ELSEVIER

Schizophrenia Research 51 (2001) 137–147

SCHIZOPHRENIA RESEARCH

www.elsevier.com/locate/schres

Temporal order and spatial memory in schizophrenia: a parametric study

J.-C. Dreher[a,*], J.-P. Banquet[a], J.-F. Allilaire[b], M.-L. Paillère-Martinot[b], B. Dubois[c], Y. Burnod[a]

[a]*INSERM U483, University of Paris VI Jussieu, Paris, France*
[b]*Adult Psychiatry Section, Hôpital de la Salpêtrière, Paris, France*
[c]*INSERM U289, Hôpital de la Salpêtrière, Paris, France*

Received 14 April 2000; accepted 10 September 2000

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,

* Corresponding author. Unit of Integrative Neuroimaging, National Institute of Mental Health, Clinical Brain Disorder Branch, Building 10, Room 4C/101, 9000 Rockville Pike, Bethesda, MD 20892-1365, USA. Tel.: +1-301-402-5483; fax: +1-301-496-7437.
E-mail address: dreherj@intra.nimh.nih.gov (J.-C. Dreher).

0920-9964/01/$ - see front matter
PII: S0920-9964(00)00151-1

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