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Temporal order and spatial memory in schizophrenia: a parametric study

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Abstract

Spatial working memory has been shown to be impaired in schizophrenia. In contrast, memory for temporal order has been poorly studied in patients with schizophrenia. The aim of this study was to compare and to further characterize spatial working memory and sequence reproduction deficits in patients with schizophrenia under stable medication by manipulating cues (pattern versus sequence), delay, set-size and response type in various recall and recognition tasks. This allowed us to dissociate processes as encoding, retention and retrieval and to compare the performance of patients with schizophrenia to the performance of patients with prefrontal lesions, who have been previously tested in the same tasks. Our results show that increase of the set-size and of the delay decreased performance of both groups, and that these factors had larger detrimental effects in patients with schizophrenia than in controls. Furthermore, comparison between tasks revealed retention and retrieval deficits in schizophrenia. Finally, patients with schizophrenia showed impairments not only in recall but also in sequence recognition tasks with delay. This is in contrast to patients with prefrontal lesions, who have previously been shown to have intact recognition of sequences after a delay. These results suggest that the working memory deficit in schizophrenia cannot be restricted to a prefrontal dysfunction.

Keywords: Frontal lobe; Spatial working memory; Executive processes; Schizophrenia; Encoding; Retention; Retrieval; Rehearsal

1. Introduction

Recent theories of schizophrenia have attempted to explain the wide range of cognitive deficits found in these patients as a disruption of behavior guided by working memory (Goldman-Rakic, 1991). Working memory is a system used for temporary storage and manipulation of information (Baddeley et al., 1986). It is divided into two general components: short-term storage (in the order of seconds) and a set of executive processes that operate on the content of storage. This division is supported by neuropsychological studies showing that some neurological patients have intact short-term storage but impaired executive processes and vice versa (D'Esposito and Postle, 1999; Smith and Jonides, 1999). The short-term storage can itself be divided into two subordinate components, the visuo-spatial sketchpad and the phonological loop,

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that are respectively responsible for short-term retention and processing of visuo-spatial and verbal information (Baddeley, 1992).

All components of working memory have been shown to be impaired in schizophrenia, and in particular, the visuo-spatial sketchpad (Park and Holzman, 1992; Fleming et al. 1997; Keefe et al., 1997; Pantelis et al., 1997) and the executive component (Sullivan et al., 1994; Hutton et al., 1998; Morice and Delahunty, 1996; Pantelis et al., 1997; Fleming et al., 1997; Stone et al., 1998; Salamé et al., 1998; Brebion et al., 1998; Smith et al., 1998; Granholm et al., 1996). The visuo-spatial sketchpad has either been tested by a spatial delayed response task, in which a pattern has to be remembered during a delay, or by a visuo-spatial memory span task (Milner et al., 1991), in which the subject has to reproduce sequences *immediately* after the examiner touched a set of squares in sequential order (Fleming et al., 1997; Brebion et al., 1998; Salamé et al., 1998; Stone et al., 1998).

The neural basis of spatial working memory in schizophrenia has been shown to be dysfunctional as compared to controls but the exact nature of the dysfunction remains controversial. Some brain imaging studies of spatial working memory support hypofrontality in patients with schizophrenia as compared with controls (Weinberger et al., 1996; Yurgelun-Todd et al., 1996; Callicott et al., 1998) while other report greater activation in patients than controls in the left dorsolateral prefrontal cortex (DLPFC) (Manoach et al., 1999, 2000). In fact, the exact role of the prefrontal cortex in spatial working memory is also controversial in normal controls, as shown by a recent review revealing the importance of the right premotor cortex but not of the DLPFC in storage of spatial information (Smith and Jonides, 1999).

The neural basis of *reproduction* and *recognition* of sequences from presented stimuli remain to be determined in schizophrenia. However, in controls *reproduction* and *recognition* of sequences after a delay would involve separate neural substrates, with no PFC activation during the delay of sequences *recognition* (Pochon et al., 1999). Another recent fMRI experiment has shown activation of the pre-SMA in visuomotor association during sequences learning (Sakai et al., 1999). The involvement of the premotor cortex in sequence *reproduction* is confirmed by neuropsychological studies showing deficits in lesioned humans (Shimamura et al., 1990; Milner et al., 1991; Kesner et al., 1994) and in non-human primates (Barone and Joseph, 1989; Tanji and Mushiake, 1996; Shima and Tanji, 1998).

The present study was designed to characterize spatial working memory and sequence reproduction in schizophrenia. For this purpose, task difficulty was systematically manipulated to determine whether spatial working memory and sequence reproduction deficits occur at the lowest or at some higher level of difficulty. The difficulty level was manipulated by increasing sequence sizes and by varying the length of the delay between the presentation of the sequence and its reproduction. To our knowledge, these parameters have never been simultaneously varied in patients with schizophrenia in the tasks presented hereafter. In particular, no previous study has investigated the performance of patients with schizophrenia when sequences have to be reproduced after a delay. Such tasks allow the testing of executive processes because they require both retention of the spatial location of the stimuli presented and their manipulation during active rehearsal of the sequence through space (Owen et al., 1996).

The second goal of this study was to define more precisely the memory deficit of patients with schizophrenia by assessing elementary processes such as encoding, retention and retrieval processes. Indeed, typical delayed response paradigms performed in patients with schizophrenia did not investigate these processes separately. In order to clearly dissociate these processes, the present study used four tasks that followed one general procedure consisting of three successive phases: presentation of a visuo-spatial stimulus (cue), a 10 s delay (or alternatively 500 ms) and a response phase that manipulated the type of responses (reproduction versus recognition). Three of these four tasks were *recall* tasks that rely on the ability to retrieve sequence or pattern from memory and to reproduce the corresponding information. One task was a *recognition* task that requires comparison of two successive sequences (identical or different). The recognition task tested whether a sequence has been correctly memorized while making the response factor independent of the organization of the response.

These four tasks can distinguish memory processes

Table 1
Means, SDs, and group comparisons of demographic data

Subject characteristics	Normal subjects ($n = 18$)	Schizophrenic subjects ($n = 18$)	t	p
Age (years)	32 ± 8	33 ± 11	1.66	0.34
Sex ratio (M/F)	10/8	10/8		
Laterality score	77.6 ± 17	75.8 ± 44	0.78	0.57
Education (years)	15 ± 4	12 ± 2	4.8	< 0.05
Age of onset		17 ± 5		
Duration of illness (years)		11 ± 5		

in the following way. First, the no-delay condition should reveal a possible encoding deficit because in this condition storage of information is reduced to immediate short-term memory and rehearsal is absent. Second, retention (storage) will be investigated by varying the delay between presentation and recall. Third, spatial cues will (in the temporal recall task) or will not (in the temporo-spatial recall task) provided before the response in order to vary the retrieval condition.

The last aim of this study was to compare the performance of patients with schizophrenia with results previously obtained in dorsolateral prefrontal lesioned patients (Teixeira-Ferreira et al., 1998). The prefrontal cortex has been proposed to play a central role in the spatial working memory deficits of patients with schizophrenia (Weinberger et al., 1986; Goldman-Rakic, 1991). This assumption is based on the fact that patients with schizophrenia show reduced performance during spatial delayed response paradigms (Park and Holzman 1992), which are also impaired in dorsolateral prefrontal lesioned monkeys (Goldman-Rakic, 1991) and prefrontal lesioned humans (Verin et al., 1993; Dubois et al., 1995). Comparison of the performance of patients with schizophrenia and DLPFC lesioned patients should pinpoint specific impairment and consequently reveal whether spatial working memory and sequences reproduction impairments are qualitatively similar in these two groups.

In summary, this study aims to better characterize the temporal order and spatial working memory deficits of patients with schizophrenia by:

1. A quantification of the influence of different parameters of difficulty (sequences length or pattern complexity, delay versus no delay) on performance in different working memory tasks.
2. An evaluation of elementary processes involved in working memory (encoding, retention, retrieval).
3. A distinction of qualitative differences in memory processes between patients with schizophrenia and dorsolateral prefrontal lesioned patients.

2. Methods

2.1. Subjects

Eighteen patients (10 males, 8 females), with a mean age of 33 years (SD 11), meeting DSM-IV (American Psychiatric Association, 1994) criteria for schizophrenia and with dominant negative signs were recruited from the adult psychiatry section of the Salpêtrière Hospital (Paris). Patients with past substance abuse or with prior head injury or a history of neurological illness were not included. All patients were under stable medication at the time of testing. All subjects were right handed, as determined by a laterality score of 70 or more on the modified Edinburgh Handedness Inventory (White and Ashton, 1976). Patients characteristics are summarized in Table 1.

A group of 18 controls (10 males, 8 females), were matched for age (mean age 32 years, SD 8) and gender. They were also screened for substance abuse and neurological or psychiatric diseases.

All subjects gave written informed consent to participate in this paradigm, which was approved by the ethics commission of the Salpêtrière Hospital, Paris.

2.2. Procedure

Subjects were seated in front of a touch-sensitive screen and responded by using the right index finger. The testing procedure consisted of a series of four

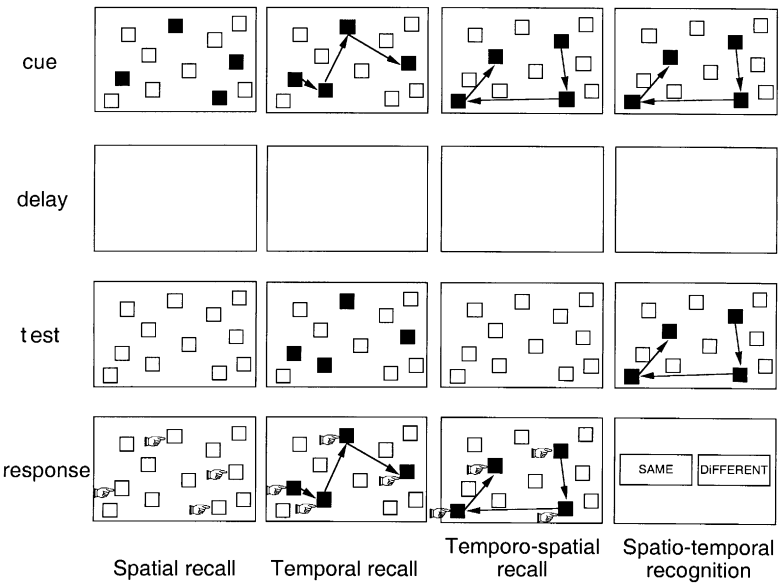

Fig. 1. Trial sequence (from up to bottom) of a trial in the spatial recall, temporal recall, temporo-spatial recall and temporo-spatial recognition tasks.

computerized tasks (15 min each). Each trial began with the same arrangement of 12 identical blue 2 cm squares displayed on the screen in a pseudo-random pattern. The structure of each task was that of a standard delayed-response task: presentation of a stimulus, a delay (or no delay) and a response stage. The stimuli consisted of squares that changed color from blue to red. The number of squares that changed color varied from 2 to 5. For each set size, 6 trials were presented, 3 with no delay (500 ms) and 3 with a delay (10 s), during which the screen remained black. After presentation of the pattern, all squares disappeared. When they reappeared on the screen, a beep indicated that the subject had to respond by touching the squares according to specific instructions on each task. Each time a square was touched, it disappeared for 2 s and then reappeared. The subject had 15 s to respond, after which the next trial began. To ensure of subject's comprehension, 2 test/practise trials were performed before each task. Task order was counterbalanced between subjects (see Fig. 1).

2.2.1. Spatial recall task

The *spatial recall task* aimed to analyze the subjects' ability to register, retain and reproduce the spatial arrangement of the items. The stimulus presentation consisted of the *simultaneous* color change of 2, 3, 4 or 5 squares depending on set size. The stimulus consisting of 2 squares remained red for 2 s. For each additional square, 0.5 s of presentation was added. At response time all squares reappeared as blue. The subject had to remember the location of the squares that had turned red during stimulus presentation.

2.2.2. Temporal recall task

The *temporal recall task* aimed to analyze the subject's capacity to register, retain and reproduce the temporal ordering of the items. The stimulus presentation was formed by the successive color changes of 2, 3, 4 or 5 squares, depending on the set size. On each trial, one square turned to red for 2 s and then returned to blue at the same time as the next square changed color. At response time, the squares that belonged to the stimulus sequence reappeared as red, while the other reappeared as blue. The subject had to reproduce the order in which the squares had changed color during stimulus presentation, by touching the red squares in that order.

2.2.3. Temporo-spatial recall task

The *temporo-spatial recall task* analyzed the subject's capacity to register, retain and reproduce

the temporo-spatial trace of the items. Stimulus presentation was the same as in the temporal recall task, but at response time, all squares reappeared as blue. Therefore, the subject had to remember both the location and the order of the squares that changed color, and respond by touching these squares in the same location and the same order as that shown during stimulus presentation.

2.2.4. Temporo-spatial recognition task

The *temporo-spatial recognition task*, which can be viewed as a delayed match-to-sample task for temporo-spatial patterns, analyzed the subject's capacity to register, retain and recognize the temporo-spatial trace of the visual items without requiring a specific motor program. Stimulus presentation was the same as in temporo-spatial recall task, but after the delay another sequence was presented in order to be compared to the first. The sequences were either identical or different. After the presentation of the second sequence, the words "SAME" and "DIFFERENT" appeared on the screen and the subject had to touch the word that corresponded to the correct response

The performance index was the percentage of correct responses produced by subjects in the recall conditions and the percentage of test sequences correctly matched to learned sequences in the recognition condition. Statistical analysis was achieved by repeated measure analysis of variance with group as inter-subject factor (controls versus patients), and task, set size and delay as intra-group factors.

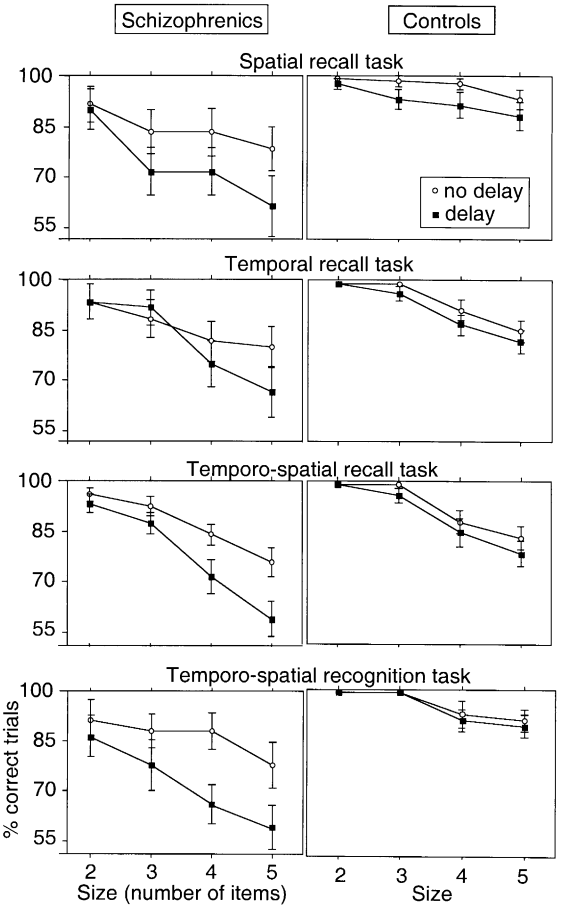

Fig. 2. Percentage of correct trials and corresponding standard deviation in patients with schizophrenia (left column) and controls (right column) for the four tasks as a function of set-size (number of items in patterns or sequences) and delay period.

3. Results

The level of performance of patients with schizophrenia was significantly reduced as compared to controls [$F(1,34) = 10.2$, $p < 0.003$] (Fig. 2). There was a significant task effect [$F(3,34) = 3.5$, $p < 0.05$], a significant delay effect [$F(1,34) = 33.7$, $p < 0.0001$] and a significant set-size effect [$F(3,34) = 46.9$, $p < 0.0001$]. The task effect was due to the fact that the mean level of performance of the temporo-spatial recall task was significantly reduced compared to the spatial recall task [$F(1,34) = 5.2$, $p < 0.05$] and the temporal recall task [$F(1,34) = 7.5$, $p < 0.05$]. The performance in the temporo-spatial recognition task was also significantly reduced compared to the temporal recall task [$F(1,34) = 4.0$, $p = 0.05$].

Significant interactions appear between group and delay [$F(1,34) = 9.5$, $p < 0.005$]. Indeed, patients with schizophrenia performed significantly worse in the delay than in the no-delay condition [$F(1,16) = 22.2$, $p = 0.0002$] while no significant difference was found between the no-delay and delay conditions in controls. Furthermore, patients were significantly impaired compared to controls in the absence of delay in the spatial [$F(1,34) = 6.0$, $p < 0.05$] and temporo-spatial recall [$F(1,34) = 9.5$, $p < 0.05$] tasks but did not differ significantly in the temporal recall task [$F(1,34) = 1.1$, $p = 0.3$] and differ only

marginally in the temporo-spatial recognition [$F(1,34) = 4.0$, $p = 0.05$].

Significant interactions were also present between task and delay [$F(3,34) = 8.7$, $p < 0.001$], because the delay significantly impaired the spatial recall task [$F(1,34) = 13.2$, $p < 0.001$], the temporo-spatial recall task [$F(1,34) = 20.4$, $p < 0.0001$] and the temporo-spatial recognition task [$F(1,34) = 42.0$, $p < 0.0001$] but did not significantly impair the temporal recall task [$F(1,34) = 1.2$, $p = 0.72$].

No group by task interaction was found [$F(3,34) = 2.3$, $p = 0.8$]. There was also no interaction between group and set-size [$F(3,34) = 1.7, p = 0.15$]. Finally, no interaction was observed between group, task and delay [$F(3,34) = 1.5$, $p = 0.22$] or between group, task and set-size [$F(9,34) = 1.6$, $p = 0.1$].

4. Discussion

Patients with schizophrenia showed significant impairment compared to controls in all the tasks. This confirms previous studies showing deficits in schizophrenia both in spatial working memory (Park and Holzman, 1992; Keefe et al., 1997; Fleming et al., 1997) and during temporal sequence reproduction (Fleming et al., 1997; Stone et al., 1998; Salamé et al., 1998; Brebion et al., 1998). However, previous temporal sequences reproduction studies in patients with schizophrenia only investigated *immediate* sequences reproduction after their presentation. In contrast, this study also investigated recall and recognition of sequences after a delay. Furthermore, this study used the same type of computerized tasks to test spatial and temporal processing, which avoids the use of different methodologies for different tasks as encountered in previous work (Fleming et al., 1997).

The absence of interaction between task and group shows that the effect of task was qualitatively similar in both groups. Thus, executive processes, assessed by the temporo-spatial recall task and spatial working memory processes, assessed by the spatial recall task, were not differentially impaired in patients with schizophrenia.

Below, we discuss in details the effect of increasing difficulty on spatial working memory and sequence reproduction, dissociate the components involved in working memory and compare the performance of patients with schizophrenia with that of dorsolateral prefrontal lesioned patients.

4.1. Difficulty effect

In the absence of delay and when all sequence size data were grouped together, patients were impaired during all tasks compared to controls, except in the temporal recall task. The deficit of patients with schizophrenia in the spatial recall with no delay is in accordance with previous studies showing deficits during reproduction of patterns in absence of delay (Fleming et al., 1997). Similarly, deficit of the temporo-spatial with no delay was found in previous studies of the Corsi span (Salamé et al., 1998; Brebion et al., 1998). To our knowledge, the temporo-spatial recognition task with no-delay has not been studied before, and thus no comparison can be made. Finally, the absence of significant difference between the two groups in the temporal recall task with no delay can be attributed to the fact that in this task, the pattern of the sequence is given before the response, thereby facilitating sequence reproduction.

Our study also evaluated the general effect of increasing difficulty (sequence size and presence of delay) on performance. We found that when sequence size increases, performance is reduced in all tasks for both groups. Furthermore, performance is reduced more rapidly in patients with schizophrenia than in controls when the set-size increases. Indeed, when the no-delay and delay conditions are grouped together, the size effect is greater in patients with schizophrenia than in controls, for each task.

When delay increases, performance is reduced in all the tasks for both groups. However, this reduction of performance only reaches significance in patients with schizophrenia in all the tasks, except in the temporal recall task. This shows that patients with schizophrenia have working memory impairments, both for spatial information and for temporo-spatial sequences.

However, the fact that patients were also significantly impaired compared to controls in the absence of delay in the spatial, the temporo-spatial recall and marginally impaired in the temporo-spatial recognition tasks suggests that they could have a dysfunction beyond the working memory deficit. Two distinct but

mutually not exclusive processes can account for the results:

1. The deficit lies partly downstream from short-term storage, at the stage of encoding or selecting the information to be processed in working memory.
2. Patients have difficulties upstream to short-term memory processing, at the stage of retrieving visuo-spatial information.

Alternatively, the impairment of patients in the no-delay condition of the tasks involving sequential presentation of stimuli might reflect in fact a working memory deficit. Indeed, these conditions do involve a time lag between the presentation of the stimuli and the presentation of the target. However, this interpretation does not explain the deficit of patients in the spatial recall task with no-delay. We therefore explore the hypothesis of a dysfunction beyond the working memory deficit.

4.2. Individualization of processes involved in delay–response paradigms

Comparison between the different task conditions enabled dissociating memory components such as information encoding, retention during the delay and retrieval of information for programming an appropriate motor response. Indeed, a specific *encoding* deficit in patients with schizophrenia should be revealed by a significant reduction of their performance as compared to controls in the no-delay condition, in which retention and rehearsal processes are minimized. The significant impairment which appears when patients with schizophrenia are compared to controls in the no-delay condition of the spatial and temporo-spatial recall tasks could suggest a possible encoding deficit, whatever the type of stimuli presentation (pattern or sequence). However, if an encoding deficit was strongly present in patients with schizophrenia, it should appear in all the tasks. The fact that the performance of patients and controls did not differ significantly in the no-delay condition for all sequence size in the temporal recall task [$F(1, 34) = 1.1$, $p = 0.3$] and differed only marginally in the temporo-spatial recognition [$F(1, 34) = 4.0$, $p = 0.05$] shows that encoding is not strongly impaired in patients with schizophrenia.

Further studies are needed to support the absence of encoding deficit in patients with schizophrenia. Indeed, it is possible that patients with schizophrenia could have an encoding deficit because the temporal recall task and temporo-spatial recognition task may have been too easy to discriminate differences between groups.

A *retention* deficit should become apparent in patients with schizophrenia by an impairment of performance as compared to controls in the delay condition. Such a retention deficit does appear in all tasks because, when all set size were grouped together, there was a significant impairment in patients with schizophrenia as compared to controls in the delay condition. This retention deficit is in accordance with previous results in which distracting stimuli impaired schizophrenic's retention (Corrigan and Addis, 1995).

In addition to a retention deficit, a *retrieval* impairment cannot be excluded in patients with schizophrenia. A retrieval deficit is more difficult to demonstrate by the between-task comparison than by encoding or retention deficits. Such retrieval deficit should become apparent by comparing the delay condition of the temporo-spatial recall and temporal recall tasks. Indeed, there is no external cue helping retrieval after the delay in the temporo-spatial recall task while in the temporal task, retrieval is primed by the presentation of the pattern constituting the sequence. A retrieval impairment is possible because schizophrenic's deficit is significantly larger during the delay condition in the temporo-spatial than in the temporal recall tasks [$F(1, 34) = 2.17$, $p < 0.05$] and because there was a significant interaction between these two conditions and the group [$F(4, 34) = 5.7$, $p < 0.05$], indicating that the difference between these two conditions are larger in patients than in controls.

Finally, a response programming deficit is difficult to prove using the current design. However, we have previously shown, with the precise temporal definition provided by electrophysiology, that a deficit of preparation to generate self-initiated motor sequences does exist in patients with schizophrenia (Dreher et al., 1999). Indeed, when compared to controls, patients with schizophrenia show a reduced focalization of activation around the SMA and/or primary motor cortex during the preparation of motor sequences.

4.3. Comparison between frontal lesioned patients and patients with schizophrenia

Immediate sequences reproduction tasks have first been assessed in frontal lesioned patients (Milner et al., 1991; Petrides and Milner, 1982). It was shown that dorsolateral prefrontal cortex lesioned patients could identify visual stimuli in an item recognition task but were unable to identify which one was the more recently presented in a recency judgment task. Furthermore, in the tasks presented in this study, dorsolateral prefrontal cortex lesioned patients showed impairments in the spatial recall and temporo-spatial recall tasks but not in the temporo-spatial recognition task (Teixeira-Ferreira et al., 1998). Therefore, the major difference between patients with schizophrenia and dorsolateral lesioned patients relies in the recognition task, which is impaired only in patients with schizophrenia during the delay condition. The lack of deficits during the delay of the temporo-spatial recognition task in dorsolateral prefrontal lesioned patients suggests that intact posterior cortical areas are sufficient to perform correctly delayed sequence recognition. Conversely, the impairment of delayed sequence recognition in patients with schizophrenia favors the view that their working memory deficit can not be reduced to a prefrontal dysfunction. This agrees with the proposition that the frontal lobes do not contribute to working memory in isolation but rather operate as a component of a distributed neural network involving posterior regions. This is also in accordance with a recent fMRI study reporting no PFC activity during the delay of the temporo-spatial recognition task (Pochon et al., 1999). In contrast, activation of a network including the right dorsolateral PFC (area 9/46), premotor and parietal areas was shown during the delay of the temporo-spatial recall task. This shows that the dorsolateral PFC is not critical to hold information in short-term memory, when no sequence reproduction is required, but is rather involved in the transformation between stored visuo-spatial information and the programming of the motor response. The fact that the recognition task did not activate the DLPFC during the delay in controls confirms our interpretation that the deficits observed in patients with schizophrenia during the recognition task with delay cannot be reduced to a prefrontal dysfunction.

Different candidate mechanisms could explain the temporo-spatial recognition deficits in schizophrenia. In particular, it could be argued that additional temporal cortex dysfunction could account for the recognition deficit found in patients with schizophrenia (Stone et al., 1998). This statement is based on classical findings involving the temporal cortex in recognition memory (for review see Suzuki and Eichenbaum, 2000). However, in the same temporal recognition task as the one used in our study, Teixeira-Ferreira et al. (1998) have not found significant impairment in temporal lesioned patients compared to a control group. Furthermore, no temporal cortex activation was found during the recognition task with delay in normal subjects (Pochon et al., 1999).

The neuropathological basis of working memory impairment in schizophrenia can not be reduced to the neuroanatomy. Another possible mechanism which could explain the temporo-spatial recognition deficit in schizophrenia involves a deficit of neuromodulation. In particular, recent work attributes a primary role to dopamine D1 receptors in schizophrenic's working memory deficit. This is supported by a PET study which showed reduced dopamine D1 receptors in the prefrontal and temporal cortices of drug-naive schizophrenics related to their cognitive deficit (Okubo et al., 1997). These results in humans are concordant with the fact that local injections of D1 receptors antagonists in rat and monkey prefrontal cortex, which induce sub-optimal level of D1 receptor stimulation, are detrimental to normal working memory performance (Zahrt et al., 1997; Sawaguchi et al., 1991; Seamans et al., 1998).

4.4. Problems related to medication in patients with schizophrenia

Finally, it is necessary to examine the possibility that the working memory deficit of patients with schizophrenia is not attributable to the disease per se but can rather be ascribed to medication. However, two important facts argue for a working memory deficit intrinsic to schizophrenia. The first is that working memory deficits are present in medication-withdrawn patients with schizophrenia (Carter et al., 1996) and in neuroleptic naive first episode samples (Saykin et al., 1994), whereas bipolar patients taking similar neuroleptics show intact working memory

(Park and Holzman, 1992, 1993). In addition, relatives of schizophrenics show working memory deficits as compared to controls (Park et al., 1995), suggesting a possible genetic deficit a fortiori valid in never medicated patients with schizophrenia. Thus, even if a negative influence of medication cannot be excluded, the observed working memory deficit is probably intrinsic to the disease per se. In fact, classical neuroleptics (chlorpromazine, haloperidol) would not improve nor damage schizophrenic's working memory (Green et al., 1997; Goldberg et al., 1995), while atypical neuroleptics (risperidone, clozapine) could improve working memory (although this remains to be firmly established) (Green et al., 1997; Goldberg et al., 1995; Weinberger and Gallhofer, 1997). More generally, cognitive deficits in patients with schizophrenia are not improved by classical neuroleptics (Sharma and Mockler, 1998; Bristow et al., 1997; Weinberger and Gallhofer, 1997; Rao and Moller, 1994) and stay remarkably constant during the course of the disease (Goldberg et al., 1991). They are positively correlated with social outcome (Breier et al., 1991; Goldberg et al., 1993; Green et al., 1997), better than symptomatic scales (Goldberg et al., 1995), and are good predictors of the length of hospitalization (Pantelis et al., 1997). The precise characterization of cognitive deficits in schizophrenia, as provided by this study, is thus important from a clinical and therapeutical point of view.

5. Conclusions

Our study has contributed to a better characterization, according to task difficulty, of spatial working memory and executive process deficits in patients with schizophrenia. It has suggested that these working memory deficits cannot be reduced to those observed in prefrontal cortex lesioned patients. The deficits of patients with schizophrenia are better understood by a general cortico-cortical or cortico-subcortical dysfunction. This view is consistent with the neurodevelopmental hypothesis of schizophrenia, which supports that this disease is a disorder of maturation of the cerebral cortex (see Harrison, 1997 for a review). Finally, the delineation of encoding, storage and retrieval processes involved in spatial working memory made in the present work could be helpful for future brain imaging studies exploring the neural basis of these processes in schizophrenia.

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