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Impaired spatial working memory maintenance in schizophrenia involves both spatial coordinates and spatial reference frames

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ABSTRACT

Spatial working memory (SWM) dysfunction is a central finding in schizophrenia; however, more evidence of impaired *maintenance* over time is required. Consequently, the present study examined SWM maintenance over short unfilled delays, and with encoding equated. The influence of a vertical reference frame to support maintenance was also investigated. The performance of 58 patients with schizophrenia and 50 healthy controls was assessed using the Visuo-Spatial Working Memory (VSWM) Test across three unfilled delays (0, 2, and 4 s). Inaccuracy of direction and distance responses was examined at each delay duration. The results showed that performance was significantly less accurate for both distance and direction responses at 2 and 4 s delays in schizophrenia, but was not significantly different from controls at the 0 s delay. Patients showed a particularly marked loss of accuracy between the time interval of 0–2 s. Furthermore, schizophrenia participants exhibited significantly greater response variability at the vertical axis of symmetry than controls at the 2 and 4 s delays, but not at the 0 s delay. These data clearly show both impaired maintenance over time and difficulty using a vertical frame of reference in schizophrenia. The latter findings may reflect, in part, dysfunctional reference-related inhibition.

1. Introduction

The centrality of working memory (WM) deficits in individuals with schizophrenia (Lee and Park, 2005; Piskulic et al., 2007; Forbes et al., 2008) has led the NIMH initiative Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) to select this cognitive domain as a target for translational research (Barch and Smith, 2008). This decision reflects, in part, the impact that impairments in WM have on social and occupational functioning (Green et al., 2000; Cervellione et al., 2007). Reflecting the multi-component nature of WM, the CNTRICS working party determined that the WM constructs of *goal maintenance* and *interference control* were ready for immediate application in clinical trials (Barch et al., 2009). In contrast, the construct of *maintenance over time* – that is, the ability to maintain target representations internally during a delay period (Park and Lee, 2002) – was recognized as having good construct validity but in need of more clinical research to determine whether this mechanism is impaired in schizophrenia (Barch and Smith, 2008).

At the neural level, recent evidence supports the notion of a time-dependent impairment during spatial working memory (SWM) maintenance in schizophrenia (Driesen et al., 2008). However, behavioral evidence concerning the effects of delay duration has been somewhat mixed. Early studies suggested that increasing the delay duration worsens the SWM deficit in patients with schizophrenia when compared to healthy controls. For example, using oculomotor and haptic delayed-response tasks, Park and Holzman (1992) showed that schizophrenia patients made more errors after a 30 s than after a 5 s delay and were thus vulnerable to increasing delay periods. Others have suggested that SWM deficits may be stable regardless of the length of delay (Keefe et al., 1995, 1997; Leiderman and Strejilevich, 2004; Lee and Park, 2005). Importantly, based on a meta-analysis of 124 studies (of both spatial and verbal WM) Lee and Park (2005) reported that increasing the delay duration beyond 1 s did not influence the performance difference between controls and individuals with schizophrenia, indicating that encoding and/or the early part of maintenance may be particularly impaired.

Differences in task methodologies have also complicated the interpretation of these mixed findings. In particular, many studies of SWM have used filled-delays (i.e., distractors presented during the

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delay period) (Park and Holzman, 1992; Stratta et al., 1999; Hartman et al., 2002), consequently poor performance by individuals with schizophrenia may be due to difficulties with interference control rather than impaired maintenance over time (Turvey, 1973; Barch and Smith, 2008). In addition, many studies have measured SWM maintenance without controlling for differences in the initial encoding of visuospatial targets; again such studies cannot be unambiguously linked to an impairment in maintenance over time. However, both Tek et al. (2002) and Badcock et al. (2008) did equate for encoding differences and found evidence of impaired maintenance of spatial information over relatively short (3 and 4 s, respectively) unfilled delays, supporting Lee and Park's (2005) proposal that the earliest part of maintenance is impaired in schizophrenia.

Basic research in spatial memory also highlights the importance of reference frames (i.e., category boundaries that divide space into smaller regions) in maintaining spatial representations over short and long delays (Huttenlocher et al., 1991; McNamara and Diwadkar, 1997; Spencer and Hund, 2002). While the precise spatial coordinates of visual targets decay rapidly after stimulus offset, perceived reference frames can support the accurate memory of spatial locations. For example, the dynamic field theory (DFT) of spatial cognition (Schutte et al., 2003; Spencer et al., 2007; Simmering et al., 2008) predicts that *variance* in WM responses near reference axes (e.g., the perceived vertical midline or symmetry axis of a target display) should be low compared to responses away from reference axes; and such predictions have been supported empirically in healthy adults (Spencer and Hund, 2002; Simmering et al., 2006), though such effects have received little attention in studies of schizophrenia.

In sum, there is a clear need for further studies examining whether maintenance over time in SWM is impaired in schizophrenia, using unfilled delays and with stimulus encoding equated (Barch and Smith, 2008). Furthermore, existing evidence suggests that maintenance over very short delays (1–2 s after stimulus offset) is of critical importance. In the current investigation, we used a modified delayed-response task, the Visuo-Spatial Working Memory (VSWM) test (Badcock et al., unpublished test), to examine this issue. The VSWM uses a staircase procedure to equate differences in the speed of encoding in working memory. Using this task, Badcock et al. (2008) showed that the performance of schizophrenia patients was equivalent to that of healthy controls at 0 s delay but less accurate compared to healthy controls at 4 s delay. The current study aimed to replicate and extend these findings, in an independent sample of individuals with schizophrenia and healthy controls, by including an intermediate delay period of 2 s. In addition, the VSWM task provides separate examination of direction and distance responses, which are distinct features of reaching movements (Gordon et al., 1994; Chieffi and Allport, 1997; Smyrnis et al., 2003), within a stimulus array that allows us to examine the variability of responses near to and away from the vertical midline axis. Consequently, the second aim of the current study was to examine whether individuals with schizophrenia are impaired in the use of a vertical reference frame, which normally supports the recall of spatial locations as delay increases. Finally, since poor SWM performance in schizophrenia may reflect general deficits in memory and attention, or side effects of (anticholinergic) medication, we also examined the influence of these variables on performance.

2. Method

2.1. Participants

A group of 58 patients (46 males) was recruited through consecutive admissions to a psychiatric hospital. All patients met both International Classification of Diseases (ICD)-10 and Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for a lifetime diagnosis of schizophrenia or schizophrenia spectrum disorder. At the time of testing, patients were taking their usual medication, $n=50$ atypical antipsychotics, $n=2$ typical antipsychotics, $n=6$ on both, $n=7$ anticholinergic, $n=17$ selective serotonin reuptake inhibitors (SSRI), $n=3$ tricyclic antidepressants (TCA), $n=16$ mood stabilizer, and $n=15$ benzodiazepines. The mean chlorpromazine equivalent dose of antipsychotics was 637 mg.

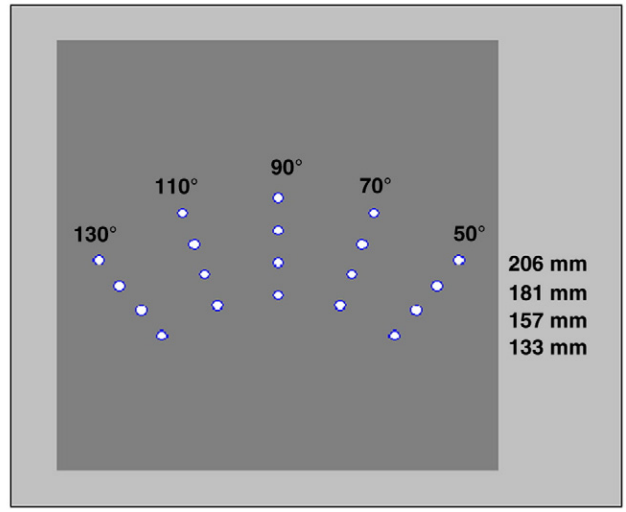

Fig. 1. Distribution of target locations in the VSWM test.

The control group comprised 50 healthy participants (33 male) screened for a personal or family history of psychotic illnesses. Exclusion criteria for all participants included head injury, neurological disorder, and substance abuse treatment at the time of testing. Written informed consent was obtained from all participants. The study was approved by the Human Research Ethics Committees of The University of Western Australia and the North Metropolitan Area Mental Health Service in Perth, Western Australia. The data for this study form part of a larger cognitive and electrophysiological study of schizophrenia patients.

2.2. Tasks

2.2.1. VSWM test

Participants were seated in front of a computer and touch-sensitive monitor. A target stimulus (white circle, 4.7 mm radius) appeared at variable locations on the monitor. The distribution of target position was determined by a hidden grid comprised of four concentric arcs and five radial arms (see Fig. 1). Stimuli could appear at one of 20 possible locations on every trial. When the target was switched off, an auditory stimulus signaled to the participants to touch the screen where the target had been located. The starting hand position was fixed in the midline at the base of the screen by a coloured marker; participants touched the screen with a pointing-stylus but a speeded response was not required. The VSWM task included two phases: pre-test (staircase), and test. The staircase phase was used to minimize the effect of differences in speed of encoding between individuals. The staircase phase began with an easily detectable target presentation time (1166 ms, or 70 frames), which quickly decreased to near threshold, which was estimated as the duration required to achieve 79% correct immediate recall of the stimulus locations (Edwards et al., 1998). These individualized target duration thresholds were used in the subsequent test phase, during which, three blocks of stimuli (counterbalanced) were presented: no delay (immediate, 0 s), 2 s and 4 s delay. Every possible stimulus location was presented twice (randomly selected), therefore each block comprised 40 targets. An advantage of the grid governing locations was that some stimuli were presented directly aligned with the perceived vertical axis of symmetry of the target display, thus allowing examination of the influence of this reference frame on working memory performance.[1] Dependent variables included speed of encoding (ms), direction inaccuracy (degree), and distance inaccuracy (mm). Inaccuracy was assessed as the difference between target location and response coordinates relative to the starting hand position. All participants responded with their preferred hand.

2.2.2. Other cognitive tests

Current intelligence was estimated with the Shipley Institute of Living Scale (Shipley, 1940; Zachary et al., 1985); which contains a 40-item vocabulary test and a 20-item test of abstract reasoning, from which estimates of Wechsler Adult Intelligence Scale (WAIS)-R full scale intelligence quotient (IQ) (Wechsler, 1981) can be derived.

[1] Due to the presence of the colored marker, indicating the starting hand position, the vertical midline axis was much more salient than the horizontal midline symmetry axis — making it more likely to be used as a reference frame to divide the task space into smaller regions (Li and Westheimer, 1997). Similarly diagonal symmetry axes are perceived less accurately (Beh et al., 1971; Wenderoth, 1997) and used less reliably than the vertical symmetry axis (Tversky and Schiano, 1989).