

## Cognitive Functioning in Schizophrenia, Methamphetamine-induced Psychotic Disorder, and Healthy People: A Comparative Study

### Abstract

**Background:** Methamphetamine-induced psychotic disorder (MIP) cannot be easily differentiated from other psychotic disorders. Some studies have reported that patients with MIP and schizophrenia have differences in their cognitive functioning. We hypothesized that their performance would be different on neuropsychological tests which assess executive functions and visual memory. **Materials and Methods:** In a cross-sectional study, 30 patients with MIP, 31 patients with schizophrenia, and 31 healthy controls were assessed by Rey–Osterrieth complex figure (ROCF) test and visual search and attention test (VSAT). One-way analysis of variance was performed to compare the mean scores of tests. Tukey's HSD test was used for *post hoc* analysis. **Results:** Three groups had significant differences according to ROCF test ( $F = 15.76, P < 0.0001$ ), VSAT ( $F = 39.78, P < 0.0001$ ), left VSAT ( $F = 37.96, P < 0.0001$ ), right VSAT ( $F = 40.40, P < 0.0001$ ), and the time of the test administration ( $F = 3.26, P = 0.04$ ). The *post hoc* analysis showed that the mean score of ROCF test and VSAT (total, right, and left) was significantly higher in the control group than in the other two groups. The time of administering the test in the control group was significantly shorter than in the MIP group ( $P < 0.03$ ) and nonsignificantly shorter than in the schizophrenia group ( $P = 0.54$ ). The mean score of right side VSAT was significantly higher in the MIP group than in the schizophrenia group. **Conclusion:** ROCF could not differentiate MIP from schizophrenia. The better performance of patients with MIP on right side VSAT that is reported in this and in the previous study needs to be reevaluated in more controlled studies.

**Keywords:** Cognitive function, executive function, methamphetamine, psychotic disorder, schizophrenia

### Introduction

The use of crystallized forms of methamphetamine has greatly increased in Iran.<sup>[1-5]</sup> It is a pharmacological stimulant of the central nervous system, which results in stimulating excessive dopaminergic transmissions in the brain.<sup>[6-9]</sup> Methamphetamine use induces a wide variety of psychiatric disorders such as psychotic,<sup>[10]</sup> mood,<sup>[11]</sup> sleep,<sup>[12]</sup> sexual,<sup>[13]</sup> cognitive,<sup>[14]</sup> and violent behaviors.<sup>[15,16]</sup> Methamphetamine-induced psychotic disorder (MIP) cannot be easily differentiated from other primary psychotic disorders.<sup>[5,17]</sup> Methamphetamine causes persistent damage to dopaminergic and serotonergic nerve terminals, gliosis, and apoptosis through various mechanisms.<sup>[18-20]</sup> The brain structures involved in cognitive functioning such as memory, attention, speed of cognitive processing, and executive functions (EFs) are damaged in

chronic methamphetamine users.<sup>[21]</sup> The psychiatric symptoms and clinical course of MIP and schizophrenia are very similar, which make it difficult to distinguish between MIP and schizophrenia.<sup>[22,23]</sup> Previous studies have not demonstrated a clinically significant distinction between schizophrenia and MIP.<sup>[5,24]</sup> The patients with schizophrenia show a wide variety of EFs deficits in verbal, working, and implicit memory, which is related to the neuronal dysfunction in the prefrontal cortex.<sup>[25]</sup> Chronic methamphetamine use is also associated with a wide range of cognitive deficits, especially in EFs.<sup>[26-31]</sup> Not surprisingly, patients with MIP also have similar cognitive dysfunctions in working memory, episodic memory, information processing speed, and other EFs.<sup>[32,33]</sup> Many developmental or accidental adverse events may affect EFs.<sup>[34]</sup> Executive dysfunctions are mainly related to neural

Mohammadrasoul Khalkhali, Mahboobeh Golshahi, Tolou Hasandokht<sup>1</sup>, Moosa Kafie<sup>1</sup>, Roghaye Zare<sup>2</sup>

From the Department of Psychiatry, Shafa Psychiatry Hospital, Guilan University of Medical Sciences, Rasht, Iran, <sup>1</sup>Department of Psychology, University of Guilan, Rasht, Iran, <sup>2</sup>Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran

**Address for correspondence:**  
Dr. Mahboobeh Golshahi,  
Department of Psychiatry,  
Shafa Psychiatry Hospital,  
Guilan University of Medical  
Sciences, Panzdah-e Khordad  
St. 4165863795, Rasht, Iran.  
E-mail: mahboobeh\_golshahi@  
yahoo.com

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dysfunctions in the frontal and parietal cortex, but many other cortical and subcortical pathways are likely to be involved in this pathology.<sup>[35,36]</sup> The previous studies have reported similarities and significant differences in the cognitive functioning and performance on neurocognitive tests between MIP and schizophrenia.<sup>[37-39]</sup> Although Jacobs *et al.*<sup>[37]</sup> did not find any differences in cognitive functioning between patients with MIP and schizophrenia, Ezzatpanah *et al.*<sup>[38]</sup> reported that the patients with MIP had significantly better performance on visual search and attention test (VSAT) than did the patients with schizophrenia. It can be an important finding and needs to be repeated in more controlled studies. Considering the brain's structural and functional abnormalities<sup>[21,40]</sup> and cognitive impairment of the patients with MIP, we hypothesized that the performance of the patients with MIP and schizophrenia would be different on VSAT and Rey–Osterrieth complex figure (ROCF) neuropsychological tests which assess EFs and visual memory-related neurologic pathways and might help us differentiate these two very similar clinical conditions. The main reasons for choosing VSAT and ROCF test were as follows: (1) the reported significant difference on the performance of the patients with MIP and schizophrenia on VSAT,<sup>[38]</sup> (2) other neuropsychological tests which assess EFs were not able to find any significant differences, (3) ROCF test is a simple test for the evaluation of visual memory and visuoconstructional; episodic memory, processing speed, motor skills, and visuoconstructional abilities in acute and chronic methamphetamine users have been studied,<sup>[26,41]</sup> but visual memory and visuoconstructional ability of patients with MIP are less properly studied, and (4) the simplicity and brevity of these tests that can be used easily in clinics. Therefore, this study aimed to ascertain whether patients with MIP, those with schizophrenia, and those in the healthy control groups have different performances on cognitive tests.

## Materials and Methods

### Participants and study design

This cross-sectional study was conducted in Shafa Psychiatry University Hospital and a psychiatry clinic in Rasht, the capital of Gilan province. Our study populations were 31 patients with schizophrenia, 30 patients with MIP, and 31 healthy controls. The participants were included in the study if they were 20–50 years old and had 5 or more years of schooling. A resident of psychiatry performed simple screening of consecutive patients and then invited those who fulfill the inclusion criteria. The patients with MIP and schizophrenia were selected from psychiatric wards (all of the patients with MIP, 25 patients with schizophrenia) or clinics of the hospital (two patients with schizophrenia) or the afore-mentioned outpatient clinic (3 patients with schizophrenia). A board-certified psychiatrist evaluated the patients and concluded that

the patients with MIP met DSM-5 diagnostic criteria for amphetamine-like use disorders and amphetamine-like induced psychotic disorders (292.89). The diagnosis was based on clinical interview. The patients with schizophrenia met DSM-5 criteria for schizophrenia. If the patients with schizophrenia had a history of substance use or the patients with MIP had a history of using any other drugs or substances in the preceding month of admission or a history of psychiatric disorders, they were excluded from the study. The controls were selected from the family of the clients or staff members of the clinic or Shafa Hospital. After a psychiatric interview, people with no history of illicit drug use or a major psychiatric disorder were enlisted as control group. All participants had normal or corrected-to-normal visual acuity and normal color vision. We asked about any history of ophthalmic problems, using eyeglasses, or any problem in color vision. Before starting the tests, we checked the visual acuity by E-charts and color vision by showing red and blue and green test-size letters at a distance of 40 cm. We matched schizophrenia and control groups on age, sex, and education with MIP group.

Neuropsychological tests were done for all three study groups. The tests were done in a silent, well-equipped, and private room. Enrolment was made after primary stabilization of the patients with schizophrenia and MIP and after confirming the final diagnosis. The patients were not sedated, confused, or aggressive and were able to take part in the tests. The MIP group members were abstinent in the time of testing. A professor of clinical psychology who was blind to diagnostic status supervised all of the procedures and also evaluated and interpreted the results of neuropsychological tests. The written informed consents were obtained both from the patient and from a responsible (legally authorized) family member in each case. This study received ethics approval from the Research Ethics Committee of the Guilan University of Medical Sciences (Ethics Approval Code No: 1930003508). All phases of this study were performed according to the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

### Measures

ROCF test is one of the most widely used neuropsychological tests for the evaluation of nonverbal memory skills, visual memory, visuospatial constructional ability, fine-motor coordination, and organizational skills. It can be considered a useful tool for the evaluation of EFs of the brain.<sup>[42]</sup> In ROCF test, examinees are asked to reproduce a complicated line drawing, first by copying it freehand (recognition), and then drawing from memory (recall). The test is not timed, but the length of time needed to complete the test is recorded. Each copy is scored for the accurate reproduction and placement of 18 specific design elements. Each patient connected to the accuracy of the draw receives between 0 and 36 scores.

This scoring system is the most commonly used in scoring copy and recall reproduction of the ROCF, but several other qualitative and quantitative scoring systems also have been proposed which focus on different aspects of reproduction, accuracy, organization, strategy, and style. The qualitative scoring methods are more sensitive to EFs, but the main disadvantage of qualitative systems is the complexity and considerable time commitment required to learn it.<sup>[43]</sup> ROCF test would be helpful for the evaluation of the EFs that is mediated by the prefrontal lobe, as well as visual construction ability and visuospatial memory.<sup>[44]</sup> Our study has measured the organizational strategies with quantitative scoring system and is not able to evaluate comprehensively EFs that are required for performing ROCF. ROCF test might be a good tool for monitoring the improvement of cognitive deficits during illness in patients with MIP. The ease of administration as well as the low cost of this test is a considerable advantage of this test.

VSAT assesses sustained attention and visual accuracy. VSAT consists of four search trials.<sup>[35,36]</sup> The examinees must search and find target signs which are written on the top of the pages in each trial. Every trial contains 10 rows and each row consists of 40 items. The first trial contains black letters on a white background and the target letter is F. The second trial consists of black symbols and the target letter is. The third trial contains colored letters (red, green, and blue) and a blue H is the target letter and the fourth trial contains colored items (red, green, and blue) and a blue/is the target item. Examinees must mark as many target items as they can in 60 s, and their practice is determined based on their results from only the last two trials and number of items they mark on the left and right side in 60 s.

### Statistical analysis

Data are expressed as mean (standard deviation [SD]) or frequency (%). Normal distribution assumption was checked by Kolmogorov–Smirnov test. Comparison of continuous demographic characteristics between three groups was checked by analysis of variance (ANOVA) or Kruskal–Wallis test. Comparison of categorical demographic characteristics between three groups was checked by Chi-square or Fisher’s exact test. One-way ANOVA was performed to compare the mean score of ROCF, VSAT, and the time of the test administration between three groups of study. Tukey’s HSD test was used for *post hoc* analysis. The effect size between two groups was calculated using Cohen’s  $d$ <sup>[45]</sup> (difference between the means divided by the pooled SD). Cohen suggested that  $d = 0.2$  be considered a “small” effect size, 0.5 represents a “medium” effect size, and 0.8 represents a “large” effect size. Study analysis was performed using Statistical Package for the Social Sciences version 23.0 (SPSS Inc., Chicago, Illinois, USA), with the level of significance being  $P < 0.05$  (two-tailed).

## Results

The average age of the participants was  $36.71 \pm 7.83$  years. The average and median years of education was  $9.59 \pm 2.96$  and 9 years. The groups were homogeneous in terms of demographic characteristics [Table 1]. As shown in Table 2, three groups had significant differences according to ROCF test ( $F = 15.76$ ,  $P < 0.0001$ ), VSAT ( $F = 39.78$ ,  $P < 0.0001$ ), left VSAT ( $F = 37.96$ ,  $P < 0.0001$ ), right VSAT ( $F = 40.40$ ,  $P < 0.0001$ ), and the time of the test administration ( $F = 3.26$ ,  $P = 0.04$ ). The *post hoc* analysis showed that the mean score of ROCF test and VSAT (total, right, and left) was significantly higher in the control group than in the other two groups [Table 2]. The time of administering the test in the control group was significantly shorter than in the MIP group ( $P < 0.03$ ) and nonsignificantly shorter than in the schizophrenia group ( $P = 0.54$ ). The mean score of right side VSAT was significantly higher in the MIP group than in the schizophrenia group. There was not a significant difference between MIP group and schizophrenia group by the other tests [Table 2].

## Discussion

The results of this study revealed that both patients with schizophrenia and MIP had lower values on VSAT and ROCF tests in comparison with those in the control group. Inconsistent with our hypothesis, ROCF test could not differentiate MIP from schizophrenia. VSAT scores (both in the right and left) were higher in patients with MIP than in patients with schizophrenia, and this difference reached a significant level, only in the right side. This finding was partly consistent with the results of Ezzatpanah *et al.*’s study that reported right VSAT is able to differentiate MIP from schizophrenia.<sup>[38]</sup> Probably, due to the small sample size, our study could not show this difference on the left side.

### Visual search and attention test

It can be concluded that sustained attention and visual accuracy in patients with schizophrenia and MIP is disrupted. Our results are consistent with the findings of previous studies that have reported executive dysfunction in schizophrenia<sup>[25,38,42]</sup> and patients with MIP.<sup>[26-28]</sup> Although the results of this study were partly consistent with the results of Ezzatpanah *et al.*’s<sup>[38]</sup> study, it must be pointed out that our inclusion criteria were different. The use of other substances that might affect cognitive functions was controlled well, and patients with transient psychosis (with symptoms lasting  $<1$  week) were not included in our study. Prefrontal and superior parietal lobes support the brain EFs, especially selective attention.<sup>[46-48]</sup> Their circuits tune out the irrelevant information and permit only a small part of the information to be processed.<sup>[49,50]</sup> The patients with schizophrenia have a poor performance on visual search tasks.<sup>[42,51]</sup> It can be concluded that the patients with

**Table 1: Demographic characteristics of patients with schizophrenia, methamphetamine-induced psychotic disorder, and healthy control**

Variables	Total (n=92)	SZ (n=31)	MIP (n=30)	HC (n=31)	P
Age (mean±SD)	36.71±7.83	34.8±8.71	38.40±7.01	36.9±7.48	0.22 <sup>a</sup>
Education (mean±SD)	9.59±2.95	9.35±3.03	10.07±2.69	9.35±3.16	0.259 <sup>b</sup>
Sex, n (%)					
Male	86 (93.5)	29 (93.5)	28 (93.3)	29 (93.5)	1.0 <sup>c</sup>
Female	6 (6.5)	2 (6.5)	2 (6.7)	2 (6.5)	

<sup>a</sup>One-way ANOVA, <sup>b</sup>Kruskal–Wallis, <sup>c</sup>Fisher’s exact test. SZ: Schizophrenia, MIP: Methamphetamine-induced psychotic disorder, HC: Healthy control, SD: Standard deviation, ANOVA: Analysis of variance

**Table 2: Univariate analysis for three tests in study population**

Test	Groups	Mean±SD	F	P <sup>a</sup>	Effect size					
					SZ-MIP	P <sup>b</sup>	SZ-HC	P <sup>c</sup>	MIP-HC	P <sup>d</sup>
ROCF	SZ	10.00±4.42	15.76	<0.0001	-0.06	0.94	-1.00	<0.0001	-0.80	<0.0001
	MIP	10.43±5.81								
	HC	16.35±4.60								
VSAT left side	SZ	28.84±7.87	37.96	<0.0001	-0.35	0.12	-1.77	<0.0001	-1.00	<0.0001
	MIP	35.13±15.65								
	HC	55.23±12.68								
VSAT right side	SZ	26.58±8.21	40.40	<0.0001	-0.43	0.04	-1.96	<0.0001	-0.98	<0.0001
	MIP	34.60±16.68								
	HC	54.55±11.63								
Total	SZ	55.42±15.51	39.78	<0.0001	-0.40	0.06	-1.89	<0.0001	-0.99	<0.0001
	MIP	69.73±31.84								
	HC	109.13±23.78								
Time	SZ	2.97±1.20	3.26	0.04	-0.25	0.30	0.20	0.54	0.49	0.03
	MIP	3.38±1.16								
	HC	2.68±0.84								

<sup>a</sup>Univariate analysis, ROCF, VSAT, <sup>b</sup>Tukey *post hoc* test between SZ and MIP, <sup>c</sup>Tukey *post hoc* test between SZ and HC, <sup>d</sup>Tukey *post hoc* test between MIP and HC. SZ: Schizophrenia, MIP: Methamphetamine-induced psychotic disorder, HC: Healthy control, ROCF: Rey–Osterrieth complex figure test, VSAT: Visual search and attention test, SD: Standard deviation

schizophrenia as well as those with MIP have problems with sustained attention and visual search and controlling distracters. The better performance of patients with MIP on VSAT right side that is reported in this and in the previous studies<sup>[38]</sup> needs to be reevaluated in more controlled studies.

### Rey–Osterrieth complex figure test

This is the first study on the use of ROCF test for the evaluation of neuropsychological problems of patients with MIP.<sup>[52]</sup> The patients with schizophrenia were deficient in visual memory and organizational deficit related to visual memory deficit.<sup>[53]</sup> The results of our study revealed that ROCF test is able to show neurocognitive deficits in patients with schizophrenia and MIP, although, inconsistent with our hypothesis, it could not differentiate schizophrenia with MIP. Interestingly, the time of administering the test was significantly longer in patients with MIP and not in patients with schizophrenia. Using the traditional scoring system, ROCF test might be helpful for the evaluation of visual construction and visuospatial memory impairments of patients with MIP, mediated by frontal and parietal lobes.<sup>[54]</sup>

It can be concluded that the patients with schizophrenia as well as those with MIP have problems with visual memory and with visual and visuospatial memory.

After the selection of cases, our sample consisted of abstinent psychotic methamphetamine users with a history of long time (at least 6 months) repeated, high-dose substance use. The acute effects of methamphetamine use occur shortly after the substance use when methamphetamine is detectable in the body, but the long-term effects of repeated methamphetamine use occur when methamphetamine is no longer detectable in the body fluids.<sup>[26]</sup> Therefore, in this study, we really assessed the cognitive effects of long-term use of methamphetamine in psychotic abstinent patients with MIP. It is important because many studies of cognitive effects of methamphetamine are based on the acute effects of methamphetamine use on the brain and cognition.<sup>[27]</sup> Methamphetamine is a neurotoxic agent that gradually damages the neural cells.<sup>[55]</sup> The impact of repeated, long-term doses of methamphetamine due to ethical limitations in laboratory studies is less clear. The study of the cognitive performance of abstinent long-term methamphetamine users has been considered

as an alternative approach.<sup>[37]</sup> Considering the increasing evidence that indicates chronic methamphetamine use has more adverse effects on the cognitive abilities of the drug users,<sup>[56]</sup> it is reasonable that neurocognitive deficits appeared a long time after substance use in our sample.

Like other studies, our study had some strengths and limitations. The main strength of our study was the carefully controlled drugs and substances use in the groups. Our study had some limitations. First, the substance and drug use is very common in patients with schizophrenia; on the other hand, the use of other substances such as cannabis and opioids is very common in Iranian patients with MIP. We evaluated many patients with schizophrenia and MIP; however, unfortunately, because of the high prevalence of substance use in the schizophrenia group and other substance use, expect methamphetamine, in the MIP group, the number of eligible patients that could be included in the study was limited. It means that we had to exclude a number of patients that might have deficits in their neuropsychological tests. Second, although the newly published researches have classified the MIP into different clinical groups according to the duration of psychotic symptoms,<sup>[5]</sup> we did not consider such classification. Chen *et al.*<sup>[33]</sup> found that cognitive functioning in persistent MIP (duration of symptoms >1 month) was worse than that in other groups. They also classified the patients according to their psychotic symptoms and found out that like schizophrenia,<sup>[57]</sup> negative symptoms are strongly correlated with a poor cognitive performance in neuropsychological tests. Whether such differences resulted from methamphetamine use or from the users' predisposing characteristics is not clear and needs further studies, but there is ample evidence that similar neurodegenerative mechanisms may exist with both patients with schizophrenia and those with MIP.<sup>[5,33]</sup> Therefore, the heterogeneous presentations of psychosis may have influenced the results of the cognitive tests. Third, antipsychotic use can cause cognitive impairments, especially EFs.<sup>[58]</sup> We did not match the use of antipsychotics between two groups. All of the patients in our sample were taking olanzapine, risperidone, and aripiprazole. The confounding effects of the medication use patterns (i.e., dosage and duration of use) were not considered. Fourth, it was a cross-sectional study and the cognitive deficits predating MIP were unable to be differentiated from those deficits that result from it. The relationships between the use of antipsychotic, psychotic symptoms and cognitive dysfunctions call for additional study. Fifth, we used only ROCF quantitative scoring system. Therefore, the results of ROCF test need to be interpreted carefully, as with other neuropsychological tests. Sixth, due to our limited number of cases, we could not match on the duration of illness, which can be considered an important confounder in both groups. Patients with prolonged duration of illness may show more deficits in their performance in neuropsychological tests,<sup>[33]</sup> which

could explain some of the observed differences. Seventh, our sample size was small. Further evaluations with greater sample sizes are recommended.

## Conclusion

Although both patients with schizophrenia and those with MIP had a poor performance on VSAT and ROCF tests in comparison to those in the healthy control group, the differences between these very similar clinical conditions were only statistically significant in right VSAT following *post hoc* testing. The ease of administration and interpretation as well as the low cost of these tests are the considerable advantages of these tests. There are many unanswered questions about the clinical diagnosis of MIP. Further evaluations with more neuropsychological tests and functional neuroimaging are recommended.

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## Conflicts of interest

There are no conflicts of interest.

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