Original Article

Cognitive functions in methamphetamine induced psychosis compared to schizophrenia and normal subjects

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Objective: The purpose of this research was to study the cognitive functions in patients with methamphetamine-induced psychosis (MIP) in comparison with schizophrenia patients and normal subjects.
Method: This was a cross-sectional study, 30 patients with MIP, 30 patients with schizophrenia and 30 normal individuals were selected via convenient sampling and were matched on age, sex and education. Wisconsin Cards Sorting, Stroop, Visual Search and Attention and Wechsler Memory Tests were used to assess the subjects.
Results: The study showed that patients with MIP and schizophrenia have more deficits in executive functions, selective attention, sustained attention and memory than normal subjects. There were no significant differences in cognitive functions between patients with MIP and schizophrenia except for visual search and attention that showed more impairment in patients with schizophrenia.
Conclusion: Although, cognitive dysfunctions of patients with MIP are mostly similar to patients with schizophrenia, some differences seem to exist, especially in those functions that are not primarily dependent on frontal lobe.

Keywords: *Methamphetamine; psychotic disorders; schizophrenia; executive function; attention; memory*

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Methamphetamine use has significantly increased in Iran in recent years and non-official estimates of experts suggest that it is currently the most widely used illegal substance in the country. As a result, methamphetamine induced psychosis (MIP) has become the reason for one of the most common emergency visits in psychiatric centers (1, 2).

Several studies have documented the presence of both structural and functional changes in the brain of methamphetamine abusers (3, 4). These changes have been associated with deficits in various cognitive functions including memory, attention, speed of information processing, executive functions, and language (3, 5-8). However, few studies have assessed cognitive functions in patients with MIP. Also, the pattern of cognitive deficits in patients with MIP has not been clearly described and compared to non-psychotic methamphetamine users on the one hand, and psychotic patients with no history of methamphetamine use on the other.

Several studies on cognitive deficits of patients with schizophrenia have consistently shown deficits in several domains of cognitive functioning including attention, working memory, information processing, and executive functions (9-12). However, we could only find one study that had compared cognitive functions between patients with schizophrenia and MIP patients, which showed no significant difference between the two groups of patients (13). This study was performed on 19 patients with paranoid schizophrenia and 20 patients with MIP and did not include a normal comparison group. The current study was designed to assess the cognitive functions in a larger group of patients with MIP compared to a sample of patients with schizophrenia and a normal control group.

Material and Methods

Participants and procedure

This was a cross sectional study. For sample size calculation alpha, beta, and the ratio of variance to the minimum detectable difference were considered 0.05, 0.8, and 2 respectively. In this way, 30 patients was estimated to be a reasonable number. Therefore, 30 patients with methamphetamine-induced psychosis (4 female), 30 patients with schizophrenia (6 female) and 30 normal individuals (6 female) were selected via convenient sampling and were matched on age, gender and education (see table 1). All of the patients were selected for the study from among inpatients of the

emergency ward of the Iran Psychiatric Hospital. Enrollment was made after primary stabilization of the patients and during the active phase of the disorders. The documented diagnoses in the patients' files, which are generally made by board certified psychiatrists, were considered as the selection criteria of the subjects. All of the patients were using antipsychotic medications .

The normal subjects were chosen from clients and staffs of the Bésat hospital. The inclusion criteria for the subjects were as follows: being 18 – 60 years old, having more than 5 years of formal education, absence of organic brain disease, having no history of traumatic brain injury, absence of physical anomalies or visual disturbance, absence of history of psychotic symptoms before methamphetamine use in patients with methamphetamine-induced psychosis, absence of history of methamphetamine abuse in patients with schizophrenia, and having no history of any psychiatric disorders or methamphetamine abuse in normal subjects.

Instrument

Wisconsin Card Sorting Test

Wisconsin Card Sorting Test (WCST) is used for assessment of executive functions (14). The short version of WCST consists of 64 cards with different geometric shapes in different colors and numbers. Each card has one to four of a colored symbol in a way that no two cards are similar. Symbols could be triangles, stars, crosses or circles in one of the colors red, green, blue, or yellow. In order to perform the test, subject needs to infer the rule of the game and keep it in mind until the rule changes, and modify her/his strategy accordingly when necessary.

Stroop Test

This test assesses selective attention and response inhibition. Three cards with 24 stimuli (6 rows and 4 columns) are used in this type of Stroop Test (15). The first card or dots card, includes several dots in green, red, blue and yellow; and subjects are asked to name the colors. The second card or word card consists of words written in the colors green, red, blue and yellow; and subjects should mention the name of the colors without paying attention to the words. The third card or colors card, contains the words green, red, blue and yellow written in colors other than what the words denote, and subjects need to name the colors without considering the meaning of words. In this test any errors and the time for reading every card are recorded.

Visual Search and Attention Test

Visual Search and Attention Test (VSAT) assesses visual accuracy and sustained attention. It consists of four search trials in which subject should find the target sign among other stimuli (16). Every trial contains 10 rows and each row consists of 40 items; the target sign is printed on top of the page. Trial number one contains black letters on a white background and the target letter is "F". Trial two consists of black symbols and the target symbol is ")". Trial three contains colored letters (in red, green and blue) and blue "H" is the target letter, and finally trial four contains colored symbols (in red, green and blue) and blue "/" is the target symbol. Subjects should cross out as many target items as they can in 60 seconds and their performance is determined based on their results from only the last two trials and the number of items they crossed out in left and right side in 60 seconds (17).

Wechsler Memory Scale

Wechsler Memory Scale (WMS) is an objective scale that is used to evaluate memory and memory disorders. It consists of seven subtests including public and personal information, awareness of time and place, mental control, logical memory, repeating digits, visual memory and association learning (18). The total score of memory is the calculated sum of scores from subtests as Memory Quotient.

Statistical analysis

Three multivariate analysis of variance were performed to assess the differences of the three groups (schizophrenia, MIP, and normal) in scores of WCST, Stroop test, and VSAT. A two way analysis of variance was used to test the difference of the three groups in the scores of WMS. Education was considered as a possibly interfering variable in all of the above analyses. Age did not have an association with the test results and therefore was not included in the analyses as a covariate. Data analysis was performed using SPSS software version 15. Effect size estimates were calculated using Cohen,s d (difference between the means divided by the pooled standard deviation).

Results

The average duration of methamphetamine use in IMP was 10.88 (SD=17.82) months. None the patients with schizophrenia had a history of methamphetamine use. History of use of the other drugs in patients with MIP was about 66% (20 person) while in patients with schizophrenia it was 10% (3 person).

Mean scores of the tests were higher in normal subjects than the other two groups (table 2). To minimize the number of comparisons we performed three MANOVAs for WCST, Stroop test, and VSAT and one ANOVA for WMS. All the three MANOVA test results (observed scores of each test was considered as dependent variables and group and education as independent variables), based on Wilks' Lambda scale, showed a significant multivariate group effect (WCST ($F(6,152) = 4.52$, $p = 0.0005$), Stroop test ($F(4,154) = 4.43$, $p = 0.002$), VSAT ($F(6,152) = 10.05$, $p = 0.0005$)). Effect of education was only significant in VSAT and no interaction effect was observed between education level and the other tests (table 3 and 4).

Results of ANOVA on score of WMS also showed a significant difference between the three groups ($F(2,90) = 11.52$, $p = 0.0005$). Education also showed a significant effect on WMS scores (table 4).

To further probe the observed difference, univariate analysis of variance was performed for these tests.

Table 1: Demographic data of the patients with methamphetamine induced psychosis, schizophrenia and normal subjects

	MIP (n=30) M (SD)	SZ (n=30) M (SD)	NL (n=30) M (SD)	*F*	χ^2	*p*
Age	30.10 (7.27)	35.63 (10.13)	33.93 (9.75)	2.88	-	0.06
Education levels	9.33 (2.9)	10.1 (2.99)	10.4 (2.58)	1.13	-	0.32
Sex ratio (M:F)	26:4	24:6	24:6	-	0.608	0.73

MIP: Methamphetamine induced psychosis; SZ: Schizophrenia; NL: Normal

Table 2: Mean, standard deviation, and effect size of the difference in the test scores for the patients with schizophrenia, methamphetamine induced psychosis, and normal subjects

variable	group	Mean	Std.Deviation	Effect Size		
				MIP-SZ	MIP-NL	SZ-NL
WCST (correct response)	MIP	28.30	10.11	0.30	-1.49	-1.81
	SZ	25.26	10.41			
	NL	41.00	6.89			
WCST (perseveration errors)	MIP	35.46	9.32	-0.16	-1.13	-0.96
	SZ	36.96	8.99			
	NL	44.16	5.96			
WCST (categories completed)	MIP	0.90	1.09	0.19	-1.06	-1.31
	SZ	0.70	1.02			
	NL	2.00	1.01			
Stroop (reaction time)	MIP	18.70	21.15	-0.24	0.61	1.91
	SZ	23.86	22.29			
	NL	9.26	5.78			
Stroop (number of errors)	MIP	2.30	3.55	-0.29	0.71	1.1
	SZ	3.33	3.58			
	NL	0.46	1.04			
VSAT (left side)	MIP	43.20	11.41	0.62	-1.95	-1.69
	SZ	34.73	15.81			
	NL	69.13	15.26			
VSAT (right side)	MIP	39.26	11.74	0.77	-1.89	-2.41
	SZ	29.13	14.57			
	NL	65.30	15.82			
VSAT (total)	MIP	82.46	22.14	0.71	-1.99	-2.37
	SZ	63.86	30.13			
	NL	134.73	30.45			
W.M.S	MIP	78.96	15.62	0.19	-1.54	-1.65
	SZ	75.73	17.32			
	NL	100.36	12.48			

MIP: Methamphetamine induced psychosis; NL: Normal; SZ: Schizophrenia; VSAT: Visual Search and Attention Test; WCST: Wisconsin Card Sorting Test; WMS: Wechsler Memory Scale

Table 3. The effect of group, education and their interaction in the scores of Wisconsin Card Sorting Test, Stroop test, and Visual Search and Attention Test in the patients with schizophrenia, methamphetamine induced psychosis, and normal subjects

Variable		***F***	**Hypothesis *df***	**Error *df***	***p*[#]**
WCST	Group	4.52	6	152	0.0005*
	Education	1.59	9	185	0.11
	Group*Education	0.42	18	215	0.98
Stroop	Group	4.43	4	154	0.002*
	Education	1.65	6	154	0.13
	Group*Education	0.8	12	154	0.64
VSAT	Group	10.05	6	152	0.0005*
	Education	2.56	9	185	0.008*
	Group*Education	1.07	18	215	0.38

[#] statistical method used in this table is MANOVA

*(α<0.05)

MIP: Methamphetamine induced psychosis; VSAT: Visual Search and Attention Test; WCST: Wisconsin Card Sorting Test

Table 4: The effect of group and education on the scores of Wisconsin Card Sorting Test, Stroop test, and Visual Search and Attention Test, and Wechsler Memory Scale in the patients with schizophrenia, methamphetamine induced psychosis, and normal subjects

	Dependent variable	*F*	*p*[#]
Group	WCST (correct response)	13.82	0.0005*
	WCST (perseveration errors)	5.29	0.007*
	WCST (categories completed)	6.67	0.002*
	Stroop (reaction time)	2.21	0.11
	Stroop (number of errors)	6.81	0.002*
	VSAT (left side)	33.21	0.0005*
	VSAT (right side)	30.96	0.0005*
	VSAT (total)	33.51	0.0005*
	WMS	11.52	0.0005*
Education	WCST (correct response)	1.02	0.36
	WCST (perseveration errors)	0.73	0.48
	WCST (categories completed)	2.9	0.06
	Stroop (reaction time)	1.32	0.27
	Stroop (number of errors)	2.008	0.12
	VSAT (left side)	5.66	0.005*
	VSAT (right side)	5.3	0.007*
	VSAT (total)	5.55	0.006*
	WMS	2.95	0.03*

[#] statistical method used in this table is ANOVA (df = 2, 90), *(α<0.05)

MIP: Methamphetamine induced psychosis; VSAT: Visual Search and Attention Test; WCST: Wisconsin Card Sorting Test; WMS: Wechsler Memory Scale

In WCST, there was a significant difference in all three dependent variables (including number of correct response, perseveration errors and number of categories completed). From two dependent variables of Stroop test (number of errors and the time) significant difference was observed only for number of errors between the three groups. In VSAT, there was a significant difference for all of its three variables (number of items crossed out in left, right side and total).

Subsequently, a Tukey's post hoc test was performed to delineate the differences of the three groups (schizophrenia, MIP, and control) in the scores of the tests. This analysis showed that patients with methamphetamine-induced psychosis and schizophrenia have more deficits in WCST, Stroop, VSAT and WMS than normal subjects. Effect size of the difference for the variables were calculated using Cohen's d method, which were from 0.61 to 2.41 (table 2). However, no significant difference was observed between patients with methamphetamine-induced psychosis and schizophrenia except for VSAT test that showed more impairment in patients with schizophrenia (Cohen's d: total: 0.71; right side: 0.77; left side: 0.62). Participants with instability in interpersonal relationship (according to item number 2 of SCID-II) had significantly lower scores in NORA (p = 0.010) than others without this problem.

Discussion

Patients with MIP and schizophrenia had a significantly poorer performance on cognitive tests (including selective attention, sustained attention, memory, and executive functions) than normal subjects. However, we found no significant difference between MIP and schizophrenia in cognitive functions, except that sustained attention was more disturbed in schizophrenia.

Therefore, cognitive dysfunctions in MIP seem to be partly comparable to schizophrenia, at least in the studied functions. The findings are in line with the study by Jacobs et al that has found no difference between cognitive functioning of the patients with paranoid schizophrenia and MIP (13). However, the current study additionally showed that patients with schizophrenia have lower scores in VSAT compared to patients with MIP. To our knowledge, this is the first time that a difference in cognitive functioning is reported between schizophrenia and MIP .

Deficits of executive functioning, selective attention, and working memory could be ascribed to dysfunction of prefrontal cortex, which is commonly present in both the patients with schizophrenia and MIP. However, performance of VSAT is more closely related to the function of parietal cortex. Therefore, the cortical damage of parietal cortex in schizophrenia might be more pronounced than the corresponding damage in patients with MIP, but injury to prefrontal cortex seems comparable in the two disorders as assessed by the applied cognitive tests. Other explanations are also possible for this finding; for example the pattern of frontal dysfunction might be different or more severe in schizophrenia patients as compared to MIP patients. It might also show that the mechanisms involved in producing brain injury in MIP are distinct from schizophrenia .

It has been shown that methamphetamine has neurotoxic effects on dopaminergic and serotonergic nerve terminals in various sites of brain (19), and deficits made in the frontostriatal system may have a role in cognitive dysfunctions associated with

methamphetamine abuse (20). For instance, Paulus et al. showed prefrontal dysfunction in methamphetamine users during a decision making task (21); additionally, lower levels of dopamine transporters in the striatum (22-24) and prefrontal cortex (25) have been reported in meth users, as well as long term changes in frontal metabolites in these patients (26). However, few reports exist on injuries caused by methamphetamine in parietal lobes (27, 28). Eisch and Marshall have shown that the mechanisms involved in methamphetamine neurotoxicity of striatal dopamine terminals in rats are not identical to those that induce damage in parietal cortical cell bodies (28). In humans, also similar or even more pronounced distinctions might exist between the mechanisms of injury in different parts of the brain that could result in different patterns of dysfunction in performance of tests .

The current study faced some limitations that should be considered. It was a cross-sectional study and it therefore suffers from the limitations of this kind of studies. Furthermore, all of the subjects were inpatients selected from a single center. Although the center was a large referral center that receives patients from various parts of the country, this could limit the generalizability of the findings. All of the patients were receiving medications including antipsychotics. Ethically, we could not discontinue their medications and it is possible that medications affected the cognitive functioning of the patients. However, the patients of the two groups had received almost the same kind and dose of medications. One of the limitations of over research was relatively small sample size .

Findings on the difference of visual attention in patients with MIP and schizophrenia need replication. Further comparisons of these two groups using various tests with an emphasis on functions of parietal lobe could be informative.

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