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•ORIGINAL RESEARCH ARTICLE•

A Comparison Study of Working Memory Deficits between Patients with Methamphetamine-Associated Psychosis and Patients with Schizophrenia

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Background: Both patients with methamphetamine-associated psychosis (MAP) and patients with schizophrenia suffer from obvious cognitive deficits in working memory, and this affects the functional prognosis of patients.

Aim: This study is to investigate the difference of working memory deficits between patients with MAP and patients with schizophrenia, especially the difference of central executive system function, and the relevance of working memory deficits and clinical characteristics.

Methods: Twenty-eight male patients with MAP and twenty-eight patients with schizophrenia were recruited. The working memory of subjects was evaluated with the n-back task edited and adapted from English language materials. The positive syndrome scale of PANSS and CGI were employed to assess psychotic symptoms and the severity of patients.

Results: According to the results of repeated measure variance analysis, it was found that both the between-group variable (group) and within-group variable (n) had significant main effects, and the interaction between the between-group variable and the within-group variable was also significant. After Z-transformation, mean (sd) working memory scores of patients with MAP and schizophrenia were 0.91 (0.77) and -0.91 (2.11) respectively, and the difference between these two groups were statistically significant (F=19.253, p<0.001). The relevance between working memory deficits and clinical characteristics was low in both the patients with MAP and patients with schizophrenia.

Conclusion: Patients with MAP were better at regulating, updating, executing and controlling active information than patients with schizophrenia.

Key words: methamphetamine-associated psychosis; schizophrenia; working memory; n-back task

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1. Introduction

Substance abuse is a global public hazard, and according to the statistics, the number of people who abuse substances globally is 250 million[1]; moreover, the number of people who abuse synthetic drugs represented by methamphetamine (MA) is significantly increasing. In China, MA has replaced heroin to be the number one most commonly used drug.[2] MA's pharmacological activities include drug dependence, excitability and can cause psychotic symptoms, such as hallucinations and delusions.[3,4] The clinical presentation of methamphetamine-associated psychosis (MAP) is very similar to that of schizophrenia with hallucinations, persecutory delusions, reference delusions and cognitive impairment.[5] Studies have found that MA can increase glutamate neurotransmitters from the cortex to substantia nigra striatum and mesencephalic limbic system, and also increase dopaminergic neurotransmitters in the mesencephalon-cortex pathway; however, excessive glutamate and dopamine in the cerebral cortex exceed the inhibitory effect of GABA, thereby causing the presence of psychotic symptoms.[6]

As the working platform of advanced cognitive function, working memory (WM) is very important in daily life. WM includes one central executive system and two subsystems, and the central executive system is characterized by functions like controlling, regulating and updating.[7] It has been found in studies from both China and abroad that patients with MAP and patients with schizophrenia show obvious WM deficits, and WM deficits have an impact on and foretell patients' functional prognosis.[8] However, there is little research on WM of patients with MAP and patients with schizophrenia; therefore, there is no clear conclusion on this topic. Jacobs and colleagues[9] evaluated verbal WM with a repetitive set of neuropsychological tests and found that degrees of WM deficits in patients with MAP and patients with schizophrenia were similar; while Chen and colleagues[10] evaluated verbal WM with cognitive assessments of simple schizophrenia and found that MAP patients' verbal WM was better than in patients with schizophrenia. The present study aimed to clarify degrees of WM deficits (especially the central executive system) in patients with MAP and patients with schizophrenia and the relevance between WM deficits and clinical characteristics with a sample of patients with MAP and patients with schizophrenia and employing the n-back task to evaluate the central executive system of WM.

2. Methods

2.1 Participants

It has been found in previous studies that there is an obvious gender difference in cognition deficits within patients with MAP, and the majority of patients who abuse substances are male.[11] Therefore, the present study only recruited male patients as subjects.

2.1.1 The MAP group

All subjects in this group were being treated at the Shanghai Compulsory Detoxification Center in 2016. Inclusion criteria: (1) subjects who met the diagnostic criteria for MAP according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-RT); (2) subjects who were not diagnosed with any other mental disorder after being interviewed with the MINI-International Neuropsychiatric Interview (M.I.N.I) 6.0; (3) aged from 18 to 45; (4) subjects with Han ethnicity and normal eye sight or corrected eye sight; (5) subjects who did not abuse any drugs other than MA; (6) subjects who were abstinent for at least 24 hours before enrollment to prevent an amphetamine poisoning effect; (7) subjects who provided consent or had consent provided by guardians. Exclusion criteria: subjects who had organic brain diseases, had severe medical conditions, or received ECT in the past 6 months, or uncooperative and/or high risk patients who had agitation, elation or suicidal ideation.

2.1.2 The schizophrenia group (SCZ group)

All subjects in this group were inpatients at the Shanghai Mental Health Center from 2014 to 2016. Inclusion criteria: (1) subjects who met the diagnostic criteria for schizophrenia according to the DSM-IV-TR; (2) subjects who were not diagnosed with any other mental disorders after being interviewed with the M.I.N.I 6.0; (3) aged from 18 to 45; (4) participants who were Han and had normal eye sight or corrected eye sight; (5) participants provided consent or consent was provided by their guardians. Exclusion criteria: subjects who had organic brain disease, severe medical conditions, used psychoactive substances before or had received ECT in the past 6 months, or uncooperative and/or high risk patients who were agitated or had suicidal ideation.

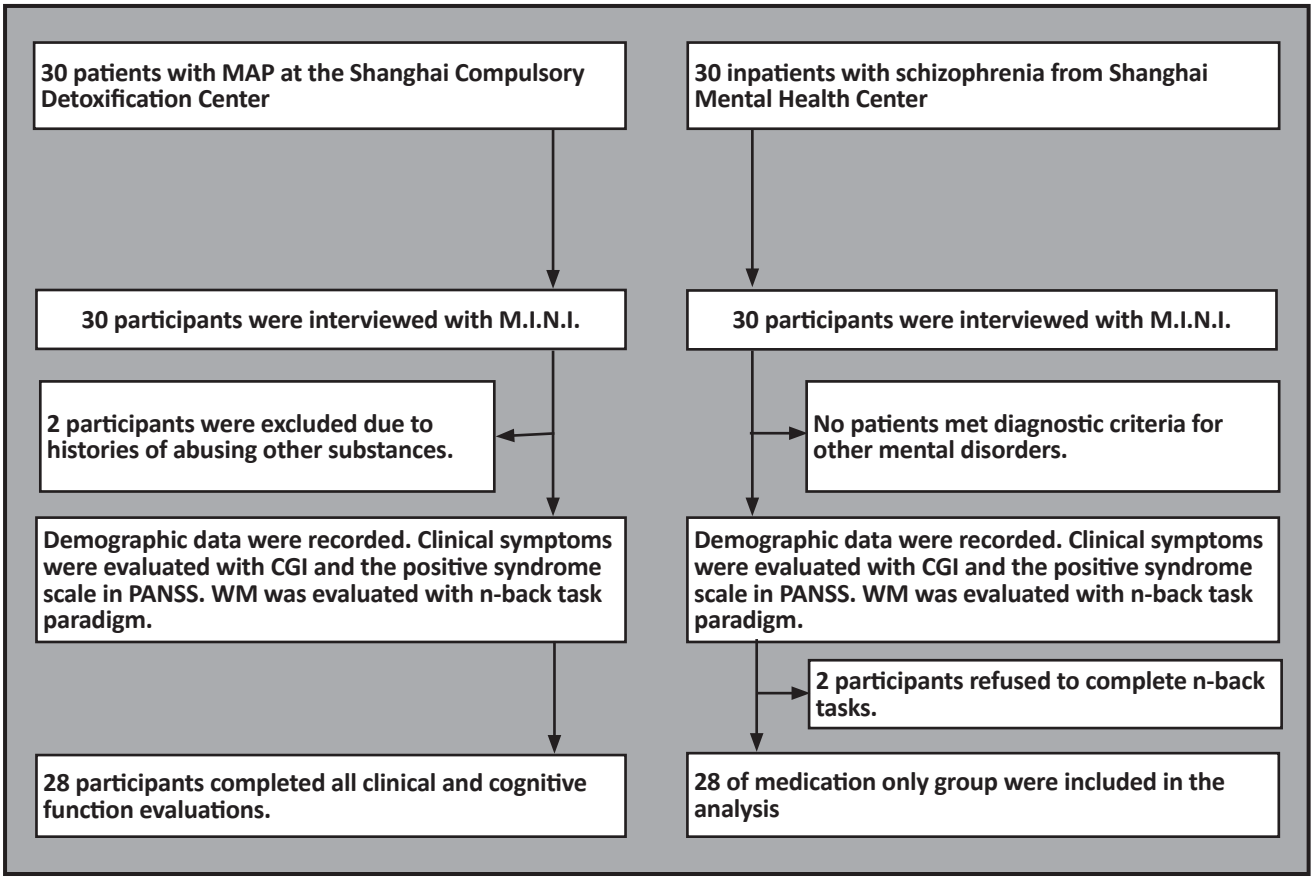
A total of 30 patients with MAP were recruited into the present study, but 2 of them were excluded due to histories of abusing other substances (one was comorbid with cocaine abuse and the other one was comorbid with marijuana). A total of 30 patients with schizophrenia were recruited, and 2 of them refused to complete the n-back task. Figure 1 shows the procedure of recruiting and evaluating participants.

2.2 Assessments

2.2.1 Evaluation of psychotic symptoms

The positive syndrome scale from the Positive and Negative Syndrome Scale (PANSS) was employed to evaluate the psychotic symptoms and severity of patients. The positive syndrome scale includes 7 items: P1 delusion, P2 disorganized concepts, P3 hallucination

Figure 1. The flowchart of the study



behaviors, P4 elation, P5 grandiosity, P6 persecutory delusions, P7 hostility; every item is on a scale of 1-7, and the theoretical range of the total score is from 7 to 49. The Chinese version of this scale has relatively good reliability and validity, and it is suitable for quantitative evaluations of schizophrenic symptoms.[13] Clinical Global Impression (CGI-S)[14] was used to evaluate subjects social function and severity of illness on a scale of 0-7: (0) no illness; (1) basically not ill; (2) extremely mild; (3) mild; (4) medium; (5) relatively severe; (6) severe; (7) extremely severe.

2.2.2 Evaluation of craving

Visual analog scales (VAS) was employed to evaluate the degrees of craving for MA of subjects with MAP. The specific steps are described as the following: A straight line with a length of 100mm was presented; 0 mm indicated that there was no craving at all, and 100 mm indicated the strongest craving. The subjects were asked to mark the position which represented their craving the most appropriately, and the length between 0 mm and the marked position indicated the degrees of craving of subjects with MAP.

2.2.3 Evaluation on working memory

The n-back task based on verbal materials was applied by the present study to evaluate subjects' abilities to regulate, update and executively control active information. This n-back task is viewed as the classic paradigm of assessing WM.[16] The variable n can be equal to 0, 1 or 2. When n=0, subjects are asked to only respond to the current task, and some scholars suggest that this mainly reflects subjects' ability to concentrate their attention.[17] When n=1, subjects are asked to compare the current task and the previous one to determine whether they are identical or not (match or not), and respond with corresponding buttons. When n=2, subjects are asked to compare the current task and the task which appeared just before the previous task to determine whether they are identical or not, and respond with corresponding buttons.

The present study employed E-prime 2.0 to code the experiment program, and 8 capital consonant letters (C, H, K, M, P, S, V and X) were chosen to be stimuli. At the beginning of the experiment, a central fixation cross "+" was presented for 500ms, and then a stimulus was presented in the center of the screen (i.e., any letter of

the 8 letters described before). After the subject pushed the button, the stimulus disappeared. If the subject did not respond within 3000ms, the stimulus would disappear automatically (i.e., the longest reaction time was 3000ms). The total number of trials were 80 with 30 percent of which were match trials, and the main result was the correct rate (%) of correctly responding to match trials. There were at least ten practice trials before every experiment, which required subjects to fully understand the purpose and procedure of trials. As for some patients who needed more practice trials, the number of practice trials could increase till the patients fully understood the experiment. Figure 2 shows the WM task when n=2.

2.3 Data analysis

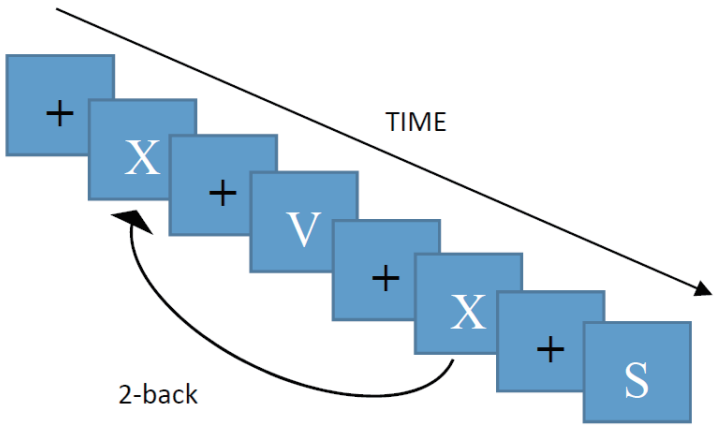
SPSS 19.0 statistics software package was used in the data analysis. Independent-sample t tests were conducted to compare the demographic and clinical characteristics between the two groups. Moreover, 2*3 repeated measure variance analysis was employed to analyze data of n-back tasks, and the group (MAP group and SCZ group) was the between-group variable with 2 levels; whereas the memory load n was the within-group variable (n was equal to 0, 1 and 2 respectively) with 3 levels. Some scholars state that when n=0, the task, which only requires subjects to respond to the current task and mainly reflects subjects' ability to concentrate, is relatively simple, and the memory load is extremely small.[17] Therefore, the present study converted the n-back task scores to standard scores, i.e., $Z_{n\text{-back}}$, and $Z_{wm}=(Z_{1\text{-back}}+Z_{2\text{-back}})$ indicating subjects' WM ability. Applied covariance analysis was conducted to compare the differences in WM between the two groups. In addition, the correlation between WM and demographic and clinical characteristics were analyzed with correlation analysis. All statistical tests were conducted as two-tailed tests, and $p<0.05$ was considered statistically significant.

3. Results

3.1 Comparisons of demographic and clinical characteristics between the MAP group and SCZ group

Table 1 shows the demographic and clinical characteristics of the MAP group and SCZ group. Participants in both groups were all male, and their ages and education levels were not significantly different from each other. The mean (SD) scores of the positive syndrome scale in PANSS of the MAP group and SCZ group were 14.32 (4.21) and 19.50 (5.47) respectively, and their mean (SD) severity of illness scores as evaluated by CGI were 4.29 (0.71) and 4.79 (0.92) respectively. The differences between the two groups were statistically significant, and it suggests that the scores of patients with schizophrenia in positive symptoms such as hallucinations and delusions are significantly higher than those of patients with MAP.

Figure2. The diagram of n-back task(n=2)



Note: The diagram shows four tests with stimulus material being X, V, X, and S, respectively. The test 3 is a matching test (the stimulus material of the test 3 is the same as test 1). Therefore, the subject is required to press the "F" key to react. The test 4 is a non-matching test (the stimulus materials of the test 4 and test 2 are different), then the subject is required to press the "J" key.

Table 1. Comparisons of demographic and clinical characteristics between the MAP group and SCZ group

	SCZ group (n=28)	MAP group (n=28)	*t*	*p*
Age (year-old)	30.32(7.09)	33.32(6.13)	1.69	0.096
Education (year)	11.25(3.90)	9.71(2.36)	1.78	0.081
Age of onset (year-old)	24.79(6.65)			
Duration of illness (year)	4.90(7.44)			
Number of episodes	2.07(2.14)			
Age of first MA abuse (year)		24.75(6.43)		
Duration of abusing MA (year)		6.88(3.93)		
Number of abstinences from MA		1.71(0.76)		
Duration of abstinence from MA (month)		3.18 (1.22)		
Craving		5.24 (2.69)		
Scores on the positive syndrome scale of PANSS	19.50 (5.47)	14.32 (4.21)	3.97	<0.001
CGI-S	4.79 (0.92)	4.29(0.71)	2.28	0.027

Note: (1) SCZ: schizophrenia; (2) MAP: methamphetamine-associated psychosis; (3) PANSS: Positive and Negative Syndrome Scale; (4) CGI-S: Clinical Global Impression-Severity Scale

3.2 Comparisons of WM between the MAP group and SCZ group

According to the results of the repeated measure variance analysis, the main effect of the between-group variable (group) was significant (F=14.56, p<0.001), and the main effect of the within-group variable (n) was also significant (F=116.38, p<0.001). Furthermore, the interaction of the between-group variable and within-group variable was significant (F=9.45, p<0.001, refer to Table 2 for more specific information). The results indicate that the accuracy of n-back tasks in the MAP group was higher than that in SCZ group, and there is an interaction between it and the n-back task loads.

After data was converted to Z scores, covariance analysis was conducted with $Z_{0\text{-back}}$ as the covariant. The results show that the Z_{wm} ($Z_{1\text{-back}}$+$Z_{2\text{-back}}$) of the MAP group and the SCZ group were 0.91 (0.77) and -0.91 (2.11) respectively, and there is a significant difference between the two groups (F=19.25, p<0.001). This indicates that the WM scores in the MAP group are higher than those in SCZ group.

3.3 Correlation between WM deficits and clinical characteristics in the MAP and SCZ groups

Correlation analysis was conducted with Z_{wm} ($Z_{1\text{-back}}$+$Z_{2\text{-back}}$) as the dependent variable, and demographic and clinical characteristics as independent variables. Results of neither MAP group nor SCZ group show any statistically significant differences, which indicates that WM deficits in both the MAP group and SCZ group have insignificant correlations with the demographic and clinical characteristics mentioned before.

4. Discussion

4.1 Main findings

It has been found in the present study that WM of the MAP group and SCZ group is significantly different from each other by comparing and studying the WM abilities in both groups, and this significant difference still exists after the attention factor being controlled, which indicates that the MAP groups' WM ability (especially the central executive ability) is significantly better than that in the SCZ group. Chen and colleagues'[10] research also drew similar conclusions that the WM ability of patients with MAP was significantly better than that of patients with schizophrenia by evaluating the cognitive functions of patients with MAP and patients with schizophrenia with cognitive assessments of simple schizophrenia. However, Jacobs and colleagues[9] concluded that the cognitive impairments of MAP patients and patients with schizophrenia were similar after evaluating the WM status of patients with MAP and patients with schizophrenia with a repetitive set of neuropsychological tests. Jacobs suggested that the small sample size (only 19 patients with schizophrenia and 20 patients with MAP), unmatched ages and races in the two groups and the low sensitivity of cognitive function assessment tools applied were possible factors that caused the negative results. Hence, based on the current results, we suggest that MAP patients'

Table 2. Comparisons of n-back accuracy between the MAP group and SCZ group

n-back task	SCZ	MAP	Load		Group		Load*Group	
			F	*P*	*F*	*P*	*F*	*P*
WM			116.38	<0.001	14.56	<0.001	9.45	<0.001
0-back	0.94(0.09)	0.96(0.03)						
1-back	0.86(0.14)	0.95(0.04)						
2-back	0.69(0.15)	0.82(0.82)						

Note: (1) SCZ: schizophrenia; (2) MAP: methamphetamine-associated psychosis

Table 3. Comparisons of Z scores between the MAP group and SCZ group

	SCZ	MAP	*F*	*p*
Z_{WM}	-0.91 (2.11)	0.91 (0.77)	19.25	<0.001

Note: (1) SCZ: schizophrenia; (2) MAP: methamphetamine-associated psychosis; (3) $Z_{WM}=(Z_{1\text{-back}}+Z_{2\text{-back}})$

regulation, update and executive control of active information are better than those of patients with schizophrenia.

WM has an important impact on both patients' treatment effectiveness and functional prognosis. A systematic review which includes 34 studies has found that the WM ability of patients with mental disorders influences their social functions and symptom recoveries positively, which means that the better the WM ability, the better the treatment effectiveness, thereby leading to better functional prognosis and social function recovery.[18] Some scholars even suggest that cognitive function can be viewed as a biomarker for the prognosis of patients with mental disorders.[19] Therefore, the different WM deficits of patients with MAP and patients with schizophrenia may influence the treatment effectiveness and functional prognosis differently, and more attention should be paid to the exercise and rehabilitation therapies of WM in the future treatments.

The present study evaluated subjects' WM with n-back tasks based on verbal materials, and it is generally believed that the parietal lobe (supramarginal gyrus) is an important brain area of voice WM; an impairment in this brain area can cause a decrease in patients' auditory-verbal memory span, so patients are unable to maintain the linguistic sequence in WM.[7] Ezzatpanah and colleagues [20] have found that compared to patients with MAP, patients with schizophrenia score lower in the visual search task which is mainly related to the functions of the parietal lobe. Therefore, the impairment of the parietal lobe in patients with schizophrenia being more severe than that in patients with MAP could be a possible basic mechanism for the present study's results. Even though there has not been any direct evidence supporting this conclusion, research on patients with schizophrenia has found that the impairment of the parietal lobe is significant[21], whereas the main brain damage of patients with MAP is located in the mesencephalon-cortex pathway and the frontal corpus striatum system.[6,22] There has been reports which state that MAP addicts have a lower level of dopamine transport protein in their corpus striatum[23-25] and frontal cortex[26], and structural brain imaging studies have also found a significant reduction in the volume of gray matter in the temporal lobe, the occipital lobe, the frontal lobe and the insula in patients who abuse MA, with the volume reduction of gray matter in the frontal lobe being the most common symptom.[27] However, there is little research reporting the impairment of the frontal lobe's function in MA addicts, and Eisch and Marshall have found that the mechanisms of nerve damage in rats' corpus striatum and the parietal cells may be different from each other in their animal experiments.[28] Therefore, one important reason for patients with MAP and patients with schizophrenia having different cognitive functions is that they have impairments in different brain areas, but this conclusion still needs more direct evidence, such as a comparison study of the brain images of patients with MAP and patients with schizophrenia.

In the present study's correlation analysis, there were no statistically significant correlations found between WM deficits and demographic data in patients

with MAP, which is in contradiction with previous studies. Salo and colleagues[22] have found that at the early stage of withdraw, MA addicts suffer from impairments in cognitive functions, and their cognitive functions improve gradually as time goes by. In addition, it has been found in a DTI study that MA can affect the nerve conduction in the white matter and fiber bundles of the brain[29], leading to the reduction of FA values in the right frontal white matter, the bilateral corona, the genu of corpus callosum, hippocampus and other parts of the brain; furthermore, the ADC value of the frontal white matter is positively correlated with the duration of abusing MA.[30] The resting state fMRI studies on MAP have also had similar findings.[31,32] The results of these studies indicate that the severity of impairments in cognitive functions in patients with MAP may be correlated with the duration of withdraw, however, the present study has not found similar results which is probably due to many factors. Combining the characteristics of patients recruited in the present study, we found that the possible main reason is that durations of withdraw of subjects are relatively similar (mainly from 2 to 4 months), whereas the longest duration of withdraw of MA addicts in Salo's study is over a year. Therefore, future studies with more diverse populations and longitudinal studies are needed to clarify the correlations between these factors. In addition, the sample size of the present study is relatively small, so the negative result is likely to be attributed to type II error. In this case, more trials should be repeated for more accurate results.

It is generally believed that the cognitive impairment in patients with schizophrenia is primary, and it has probably already taken place during the latent period or early stage of schizophrenia,[33] being a type of psychopathology independent of positive and negative symptoms to some extent.[34] The results of the present study support this theory. In the meantime, the present study's results also suggest that the impairment of cognitive function in patients with MAP is probably a relatively independent clinical symptom, which is in line with the results of Salo and colleagues[35] who did not find significant results in the correlation analysis after evaluating subjects' selective attention with Stroop trials and evaluating subjects' psychotic symptoms with PANSS. However, there has been research reporting that the cognitive deficits of MA addicts are correlated with the severity of anxiety, depression[36] or negative symptoms.[10] Currently, there is little research on the correlation between the cognitive function of MA addicts and their clinical characteristics, therefore any conclusions on this topic are unclear. The negative results of the present study may be related to the relatively limited clinical symptoms assessed and some potential correlations not being considered, therefore, further studies are needed.

4.2 Limitations

The present study has several limitations. Even though the present study employed the n-back task which is a classic paradigm of assessing WM, there are many other paradigms and scales available to assess WM. Therefore, it is necessary to evaluate patients' WM ability using multiple assessment tools together, which will make the research results more reliable. The present study is a cross-sectional study without longitudinal follow-up, so it cannot explore the dynamic changes in cognitive function by comparing the WM abilities of subjects at different stages. Moreover, the sample size of the present study is very small with only 28 subjects in each group. Therefore, some negative results (i.e., not being able to detect the differences between the two groups) may be attributed to type II error. Hence, more detailed follow-up studies with larger sample sizes are needed to lend evidence to the results of the present studies.

4.3 Implications

As a working platform for advanced cognitive functions, WM represents a psychological process which saves (maintains) and processes information with limited volume, and it is extremely important for daily life. WM mainly includes a central executive system and two subsystems, and the central executive system's functions involve executive control, regulation, updating and so on.[7] Studies published in China and abroad have found that both patients with MAP and patients with schizophrenia suffer from obvious WM deficits.[8] However, as of now, there have not been studies focusing on the WM of patients with MAP and patients with schizophrenia. The present study employed a neuropsychological assessment paradigm (n-back task) to evaluate subjects' WM abilities, and clarified the severity of impairment in WM function (especially the central executive system) in patients with MAP and patients with schizophrenia, along with the correlation between these WM deficits and clinical characteristics.

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Conflict of interest statement

The authors declare no conflict of interest related to this manuscript.

Informed consent

All participants and their legal guardians provided written informed consent before they participated in this study.

Ethical approval

The study was approved by the Ethics Committee of Shanghai Mental Health Centre (Approval number given by the Ethics Committee: 2016-33).

Authors' contributions

Dengtang Liu and Min Zhao participated in the study design process, and revisions of the drafts and the final paper; Hong Gan, Peiwei Xu and Hang Su recruited subjects and evaluated the clinical symptoms and cognitive function; Peiwei Xu and Yingying Pan entered the data; Hong Gan and Zhenhua Song analyzed the data and wrote the draft. All authors read and agreed upon the final version of this article.

甲基苯丙胺所致精神病性障碍与精神分裂症患者工作记忆缺陷的比较研究

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背景： 甲基苯丙胺所致精神病性障碍（methamphetamine-associated psychosis，MAP）患者和精神分裂症患者均存在明显的工作记忆等认知功能缺陷，并且均影响患者的功能预后。

目的： 探讨 MAP 患者和精神分裂症患者工作记忆缺陷，尤其中央执行系统功能的差异，以及工作记忆缺损与临床特征的相关性。

方法： 共入组了 28 例男性 MAP 患者及 28 例男性精神分裂症患者。应用基于语言材料编制的 n-back 任务评估被试的工作记忆。应用阳性与阴性症状量表（PANSS）的阳性量表及临床总体印象量表（CGI）评估患者的精神症状及其严重程度。

结果： 对 n-back 数据进行重复测验方差分析，结果发现组间变量（组别）及组内变量（n）的主效应均显著，组间变量与组内变量的交互作用亦显著。经 Z 转换后，MAP 患者及精神分裂症患者的工作记忆成绩分别为 0.91（0.77）和 -0.91（2.11），组间差异有统计学意义（F=19.253，p<0.001）。无论 MAP 患者或精神分裂症患者，其工作记忆缺陷与临床特征均缺乏相关性。

结论： MAP 患者对激活信息的管理、更新及执行控制能力优于精神分裂症患者。

关键词： 甲基苯丙胺所致精神病性障碍，精神分裂症，工作记忆，n-back 任务

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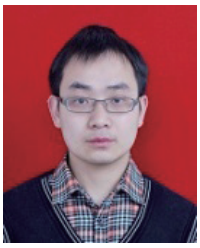

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Notice: Shanghai Archives of Psychiatry soon to be renamed General Psychiatry

Shanghai Mental Health Center will publish its last issue of the journal *Shanghai Archives of Psychiatry*, 2018 volume 30 issue 3, on 30th June 2018. The postal code is 4-798. The journal will be renamed *General Psychiatry* and presented to the readers as issue 4 on 30th August 2018.

Changing the name of the journal is a magnificent make-over. We aim to publish a high quality and international journal by cooperating with the BMJ publishing group. The mission of our journal will not change, however the new content and research will be much more innovative and comprehensive. This journal will continue to spotlight important academic exchanges between China and the rest of the world that promote the international development of mental health research.

General Psychiatry Editorial Department