A NEW LOOK AT WORKING MEMORY DEFICITS IN SCHIZOPHRENIA

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CHAPTER I

OVERVIEW

This dissertation aims to augment our understanding of working memory deficits in schizophrenia. Working memory deficit, first reported in the early 90s (e.g., Park & Holzman, 1992), has become an important cornerstone in understanding the pathophysiology of schizophrenia. The working memory deficit has been suggested to be a central underlying factor of cognitive dysfunctions observed in schizophrenia patients (e.g., Goldman-Rakic, 1994; Silver, Feldman, Bilker, & Gur, 2003). Cognitive dysfunctions in schizophrenia patients are more predictive of the functional outcome than clinical symptoms (i.e., positive or negative symptoms) (e.g., Addington & Addington, 2000; Green, 1996; Liddle, 2000), and therefore have become the focus of pharmacological and neurobiological research efforts in recent years. In addition, the working memory deficit has been linked to both the frontal lobe dysfunction and the dopamine system abnormalities that may be central to the etiology of schizophrenia (e.g., Abi-Dargham, Mawlawi, Lombardo, Gil, Martinez, Huang, Hwang, Keilp, Kochan, Van Heertum, Gorman, & Laruelle, 2002; Goldman-Rakic, 1991; Perlstein, Carter, Noll, & Cohen, 2001). Considering the utmost important role of working memory in understanding schizophrenia, it is rather surprising to find that the etiology of working memory deficits in schizophrenia remains to be determined. Moreover, the role of the dorsolateral prefrontal cortex in working memory deficits of schizophrenia is not well understood (for a review see Manoach, 2003). In addition, recently, it has been suggested

that poor encoding plays an important role in working memory deficits in schizophrenia (Hartman, Steketee, Silva, Lanning, & McCann, 2003; Lencz, Bilder, Turkel, Goldman, Robinson, Kane, & Lieberman, 2003; Tek, Gold, Blaxton, Wilk, McMahon, & Buchanan, 2002), though the role of other components of working memory such as maintenance still remains to be studied thoroughly.

The goal of this dissertation is to expand the current understanding of working memory deficits in schizophrenia. I will start by reviewing previous studies on working memory deficits in schizophrenia and, then, propose theory-driven hypotheses in CHAPTER II. First, I will focus on specific cognitive components of working memory and consider the effects of contextual modulation on working memory in schizophrenia in CHAPTER III and CHAPTER IV. I will then examine the neural correlates of working memory deficits in schizophrenia patients, using both functional and structural brain imaging techniques including functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS) and diffusion tensor imaging (DTI) in CHAPTER V. These imaging methods will be used to uncover the brain mechanisms related to working memory process in schizophrenia patients and healthy normal individuals. Finally, I will attempt to describe implications of behavioral and imaging results in CHAPTER VI.

CHAPTER II

WORKING MEMORY DEFICITS IN SCHIZOPHRENIA

Working memory and schizophrenia

Schizophrenia is a complex and severe mental disorder that affects about 1% of the population worldwide. It has been traditionally characterized by clinical symptoms such as delusions, hallucinations, thought disorders, apathy, and flat or inappropriate affect. However, more recently, the importance of cognitive deficits such as attention deficit, abnormal language, memory impairment, and disinhibition has become evident. Cognitive dysfunctions are better at predicting prognosis of schizophrenia patients than clinical symptoms (Green, 1996; Green, Kern, Braff, & Mintz, 2000; Liddle, 2000; Meltzer, Thompson, Lee, & Ranjan, 1996). Among the cognitive dysfunctions present in schizophrenia patients, working memory deficit has been suggested to be an underlying causal factor for other deficits (Goldman-Rakic, 1991). Accumulating evidence indicates that the working memory deficit is a core feature of schizophrenia (e.g., Goldman-Rakic, 1994; Lee & Park, in press) but the source of working memory deficits is not yet clearly elucidated.

Conceptualizing working memory

Working memory was originally defined as " a system for the temporary holding and manipulation of information during the performance of a range of cognitive tasks such as comprehension, learning, and reasoning" (Baddeley, 1986). In this model,

working memory consisted of an active attentional control system called the central executive, sub-served by modality-specific sub-systems: the phonological loop and the visual-spatial sketchpad. Since then, the concept of working memory has evolved into different forms depending on the theoretical research framework. For example, Kieras, Meyer, Mueller, and Seymour (1999) describe working memory as an entire system of temporary stored codes, human knowledge representation and procedures, whereas Ericsson and Delaney (1999) conceptualize working memory as a component of long-term memory system the function of which is to maintain selective access to information that is needed to complete a task with unlimited capacity. Engel et al. (Engel, Tuholski, Langheim, & Conway, 1999) also consider working memory to be a system consisting of active long-term memory traces above threshold plus controlled attention. In neurophysiology or behavioral neuroscience literature, working memory is often defined as the system that maintains information 'on-line' for a short period of time (e.g., Goldman-Rakic, 1991). Although the definition of working memory and the methods used to study it may differ, the core part of the concept of working memory across these theories may be summarized as the system or procedure for maintaining mental representation actively for further processing of the representation (Miyake & Shah, 1999 for a detailed account). In this dissertation, I will define working memory as *a system or mechanism for representation and active maintenance of information during a short period of time for further processing*.

Working memory deficits in schizophrenia: A brief summary

The working memory deficit in schizophrenia is well documented across diverse paradigms, methods, and techniques. A recent meta-analytic study showed that working memory deficit was not modality-specific and present regardless of the duration of the delay period (Lee & Park, in press). More importantly, working memory deficits in schizophrenia do not seem to be a mere artifact of antipsychotic medication since it was found in unmedicated patients with schizophrenia (e.g., Carter, Robertson, Nordahl, Chaderjian, Kraft, & O'Shora-Celaya, 1996). In addition, some studies found improvement in working memory deficits in schizophrenia patients after a certain period of time in atypical antipsychotic treatment (Green, Marshall, Wirshing, Ames, Marder, McGurk, Kern, & Mintz, 1997; McGrath, Chapple, & Wright, 2001; McGurk, Carter, Goldman, Green, Marder, Xie, Schooler, & Kane, 2005), although different types of medication may have differential effect on working memory deficit (McGurk et al., 2005). Working memory deficits have also been found in healthy, unmedicated biological relatives of schizophrenia patients (e.g., Conklin, Curtis, Katsanis, & Iacono, 2000; MacDonald, Pogue-Geile, Johnson, & Carter, 2003; Myles-Worsley & Park, 2002; Park, Holzman, & Goldman-Rakic, 1995a) as well as healthy individuals with schizotypal characteristics (Park, Holzman, & Lenzenweger, 1995b; Park & McTigue, 1997; Tallent & Gooding, 1999). These studies suggest that working memory deficit may be present at all stages of illness as well as in those who may carry latent liability for the disorder. Hence, working memory deficit is a strong candidate for an endophenotypic marker for schizophrenia.

Past studies of working memory in schizophrenia suggest that working memory deficit may be a central feature of the disorder; yet, the causal factors of this deficit remain obscure. Therefore, the next logical step is to investigate the etiology of the deficit. Identifying the underlying cause(s) of working memory deficits in schizophrenia may help to develop more focused pharmacological interventions and other types of remediation.

Putting working memory in context

One way to understand the working memory deficit in schizophrenia is to study each component of working memory. To perform a working memory task successfully, one must encode target information correctly, store a representation of the target in working memory for a brief period while resisting distraction, and retrieve the stored representation and initiate appropriate behavioral response when necessary. Failure to perform successfully in any of these processes may result in working memory errors. Several studies suggest that poor encoding might contribute to working memory deficits in schizophrenia patients. Schizophrenia patients may show working memory deficit because they have impaired perceptual processing, which can cause inefficient encoding (Tek et al., 2002), or because they are slower to encode a target (Hartman et al., 2003). These studies suggest that inefficient encoding is partially responsible for working memory deficit in schizophrenia. However, this does not dismiss the role of the other components of working memory (i.e., maintenance and retrieval) in working memory deficits in schizophrenia. Schizophrenia patients showed working memory deficit even when their perceptual incompetence (that can result in inefficient encoding) was

controlled (Lencz et al., 2003; Tek et al., 2002). A component analysis of error response (Park & O'Driscoll, 1996) also showed that schizophrenia patients seemed to be susceptible both to maintenance of representation during the delay period and to interference from competing response tendencies, leading to an inappropriate response choice. In summary, previous studies have demonstrated that schizophrenia patients have deficits in encoding and maintenance.

However, previous theories did overlook one important factor of target processing in working memory: context. Contextual information affects short-term memory or working memory (Gorfein, 1987; Postle, 2003) as well as long-term memory (for a review, see Smith & Vela, 2001). Context can also guide attention to a target more efficiently (e.g., Chun, 2000; Chun & Jiang, 1998; Mathis, 2002), which may affect target encoding in working memory. In addition, context can modulate the neural activation in relation to target processing (Ghose & Maunsell, 2002; Gilbert, Ito, Kapadia, & Westheimer, 2000; Ito & Gilbert, 1999; Kastner & Ungerleider, 2000; Olson, Chun, & Allison, 2001; Toth & Assad, 2002; Williams, Singh, & Smith, 2003). Hence, it seems logical to hypothesize that contextual information could affect working memory in schizophrenia; yet, the association between context and encoding in working memory has not been elucidated very well in schizophrenia studies. In addition, a dominant theory of schizophrenia states that schizophrenia is a disorder of context processing (Cohen, Barch, Carter, & Servan-Schreiber, 1999; Cohen & Servan-Schreiber, 1992; Servan-Schreiber, Cohen, & Steingard, 1996). The question we should answer is: Is working memory deficit in schizophrenia a consequence of abnormal context processing? Before we can address this question, we need to examine what is meant by context processing. Context

as defined by Cohen and his colleagues seems to be restricted to verbal information given in the form of task instruction (Barch, personal communication) and context processing itself is a form of 'executive control' (Carter, personal communication). That is, 'context' in this theory is limited to the task instruction that has to be maintained during the task for successful performance. So the conceptualization of context in this theory can be considered as 'task set,' or 'task context.' It is directly related to the goal of the current task and it provides the rule for guiding participants to perform the task successfully. This theory may be able to describe how schizophrenia patients utilize the goal of the task or task instruction during the task, but it excludes all other forms of context processing. Therefore, one of goals of this dissertation is to deconstruct the amorphous concept of 'context' in the field of schizophrenia research and begin to examine each component systematically.

A review of context processing in schizophrenia

Fragmented experience in perception, language processing, thought processes, and behavioral actions is one of the characteristic phenomena described by schizophrenia patients since the beginning of the last century (i.e., Kraepelin, 1896/1987; Matussek, 1952/1987). Though Shakow (1962) proposed that these phenomena could be explained by an inability to process context, it was not until recently that context processing became a central framework for understanding cognitive deficits of schizophrenia. At present, there are three major theories of schizophrenia that are centered around the concept of context processing. I will discuss each theory briefly in turn.

Gray and his colleagues proposed that the core deficit of schizophrenia patients is 'impaired context processing,' an inability to integrate stored memories of past regularities of perceptual input (e.g., associations among stimuli) with ongoing motor programs due to excessive dopamine activity in the limbic system (including hippocampus) and the basal ganglia (Gray, 1998; Gray, Feldon, Rawlins, & Hemsley, 1991; Gray, Joseph, Hemsley, Young, Warburton, Boulenguez, Grigoryan, Peters, Rawlins, Taib, Yee, Cassaday, Weiner, Gal, Gusak, Joel, Shadach, Shalev, Tarrasch, & Feldon, 1995; Gray, Williams, Fernandez, Ruddle, Good, & Snowden, 2001; Hemsley, 1987). Context processing was typically assessed with latent inhibition (LI) or Kamin blocking (KB) paradigms. Both LI and KB examine latent effects of implicitly presented context on target processing. The impaired context processing was hypothesized to be more prevalent among acute schizophrenia patients because acute schizophrenia patients show more positive symptoms that are closely related to excessive dopaminergic activity, but evidence from acute schizophrenia patients is mixed. Some studies found reduced or abolished latent inhibition or Kamin blocking effects (Baruch, Hemsley, & Gray, 1988; Rascle, Mazas, Vaiva, Tournant, Raybois, Goudemand, & Thomas, 2001), but others found normal latent inhibition in acute schizophrenia patients (Swerdlow, Braff, Hartston, Perry, & Geyer, 1996; Swerdlow, Stephany, Wasserman, Talledo, Sharp, Minassian, & Auerbach, 2005; Williams, Wellman, Geaney, Cowen, Feldon, & Rawlins, 1998). In Gray's theory, context is viewed as the representation of stored regularities in the long-term memory acquired by previous experience that can affect current, ongoing activity. Acute psychotic schizophrenia patients may have difficulties applying stored regularities in the current task appropriately. That is, 'intact context processing' is

associated with an ability to use previous experience in long-term memory appropriately in the current situation. Although this theory accounts for how previous experience may affect task performance in the current situation, studies on impaired episodic long-term memory in schizophrenia patients (e.g., Aleman, Hijman, de Haan, & Kahn, 1999) raises the question of whether impaired context processing of acute schizophrenia patients is just another expression of defective long-term memory. This remains to be debated further. In addition, 'context processing' in this theory is a multifaceted concept; learning 'a rule' or 'knowledge' from experience, having intact long-term memory, appraising current motor program, and applying previous experience from long-term memory to the current motor program. Further studies are necessary to examine at which step schizophrenia patients are most vulnerable and how context processing in this theory is related to other cognitive functions.

Cohen's theory of context processing in schizophrenia proposed that schizophrenia patients suffer from a disturbance in the internal representation of context, the task-relevant information held in mind that can be used to produce an appropriate behavior while inhibiting strong, prepotent inappropriate responses, and, as a result, they produce contextually inappropriate response (i.e., Cohen et al., 1999; Cohen & Servan-Schreiber, 1992; Servan-Schreiber et al., 1996). Here, context is task-relevant information held in working memory such that context amounts to specific, verbal task instruction (Barch & Carter, 1998b; Barch, Carter, MacDonald, Braver, & Cohen, 2003; Barch, Carter, Perlstein, Baird, Cohen, & Schooler, 1999a; Cohen et al., 1999; Perlstein, Carter, Barch, & Baird, 1998), or the result of processing a sequence of prior stimuli that is critical to the current task (Cohen et al., 1999; Cohen & Servan-Schreiber, 1992;

Servan-Schreiber et al., 1996). 'Context' in this theory is similar to a task set, which defines how to perform the task. Hence, to produce contextually appropriate behavior, one must 1) be sensitive to context information, 2) hold this information in working memory during the task, and 3) respond appropriately while inhibiting strong, prepotent behavior. In other words, intact context processing is similar to the notion of the central executive and includes intact sensitivity to context information, intact working memory and intact inhibition. This theory did not specify the step at which schizophrenia patients show vulnerability and it is well known that schizophrenia patients suffer from working memory deficit and disinhibition. Another weakness of this theory is that it completely ignores non-verbal behavior. It is necessary to examine which component(s) of 'context processing' in schizophrenia patients is (are) are most impaired. Recently Titone and her colleagues showed that schizophrenia patients were able to detect contextually relevant information under conditions that minimize the need for controlled processing (Titone, Holzman, & Levy, 2002; Titone, Levy, & Holzman, 2000). These studies suggest that schizophrenia patients may be sensitive to context information but are not able to use this information appropriately under certain conditions (resulting in 'impaired context processing') due to other cognitive deficits (i.e., disinhibition). This suggests that the broad definition of context processing in Cohen's theory made it difficult to locate specific deficit of schizophrenia patients in those tasks.

Recently Phillips and Silverstein (2003) proposed a theory that explains cognitive deficits of schizophrenia as a manifestation of discoordination between/ or within areas of the brain. Coordination or contextual processing is the modulational process that affects the salience or dynamic processing of neuronal signals without changing what they mean.

Impaired 'dynamic' perceptual grouping found in schizophrenia patients can be viewed as an example of a product of discoordination (Keil, Elbert, Rockstroh, & Ray, 1998; Peters, Nunn, Pickering, & Hemsley, 2002; Place & Gilmore, 1980; Silverstein, Kovacs, Corry, & Valone, 2000). Impaired dynamic grouping has been found in schizophrenia patients despite intact form recognition or discrimination (O'Donnell, Swearer, Smith, Nestor, Shenton, & McCarley, 1996) and intact perceptual grouping using the Gestalt Principles (proximity, collinearity, and similarity) (Chey & Holzman, 1997). However, impaired dynamic perceptual grouping in schizophrenia can be ameliorated when the task requires less top-down control (Silverstein, Bakshi, Chapman, & Nowlis, 1998b; Silverstein, Knight, Schwarzkopf, West, Osborn, & Kamin, 1996a; Silverstein, Matteson, & Knight, 1996b). That is, schizophrenia patients may show impaired dynamic perceptual grouping because of their deficits in top-down control and not because they have 'pure' impaired perceptual processes per se. Additionally schizophrenia patients were able to benefit from a salient environment represented by being physically different from background stimuli (Cox & Leventhal, 1978), suggesting that schizophrenia patients may be able to use 'simple modulational' processes. It is necessary to understand the scope of coordination or context processing before examining whether schizophrenia patients show impaired contextual processing or not.

These three major theories of context processing in schizophrenia conceptualize the core deficit of schizophrenia as impaired context processing. Though each theory tries to provide a comprehensive approach, unconstrained definition of context in these theories presents a clear limitation in elucidating the underlying mechanism of cognitive dysfunctions in schizophrenia in relation to 'impaired context processing.' The

definitions of context processing in these theories include multiple related cognitive functions (e.g., working memory, inhibition, or executive control), which make it difficult to assess whether context processing in these theories is indeed different from these cognitive constructs. In fact, some of the previous findings on impaired context processing in schizophrenia can be explained by impaired top-down control (executive control) or working memory deficit. Although the idea of impaired context processing provides a very appealing and attractive global framework for explaining schizophrenia, diffuse and amorphous definitions of context makes it difficult to appreciate the importance of its specific role in understanding schizophrenia. Therefore, to investigate the effect of context on working memory in schizophrenia, it is necessary to use a constrained, specific definition of context. It is also important to examine each aspect of context separately with the specific definition of context.

Context-dependent working memory in schizophrenia

To investigate how contextual processing may affect working memory (context-dependent working memory) in schizophrenia, this dissertation plans to focus on a constrained definition of context in contrast to ones proposed in previous studies. One of the goals of this dissertation is to investigate whether context affects target processing in working memory in schizophrenia patients. Therefore, context is defined as *task-irrelevant information in the current task* that is not critical to performing the current task but may affect the current task performance. That is, context in this dissertation is not directly related to the goal of the current task explicitly. I will also focus on the context that is *presented concurrently with the target* in order to minimize the effect of long-term

memory or other kinds of pre-existing knowledge that might affect performance of the current task. Defining context as the concurrently presented, task-irrelevant information allows me to investigate context processing in schizophrenia patients while minimizing or eliminating additional cognitive demands on the participants. Context information is task-irrelevant and is not critical to the current task; therefore, it does not burden individuals' current information processing further. And yet, it may affect the current task performance without individuals being explicitly aware of its effect. I will investigate two specific types of context in this dissertation: context embedded within the target (i.e., the dimensions or the features of the target that is not task-relevant) and context surrounding the target (i.e., the visuospatial layout around the target). If context information affects working memory performance of schizophrenia patients, we should be able to observe its effect as the change in performance of schizophrenia patients in the task when contextual information is manipulated. However, if context information does not affect working memory in schizophrenia, schizophrenia patients would show the similar degree of performance in the current task performance regardless of the contextual manipulation.

Neurobiological mechanisms of working memory in schizophrenia

Neural correlates of working memory: A brief summary

Studies of the neurobiological correlates of working memory in monkeys and humans showed that the prefrontal cortex plays a key role. Studies on monkeys using single cells in the dorsolateral prefrontal cortex (DLPFC) indicate that there are cellular correlates of maintaining mental representation in working memory (e.g., Funahashi,

Bruce, & Goldman-Rakic, 1989, 1990). The increased activation of the DLPFC associated with maintenance has also been found in studies on humans using fMRI and positron emission tomography (PET) (e.g., Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Courtney, Ungerleider, Keil, & Haxby, 1996; Leung, Gore, & Goldman-Rakic, 2002; Sakai, Rowe, & Passingham, 2002; Ungerleider, Courtney, & Haxby, 1998). Studies also suggest that the division of the dorsal vs. ventral visual processing continues to the prefrontal cortex, such that spatial working memory is associated with more superior part of the prefrontal cortex (the DLPFC and the superior frontal gyrus) whereas object working memory is associated with more ventrolateral prefrontal cortex (Levy & Goldman-Rakic, 2000; Sala, Rama, & Courtney, 2003; Ungerleider et al., 1998; Wilson, Scalaidhe, & Goldman-Rakic, 1993). However, other studies (e.g., D'Esposito, Aguirre, Zarahn, Ballard, Shin, & Lease, 1998; D'Esposito, Postle, Ballard, & Lease, 1999; D'Esposito, Postle, & Rypma, 2000) suggest that the functional architecture of the prefrontal cortex is better described in terms of processing rather than the stimulus modality. Thus, they argue that the manipulation of mental representation in working memory is associated with the DLPFC, whereas the 'simple' maintenance function of working memory is more related to the inferior prefrontal cortex. These two approaches do not agree with the functional organization of the prefrontal cortex in relation to working memory, but there is no doubt that the prefrontal cortex is critical to working memory process. Further studies are necessary to understand whether these two approaches are, in fact, qualitatively distinct from each other (i.e., maintenance from domain specific approach may be a combination of manipulation and maintenance of

process-oriented approach), and what specific role of the sub-areas of the prefrontal cortex plays in working memory.

It is important to note that the prefrontal cortex is a part of a large network of cortical and subcortical areas that support working memory (Chafee & Goldman-Rakic, 1998, 2000; Olesen, Westerberg, & Klingberg, 2004; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Todd & Marois, 2004), including the inferior temporal cortex (Chelazzi, Duncan, Miller, & Desimone, 1998), and the premotor cortex (Bruce & Goldberg, 1985; Rowe et al., 2000). Several areas in the brain found to be related to working memory suggest that a widely spread network, instead of a single area, in the brain is crucial. Especially a network of frontoparietal regions seems to play an important role in visuospatial working memory. Pessoa et al. (2002) showed that the magnitude of neural activity in a network of frontoparietal regions predicted successful performance in visual working memory task. Sakai et al. (2002) also showed that the magnitude of neural activity in the prefrontal cortex was higher in correct trials than in error trials, whereas the correlation of activity between the prefrontal area 8 and the intraparietal area was associated with correct working memory performance. In summary, a network of areas in the brain including the prefrontal cortex has been associated with successful performance in working memory task in monkeys and healthy individuals.

Neural correlates of working memory deficit in schizophrenia

Studies with monkeys (e.g., Funahashi et al., 1989) and healthy individuals (e.g., Smith & Jonides, 1999; Ungerleider et al., 1998) have shown the important role of the prefrontal cortex in working memory. Thus, it is not surprising to find that most previous

studies on the neural correlates of working memory in schizophrenia have been heavily focused on the prefrontal cortex. Past studies have showed that compared to healthy individuals, schizophrenia patients show abnormal activation in the prefrontal cortex during working memory tasks. However, they do not agree on the exact pattern of abnormal activation in the prefrontal cortex in schizophrenia patients (for a review, see Manoach, 2003). The majority of studies found task-related hypofrontality in schizophrenia patients during working memory tasks (e.g., Barch, Carter, Braver, Sabb, MacDonald, Noll, & Cohen, 2001; Callicott, Ramsey, Tallent, Bertolino, Knable, Coppola, Goldberg, van Gelderen, Mattay, Frank, Moonen, & Weinberger, 1998; Carter, Perlstein, Ganguli, Brar, Mintun, & Cohen, 1998; Weinberger & Berman, 1996; Wexler, Anderson, Fulbright, & Gore, 2000). However, studies showing evidence of increased activation in the prefrontal cortex ('hyperfrontality') in schizophrenia patients make it difficult to draw a clear conclusion (Callicott, Bertolino, Mattay, Langheim, Duyn, Coppola, Goldberg, & Weinberger, 2000; Manoach, Gollub, Benson, Searl, Goff, Halpern, Saper, & Rauch, 2000; Manoach, Press, Thangaraj, Searl, Goff, Halpern, Saper, & Warach, 1999; Perlstein et al., 2001).

There are several possibilities that may explain these discrepancies. Schizophrenia patients show working memory deficits in many of these studies (i.e., they have higher error rates). Therefore, unmatched performance may contribute to the discrepancy. The block-design used in most studies has made it difficult to take this behavioral discrepancy into account. Some studies (e.g., Callicott et al., 2000) tried to control for the performance difference by correlating the performance with the hemodynamic functions in the relevant area of the brain, but this still does not give us a clear picture of the brain

activation pattern in schizophrenia patients when they are able to perform accurately vs. when they fail. The magnitude of activation sustained in the prefrontal cortex during working memory task was significantly greater in correct trials compared with that in error trials in healthy individuals (Sakai et al., 2002). Thus, schizophrenia patients might show reduced activation in the prefrontal cortex because they produce more error responses, and not because they do not recruit the prefrontal cortex when they were able to perform the task successfully. Indeed, schizophrenia patients actually do show normalized task-related activation in the prefrontal cortex after behavioral improvement in a verbal working memory task (Wexler et al., 2000). These studies suggest that poorer working memory performance of schizophrenia patients may explain the hypofrontality reported in previous studies. Therefore, it is important for future neuroimaging studies to control for the behavioral discrepancy between schizophrenia patients and healthy controls in order to examine the neural correlates of working memory in patients with schizophrenia.

The relatively good temporal and spatial resolutions of fMRI make it an ideal tool in investigating cognitive functions in humans. However, fMRI is not ideal for psychiatric patients. There are several practical problems that make it difficult for psychiatric patients to participate in fMRI studies. Many patients are paranoid and delusional and, hence, do not wish to participate in neuroimaging studies. Therefore, fMRI studies may exclude an important subpopulation of schizophrenia patients. Another practical problem is the weight limit of the scanner. Many schizophrenia patients exceed the safety weight limit of the scanner partly because one of the more common side effects of antipsychotic medication is serious weight gain (Allison, Fontaine, Heo, Mentore,

Cappelleri, Chandler, Weiden, & Cheskin, 1999a; Allison, Mentore, Heo, Chandler, Cappelleri, Infante, & Weiden, 1999b). Weight gain is more prevalent in patients treated with atypical antipsychotics than typical antipsychotics (Allison et al., 1999b; Weiden, Mackell, & McDonnell, 2004), and at present most schizophrenia patients are treated with atypical antipsychotic drugs in America. In addition, schizophrenia patients tend to be more anxious than healthy controls, especially when they are exposed to a new technique. High anxiety in schizophrenia patients, furthermore, can cause them to move when they are in the scanner, which can result in motion artifacts and poor quality of data. These practical problems call for an alternative functional brain imaging method.

Near Infrared Spectroscopy (NIRS) is a relatively new, non-invasive method that allows us to investigate functional brain activation patterns. Since light has been found to be sensitive to the hemoglobin concentration and oxygenation in the blood (Milliken, 1942), imaging of reflected light has been widely used in studies of animals to examine the functional architecture of the cortex. NIRS uses light from the near infrared spectrum (700-1000 nm wavelength) to monitor the changes in oxyhemoglobin and deoxyhemoglobin in the brain tissue. Light from the near infrared spectrum can penetrate the skull and is absorbed mainly by oxyhemoglobin and deoxyhemoglobin which have different absorption spectra. Changes in the oxyhemoglobin and deoxyhemoglobin in the brain tissue can be calculated from the amount of absorbed near infrared light using the modified Lambert-Beer Law (Obrig, Wenzel, Kohl, Horst, Wobst, Steinbrink, Thomas, & Villringer, 2000). Non-invasiveness of NIRS and its sensitivity to cerebral oxygen change caused by cortical activation make it a useful tool in investigating the neural mechanisms of cognitive processes in infants (e.g., Brown, Hadway, & Lee, 2003;

Nicklin, Hassan, Wickramasinghe, & Spencer, 2003; Wilcox, Bortfeld, Woods, Wruck, & Boas, 2005). Several strengths that made NIRS ideal in infant neuroimaging studies also apply to the studies of psychiatric population; it has good temporal resolution (0.1 seconds) and acceptable spatial resolution (20-30 mm); furthermore, it tolerates head movement, and allows experiments to have more 'normal' setting (e.g., sitting in front of a computer in a normal chair) where patients may experience less anxiety than in the scanner. In addition, its quiet operation removes auditory confounds inherent in studies with fMRI. It also separates out the oxyhemoglobin and deoxyhemoglobin contributions to the hemodynamic function, which helps us to better understand the relationship between the hemodynamic function in the brain and the behavior. However, there are some disadvantages as well. One important limitation of the NIRS is that the properties of infrared absorption spectra did not allow researches to detect hemodynamic changes deeper than 2 cm below the surface of the cortex (e.g., Strangman, Boas, & Sutton, 2002a). For example, localizing activation of the thalamus is not feasible, but the superficial cortex including the dorsolateral prefrontal cortex and the superior parietal cortex can be studied with NIRS. In summary, NIRS may be a useful brain imaging technique to study the neural correlates of working memory deficit in schizophrenia. Therefore, it is necessary to examine the validity of NIRS results by comparing the activation pattern of NIRS data to results from fMRI.

Summary

Past studies of working memory in schizophrenia suggest that encoding, maintenance as well as retrieval may be impaired in schizophrenia patients and that these

deficits are associated with abnormal prefrontal function. However, it is unclear why these deficits occur. For example, the role of context in working memory has not been carefully studied and we do yet understand the nature of abnormal prefrontal activation pattern in schizophrenia patients. The major goal of this dissertation is to answer the following questions: What is the role of context in working memory? How should "context" be defined so that we can begin to examine specific contextual effects on working memory? What are the neural correlates of maintaining the mental representation as compared to forgetting in working memory in healthy individuals and schizophrenia patients? These questions were investigated in studies using both behavioral and neuroimaging methods.

CHAPTER III

CONTEXT-DEPENDENT WORKING MEMORY IN SCHIZOPHRENIA: CONTEXT EMBEDDED WITHIN THE TARGET

Introduction

Previous studies on the causal factors of working memory deficits in schizophrenia have mainly focused on the temporal dynamics of target processing in working memory. Although context can greatly affect the way a target is processed (e.g., Chun, 2000; Postle, 2003), the relationship between context and working memory has not received much consideration in schizophrenia research. In CHAPTER II, I proposed a more constrained definition of context to investigate the effect of context on working memory deficit in schizophrenia. Specifically, I pointed out the importance of *task-irrelevant information presented concurrently with the target*. CHAPTER III will focus on the effect of context on working memory in schizophrenia patients when context is embedded within the target. Here, contextual information is provided within the target, but it is not task-relevant in that it does not provide any information that is critical to the task. For example, in a visual search task where one must detect a letter 'L' among other letters, the color of the 'L' is a task-irrelevant feature and not critical to the visual search task; yet, is the information embedded within the target and may affect target processing. That is, the color of the stimulus renders contextual information that may in turn influence the task performance. CHAPTER III investigates how contextual information embedded within the target affects target processing in working memory. In Experiment 1 and Experiment 2, the continuous performance task (CPT) and a spatial delayed-

response task were used to assess working memory, respectively, and contextual information was provided by changing the task-irrelevant features of the target (e.g., color).

Experiment 1: The effect of contextual modulation on the continuous performance task (CPT)

Schizophrenia patients show impaired performance on the continuous performance task (CPT). Among the several versions of CPT, CPT-AX is thought to be sensitive to working memory (Chen & Faraone, 2000; Elvevag, Weinberger, Suter, & Goldberg, 2000). In CPT-AX, individuals are asked to respond to letter 'X' only when it follows the letter 'A'. Thus, in CPT-AX, individuals must maintain the mental representation of the cue ('A') in working memory while attending continuously to the letters that are presented in sequence. In Experiment 1, CPT-AX was used to examine the effect of context embedded within the target on working memory performance of schizophrenia patients. Context information was manipulated by changing the color of the cue (i.e., red A instead of black A). In CPT-AX, the identity of the cue is critical but the color of this letter is task-irrelevant. Although the color is irrelevant to the CPT-AX, changing the color of the cue on some trials can make these trials more "salient" than others. If such contextual information affects performance of schizophrenia patients in CPT-AX, their accuracy and response time on the trials where the cue was red (i.e., salient) would be different from these on the trials where the cue was black (i.e., regular).

Methods

Participants: Sixteen outpatients (5 women and 11 men), who met the criteria for schizophrenia or schizoaffective disorder of the Diagnostic and Statistical Manual of Mental Disorder – 4th edition (DSM-IV) (American Psychiatric Association, 1991), were recruited from the Outpatient Clinic of Vanderbilt Psychiatric Hospital, Nashville, TN. Fourteen healthy controls (7 women and 7 men) were recruited through advertisements from the local community. The exclusion criteria for all participants were (1) current substance use (2) brain injury, (3) neurological disorder and (4) mental retardation. In addition, control participants were excluded if they had (1) past or present DSM-IV Axis I or Axis II disorder or (2) a family history of psychotic illness. The Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) were used to evaluate symptom severity in the patients. Mean BPRS total score was 27.0 (±16.7). Means SANS score was 30.2 (±20.7), and mean SAPS score was 29.8 (±25.4). All patients were taking atypical antipsychotic drugs (clozapine, risperidone or olanzapine) at the time of testing. Mean illness duration of the patients was 12.8 (±8.2) years.

SZ group and CO group were comparable in age (38.5 years, SD = 9.9 and mean=34.5 years, SD= 9.8, respectively, t_{28}= 1.1, NS) and education (12.6 years, SD = 1.9 and mean=14.6 years, SD= 1.8, respectively, t_{28}= -2.9, NS). There were three left-handed and one ambidextrous patients in SZ group. All other participants were right-handed. There was no significant group difference in the proportion of women (χ^2 = 1.55, NS) or of right-handedness (χ^2 = 1.91, NS). All participants were provided a complete

description of the procedure and they gave written informed consent. The Institutional Review Board of the Vanderbilt University, Nashville TN, approved the study protocol and consent procedure. All participants were compensated for study participation.

Apparatus and Procedure: The experiment was conducted on a Macintosh iMac computer with a 15-inch screen. The experiment was programmed with MacStim software (White Ant Publishing, Melbourne, Australia). Participants were tested individually in a quiet room with normal interior lighting. The unrestricted viewing distance to the screen was 50 cm.

At the beginning of each task, participants fixated at the center of the screen. When they were ready to begin, they pressed the spacebar to initiate the trial. Then a letter (1.1°) was presented at the center of the screen for 250 milliseconds (ms) with an interstimulus interval (ISI) of either 1000 ms or 3000 ms before the next letter appeared. For CPT-AX, participants were asked to press the key if the target (letter X) was followed by the cue (letter A) regardless of the color of a cue (red or black). For CPT-Single, participants were asked to press the key whenever they saw the target letter (X) regardless of its color. It is important to note that participants were told that the color of the letters is not important in performing the task.

Continuous Performance Task (CPT): Three versions of the CPT were administered and the order of three tasks was counterbalanced across participants. Three tasks were CPT-AX with short ISI, CPT-AX with long ISI and CPT-Single. To test the effect of target salience on CPT performance, 20% of trials in each task presented salient stimuli; in CPT-AX red cue (red A) was used in 20% of cue-target sequence trials and red target (red X) appeared 20% of target trials of CPT-Single. The standard procedure for

CPT-AX was modified in 2 ways. First, the frequency of the cue-target sequences (A-X) was increased so that these occurred 70% of the total trials. A randomly chosen non-cue letter preceded the target (e.g., B-X) in 10% of trials, the cue was followed by a distracter (e.g., A-Y) in another 10% of trials, and a randomly chosen non-cue letter preceded a distracter (e.g., B-Y) in the remaining 10% of trials. Increasing the frequency of the cue-target sequences introduced a strong bias or tendency to respond after the presentation of the cue and to engage participants more actively in the task. The second modification involved varying the ISI (i.e., delay) to test participants' ability to maintain cue information over time in working memory. Two ISIs were used: 1000 ms and 3000 ms. Each participants was tested in 2 blocks of CPT-AX task, one with the short ISI (delay=1000 ms) and the other with the long ISI (delay=3000 ms). In each condition, the proportion of the target and non-target events remained the same (A-X, 70%; B-X, 10%; A-Y, 10%; B-Y, 10%). CPT-AX with ISI of 3000ms had 100 trials. CPT-AX with ISI of 1000 ms had 200 trials. CPT-AX with 3000ms ISI had fewer trials than CPT-AX with 1000ms ISI so that the total task time could be equal per condition.

In CPT-Single, single letters were presented centrally on screen for 250 ms each with an ISI of 1000 ms and participants were asked to identify the target (letter X) regardless of its color. There were 273 trials in CPT-Single.

Results

Overall hit rate, overall false alarm rate, and reaction time (RT) are presented in Table 1 and % error for specific error types is presented in Table 2. Repeated-measures ANOVA was used to examine whether the SZ group showed different performance in the

Table 1. Performance of SZ and CO groups in CPT

	SZ	CO
CPT-AX with ISI 3000 ms		
Hit rate	.89 (.10)	.96 (.03)
False alarm rate	.07 (.11)	.02 (.04)
RT (ms)	661 (211)	461 (85)
CPT-AX with ISI 1000 ms		
Hit rate	.91 (.08)	.98 (.02)
False alarm rate	.09 (.11)	.03 (.04)
RT (ms)	479 (85)	400 (83)
CPT-Single		
Hit rate	.95 (.06)	.99 (.01)
False alarm rate	.12 (.08)	.05 (.06)
RT (ms)	419 (78)	407 (84)

† Values are given as mean (SD).

overall hit rate, overall false alarm, and RT of CPT-AX compared with the CO group. For overall hit rate, there was a main effect of the diagnostic group in CPT-AX; SZ patients were less accurate in detecting the AX sequence than controls ($F(1,28)=8.84$, $p<.01$). There was no other significant effect. For RT on the CPT-AX, SZ patients were slower than the CO participants ($F(1,28)=12.30$, $p<.01$). There was also a main effect of the delay; both groups showed longer RT with the longer ISI condition ($F(1,28)=20.68$, $p<.001$). A significant delay-by-group interaction ($F(1,28)=5.08$, $p<.05$) indicated that increasing the delay between the cue and the target had a larger effect on SZ patients than in CO.

Table 2. % error in non-target trials in CPT-AX

		SZ	CO
CPT-AX with ISI 3000 ms	A-Y	1 (3)	2 (6)
	B-X	15 (26)	4 (7)
	B-Y	3 (5)	0 (0)
CPT-AX with ISI 1000 ms	A-Y	7 (8)	4 (6)
	B-X	17 (26)	3 (6)
	B-Y	4 (8)	0 (0)

† Values are given as mean (SD).

No significant main effect was found in the overall false alarm rate. However, when we separated each type of errors, SZ group made more BY errors than did CO group in CPT-AX with ISI 3000 ms (t_{28}=-2.4, p<.05; see Table 2). In CPT-Single, group difference was significant only in the false alarm rate (t_{21}=2.25, p<.05), showing that SZ group made more false alarm responses than did the CO group (see Table 1).

The effects of the stimulus salience were examined by comparing the trials with the salient stimuli (i.e., infrequent red letters) with those trials with regular stimuli (i.e. black letters) using repeated measures ANOVA (see Figure 1).

For CPT-AX with ISI 3000 ms, SZ patients were less accurate than the CO (F (1,28)=5.01, p<. 05) in detecting the AX sequence, regardless of cue saliency (i.e., the color of the cue). The main effect of the cue saliency (F (1,28)=12.28, p<. 001) showed that salient cues (i.e., red cues) improved the performance of both groups (Figure 1A). The group-by-cue saliency interaction was not significant. SZ patients showed slower RT than did the CO (F (1,28)=10.89, p<. 01) but there was no main effect of cue saliency and no group-by-cue saliency interaction on the RT.

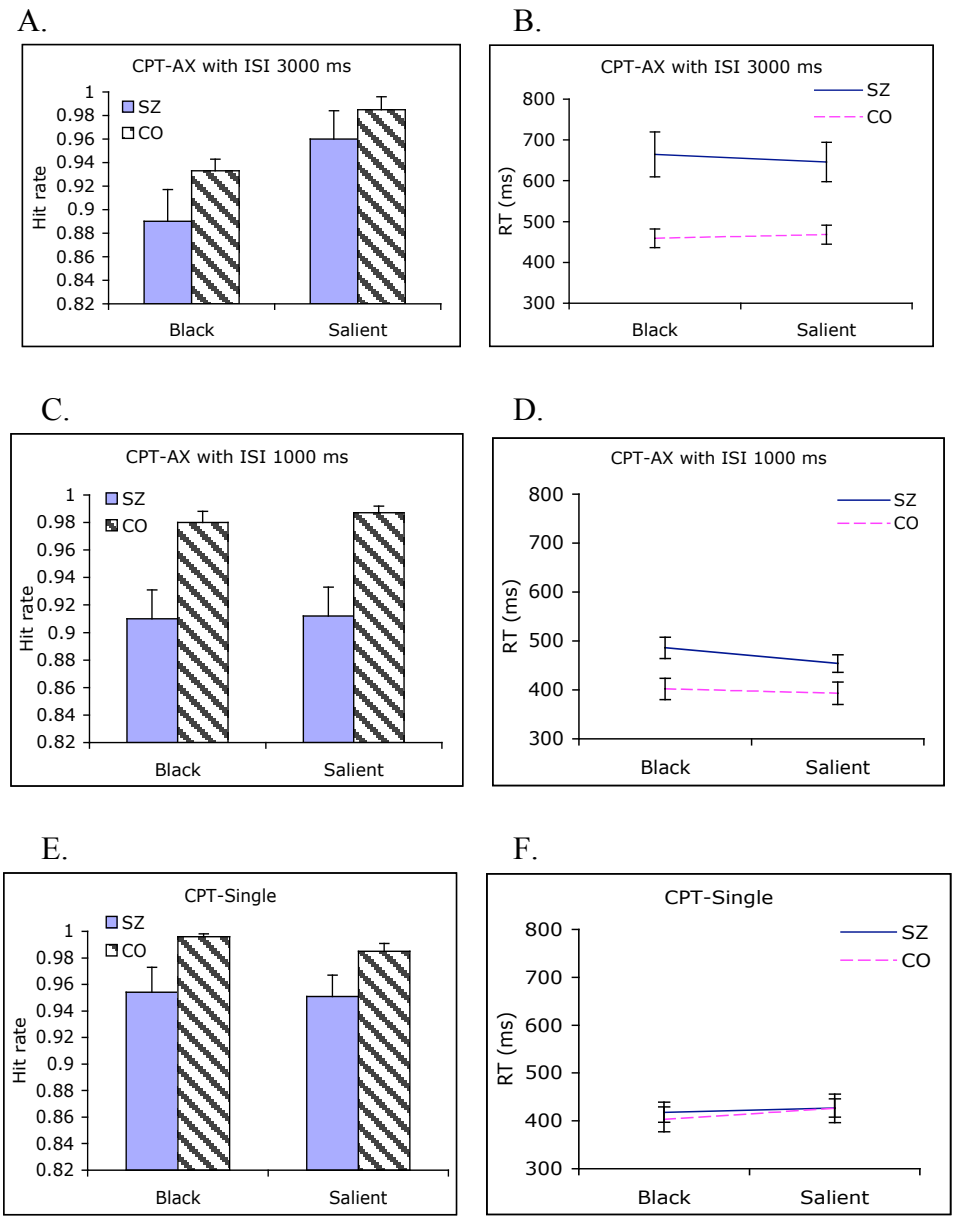

Figure 1. Performance of CO group and SZ group in CPT. A. accuracy in CPT-AX with ISI 3000ms; B. RT in CPT-AX with ISI 3000 ms; C. accuracy in CPT-AX with ISI 1000ms; D. RT in CPT-AX with ISI 1000 ms; E. accuracy in CPT-Singe; F. RT in CPT-Single. Error bars represent the standard error of the mean.

For CPT-AX with ISI 1000 ms, SZ group was less accurate than CO group ($F(1,28)=10.98$, $p<.01$), but there was no main effect of cue saliency and no group-by-cue saliency interaction (Figure 1C). There was a main effect of the diagnostic group on the RT ($F(1,28)=5.95$, $p<.05$) and a main effect of cue saliency on RT ($F(1,29)=16.58$, $p<.$

001). SZ group were slower than CO group in detecting targets and both groups were faster at detecting the target in salient cue trials. There was also a group-by-cue saliency interaction on RT ($F(1,28)=5.32$, $p<.05$) such that the saliency effect was larger for the SZ group (Figure 1D).

In CPT-Single, there was neither group difference nor cue saliency effect on accuracy. Unexpectedly, both groups were slower when the salient stimulus (i.e., red X) was presented ($F(1,21)=7.57$, $p<.05$).

Discussion

Experiment 1 investigated the effects of contextual modulation on CPT-AX performance by manipulating the cue salience. In CPT-AX, schizophrenia patients showed an improvement in target detection when the salient cue was presented (i.e., the red cue). Although the effect of cue saliency was found in both ISI conditions of CPT-AX, its effect was manifested differently. In the longer delay condition, the effect of contextual modulation was observed in the increased accuracy of both groups. This effect was not a result of a speed-accuracy trade-off. Contextual modulation also affected both groups in a similar way. In the CPT-AX with short delay, the effect of context was observed in faster RTs while the accuracy remained unchanged. The effect of contextual modulation on RT was larger in schizophrenia patients than controls, and as a result group difference got smaller when contextual information was provided. The findings of CPT-AX shows that contextual information embedded within the target influenced target processing in working memory for both SZ and CO participants. They also suggest that

the effect of contextual modulation of working memory may depend on the duration of the delay period.

The contextual information did not have the same effect in CPT-single, which is thought to tap mostly sustained attention rather than working memory (Chen & Faraone, 2000; Oades, 2000). Salient targets in CPT-Single did not affect accuracy, but surprisingly they slowed down performance of both groups. It is unclear why increased RT for salient targets was observed. Although this result is completely unexpected, similar finding has been reported. Goodin, Aminoff, Chequer and Ortiz (1996) showed that reaction time for rarely presented stimuli was slower than for frequent stimuli in the choice reaction time task. It is possible that the novelty of the salient target may momentarily inhibit the behavioral response while participants decide on the correct identity of the target. Further studies are necessary to examine the underlying mechanism of slow RT for salient stimuli.

One of the main findings of this experiment was that contextual modulation aided performance in CPT-AX but not in CPT-Single. In CPT-Single, both groups had over 95% of accuracy when they were given non-salient stimuli so there is a ceiling effect on accuracy. It might have been difficult to observe improvement in performance. It is also important to note that CPT-Single does not tap into the same cognitive function as CPT-AX. CPT-AX requires greater goal-directed attention and working memory than CPT-Single. One must maintain the preceding cue during the delay in CPT-AX, and actively use this cue to direct attention to the target. In contrast, CPT-Single does not require working memory and consequently, contextual information that may aid working memory would play a reduced or negligent role in CPT-Single.

To summarize, contextual modulation improved the performance of schizophrenia patients in CPT-AX. Importantly, schizophrenia patients were sensitive to context information embedded within the target (e.g., the color of the stimulus when the color is not a task-relevant feature) just as normal controls were. In addition, the effect of contextual modulation in schizophrenia was observed differently as a function of working memory delay. Contextual information did not affect performance of schizophrenia patients in CPT-Single that mostly taps sustained attention. These findings suggest that it is necessary to specify and elaborate the definition of "context" for a better understanding of context processing in schizophrenia and how it may be related to working memory deficits.

Experiment 2: The effect of contextual modulation on a spatial delayed response task

Experiment 2 further examined the effects of context in other tasks that tap working memory to see if the results observed in Experiment 1 can be generalized across other paradigms. A spatial delayed response task (DRT) was employed to test the effect of context embedded within the target. Similar to Experiment 1, context information was manipulated by changing the task-irrelevant feature of the target. The location of the target is critical on the spatial DRT. Other features (e.g., the identity or the color of the target) are task-irrelevant but may provide contextual information. The strategy in this experiment was to change the identity or the color of the target to observe the effects of context on spatial working memory.

Methods

Participants: Eighteen outpatients with schizophrenia (6 women), who met the criteria for schizophrenia or schizoaffective disorder of DSM-IV (American Psychiatric Association, 1991), were recruited from the Outpatient Clinic of Vanderbilt Psychiatric Hospital, Nashville, TN. Fifteen healthy controls (8 women) were recruited through advertisements from local community. The exclusion criteria for all subjects were (1) current substance use, (2) brain injury, (3) any neurological disorder and (4) mental retardation. In addition, control subjects were excluded if they had (1) past or present DSM-IV Axis I or Axis II disorder, or (2) a family history of psychotic illness. The Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) were used to evaluate symptom severity in the patients. Mean BPRS total score was 28.0 (±15.5). Means SANS score was 33.6 (±24.1), and mean SAPS score was 31.0 (±23.4). All patients were taking atypical antipsychotic drugs (clozapine, risperidone or olanzapine). Mean illness duration of the patients was 13.8 (±7.8) years.

Schizophrenia patients (SZ) group and healthy control (CO) groups were comparable in age (38.2±9.4 and 32.4±9.7, respectively; t_{32}=1.71, NS), but not for education (12.6±1.9 and 14.0±2.1, respectively; t_{32}=-2.03, p=.05). There were three left-handed and one ambidextrous patients in SZ group. All other participants were right-handed. There was no significant group difference in the proportion of right-handedness (χ^2 = 3.5, NS) or of women (χ^2 = 1.3, NS). All participants were provided a complete description of the procedure and they gave written informed consent. The Institutional

Review Board of the Vanderbilt University, Nashville, TN approved the study protocol and consent procedure. All participants were compensated for study participation.

Apparatus: The experiment was conducted on a Macintosh iMac computer with a 15-inch screen. The experiment was programmed with MacStim software (White Ant Publishing, Melbourne, Australia). Participants were tested individually in a quiet room with normal interior lighting. The unrestricted viewing distance to the screen was 50 cm.

Spatial working memory task: To test the hypothesis that contextual information may affect working memory performance of schizophrenia patients, two modified spatial DRTs were used: Color spatial DRT and Novel spatial DRT. Contextual information in each DRT was manipulated by varying the task-irrelevant feature of the target: the identity of the target in the Novel spatial DRT and the color of the target in the Color spatial DRT. In the Novel spatial DRT, 80% of the targets were regular black dots and 20% were novel stimuli (Korean characters) that could not be labeled or verbalized by non-Korean speakers[1]. In the Color spatial DRT, 80% of the targets were regular black dots and 20% were colored dots (red). In each task, participants were instructed to remember the location but to ignore the identity/color of the target.

There were total 50 trials in the working memory condition in the Novel spatial DRT and the Color spatial DRT and contextual information was manipulated in 10 trials (20% of total number of trials). There were 30 trials in the control condition in each task and the contextual information was changed in 6 trials (20% of total number of trials). The control condition was introduced to make sure that participants could perform these

[1] It must be noted that none of participants in Experiment 2 spoke Korean or recognize novel stimuli of the Novel DRT as Korean characters.

tasks without any working memory load. Error distance (pixels), and response time (RT; ms) were measured.

Procedure: The sequence of events in a single trial of the spatial DRT was as follows: (a) an appearance of a cross at the center of the screen marked the beginning of each trial. Participants were told to press the space bar if they were ready to start a trial. (b) After participants pressed the space bar, the target (1.4°; black dot or Korean character in the Novel spatial DRT, and black dot or color dot in the Color spatial DRT) was presented for 250ms. The potential locations of target included 12 equally spaced positions on a small imaginary concentric circle (12.6° in diameter) and 20 equally spaced positions on a large imaginary concentric circle (20° in diameter). Thus, there were 32 equally likely positions of the presentation of the target stimulus. (c) After the target disappeared, there was a delay period of 7000ms. During this period, participants performed an intervening task (the Size Discrimination task), which does not interfere with the main working memory task but prevents idiosyncratic rehearsal. In the Size Discrimination task, a series of squares appeared at the center of the screen at the rate of one per second. These squares changed size sometimes. Participants were required to count how many times the square changed size during the delay. (d) After the delay period, 32 blank circles were presented at the potential target locations and participants were required to remember the location of the target that they had seen and used the mouse to indicate the target location. Then, they were asked to answer how many times the square changed size. The sequence of events in a single trial in the control condition was the same, except that the target was present during the delay period (7000 ms). After

the delay period, participants were asked to locate the target with the mouse and click once.

Results

The performance of SZ group and CO group in the Color spatial DRT and the Novel spatial DRT are presented in Table 3. A repeated measures ANOVA was conducted for error distance and RT of the DRTs separately, with the diagnostic group as the between-subjects variable and the task type (control condition vs. memory condition) and the stimulus condition (black target vs. salient target) as within-subjects variables.

Table 3. Performance data of SZ and Co groups in the spatial DRT

		Target Type	SZ	CO
Color spatial DRT				
Control	Error distance	Black	32.95 (25.99)	12.42 (6.89)
		Red	29.30 (21.18)	12.96 (11.10)
	RT (ms)	Black	2695 (1404)	1707 (485)
		Red	2729 (1766)	1565 (466)
Memory				
	Error distance	Black	53.08 (30.52)	23.14 (15.28)
		Red	52.39 (30.33)	17.73 (12.36)
	RT (ms)	Black	2709 (1137)	1657 (538)
		Red	2533 (868)	1619 (638)
Novel spatial DRT				
Control	Error distance	Black	30.25 (19.93)	12.73 (9.21)
		Korean	44.71 (38.93)	12.82 (11.62)
	RT (ms)	Black	2319 (1152)	1591 (560)
		Korean	2607 (1545)	1564 (740)
Memory				
	Error distance	Black	58.66 (32.28)	26.90 (25.80)
		Korean	52.28 (43.91)	31.15 (30.47)
	RT (ms)	Black	2503 (1076)	2009 (1692)
		Korean	2578 (953)	1938 (1358)

† Values are given as mean (SD).

For error distance of the Color spatial DRT, the main effect of the diagnostic group ($F(1,29)=14.29$, $p<.001$) and the main effect of the task type ($F(1,29)=28.23$, $p<.001$) were significant. SZ group showed worse performance than CO group and both groups showed worse performance in the memory condition compared to the control condition. A significant group-by-task type interaction ($F(1,29)=6.31$, $p<.05$) indicated that the performance difference between groups was larger in the memory condition than in the control condition. Stimulus condition did not have any effect in the Color spatial DRT. For RT, there was only a significant main effect of group ($F(1,29)=8.66$, $p<.05$). SZ group showed slower RT than CO group overall.

For error distance of the Novel spatial DRT, the main effect of group ($F(1,30)=9.44$, $p<.01$) and the main effect of task type ($F(1,30)=12.11$, $p<.001$) were significant, showing that SZ group performed worse than CO group and that both groups were less accurate in the memory condition. There was a trend towards significance for an interaction of group by task-type by stimulus condition ($F(1,30)=3.91$, $p=.057$, power=.47). A contrast analysis showed that a significant group difference was found with regular targets ($t_{30}=3.10$, $p<.01$) as well as Korean characters ($t_{30}=3.12$, $p<.01$) in the control condition. SZ group also performed worse than CO group with regular targets in the memory condition ($t_{30}=3.06$, $p<.01$). However, with the novel Korean characters in the memory condition, SZ group showed comparable performance to the CO group ($t_{31}=1.55$, NS), suggesting that the task-irrelevant, contextual feature of the target (i.e., novel Korean character) facilitated spatial working memory in the SZ group. No significant effect was found for the RT of the Novel DRT.

Discussion

Experiment 2 further examined the question of whether context embedded within the target might affect working memory performance of schizophrenia patients. In the prototypical spatial DRTs, participants are required to maintain the internal representation of the target location during the delay. Thus, the identity or the color of the target should neither hinder nor aid the spatial working memory performance. In the Color spatial DRT, task-irrelevant information (contextual information) did not affect the performance overall. Schizophrenia patients showed impaired spatial working memory performance regardless of the color of the target. However, when the identity of the target was manipulated in the Novel spatial DRT, the performance of schizophrenia patients improved on the salient trials. Novel Korean characters in the spatial DRT facilitated working memory performance of schizophrenia patients, such that they showed no spatial working memory deficits. They showed spatial working memory impairment when regular black dots were presented as targets in the same DRT.

In this study, using novel stimuli as targets facilitated spatial working memory of schizophrenia patients even though the identity of the target was irrelevant to the task. Novel targets (Korean characters) were infrequently presented and they were salient compared with the black dot stimuli. Although the target location was critical feature and participants were instructed to remember the location but not any other features of the target, schizophrenia patients remembered target locations better when they were novel shapes. Novel shapes may be effective in capturing spatial attention, thereby indirectly facilitating the encoding of the target in schizophrenia patients. In other words, attentional capture aided by the contextual information may have helped schizophrenia

patients to better encode and maintain the target location. The results of Experiment 1 showed a strong association between context processing and working memory in schizophrenia patients, supporting the hypothesis that schizophrenia patients are able to process contextual information.

One may argue that the enhancing effect of novel Korean characters on working memory originates from the infrequency or rarity of their occurrence rather than its attentional salience. However, the null effect of the red dots in the Color spatial DRT does not support this alternative hypothesis. In the Color spatial DRT, the red dot was presented in 20% of the trials (i.e., infrequently). However, the red dots failed to affect spatial working memory of schizophrenia patients. That is, even though the red dot appeared in only 20% of the trials, it did not facilitate spatial working memory of schizophrenia patients. This result suggests that the facilitation of spatial working memory in schizophrenia patients in the Novel spatial DRT probably results from the attentional salience of Korean characters (i.e., novelty) rather than from the infrequency of presentation.

Considering the important role of cognitive dysfunctions in functional outcome in schizophrenia (e.g., Green, 1996), normalized working memory performance of schizophrenia patients in the Novel spatial DRT has a very significant implication for rehabilitation. Previous studies of cognitive remediation have heavily focused on exercises and drills that require repeated practice on cognitive tasks. For example, Bell et al. (2003) reported improved working memory performance in schizophrenia patients after cognitive training of up to 5 hours a week for 26 weeks. But the effect sizes of their study were weak even after such lengthy and arduous training and only about 60% of the

patients who enrolled in this program showed any improvements. Even though cognitive exercises may be effective, it is not easy to train and drill schizophrenia patients for months using computerized exercises. The results of Experiment 2 suggest that by increasing attentional salience of the targets or the task at hand, certain key cognitive functions may be facilitated effortlessly. Such knowledge can be adapted to design more effective cognitive exercises. In addition to the facilitation of working memory observed under the laboratory conditions, the results of this study suggest that in real life it might be possible to improve adaptive functioning in schizophrenia patients by having them exposed to encountering more salient stimuli. That is, salient stimuli in the environment may help schizophrenia patients to compensate for some of their impaired cognitive functions and therefore to produce more adaptive behaviors. Further studies are needed to examine how manipulating context may facilitate cognitive rehabilitation and whether the facilitation of spatial working memory observed in Experiment 2 may also be observed in the natural environment outside the laboratory.

In summary, Experiment 2 showed that the facilitation of working memory by contextual information embedded within the target generalizes to different paradigms. Schizophrenia patients showed normalized performance in the spatial DRT when the target was novel. These results show that schizophrenia patients are sensitive to contextual information in contrast to the results reported by Cohen and his colleagues (1999) and provide novel approach for cognitive rehabilitation techniques for schizophrenia patients.

General discussion

In CHAPTER III, the role of contextual information embedded within the target in working memory in schizophrenia was investigated with two different experiments. The contextual information was manipulated by changing one of the features of the target that was not critical to the task at hand. Though the effect of context on working memory in schizophrenia patients varied depending on the task condition, contextual information overall facilitated working memory performance of schizophrenia patients. Results of this study showed that context affected working memory performance of schizophrenia patients, suggesting that schizophrenia patients may have intact ability to process context.

Contextual information manipulated in two experiments of CHAPTER III is task-irrelevant (i.e., not critical to the current task). For Experiment 1, the color of the stimulus was the task-irrelevant feature because in the CPT-AX, it is the identity of the letters that is crucial to the successful performance. For the spatial DRT in Experiment 2, the target location was the critical, task-relevant information whereas the other features of the target, such as its identity or color, were irrelevant to the task. Even though the contextual information was irrelevant to the task, it facilitated processing of task-relevant, critical feature of a target of both experiments in schizophrenia patients and to some extent, some improvements were observed in normal controls as well. What the contextual information embedded within the target seem to do is to increase the attentional salience of the target. As result, stimulus-driven attentional salience of the target may have helped in encoding and maintenance of the target in schizophrenia patients.

The results reported in CHAPTER III support the hypothesis of encoding difficulties as a causal factor of working memory deficits of schizophrenia patients.

Previous studies showed that impaired perception or slow information processing may result in inefficient encoding (Hartman et al., 2003; Tek et al., 2002). The results reported in this chapter further suggest that impaired attentional orienting to the target may partly be responsible for defective encoding and that by increasing attentional salience of the target, this problem may be partially remediated in schizophrenia patients. In addition to improved encoding, contextual information may be useful in improving abnormal consolidation processing during encoding in schizophrenia patients (Fuller, Luck, McMahon, & Gold, 2005).

It has been shown that in healthy individuals the nature of representation in working memory may be object-based rather than feature-based (Vogel, Woodman, & Luck, 2001; but see Wheeler & Treisman, 2002). When one feature of an object is processed in working memory, other features of the same object are likely to be processed. The results reported in this chapter suggest that object-based representation in working memory is likely to be intact in schizophrenia patients and their working memory deficits are probably due to other problems such as attentional orienting to the target during encoding and maintaining attention to the target during maintenance. Recent study supports this view. Gold et al. (2003) showed that schizophrenia patients have normal feature binding in working memory even though their working memory capacity is smaller than that of normal controls. The results reported in CHAPTER III further support the view that schizophrenia patients have intact object-based representation in working memory.

The facilitatory effect of context on working memory in schizophrenia patients suggests an important and novel implication of the relationship between stimulus-driven

attention and goal-driven attention systems in schizophrenia. In healthy individuals, "bottom-up" factors that are related to stimulus-driven attention system, can bias encoding of stimuli into working memory (Schmidt, Vogel, Woodman, & Luck, 2002; Woodman, Vecera, & Luck, 2003). It is well-known that schizophrenia patients have difficulties with cognitive control or top-down control (e.g., Braver, Barch, & Cohen, 1999). Schizophrenia patients have difficulties guiding and controlling their attention via internal goals (or intention) and, as a result, may have difficulties in processing task-relevant information at the encoding stage. However, little is known about the stimulus-driven attentional system in schizophrenia. Results of Experiment 1 and Experiment 2 suggest that schizophrenia patients have relatively intact stimulus-driven attention system compared to their goal-driven attention system. Facilitation of working memory by contextual information in working memory may result from enhanced attentional orienting to the target. The facilitating effects of stimulus saliency in schizophrenic subjects have also been observed in visual search tasks (Carr, Dewis, & Lewin, 1998; Mori, Tanaka, Ayaka, Michitsuji, Niwa, Uemura, & Ohta, 1996). These studies suggest that intact stimulus-driven attention system can be used to compensate for impaired goal-driven attention system in schizophrenia. Schizophrenia patients may benefit from an extrinsically salient stimuli (i.e., bottom-up factors) even when they have difficulties with assigning salience to stimuli based on internal goals (Kapur, 2003). Future studies should investigate the relationship between stimulus-driven attention and goal-driven attention in schizophrenia more thoroughly.

In summary, schizophrenia patients were sensitive to contextual information embedded within the target. Contextual information facilitated working memory

performance of schizophrenia patients probably by increasing encoding efficiency. The effect of context on working memory in schizophrenia patients also suggests new strategies for rehabilitation. Finally, contextual modulation of working memory may help us better understand how the attentional system works in schizophrenia.

CHAPTER IV

CONTEXT-DEPEDENT WORKING MEMORY IN SCHIZOPHRENIA: CONTEXT SURROUNDING THE TARGET

Introduction

CHAPTER III described the role of context embedded within the target in facilitation of working memory in schizophrenia patients. In CHAPTER IV, I extended this line of inquiry further by investigating the effects of other types of context on working memory to better understand the scope and the extent of contextual effects on working memory. Specifically, I focused on the visuospatial context surrounding the target when it was irrelevant to the task.

Previous studies with healthy undergraduate students (Chun, 2000; Chun & Jiang, 1998; Jiang, Olson, & Chun, 2000) showed that visual short-term memory for individual locations was bound to the consistency of global configuration of individual locations (i.e., spatial context). Considering the fact that schizophrenia patients show consistent spatial working memory deficits, it seems logical to ask whether spatial context might affect spatial working memory in these patients. Spatial configuration of a stimulus array provides spatial context for the location of a target presented within this array. If schizophrenia patients were sensitive to spatial context, they might benefit from having spatial context information. However, if spatial context has no effect on location memory in schizophrenia patients, their performance would remain unchanged with or without spatial context.

Experiment 1: The effects of spatial context on spatial working memory: short delay

In Experiment 1, the effect of spatial context on working memory was examined using a spatial context task with a short delay. The general outline of this task is simple. Participants are presented with two spatial arrays separated by a short delay and are required to decide whether one of the stimulus locations remains the same or not. Spatial configuration in Experiment 1 was manipulated two ways: varying the memory set size and the probe condition. The memory set size varied from 3 to 8 items. There were three probe conditions: consistent configuration, inconsistent configuration and single probe condition. The global spatial configuration was preserved across the two image displays in the consistent configuration condition, providing consistent spatial context information. Spatial context was absent in the single probe condition. In the inconsistent configuration condition, a new configuration was presented at the second, probe image display, and as a result spatial context information was changed. If spatial context facilitates location memory, then participants should benefit from the consistent spatial context condition.

Methods

Participants: Seventeen outpatients with schizophrenia (SZ; female = 6, male = 11), recruited from the Outpatient Clinic of Vanderbilt Psychiatric Hospital, Nashville, TN, participated in Experiment 1. SZ patients met the criteria for schizophrenia or schizoaffective disorder of DSM-IV (American Psychiatric Association, 1991), based on clinical interviews and chart reviews. Schizophrenia patients were excluded if they had past or current alcohol and other substance abuse, brain injury, or possible neurological

disease and any other medical illness known to affect brain function. The Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) were used to evaluate symptom severity. Mean BPRS total score was 26.3 (±12.1). Means SANS score was 31.3 (±21.1), and mean SAPS score was 29.4 (±20.3). All patients underwent testing while receiving atypical antipsychotic drugs (clozapine, risperidone, or olanzapine).

Eighteen healthy controls (CO; female = 10, male = 8), recruited through advertisements in the university and local community, participated in Experiment 1. Controls were excluded if they had (1) past or present DSM-IV Axis I or Axis II disorder; (2) a family history of psychotic illness in their first- or second-degree relatives; (3) any other medical illness known to affect brain function; and (4) any possible brain damage.

SZ patients and COs were matched in age (years, 38.1 ±9.6 and 35.3 ±13.1, respectively; t_{32}=-0.71, NS), and education (years, 12.8 ±1.9 and 12.8 ±1.7, respectively; t_{32}=-.07, NS). Although there were more female participants in the CO group, there was no significant group difference in the proportion of male vs. female participants (χ^2 = 1.07, NS). Two participants in the CO group were left-handed. Three SZ patients were left-handed, one was ambidextrous but all other SZ patients were right-handed. No significant group different was found in handedness (χ^2 = 1.20, NS). All participants were provided a complete description of the proposed study and gave written informed consent before study participation. The Institutional Review Board of the Vanderbilt University, Nashville TN, approved the study protocol and consent procedure. All participants were compensated for study participation.

Apparatus: The experiment was conducted on a Macintosh iMac computer with a 15-inch screen. The experiment was programmed with the MacProbe software (Hunt, 1994). Participants were tested individually in a quiet room with normal interior lighting. The unrestricted viewing distance was about 50 cm.

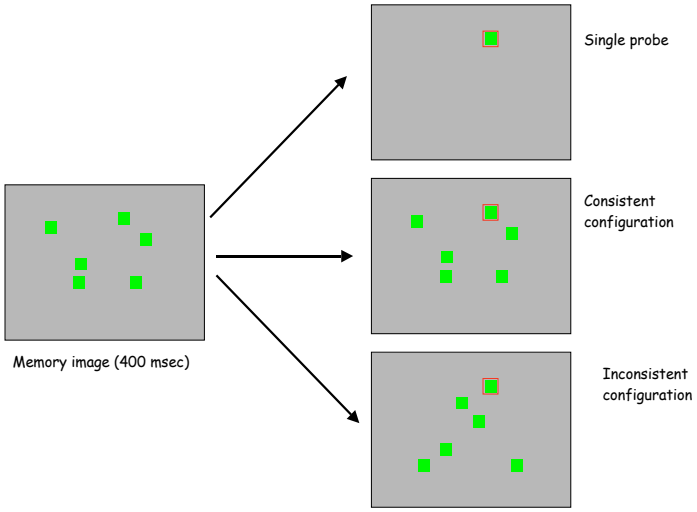

Figure 2. A schematic diagram of a spatial context task with short delay. The memory image was presented for 400 ms. After a delay of one second, the probe image was presented and one of greens squares was enclosed by a red box ('a target'). Participants were asked to decide whether a target was located in one of previously occupied locations or not.

Spatial Context Task: In the spatial context task, two images were presented (the memory image and the probe image), separated by a delay period of one second. See Figure 2 for a schematic diagram. The memory set sizes varied from 3 to 8 (set 3, 4, 6, and 8). The memory image (the first image) contained 3 to 8 green squares, depending on the memory set size; the probe image (the second image) contained either same numbers of green squares as the memory image (consistent configuration and inconsistent configuration conditions) or a single green square (single probe condition). A target in the probe image was cued by a red outlined box (1.1cm x 1.1 cm, 1.18° x 1.18°). Each

green square (1cm x 1cm, 1.1° x 1.1°) was randomly positioned in an 8 by 8 invisible matrix (14cm x 14cm, 16° x 16°). The position of each square inside a cell was slightly jittered. The session consisted of 16 practice trials and 240 experimental trials. Trials were presented in a random order.

Procedure: The procedure of each trial was as follows. At the beginning of each trial, a white cross was presented against a light gray background. When participants pressed a space bar to indicate that they were ready for the task, a memory image of an array of green squares was presented for 400 ms. After one second of delay, a probe image was presented. In the probe image, one of green squares was the target and it was marked by a red outlined box. Participants were asked to decide whether the target location coincided with one of the locations presented in the memory image. 50% of the trials contained overlapping locations. Participants were especially instructed to ignore non-target green squares in the probe image. The probe image remained until the participants responded and a sound feedback was provided immediately after a response was made to indicate whether it was correct or not. The accuracy and reaction time (RT; ms) were measured at each trial.

Statistical Analysis Reaction time (RT) and A-prime (*A´),* a nonparametric measure of sensitivity (comparable to the parametric measure *d´*), were acquired to examine the effect of spatial context on working memory. *A´* was computed based on the hit and false alarm rates for each condition. *A´* has a maximum value of 1.0 and a value of .50 represents chance performance. *A´* scores were calculated for each participant at each probe condition and the memory set size, using the formulae: $A' = .50 + (H - FA)(1 + H - FA)/4H(1 - FA)$, when hit rate (H) is ≥ false alarm rate (FA); and $A' = .50 - (FA - H)(1 +$

FA - H)/4FA(1 - H), when FA > H (Stanislaw & Todorow, 1999, equation 2). The hit rate was computed as the proportion of correct responses in trials where the target was presented in one of the old locations. The false alarm rate was computed as the proportion of incorrect responses in trials where the target was at a new location. *A´* cannot be computed when either H or F has a value of 0 or 1, so values of 0 was replaced with .50/*n*, and values of 1 were replaced with (*n* - .50)/*n*, where *n* was the number of trials contributing to the score.

Results

A´ values are presented in Figure 3 and RTs are presented in Table 4. A repeated measures ANOVA was performed to examine the effect of spatial context on working memory.

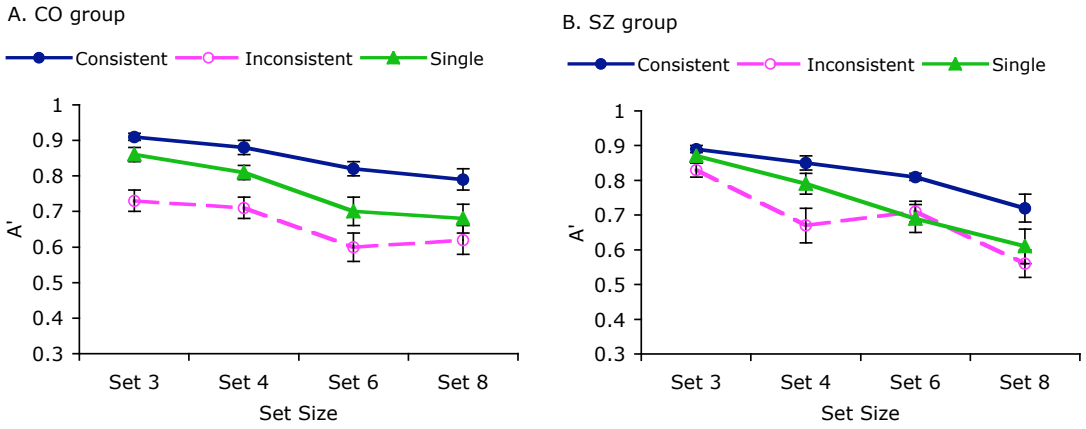

Figure 3. Performance of CO group (A) and SZ group (B) in a spatial context task with short delay. The solid line with closed circle indicates the performance of consistent configuration condition. The solid line with triangle showed the performance of single condition. Performance of inconsistent condition was shown with dotted line with open circle. Both groups showed better performance when a spatial configuration remained the same between two images and when the set size was small. No group difference was found. Error bars represent the standard error of the mean.

Table 4. RT of SZ and CO groups in a spatial context task with short delay

		SZ	CO
Set Size	Spatial Configuration		
	Consistent	1452 (305)	1331 (362)
Set 3	Inconsistent	1534 (384)	1335 (293)
	Single	1412 (370)	1227 (205)
Set 4	Consistent	1475 (319)	1314 (277)
	Inconsistent	1560 (343)	1419 (299)
	Single	1430 (284)	1272 (363)
Set 6	Consistent	1547 (266)	1346 (284)
	Inconsistent	1571 (316)	1484 (412)
	Single	1549 (575)	1315 (399)
Set 8	Consistent	1522 (372)	1361 (275)
	Inconsistent	1619 (489)	1468 (392)
	Single	1592 (469)	1299 (309)

† Values are given as mean (SD).

For *A´*, the main effect of set size and main effect of context were significant ($F(3,99)=32.85$, $p<.0001$ and $F(2,66)=36.20$, $p<.0001$, respectively). The main effect of group was not significant ($F(1,33)=.18$, NS). See Figure 3 for detailed information. A series of Scheffé test was used to examine the significant difference between the levels of set size and spatial context. For set size, significant differences were found between set 3 vs. set 4 ($p<.05$), set 4 vs. set 6 ($p<.05$) and set 6 vs. set 8 ($p<.05$). For spatial context, both groups also remembered best when the spatial configuration remained the same between two images and worst when the spatial configuration changed from the memory image to the probe image (consistent configuration vs. single probe, $p<.001$; single probe vs. inconsistent configuration, $p<.001$). There were no other significant effects. For RT,

the main effect of set size and the main effect of context were significant ($F(3,99)=8.43$, $p<.0001$, and $F(2,66)=15.74$, $p<.0001$, respectively). Both groups showed longer reaction time as the set size increased (set 3 vs. set 4, $p=.59$; set 3 vs. set 6, $p<.01$; set 4 vs. set 6, $p=.10$; set 4 vs. set 8, $p<.05$; set 6 vs. set 8, $p=.98$). They also responded slower in inconsistent condition (inconsistent configuration vs. single probe, $p<.001$; inconsistent configuration vs. consistent configuration, $p<.001$), but there was no difference between consistent configuration and the single probe condition ($p=.29$).

Discussion

In Experiment 1, both groups showed better performance when the spatial configuration surrounding the target remained the same between the two images and when the set size was smaller. It is important to note that the effect of spatial configuration and set size affected performance of both groups similarly. In other words, there was no main effect of the diagnostic group. This is an important finding in that schizophrenia patients have been known to show deficits in spatial working memory across a wide range of task (see Lee & Park, in press, for a review). However, when spatial context was provided, they seem to show no deficit in spatial working memory. Moreover, their use of spatial context information is comparable to that of normal controls. That is, schizophrenia patients remembered target locations better when the spatial context remained the same, just as the normal controls did.

In this study, multiple green squares were presented in the memory image and individuals were asked to remember the location of each square but not to pay attention to the global configuration. At the retrieval stage of the consistent configuration

condition, they were provided with the same spatial configuration surrounding the target. In the single probe condition, there was no spatial configuration at the retrieval stage. The different spatial configuration was presented at the retrieval stage of the inconsistent configuration condition. It was found that schizophrenia patients were sensitive to the spatial configuration surrounding the target. They remembered the target location best when the spatial configuration remained the same. However, even when there was no spatial context at retrieval stage, they still performed better compared to the inconsistent condition. In other words, even when the task did not ask directly to compare the configuration pattern of individual squares, schizophrenia patients still remembered the global pattern and as a result they showed poorest performance when the configuration surrounding the target was disturbed. This suggests that schizophrenia patients may remember the target locations based on the spatial relations between items instead of remembering each independently. It has been suggested that stimulus-related contextual information is automatically and obligatory encoded and stored in working memory (Jiang, Chun, & Olson, 2004; Jiang et al., 2000; Postle, 2003). In other words, the spatial configuration in relation to the target locations can be automatically encoded and maintained in visuospatial working memory. The findings of Experiment 1 raise a possibility that schizophrenia patients may also encode and maintain contextual information automatically in working memory. Further studies are necessary to determine how 'obligatory' the encoding and maintenance of spatial context is in spatial working memory of schizophrenia patients. However, before examining further how schizophrenia patients encode and maintain spatial context in working memory, we need to understand how strongly the representation of spatial context is maintained in working

memory of schizophrenia patients. For example, the representation may get weaken as schizophrenia patients have to hold it longer than 1 second. To examine whether the effect of spatial context endures across longer delay periods, Experiment 2 investigated the effect of spatial context in working memory with long delay using the same paradigm.

Experiment 2: The effects of spatial context on spatial working memory: Long delay

Experiment 2 tested whether the effect of spatial context found in Experiment 1 may be sustained for longer periods. The task was modified in the following way. Two spatial configuration conditions (consistent and inconsistent configuration conditions) and three memory set sizes (set size 4, 6, and 8) were employed with a delay of 7 seconds between the memory and probe images.

Methods

Participants: Seventeen patients with schizophrenia (SZ; female = 5, male = 12), recruited from the Outpatient Clinic of Vanderbilt Psychiatric Hospital, Nashville, TN, participated in Experiment 2. SZ patients met the criteria for schizophrenia or schizoaffective disorder of the DSM-IV (American Psychiatric Association, 1991), based on clinical interviews and chart reviews. Schizophrenia patients were excluded if they had past or current alcohol and other substance abuse, brain injury, or possible neurological disease and any medical illness known to affect brain function. The Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), and the Scale for the

Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) were used to evaluate symptom severity. Mean BPRS score was 30.1(±15.1). Mean SAPS score was 31.1(±20.4) and mean SANS score was 32.9(±15.6). All patients underwent testing while receiving atypical antipsychotic drugs (clozapine, risperidone, or olanzapine).

Sixteen healthy controls (CO; female = 10, male = 6), recruited through advertisements from the university and local community, participated in Experiment 2. Controls were excluded if they had (1) past or present DSM-IV Axis I or Axis II disorder; (2) a family history of psychotic illness in their first- or second-degree relatives; (3) any other medical illness known to affect brain function; and (4) any possible brain damage.

SZ and CO groups were comparable in age (37 ±8.7 and 36 ±11.4 years, respectively; t_{31}=--0.28, NS), and education (13.1 ±1.9 and 12.9 ±1.6 years, respectively; t_{31}=-0.18, NS). Although there were more female participants in CO group, there was no significant group difference in the proportion of female vs. male participants (χ^2 = 3.64, NS). One participant in CO group was left-handed. Two SZ patients were left-handed, one was ambidextrous but all other patients were right-handed. There was no group difference for handedness (χ^2 = 0.97, NS). All participants were provided a complete description of the proposed study and gave written informed consent before study participation. The Institutional Review Board of the Vanderbilt University, Nashville TN, approved the study protocol and consent procedure. All participants were compensated for study participation.

Apparatus and Procedure and Statistical Analysis: Apparatus and procedures were similar to those in Experiment 1, unless otherwise noted. Similar to Experiment 1, Reaction time (RT; ms) and *A′* were analyzed.

Spatial Context Task: Two images were presented, separated by a delay of 7 seconds. The memory set sizes varied from 4 to 8 items (set 4, 6, and 8). The memory image (the first image) contained 4 to 8 green squares, depending on the memory set size; the probe image (the second image) contained the same numbers of green squares as the memory image (consistent and inconsistent configuration condition). A target in the probe image was cued by a red outlined box. The whole session consisted of 16 practice trials and 120 experimental trials. Trials were presented in a random order.

Result

A′ values are presented in Figure 4 and RTs are presented in Table 5. A repeated measures ANOVA was performed to test the effect of spatial context on working memory.

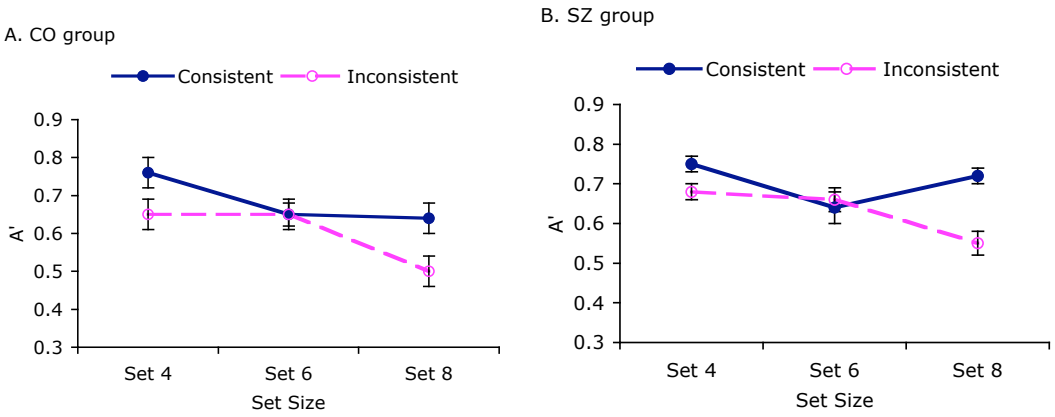

Figure 4. Performance of CO group (A) and SZ group (B) in a spatial context task with long delay. The solid line with closed circle indicates the performance of consistent configuration condition. Dotted line with open circle shows the performance of inconsistent configuration condition. Both groups showed better performance when a spatial configuration remained the same between two images and when the set size was small. No group difference was found. Error bars represent the standard error of the mean.

Repeated measures ANOVA for *A´* found a significant main effect of set size ($F(2,62)=10.60$, $p<.0001$), a significant main effect of context ($F(1,31)=13.7$, $p<.000$). The main effect of group was not significant ($F(1,31)=.61$, NS). In addition, there was a significant interaction between set size and context ($F(2,62)=5.80$, $p<.01$). Both groups performed better with smaller set size and with consistent spatial configuration. The effect of spatial context was not strongly present at set size 6 ($t_{32}=.38$, NS) compared to set size 4 and 8 ($t_{32}=-2.60$, $p<.05$, and $t_{32}=-4.41$, $p<.001$, respectively). That is, the performance of both groups in the consistent configuration condition was not different from in inconsistent configuration condition at set size of 6 (see Figure 4).

Table 5. RT of SZ and CO groups in a spatial context task with long delay

		SZ	CO
Set Size	Spatial Configuration		
Set 4	Consistent	2028 (728)	1686 (499)
	Inconsistent	1933 (565)	1694 (553)
Set 6	Consistent	2110 (793)	1839 (797)
	Inconsistent	2032 (635)	1739 (722)
Set 8	Consistent	2264 (876)	1971 (900)
	Inconsistent	2332 (1349)	1670 (665)

† Values are given as mean (SD).

For RT, the main effect of set size and the main effect of spatial configuration were significant ($F(2,62)=3.42$, $p<.05$ and $F(1,31)= 5.45$, $p<.05$, respectively). Both groups showed faster RT with a smaller set size and with inconsistent spatial configuration.

Discussion

Experiment 2 examined the effect of spatial context on working memory when the task was made more difficult by increasing the delay to 7 seconds. The results showed that both groups were better at remembering the target location, with smaller set size and consistent spatial context. No significant effect related to the diagnostic group showed that the set size and the spatial configuration affected both groups similarly. Schizophrenia patients benefited from the consistent spatial configuration information when remembering the target location even with a long delay (7 seconds) as normal controls did. That is, schizophrenia patients seemed to be capable of keeping spatial configuration information during a long delay period, and, as a result, they benefited from the consistent spatial configuration surrounding the target. These results show that the effect of spatial context can be sustained for a long delay in schizophrenia patients.

In the inconsistent configuration condition, schizophrenia patients as well as normal controls showed a speed-accuracy tradeoff (e.g., faster RT and lower *A'*). They made more faster but inaccurate responses when the spatial configuration in the probe image was changed from the memory image. It is possible that they might have been careless at deciding the target location with the inconsistent spatial configuration surrounding the target if they had used the spatial configuration as a retrieval cue. In other words, because the global configuration surrounding the target was new, they might have made a quick but inaccurate judgment that the target was not at the location that was occupied previously without examining the target location carefully (that would result more miss responses). A contrast analysis for comparing hit and false alarm rates between two configuration conditions showed that participants made less hit responses in

the inconsistent configuration compared to the consistent configuration condition (t_{32}=-3.02, p<.01). No difference was found in the false alarm rate between two conditions (t_{32}=.56, NS). This finding raises a question whether context also has effect on the way we respond. Further studies are necessary to examine the scope and the extent of the effects of context on our behavior.

An important finding from Experiment 2 is that schizophrenia patients did show comparable performance to normal controls when they were asked to remember the location of several dots for a delay (7 seconds). In other words, schizophrenia patients did not show spatial working memory deficit when spatial context information was provided. This finding is very unusual considering that previous studies have reported working memory deficit in schizophrenia patients even with relatively short delays (Lee & Park, in press). The difference between spatial context task used in Experiment 2 and other spatial working memory tasks may explain why schizophrenia patients showed no spatial working memory deficit in Experiment 2. The spatial context task used in Experiment 2 provided several squares in the memory image and asked them to remember the location of these dots. Previous studies with spatial working memory tasks in schizophrenia patients mainly presented one item at the encoding stage. It seemed that schizophrenia patients did not show impaired spatial working memory performance when there were multiple targets to be remembered at the encoding stage. It is puzzling why schizophrenia patients perform better when they have to encode more locations in working memory. Does having spatial context help encoding in working memory? The relationship between spatial context and encoding in working memory must be studied thoroughly in the

future. But first, we must test the same patients to see if they indeed show deficits in spatial working memory when they are asked to remember one location.

Experiment 3: Spatial working memory for single target

Experiment 2 suggested that providing the spatial context at encoding stage could normalize spatial working memory performance of schizophrenia patients. If this is true, without the spatial configuration information at encoding stage, schizophrenia patients should show spatial working memory deficits. In Experiment 3, only one target was presented at the encoding stage. At retrieval stage, there were two spatial configuration conditions: single target and distracter conditions. In the single target condition, only one green square enclosed by a red box ('a target') was presented at the retrieval stage. In the distracter condition, a target was presented with several distracters at the retrieval stage. Three memory set sizes were employed to vary the number of distracters at the retrieval stage: set 4, 6 and 8.

Methods

Participants: Twelve patients with schizophrenia (SZ; female = 3, male = 9), who finished Experiment 2, participated in Experiment 3. Characteristics of SZ patients are similar to those in Experiment 2, unless otherwise noted. Mean BPRS total score was 26.1 (±15.1). Mean SANS score was 23.7 (±15.3) and mean SAPS score was 28.6 (±21.1). All patients underwent testing while receiving atypical antipsychotic medications (clozapine, risperidone, or olanzapine).

Thirteen healthy controls (CO; female = 8, male = 5), recruited through advertisements from the university and local community, participated in Experiment 3. Controls were excluded if they had (1) past or present DSM-IV Axis I or Axis II disorder; (2) a family history of psychotic illness in their first- or second-degree relatives; (3) any other medical illness known to affect brain function; and (4) any possible brain damage.

SZ and CO groups were comparable in age (37.5 ±8.9 and 33.8 ±9.3 years, respectively; t_{23}=-1.0, NS), and education (13.3 ±2.3 and 13.0 ±1.4 years, respectively; t_{23}=-.43, NS). Although there were more females in CO group than in SZ group, there was no significant different in the proportion of female vs. male between groups (χ^2 = 3.8, NS). All participants in the healthy control group were right-handed. Two participants in patient group were left-handed, one was ambidextrous and other participants were right-handed. There was no group difference in handedness (χ^2 = 3.69, NS). All participants were provided a complete description of the proposed study and gave written informed consent before study participation. The Institutional Review Board of the Vanderbilt University, Nashville TN, approved the study protocol and consent procedure. All participants were compensated for study participation.

Apparatus and Procedure: Apparatus and procedures were similar to those in Experiment 1, unless otherwise noted. Similar to Experiment 1, reaction time (RT; ms) and *A′* were analyzed.

Spatial Working Memory Task: On each trial, two images were presented, separated by a delay period (7 seconds). The number of distracters in the probe image varied from 4 to 8 (set 4, 6, and 8). The memory image (the first image) contained one green square; the probe image (the second image) contained either one green square

(single condition) or several green squares depending on the set size of the probe image (distracter condition). Targets were cued by a red outlined box. The whole session consisted of 16 practice trials and 120 experimental trials. Trials were presented in a random order.

Results and Discussion

Table 6. RT of SZ and CO groups in a spatial working memory task with single target

		SZ	CO
Presence of Distracter			
Single Probe		1487 (807)	1128 (358)
Distracter	Set 4	1421 (481)	1206 (411)
	Set 6	1427 (493)	1170 (358)
	Set 8	1684 (1336)	1198 (423)

† Values are given as mean (SD).

A′ values are presented in Figure 5 and RTs are presented in Table 6. A repeated measures ANOVA was performed with groups as the between-subject variable and the presence of distracter was as the within-subject variable. For *A′,* the main effect of group showed a trend towards significance ($F(1,23)=3.37$, $p=.07$, power=.40). SZ showed impaired performance compared to CO group although both groups showed above 90% of sensitivity. The presence of distracter in the retrieval image did not have any effect. For RT, the main effect of the presence of distracter in the retrieval images was significant ($F(1,23)=5.63$, $p<.05$), showing that both groups showed faster RT when there was no distracter in the retrieval image.

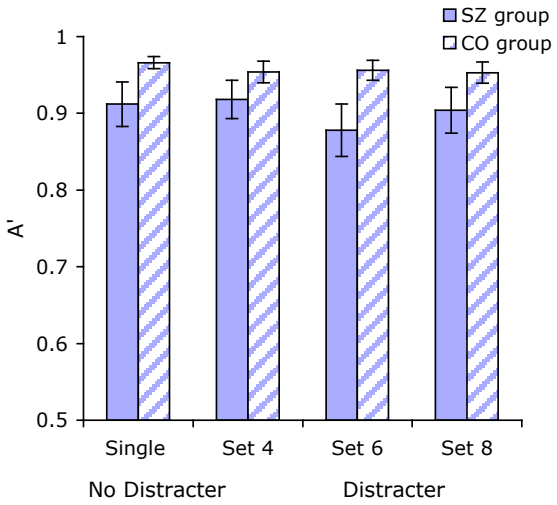

Figure 5. Performance of CO group and SZ group in a spatial WM task with single target. The solid bar indicates the performance SZ group and the stripped bar indicates the performance of CO group. SZ group showed worse performance than CO group. Neither the presence of distracter nor the number of distracters at retrieval affected performance of both groups. Error bars represent the standard error of the mean.

In Experiment 3, schizophrenia patients showed relatively poor spatial working memory performance when they were given only one item at the encoding stage. Having one item to memorize should have made this task easier than the other spatial context tasks but surprisingly they seemed to have more difficulty in this task. In addition, having distracters at retrieval image did not affect the working memory performance of schizophrenia patients and normal controls. The results of Experiment 3 suggest that spatial context provided by spatial relations of individual items may contribute to normalized working memory performance of schizophrenia patients in Experiment 2.

General Discussion

CHAPTER IV examined the effects of spatial context on working memory in schizophrenia patients. This study found that when spatial context was provided,

schizophrenia patients showed normal performance. This study also found that schizophrenia patients, similar to normal controls, did show facilitated performance in spatial context task when the spatial configuration at the retrieval stage was the same as at the encoding stage. They also showed better performance with smaller set size compared to larger set sizes. The effect of spatial configuration on working memory in schizophrenia patients was observed with a short delay as well as a long delay, suggesting that the spatial context effect is robust.

The beneficial effect of consistent spatial configuration in visuo-spatial working memory suggests that schizophrenia patients are capable of forming the global configuration of the spatial array based on individual items during a very short period of time (400 ms) and maintaining the representation of configuration for a delay up to 7 seconds. To be benefit from consistent spatial configuration, schizophrenia patients might have organized individual squares into one group during the encoding stage. By maintaining the spatial context (spatial configuration) during the delay, schizophrenia patients may have benefited at the retrieval stage. If they remembered individual location independently, they probably would not have showed better performance in the consistent configuration compared to the inconsistent configuration condition and the single probe condition. The results of this study show that schizophrenia patients do process spatial context.

Previous studies on visuospatial working memory in schizophrenia focused on the presence of working memory deficit in schizophrenia. However, little is known about *how* schizophrenia patients remember the mental representation of location in working memory. Results of the three experiments in this chapter using spatial context tasks

provide new information on how the memory representation for spatial location may be organized in schizophrenia patients. It is suggested that the visuospatial short-term memory or working memory for the location is organized based on the spatial configuration (Jiang et al., 2004; Jiang et al., 2000; Sebrechts & Garner, 1981). In other words, we remember the location of individual item in relation to other items by forming the spatial configuration of individual items. Since items are represented within this configuration, we remember better when the spatial configuration remains, but show impaired memory performance when the spatial configuration is distorted. In the studies included in this chapter, schizophrenia patients also remembered the target location better when the spatial configuration surrounding the target was consistent. These findings suggest that the mental representation of visuospatial working memory in schizophrenia may be organized based on the global, spatial configuration.

The beneficial effect of spatial context on working memory observed in schizophrenia patients is hard to reconcile with the previous findings of impaired perceptual grouping in schizophrenia patients. Schizophrenia patients have shown relatively adequate performance on tasks where the grouping between items was relatively easy using continuous contour or strong configural properties such as the Gestalt Principle (Chey & Holzman, 1997; Knight & Silverstein, 1998; Silverstein et al., 1998b). However, when perceptual grouping may interfere with the current task, schizophrenia patients showed no impairment due to grouping (i.e., counting the number of items, searching a target among distracter when grouping may interfere) whereas normal controls showed less accurate performance when the perceptual grouping was strong (Place & Gilmore, 1980; Rabinowicz, Opler, Owen, & Knight, 1996; Silverstein et

al., 1998b; Silverstein et al., 1996a; Silverstein et al., 2000). These studies suggest impaired perceptual grouping in schizophrenia since schizophrenia patients did not show impaired performance compared to controls on conditions where perceptual grouping interfered with the task. Mixed findings reported in previous studies of perceptual grouping in schizophrenia may be explained by appealing to the notion of the strength of grouping cue. It is hypothesized that schizophrenia patients have impaired ability to organize individual items into a coherent group, especially when the grouping cue is weak and as a result more top-down cognitive control is necessary to create perceptual grouping (Phillips & Silverstein, 2003). However, the results reported in this chapter showed that schizophrenia patients benefited from consistent global configuration condition even though the grouping cue was weak. The global configuration of individual items in the experiments of this chapter was an emergent property of the stimulus array. Unlike the perceptual grouping based on the Gestalt Principles, the global configuration in the experiments of this chapter was neither familiar nor simple. Rather, the stimuli can be described as disorganized and ill-configured (see Figure 2 of Experiment 1). In addition, the configuration varied greatly from trial to trial. Yet, schizophrenia patients benefited from perceptual grouping based on the spatial locations of individual items.

The findings reported in this chapter cannot be explained by the hypothesis of the strength of grouping cue. The experiments reported in this chapter are different from studies showing impaired perceptual grouping in two ways and these differences may explain why schizophrenia patients showed intact ability to use the spatial configuration. First, it is possible that schizophrenia patients may need more time to construct the global configuration of the stimulus array compared with normal controls. It has been suggested

that problems with integrating stimulus components into object representation occurs within the first 200 ms after stimulus presentation (Symond, Harris, Gordon, & Williams, 2005). In studies where schizophrenia patients showed normal ability of perceptual grouping, they were given enough time to form the mental representation (e.g., 400 ms for experiments included in this chapter and 1 seconds for Chey & Holzman's study (1997)). In studies where schizophrenia patients showed impaired perceptual grouping, the stimuli were presented for less than 150 ms (Place & Gilmore, 1980; Rabinowicz et al., 1996; Silverstein et al., 1998b; Silverstein et al., 1996a). If schizophrenia patients need more time to form the global configuration but were given a very brief time, they would not be able to perform perceptual grouping. Therefore, if the memory image (the stimulus array) had been presented for less than 150 ms in the experiments included in this chapter, schizophrenia patients may not have shown facilitated performance in the consistent configuration condition. Second, clinical symptoms may play a role in perceptual grouping. Abnormal pattern in perceptual grouping reported in some studies (e.g., Silverstein et al., 1996a; Silverstein et al., 2000) may be associated with sub-population of schizophrenia patients (i.e., acutely psychotic schizophrenia patients with poor premorbid function or schizophrenia patients with disorganized symptoms). Schizophrenia patients who participated in the studies of this chapter were not acutely psychotic and did not tend to have disorganized symptoms. Further studies are necessary to test these hypotheses.

The beneficial effects of spatial context on working memory in schizophrenia patients suggest that it is important to specify the nature of context processing required in the task when investigating context processing in schizophrenia. For example, "context"

referred in Cohen and colleagues' theory is closely associated with the task instruction and is given explicitly. For example, the "context" in their CPT-AX task is the presentation of the letter A. Participants are asked to hold this letter in mind (i.e., maintaining context) until the next letter is presented and to decide whether the sequence is AX or not. Therefore, their interpretation of context is explicit and basically equivalent to working memory. These studies showed that schizophrenia patients have difficulties in processing the task context in the CPT-AX and the Stroop task (Barch et al., 2003; Braver, Barch, Keys, Carter, Cohen, Kaye, Janowsky, Taylor, Yesavage, Mumenthaler, Jagust, & Reed, 2001; Cohen & Servan-Schreiber, 1992; Servan-Schreiber et al., 1996). Based on these studies, they argue that the core deficit of cognitive dysfunctions in schizophrenia is impaired context processing. However, the results reported here showed that schizophrenia patients are capable of using spatial context information when context is implicit and is not task-relevant. A recent study also showed that schizophrenia patients are sensitive to social context information when performing the spatial working memory task (Park, Gibson, & McMichael, in press). It is possible that schizophrenia patients may show deficit in processing certain type of context information but not other type of context information. Studies showing intact context processing argues that it is necessary to investigate specific types of context carefully for a better understanding of context processing in schizophrenia (Hemsley, 2005; Park, Lee, Folley, & Kim, 2003).

In summary, schizophrenia patients showed facilitated performance during working memory task when spatial context information was provided. These findings suggest that schizophrenia patients are able to use the global representation formed from individual items when they are required to remember locations, instead of remembering

each item independently. In other words, they may be able to use spatial relations among individual items as well as the global form of the whole stimulus array when they are asked to remember spatial locations.

CHAPTER V

NEURAL CORRELATES OF WORKING MEMORY IN SCHIZOPHRENIA: FUNCTIONAL AND STRUCTURAL BRAIN IMAGING STUDIES

Introduction

The role of the prefrontal cortex in the working memory deficits of schizophrenia is firmly established in the literature (e.g., Callicott et al., 2000; Goldman-Rakic, 1991; Perlstein et al., 2001; Stevens, Goldman-Rakic, Gore, Fulbright, & Wexler, 1998). Numerous functional imaging studies have provided evidence for abnormal patterns of activation in the prefrontal cortex during working memory tasks in schizophrenia patients (for a review, see Manoach, 2003). However, they do not agree the nature of the abnormal activation pattern. While a majority of studies reported 'hypofrontality' during working memory tasks, others showed 'hyperfrontality.' Although it has been proposed that the performance level of schizophrenia patients or task demands may contribute to inconsistent findings of previous studies (Callicott et al., 2000; Curtis, Bullmore, Morris, Brammer, Williams, Simmons, Sharma, Murray, & McGuire, 1999), it has not resolved clearly how these factors may be associated with the degree or the direction of activations of the prefrontal cortex in schizophrenia patients. It is therefore crucial to consider the specific characteristics of schizophrenia patients (i.e., the performance level, limited selection of sample due to restrictive exclusion criteria) when conducting brain imaging studies and interpreting the data. The goal of the functional imaging experiments reported in this chapter was to understand how the brain activation pattern might reflect cognitive dysfunctions (especially working memory) in schizophrenia patients.

Experiment 1: The role of the prefrontal cortex in spatial working memory in schizophrenia patients: An event-related fMRI study

Experiment 1 investigated the neural correlates of spatial working memory in schizophrenia patients using an event-related fMRI design. Previous studies of working memory in schizophrenia patients failed to provide a satisfactory explanation of how the activity of the prefrontal cortex may be related to the performance of schizophrenia patients. It is possible that impaired performance of schizophrenia patients in those studies may have contributed to inconsistent findings. In healthy individuals, working memory performance is strongly associated with the degree of activation of the prefrontal cortex (Olesen et al., 2004; Sakai et al., 2002; Wexler et al., 2000), but it is not clear whether there is a tight coupling of working memory accuracy and prefrontal activation in schizophrenia patients. Schizophrenia patients show working memory deficits in general, but their poor performance may not be associated with reduced prefrontal activation. In other words, it is unclear whether the hypofrontality or hyperfrontality observed in the past fMRI studies of working memory in schizophrenia stems from their general poor performance, inefficiency or some other factors. For example, the activation in the prefrontal cortex may be observed if these patients are maintaining internal representations during the delay period even if they are remembering wrong things. On the other hand, if they encoded nothing and therefore maintained no representation during the delay, one would expect reduced prefrontal activation in such trials. It still remains to be determined how schizophrenia patients utilize their brain when they maintain an internal representation in working memory successfully vs. unsuccessfully.

Another factor related to poor performance of schizophrenia patients is the nature of the errors they produce. Schizophrenia patients have encoding and maintenance difficulties, which may result in different types of errors. First, encoded representation may not be consolidated in working memory or it may be lost during maintenance. In this case, schizophrenia patients may produce incorrect responses because they simply lost the mental representation. This type of error should be correlated with reduced frontal activation. A second possible error type due to encoding problem is that participants may encode the wrong object or location. In this case, they will maintain accurate representation during the delay period but they will produce error responses. This is akin to false memory and should be correlated with increased prefrontal activation because they are maintaining representation in working memory. In addition, participants should be confident of their responses. Finally, an encoding problem may result in degraded or inaccurate representation. Instead of sharply defined target representation, blurred and imprecise representation may be formed. When errors result from blurred and imprecise representation, they may not radically and qualitatively different from correct responses. Participants also may not be confident of their response even though they produce correct response. Any response due to degraded and blurred representation may result in reduced frontal activation. Therefore, depending on how one encodes and maintains the stimuli, there may be hyper or hypo prefrontal activation.

The goal of Experiment 1 was to investigate the neural correlates of working memory in schizophrenia in relation to their behavioral performance. An event-related fMRI design made it possible to separate each individual trial and compare only the relevant trials based on the behavioral performance. Experiment 1 addressed two

questions. The first question was whether schizophrenia patients show increased activation when they correctly maintain targets in working memory. The second question was concerned with the brain activation pattern on error trials when participants were maintaining wrong target representations.

Methods

Participants: Nine outpatients with schizophrenia (SZ) and 9 healthy normal controls (CO) participated. All participants were right-handed. Schizophrenia patients were recruited from the Outpatient Clinic of Vanderbilt Psychiatric Hospital, Nashville, TN. SZ patients met the criteria for schizophrenia or schizoaffective disorder of the DSM-IV (American Psychiatric Association, 1991), based on clinical interviews and chart reviews. Schizophrenia patients were excluded if they had past or current alcohol and other substance abuse, brain injury, or possible neurological disease and any medical illness known to affect brain function. The clinical symptom severity of schizophrenia patients was evaluated with the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). Participants in CO group were recruited through advertisements from the university and local community. Healthy normal controls were excluded if they had (1) past or present DSM-IV Axis I or Axis II disorder; (2) a family history of psychotic illness in their first- or second-degree relatives; (3) any other medical illness known to affect brain function; and (4) any possible brain damage. Among participants who finished the behavioral task during scanning, one patient with schizophrenia was

excluded from data analysis due to motion artifact and two healthy normal controls were excluded due to the hardware problems during the image acquisition.

For participants who were included in data analysis, SZ group was older and less educated than the CO group (age, 34.5±9.3 and 25±4.5 years, respectively, t_{13}=-2.43, p<.05; education, 12.8±1.2 and 15.1±2.3 years, respectively, t_{13}=2.4, p<.05). All schizophrenia patients were stable chronic outpatients with 12.5 (±5.3) years of duration of illness, total 19.5 (±4.4) score of BPRS, total 20 (±3.4) scores of SAPS, and total 32.8 (±3.8) scores of SANS. All patients were taking atypical antipsychotics (clozapine, risperidone, or olanzapine) when they participated in this study. Although there were more female participants in the CO group (female=3) compared to SZ group (female=2), no significant group difference was found (χ^2=.62, NS). All participants were provided a complete description of the proposed study and gave written informed consent before study participation. The Institutional Review Board of the Vanderbilt University, Nashville TN, approved the study protocol and consent procedure. All participants were compensated for study participation.

Spatial Working Memory Task: The blood-oxygenation-level-dependent (BOLD)-sensitive functional images were obtained concurrently with a spatial delayed response task (spatial DRT, Figure 6) to examine task-related changes in cortical activity. The spatial DRT was adopted from Leung et al. (2002). The procedure of each trial of the spatial DRT is as follows: At the beginning of each trial, a fixation cross was presented for 1000ms. Then 3 targets (identical black circles) were flashed sequentially on a dark gray background, each in a different location (750 ms per target) with the interstimulus interval of 250 ms, followed by a delay of 12 seconds. Then, a probe was presented for 3

seconds. Participants were asked to decide whether the probe was at one of the three target locations by pressing their thumb or index finger, which indicates 'yes' and 'no' respectively. After the response, participants were also asked to rate their confidence level for the response they had just made on a 5-point rating scale that ranges from 1 (most confident) to 5 (least confident) by pressing a button corresponding to the digits. "1" corresponded with the thumb press, "2" with index finger and so on. An inter-trial interval (ITI) of 8.25 s followed the participants' confidence rating response. There were seven runs and each run contained 14 DRT trials.

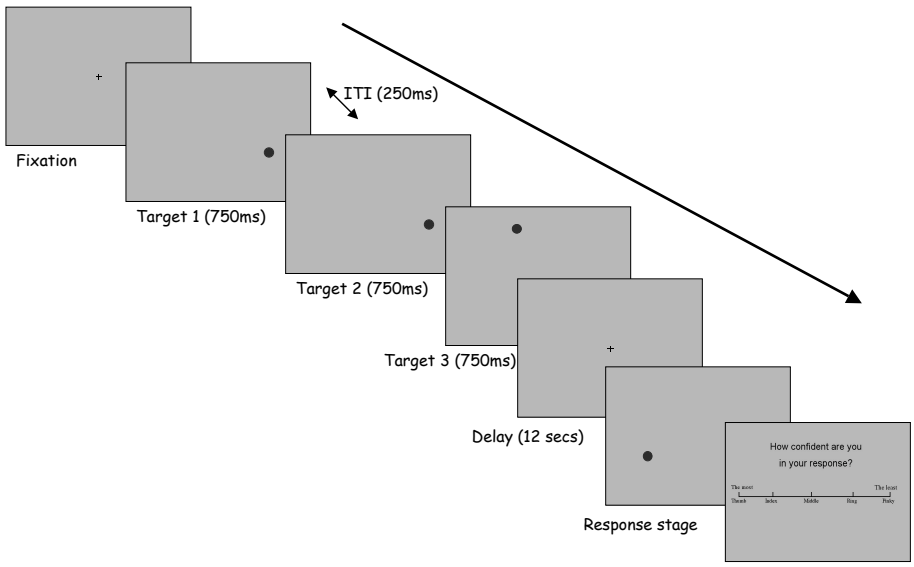

Figure 6. A schematic diagram of a spatial working memory task. After a fixation point (1000 ms), three targets appeared for 750 ms with the interstimulus interval of 250 ms. A delay of 12000 ms ensued. Participants were asked to decide whether a probe was located in one of previously occupied locations by targets or not. Then they were asked to rate their confidence level for the response they just made.

Image acquisition: All brain images were collected on a 3 Tesla whole-body GE Signa MRI system with a birdcage head coil at the Vanderbilt University Medical Center

(Nashville, TN USA). 19 T1-weighted anatomical images parallel to the anterior-posterior commissural (AC-PC) were acquired, along with T2*-weighted functional images parallel to the (AC-PC) line for blood oxygen-level-dependent (BOLD)-based images (gradient echo planar imaging sequence, TR=2000ms, TE=35ms, flip angle=90º, matrix=64x64, slice thickness=5mm, slice gap=1mm, FOV=24x24cm). High-resolution T1-weighted anatomical volumes were also acquired with a magnetization-prepared 3D SPGR imaging sequence. Stimuli were presented through MR-compatible LCD goggles (VisualStim, XGA, Resonance Technology).

fMRI data analysis: Imaging data were preprocessed and analyzed using the Brain Voyager 4.9 and QX (Brain Innovation, Masstricht, The Netherlands). The anatomical volumes were transformed into a stereotactic space that was common for all participants (Talairach & Tournoux, 1988). Functional volumes for each subject were aligned to the transformed anatomical volumes, thereby transforming the functional data into a common brain space across participants. Data pre-processing for functional volumes included image realignment, three-dimensional motion correction, linear de-trending, temporal frequency filtering with high pass filter, and spatial smoothing with a 4-mm Gaussian kernel (full width at half-maximum). The statistical analysis is based on the application of the multi-study general linear model (GLM) to time-series of task-related function volumes. The GLM allows the correlation of predictor variables with the recorded activation data (criterion variables) across scanning sessions on grouped datasets. The GLM in the Brain Voyager with predictors of interest (i.e., correct vs. incorrect trials that were determined from the behavioral performance on the spatial working memory task) was applied for the individual Z-normalized volume time courses, to investigate the

delay-related maintenance activity. The overall model of fit was assessed by using an F statistic. Significant differences between the conditions (i.e., correct vs. incorrect) were assessed by using contrast (*t*) maps. The obtained *p* values are corrected for multiple comparisons by using False Discovery Rate (FDR) of .05. The FDR controls the expected proportion of false positives among suprathreshold voxels instead of controlling for the change in any false positives as Bonferroni correction method does (Genovese, Lazar, & Nichols, 2002; Nichols & Hayasaka, 2003).

Results

The behavioral responses of each group on spatial working memory task were analyzed based on the accuracy and confidence ratings. The 5-scale of confidence rating allowed the behavioral responses to be divided into two categories, 'confident response' for the ratings 1 and 2 and 'non-confident' response for the ratings 4 and 5. For accuracy, CO group showed better performance than SZ group (mean accuracy, 86±9% and 75±9%, respectively, t_{13}=2.39, p<0.05). For confidence rating, CO group rated 84% of their total responses as confident. Among the confident responses, 92% were correct responses. SZ group rated 86% of their total responses as confident, but only 77% of the confident responses were correct responses. SZ patients produced more incorrect but confident responses compared to the CO (χ^2=17.41, p<0.001). This result suggests that schizophrenia patients might have encoded and maintained 'wrong' representation during the spatial working memory task and as a result produced incorrect but confident response ("false memory" response).

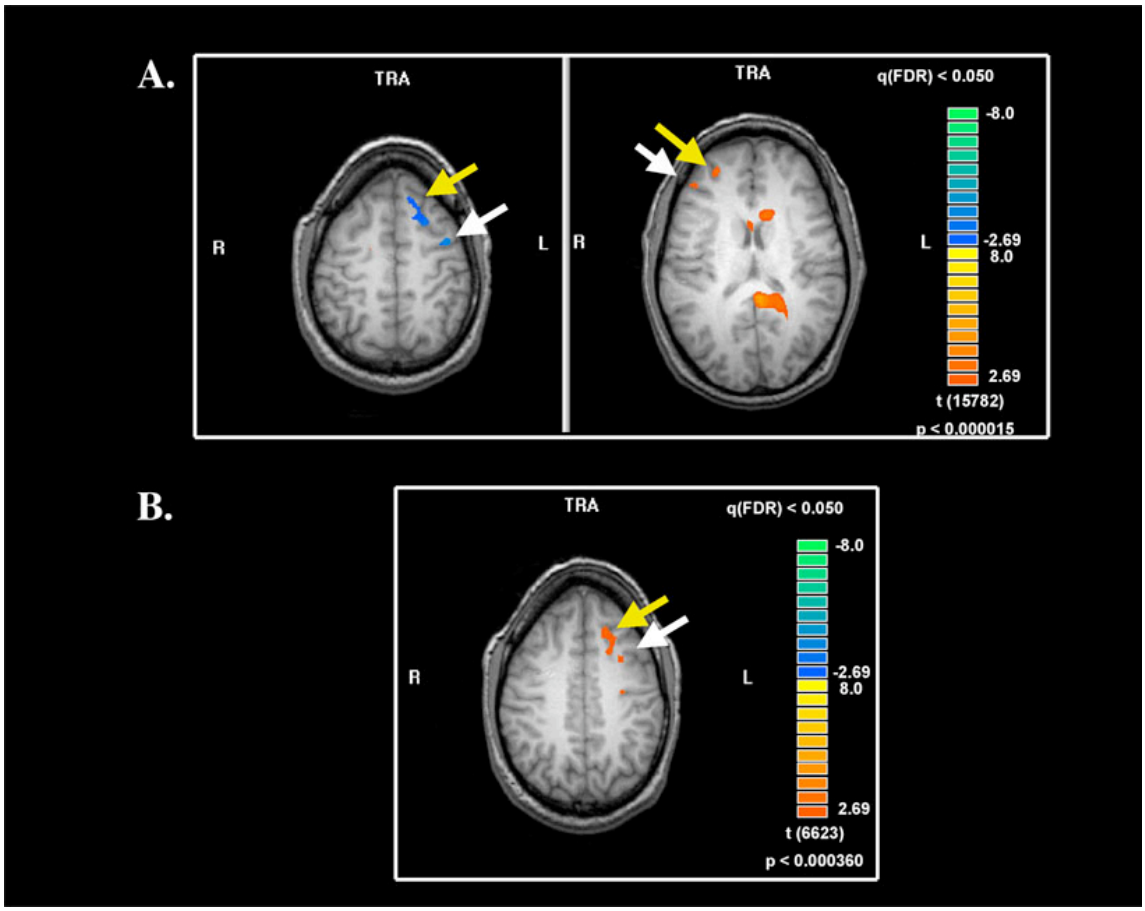

Figure 7. Activation map of the delay-related BOLD data in the prefrontal cortex during spatial working memory task. (A) SZ group showed more activation in the middle frontal gyrus (white arrow) and the superior frontal gyrus (yellow arrow) in the left hemisphere whereas CO group showed more activation in the middle frontal gyrus and the superior frontal gyrus in the right hemisphere. (B) SZ showed increased activation in the middle frontal gyrus and the superior frontal gyrus during false memory trials.

For functional imaging data, the delay-related BOLD activity of the SZ group was compared with that of the CO group, to investigate whether schizophrenia patients show similar patterns of activation when they perform the spatial working memory task correctly. Table 7 presents areas of the brain activated during the maintenance in CO and SZ group. During the maintenance period, both SZ and CO groups showed activation in the right middle frontal gyrus (MFG) and the right superior frontal gyrus (SFG) (Figure 7). In addition to these two areas, CO group showed greater activation in the right

posterior cingulate gyrus (PCG) and the right superior temporal gyrus (STG) compared to SZ. Areas where SZ patients showed greater activation compared to the CO included the anterior part of the right CG, the right insular, the left MFG, the left medial frontal gyrus, the left inferior frontal gyrus (IFG), the left CG as well as the left inferior parietal lobule (IPL) and the left STG.

Table 7. Talairach sterotaxic coordinates for the peak of activated areas in the brain during spatial working memory task.

	x	*y*	*z*	*t*
CO group > SZ group				
Right middle frontal gyrus	41	38	15	2.6
Right superior frontal gyrus	25	46	15	3.0
Right posterior cingulate gyrus	13	-42	7	3.1
Right superior temporal gyrus	53	-3	-11	2.9
CO group < SZ group				
Right middle frontal gyrus	19	32	43	-2.7
Right superior frontal gyrus	16	12	48	-2.3
Left middle frontal gyrus	-39	3	48	-7.6
Left inferior frontal gyrus	-47	1	1	-7.7
Left medial frontal gyrus	-4	9	47	-2.6
Left superior temporal gyrus	-44	12	-12	-7.2
Left inferior parietal lobule	-34	-47	43	-7.0
Right cinculate gyrus	9	21	32	-3.5
Left cingulate gyrus	-7	-3	42	-3.8
Right insular	43	1	1	-6.0

To determine whether the SZ group indeed maintains mental representations during “false” memory trials, the delay-related BOLD activity for false memory trials was examined in SZ (see Figure 7). Similar analysis for the CO group could not be

performed due to the small number of false memory trials. For false memory response, schizophrenia patients activated MFG, SFG, CG, and IFG in the left hemisphere and the right medial frontal gyrus. These areas are similar to the areas schizophrenia patients activated during the successful working memory trials. This suggests that during the false memory trials, schizophrenia patients maintained the representation of a stimulus that is not a target.

Discussion

This study examined the neural correlates of working memory in schizophrenia while controlling for their performance level by selecting the correct trials. When schizophrenia patients maintained the mental representation successfully in working memory, they, as well as normal controls, activated the right MFG, which is associated with spatial working memory maintenance (e.g., Leung et al., 2002). However, schizophrenia patients also activated the left MFG, the left IFG and other areas in the left hemisphere during the spatial working memory task.

Normal controls showed the expected lateralized pattern of activation of the right hemisphere during the spatial working memory task. However, this pattern was not observed in schizophrenia patients. The bilateral activation in the prefrontal cortex of schizophrenia patients in this study suggests that a 'simple' explanation of hypofrontality or hyperfrontality is not sufficient to determine the neural correlates of working memory in schizophrenia. A recent meta-analysis study indicates that there is a complex pattern of hyper- and hypo- activation in the areas of the brain associated with working memory in schizophrenia (Glahn, Ragland, Abramoff, Barrett, Laird, Bearden, & Velligan, 2005).

Since the performance level of both groups was matched (by comparing only the correct trials), this finding is not an artifact of different performance level in schizophrenia patients. Rather this suggests that schizophrenia patients seem to engage different areas of the brain to perform spatial working memory tasks.

This study suggests that the brains of schizophrenia patients may do things differently even when the resulting, observed behaviors are the same as those of normal controls. There could be several possible explanations for the different pattern of activations in the prefrontal cortex in schizophrenia patients. First, it may be a result of a compensatory mechanism for dysfunctional right hemisphere in schizophrenia. Schizophrenia patients do *not* show right hemisphere advantage for processing visuospatial information as normal controls do (Heckers, Goff, & Weiss, 2002; Nuechterlein, Buchsbaum, & Dawson, 1994; O'Donnell, Potts, Nestor, Stylianopoulos, Shenton, & McCarley, 2002; Walter, Wunderlich, Blankenhorn, Schafer, Tomczak, Spitzer, & Gron, 2003; Wynn, Light, Breitmeyer, Nuechterlein, & Green, in press). Dysfunctional right hemisphere in schizophrenia patients may be due to reduced or absent brain asymmetry including reduced or absent torque (Bilder, Wu, Bogerts, Degreef, Ashtari, Alvir, Snyder, & Lieberman, 1994; Crow, 1997; Crow, Done, & Sacker, 1996; DeLisi, Sakuma, Kushner, Finer, Hoff, & Crow, 1997) and/or abnormal hemispheric interaction (David, 1994). If schizophrenia patients have less lateralized brain (i.e., less specialized compared to the brains of healthy individuals), they may activate widespread areas of the brain during a task, which activates selectively specialized areas in healthy individuals. It has also been suggested that schizophrenia patients have abnormal cortico-cortical connectivity in the brain (David, 1994; Friston,

1998, 1999; Hoffman & McGlashan, 1993, 1994; McGlashan & Hoffman, 2000). Abnormal cortico-cortical connectivity can be seen as reflecting reduced synaptic connectivity (David, 1994; Hoffman & McGlashan, 1994; McGlashan & Hoffman, 2000) or impaired modulation of associative changes in synaptic efficacy, especially in the modulation of plasticity in the brain (Friston, 1998, 1999). Abnormal connectivity in the brain may interfere with the functioning of the system as a whole, and as a result schizophrenia patients may show less specialized activation in the brain.

Another possibility is that the bilateral activation observed in Experiment 1 may be a result of a compensatory mechanism including increased cognitive effort in schizophrenia patients. It is possible that schizophrenia patients experienced more difficulty of performing the task compared to normal controls even though they eventually performed the task successfully, considering that they have reduced working memory capacity compared with normal controls (Chey, Lee, Kim, Kwon, & Shin, 2002; Gold et al., 2003). It has been shown that increasing task difficulty can result in bilateral pattern of activation in the brain during a working memory task (Klingberg, O'Sullivan, & Roland, 1997; Rypma & D'Esposito, 1999; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). If schizophrenia patients have reduced working memory capacity, they may need to exert more effort to perform the task to achieve the same level and, consequently, they may have to activate more areas in the brain.

As described above, there are several possible explanations for the bilateral activation in the prefrontal cortex in schizophrenia patients during the spatial working memory task. Each explanation is plausible but there is not enough evidence to decide

which hypothesis best accounts for the data. Future studies are necessary to test each hypothesis.

This study also showed that for "false" memory trials where errors were coupled with a high degree of confidence, schizophrenia patients activated similar brain areas where they showed activation during the correct trials. This finding suggests that schizophrenia patients may have encoded 'wrong' targets and maintained the representation on these trials and that there is corresponding prefrontal activation on these false memory trials. Therefore, if schizophrenia patients make a large number of such errors, there will be normal or even hyperfrontal activation during working memory task. In contrast, if the encoding process was degraded and the ensuing memory representation weakened or lost, the resulting errors should be accompanied by reduced frontal activation. The finding of robust activation in the brain during such false memory trials may partly account for the inconsistent findings of previous studies that have reported both hyper and hypofrontality. Schizophrenia patients produce errors in some studies because they may have maintained a representation of a wrong targets (as a result, they show robust activation in the prefrontal cortex), but in other studies they failed to encode and/or maintain the mental representation (i.e., they may not show activation in the prefrontal cortex).

In summary, both schizophrenia patients and normal controls activated the right MFG during the spatial working memory task, but schizophrenia patients activated additional areas including the left MFG and the left IFG. Lateralized activation in the prefrontal cortex during the spatial working memory task was only observed in the CO group. In addition, SZ patients activated similar areas of the brain when they maintained

the representation of 'wrong' targets. This finding suggests that event-related fMRI experiments are necessary to understand the nature of working memory deficits in schizophrenia patients.

Experiment 2: Near Infrared Spectroscopy (NIRS) study of spatial working memory

Experiment 1 showed that the fMRI provides a powerful methodology towards the neural correlates of working memory deficit in schizophrenia. However, there are practical hurdles that fMRI presents for psychiatric patients. The exclusion criteria for MRI rule out many of the available patients who are able to participate. Atypical antipsychotic medications are associated with weight gain and unfortunately a large proportion of schizophrenia patients are obese and exceed the safety weight limit of the scanner. In addition, some patients are paranoid and delusional and therefore they do not want to participant. Even when some patients meet the inclusion criteria for MRI and are less paranoid, they may not be able to participate because they are anxious and claustrophobic. Therefore, there is a dire need to develop a safe, alternative imaging method for psychiatric population. The NIRS provides a safe and non-invasive brain imaging technique for infants, small children and psychiatric population (e.g., Hebden, 2003). NIRS also has several advantages over fMRI including good temporal resolution, reasonable spatial resolution, better motion tolerance, no auditory confounds due to quiet operation, and increased comfort for the participants. In addition, less strict exclusion criteria allow participants with weight problem or metal implant to be included in studies with NIRS. Therefore, NIRS may be a suitable alternative method, but before it can be used widely in psychiatric setting, it must be validated against fMRI and other imaging

methods. Hence, Experiment 2 was planned to use NIRS to examine the neural correlates of working memory in schizophrenia. By using the same spatial working memory task from Experiment 1, it would be possible to compare the brain activation patterns from NIRS to the results of Experiment 1.

Methods

Participants: Thirteen outpatients with schizophrenia (SZ, female=4) and 11 healthy normal controls (C0, female=4) participated in the study. Schizophrenia patients were recruited from the Outpatient Clinic of Vanderbilt Psychiatric Hospital, Nashville, TN. SZ patients met the criteria for schizophrenia or schizoaffective disorder of the DSM-IV (American Psychiatric Association, 1991), based on clinical interviews and chart reviews. Schizophrenia patients were excluded if they had past or current alcohol and other substance abuse, brain injury, or possible neurological disease and any medical illness known to affect brain function. The clinical symptom severity of schizophrenia patients was evaluated with the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). Total BPRS score was 12.0 (±8.5). Total SANS score was 13.6 (±9.2) and total SAPS score was 11.76 (±12.3). All patients were taking atypical antipsychotics (clozapine, risperidone, and olanzapine) when they participated in this study. Participants in CO group were recruited through advertisements placed in the university and local community. Healthy normal controls were excluded if they had (1) past or present DSM-IV Axis I or Axis II disorder; (2) a family history of psychotic illness in their first- or

second-degree relatives; (3) any other medical illness known to affect brain function; and (4) any possible brain damage.

SZ and CO group were comparable in age (34.7 ±8.0 and 36.6 ±6.4, respectively, t_{21}=.58, NS) and education (13.0 ±1.0 and 14.1 ±2.4, respectively, t_{21}=1.37, NS). Three participants in SZ group were left-handed and all COs were right-handed, but there was no group difference in handedness (χ^2=2.65, NS) and in the proportion of female vs. male (χ^2=0.08, NS). All participants were provided a complete description of the proposed study and gave written informed consent before study participation. The Institutional Review Board of the Vanderbilt University, Nashville TN, approved the study protocol and consent procedure. All participants were compensated for study participation.

Spatial Working Memory Task: The spatial working memory task used in Experiment 1 was administered. For detailed information, see the Method section of Experiment 1.

NIR Measurement: NIRS was performed using a 24-channels (maximum) 780-830 nm spectrometer (ETG-100 system; Hitachi Medical Corp.), composed of emitter-detector pairs that can be set up for 12, 22 or 24 channels. Each emitter is composed of two continuous laser diodes (3mW± 0.15mW on 'high' power) with different wavelengths (780±20 and 830±20 nm) that are amplitude modulated (0.6 and 1.5 Khz). NIR signals are mixed and transmitted through a multi-component glass bundle optical fiber cable that is placed on the scalp using a spring-loaded probe that is attached to the probe holder through an adjustable socket. Another optical fiber carries the scattered signal picked up by the optical sensor to a photodiode. An inter-fiber spacing of approximately 27 mm produces a light penetration close to 20 mm. Signals were acquired

at a sample rate of 10 Hz from 22 cortical regions on the bilateral prefrontal cortex using the 3 x 5 probe holder and the corresponding optodes. The signal was amplified, demodulated, and then digitized. The detected signals were converted to chromophore concentrations using the modified Beer-Lambert Law (Obrig et al., 2000).

Anatomical Localization: Probes were placed on the forehead according to the international 10-20 system of electrode placement used for EEG and ERP. The middle vertical band of optodes was placed along the z (midline) axis extending from the Fp position ventrally (just superior and horizontal to the Obicularis oculi muscles) towards a caudal position proximal to the Fz position along the Frontalis muscles. However, unlike EEG electrode placement that uses relative (10-20% distance from nasion and inion) place of electrodes in individual skulls, the NIRS optodes were placed in a fixed holder that cannot be stretched or compressed for individual variation in skull measurements. Therefore, some anatomical variation inevitably exists among individuals. However, this method assures a high level of standardization across participants with the right hemisphere probes covering areas Fp2, F4 and F8 and the left hemisphere probes covering area Fp1, F5 and F7.

NIR data analysis: NIR data were analyzed using the Matlab (The Mathworks) and the Brain Voyager-QX version (Brain Innovation, Masstricht, The Netherlands). First, a temporal filter was applied to remove any artifact due to respiration and cardiac variation using a bandpass filter with a range 0.01-0.5 Hz. Then, NIR data were converted to the measurement of oxyhemoglobin (oxy-Hb), deoxyhemoglobin (deoxy-Hb), and total hemoglobin (total-Hb) levels according to the modified Beer-Lambert Law, arranged into epoch focusing on the delay period of the spatial working memory

task and imported into the Brain Voyager-QX for further analysis. To remove overall linear drifts, the linear trend removal was performed. The general linear model was used to compare whether schizophrenia patients show different pattern of activation in the brain compared to controls when they performed the working memory task correctly vs. incorrectly. The obtained *p* values were corrected for multiple comparisons by using False Discovery Rate (FDR) of .05. Results are reported for statistical map clusters that passed a threshold criterion of 20+ voxels.

Results

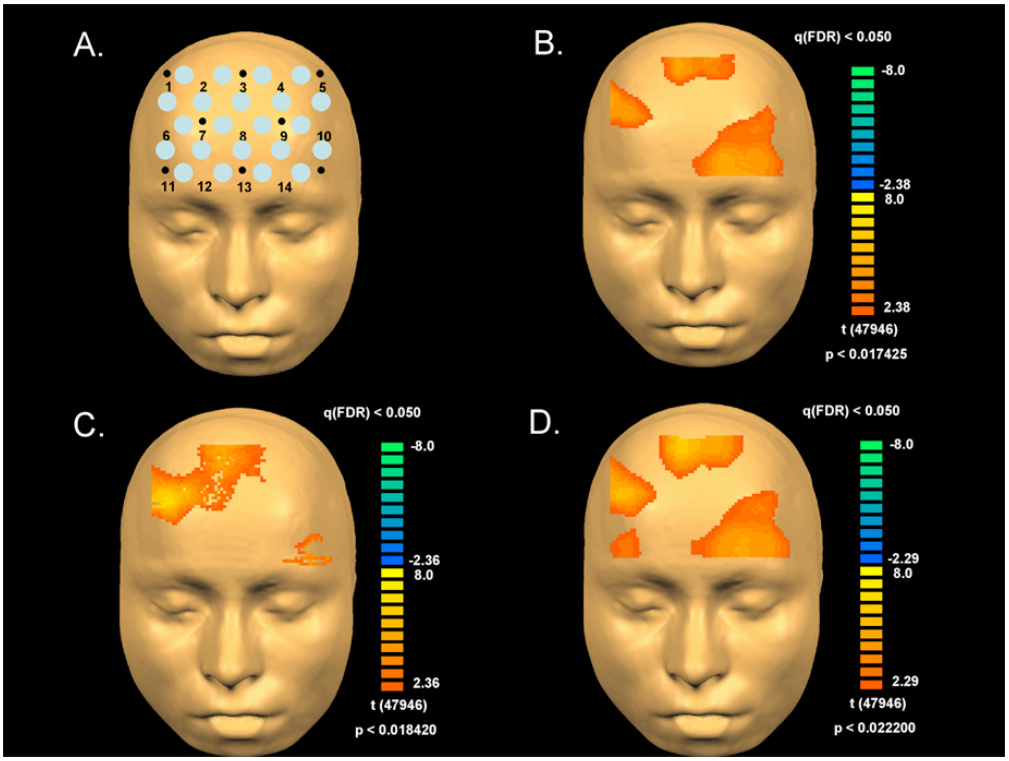

Figure 8. NIRS results comparing the delay-related NIRS measurements between CO group and SZ group. (A) Location of the 22-channel placement with 3 x 5 probe holder. Small circles represent emitters (closed) and detectors (open). Large circles represent measurement channels (22); (B) Co group showed more activation in the prefrontal cortex in oxy-Hb; (C) In deoxy-Hb, CO group showed lateralized activation in the right hemisphere; (D). Total-Hb showed similar activation pattern to oxy-Hb.

The behavioral responses of each group on spatial working memory task were analyzed based on the accuracy and confidence rating. The 5-scale of confidence rating allowed behavioral responses to be divided into two categories, 'confident response' for scale 1 and 2 and 'non-confident' response for scale 4 and 5.

For accuracy, group difference showed a trend toward significance (CO group, 88±7%, SZ group, 80± 2%, t_{21}=1.83, p=0.08). For confidence rating, CO group rated 81% of the total responses as confident. Among the confident responses, 91% were correct responses. SZ group rated 74% of the total responses as confident, and 81% of the confident responses were correct responses. SZ group produced more incorrect but confident responses compared to CO group (χ^2=14.2, p<0.001). This result suggests that schizophrenia patients might maintain 'wrong' representation during the spatial working memory task and as a result produce incorrect but confident response.

To examine whether SZ group showed differential activation during the spatial working memory task, the delay-related NIRS data of SZ group was compared with that of CO group when they performed the task correctly. The delay-related NIRS data were analyzed for oxy-Hb, deoxy-Hb, and total-Hb separately. Figure 8 presents statistical maps for the oxy-Hb, deoxy-Hb and total-Hb that were overlaid onto the position for the 22 channel probes on the head. For oxy-Hb, CO group showed greater activation in the superior part of the right frontal cortex, in the superior junction of both hemispheres, and in the inferior part of the left frontal cortex compared to SZ group. CO group also showed more activation in the superior part of the right frontal cortex compared to SZ group in deoxy-Hb. Analysis of total-Hb showed similar pattern of activation as the oxy-Hb data.

The superior part of the right frontal cortex where CO group showed greater activation corresponds to the right lateral prefrontal cortex.

Since SZ patients produced confident but incorrect responses ('false memory' response) during the spatial working memory task, the delay-related NIRS data for false memory response was examined in the SZ group. Similar analysis in the CO group could not be performed due to the small number of false memory trials. SZ showed decreased oxy-Hb during the false memory trials in the inferior part of both hemispheres. For deoxy-Hb, increased activation in the left frontal cortex and decreased activation in the superior part of the right frontal cortex were observed. SZ showed increased total-Hb in both hemispheres (especially in the inferior frontal cortex) during the false memory trials.

Discussion

In Experiment 2, the functional activations in schizophrenia patients using the NIRS were examined to evaluate whether NIRS can match fMRI. During the spatial working memory task, CO group showed greater activation in the right frontal cortex compared to the SZ group and this pattern was observed in oxy-Hb, deoxy-Hb and total-Hb data. In addition, oxy-Hb and total-Hb showed that CO group showed greater activation in the inferior part of the left frontal cortex. NIRS data suggest that schizophrenia patients show different pattern of activation from normal controls even though the behavioral performance was equivalent. These results also suggest that the NIRS may present a viable, alternative method to be used in psychiatric research.

In this study, the deoxy-Hb data was the most similar to the delay-related BOLD activity from Experiment 1. This is intriguing considering that the 780 nm used in this

experiment may not have the optimal sensitivity for the deoxy-HB (Sato, Kiguchi, Kawaguchi, & Maki, 2004). In addition, the activation patterns obtained from the oxy-Hb and total-Hb data were slightly different from that obtained from the deoxy-Hb data. It is not clear why each measure produced different patterns of activation during the spatial working memory task. The oxygenation changes detected by NIRS in response to functional stimulation consist of decreased deoxy-Hb accompanied by increased oxy-Hb. In addition, the magnitude of changes in oxy-Hb is approximately two to three times larger than the magnitude of that in deoxy-Hb. This pattern of association between deoxy-Hb and oxy-Hb has been found during the spatial working memory task (Fuster, Guiou, Ardestani, Cannestra, Sheth, Zhou, Toga, & Bodner, 2005) and the Wisconsin Card Sorting Task (Fallgatter & Strik, 1998). Among the three Hb measures, the deoxy-Hb is proposed to be the most accurate indicator of measuring cortical activation because increased oxy-Hb may indicate a change in blood pressure or an increase in skin blood volume (Obrig & Villringer, 2003). Deoxy-Hb has also been proven to be associated with the BOLD contrast of fMRI (Mehagnoul-Schipper, van der Kallen, Colier, van der Sluijs, van Erning, Thijssen, Oeseburg, Hoefnagels, & Jansen, 2002; Obrig & Villringer, 2003). However, other studies suggest that oxy-Hb is better than deoxy-Hb (Kennan, Kim, Maki, Koizumi, & Constable, 2002). Oxy-Hb has been found to be more closely related to the BOLD signal of fMRI than deoxy-Hb (Strangman, Culver, Thompson, & Boas, 2002b). Moreover, some studies have found that there are changes in oxy-Hb during cognitive tasks, but not in deoxy-Hb (Strangman et al., 2002b; Tsujimoto, Yamamoto, Kawaguchi, Koizumi, & Sawaguchi, 2004). To summarize, these studies show that NIRS is useful in study cortical activation in relation to cognitive functions, but there is still

much disagreement on what it is measuring and which parameters may best reflect cortical functions. Recent study suggested that different combination of the wavelengths may affect the noise level of each parameter differently (Sato et al., 2004; Yamashita, Maki, & Koizumi, 2001). That is, if some studies used different combinations of wavelengths, they may show favorable results for some NIRS measures and less favorable results for other NIRS measurements. Lack of standardized combinations of wavelengths makes it difficult to determine which measurement is better than others simply by comparing findings across studies. Further studies are necessary to investigate the possible variables that may affect each NIRS measurement differently and how these factors may influence the findings related to functional activations in the brain.

Experiment 3. Connectivity in the brain in relation to spatial working memory

Experiment 1 and 2 showed that schizophrenia patients may use their brain differently compared to healthy normal controls. In the fMRI study of spatial working memory, schizophrenia patients show the bilateral activation in the prefrontal cortex whereas healthy controls predominantly activated the right MFG. One possible explanation for the observed bilateral activation in the prefrontal cortex is the abnormal cortico-cortical connectivity in schizophrenia patients (David, 1994; Friston, 1998, 1999; Hoffman & McGlashan, 1993, 1994; McGlashan & Hoffman, 2000). Abnormal connectivity in the brain may interfere with the functioning of the system as a whole and as a result schizophrenia patients may engage or recruit their brain areas differently. Thus, Experiment 3 investigated whether schizophrenia patients have abnormal

connectivity in areas associated with working memory in the brain, focusing on the white matter of the brain.

Diffusion Tensor Imaging (DTI) is a relatively new technique that is very useful for evaluating abnormalities of the white matter in the brain (Basser & Jones, 2002; Kubicki, Westin, Maier, Mamata, Frumin, Ersner-Hershfield, Kikinis, Jolesz, McCarley, & Shenton, 2002b; Le Bihan, Mangin, Poupon, Clark, Pappata, Molko, & Chabriat, 2001; Melhem, Mori, Mukundan, Kraut, Pomper, & van Zijl, 2002). DTI measures the diffusion of water molecules based on the principle that the movement of water molecules can represent the structure of the tissue environment. In a liquid or gas, individual molecules move randomly without any restriction (i.e., Brownian movement) and therefore the diffusion is isotropic. In brain tissue, such as the white matter, however, the movement of water molecules is restricted by the fiber structure such that it is more likely to move along the longitudinal direction of the axons compared to other directions due to the presence of myelinated white matter fibers, i.e., the diffusion is anisotropic. Diffusion anisotropy provides important information about the structure of the white matter. This can be done by measuring the mean diffusivity (D) and the fractional anisotropy (FA), but both measures are independent of the orientation of the diffusion tensor. The mean diffusivity represents the overall displacement of the water molecules. The factional anisotropy represents the fraction of the magnitude of the tensor that can be ascribed to the anisotropic diffusion (i.e., the FA value of '1' indicates the perfect state of anisotropy and the FA value of '0' indicates the perfect state of isotropy). Due to its sensitivity to the structure of white matter in the brain, DTI can estimate the connectivity between the structures interconnected by the white matter fiber tracts by modeling the

diffusive transport of water molecules between them. Recent studies using DTI showed that indeed schizophrenia patients have abnormal white matter in general (Minami, Nobuhara, Okugawa, Takase, Yoshida, Sawada, Ha-Kawa, Ikeda, & Kinoshita, 2003), and specifically in the uncinate fasciculus that connects the frontal lobe to the temporal lobe (Burns, Job, Bastin, Whalley, Macgillivray, Johnstone, & Lawrie, 2003; Kubicki, Westin, Maier, Frumin, Nestor, Salisbury, Kikinis, Jolesz, McCarley, & Shenton, 2002a), in the anterior cingulum areas (Kubicki, Westin, Nestor, Wible, Frumin, Maier, Kikinis, Jolesz, McCarley, & Shenton, 2003; Wang, Sun, Cui, Du, Wang, Zhang, Cong, Hong, & Zhang, 2004), and in the arcuate fasciculus that connects the frontal and parietal areas (Burns et al., 2003).

The goal of Experiment 3 was to investigate whether schizophrenia patients show abnormal connections between the areas of the brain associated with spatial working memory, focusing on the superior longitudinal fasciculus. The superior longitudinal fasciculus (SLF) is considered to be a major association fiber pathway that connects the posterior association area (i.e., parieto-temporal areas) to the frontal lobe. Using DTI, Makris et al. (Makris, Kennedy, McInerney, Sorensen, Wang, Caviness, & Pandya, 2004) showed that the SLF is composed of four parts. Among these four parts, SLF II originates from the posterior-inferior parietal regions and terminates in the prefrontal area (BA 46 and 9). Considering its location, it is possible that SLF II is the main link transferring information between the prefrontal cortex and the parietal cortex and as a result may play an important role in working memory.

Methods

Participants: Six outpatients with schizophrenia (SZ, female=3) and 6 healthy normal controls (CO, female=3) who finished Experiment 1 participated in the study. All schizophrenia patients were stable chronic outpatients with 13.8 (±7.3) years of duration of illness, total 18.5 (±14.7) score of BPRS, total 19.6 (±17.5) scores of SAPS, and total 22.3 (±21.6) scores of SANS.

SZ and CO group were comparable in age (32.8 ±8.0 and 31.5 ±7.3, respectively, t_{10}=-0.29, NS) and education (13.1 ±1.1 and 14 ±2.0, respectively, t_{10}=0.85, NS). All participants were provided a complete description of the proposed study and gave written informed consent before study participation. The Institutional Review Board of the Vanderbilt University, Nashville TN, approved the study protocol and consent procedure. All participants were compensated for study participation.

Imaging Data Acquisition: All diffusion tensor images were collected on the General Electric 3.0 T MRI scanner at Vanderbilt University Medical Center (Nashville, TN, USA). Diffusion images were collected using a spin echo EPI sequence. The following scanning parameters were used: square field of view (FOV)=260x260 mm; 128x128 scan matrix; slice thickness = 4mm; interslice distance = 0mm; echo time = 88.5 msec (minimum); TR=9000 ms; ramp sampling=1; b=1000s/mm^2; number of directions =33. Twenty nine axial slices were acquired, covering the entire brain.

Diffusion Data Analysis: After reconstruction, the diffusion-weighted images were analyzed using Matlab to calculate eigenvalue, eigenvector, Trace, and FA maps of the diffusion tensor. Based on previous studies (Makris et al., 2004; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004), regions of interest (ROIs) were placed in the

SLF on the axial slice that is one slice superior to the body of corpus callosum on the color FA map (see Figure 9). ROIs (9.283 x 9.283 mm, 3x3 voxels) were selected on the anterior and posterior part of SLF II on each hemisphere and FA and D were measured.

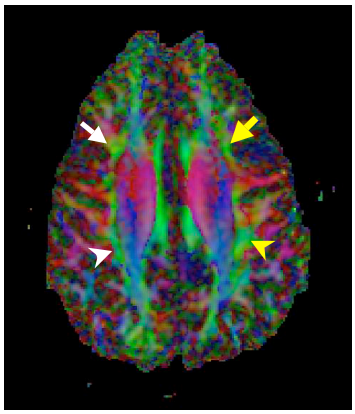

Figure 9. Placement of regions of interest (ROIs) on the colored FA map. On this map, red, green, and blue represent fibers running along right-left, anterior-posterior, and superior-inferior axes, respectively. The brightness of each color is proportional to FA. ROIs were placed on the axial slice right that is one superior to the body of corpus callosum: the anterior ROI of the left SLFII (yellow arrow), the posterior ROI of left SLFII (yellow arrowhead), the anterior ROI of the right SLFII (white arrow), and the posterior ROI of the right SLFII (white arrowhead).

Table 8. FA and D of SLFII in SZ group and CO group

		SZ		CO	
		FA	D	FA	D
R.SLFII	Anterior	0.397 (0.09)	8.35E-06 (6.86E-07)	0.409 (0.08)	6.79E-06 (2.94E-06)
	Posterior	0.511 (0.099)	8.43E-06 (1.55E-07)	0.498 (0.107)	8.04E-06 (3.88E-06)
L.SLFII	Anterior	0.392 (.072)	8.47E-06 (8.43E-07)	0.351 (0.06)	8.69E-06 (5.03E-07)
	Posterior	0.601 (0.11)	7.89E-06 (5.59E-07)	0.531 (0.096)	8.31E-06 (4.15E-07)

† Values are given as mean (SD).
† R.SLFII, the superior longitudinal fasciculus II in the right hemisphere; L.SLFII, the superior longitudinal fasciculus II in the right hemisphere; FA, fractional anisotropy; D, mean diffusivity.

Results

Table 8 presents FA and D from ROIs in each hemisphere. SZ group showed larger D in the posterior part of the right SLFII compared with the CO group (t_{10}=-2.24, p<0.05). No significant group difference was found in other ROIs.

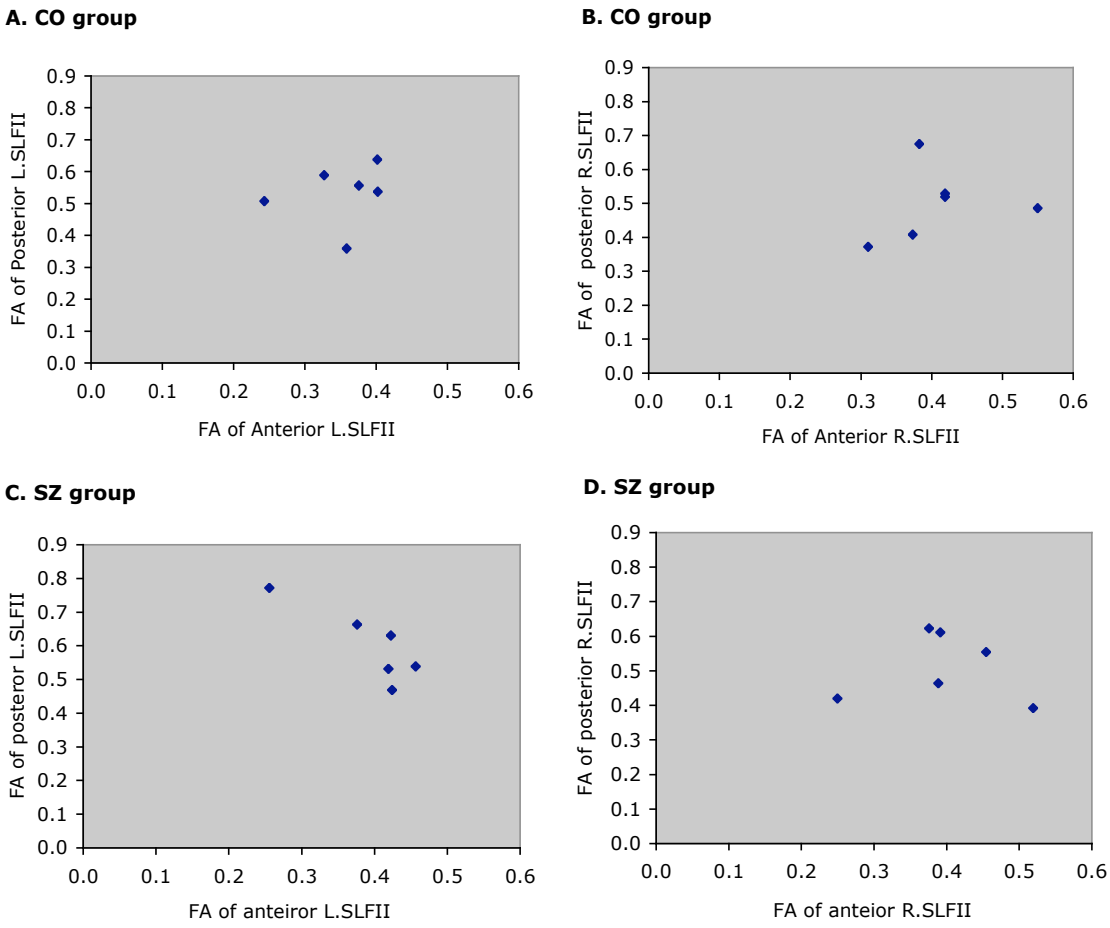

Figure 10. Scatter plot of FA in the right SLFII (R.SLFII) and the left SLFII (L.SLFII) in CO group (A and B) and SZ group (C and D). CO group showed positive association between the anterior and posterior parts of SLFII in both hemispheres. However, SZ showed negative association between the anterior and posterior parts of SLFII in both hemispheres.

A correlation analysis between FA values of anterior SLFII and posterior SLFII in each hemisphere was performed. In SZ group, a negative correlation between anterior and posterior parts of the left SLFII was found (FA, r=-.854, p<0.05). Although other

correlations were not significant, SZ group showed negative association between the anterior and posterior SLFII in both hemispheres whereas CO group showed positive association (see Figure 10).

Discussion

Experiment 3 examined whether SZ group showed different organization in the brain in relation to areas associated with spatial working memory. The SLF that connects the parietal cortex to the frontal cortex was compared between the two groups. A correlation analysis based on ROIs suggested that the SZ group might have different association between anterior and posterior SLFII compared to CO group. It is possible that this difference may contribute to the different pattern of activation in schizophrenia patients during spatial working memory task.

Although Experiment 3 proposed a possibility that the organization of SLF II in SZ group may be different from that of healthy individuals, this finding is preliminary and the interpretation of this finding is uncertain at best. First, the sample size of this study was small. Though a correlation analysis showed a pattern, it is possible that this difference may disappear with a larger sample size. Second, ROIs in this study were selected only from one slice. The SLFII is one of the major association fiber tracks that extends from the angular gyrus to the caudal-lateral prefrontal regions (Makris et al., 2004). Thus it is possible that limited ROIs in this study may not represent the entire characteristics of the SLFII in general. In addition, it is possible that the shape of the SLFII or the 'exact' position of the SLFII may differ between schizophrenia patients and healthy individuals. It has been reported that schizophrenia patients show shape

deformations in several areas of the brain (Csernansky, Schindler, Splinter, Wang, Gado, Selemon, Rastogi-Cruz, Posener, Thompson, & Miller, 2004; Falkai, Tepest, Honer, Dani, Ahle, Pfeiffer, Vogeley, Schulze, Rietschel, Cordes, Schonell, Gaebel, Kuhn, Maier, Traber, Block, Schild, & Schneider-Axmann, 2004; Frumin, Golland, Kikinis, Hirayasu, Salisbury, Hennen, Dickey, Anderson, Jolesz, Grimson, McCarley, & Shenton, 2002; Kim, Lee, Kim, Jang, Shin, Ha, Kim, Kim, Kwon, & Kim, 2005). If the SLF in schizophrenia patients is shaped differently from that in normal controls, the selection of ROIs in this study may not be the most appropriate way to examine the SLF.

This study examined the abnormal connectivity of the SLFII in schizophrenia patients. Although this finding is preliminary with a small sample size, it suggests that schizophrenia patients may have disrupted SLFII that connects the parietal lobe to the frontal lobe. Further studies are necessary to investigate whether schizophrenia patients show abnormal connectivity in SLF with a large sample size with a better way to define the ROIs.

General Discussion

CHAPTER V investigated the neural correlates of working memory in schizophrenia using fMRI, NIRS and DTI. In Experiment 1, the neural correlate of working memory in schizophrenia patients was examined using an event-related fMRI design. To control for the poor working memory performance of schizophrenia patients, only the correct responses were compared across groups. Schizophrenia patients did not show a clear pattern of lateralized activation in the prefrontal cortex during the spatial working memory task. Schizophrenia patients showed activation in the right and left

MFG during the maintenance of spatial information whereas normal controls showed activation only in the right MFG. Similar finding was also observed in the NIRS data. This finding suggests that simplistic accounts of hypofrontality or hyperfrontality in relation to working memory deficit in schizophrenia should be revised.

The bilateral pattern of activation observed in schizophrenia patients is consistent with previous data on the lack of asymmetry pattern in schizophrenia. The prevalence of left-handedness or mixed-handedness is much higher in schizophrenia patients compared to that in general population (Sommer, Ramsey, Kahn, Aleman, & Bouma, 2001). For hemispheric specialization related to information processing, schizophrenia patients do not show right hemisphere advantage for processing visuospatial information (Heckers et al., 2002; Nuechterlein et al., 1994; O'Donnell et al., 2002; Walter et al., 2003; Wynn et al., in press) nor left hemisphere advantage for processing verbal information (Gur, 1978; Walter et al., 2003). It has also been found that schizophrenia patients show anomalous cerebral asymmetry (e.g., Bilder et al., 1994; Chance, Esiri, & Crow, 2005; DeLisi et al., 1997). However, there is very little information available that can be used to discern whether schizophrenia patients have simply reduced asymmetry or reversed asymmetry. Studies combining behavioral tasks with brain imaging methods will help us unveil the functional and structural characteristic of the brain in schizophrenia (e.g., a brain imaging study using matched verbal and spatial working memory tasks).

Furthermore, it has been suggested that the organization of the brain in schizophrenia is altered anatomically (e.g., Burns et al., 2003; Kubicki et al., 2002a) or functionally (Ford, Mathalon, Whitfield, Faustman, & Roth, 2002; Peled, Geva, Kremen, Blankfeld, Esfandiarfard, & Nordahl, 2001; Schlosser, Gesierich, Kaufmann, Vucurevic,

Hunsche, Gawehn, & Stoeter, 2003; Schlosser, Gesierich, Kaufmann, Vucurevic, & Stoeter, 2003; Spencer, Nestor, Perlmutter, Niznikiewicz, Klump, Frumin, Shenton, & McCarley, 2004). The DTI data from Experiment 3 also suggest that there may be abnormal connectivity in the brains of schizophrenia patients. Reduced organization in the brain is also proposed to be associated with clinical characteristics of schizophrenia. Structural abnormalities may be associated with positive symptoms such as hallucinations (Hoffman & McGlashan, 1993, 1994) and disorganized symptom may be closely related to abnormal cortico-cortical connectivity (Phillips & Silverstein, 2003; Spencer et al., 2004). It is possible that abnormal connectivity may play a pivotal role in cognitive dysfunctions and clinical symptoms in schizophrenia. Further studies are needed to determine the relationship between abnormal connectivity in the brain, cognitive dysfunctions and the clinical characteristics of schizophrenia patients.

In summary, CHAPTER IV investigated the neural correlates of spatial working memory in schizophrenia using event-related fMRI, NIRS and DTI. In event-related fMRI and NIRS experiments, schizophrenia patients showed bilateral activation in the prefrontal cortex compared to healthy controls even though their performance level was equivalent. Its implication in relation to reduced cerebral asymmetry in schizophrenia patients was discussed. In addition, the possibility of abnormal connectivity in the brain in relation to working memory process was suggested in the DTI study. Finally the findings of NIRS study suggest that NIRS emerges as an alternative and viable brain imaging method for studying psychiatric population although the methodology of NIRS needs to be improved and refined.

CHAPTER VI

CONCLUSIONS

Working memory deficit may be a core feature of schizophrenia that cascades into a wide range of cognitive and social impairments; yet, our current understanding of the nature of this deficit is limited. The major goal of this dissertation was to expand our understanding of the etiology of working memory deficits in schizophrenia. The behavioral studies described in CHAPTER III and CHAPTER IV focused on elucidating the relationship between context processing and working memory in schizophrenia. The results from these experiments indicate that task-irrelevant contextual information facilitates working memory performance of schizophrenia patients whether the contextual information is embedded within the target or is provided by the spatial layout that surrounds the target. In CHAPER V, both functional and structural imaging experiments were conducted to examine the neural correlates of spatial working memory. It was observed using fMRI and NIRS that schizophrenia patients engage different areas of the brain during spatial working memory compared with normal controls. In addition, preliminary evidence concerning abnormal connectivity of the frontal and parietal cortices was obtained using the DTI method.

The results of the behavioral experiments open up an important debate concerning context processing and working memory deficit in schizophrenia. A current, dominant theory of schizophrenia proposed by Cohen and his colleagues states that the core deficit of schizophrenia is impaired context processing (e.g., Cohen et al., 1999; Cohen &

Servan-Schreiber, 1992). Their argument rests on the experimental results obtained with CPT-AX and Stroop tasks. In their framework, 'context' is closely tied to the task instruction that one must maintain in working memory. This definition of context, however, does not generalize to other paradigms (i.e., spatial memory) and is not clearly differentiated from that of working memory. What they have failed to do is to provide a clear definition of context in their theory. Unfortunately, the idea of 'context processing' has since become a convenient, catch-all phrase to describe all kinds of deficits in schizophrenia. However, unconstrained and loose definition of context does not help us understand the nature of the problems faced by schizophrenia patients. The findings from behavioral experiments suggest that schizophrenia patients are sensitive to task-irrelevant "context" information presented concurrently with or as an intrinsic feature of the target. Furthermore, when they are able to process or use contextual information, their working memory performance improves. The findings reported in this dissertation suggest that schizophrenia patients may have an intact ability to process certain types of context and therefore, it is rather inaccurate to characterize 'context processing' deficit as the fundamental core feature of schizophrenia as previously proposed. Thus, it is necessary to examine context processing in schizophrenia patients systematically because there are levels and types of context processing (Gorfein, 1987; Hemsley, 2005; Wickens, 1987).

Returning to the finding of normalized working memory performance in schizophrenia patients in contextual condition, it is of utmost importance to note the lack of success in pharmacologically treating working memory deficits. Yet, we observed reduced or remediated working memory deficits when the task condition enabled participants to use contextual information. Working memory deficits are found in a

majority of schizophrenia patients and lead to poor functional outcome (e.g., Green, 1996; Lee & Park, in press; Liddle, 2000). Therefore, any methods that lead to an improvement in working memory should be of interest to those working in treatment or outcome research. Recently, Silverstein and Wilkniss (2004) suggested that it is important to manipulate the stimulus and context structure in rehabilitative intervention. The results of this dissertation provide an empirical support for Silverstein and Wilkniss's hypothesis by showing that manipulating context structure ameliorated working memory deficits in schizophrenia patients. Future studies are needed to develop efficient methods and strategies that allow schizophrenia patients to use context information in rehabilitation program outside the laboratory. Overall, the results of the behavioral studies suggest a more dynamic picture of working memory deficit in schizophrenia that had previously been portrayed, and hint at the possibilities of remediation in the future.

The functional and structural brain imaging results also paint a dynamic picture of the neural correlates of working memory deficit that is neither a simple result of hypofrontality nor hyperfrontality but probably an outcome of a combination of recruitment of wider cortical network, altered connectivity between cortical areas, and altered cognitive strategies. The fMRI and NIRS results reported in CHAPTER V suggest that schizophrenia patients may recruit a different and wider network of areas to during working memory tasks compared with healthy controls. Interestingly, while normal controls show clear right hemispheric advantage for processing visuospatial information, schizophrenia patients tend to activate bilateral cortical areas for the same task. In addition, evidence for faulty encoding was discussed. Several possible explanations were presented, including reduced hemispheric asymmetry, right hemisphere deficit, use of

compensatory strategies and others. In relation to the results obtained in the behavioral experiments, it is important to note that using encoding strategies increases activation of the prefrontal cortex even though chunking or grouping may make the task easier (Bor, Duncan, Wiseman, & Owen, 2003). However, the neural correlates of the effect of context on working memory remain to be determined.

Lastly, there are several limitations and caveats. First, I intentionally chose to constrain the definition of "context" in order to understand the role of this specific type of context processing in working memory, but a limitation of this approach is that the effects of other types of context (e.g., temporal context, social context, etc) on working memory are still obscure to us. Though the findings clearly showed intact context processing in schizophrenia for this specific type of context, it does not mean that schizophrenia patients are able to process other types of context. Therefore, it is necessary to study the effects of other types of context on working memory systematically in the future.

Second, schizophrenia patients in these studies were chronic and clinically stable. They have also been taking atypical antipsychotic medication for a long period of time. The effects of atypical antipsychotic drugs on the frontal function and working memory are hotly debated. Although some have reported that risperidone improves verbal working memory (Green et al., 1997), others found that clozapine worsens working memory in the first a few weeks of administration (McGurk et al., 2005). However, the finding that the first episode patients healthy first degree relates of schizophrenia patients, and psychometrically-ascertained schizotypal participants show working memory deficits (e.g., Carter et al., 1996; Myles-Worsley & Park, 2002; Park et al., 1995a; Park et al.,

1995b), suggests that the effects of antipsychotic medication on working memory may not be the central factor. Even if the effects of antipsychotic medication on working memory are peripheral, we should still be mindful of the potential long-term consequences of administering potent dopamine and serotonergic drugs in the brain function. Future studies are needed to dissociate the consequences of atypical drug effects from intrinsic abnormalities of the brain in schizophrenia patients.

Third, the schizophrenia patients participated in studies included in this dissertation are chronic and relatively high functioning. It is not clear whether the results reported can be generalized to acutely psychotic patients. A related issue is the small sample size. Schizophrenia is a heterogeneous disorder, but with a relatively small number of patients it was not possible to examine working memory deficits of different subtypes of schizophrenia patients or to test for association among clinical symptoms and working memory performance.

Despite the importance of working memory deficits in the pathophysiology of schizophrenia, we do not yet understand what factors cause these deficits and how they may be ameliorated. The major goal of this dissertation is to move closer to elucidating the etiology of working memory deficits using both behavioral and brain imaging methods. While there are caveats, the results reported here clearly indicate that schizophrenia patients are able to process context, and working memory deficits can be partly remediated by manipulating contextual information. It is also clear that cortical activation pattern associated with working memory is altered in schizophrenia patients but it is not a simple matter of reduced activation. They recruit a larger, more bilateral network to support working memory. These findings provide a new perspective towards

understanding working memory deficit and context processing in schizophrenia.

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