ORIGINAL ARTICLE

Working memory assessment in schizophrenia and its correlation with executive functions ability

Avaliação da memória de trabalho na esquizofrenia e sua correlação com habilidades de funções executivas

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Abstract

Objective: *Working memory impairment is common in schizophrenia and is possibly a cause of multiple features of the disorder. However few studies have replicated such findings of impairment patterns in Brazilian samples. The main target of this study was to assess auditory and visual working memory in patients with schizophrenia, to assess if they work as separate systems, and to correlate working memory deficits with executive functions.* ***Method:*** *Twenty subjects with schizophrenia and twenty healthy subjects matched by gender, age, and schooling have participated. The abilities assessed were auditory and visual working memory, selective attention, inhibitory control, cognitive flexibility, and planning.* ***Results:*** *Patients showed declines in all measures evaluated, except for a measure reaction time of inhibitory control. Auditory working memory was correlated to selective attention, inhibition, flexibility and planning while Visual working memory to planning and flexibility.* ***Conclusion:*** *The present study suggests that working memory and executive functions deficits are present in patients with schizophrenia in the Brazilian sample evaluated. Alterations in executive functions may lead to incapacity of operation of processes of working memory. These findings may contribute to delineate and develop new strategies of schizophrenia treatment in the Brazilian population.*

Descriptors: *Memory; Cognition; Schizophrenia; Attention; Evaluation*

Resumo

Objetivo: *Prejuízos em memória de trabalho são comuns na esquizofrenia e possíveis causas de múltiplas características do transtorno. Entretanto, poucos estudos reproduziram achados de padrões específicos de déficits em amostras brasileiras de pacientes com esquizofrenia. O objetivo desta pesquisa foi avaliar a memória de trabalho auditiva e visual na esquizofrenia, verificar se estas habilidades operam como dois sistemas separados, e relacionar possíveis déficits de memória de trabalho com habilidades de funções executivas.* ***Método:*** *Foram incluídos 20 indivíduos com esquizofrenia e 20 indivíduos saudáveis pareados quanto a sexo, idade e escolaridade. As habilidades avaliadas foram memória de trabalho auditiva e visual, atenção seletiva, controle inibitório, flexibilidade cognitiva e planejamento.* ***Resultados:*** *Os pacientes demonstraram prejuízos em todas as medidas dos testes, exceto em tempo de reação de controle inibitório. Pacientes apresentaram significante correlação entre MT auditiva com medidas de atenção seletiva, controle inibitório, flexibilidade e planejamento. Memória de trabalho visual apresentou correlações com planejamento e flexibilidade.* ***Conclusão:*** *Este estudo sugere que déficits em memória de trabalho e funções executivas estão presentes em pacientes esquizofrênicos na amostra brasileira avaliada. Alterações nas funções executivas podem levar a incapacidade de adequadas operações de memória de trabalho. Esses achados podem contribuir no delineamento de novos procedimentos de intervenção na esquizofrenia em populações brasileiras.*

Descritores: *Memória; Cognição; Esquizofrenia; Atenção; Avaliação*

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Introduction

Many studies have shown that cognitive deficits are core characteristics of schizophrenia.[1,2] These impairments span a wide range of information processing, including attention, memory, and executive functions (EF). It has been suggested that the working memory (WM) may underlie several of these deficits and contribute to multiple features of the disorder.[3-5] The concept of WM refers to a temporary repository of mental representations for different specialized cognitive systems. These representations are sustained, integrated and manipulated, enabling adaptation, response and direction of the behavior in response to life experiences and environmental demands. In fact, the cooperation between WM and many other cognitive functions is required for a good daily life functioning.[6]

According to the Baddeley and Hitch[7] model there are three specialized subsidiary systems involved in WM: the phonological loop, the visuospatial sketchpad, and the episodic buffer. The phonological loop is a system to process and retain the linguistic representations and the visuospatial sketchpad is an operating subsystem of imaging representation of objects and their spatial position. The episodic buffer[8] allows temporary storage and integration of sensory information from different modalities in an organized, coherent and sequential episode. These three subsidiary systems serve to a central executive component that is a fractionated system for the control and regulation of voluntary behavior to achieve internally generated goals. More specifically, it controls and coordinates the relationship between the phonological loop, the visuospatial sketchpad, long-term memory and a diversity of abilities of EF necessary for action planning.

EFs are intrinsic cognitive processes which contribute for the ability to adaptively respond to novel situations and are also the basis of many cognitive, emotional, and social skills.[9] They comprise a cluster of abilities necessary for goal-directed behaviors. Both central executive of WM and EF have been reported to be related to the Supervisory Attentional System (SAS),[10,11] originally constructed as a model of attentional control of behavior in healthy individuals as well as in neuropsychological patients.[12] SAS model provides a stronger theoretical link to both neurocognitive function and clinical symptoms in schizophrenia. For example, the presence of avolition may be due to inabilities to sustain mental representations in the mental buffer of WM, while negative symptoms may be associated with deficits in conscientious action.[13,14] In this context, different authors have suggested that disturbances of EF such as distractibility, perseveration and failure to inhibit irrelevant responses may underlie malfunction of WM operations, and these disturbances may reflect an inability to utilize WM or internal representations to guide the context behavior.[14,15]

The neural bases for both WM and EF are located in the prefrontal cortex (PFC), a large structure that corresponds to almost one-third of the total cortex and establishes multiple relations, usually reciprocal, with a number of other encephalic structures, including motor, perceptive and limbic regions.[3] The function of the PFC and its relation to other encephalic regions and systems may be related to the coordination of different processes through integration and manipulation, acting upon response to internal and external stimuli, goal oriented behavior, and cognitive and behavioral adaptation.[15,16] There is solid evidence for functional and structural abnormalities of the PFC and its related systems in schizophrenia.[17,18]

Besides all the body of evidence supporting that schizophrenia patients have poor performance on WM and EF tasks,[18,19] the identification of specific impaired cognitive patterns and interactions between them still remain inconsistent.[20,21] The discrepancies may be due to the methodological variability between the studies, to a lack of common classifications and definitions of cognitive constructs, and to different forms of evaluations applied. For example, tasks such as the Wisconsin Card Sorting Test and the Tower of Hanoi, among others, are sensible to detect global EF impairment; however they are scarcely specific to identify at which stage takes place the breakdown of the EF process.[9] Although such tasks are complex and poorly performance on them could arise for many reasons, they have nonetheless become the primary research tools for studying the organization and roles of EF. In parallel, through them, it is possible to use different and broad concepts of EF. Thus, a better method to verify possible patterns between EF and other cognitive measures, such as WM, may be the use of a very comprehensive battery to assess different specific abilities related to EF.

The current study aimed to investigate the performance of the two different forms of WM in schizophrenia patients. Based on previous findings of the international literature, it was hypothesized that patients would perform worse than a healthy comparison group would in such abilities. It was also hypothesized that both measures of WM would be correlated to specific measures of EF, including selective attention, inhibitory control, flexibility, and planning.

Performance on WM tasks was expected to be related to the performance on EF tasks, because of the fractionated central executive, the most prominent cognitive framework that has been associated with EF, wich is a common component coordinating the different aspects of WM. However, since the phonological loop and visuospatial sketchpad seem to be distinct, differential relationship patterns among them with EF might be observed. Using a battery composed by specific EF tasks it may be possible to dissect which abilities are more related to both types of WM.

Method

1. Participants

The participants were 20 chronic and stable schizophrenia outpatients and 20 healthy comparison subjects. Patients were recruited from a private psychiatric clinic that is established in a town in São Paulo state, Brazil, which receives patients by self referral and referral from local general and specialist practitioners. Patients were recruited based on a diagnosis of schizophrenia in accordance to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. This diagnosis was subsequently confirmed by one of the authors that was trained and conducted the application of the structured clinical interview for the DSM-IV. In the schizophrenia group (SG) all participants were under pharmacological treatment with atypical antipsychotics and medication doses were stable for at least 4 weeks prior to the evaluation. The SG had a mean age of 39.9 (SD = 13.47, range = 18-62), the schooling varied from 3 and a half years of primary school to complete high school mean number of years of formal schooling was 8.9 (SD = 3.17). Mean number of years of disease duration was 11.8 (SD = 9.59, range = 1-35).

The healthy comparison group (HCG) was composed by 20 individuals with no mental health disorder also in accordance to the DSM, 4th ed. The HCG was exactly matched with the SG by sex, schooling years and age. For this reason, no statistical test was conducted to verify possible differences on demographic characteristics between groups. All subjects in both groups aged 18 years or older, spoke Portuguese as their first language, and had an estimated IQ of at least 80 according to a non-verbal intelligence evaluation.

The administration of tests occurred in two sessions which lasted for approximately one hour. For all participants testing sessions was conducted in a proper room with adequate conditions. The present study was approved by the Research Ethics Committee of the Universidade São Francisco and written informed consents were obtained from all participants (CEP 098/06).

2. Neuropsychological tests

General information. For information regarding validity evidences of the tests used in the presented study, see Berberian (2007),[22] Capovilla et al. (2008),[23] Menezes (2008),[24] Montiel, (2005)[25] and Tortella et al. (2008).[26]

Auditory and Visual Working Memory Tests. Auditory Working Memory Test (AWM)[27] involves repeating a series of 2 to 10 stimuli that may be ether letters or numbers presented auditorily to the participant at the rate of one digit per second, with digitalized sound. Participants were asked to repeat the stimuli organizing them in a predetermined order: first letters and then numbers in a crescent order. In the Visual Working Memory Test (VWM)[27] a subject is asked to pay attention to a computer screen where one to four 3X3 matrices are displayed. A stimulus appears within each matrix for a brief period of time, then arrows start indicating special manipulations that the subject will be asked to perform with the stimuli within each matrix. An arrow pointing to the upward position followed by an arrow pointing to the left indicates that the stimuli should be dislocated one row above and one column to the left from its original position. There is no limit of time for each answer.

Computerized Stroop Test. The computerized version of the Stroop Test[28] was used to assess selective attention. Three parts composes this test, each comprising 24 stimuli. In the first part the subject is asked to read the word that appears in the computer display and the stimuli are names of four colors (yellow, blue, green and red) written in capital black font. The objective of this part is to evaluate the automation of reading, which is essential for the expected effect. The second part comprises 24 colored circles, six drawn in each of the four colors. Each circle is displayed for 40 milliseconds and the participant has to name the color of the circle as fast as he/she can. The objective of this part is to provide a baseline measure for analyses of errors and reaction times. In the third part of the test the subject has to read the color name but the stimuli are divergent, the word is displayed in a color different from the color it actually names. Each word is displayed for 40 milliseconds and the participant has to name the color in which the word is written as fast as he can. In all the three parts the reaction time (RT_Stroop Test) and the number of correct answers are recorded using a microphone.

The performance in the Stroop Test depends on the interference of automatic processing of reading in the color identification. The scores both for reaction time and for the number of correct answers are based on the subtraction between the mean results in parts three and two.

Semantic Generation Test. Inhibitory control was evaluated by the Semantic generation test.[25] We used a computerized version with 120 items.[29] For each item a figure appears in the screen and the participant has to utter an action (verb) semantically associated with it. The items may demand ether a "high selection" effort or a "low selection" effort. The "high selection" figures are those associated with several options of actions, demanding the subject to choose one among many concurrent stimuli and to inhibit all others. Responses and reaction times (RT_Semantic Generation) are recorded by the software. The overall scores are based on the subtraction between the higher and lower selection conditions, reflecting the differences in the performance that may be attributed to the higher selection demand.

Trail Making Test. Trail Making Test (TMT) - Part B.[25] This test is considered to measure mental flexibility. The TMT-B requires an individual to draw lines sequentially connecting 24 encircled numbers and letters distributed on a sheet of paper in a numerical/ alphabetical sequence. Numbers and letters must be alternately connected (i.e.: 1 – A – 2 – B – 3 – C, …). The maximum response time allowed is 1 minute. Three scores are calculated; the first score represents the total number of items correctly linked, the second is the number of correct links among two items and the third is the sum of both.

Tower of London Test. The Tower of London Test (TOL) was used to assess the ability of planning.[30] Three colored discs are arranged in three pegs. The colored discs must be moved one-by-one from an initial state to matched goal states determined by the examiner. Subjects are instructed to use as few movements as possible to reach the goal and to never move more than one disc simultaneously or to place a disc out of the peg. The complete test comprises 12 items, with a rising complexity level.

Nonverbal Intelligence Test. The non-verbal intelligence task (R-1)[31] was used to assess intelligence. This scale was created to allow measures of intelligence in low literacy populations. This test highly correlates with the Raven's Colored Progressive Matrices Test ($r = 0.76$, $p = 0.001$), and was chosen for the high frequency of low literacy found in the Brazilian schizophrenic population.

3. Statistical analysis

Data were registered and analyzed using the Statistical Package for Social Sciences (SPSS), version 13.0. Proportion differences were compared using the chi-square test. To verify symmetry of the distribution probability and homogeneity of variance, skewness measures and Levene Test were applied, respectively. All measures that reached an adequate variation of the distribution and constant homogeneity of variance, were submitted to analysis of covariance (ANCOVA) with nonverbal intelligence as covariant, and Pearson's correlation. Nonparametric techniques consisted of Mann-Whitney U and Spearman's correlation and they were applied to the data that did not presented symmetry and constant homogeneity of the variance.

For VWM and AWM tests only the scores in the tests were considered but not the reaction time since the examiner manipulated the software. For the analysis of the reaction time for the Stroop and the Semantic Generation Tests, it was stipulated a mean response time in convergent situations and in situations in which there is a low probability to chose one response, respectively. This mean time is discounted from the response time in the divergent situation and from the time in the situation that demands a decision between concurrent stimuli. The mean time lasting after the discount is the exact time interval that the subject used to select or choose an answer. Pearson correlations analysis of AWM and VWM scores with EF measures were conducted considering the groups separately, and Spearman correlations considering all participants together. For all statistical analysis, significance was set at $p < 0.05$, two-tailed.

Results

The SG significantly differed in the distribution of clinical diagnoses ($X^2 = 26$, $p < 0.001$), being 44.8% of paranoid subtype, 17.2% of undifferentiated subtype, 3.4% of catatonic subtype, and 3.4% of disorganized subtype. However, no discrepancies of discharges were observed when considered the subtype as the independent

Table 1 - Descriptive analysis of tests scores results for both schizophrenia (n = 20) and comparison group (n = 20)

Subtest	SG (SD)	HCG (SD)	SG Mode	HCG Mode	SG Median	HCG Median
AWM Test	6.50 (3.4)	12.35 (2.9)	8	13	7	13
VWM Test	5.58 (4.5)	9.37 (3.5)	1	12	5.50	12
Computerized Stroop Test	63.99 (7.8)	70.77 (1.0)	71	71	66.50	71
RT_Stroop Test	-13.00 (12.0)	-20.28 (2.7)	-35	-24	-16.48	-19.65
Semantic Generation Test	80.94 (48.3)	114.26 (3.0)	111	115	111	114.50
RT_ Semantic Generation Test	18.15 (20.2)	32.37 (25.0)	32	33	16.67	27.33
Connection score of TMT	8.23 (6.3)	11.77 (6.6)	6	7	6	10
Sequence score of TMT	6.12 (7.2)	10.13 (8.0)	2	2	2	9.5
Total score of TMT	14.34 (8.2)	21.91 (10.2)	8	47	9	19
TOL	23.55 (6.3)	31.40 (2.7)	22	30	23.50	32

SG = schizophrenia group; HCG = healthy comparison group; SD = standard deviation.

variable and measures of neuropsychological performance as the dependent variables. Regarding the time since the first episode, the performances did not follow a linear time pattern of decline. Furthermore, no significant correlations were found between the time of the first episode or illness and the neuropsychological performances. The scores for both WM of comparison and patients groups together were correlated to age and education. None measures of correlation reached significant value. Table 1 shows all descriptive analysis of tests utilized.

Skewness measures were medium or high for all variables, except for AWM and VWM. It means that only these last two variables reached an adequate level of symmetry of distribution. Measures of reaction time of the Stroop Test and TOL also presented adequate symmetry of distribution, but only among HCG. Levene's Test showed that the score of Stroop Test and the two measures of Semantic Generation Test did not reach variability constant of residuals.

The first part of the results descriptions is regarding to parametric techniques. SG showed significantly poorer performance on AWM and VWM. Pearson's correlations revealed moderated and significant relationships between AWM and VWM. TOL and reaction time of Stroop Test did not reach significant correlations among HCG. The descriptive measures and statistical analysis are presented in Table 2 and 3, respectively.

The second part of the descriptions refers to the nonparametric analyses. According to the mean ranks provided by the Mann-Whitney U, SG showed significantly poorer performance on all measures of neuropsychological tests except for those of reaction time of Stroop and Semantic Generation Tests. However, for the reaction time of the Stroop Test, the p value was marginal, what indicates a tendency of the SG be slower than HCG for situations in which response selection was needed.

Table 2 - Descriptive analysis of AWM and VWM scores for both schizophrenia (n = 20) and comparison group (n = 20) after correction using ANCOVA with non verbal intelligence IQ as covariant

Subtest	SG (SD)	HCG (SD)	F-value (df = 1.37)	p-value
AWM Test	6.50 (3.4)	12.35 (2.9)	29.72	0.001
VWM Test	5.58 (4.5)	9.37 (3.5)	8.45	0.006

SG = schizophrenia group; HCG = healthy comparison group; df = degrees of freedom; SD = standard deviation.

The Spearman's correlation, considering all participants together, revealed significantly correlation of AWM with TOL, TMT, Stroop, and Semantic Generation. For VWM only measures of TOL and sequence score of the TMT reached significant correlations. The correlations are presented in Table 5.

Discussion

1. Performance differences between patients and healthy participants

In this study, AWM and VWM, and four abilities related to EF (three specific ones and a complex task) were assessed among 20 patients with schizophrenia and 20 healthy individuals matched for gender, age and schooling. Parametric analyses showed that both WMs were impaired in patients with schizophrenia. Nonparametric analysis revealed that patients had lower performances in all measures except for reaction time of inhibitory control. Reaction time of selective attention was marginal, what reveals a tendency in the SG to require longer duration to give an answer on selective attention tasks.

The main hypothesis was that schizophrenia patients would perform worse than HCG in both measures of WMs. Besides the fact that WM impairment is common in schizophrenia being possibly a cause of multiple features of the disorder, few studies have replicated such findings of declining patterns in a Brazilian sample. Patients, indeed, performed worse than controls in their capacity to hold a mental representation for a short time, and either to use it after a short delay or to process or manipulate it mentally in order to guide their behavior in a context. This evidence corroborates previous studies[11,17,20] and supports the idea that such

Table 3 - Patterns of correlations of AWM and VWM with EF measures considering each group separately, SG (n = 20) and HCG (n = 20)

			VWM	TOL	RT_Stroop
SG	AWM	r	**0.60**		
		p	**0.005**		
	VWM	r			
		p			
HCG	AWM	r	**0.50**	0.16	0.25
		p	**0.02**	0.49	0.29
	VWM	r		0.24	-0.04
		p		0.29	0.85

AWM = Auditory working memory; VWM = Visual working memory; TOL= Tower of London Test; RT_Stroop = Reaction Time of Stroop Test. p-value > 0.05

Table 4 - Mean rank on the Mann-Whitney U measures for both SG (n = 20) and HCG (n = 20)

Subtest	SG (Mean rank)	HCG (Mean rank)	Man-Whitney U	Z	Sig.
AWM Test	12.13	29	32.50	-4.56	0.001
VWM Test	15.25	25.25	95.00	-2.85	0.004
Computerized Stroop Test	14.53	26.50	80.50	-3.50	0.001
RT_Stroop Test	23.90	17.10	132.00	-1.84	0.06
Semantic Generation Test	15.75	25.25	105.00	-2.60	0.01
RT_ Semantic Generation Test	18.00	23.00	149.00	-1.40	0.17
Connection score of TMT	15.90	25.10	108.00	-2.50	0.01
Sequence score of TMT	15.43	25.58	98.50	-2.81	0.005
Total score of TMT	15.33	25.68	96.50	-2.80	0.005
TOL	12.00	29.00	30.50	-4.60	0.001

a pattern of WM impairment in schizophrenia may also happen in Brazilian samples.

AWM is essential to monitor one's own speech. Thus, an individual who shows a poor performance on AWM might find it difficult to remember the first intention of his/her current speech. By doing this, the individual's speech might be filled in with loose associations, for example. Another important influence of AWM occurs in the learning process. There is much evidence from the international literature[24] showing the importance of this ability for the achievement of academic activities and the acquisition of new information.[11,20] Regarding VWM, previous studies have shown that schizophrenia patients show persistent deficits on that ability over time. Such ability is mediated by a neural circuitry that includes processing streams of dorsal visual information and dorsolateral prefrontal cortex, and it occurs whether individuals are acutely psychotic or in partial remission. Furthermore, there is robust neuropsychological and imaging evidence that frontal function is disturbed in schizophrenia.[16,17]

Another goal of the present study was to verify which separated ability of EF was impaired in patients. Although the present data suggests that SG showed deficits in selective attention and required longer duration to give an answer. Patients may possibly need longer stimulus exposure duration to better select information among many others, the heterogeneity of the data distribution and inconstant variance of the residuals do not allow reliable and further interpretations.

Patients also performed worse in planning, a complex task, that necessarily is manifested by operating on others cognitive processes such as selective attention, inhibitory control, flexibility and WM, among others. Most of these abilities were impaired according to the Mann-Whitney U analysis. Levin e Yegerlun-Todd[32] suggested that schizophrenic patients are likely to have reduced cognitive flexibility, experiencing, thus, problems to adapt choices according to demands and to monitor the course of a given task. Authors also suggest that distractibility and failure to inhibit irrelevant responses may underlie malfunction of WM operations, and that these disturbances may reflect an inability to utilize WM or internal representations to guide context behavior.[10,12,33]

An unexpected result was that patients did not perform worse than controls reaction time for choosing an answer among many concurrent stimuli, assessed by **Semantic Generation Test.** Authors also suggest that distractibility and failure to inhibit irrelevant responses may underlie malfunction of WM operations, and these disturbances may reflect an inability to utilize WM or internal representations to guide context behavior.[10,12] A possible explanation of the lack of differences on reaction time of the Semantic Generation Test is that such task may not be a adequate way to evaluate and distinguish differences for such a measurement. However, the limited number of subjects evaluated by the present study, do not allow further conclusion. It is also possible that the heterogeneity of cognitive patterns in schizophrenia could interfere in this result.

Summing up, both WMs and all measures of EF were impaired among patients. The use of a very comprehensive battery of EF could contribute to the understanding of specific correlations of WM and EF. Such knowledge is relevant to the identification of impaired cognitive patterns and interactions between them and it may contribute to the understanding for the etiology of WMs deficits and planning. According to previous findings about neurocognitive performances in schizophrenia, these abilities may be a possible predictor of schizophrenia development, once such impairments are already present on prodromal phase of the disorder.

2. Different patterns of correlations between AWM and VWM with EF abilities

The moderate correlations between both WMs reveal strong relationships between them. Such outcome also shows dissociations

Table 5 - Spearman correlations of AWM and VWM with EF measures considering all participants together (n = 40)

		TOL	C_TMT	S_TMT	T_TMT	RT_Stroop	Stroop	Semantic Generation	RT_Semantic Generation
AWM	p	**0.58**	**0.31**	**0.36**	**0.35**	0.01	**0.40**	**0.32**	0.19
	p	**0.001**	**0.04**	**0.02**	**0.02**	0.90	**0.009**	**0.04**	0.23
VWM	p	**0.44**	0.24	**0.40**	0.28	0.04	0.10	0.14	0.15
	p	**0.005**	0.13	**0.01**	0.08	0.81	0.53	0.38	0.36

TOL = Tower of London Test; C_TMT = Connection score of the Trial Making Test; S_TMT = Sequence score of the Trial Making Test; T_TMT = Total score of the Trial Making Test RT_Stroop = Reation Time of Stroop Test; RT_ Semantic Generation = Reation Time of Semantic Generation Test. p-value > 0.05 and may confirm the hypothesis that AWM and VWM act as two separate storage system domains. AWM actively sustains and manipulates acoustic stimulus while VWM manipulates visual mental representations. The strong relation probably occurred because of the common component that coordinates these different processing representations, the central executive.

Since both WMs act separately, different patterns of correlation with the EFs should occur. AWM were correlated to all measures of EF except to reaction time in the Stroop and Semantic Generation Tests. On the other hand, VWM reached a significant correlation with planning and cognitive flexibility. Silver et al. evaluated twenty-seven patients with chronic schizophrenia with several neuropsychological tests.[20] Their intention was to verify different patterns of correlation between both WMs and other cognitive abilities. Results showed that AWM scores were correlated to visual retention, visual orientation, simple motor function, visuomotor coordination, and EF but not with memory for objects, memory for faces, recognition of facial emotions, or attention. VWM correlated significantly with visual retention and orientation, memory for objects, memory for faces and simple motor function. No correlation was found though VWM with attention, EF, or visuomotor coordination.

Regarding selective attention and inhibitory control, Kim et al. suggested that these abilities are important to create internal representations and that attention mediates the encoding process by selecting the target or its features.[4] It contributes to the active maintenance of the internal representations. In this context, problems in selecting a stimulus among others or inhibit those that are irrelevant, may be implicated in the etiology of WM decline. The correlations among AWM, selective attention, and inhibitory control presented by the present study corroborate these hypotheses.

Cognitive flexibility reached significant correlation with VWM. Such outcome corroborates theoretical models and previous findings that show flexibility as a relevant component for adequate performance in WM.[9,10]

In the present study, it is possible make two kinds of interpretations of the relationships found. The first one is that lower or limited buffer capacity directly interferes on performance of other cognitive operations. The second view privileges the primacy of necessary operations to fill the WM buffer. Thus, alterations on this set of attentional capacities that enable someone to identify relevant and inhibit irrelevant stimuli, focus on that stimulus, and sustain this focus until it is processed to higher level processes, may lead to WM deficits.

3. Implications for treatment

It is clear that schizophrenia treatment is beyond control of symptoms, and evidence has shown that decline in WM is directly related to long-term clinical and functional outcomes, such as employment and social skills acquisition.[34] However, there are different domains of deficits that may function independently from each other. Since cognitive impairment is a core feature of schizophrenia, no intervention can be considered effective unless it also targets this domain. Consequently, interventions must occur together, being necessary many supporting measures to achieve real and durable improvement. The treatment domains can be summarized as pharmacological treatment, cognitive training, psychosocial intervention, improvement and training of social cognition, occupational therapy, and psychotherapy.[35]

Several researchers have demonstrated that cognitive deficits are not immutable. The present data suggest that this small sample of Brazilian patients show both AWM and VWM deficits and measures of EF, except for cognitive flexibility.

Bell, Bryson and Wexler, tested a program of neurocognitive enhancement therapy in schizophrenic patients, and verified whether this program combined with work therapy yielded greater improvement in WM performance than did work therapy alone.[36] The neurocognitive program consisted of cognitive training exercises in attention, memory, EF, and social information processing. Work therapy was a six-month program. Participants in both programs demonstrated significantly greater improvement in WM than did groups that received work therapy alone. This improvement persisted for 6 months after the conclusion of treatment, considering that within the first 6 months all the interventions had occurred. The authors concluded that it is not possible to affirm that neurocognitive enhancement therapy alone improves the measures of WM, because their study tested this program in combination with other training tasks, such as attention training, or because it was embedded in a work program. They did not mention any differences on visual or verbal WM performances before or after the program.

The present study showed deficits in both WMs and most EF in the SG, but the data did not suffice to establish a relationship between them. In clinical practice or family orientation this outcome may be useful in the elaboration of activities, family orientation, and cognitive remediation.

4. Positive aspect

A positive aspect of our study to be highlighted was the use of a computerized neurocognitive battery of tests that allows measuring the reaction time, a battery few studies have used. The method used to register the reaction time in selective attention and inhibitory control tasks allows more pure and sensible measures and may provide relevant information that can inform complementary data of the group's performances. It was also utilized a very comprehensive battery to test different abilities related to EF and two different measures for WM, what might contribute for the availability of valid instruments of WM and EF assessment in the Brazilian context. Another point is that these findings highlight the importance of cognitive deficits as a core characteristic of schizophrenia.[1,36,37]

5. Limitations

One limitation of the present study was that sustained attention was not assessed. This ability is a relevant component of the set of attentional operations of the SAS model, and plays an important role to maintain the representations within the WM buffer. Another weakness, besides the considerable heterogeneity in the severity and range of cognitive deficits in schizophrenia, was the small number of participants assessed in each group, which could increase the probability of type 2 errors and decrease the effect sizes.

One hypothesis that may explain the lack of correlation between VWM and most EF, may occurred because great part of the tasks used primarily demands of verbal instead of visual representations. It could challenge the correlation between VWM and EF. Interpretation for the correlation between VWM and flexibility in the HCG may have occurred due to the particularities of TMT's task way. Besides the need to draw lines linking alternatively among letters and the numbers in alphabetical or ascending order (flexibility), subjects must also retain the localization of a particular stimulus, and then, keep visually screening the area until findings out where the next stimulus is. It is possible that this type of task demands VWM processes. More evidence in support for this last consideration is needed.

Another relevant point was that SG presented a bigger standard deviation in all cognitive performances assessed. It reveals that the variability of cognitive performance of schizophrenic patients did not obey a linear pattern of impairment, so, it is possible that different cognitive profiles may be present in this sample and studies which seek for these different patterns of cognitive expressions must be conducted. Once established these profiles, they also must be correlated to clinical manifestations. Such variability also contributed to the use of nonparametric techniques, what makes some of the data interpretation weaker than parametric techniques.

Conclusion

AWM and VWM, as well as abilities related to EF such as selective attention, inhibitory control, flexibility, and planning, were impaired in patients with schizophrenia in comparison to the healthy comparison group. The dissociations between both WM and EF abilities confirm the hypothesis that VWM and VWM act as two separate storage systems domains. The correlations between WM and EF also contribute to the understanding of the interactions between them, and it may contribute to the understanding for the etiology of WMs deficits. Many studies apply complex tasks as the Wisconsin Card Sorting Test and the Tower of Hanoi as a measure of EF without consider all the specific or purer abilities related to the EF. Thus, the understanding of specific relationship between WM and EF cannot be made. The present data suggest that alterations on the EF contributes to abnormalities on the identification of relevant stimuli, inhibition of irrelevant, and capacity of flexibility may lead to an incapacity of operation of cognitive processes in a higher level (WMs).

Finally, the heterogeneity of schizophrenia must be considered. Future studies with larger samples should be conducted, and cognitive deficits must also be correlated with symptoms and brain functioning in schizophrenia, what may help the further understanding of the cognitive aspects of this disorder. Cognitive dysfunction is a core feature of schizophrenia and the possible main cause of functional outcome.[1,2] The study of these impairment patterns is relevant because it can be used to understand their etiology and pathogenesis.[37] Concomitantly, it is also important to provide data that may underlie the development of futures treatment strategies of schizophrenia.

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Disclosures

Writting group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Speaker's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Arthur A. Berberian	UNIFESP	-	-	-	-	-	-
Bruna T. Trevisan	Universidade Mackenzie	-	-	-	-	-	-
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José M. Montiel	Universidade São Francisco	-	-	-	-	-	-
José Ari C. Oliveira	Universidade São Francisco	-	-	-	-	-	-
Alessandra G. Seabra	Universidade Mackenzie	-	-	-	-	-	-

** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: UNIFESP = Universidade Federal de São Paulo; HIAE = Hospital Israelita Albert Einstein.
For more information, see Instructions for authors.

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