ORIGINAL PAPER

Verbal Working Memory in Schizophrenia: Relationship to Cigarette Smoking and Psychopathology

Hazura H[1], Wan Norhaida WA[2], Ruzita J[3], Zahiruddin O[2]

[1]Department of Psychiatry and Mental Health, Hospital Raja Perempuan Zainab II, 15000 Kota Bharu, Kelantan, Malaysia
[2]Department of Psychiatry, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia
[3]Department of Psychiatry and Mental Health, Hospital Tuanku Fauziah, 01000, Kangar, Perlis

Abstract

Introduction: **A number of researches suggest *s*moking serves as a form of self-medication to reduce the side effects of antipsychotic medications, to alleviate negative symptoms, and/or to ameliorate a number of cognitive deficits associated with schizophrenia.** ***Objective:*** **The aim of this study was to investigate the association of cigarette smoking with verbal working memory and psychopathology of patients with schizophrenia.** ***Methods:*** **Fifty-three patients with schizophrenia were assessed by a single rater using the Malay Version of Auditory Verbal Learning Test (MVAVLT) and Positive and Negative Syndrome Scale (PANSS). Smokers (n=30) were compared with nonsmokers (n=23) on socio-demographic, clinical, psychopathology and verbal memory variables. Single linear and multiple regression analysis were performed to determine factors associated with verbal memory performance.** ***Results:*** **Verbal working memory performance is associated with lower number of admission to ward, lesser severity of the negative symptoms or general psychopathology of schizophrenia and use of atypical antipsychotics in all schizophrenic subjects. Smokers with schizophrenia scored higher than non- smoker in measures that reflect immediate memory, delayed recall and recognition memory. However, the association between verbal working memory performance and smoking status was found to be not significant.** ***Conclusion:*** **Verbal working memory performance is associated with negative symptoms but not positive symptoms. This study failed to detect association of smoking on verbal working memory.**

Keywords: Schizophrenia, Smoking, Working Memory

Introduction

Prevalence of smoking in patients with schizophrenia is up to four-fold higher compared the general population[1]. These observations remain true across cultures and countries and when controlling for possible confounders, such as marital and socio-

economic status, alcohol use, antipsychotic use, or institutionalism[2]. Patients with schizophrenia smoke more, favour stronger cigarettes and extract more nicotine from their cigarettes[3]. Several possible mechanisms have been hypothesized to explain the high prevalence of smoking seen in schizophrenia. Most of these suggest that nicotine serves as a form of self-medication to reduce the side effects of antipsychotic medications, to enhance the therapeutic effect of antipsychotics and so alleviate negative symptoms, and/or to ameliorate a number of cognitive deficits associated with schizophrenia[4].

Smoking high-nicotine cigarettes, compared to smoking de-nicotinized cigarettes was found to reduce negative symptoms without affecting positive symptoms[5]. This effect is thought to reflect nicotine's ability to raise dopamine levels in the nucleus accumbens and prefrontal cortex[6]. Following from the view that negative symptoms results from hypodopaminergic tone in the frontal cortex[7], it has been suggested that smoking provides a way of temporarily reducing these negative symptoms by raising dopamine levels in these regions[8]. In a phase 2 trial of a nicotinic agonist in schizophrenia, DMXB-A which activates α7-nicotinic receptor was found to improve negative symptoms that are generally resistant to treatment with antipsychotics[9]. Cognitive impairment whilst less obvious than positive symptoms such as hallucinations and delusions, is now thought to be a core component of schizophrenia. Neuropsychological studies have consistently described deficits affecting attention, working memory, executive functioning, learning and memory in patients with schizophrenia[10].

Working memory provides a crucial interface between perception, attention, memory, and action, due to its involvement in complex cognitive functions such as learning, reasoning and comprehension[11]. It is limited in volume and time span, allowing the subject to operate with bits of recent information. Two subsystems namely the visuo-spatial sketchpad and the phonological loop have been described. The first one is represented by the working memory for visual and spatial information, and the second one is the short term memory for acoustic or speech based information. The two aforementioned subsystems are under the control of a central executive system[11]. Verbal memory is therefore regarded as a distinctive type of working memory, underlying encoding through language[12].

In a study by Cosman, patients with schizophrenia performed significantly poorer in all three working memory tests comprised of Word List Memory Test, Face Memory Test, and Spatial Working Memory[13]. On the other hand, studies have suggested that nicotine administration can improve attention and working memory deficits[14,15]. Overall, existing evidence points consistently towards the beneficial effect of smoking or nicotine on sustained attention and working memory functions in schizophrenia, perhaps to a greater extent than seen in healthy populations. Other cognitive functions may be less sensitive to the effects of nicotine or smoking.

The assessment of working memory subsystems has been shown to provide invaluable information for the strategy of cognitive rehabilitation of schizophrenia patients, due to the fact that cognitive training exercises mainly involve working memory subsystems[16]. Therefore, this study aims to investigate the association of cigarette smoking with verbal memory (a part of working memory) and

psychopathology of patients with schizophrenia.

Methods

Subject

This is a cross sectional study on 30 smokers and 23 non-smokers with schizophrenia. Subjects were grouped into smoker if they smoke > 20 cigarettes per day and non-smoker if they do not smoke or smoke less than 5 cigarettes for the previous 6 months. They were recruited from the outpatient clinic and psychiatric wards in Hospital Universiti Sains Malaysia (HUSM) within a six-month period (1st July 2011 till 31st December 2011). They were cooperative and able to understand the Malay language. Patients were excluded if they have mental retardation, neurological or significant medical problems; current or past histories of substance abuse other than nicotine, or were regularly prescribed with anticholinergic medication such as benzhexol. Anticholinergic drugs have been shown to have significant negative effects on the immediate memory and the verbal working memory[17].

The age limit of all subjects was set between 15 and 65 years to minimize the effect of normal aging process on the cognitive performance. The study protocol was approved by the Research & Ethics Committee, Universiti Sains Malaysia and Ministry of Health. A single researcher (the first author) trained in psychiatric interview and rating scale interviewed all the subjects and administered the test individually.

Assessment

The Malay Version of Auditory Verbal Learning Test (MVAVLT) is a translated and validated Malay version of the Rey Auditory Verbal Learning Test, developed to suit the Malaysian population. It has good validity (factor analysis 0.66 to 0.98), test-retest reliability (pearson correlation 0.24 to 0.84) and sensitive in discriminating between normal and schizophrenia patients[18]. The MVAVLT consists of two different lists (A and B) of 15 concrete nouns each. Participants were asked to read the first list (A) five times (A1-A5) at a rate of one item per second (tape recording was used to standardize the rate). Free verbal recall (immediate memory) was tested immediately after each presentation. Total learning (A1 + A2 + A3 + A4 + A5) reflects the acquisition phase in the memory information processing operations. Then a second list (B) was presented followed by its free recall which acted as interference for A6. Thereafter, recall of list A (A6) was examined without prior presentation of list A. After 20 minutes of rest, recall of list A (A7) was repeated without its prior presentation. Finally, the participants had to recognize the words from list A interspersed among semantically or phonetically related words in a third list that comprised 30 words.

The Positive and Negative Syndrome Scale (PANSS) scale is a 30-item semi structured clinical interview specifically developed to assess for typological and dimensional assessment of schizophrenia. It has good psychometric properties with coefficients ranging from 0.73 to 0.83 for each of the scale[19]. There are 7 items for PANSS positive scale, 7 items for PANSS negative scale and 16 items for general psychopathology scale. Each items are rated on a 7-point scale (1= absent, 7 extreme). Rating is based upon information related to the past week. Total score for each group of symptoms were calculated by adding all the scores for the items in each group.

Results

Table 1 shows the socio-demographic and clinical variables of the study participants. The smoker and non-smoker groups did not differ significantly in age, age at first treatment, duration since first treatment and number of admission. The median age were 35.5 and 38.6 years old, median age at first treatment 21.5 and 20 years old, median duration of treatment 12.5 and 17 years and median number of ward admission 5 and 6 respectively. Both groups also did not differ significantly in ethnicity, marital status, employment status, educational level and type of antipsychotics. Majority of the participants was Malay (98.1%) and there was only one Chinese participant who is a smoker. Male comprised of 90% in smoker group compared to 39% in non-smoker group which is statistically a significant difference. Effect of gender on verbal learning from previous study has been inconclusive. A local study found that male patients performed better in verbal learning performance compared to female[20].

Table 1. Socio-Demographic and Clinical Characteristics of the Sample (n=53)

		Smokers (n=30)	Non-smokers (n=23)		
		Frequency (%)	Frequency (%)	Z*	*p*-value†
Gender	Male	27 (90)	9 (39)		<0.010
	Female	3 (10)	14 (61)		
Ethnic	Malay	29 (97)	23 (100)		0.566
	Others	1 (3)	0 (0)		
Marital status	Married	7 (23)	4 (17)		0.543
	Single	15 (50)	15 (65)		
	Divorced	8 (26)	4 (17)		
Employment status	Full time	1 (3)	2 (8)		0.460
	Part time	12 (40)	6 (26)		
	Unemployed	17 (57)	15 (66)		
Educational level	Tertiary	0 (0)	1 (4)		0.051
	Secondary	29 (97)	17 (74)		
	Primary	1 (3)	5 (22)		
Type of antipsychotics	Atypical only	14 (47)	10 (43)		0.460
	Typical Only	4 (13)	1 (4)		
	Combination	12 (40)	12 (52)		
		Median (IQR)	Median (IQR)		
Age (year)		35.5 (8.0)	38.7(8.0)	-1.92	0.542
Age at first treatment (year)		21.5 (11)	20 (10)	-0.70	0.481
Duration since first treatment (year)		12.5 (16)	17 (10)	-1.21	0.230
Number of ward admission		5 (8)	6 (9)	-1.69	0.493

*Mann-Whitney test.

† Chi-Square test, P<0.05 as significant at 95% CI.

Table 2 shows that all of the participants had only minimal to mild psychiatric symptoms. For smokers the means (SD) scores in PANSS positive, negative and general psychopathology were 15.3 (5.12), 11.5 (5.81) and 24.9 (7.17) while for non-smokers the score were 14.0 (5.9), 12.9(4.79) and 24.9 (5.25) respectively. Even though, smokers scored higher on PANSS positive and non-smokers scored higher on PANSS negative, these were not statically significant. Assessment with MVAVLT showed that there were significant differences in total A1-A5, A6, A7 and recognition between the 2 groups although the scores in smoker group were consistently higher than the non-smoker group in all 4 measures of immediate memory (total A1-A5), post-interference immediate memory (A6), delayed recall (A7) and recognition memory.

Table 2. Psychopathology and Verbal Memory among Smokers and Non-Smokers with Schizophrenia

	Smokers (n=30)	Non-smokers (n=23)	Statistical Analysis	
	Mean (SD)	Mean (SD)	Mean differences (95% CI)	*p*-value
PANSS				
Positive	15.41 (5.12)	14.03(5.91)	1.37 (-1.691,4.421)	0.380
Negative	11.50 (5.81)	12.90(4.79)	-1.42 (-4.350,1.501)	0.352
General Psychopathology	24.93 (7.17)	24.90 (5.25)	0.01 (-3.562,3.583)	0.901
MVAVLT				
Total A1-A5	42.71(11.03)	37.52(11.53)	0.6 (-0.591,1.710)	0.260
A6	8.50(2.51)	7.84((1.50)	0.2 (-0.680,1.052)	0.671
A7	9.41(2.53)	8.43(2.562)	0.9 (-0.490,2.351)	0.190
Recognition	14.00(2.02)	13.10(1.421)	0.6 (-0.191,1.400)	0.140

Simple linear regression analysis was done to determine the potential associated factors for verbal working memory among the subjects. Total A1-A5 scores of MVAVLT were chosen as dependent factor for the analysis since the scores measure immediate memory which reflects the verbal working memory of the subjects. Eight variables with p-value of less than 0.25, which include employment status, educational level, smoking status, number of admission, type of antipsychotics and all PANSS subscales, were further analysed using multiple linear regression. In the final model, the result shows that the higher the number of admission to ward and also, the more severe the negative symptoms or general psychopathology of schizophrenia, the lower the memory performance. There was also association between type of antipsychotics and memory, atypical showing better memory performance compared to typical antipsychotics or combination.

Table 3. Simple and Multiple Linear Regression Analysis to Determine Factors Associated with Verbal Working Memory in Patients with Schizophrenia

	SLR*			MLR‡		
	B† (95% CI)	t Stat	*p*-value	B§ (95% CI)	t Stat	*p*-value
Age	0.151 (-0.285,0.596)	0.69	0.491			
Gender	-0.574 (17.397,6.25)	-0.167	0.870			
Ethnicity	3.635 (-19.759, 27.028)	0.312	0.762			
Marital status	1.330 (-3.494, 6.154)	0.554	0.582			
Employment status	-5.153 (-10.254, -0.052)	-2.028	0.048	-0.054 (-5.526, 3.503)	-0.452	0.654
Educational level	-7.072 (-45.929, 1.785)	-1.603	0.115	-4.198 (-11.610, 3.215)	-1.139	0.260
Smoking status	-5.145 (-11.408, 1.118)	-1.65	0.108	-0.149 (-8.443, 1.616)	-1.368	0.178
Age at first treatment (year)	0.075 (-0.435, 0.585)	0.295	0.773			
Duration since first treatment (year)	0.022 (-0.335, 0.379)	0.123	0.902			
Number of ward admission	-0.810 (-1.427, -0.193)	-2.63	0.011	-0.623 (-1.120, -0.126)	-2.52	0.015
Type of antipsychotics	2.771 (-0.485, 6.027)	1.709	0.094	3.080 (0.598,5.562)	2.49	0.016
PANNS positive	-0.533 (-1.100, 0.035)	-1.885	0.065	-0.052 (-0.552, 0.449)	-0.207	0.837
PANSS negative	-1.170 (-1.669, -0.672)	-4.711	0.000	-1.011(-1.460,-0.562)	-4.59	0.000
PANSS general	-0.590 (-1.069, -0.111)	-2.475	0.017	-0.450 (-0.796, -0.034)	-2.19	0.034

*Simple Linear Regression (outcome as mean stigma score)

† Crude regression coefficient.

‡ There is no significant interaction; no multi colinearity problem; and linearity, normality and equal variance assumptions were made.

§ Adjusted regression coefficient.

Discussion

This study found better verbal working memory performance is associated with lower number of admission, use of atypical antipsychotics, lower negative symptoms and general psychopathology among patients with schizophrenia. No significant association was found between verbal working memory performance and smoking status.

The association between verbal working memory performance and lower negative symptoms is consistent with a previous study by Cameron[21] which measure psychopathology using PANSS in a sample of 58 patients with schizophrenia. It was concluded that working memory deficit was associated with severity of negative symptoms but not with positive symptoms. Working memory deficit was also associated with severity of disorganised dimension comprised of conceptual disorganization (P2), difficulty in abstract thinking (N5), disorientation (G10), and poor attention (G11) which also explained the positive association with general psychopathology subscale in this study. A more recent study by McDowd et al indicated that verbal memory, processing speed and negative symptoms were inter-related and significantly contributed to functional status directly and mediated by the other factors[22].

The association between verbal working memory performance and use of atypical antipsychotics is consistent with many previous studies. For example a study by Mori et al[23] suggested that switching chronic schizophrenic patients to risperidone or olanzapine improved the immediate memory. Risperidone and olanzapine have been suggested to promote the release of acetylcholine in the medial prefrontal cortex[24]. Improvement of the immediate memory by olanzapine and risperidone increased further when anticholinergic drugs were withdrawn. On the other hand, the immediate memory became worse after switching to quetiapine suggesting a strong connection between the immediate memory and the anticholinergic effect of drug therapy.

This study did not find significant association between verbal memory performance and smoking status which is consistent with study by Harris et al[25] which failed to detect positive effects of nicotine on tests of immediate or delayed memory, language or visuo-spatial attention. Nicotine nasal spray was reported to improve spatial accuracy and verbal memory[5]. Nicotine administered via patches to smoking deprived schizophrenia patients was reported to improve their performance on a task involving working memory and attention[26].

The main limitations of this study are its cross sectional design and small sample size. A better design will compare cognitive performance during nicotine abstinence and administration in subjects with schizophrenia. The use of nicotine spray or patch is preferable compared to patient's verbal report on the amount of cigarettes smoke which may not be accurate. Another poorly controlled confounder in this study is the use of antipsychotics. Antipsychotics use is different not only with regard to atypical, typical and combined, but also in their intrinsic anticholinergic activity[23]. Future study should consider all the subjects using only one or a few but very similar antipsychotics.

References

1. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res. 2005; 76:135–157

2. de Leon J, Becona E, Gurpegui M, Gonzalez-Pinto A, Diaz FJ. The association between high nicotine dependence and severe mental illness may be consistent across countries. J Clin Psychiatry 2002; 63:812–816

3. Olincy A, Johnson LL, Ross RG. Differential effects of cigarette smoking on performance of a smooth pursuit and a saccadic eye movement task in schizophrenia. Psychiatry Res. 2003; 117:223–236

4. Kumari V, Postma P. Nicotine use in schizophrenia: The self-medication hypotheses. Neuroscience & Biobehavioral Reviews, 2005; 29(6):1021-1034

5. Smith RC, Singh A, Infante M, Khandat A, Kloos A (2002) Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia. Neuropsychopharmacology 2002; 27:479–497

6. Corrigall WA, Coen KM. Selective dopamine antagonists reduce nicotine self-administration. Psychopharmacology (Berl), 1991; 104(2), 171-6

7. Weinberger DR, Berman KF. Speculation on the meaning of cerebral metabolic hypofrontality in schizophrenia. Schizophr. Bull. 1988; 14(2): 157–168

8. Dalack GW, Healy DJ, Meador-Woodruff JH. Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. Am J Psychiatry. 1998; 155(11), 1490-501

9. Freedman R, Olincy A, Buchanan RW; Harris JG, Gold JM, Johnson L, et al. Initial phase 2 trial of a nicotiniv antagonist in schizophrenia. Am J Psychiatry. 2008; 165(8):1040-1047

10. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology. 1998; 12:426–445

11. Baddeley AD. The fractionation of working memory. Proceedings of the National Academy of Sciences of the United States of America. 1996; 93: 13468–13472

12. Barch DM, Csernansky JG. Abnormal parietal cortex activation during working memory in schizophrenia verbal phonological coding disturbances versus domain-general executive dysfunction. Am J Psychiatry. 2007; 164: 1090-1098

13. Cosman D, Nemes B, Nica S, Herła DC. Verbal, visuo-spatial and face working memory impairment in multiple episode schizophrenia patients. Journal of Cognitive and Behavioral Psychotherapies. 2009; 9(1), 21-32

14. Zabala A, Eguiluz JI, Segarra R, Enjuto S, Ezcurra J, Gonzalez PA, Gutierrez M. (2009). Cognitive performance and cigarette smoking in first-episode psychosis. Eur Arch Psychiatry Clin Neurosci. 2009; 259(2), 65-71

15. Barr RS, Culhane MA, Jubelt LE, Mufti RS, Michael A Dyer MA, Weiss AP, Deckersbach T, Kelly JF, Oliver Freudenreich O, Goff DC, and Evins AE. The Effects of Transdermal Nicotine on Cognition in Nonsmokers with Schizophrenia and Nonpsychiatric Controls Neuropsychopharmacology. 2008; 33: 480–490

16. Wykes T, Brammer M, Mellers J, Bray P, Reeder C, Williams C, Corner J. Effects on the brain of a psychological treatment: cognitive remediation therapy. Functional magnetic resonance imaging in schizophrenia. Br J Psychiatry. 2002; 181, 144-152

17. Mori K, Yamashita H, Nagao M, Horiguchi J, Yamawaki S. Effects of anticholinergic drug withdrawal on memory, regional cerebral blood flow and extrapyramidal side effects in schizophrenic patients. Pharmacopsychiatry. 2002; 35, 6–11

18. Ruzita J, Zahiruddin O, Kamarul IM, Muhammad Najib MA. Validation of the Malay Version of Auditory Verbal Learning Test (MVAVLT) among schizophrenia patients in Hospital Universiti Sains Malaysia (HUSM), Malaysia, ASEAN J Psychiatry. 2009; 10(1)

19. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987; 13(2):261-76

20. Zahiruddin O, Ruzita J, Muhammad Najib M A, Hasanah CI. Demographic and clinical factors associated with verbal memory performance in patients with schizophrenia in Hospital Universiti Sains Malaysia (HUSM), Malaysia. ASEAN J Psychiatry, 2011; 12(2)

21. Cameron AM, Oram J, Geffen GM, Kavanagh DJ, McGrath JJ, Geffen LB. Working memory correlates of three symptom clusters in schizophrenia. Psychiatry Res. 2002; 110(1), 49-61

22. McDowd J, Tang TC, Tsai PC, Wang SY, Su CY. The association between verbal memory, processing speed, negative symptoms and functional capacity in schizophrenia. Psychiatry Res 2011;187: 329–334

23. Mori K, Nagaoa M, Yamashita H, Morinobu S, Yamawaki S. Effect of switching to atypical antipsychotics on memory in patients with chronic schizophrenia. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2008;28: 659– 665

24. Ichikawa J, Dai J, O'Laughlin IA, Fowler WL, Meltzer HY. Atypical, but not typical, antipsychotic drugs increase cortical acetylcholine release without an effect in the nucleus accumbens or striatum. Neuropsychopharmacology. 2002; 26: 325–339

25. Harris JG, Kongs S, Allensworth D, Martin L, Tregellas J, Sullivan B, Zerbe G, Freedman R. Effects of nicotine on cognitive deficits in schizophrenia. Neuropsychopharmacology 2004; 29 (7): 1378–1385

26. Jacobsen LK, D'Souza DC, Mencl WE, Pugh KR, Skudlarski P, Krystal JH. Nicotine effects on brain function and functional connectivity in schizophrenia. Biol. Psychiatry. 2004; 55 (8): 850–858

Corresponding Author
Dr. Zahiruddin Othman
Department of Psychiatry,
School of Medical Sciences,
Universiti Sains Malaysia,
16150 Kubang Kerian, Malaysia

Email: zahir@kb.usm.my