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ScienceDirect
Schizophrenia Research 92 (2007) 160–167
SCHIZOPHRENIA RESEARCH
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The dynamic architecture of working memory in schizophrenia☆

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Received 19 September 2006; received in revised form 25 January 2007; accepted 26 January 2007
Available online 21 March 2007

Abstract

Background: The capacity to hold information in working memory is greater for the first and/or last items of a sequence of information (architecture), and varies according to the retention interval (dynamic) and the type of stimuli. Although working memory deficits in schizophrenia have been documented widely, it is not clear how its architecture and dynamics are affected by the disease.
Methods: Using two Sternberg paradigms – the recognition and the context-recall tasks – we investigated the effect of serial position, retention interval, type of stimuli, and task (type of encoding for the serial position) on working memory capacity in 26 schizophrenia patients and 20 healthy control subjects. A mixed model analysis of variance was applied to the proportion of correct responses and reaction time data.
Results: All the experimental factors had significant effects. However, the most important effects were those of group, group × serial position, and group × delay interactions. The last two effects were driven by a reduced primacy effect and by a reduced performance with longer delay in schizophrenia compared to control subjects. The serial position × delay interaction was significant without triple interaction with group. Group × type of stimuli and group × task for the serial position interactions were not significant.
Conclusion: Schizophrenia patients exhibited normal dynamics but abnormal architecture of working memory (reduced primacy effect), and faster decay of information. These impairments affected equally verbal, spatial and object stimuli and operated with implicit and explicit encoding of the serial position. Although these impairments were not correlated with the clinical picture, they are likely to contribute to the pathogenesis of the difficulties with which schizophrenia patients are faced. Consequently, addressing these specific impairments could alleviate these difficulties.

Keywords: Schizophrenia; Working memory; Serial position; Recognition; Context-recall; Delay; Primacy effect; Recency effect

The dynamic architecture of working memory (WM) refers to the change of WM capacity according to the position of a stimulus in a sequence (architecture), and that this change is modulated by the length of the memorization and the type of stimuli (dynamic). First, it has been shown that WM capacity is greater for the first (i.e., primacy effect) and for the last items (i.e., recency effect) in a sequence of stimuli. Second, this effect of serial position is modulated by the duration of memorization (retention interval) and according to the type of information. With visual stimuli, the primacy effect is more prominent when the memorization duration is long, whereas the recency effect is more

☆ Supported by a grant-in-aid from the University of Minnesota and grants from the VA Medical Center.
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doi:10.1016/j.schres.2007.01.021

prominent when the memorization duration is short (Wright et al., 1985). With auditory stimuli, the reverse modulation was found (Wright, 2002).

Of particular interest is that the primacy and recency effects could be crucial for the memory of serial order. It has been shown that the first and last positions of a sequence could serve as anchor points for coding for the intermediate positions (Henson, 1998). Therefore, altered primacy and recency effects could affect the memory for the serial order. Since Lashley (1951), it has been recognized that memory for the serial order is crucial for the organization of purposeful actions, including motor control (Rosenbaum, 1990) and language (Levelt, 1989; Dell et al., 1997). Interestingly, in effective writing, it is recommended to place the most important sentences at the beginning or end of the paragraph (Strunk and White, 2000). This indicates that the effects of primacy and recency can be used advantageously.

WM impairment is considered to be a core cognitive deficit in schizophrenia (Goldman-Rakic, 1999). It could also contribute to the cognitive (Hemsley, 2005; Gold et al., 1997), language (Stephane et al., in press), and general function impairments in this illness. Some studies have examined the primacy and recency effects and the memory of serial order; however, the findings have been inconsistent.

Frame and Oltmanns (1982) examined the recall of the first and last words of seven-word lists and found impairment in the primacy effect that was independent, unlike overall recall, from the level of symptomatology. Similar findings were reported when subjects were required to reproduce 20-word lists (Manschreck et al., 1991). Other studies examined only the recency effect using recency discrimination tasks, and found that schizophrenia patients were impaired in recency judgment despite normal recall (Rizzo et al., 1996) or recognition (Schwartz et al., 1991).

Other studies evaluated the memory of the serial order by examining the correlation between the remembered and actual test word-lists, and found impairment (Schwartz et al., 1991; Stone et al., 1998; Elvevag et al., 2000). As the impairment co-varied with measures like recall, primary deficit of the memory of the serial order could not be ascertained.

Memory of the serial order in schizophrenia was investigated by two additional methods. In one method, subjects reproduced 4–7 letter sequences (Elvevag et al., 2001). The patients in this study made more omission errors toward the end of the list. The other method required subjects to recall items appeared in specific serial positions in 4–7 letter lists (Elvevag et al., 2003). In this study, the difference in last positions disappeared, and impairment in recalling items in earlier positions emerged. The authors attributed these findings to a greater forgetting during the recall process, and impairment in maintaining information respectively. However, as only one memorization delay was used in the latter study, the finding can be related to a problem in encoding for the first position, or/and decay of information.

Contrary to the above, in an earlier study (Wexler et al., 1998), the effect of serial position did not differentiate between patients and controls in the verbal WM task. In this study, the interaction between serial position and group was not examined in the non-verbal WM task; however, examination of the plot of performance against serial position showed a similar effect of serial position in patients and controls.

The inconsistency between these studies is likely related to methodological differences between studies, and/or methodological limitations. First, some studies used memory loads much higher than the usual working memory span (Manschreck et al., 1991; Elvevag et al., 2000). Consequently, memory resources other than WM might have been called upon in these tasks. Second, many studies did not control for experimental factors that could affect the primacy and recency effects, such as memorization duration and type of stimuli. Third, some studies used explicit instructions to remember the serial position of the stimuli (Wexler et al., 1998), whereas others did not (Manschreck et al., 1991). In the former paradigm the serial position was explicitly encoded, while in the latter paradigm, the encoding for the serial position is implicit (given the sequential presentation, the order of stimuli is part of the information with which the subjects are presented; however, no explicit attention to the order is paid).

The memorization duration, as mentioned above, modulates the primacy and recency effects. However, many of the above studies used one memorization duration (delay) (Elvevag et al., 2003), or allowed as much time as needed to reproduce a list (Manschreck et al., 1991; Stone et al., 1998; Elvevag et al., 2000, 2001), which implies that the memorization duration across trials and across subjects is likely variable and accordingly has a variable effect on the serial position. In addition, the neural network engaged in these tasks depends on the type of information held in WM (Farah, 1988a,b). As many studies used different types of stimuli, they are not readily comparable. Furthermore, the implicit and explicit encodings of the serial position affect the reaction time (RT) differentially (Luce, 1986). Therefore, studies that used implicit encoding (Elvevag et al., 2001), or explicit encoding (Elvevag et al., 2003) are not comparable either.

Table 1
Demographic and clinical data

	Group			
	Control (N=20)		Patient (N=26)	
Age[a], years	48.0	(11.1)	49.3	(7.6)
Sex, male/female	16/4		25/1	
Handedness, left/right	1/19		1/25	
Subject's education[a], years	14.6	(1.9)	13.1	(1.6)
Average parents education[a], years	12.8	(2.8)	11.6	(2.6)
NART-estimated IQ[a]	108.5	(8.1)	101.5	(9.4)
BPRS[a]	–	–	43.8	(9.0)
Negative symptoms[a]	–	–	7.8	(4.5)
Psychotic symptoms[a]	–	–	5.8	(2.7)
Disorganized symptoms[a]	–	–	2.0	(2.6)
Duration of illness[a], years	–	–	19.4	(10.3)
Medication[a], chlorpromazine equivalent, mg/day	–	–	367	(242)
Diagnostic, schizophrenia/ schizoaffective	–		18/8	

[a] Mean (SD).

In summary, to date, studies in schizophrenia examined some factors known to affect the dynamic architecture of working memory, but neglected others. Therefore, a comprehensive evaluation of all these factors on working memory capacity in schizophrenia is necessary for accurate conclusions. In this study, we investigated the effects of serial position, stimulus type, memorization delay, and the implicit and explicit encoding of the serial position of the stimuli on working memory in schizophrenia.

1. Methods

1.1. Subjects

We studied 26 patients (18 with schizophrenia and 8 with schizoaffective disorder), and 20 healthy control subjects. The patients were recruited from the outpatient clinic at the Minneapolis VA Medical Center (MN), whereas the control subjects were recruited through flyers placed in the VA Medical Center. All subjects gave their informed consent before their participation in the study. The experimental protocol was approved by the Institutional Review Boards of the VA Medical Center and the University of Minnesota. The diagnostic evaluation was carried out by a master's level research assistant who was trained to use the Structured Clinical Interview for DSM IV (SCID). Consensus diagnosis was established with the treating psychiatrist or by three other psychiatrists when the treating psychiatrist was not available. Table 1 shows the demographic data for all subjects. The two groups of subjects did not differ significantly in the number of male and female subjects (Fisher's exact test, p=0.151), in the number of right and left-handed subjects (Fisher's exact test, p=1.000), in age ($t(44)=-0.48$, p=0.637) or in the average education level of the parents ($t(44)=1.45$, p=0.154). On the other hand the two groups differed significantly in education level ($t(44)=2.77$, p=0.008, and premorbid level of intellectual functioning ($t(42)=2.65$, p=0.011), which was evaluated using the National Adult Reading Test (NART).

The severity of illness was evaluated with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). The scores from the SANS/SAPS were used to provide ratings for negative symptoms, psychotic symptoms and disorganized symptoms (Andreasen et al., 1995). Duration of illness was derived from records' reviews, and the chlorpromazine equivalent doses of medications were estimated according to the methods of Woods (2003) and Van Kammen and Marder (1995). The clinical data are summarized in Table 1 also. The subjects performed the two tasks described in the

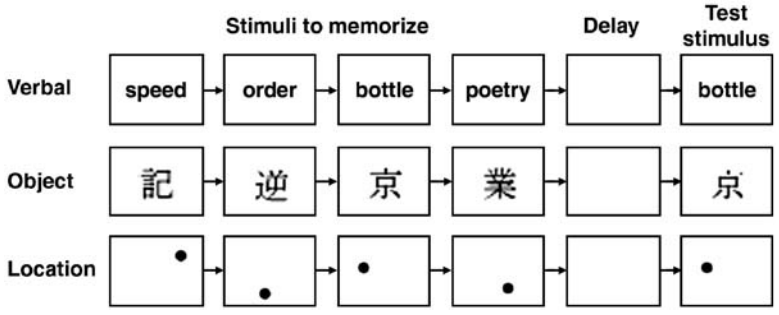

Fig. 1. Examples of stimuli presentation in the working memory tasks with verbal, object and spatial stimuli. In the task with implicit encoding for serial position, subjects had to indicate whether the test stimulus was present in the list to memorize, whereas in the task with explicit encoding for serial position, subjects had to indicate the serial position of the test stimulus in the list.

Appendix, Fig. 1. These two tasks and their constituent components were presented in random order.

1.2. Data analyses

Mixed model analyses of variance were performed to determine the significance of the effects of group (patient, control), type of encoding for the serial position (implicit, explicit), type of stimuli (verbal, object, spatial), serial position (1, 2, 3, 4), delay (0.5 s, 5 s, 10 s) and their interactions on the percent of correct responses and on the reaction time (RT) of correct responses. For the recognition task, the serial position can be determined only when the test stimulus was part of the list of stimuli to memorize, therefore only those trials (i.e., expected response 'Yes') were used in the analyses. The analysis of the percent of correct responses was done using Anscombe angular transformation to stabilize the variance (Chanter, 1975). The RT of correct trials were averaged using the harmonic mean, which is robust to potential outliers (Ratcliff, 1993). The statistical analyses were implemented using SPSS 13.0 (SPSS Inc., Chicago, IL).

2. Results

2.1. Control tasks

The control tasks were performed almost flawlessly by the two groups, with an average correct performance exceeding 99%. In contrast, RT was not homogeneous across experimental factors. Table 2 presents the average RT and standard error of the mean. In the two-choice task, the RT was significantly longer for the patient group than for the control group ($F(1,44)=6.33$, $p=0.016$). Similarly, in the four-choice task, RT was longer for the patient group than for the control group ($F(1,43)=11.710$, $p<0.001$). In addition, there was a significant effect of finger ($F(3,129)=24.53$, $p=0.016$), but not of interaction group × finger ($F(3,129)=0.92$, $p=0.433$). The effect of finger resulted from shorter RT with the index finger than with the other fingers.

The differential effects found in the control tasks should be taken into account in the analyses of RT in WM tasks. Therefore, RT from the control tasks was subtracted from the corresponding RT in the WM tasks.

2.2. Working memory tasks

The results of the analyses of variance on the percent of correct responses and on the adjusted RT are indicated in Table 3. Although the five experimental factors and their interactions produce a complex table of effects, the effects of importance for this study can be summarized quite briefly. For one thing, all the experimental factors associated with the working memory tasks (i.e., type of encoding for the serial position, type of stimuli, serial position, and delay) had a significant effect on the percent of correct responses and reaction time. The fourth-level interaction of all these factors was significant for the percent of correct responses ($p=0.033$) and marginally significant for the adjusted RT ($p=0.051$).

More importantly, three effects significantly differentiated patients from control subjects: (1) the schizophrenia group had a significantly lower percent of correct responses than the control group ($p<0.001$); (2) the percent of correct responses was significantly affected by the interaction delay × group ($p=0.004$); and (3) the percent of correct responses was significantly affected by the interaction serial position × group ($p=0.038$). Adjusting the RT in the working memory tasks to that in the control task eliminated any significant effect for the factor group. Fig. 2 illustrates the significant effects: the average percent of correct responses of the two groups is plotted against delay in A, and against serial position in B. The two plots show that the schizophrenia group was systematically less accurate than the control group. In addition, Fig. 2A shows that the percent of correct responses dropped more quickly with delay for the schizophrenia group than for the control group. Finally, Fig. 2B shows that the primacy effect was less pronounced in the schizophrenia group than in the control group.

Table 2
Reaction time in the control tasks

Group	Two-choice RT task				Four-choice RT task							
	Index		Middle[a]		Index		Middle		Ring		Little	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Control	471	(19)	468	(20)	529	(20)	619	(26)	633	(29)	620	(28)
Patient	578	(34)	574	(36)	698	(40)	802	(40)	834	(52)	840	(61)

[a] Not used in the analyses.

Table 3
Results of ANOVA on percent of correct responses and on adjusted response time

Effect	*df*	Percent of correct responses		Adjusted response time	
		F	*p*	*F*	*p*
Group (Gr)	1,44	15.23	<0.001 [a]	1.33	0.255
Type of encoding (TE)	1,44	1.84	0.182	6.95	0.012 [b]
TE × Gr	1,44	0.57	0.456	0.12	0.727
Type of stimuli (TS)	2,88	221.02	<0.001	33.73	<0.001 [b]
TS × Gr	2,88	0.36	0.697	0.20	0.820
Delay (D)	2,88	207.74	<0.001 [b]	17.11	<0.001 [b]
D × Gr	2,88	5.91	0.004 [a]	0.94	0.394
Serial position (SP)	3,132	60.25	<0.001 [b]	35.23	<0.001 [b]
SP × Gr	3,132	2.887	0.038 [a]	0.47	0.703
TE × TS	2,88	16.48	<0.001 [b]	18.57	<0.001 [b]
TE × TS × Gr	2,88	0.06	0.945	2.27	0.109
TE × D	2,88	65.50	<0.001 [b]	0.24	0.786
TE × D × Gr	2,88	1.04	0.358	1.00	0.373
TS × D	4,176	23.36	<0.001 [b]	9.64	<0.001 [b]
TS × D × Gr	4,176	0.31	0.874	0.67	0.617
TE × TS × D	4,176	2.24	0.067	2.01	0.095
TE × TS × D × Gr	4,176	0.92	0.454	0.70	0.594
TE × SP	3,132	13.94	<0.001 [b]	23.73	<0.001 [b]
TE × SP × Gr	3,132	0.42	0.738	0.71	0.550
TS × SP	6,264	11.94	<0.001 [b]	16.74	<0.001 [b]
TS × SP × Gr	6,264	1.29	0.262	0.38	0.892
TE × TS × SP	6,264	3.95	0.001 [b]	4.99	<0.001 [b]
TE × TS × SP × Gr	6,264	0.46	0.840	0.76	0.602
D × SP	6,264	25.75	<0.001 [b]	10.57	<0.001 [b]
D × SP × Gr	6,264	1.13	0.344	1.65	0.133
TE × D × SP	6,264	8.75	<0.001 [b]	2.01	0.054
TE × D × SP × Gr	6,264	1.49	0.182	0.92	0.483
TS × D × SP	12,528	11.30	<0.001 [b]	2.17	0.012 [b]
TS × D × SP × Gr	12,528	1.13	0.336	1.31	0.210
TE × TS × D × SP	12,528	1.89	0.033 [b]	1.77	0.051 [b]
TE × TS × D × SP × Gr	12,528	0.65	0.797	1.33	0.196

[a] Denotes a significant effect that includes group.
[b] Denotes a significant effect of experimental factors that does not include group.

2.3. Correlation analyses

The characteristics of performance of schizophrenia patients that were significantly different from those of the control subjects (i.e., accuracy, decay and primacy) are potential indicators of the severity of the illness. For this reason, we analyzed the correlation between these characteristics and the clinical data. First, we computed estimates of (a) accuracy, as the average percent of correct responses across conditions for each patient; (b) decay, as the least-squares slope between the angular-transformed percent of correct responses and delay for each patient; and (c) primacy, as the difference between percent of correct responses for serial position 1 and the average percent of correct responses for serial positions 2 and 3. Second, we computed the rank correlation (Spearman rho) between these scores and the clinical data (i.e., BPRS score, negative, psychotic and disorganized symptoms, duration of illness, and chlorpromazine equivalent doses of medication). The results showed no significant correlation.

2.4. Classification analysis

We investigated whether the scores of accuracy, decay, and primacy could discriminate effectively schizophrenia patients from healthy control subjects. For this purpose, we performed a binary logistic regression analysis, with group as the dependent variable

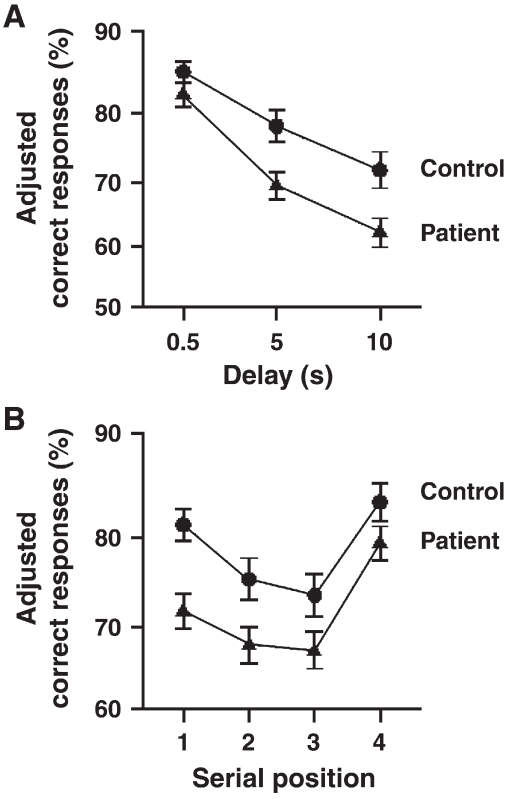

Fig. 2. A. Percent of correct responses averaged across conditions and across subjects for each group as a function of memory delay. The decrease of the percent of correct responses with delay was more pronounced for the patient group than for the control group. B. Percent of correct responses averaged across conditions and across subjects for each group as a function of serial position. The primacy effect (i.e., advantage for the first stimulus in the list compared to the stimuli in the middle) was less marked in the patient group than in the control group. The recency effect (i.e., advantage for the last stimulus in the list compared to the stimuli in the middle) was similar in both groups. In each plot the vertical lines represent the standard error of the mean calculated across subjects.

Table 4
Classification results based on the logistic regression analysis

Observed group	Predicted group		Percent correct
	Control	Schizophrenia	
	N	*N*	
Control	15	5	75
Schizophrenia	5	21	81

and the scores of accuracy, decay, and primacy as covariates (Hosmer and Lemeshow, 2000). We performed the regression using a stepwise procedure to select the covariates that can be used to classify subjects. We performed the stepwise procedure both forward and backward, and obtained the same final results. These analyses indicated that the scores of accuracy (Wald-test, $\chi^2(1)=9.25$, $p=0.002$) and primacy (Wald-test, $\chi^2(1)=3.96$, $p=0.047$) provided a model that fitted the data well (Hosmer and Lemeshow-test, $\chi^2(7)=5.70$, $p=0.575$). Expressed in odd-ratio, the parameters of the model indicate that a decrease of 10% in accuracy increased the odds of being part of the schizophrenia group by 7.4 to 1; and a decrease of 10% of the primacy effect increased the odds of being part of the schizophrenia group by 4.6 to 1. We used this model to classify individuals in the control group or in the schizophrenia group, and obtained a correct classification of 78% of the cases. The results of the classification for each group are presented in Table 4.

3. Discussion

The experimental factors of group, serial position, delay, type of stimuli, and type of encoding were all found to affect WM capacity. Schizophrenia patients performed less well than controls, but more importantly, this impairment in WM capacity was affected by the serial position and delay factors. Patients exhibited a primacy impairment that was independent from the delay. In fact, there was a significant delay × serial position interaction without triple interaction with the group factor, which suggests that the delay modulates the serial position effect in schizophrenia in the same way as in controls. This can be seen in Fig. 3, which plots the difference between primacy and recency regarding the percent of accuracy for both groups and across delay. This figure shows that the prominence of the recency effect at the shortest delay changed progressively toward a greater primacy effect in both groups. In addition, the schizophrenia group had a bias toward less primacy at all delays. These results indicate that schizophrenia patients had abnormal architecture of WM (impaired primacy effect); however, the dynamic properties of this architecture were not different from that of healthy controls.

The impairment of schizophrenia patients was also greater for the longer delays however, as mentioned above, this was independent from the serial position effect. Furthermore, the classification analyses showed that the overall accuracy and the impairment of the primacy effect, but not the delay effect discriminated significantly between patients and controls. Given these findings, it is reasonable to conclude that the delay and serial position effects reflect distinct impairments of working memory in schizophrenia. One finding indicates that encoding of serial position and more particularly the encoding of the first position in a sequence is deficient, and the other finding indicates that information decays faster in schizophrenia patients than in healthy control subjects.

The differences between groups were found in the accuracy but not in the reaction time, which indicates that the effects on accuracy were not determined by a speed–accuracy tradeoff. Furthermore, these findings are consistent with previous studies in the literature. One study (Elvevag et al., 2003) examined the serial position, but not delay, and found primacy impairment. Another study (Dreher et al., 2001) investigated the delay, but not the serial position effects, and reported a

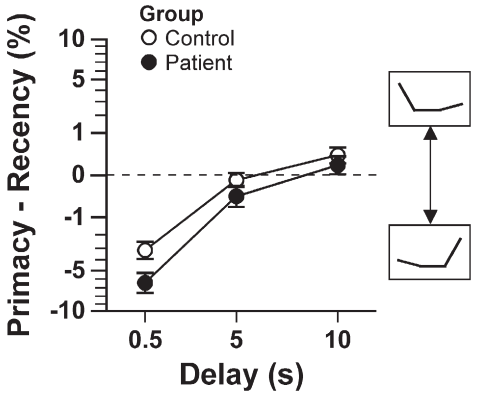

Fig. 3. The difference between primacy and recency for both groups is plotted across delay. The primacy effect was estimated by the difference between the percent of correct responses for serial position 1 and the average of percent of correct responses for serial positions 2 and 3. The recency effect was estimated as the difference between the percent of correct responses for serial position 4 and the average of percent of correct responses for serial positions 2 and 3. The change of the serial position effect was similar in patients and healthy controls. The prominence of the recency effect at the shortest delay changed progressively toward a greater primacy effect. In addition, the schizophrenia group had a bias toward less primacy at all delays.

delay effect independent of memory load and type of stimuli.

Of interest is that while the type of stimuli and the type of encoding for the serial position affected working memory capacity, these factors did not differentiate schizophrenia patients from healthy controls, and did not affect the between group differences with respect to the serial position and delay factors. This indicates that the abnormal architecture of working memory and the faster decay of information were present in schizophrenia patients irrespective of the type of information memorized and the type of encoding for the serial position.

Although some work (Szendi et al., 2006) reports positive correlation between spatial working memory capacity and negative symptoms, this data do not show any significant correlation between the specific WM impairments and the measures of severity of illness. In our view, due to the inherent imprecision of the assessment of the severity of symptoms, a relationship cannot be ruled out. It could be argued that the WM impairments could play a role in the pathogenesis of symptoms, have repercussions on the cognitive operations, and have a direct impact on the social and professional functioning of schizophrenia patients. The WM impairments could also suggest specific ways to alleviate the difficulties of these patients. For example, it is well known that working memory capacity predicts the ability to comprehend language in healthy subjects (Just et al., 1996), and in schizophrenia patients (Condray et al., 1996). The primacy impairment found in this study points to a specific way that schizophrenia patients might miscomprehend language, by less than adequate encoding for the earlier part of sentences or discourse. Consequently, this difficulty could be alleviated by placing the most important sentence at the end, rather than at the beginning, of the discourse (i.e., making use of the normal recency effect). The faster decay of information seen in schizophrenia patients may contribute to comprehension difficulty, and implies that these patients could benefit from repetitive reminders. Furthermore, the impaired primacy, along with the faster decay, could explain the loose association between propositions observed in schizophrenia. Poor encoding and forgetting of earlier propositions, resulting from the impaired primacy effect and from the faster decay of information, respectively, could result in making latter propositions with marginal relatedness to the earlier one.

The patients in this study were medicated. Nonetheless, the chlorpromazine equivalent doses were not correlated with working memory impairments. This makes medication effect an unlikely explanation for the impairments seen in this study.

In summary, the results indicate that schizophrenia patients had normal dynamics but abnormal architecture of working memory, and faster decay of information in WM. These impairments affected equally verbal, spatial, and object stimuli, and operated with implicit and explicit encoding of the serial position. Although these impairments were not correlated with the clinical picture, they are likely to contribute to the pathogenesis of the difficulties with which schizophrenia patients are faced. Consequently, addressing these specific impairments could alleviate these difficulties.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi: 10.1016/j.schres.2007.01.021.

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