



A Voxel-Based Morphometric Brain Study of Patients with Methamphetamine Dependency: A Case Controlled Study

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Methamphetamine (MA) use has been an important health problem in Iran in recent decade. Previous studies have suggested brain structural abnormalities in MA users. Increasing knowledge about the MA induced structurally and possible structural brain changes is important for better management of this disorder. The aim of the present study was to investigate the possible structural brain structural changes in MA dependent patients. This was a case-control study, which conducted in Farabi mental hospital in the west of Iran. Voxel-based-morphometry (VBM) as a whole-brain technique for characterizing regional cerebral volume and tissue concentration differences in structural MRI was administered. We used VBM to assess regional brain differences in 25 MA dependent patients and 20 age, sex matched healthy controls. In MA dependent patients hippocampus, parahippocampus, left frontal lobe, right frontal lobe, left temporal lobe, and right temporal lobe volumes were significantly lower than healthy control subjects ($P < 0.05$). Also caudate and amygdala volume in MA dependent patients were smaller than healthy subjects ($P < 0.05$). The brain volume reduction of MA dependent patients compared to control subjects may explain the prevalence of psychiatric disorders in these patients, and could help to provide therapeutic strategies for drug-induced brain injury.

Key Words: Methamphetamine, Brain, Magnetic Resonance Imaging, Voxel-Based-Morphometry (VBM)

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Introduction

Methamphetamine (MA) has become the second most used drug globally (Vienna, 2013). According to the report of the United Nations Office on Drugs and Crime Vienna, 2012, MA use has increased 400% in Iran between 2010 and 2011 (Vienna, 2012). It is estimated that 1.6–2.67% of the Iranian population (75.1 million in 2011) using illicit drugs regularly (Alam-Mehrjerdi, Abdollahi, Higgs, & Dolan, 2015), so MA use has been an important health problem in Iran recently.

In recent decade several neuroimaging studies with different volumetric and pattern analysis

methods have suggested significant structural abnormalities within different regions of the brain system in stimulant-dependent individuals (Barros-Loscertales *et al.*, 2011; Chang *et al.*, 2005; Chang *et al.*, 2004; Jacobsen, Giedd, Gottschalk, Kosten, & Krystal, 2001; Kim *et al.*, 2006; Thompson *et al.*, 2004). In contrast, some other studies could not identify any brain structural abnormalities in stimulant users at all (Narayana *et al.*, 2010; Weller *et al.*, 2011).

Magnetic resonance imaging (MRI) is a highly sensitive modality for brain morphometric studies, as the resolution of an anatomical scan of a whole brain increases with shorter acquisition time. Voxel-based morphometry (VBM) as a relatively easy technique

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is used to provide biologically plausible results. VBM basically uses T1-weighted volumetric MRI scans and by performing statistical analysis between all voxels in the image could assess volume differences between groups(Whitwell, 2009).

Certainly more comprehensive understanding of the neuropathology underlying the clinical symptoms of MA use is necessary to develop better strategies for more effective interventions; and well-organized neuroimaging studies and robust data could be helpful in this way(Hanlon and Canterberry, 2012).

Accordingly we aimed to investigate the possible brain anatomical abnormalities of MA dependent patients compare to healthy controls in an Iranian population in the present study.

Methods

The present case-control study, which assessed the brain MRI findings of subjects with MA use compare to control group, was carried out between March 2016 and January 2018 in Kermanshah (Iran). Written informed consent provided by all of participants. The study was approved by the Medical Research and Ethical Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran with registration No. Kums. REC.1396.150 at the date of 9 June 2017 and was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki.

All participants were healthy according to physical examination, and medical history. Inclusion criteria were as follow: (a) current diagnosis of amphetamine use according to the structured clinical interview for psychiatric disorders(Shreehan *et al.*, 1998), (b) a positive MA urine test for patients in case group, (c) age between 18 and 60 years; (d) written informed consent.

Subjects were excluded for the following reasons: (a) not meeting the inclusion criteria; (b) history of any other psychiatric disorder (c) in the case of female patients, (planned) pregnancy or breastfeeding (d) using of psycho-active medications or other substances(except MA in case group), and (e) history of cardiovascular, pulmonary, systemic disease; and neurological diseases.

Finally forty-three subjects were selected for the study. Twenty-Five MA dependent patients with a history of MA use (mean age, 30.5+-6.5 years; 18 men and 7 women) and 20 comparison subjects without a history of MA abuse (mean age, 31.7+-9.1 years; 15 men and 5 women) were analyzed.

Assessments

The diagnoses were made by trained psychiatrists using psychiatric interview and clinical exams. Socio-demographic and historical data were gathered. Laboratory urine samples were screened for drugs using thin-layer chromatography for benzodiazepines, barbiturates, opiates, methadone, cocaine, amphetamines and Lysergic Acid Diethylamide (LSD).

Image acquisition and pre-processing

Magnetic resonance imaging was obtained in all subjects using a 1.5-T Siemens scanner and the head coil. A strict imaging protocol was used, including a 3-dimensional inversion recovery preparation spoiled gradient recalled echo sequence of the entire brain in the axial plane, and the following parameters: repetition time, 17 milliseconds; echo time, 5 milliseconds; inversion time, 300 milliseconds; section thickness, 1.5 mm; field of view, 24 × 256 cm; and number of excitations, 1.

All MRI processing was carried out according to the optimized VBM protocol (Good *et al.*, 2001). The MRIs were analyzed using SPM8 (WDCN, London or <http://www.fil.ion.ucl.ac.uk/spm>), and MATLAB software.

Statistical analyses

First, a series of T-tests and Chi square tests were administered to compare socio-demographic variables between case and control groups. Next, Kolmogorov Smirnov test was performed to assess the normal distribution of demographic and imaging data. Finally the brain regions volumes between two groups were compared using a series of independent sample T-tests. All computations were performed with SPSS -22.0 (IBM Corporation, Armonk NY, USA) for Apple Mac.

Results

Socio-demographic data: comparisons between MA dependent patients and healthy controls. All descriptive and inferential statistical indices are summarized in Table 1. The mean age of MA dependent patients was lower than healthy controls, but the differences was not statistically significant ($p=0.61$). The differences related to gender, education, marital status, and employment between two groups were not statistically significant.

VBM analyses: comparisons between MA dependent patients and healthy controls



To investigate the differences of the brain regions volume between MA dependent patients and healthy controls Kolmogorov Smirnov test was performed. The results are summarized in Table 2. There were no group differences in total cerebral volumes between two groups ($p > 0.1$). The

Table 1. Demographic and Basic Characteristics of the MA dependent patients and healthy controls

Variable	Group		Sig
	MA dependent patients(n= 25)	Healthy controls(n=20)	
Age	30.5+-6.5	31.75+-9.1	0.61
Gender	Male	18(0.72)	0.55
	Female	7(0.28)	
Level of education	High School	11(0.44)	0.63
	Diploma	11(0.44)	
	Academic	3(0.12)	
Marital status	Single	12(0.48)	0.06
	Married	7(0.28)	
	Widowed/ Divorced	6(0.24)	
Occupation status	Employed	18(0.72)	0.15
	Non- employed	7(0.28)	

Table 2. Comparison of the brain volumes regions between MA dependent patients and healthy controls

		Volume (mm3) Mean±SD	T-test	sig
Whole brain volume	MA dependent patients	1562112.5 ± 131678.2	-0.82	0.42
	Healthy controls	1598195.5±160702.4		
Gray matter	MA dependent patients	717165.7±61758.2	-1.25	0.22
	Healthy controls	741395.2±66339.4		
White matter	MA dependent patients	2532281.5±52547.7	-0.81	0.42
	Healthy controls	546315.3±62097.9		
Cerebrospinal fluid	MA dependent patients	312665.1±29431.8	0.20	0.84
	Healthy controls	310484.8±42201.4		
Left amygdala	MA dependent patients	949.1±266.6	-2.31	0.038*
	Healthy controls	1083.6±92.8		
Right amygdala	MA dependent patients	2035.7±1022.3	-1.45	0.15
	Healthy controls	1095.9±111.0		
Left caudate nucleus	MA dependent patients	2618.5±648.4	-2.34	0.024*
	Healthy controls	2998.4±353.2		
Right Caudate nucleus	MA dependent patients	2728.8±556.0	-1.69	0.099
	Healthy controls	2977.8±387.1		
Left frontal lobe	MA dependent patients	83600.2±15817.1	-2.44	0.019*
	Healthy controls	93332.9±8922.2		
Right frontal lobe	MA dependent patients	81377.0±15198.0	-2.30	0.026*
	Healthy controls	90249.7±8884.7		
Left hippocampus	MA dependent patients	3264.6±773.6	-1.98	0.055
	Healthy controls	3618.9±221.7		
Right hippocampus	MA dependent patients	3023.0±590.6	-1.22	0.23
	Healthy controls	3195.1±240.2		
Left parahippocampus	MA dependent patients	3362.2±841.1	-2.52	0.016*
	Healthy controls	3855.9±261.1		
Right parahippocampus	MA dependent patients	4297.5±1019.4	-2.64	0.012*
	Healthy controls	4938.3±406.2		
Left putamen	MA dependent patients	2593.5±708.1	-0.65	0.52
	Healthy controls	2702.3±269.5		
Right putamen	MA dependent patients	3355.8±784.8	-0.67	0.51
	Healthy controls	3481.2±330.1		
Left temporal lobe	MA dependent patients	50442.7±8125.5	-2.67	0.01**
	Healthy controls	56015.6±5034.9		
Right temporal lobe	MA dependent patients	50549.8±5799.7	-1.96	0.057
	Healthy controls	53927.6±5575.9		



analyses revealed significantly differences in some brain regions between two groups. In subjects with history of chronic MA use the hippocampus, par hippocampus, left frontal lobe, right frontal lobe, left temporal lobe, and right temporal lobe were significantly smaller than control subjects ($P < 0.05$).

Discussion

In the present study, the brain regions volume in 25 patients with MA dependence and 20 healthy subjects were studied. Both groups were comparable in terms of demographic and basic characteristics variables. According to our study results no significant differences was found in whole brain volume between two groups. However, compared to healthy controls, patients with MA dependence showed several regions of lower brain volume. In particular, differences in the hippocampus, parahippocampal, left frontal lobe, right frontal lobe, left temporal lobe, and right temporal lobe were found between two groups. Previous studies reported some structural brain alterations in cortex, and hippocampus, thalamic and hypothalamic structures among MA users (Marinelli-Casey *et al.*, 2008; Mobius, Kustermann, Struffert, Kornhuber, & Muller, 2014; Rawson, Gonzales, Marinelli-Casey, & Ang, 2007). Also two studies reported larger grey matter volumes in the striatum and bilateral parietal cortices (Chang *et al.*, 2005; Jernigan *et al.*, 2005). These brain deficits may help to better understanding the underlying psychopathology of MA induced psychiatric symptoms, and disorders. For examples, brain deficits in temporal cortex and in the visual association area of the occipital cortex in our MA users may contribute to psychiatric symptoms, such as psychosis or hallucinations that are often reported in these patients (Mahoney, Kalechstein, De La Garza, & Newton, 2008; McKetin, McLaren, Lubman, & Hides, 2006). Future studies are necessary to investigate the relationship between change in regional brain volume and psychiatric symptoms in MA users.

Conclusion

VBM as a sensitive modality could help to find brain deficits in MA users. Summarizing, findings from our study suggest that chronic use of stimulants like MA could induce permanent severe brain damages, and considering growing MA use worldwide informing mental practitioners about these possible brain alternations seems necessary to better treatment of this health problem.

Limitations

Our findings should be interpreted with few limitations. First the sample size of the study was relatively small to generalize the results. Next, the medical history data were gathered by self-reports, though the present data will involve memory bias. Last future neuroimaging studies include additional measures and larger sample-sizes should be perform to prove our findings.

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Reference

- Alam-Mehrjerdi Z, Abdollahi M, Higgs P, Dolan K. Drug use treatment and harm reduction programs in Iran: A unique model of health in the most populated Persian Gulf country. *Asian J Psychiatr* 2015; 16: 78-83.
- Barros-Loscertales A, Garavan H, Bustamante JC, Ventura-Campos N, Llopis JJ, Belloch V, Avila C. Reduced striatal volume in cocaine-dependent patients. *Neuroimage* 2011; 56(3): 1021-1026.
- Chang L, Cloak C, Patterson K, Grob C, Miller EN, Ernst T. Enlarged striatum in abstinent methamphetamine abusers: a possible compensatory response. *Biol Psychiatry* 2005; 57(9): 967-974.
- Chang L, Smith LM, LoPresti C, Yonekura ML, Kuo J, Walot I, Ernst T. Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. *Psychiatry Res* 2004;132(2): 95-106.
- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 2001; 14(1): 21-36.
- Hanlon CA, Canterberry M. The use of brain imaging to elucidate neural circuit changes in cocaine addiction. *Substance Abuse and Rehabilitation* 2012; 3: 115-128.
- Jacobsen LK, Giedd JN, Gottschalk C, Kosten TR, Krystal JH. Quantitative morphology of the caudate and putamen in patients with cocaine dependence. *Am J Psychiatry* 2001; 158(3): 486-489.
- Jernigan TL, Gamst AC, Archibald SL, Fennema-Notestine C, Mindt MR, Marcotte TD, Grant I. Effects of methamphetamine dependence and HIV infection on cerebral morphology. *Am J Psychiatry* 2005;162(8): 1461-1472.
- Kim SJ, Lyoo IK, Hwang J, Chung A, Hoon Sung Y, Kim J, Renshaw PF. Prefrontal grey-matter changes in short-term and long-term abstinent methamphetamine abusers. *Int J Neuropsychopharmacol* 2006. 9(2): 221-228.



- Mahoney JJ 3rd, Kalechstein AD, De La Garza R 2nd, & Newton TF. Presence and persistence of psychotic symptoms in cocaine-versus methamphetamine-dependent participants. *Am J Addict* 2008; 17(2): 83-98.
- Marinelli-Casey P, Gonzales R, Hillhouse M, Ang A, Zweben J, Cohen J, Rawson RA. Drug court treatment for methamphetamine dependence: treatment response and posttreatment outcomes. *J Subst Abuse Treat* 2008; 34(2): 242-248.
- McKetin R, McLaren J, Lubman DI, Hides L. The prevalence of psychotic symptoms among methamphetamine users. *Addiction* 2006; 101(10): 1473-1478.
- Mobius C, Kustermann A, Struffert T, Kornhuber J, Muller HH. c-MRI findings after crystal meth abuse. *J Addict Med* 2014; 8(5): 384-385.
- Narayana PA, Datta S, Tao G, Steinberg JL, Moeller FG. Effect of Cocaine on Structural Changes in Brain: MRI Volumetry using Tensor-Based Morphometry. *Drug and alcohol dependence* 2010; 111(3): 191-199.
- Rawson RA, Gonzales R, Marinelli-Casey P, Ang A. Methamphetamine dependence: a closer look at treatment response and clinical characteristics associated with route of administration in outpatient treatment. *Am J Addict* 2007; 16(4): 291-299.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59(20): 22-33.
- Thompson PM, Hayashi KM, Simon SL, Geaga JA, Hong MS, Sui Y, London ED. Structural abnormalities in the brains of human subjects who use methamphetamine. *J Neurosci* 2004; 24(26): 6028-6036.
- Vienna U. N. O. o. D. a. C. World Drug Report. New York: united Nations 2012.
- Vienna, U. N. O. o. D. a. C. World Drug Report. New York: united Nations 2013.
- Weller RE, Stoeckel LE, Milby JB, Bolding M, Twieg DB, Knowlton RC, Ding Z. Smaller Regional Gray Matter Volume in Homeless African American Cocaine-Dependent Men: A Preliminary Report. *The Open Neuroimaging Journal* 2011; 5: 57-64.
- Whitwell JL. Voxel-based morphometry: an automated technique for assessing structural changes in the brain. *J Neurosci* 2009; 29(31): 9661-9664.

