	0.03	-3.18*	-2.23*
Local	Parahippocampa Gyrus	-21,-51,0	-2.32*	-4.89*	-1.51
	Right Lingual	12,-69,-3	-0.08	-3.64*	-2.88*
Long-range	Medial frontal gyrus	0,63,-6	-5.07*	-1.97	1.64
	VMPFC	6,45,-24	-0.99	-4.28*	-2.62*

3.3 Association with clinical symptoms

We found significant association between altered FCD with clinical symptoms (Figure 3). Specifically, the global FCD values in left medial frontal gyrus and that in left inferior occipital lobe were correlated with MMSE ($r = -0.440$, uncorrected $p < 0.001$) and ADS ($r = 0.285$, uncorrected $p = 0.026$) respectively.

4. Discussion

In the current study, we explored local, long-range and global FCD maps which come from healthy controls and patients with AUD, and we extracted mean FCD values presenting significant difference among three groups. Besides, we found main effect of global FCD was located in brain regions and local FCD of three groups exhibited significant difference in brain regions. Through statistical analysis of relevant data, we found significant association between altered FCD with clinical symptoms. Specifically, the global FCD values in left medial frontal gyrus and that in left inferior occipital lobe were correlated with MMSE and ADS respectively, long-range FCD values in left medial frontal gyrus were correlated with MMSE. This suggests that alternations of FCD might be associated with AUD.

Our study finds that the left medial frontal gyrus is significantly deviated among HC, ARCI and AUD-NCI in gFCD, indicating a disrupted function of left hippocampal gyrus. This change in gFCD possibly stems from a significantly lower density of medial frontal gyrus in AUD patients found in a previous finding[25]. Significant differences in left hippocampal gyrus in gFCD and IFCD are also discovered. The aberrant pattern in IFCD reveals an impaired within-region activity, supported by earlier researches find that AUD subjects exhibit a parahippocampal gyrus volume shrinkage and a regional cerebral blood flow decrease[26], together with a prominent loss of white matter[27]. In addition to anatomy, parahippocampal gyrus is also an crucial node linking the default mode network(DMN) and medial temporal lobe[28]. In AUD patients, the effective connectivity within DMN is lower than HC[29], thus impaired parahippocampal gyrus might associate with this contraction in connectivity. Current study also

recognizes a significant difference in VMPFC's long-range FCD, representing a disrupted functional connectivity between VMPFC and other brain regions. This change accords with general ideas that VMPFC is blunt towards stress in AUD patients[30, 31]. Moreover, left inferior occipital lobe and left calcarine also present significant gFCD differences, and right lingual as well regarding to IFCD. These three regions all contribute to the visual information processing, while visual processing deficits is a common symptom for AUD patients[32]. The volume of gray matter in left occipital lobe in AUD subjects have been found significantly decreased, which might be a casual factor of impairment[33].

The post-hoc analysis results among HC, ARCI and AUD-NCI reveal more details. Left inferior occipital lobe, calcarine, right Lingual and VMPFC all exhibit significant differences between HC and both AUD groups, but no significance between AUD groups. As for left inferior occipital lobe and calcarine, AUD groups show significant decreases in gFCD than HC. The right lingual's IFCD and VMPFC's long-range FCD present a similar pattern with higher activity in HC. Since left inferior occipital lobe, calcarine and right lingual all play roles in visual information processing, this indifference might imply a visual processing deficit in AUD regardless of cognitive state. The decreased long-range FCD in VMPFC is consistent with the consensus that VMPFC is hypo-activated in AUD patients[34]. Moreover, this decrease in VMPFC connectivity can also be found in other substance use disorders(SUD) like cocaine addiction[35]. It is intriguing to posit that this decreased activity in VMPFC might be a prevalence phenomenon in SUD. In terms of medial frontal gyrus, there is no significance between AUD-NCI and HC, but ARCI's gFCD is significantly higher compared to both AUD-NCI and HC. Medial frontal gyrus participate in cognition, assisting high-level executive functions and decision-related process[36]. This increased connectivity is in consonance with an earlier study on mild cognitive impairment (MCI), proposed that HC contains a negative functional connectivity peak in medial frontal gyrus, while MCI patients peak in opposite direction[37]. However, it is unusual that significance exists in NCI-ARCI and NCI-HC for parahippocampal gyrus, probably suggesting a compromise between parahippocampal gyrus function and cognitive impairment in AUD population, namely AUD without CI might suffer more severe disruption in parahippocampal gyrus activity than ARCI.

The results of pearson correlations showed that gFCD values in the left medial frontal gyrus was negatively correlated with MMSE scores in AUD groups, namely a higher gFCD indicates a more severe cognitive impairment. Current study clarifies that ARCI group has higher gFCD values in left medial frontal gyrus than AUD-NCI group, consistent with the division of AUD subgroups. This abnormally increased activity in left medial frontal gyrus is not limited to AUD patients, but also exists in Alzheimer's and MCI patients during working memory tasks[38], probably stems from an increased fiber density between medial frontal gyrus and superior frontal gyrus[39]. However, AUD-NCI group has significantly smaller gFCD values than the ARCI group, in consensus with the previous finding that the gray matter volume in left medial frontal gyrus is decreased in AUD patients[40]. The contradiction between AUD-NCI and ARCI group possibly suggesting different pathological mechanisms. The variance between the two AUD groups was also seen in the left inferior occipital lobe. The Pearson correlation demonstrates that left inferior occipital lobe gFCD values are positively correlates with ADS scores, meaning the AUD-NCI group with lower gFCD values has a lighter dependence on alcohol. According to Yang et al., the

shrinkage in the gray matter volume of medial frontal gyrus is positively associated with the heavier alcohol consumption[40]. Together with the results of current study, it is intriguing to hypothesize that although ARCI have more severe damage in cognitive abilities, as a compensate, ARCI patients have less alcohol dependence and hence less impairment in the left medial frontal gyrus gray matter. In addition, although we didn't take the ADS score of HC, HC has the highest gFCD in left inferior occipital lobe, which means the correlation between ADS and gFCD in left inferior occipital lobe cannot fit in HC. These alterations in mechanisms between HC and AUD indicating an unseen functional role played by left inferior occipital lobe, which needs further explorations in future studies.

Nevertheless, some limitations still exist in current study. First of all, the sample size of current study is not adequate, future studies with an enlarged subjects number are required to assess whether the results are reproducible in large clinical population. In addition, the significant difference between subject groups damaged the reliability of results and needs to be balanced in future studies for unbiased results. Besides, we didn't record the MMSE and ADS scores of HC, nor did we calculate the Pearson correlation for each subjects group, thus it is uncertain that if the correlation between clinical symptoms and FCD in specific brain regions is specific towards AUD patients or universal in all populations. It is also notable that we didn't identify whether the altered FCD pattern found in AUD patients is a consequence of alcohol addiction or indicating as an addiction risk factor. Future studies that exploring the casual relationships between this abnormal FCD pattern and AUD are required to elucidate the role of altered FCD. Furthermore, longitude studies that explore the correlation between the deviation of FCD from HC and the length of the course of AUD, and dynamic FCD under tasks should be involved in future investigation instead of stationary FCD order to promote the validity in real-life activities.

5. Conclusion

In conclusion, in this FCD study, AUD patients were found to significantly altered in the rs FCD in AUD patients with or without cognitive impairment compared to healthy controls AUD patients suffered from a significant decrease in whole-brain functional connectivity in left medial frontal gyrus, the left parahippocampa gyrus, the left inferior occipital lobe and the left cerebellum. Besides, the functional connectivity within the left parahippocampa gyrus and the right lingual gyrus are damaged in AUD patients as well. In addition, these alterations are associated with clinical symptoms of AUD patients, with more severely impaired brain region contributing to higher alcohol dependency or lower cognitive ability. These abnormal patterns in FCD provide evidence for the potential neurological mechanisms contributing to AUD, indicate that different AUD subgroups have distinct pathological pathways, and assist further understanding towards the brain network activities in AUD patients.

Abbreviations

AUD, alcohol use disorders; FCD, functional connectivity density; rs-fMRI, resting state functional MRI; gFCD, global FCD; lFCD, local FCD; lrfCD, long-range FCD; HC, healthy controls; ARCI, alcohol-related cognitive impairment group; AUD-NCI, non-cognitive impairment group; DMN, default mode network

function; ROI, region of interest; ICA, independent component analysis; rsFCD, resting state functional connectivity density; CIWA-Ar, Clinical Institute Withdrawal Assessment-advanced Revised; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SCID, Structured Clinical Interview; ADS, Alcohol Dependence Scale; VAS, Visual Analog Scale; OCDs, Obsessive Compulsive Drinking Scale; GAD-7, Generalized Anxiety Disorder; PHQ-9, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; GRF, Gaussian random field; SUD, substance use disorders; MCI, mild cognitive impairment;

Declarations

Ethics approval and consent to participate

This present study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2018-KY-91) and complied with the declaration of Helsinki, as revised in 2008, and all participants provided informed written consent before completing the survey.

Consent for publication

1. We have obtained the informed consent for publication from subjects. 2. All of the authors agreed to publish this manuscript.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YJJ designed and supervised all aspects of the study including the fMRI protocol, fMRI data processing and analysis and drafted the manuscript and subsequent revisions. RRD conducted all the fMRI data analysis and drafted the manuscript, created all tables and figures, and assisted with manuscript preparation and revision. YFL, LJJ, ZG, YBY, YZS and YJS assisted in data analysis and revised the manuscript. WJW, YZ, JLC, XFZ, YP provided guidance on study design and analysis, assisted with the fMRI acquisition protocol, and reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Altered FCD among the three groups (ANOVA results).

Figure 2

Post hoc analysis results.

Figure 3

The association between altered FCD with clinical symptoms.