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Inferior Frontal-Occipital Fasciculus (IFOF) is the Main Neural Pathway in Psychotic Symptoms induced by Methamphetamine Abuse: A Tract-based Spatial Statistics Study

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Abstract

Background: *Chronic methamphetamine abuse can lead to white matter changes and increased levels of psychotic symptoms. This study aimed to investigate which neural pathway is most associated with the psychological symptoms of chronic Methamphetamine abuse.*

Methods: *We recruited 42 chronic methamphetamine abuse subjects meeting DSM-5 criteria and 21 healthy controls. Psychotic signs were measured using the positive and negative syndrome scale (PANSS). We applied tract-based spatial statistics (TBSS) to investigate group differences in alteration DTI parameters and their association with psychotic symptoms.*

Results: *Chronic methamphetamine abuse group had significantly lower FA and higher AD, RD, and MD in a wide range of white matter mainly IFOF, and subjects in the methamphetamine abuse group had significantly higher PANSS total scores when compared to the control group.*

Conclusions: *Chronic methamphetamine abuse shows subtle patterns of impaired white matter integrity of distinct cerebral nerve pathways, mainly IFOF relative to controls. The results are further suggested that neuronal tract-based pathology plays the main role in psychotic symptoms in methamphetamine abuse disorders.*

Keywords: Methamphetamine, Psychotic symptoms, Tract-Based spatial statistics (TBSS), Inferior frontal-occipital fasciculus (IFOF).
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Introduction

Methamphetamine (METH) is an attractive drug of abuse with easy availability because of the inexpensive production and distribution of the drug in various communities.[1] Methamphetamine increases activation of the dopamine, norepinephrine, and serotonin systems. METH use causes the release of dopamine into the synaptic cleft, increasing dopamine concentration.[2] Early research into the METH syndrome has identified delusions and hallucinations as core components of the symptom profile, which are often accompanied by affective symptoms (anxiety, depression, and hostility) and to a lesser extent disorganized psychotic symptoms (defined as fragmentations in logical and goal-directed capacities for speech, thought, affect, or movement).[3] In some study METH addicts exhibit a globally diminished white matter integrity includes lower FA, and higher AD, RD, and MD in a wide range of white matter, which mainly included corona radiata, internal capsule, superior longitudinal fasciculus, external capsule, inferior frontal-occipital fascicules, posterior thalamic radiation, sagittal stratum, fornix and stria terminalis, cerebral peduncle, superior cerebellar peduncle, corpus callosum, and corticospinal,[4] but it is not clear which nerve pathway is most associated with psychological disorders.

Some studies have shown that nerve pathway destruction can play a role in the development of disorders caused by psychological stimuli and stimulant dependence was related to FA disturbances within tracts consistent with a role in addiction. The multivariate pattern of white matter differences proved sufficient to identify individuals with stimulant dependence, particularly for cocaine and methamphetamine and these findings confirm that nerve stimulants can produce unique destructive changes in district neural pathways.[5] In multimodal imaging study show that broadly, corticolimbic brain areas (incorporating dorsolateral prefrontal cortex, anterior cingulate cortex, dorsal and ventral striatum, hippocampus, insular cortex, cerebellum, and brainstem neuromodulatory dopaminergic and glutamatergic systems) disruption, with implications for cognitive deficits in working memory, response inhibition, delay discounting, decision-making, dysfunctional interoceptive awareness, altered reward, and emotion processing.[6]

The inferior frontal-occipital fasciculus (IFOF) is a large white matter tract that originates in the occipital and parietal lobes and terminates in the inferior frontal lobe. This white matter tract courses, along with the uncinate fasciculus, adjacent to the inferolateral insula via the extreme and external capsules. While its role is primarily associated with semantic language processing and transmission, other studies have demonstrated that the IFOF connects the salience network to the executive control network, thus potentially playing an important role in goal-oriented behavior.[7] DT-MRI tractography was used to study frontotemporal fasciculi (the superior longitudinal fasciculus, the uncinate fasciculus, the inferior frontal-occipital fasciculus, and the cingulum) in subjects with schizophrenia and subjects with late-onset schizophrenia-like psychosis reduced anisotropy in left-hemispheric frontotemporal fasciculi in schizophrenia, which is not mirrored in late-onset schizophrenia-like psychosis.[8]

Structural alterations of the IFOF correlate with patients' semantic processing impairments in schizophrenia spectrum disorders and functional disruption of the IFOF may well participate in verbal semantic processing disturbances; inhibitory electrical stimulation of the IFOF during awake surgery induces semantic disturbances and reduced integrity of the left IFOF was found to correlate with subjects' semantic performance in healthy elderly as well as brain-injured individuals.[9] First-episode schizophrenia shares similar brain abnormalities with chronic schizophrenia; patients showed significantly decreased volume of left temporal lobe and disarray of all major white matter tracts. Disorganization implies gray and white matter disruption of the left cerebellum; negative symptoms were inversely related to white matter disarray of the major cortico-cortical association tracts, bilaterally. Impairment in social cognition is related to gray and white matter abnormalities of right temporal-occipital regions. Reduced speed of processing and visual memory is related to WM disarray of frontotemporal tracts.[10]

Diffusion tensor imaging is the only non-invasive method to measure the microstructural integrity of brain tissue by detecting the diffusion of water molecules in it. Fractional anisotropy, MD, AD, and RD are four common indicators. Changes in the properties of DTI may be the potential mechanism of WMH-related MCI, especially the right IFOF and the right ILF, which may become imaging markers for predicting WMH-related cognitive dysfunction.[11]

The present study evaluated the correlation between the incidence and severity of psychological symptoms and the degeneration of main nerve pathways in the brain of people with methamphetamine abuse.

Based on the findings of previous studies and the design of the present study, which is a TBSS DTI analysis, we investigate the destruction of distinct neural pathways, mainly IFOF, to play a significant role in the development of psychological disorders in people with methamphetamine abuse compared to controls.

Materials and Methods

This study was designed and conducted in October 2019 at Shahroud university of medical sciences. 42 methamphetamine abusers and 21 healthy individuals with DSM-5 criteria[12] with the help of MMT centers in Shahroud university of medical sciences were selected by advertisement and from all of them, a voluntary participation consent form was obtained in this project. Inclusion criteria in this study include age 20 to 50 years, continuous use of methamphetamine for at least 5 years, diagnosis of methamphetamine use according to a structured clinical interview for DSM-5 and no use of drugs or herbal medicines that affect the brain. Exclusion criteria in this study include having a systemic illness or psychiatric disorders not related to current or past drugs; Severe liver, respiratory, kidney, endocrine, AIDS or loss of consciousness for 30 minutes or more, medical disorder, neurological, or significant current or past trauma affecting the brain (cerebrovascular disease or seizures). All patients were evaluated by a psychiatrist by PANSS test[13] and the total scores and the level of disorders and scores of each of the scales of negative, positive, and general symptoms were determined and recorded.

Data acquisition of this study was performed using a 1.5 Tesla Siemens (AVANTO) scanner in Imam Hossein hospital in Shahroud university of medical sciences. Written consent was obtained from all participants in the study for imaging. The data obtained consisted of two parts, the first part was high resolution structural or anatomical images using MPRAGE protocol and the second part was raw images with diffuse weight (DWI).

Parameters related to T1 images are repeat time (TR) of 2200 milliseconds, echo time (TE) of 2.82 milliseconds, screen resolution about one millimeter by one millimeter, the field of view (FOV) of 250 by 250 millimeters, the matrix size of 256 by 256 and the thickness of the slices of 1 mm.

Parameters related to DWI images also include repeat time of 12-seconds, echo time of 108-millisecond, 2000 b-value per square millimeter, 30-direction gradient vector orientation, screen resolution of about 1.6 mm by 1.6 mm, the slices thickness of 2 mm, the field of view of 20 by 20 square centimeters and the matrix size of 128 by 128.

Image analysis in this study was performed according to ENIGMA protocol[14] and TBSS[15] method. In T1 images, elimination of the destructive effects of eddy currents, correction of sample head motion on DWI images in FSL software environment, data preprocessing and then preprocessed DWI images on T1 images in linear data matching were performed.

After that, the quantification of the desired parameters including FA, MD, RD, and AD for each individual, was extracted, then different stages of the TBSS technique according to the standards and values defined by ENIGMA protocol and based on Atlas[16] the-White Matter 1 mm was performed and finally, the values of FA, MD, RD and AD quantities in different areas of white matter were calculated according to the mentioned atlas and their values were recorded in the final report table. Metadata analysis with SPSS statistical software (version 24) was used to examine the data statistics. Because the number of studied samples is more than 30 samples, according to the central limit theorem in the statistics, parametric tests were used to measure the data. Data were used between two healthy groups and the group with substance abuse. An independent t-test was used with a Pvalue less than 0.05. Pearson statistical test was also used to examine the correlation of data between the studied variables.

Results

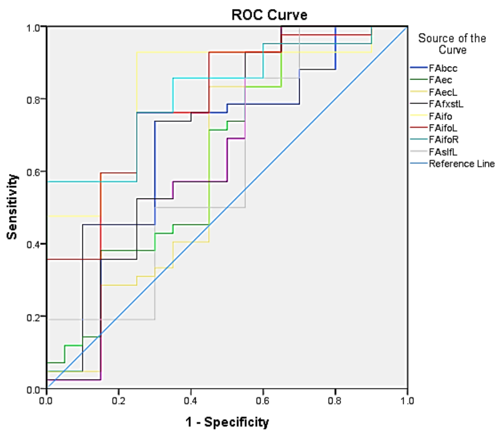
Table1 shows the demographic characteristics of the study participants (42 people with methamphetamine abuse and 21 controls (healthy).

This diffuse weighted imaging (DTI) study was performed on TBSS based white matter integration and its association with psychological symptoms and showed two main findings in the group of addicts. (A) Subjects with methamphetamine abuse had significantly lower FA and higher AD, RD, and MD in a wide range of white matter. (B) Also, individuals in the methamphetamine abuse group had a significantly higher total PANSS score compared to the control group (Table 1).

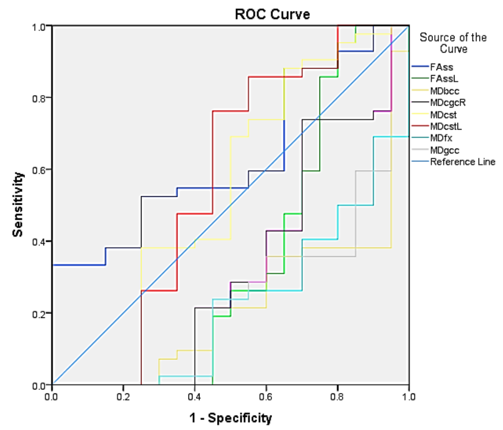
Figure 1 shows the sensitivity and specificity of diffusion parameters between different neural pathways analyzed by TBSS. FA in IFOF is the main neuronal pathway in methamphetamine abuse compared to the healthy subjects. According to the results of the ROC curve shown in figure 1(A, B, C, D), the highest accuracy, sensitivity, and specificity for identifying addicts people from healthy individuals are related to the variables that are highlighted.

Table1. The demographic characteristics of the study participants

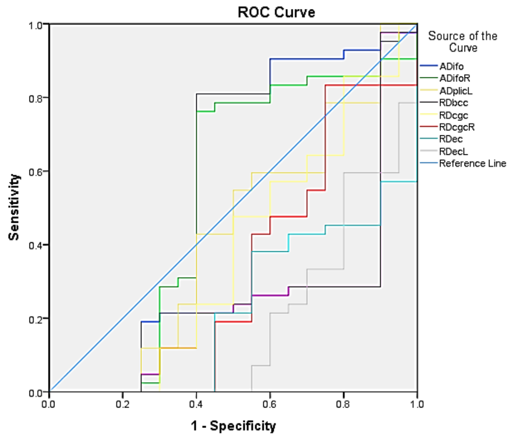
	Addict (N=42)				Normal (N=20)			
	Mean	SD	Min	Max	Mean	SD	Min	Max
Age	38.80	8.106	27	59	39.80	12.76	23	67
Dose	0.2940	0.527	0.20	2	-	-	-	-
Abuse Duration	7.78	2.30	4	15	-	-	-	-
Positive	27.42	7.55	10	40	-	-	-	-
Negative	29.28	7.54	14	43	-	-	-	-
General	58.85	13.37	32	86	-	-	-	-
Total	114.380	20.92	75	165	-	-	-	-
Age of onset	31	8.21	18	52	-	-	-	-
Education	1.26	1.03	1	4	1.90	0.640	1	3

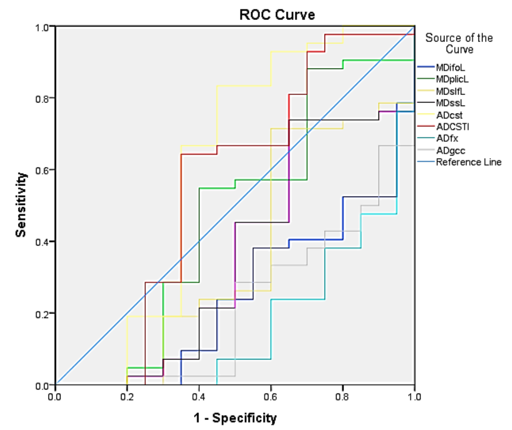


A



B





C

Figure 1. The results of the ROC curves

Table 2 shows the accuracy, sensitivity, and specificity of diffusion parameters between different neural pathways analyzed by TBSS. It is observed that IFO shows the highest sensitivity and specificity among all neural pathways to reduce FA and can be considered as an anatomical biomarker in methamphetamine abuse.

Table 2. The accuracy, sensitivity, and specificity of diffusion parameters between different neural pathways were analyzed by TBSS

	Accuracy	Sensitivity	Specificity
FAbcc	%69	%71	%70
FAec	%64	%61	%55
FAecL	%62	%81	%55
FAfxstL	%65	%85	%45
FAifo	%83	%90	%75
FAifoL	%79	%92	%55
FAifoR	%81	%81	%65
FAslfL	%61	%71	%45
FAss	%63	%71	%45
FAssL	%34	%57	%30
MDbcc	%22	%35	%30
MDcgcR	%32	%31	%40
MDcst	%53	%71	%45
MDcstL	%56	%85	%45
MDfx	%22	%11	%55
MDgcc	%24	%35	%40
MDifoL	%47	%38	%45
MDplicL	%36	%54	%50
MDslfL	%36	%71	%40
MDssL	%60	%45	%45
ADcst	%55	%83	%55
ADCSTl	%17	%64	%55
ADfx	%22	%23	%40
ADgcc	%56	%33	%40
ADifo	%53	%81	%60
ADifoR	%43	%76	%60
ADplicL	%24	%42	%60
RDbcc	%38	%21	%50
RDcgc	%32	%47	%50
RDcgcR	%22	%42	%45
RDec	%18	%35	%45
RDecL	%31	%31	%30
RDedR	%15	%40	%55
RDfx	%24	%28	%25
RDfxstL	%11	%38	%35
RDifo	%11	%19	%25
RDifoL	%10	%16	%25
RDigoR	%15	%23	%25
RDslfL	%18	%35	%25

Discussion

The findings of the present study using TBSS DTI analysis showed that there are subtle microstructural changes in a wide range of neural tracts in subjects with methamphetamine abuse that does not appear in routine imaging studies. We examined specific tracts such as IFOF and coloration with symptoms severity in methamphetamine abusers. Major changes in FA reduction in the IFOF neural tract and several other tracts were seen in individuals with methamphetamine abuse compared to controls, which was consistent with our initial hypothesis (Table 2).

According to a study by Mr. Conner and colleagues, IFOF is a large and complex white matter tract connecting the parietal and occipital lobes to the frontal lobe via its complex route lateral to the insula. It plays a critical role in semantic language processing, goal-oriented behavior, and visual switching tasks.[7] As supported by multiple other studies, Rollans and colleagues demonstrate that the IFOF more or less begins in the parietal and occipital lobes, traverses anteriorly lateral to the insula via the extreme and external capsule, and terminates in the inferior frontal lobe along the opercular gyri. Given this anatomic course, it can be hypothesized that the IFOF might play an important role in language processing and transmission.[17] While the IFOF is thought to be a key contributor to the language network, others have described the tract’s role in the visual recognition system. This idea likely stems from the tract’s anatomic terminations in the occipital lobe, along with the theory of the dual-stream model of speech and language processing.[18]

Rigucci studies demonstrate IFOF degeneration has also been demonstrated in patients with neuropsychological behavioral disorders, including antisocial personality disorder and obsessive-compulsive disorder and progressive supranuclear palsy has also been shown to correlate with IFOF degeneration.[10]

DT-MRI tractography was used to study frontotemporal fasciculi (the superior longitudinal fasciculus, the uncinate fasciculus, the inferior frontal-occipital fasciculus, and the cingulum) in subjects with schizophrenia and subjects with late-onset schizophrenia-like psychosis reduced anisotropy in left-hemispheric frontotemporal fasciculi in schizophrenia, which is not mirrored in late-onset schizophrenia-like psychosis[8] and Structural alterations of the IFOF correlate with patients' semantic processing impairments in schizophrenia spectrum disorders.[9]

Functional disruption of the IFOF may well participate in verbal semantic processing disturbances: inhibitory electrical stimulation of the IFOF during awake surgery induces semantic disturbances and reduced integrity of the left IFOF was found to correlate with subjects' semantic performance in healthy elderly as well as brain-injured individuals.[19]

Rigucci and colleagues showed how the structural development of key brain regions is related to neuropsychopathological dysfunction in first-episode schizophrenia, consistently with a neurodevelopmentally derived misconnection syndrome.[10] The other study demonstrates how changes in the properties of DTI may be the potential mechanism of WMH-related cognitive dysfunction, especially the right IFOF and the right ILF, which may become imaging markers for predicting WMH-related cognitive dysfunction(20). Besides, many studies have confirmed the relationship between the integrity of ILF/IFOF and multiple cognitive functions including memory, reading, attention, and visual processing.[20]

The IFOF role seems to be primarily associated with semantic language processing and transmission but some authors have described that the IFOF connects the salience network to the executive control network, thus potentially playing an important role in goal-oriented behavior[7] and recent publications report high rates of learning and memory impairment after insula glioma surgery, probably due to the IFOF damage suggesting its role also in memory.[21]

According to the present reported studies, IFOF can be named as one of the main neural pathways in psychotic disorders and a wide range of brain dysfunction.

The present study, according to table 3, shows that the IFOF between the methamphetamine group and the healthy group has the highest reduction in FA and the highest sensitivity and specificity. These findings confirm that the reduction in integrity in IOFO can be considered a microstructural biomarker in assessing the psychological effects of methamphetamine abuse.

It was found that measuring the microstructural parameters of diffusion tensor imaging mainly, FA in different neural pathways and especially IFOF can be useful as a microstructural biomarker in the study of psychiatric disorders derived by methamphetamine abuse. Study with a larger sample size and integration with functional connectivity assessment methods such as rest-fMRI may be helpful in future studies.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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