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Multi-Region Neurodegenerative Changes in Methamphetamine Dependence Reveal by Magnetic Resonance Spectroscopy: A Psychological Aspects

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Abstract

Background: *Methamphetamine (METH) is an illicit psychostimulant that is widely abused in the world. Several lines of evidence suggest that chronic METH abuse leads to neurodegenerative changes in the human brain. These include damage to dopamine and serotonin axons, loss of gray matter accompanied by hypertrophy of the white matter, and microgliosis in different brain areas.*

Methods: *Magnetic resonance spectroscopy measures of N-acetyl aspartate (NAA), Creatine (Cre), Choline (Cho), Myo-inositol (Ml), were obtained in the dopamine circuit (Ventral Tegmental Area, Nucleus Accumbens, Substantia nigra, Striatum, Frontal Cortex, Hippocampus) of the brain in participants in 30 abstinent methamphetamine-addicted people with psychosis (METHp+), and 10 healthy controls (HCs) (age ranges of 18 to 50 years old). Psychotic symptoms were assessed with the positive and negative Syndrome scale (PANSS) and analyzed using a five-factor model. All participants were also assessed for physical and mental illnesses as well as recent substance use.*

Results: *The METHp+group displayed robust alteration in basic metabolite concentration levels (NAA, cho, Cr, mI, and GLX) relative to HCs. This suggests that cellular metabolism is altered in both conditions but in METHp+group is seeing more dramatic changes. Significant decrease in the concentration of NAA metabolites (mean of 18.56) in the methamphetamine group with high psychological symptoms (mean of 111.9) in the studied areas compared to the control group which is a neurotransmitter and biomarker, indicates chronic neurological degeneration in the test areas and its relationship with the incidence of mental disorders in these individuals (Pvalue<0.01).*

Conclusions: *These data support the assumption that cellular abnormalities differ between methamphetamine addiction psychosis and healthy controls people despite not different in normal imaging acquisition.*

Keywords: Methamphetamine, Abstinence, Neurodegeneration, Magnetic resonance spectroscopy, Dopamine circuit.
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Introduction

Methamphetamine (METH) abuse is a disorder characterized by compulsive METH-craving and consumption despite an apparent awareness of serious negative consequences.[1] METH use has been linked to the emergence of psychotic symptoms as well as morphological, functional, and neurochemical abnormalities in multiple brain regions.[2] Multiple lines of preclinical evidence suggest that chronic methamphetamine use may cause a series of cellular effects that are local to dopamine and serotonin synapses, and eventually, lead to neurotoxic damages resulting from the pathological mechanisms that include oxidative stress and mitochondrial dysfunction.[3] These cellular changes may be associated with macroscopic structural abnormalities of both cortical and subcortical brain regions in methamphetamine-dependent subjects.[4] Acute administration of MA increases extracellular DA levels via the reverse transport of DA and also by the displacement of DA from vesicular stores.[5] The displaced monoamine is then oxidized and converted to reactive oxygen species which ultimately contribute to necrotic cell death.[6] The lipophilic nature of MA allows it to penetrate cellular membranes and disrupt the electrochemical gradient of key organelles such as mitochondria resulting in neurotoxicity driven by apoptosis.[7] The monoamines released due to the presence of methamphetamine act on the major dopaminergic, noradrenergic, and serotonergic pathways of the brain. In the case of dopamine, methamphetamine activates the mesolimbic, mesocortical circuit, and the nigrostriatal pathways, which have been related to the euphoric effects observed immediately after the ingestion of the drug.[8] Due to its structural similarity, methamphetamine substitutes for the dopamine transporter (DAT), noradrenaline transporter (NET), serotonin transporter (SERT), and vesicular monoamine transporter-2 (VMAT-2) and reverses their endogenous function, thereby redistributing monoamines from storage vesicles into the cytosol.[9] This process results in the release of dopamine, noradrenaline, and serotonin into the synapse, which then stimulates postsynaptic monoamine receptors.[10] Methamphetamine also attenuates the metabolism of monoamines by inhibiting monoamine oxidase further enabling the buildup of excess monoamines in the synapse.[11] Human positron emission tomography (PET) studies have reported a significant reduction of dopamine transporter density in methamphetamine users and that the reduction observed in methamphetamine users is associated with psychomotor impairment. Recently, we have also found that the dopamine transporter density in methamphetamine users is inversely related to the length of methamphetamine use and the magnitude of psychiatric symptoms, including psychotic symptoms.[12] In addition, it has been hypothesized that brain damage resulting from methamphetamine abuse outlives the duration of drug use and can be documented objectively by structural and chemical changes in abstinent methamphetamine-dependent subjects. Specifically, enlarged brain volume was observed in recently abstinent (4 months) methamphetamine users and relatively normal volume with

longer than 20 months of abstinence.[13] MRS of N-acetylaspartate (NAA), an axonal marker in white matter and a neuronal marker in gray matter, indicates a significant decrease in NAA levels in abstinent methamphetamine-dependent subjects whose abstinence periods were between 8 to 20 weeks, consistent with neuronal and/or axonal damage which lasts beyond the immediate period of drug abuse. Furthermore, reduction of Glx (glutamine plus glutamate), in the frontal brain was observed in early abstinent methamphetamine users, followed by relatively normal Glx concentration after 2 months of abstinent. Structural abnormalities in the corpus callosum were also observed in methamphetamine abusers who were abstinent for a longer time (mean=21 months). White matter abnormalities in amphetamine abusers have now been reported more often than gray matter abnormalities. A single MRI session can incorporate several sequences that assess several tissue parameters (volumes of gray and white matter, T1, T2, DTI, iron measures, etc), and also collect functional information.[14] Exploration of such multimodal datasets will increase our understanding of both the underlying pathophysiology and the techniques themselves.[15] Understanding of the technical aspects of brain imaging tools that we use on clinical patients must progress towards increasing the specificity of measures or combinations of measures to further the twin goals of using brain imaging to inform both medication development and clinical decision making.[6,7] The psychiatric research interview for substance and mental disorders (PRISM), which employs the diagnostic and statistical manual of mental disorders (DSM-IV) criteria for psychotic disorders, was utilized to discriminate between substance-induced and primary psychosis. Of note, a diagnosis of primary psychosis was made if there was "no evidence of heavy substance uses or withdrawal, when psychotic symptoms persisted for at least 4 weeks in the absence of heavy substance use, or when psychotic symptoms preceded the onset of heavy use". Parental substance abuse, drug dependence (rather than abuse or use), and visual hallucinations were predictive of a substance-induced psychosis. Additionally, persons with substance-induced psychosis had lower positive and negative syndrome scale (PANSS) scores, greater awareness of psychotic symptoms, and were more likely to have suicidal ideation.[16] Clinical symptoms of MA-induced psychosis include paranoia, delusions, and hallucinations. Psychosis occurs at least intermittently in a significant proportion of MA users, with wide variation in the severity and clinical course of symptoms.[17] Methamphetamine-associated psychiatric impairment may occur in several domains of cognitive, intellectual, or affective. Psychiatric impairment appears to correlate with duration of use as well as total and peak amounts of MA absorbed. Neurocognitive deficits associated with chronic MA use include impairments in episodic memory, executive functions, and psychomotor tasks related to frontostriatal and limbic circuits. Methamphetamine use may also be associated with deficits in attention, memory, and language. Neurocognitive impairment may persist for nine months or longer following cessation of MA use, but a recovery in dopamine transporter activity and improvement in cognitive functioning is possible with sustained abstinence.[18,19,20] Psychiatric symptoms have been well-documented in MA users. Anxiety, depression, insomnia, and psychosis are among the most commonly reported symptoms associated with MA dependence, and individuals presenting to the emergency department in the context of MA intoxication may be agitated, violent, or suicidal.[21] Hydrogen 1 (1H) MR spectroscopy is complementary to MR imaging and adds clinically relevant information about metabolites in common brain abnormalities. Also, NAA levels may reflect mitochondrial (dys) function. Elevated mIns is generally considered a marker for gliosis. High tCho may be a marker for cellular proliferation, increased membrane turnover, or inflammation. Elevated Lac is indicative of anaerobic glycolysis and may be considered an unspecific MR spectroscopy biomarker for several abnormalities.[22] Conventional MR imaging is not able to depict changes in cell density, cell type, or biochemical composition—all of which can be investigated with MR spectroscopy.[23] Furthermore, lesions of different underlying pathophysiology often manifest with a similar MR imaging appearance. Accordingly, MR imaging and MR spectroscopy are complementary tools for diagnosing disease and monitoring disease progression and response to therapy. MR imaging alone cannot provide the answer to many important clinical questions.[24] These include differentiating tumor from other focal lesions (giant demyelinating plaques, encephalitis), obtaining a definitive diagnosis of atypical ring-enhancing focal lesions (i.e. high-grade gliomas, metastasis, lymphoma, and abscess), identifying the optimal biopsy sites in heterogeneous gliomas, monitoring the response to treatment, and differentiating between treatment-induced changes and recurrent tumor.[22,23,25] MR spectroscopy can provide information in all of these key clinical areas, and it is increasingly being used as an adjunct to MR imaging.[21]

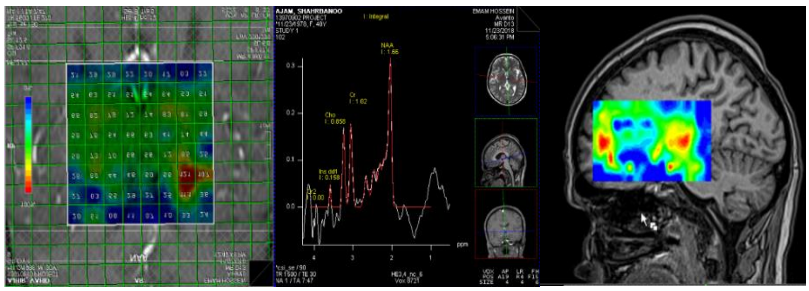
Materials and Methods

Participants were selected from among healthy subjects without a history of cerebrovascular and psychiatric illnesses, as well as methamphetamine users with the help of Shahroud university of medical sciences drug abuse collaboration team, considering the entry conditions (table 1). Written consent was obtained from all participants before the study began.

Proton MRS imaging (MRSI), the multivoxel version of MRS, and prescriptive structural MRI were acquired together in a single session. In addition to MRSI, scanning sequences included a localizer scout and a high-resolution T1-weighted whole-brain MRI. MRSI spectra of the dopamine circuit (VTA, NAc, Substantia nigra, Striatum, Frontal cortex, Hippocampus) acquired on a 1.5 T Siemens (Avanto, Imam Hossein hospital in Shahroud university of medical sciences) using standard head coil (18 channel) with the following parameters: High resolution T1 image (MPRAGE) measured with parameters (TR=1500, TE=1.53.3.21.4.89.6.57 ms) (FA=7) (FOV=256 mm), cross-sectional thickness of 1 mm 160 slice and scan time of 10 minutes. Then 3DCSI imaging acquired with parameters TE=30, TR=1500, with NEX=2, FOV=160.160.160, VOI=100.50.80, sectional thickness equal to 15 mm. CHESS automatic pulse twice with two TE and two VOIs took place in 15 minutes. Analysis using the console Siemens syngo software was done by measuring the curvature of the NAA, cho, Cr, mI, with two VOIs (including 5 anatomical regions) with two TE high and short, and after obtaining the corresponding curve. The spectrum of metabolites was presented to the radiologist with experience in the field of spectroscopy for interpretation (figure 1).

Table 1. Demographic data of participants and scores of PANSS in METH users group

	Abstinent methamphetamine-dependent (n=30)	Controls (n=10)
Age (years)	35.0±15	35±15
Gender (female/male)	10/20	5/5
Total meth used (gr)	2±2	
Duration of abstinence	4±3	
Total PANSS	80±70	



Figurer 1. MRSI spectra extracted using spectroscopic evaluation software (syngo simens) and concentrations of metabolites were extracted in the regions of interest using statistical analysis

For comparison of the mean values of the metabolite ratios between methamphetamine users and comparison subjects, the Student's t -test was used. Correlations between the metabolite ratios and each of the clinical parameters, including the duration of methamphetamine use, duration of the abstinence, and panss score, were evaluated using Pearson's correlation coefficient. Statistical significance was set at 0.05. We measured metabolite ratios in the dopamine circuit (ventral tegmental area, nucleus accumbens, substantia nigra, striatum, frontal cortex, and hippocampus). To avoid such errors, we used repeated measures analysis of variance (ANOVA) in which repeated measures were the left and right metabolite ratios.

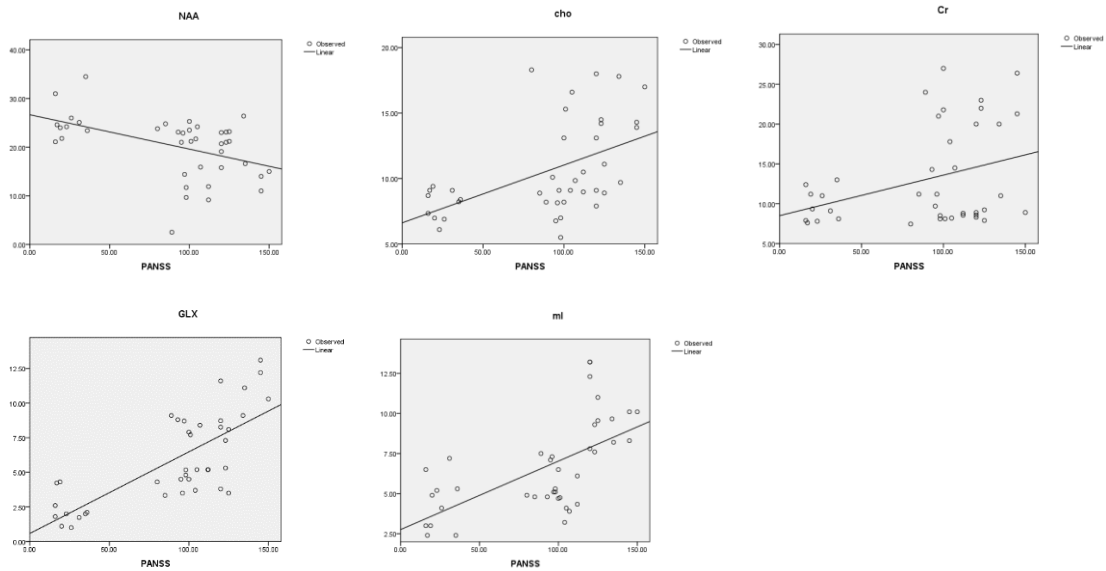
Results

Statistical analysis revealed significant relationship between the mean concentration of brain metabolites in the studied areas and the incidence of psychological disorders between the control group and methamphetamine dependence group.

Significant decrease in the concentration of NAA metabolites in the methamphetamine group with high psychological symptoms (Figurer 2) (PANSS) in the studied areas compared to the control group, which is a neurotransmitter and biomarker, indicates chronic neurological degeneration in the test areas and its relationship with the incidence of mental disorders in these individuals (Pvalue<0.01). Changes in the concentration of choline metabolite representing cell membrane changes are associated with a degree of mental disorder. There was also no significant correlation between Choline changes with dose and duration of use. (Pvalue<0.01). The amount of changes in the GLX metabolite, which represents changes in the level of neurotransmitters, has a positive correlation with the amount of psychiatric disorders (Pvalue<0.01). There is a relationship between the changes in the metabolism of mayoinozitol, which represents glial cells, and the incidence of the psychiatric disorders (Pvalue<0.01). Also, there was a positive relationship between the changes in keratin metabolism and the incidence of the psychiatric disorders. (Pvalue<0.01) (Table 2).

Table 2. Pearson r correlations between Subscale PANSS scores and mean total metabolite concentration in five regions for participates (n=30)

	Group	N	Mean	Std. Deviation	Sig. (2-tailed)
NAA	Abuser	30	18.5603	5.91551	.001
	Normal	10	25.5700	4.13415	.000
Cr	Abuser	30	14.1910	6.60855	.044
	Normal	10	9.7430	2.01238	.002
cho	Abuser	30	11.4377	3.73582	.008
	Normal	10	8.0250	1.12411	.000
GLX	Abuser	30	7.0790	2.85727	.000
	Normal	10	2.2870	1.14148	.000
mI	Abuser	30	7.3270	2.84909	.004
	Normal	10	4.4000	1.69837	.001
PANSS	Abuser	30	111.90	18.40418	.000
	Normal	10	23.9000	7.72370	.000



Figurer 2. Linear curve estimation of PANSS and metabolite concentration correlation

Discussion

The findings suggest that following the use of methamphetamine and the sustainability of this condition, nerve degradation processes (a decrease in the metabolism of NAAs) spread across the different regions of the brain, particularly serotonergic and dopaminergic regions. The severity and extent of this degradation is related to the incidence and severity of psychological symptoms and is clearly visible even in the early stages of the disorder.[13] Also, changes in the level of other biochemical markers such as keratin and choline indicate neural toxicity and changes in cell membrane in the studied areas.[10] The rate of changes in the marker mayoinozitol (mI) in the studied areas and its reduction, especially in the basal ganglia, also indicate the beginning of neurodegenerative processes and neuronal death.[14] Also, changes in neurotransmitters that have been reported in positron release studies in previous studies have significantly shown changes in glutamate and glutamine levels as well as GABA, which is consistent with the results of our study.[21] Behavioral changes in mood and also the incidence of violent and pseudo-schizophrenic behaviors and adaptation of these pathological findings with the PANSS psychoanalysis test indicate the severity and extent of the disorders.[14]

According to previous studies, patients with chronic METH psychosis who had been abstinent from METH for more than 1 month qualitatively reported experienced visual hallucinations, delusions, and persecutory delusions, while all experienced auditory hallucinations. They found no difference in the patterns of delusions experienced between those with chronic METH psychosis and schizophrenia and that auditory hallucinations were the most common type of hallucination experienced between groups.[12] Our findings also support this idea, there is a decrease in the level of NAA consistent with an increase in visual hallucinations and delusion in the meth dependence group.

Another study described persistent METH psychosis and schizophrenia demonstrated comparable severity and frequency of positive symptoms, and both of these groups had PANNS scores that were significantly higher than those in the acute METH psychosis group.[13] According to the results of PANSS Scales in our study, it was observed that the severity and frequency of positive symptoms were more strongly related to metabolite concentration than negative symptoms. Negative symptoms such as flat affect, social withdrawal, apathy, loss of drive, anhedonia, and poverty of speech have also been reported in METH psychosis samples.[4] However, in our study, no significant relationship was found between these symptoms and study variables.

The key role of the dopamine circuit (VTA, NAc, substantia nigra, striatum, PFC, hippocampus) and the mesocorticolimbic pathway in substance abuse has been proven in previous studies. However, the evaluation of all these areas together has received less attention. The Accumbens (NAc) has been implicated in numerous neurological and psychiatric disorders, including depression, obsessive-compulsive disorder, bipolar disorder, anxiety disorders, Parkinson's disease, Alzheimer's disease, Huntington's disease, obesity, and drug abuse and addiction (Accumbens).[24,25] The NAc has dopaminergic inputs from mesolimbic structures as well as prefrontal areas including the medial prefrontal cortex (MPFC) and anterior cingulate (ACC), which may be responsible for the NAc response to reward via pain relief. The NAc is functionally connected to ACC and MPFC at rest and coactivated with basal ganglia, ACC, and insula.[10] Nucleus accumbens is a major input structure of the basal ganglia and integrates information from cortical and limbic structures to mediate goal-directed behaviors.[11]

Chronic exposure to several classes of drugs of abuse disrupts plasticity in this region, allowing drug-associated cues to engender a pathologic motivation for drug seeking.[9] The

NAc is a major component of the ventral striatum and has long been thought to be a key structure involved in mediating motivational and emotional processes, the limbic-motor interface, and the effects of certain psychoactive drugs.

Overall, however, the NAc appears to be a key structure in the natural reward system, which includes modulation of motivation and incentivized learning.[16] Coupled with connectional studies, these findings have led to the suggestion that the NAc plays a central role in a positive emotional response pathway, counterbalanced by a negative emotional response pathway mediated by the amygdala,[13] although others believe the NAc itself may play a vital role in aversive motivation.[18]

Synthesizing centers, as well as dopamine and serotonin action centers, which are both causes of pleasure and a good sense of humans in methamphetamine users, were identified as the main places of occurrence of these metabolic and biochemical disorders in this study, although changes in other areas and in multiple studies have been reported the main system for these disorders is double-headed and serotonin systems.[21]

Methamphetamine use is associated with decreased neuronal integrity and viability, specifically dopamine circuit (ventral tegmental area, nucleus accumbens, substantia nigra, striatum, frontal cortex, and hippocampus). Methamphetamine dependence is associated with active neurodegeneration in the dopamine circuit, but this was not found in the control group, and in the chronic phase and the sustained nerve damage, it causes severe psychiatric disorders. MRS can be very helpful in detecting the progression of disease and degree of deterioration as well as follow-up treatment in patients with methamphetamine abuse.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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