Spatial Working Memory Function in Schizophrenia

Sohee Park and Junghee Lee

Brendan Maher loves mysteries of all kinds, and psychosis is one of the greatest unsolved mysteries of all ages. So it is not surprising that he is one of the creators of the field of experimental psychopathology, which provides the scientific framework for investigating the seemingly intractable world of schizophrenia. I was initiated into experimental psychopathology by Brendan during graduate school. He taught me directly and indirectly three essential principles that I have carried with me ever since. First, he emphasized the importance of looking for differences in patterns of behavior rather than a simple deficit. Patients with schizophrenia have deficits in a wide range of domains, so new interesting questions are how their patterns of behavior deviate from the normal range and whether pockets of better performance can be found. To answer these questions, one may need to search for the imperceptible clues in the background rather than the foreground. For example, it may be more informative to see what people do after they make errors rather than counting the errors themselves. The second Maher principle has to do with cognitive flexibility: See the forest rather than the trees most of the time, but do pay attention to the trees when the forest begins to move. I found this to be very useful advice not only for research but for all aspects of my life (and, I believe, would have been wise and have listened to Brendan). The third principle concerns generosity toward the next generation. Brendan was always the champion of the lost causes and lost students. In my own small ways, I have tried to follow his principles, and I have both succeeded and failed. However, even failures seem useful to me because I apply his first principle and see what happens after one fails at something. There just might be interesting data.

—Sohee Park

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inhibit irrelevant responses, may be understood in terms of the inability to use internal representations or working memory to guide behavior (Goldman-Rakic, 1987, 1991). Working memory is mediated by a circuitry involving the dorsolateral prefrontal system, and it has been argued that some of the most profound cognitive symptoms of schizophrenia can be attributed to a deficit in working memory (e.g., Goldman-Rakic, 1988). To investigate the nature of prefrontal deficits in schizophrenia, our laboratory adopted a theoretical framework of working memory (e.g., Baddeley, 1986; Roitblat, 1987) and developed cognitive methods comparable to those tasks used in lesion studies as tools for analyzing the functions of the frontal cortex.

The main question was whether patients with schizophrenia show deficits in behaviors that are guided by internal representations while sensory–motor functions involved in such behaviors remain intact. A series of studies was launched to address this question. In the following sections, we sketch a brief review of the frontal-lobe hypothesis of schizophrenia, followed by a review of cognitive and neuroanatomical models of working memory, before we present a summary of the spatial working memory studies in patients with schizophrenia, their first-degree relatives, and schizotypal individuals.

**Frontal-Lobe Dysfunction in Schizophrenia**

A 23-year-old male with acute onset of blunted affect, loosening of associations and auditory hallucinations presented to a tertiary care hospital. . . . The patient received a diagnosis of schizophrenia and treatment with haloperidol was started. . . . Examination led to a diagnosis of a ruptured cerebral aneurysm in the left frontal lobe. (Hall & Young, 1992, p. 1207)

Schizophrenia may be characterized by delusion and hallucinations, thought disorders, anergia, apathy, and flat or inappropriate affect, as well as more cognitive impairments, including concrete thinking, attentional deficit, and memory impairment. Neuropsychological testing of patients with schizophrenia typically yields symptom profiles that are similar to frontal- and temporal-lobe dysfunction but dissimilar to parietal-lobe disorders (e.g., Gur, Saykin, & Gur, 1991; Koh & Washah, 1983; Parcell et al., 1997). Conversely, patients with lesions in the frontal lobes tend to display anergia, inappropriate affect, and attentional and recall problems (Stuss & Benson, 1984) similar to those observed in a large proportion of patients with chronic schizophrenia.

Frontal-lobe lesions cause a disturbance of mnemonic activity, which often leads to inefficient recall (Stuss & Benson, 1984, 1985). Recognition memory is believed to be dependent on a neural circuitry that includes the hippocampus, amygdala, medial thalamus, and nucleus basalis, whereas effortful recall may involve the prefrontal cortex in addition to other cortical and subcortical systems (Bachevalier & Mishkin, 1986; Kowalska, Bachevalier, & Mishkin, 1991; Mishkin, 1957; Taylor, Saint-Cyr, & Lang, 1986). Patients with schizophrenia show relatively intact recognition memory coupled with impaired recall (e.g., Calev, 1984; Koh & Petersen, 1978). In addition, anergia in patients with schizophrenia is correlated with recall but not with recognition memory (Goldberg, Weinberger, Fluskin, Berman, & Podd, 1980).
Demonstrations of frontal-lobe deficits in schizophrenia have also been obtained from functional imaging studies. Medicated patients with schizophrenia do not show hyperfrontal regional cerebral blood flow (rCBF), typically manifested by control participants, which suggests that the frontal system in patients with schizophrenia may be hypofrontal at rest. In addition, hypofrontality seems to be specifically related to negative symptoms (Andreasen et al., 1992; Wolk et al., 1992). Hypofrontality and specific cognitive deficits are often associated. During the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1988), the rCBF to the dorsolateral prefrontal cortex (DLPFC) was significantly increased in normal controls but not in patients with schizophrenia (Sagawa et al., 1990; Weinberger, Berman, & Mawsky, 1988; Weinberger, Berman, & Zee, 1986). However, during a number matching task, which requires cognitive effort but is not mediated by the prefrontal cortex, there was no difference in rCBF pattern between normal controls and patients (Weinberger et al., 1988; Weinberger et al., 1986). During the Tower of Hanoi task (Lezak, 1996), which is also widely used to assess frontal functions, schizophrenic patients with negative symptoms (both drug-naive and chronic, medicated patients failed to show activation in the left medial frontal region, the same area that is specifically and significantly active in normal control participants performing the same task (Andreasen et al., 1992). These results substantiate the claim that the abnormal metabolic activity of the prefrontal cortex during a frontal-lobe-dependent task correlates with impaired performance (Berman, Mawsky, & Weinberger, 1988).

Structural abnormalities in the frontal cortex of patients with schizophrenia have also been observed (e.g., Benes, McSparron, Bird, Santi, & Vincent, 1991; Breier et al., 1992; Breier, Davis, Buchanan, Miledi, & Hunscher, 1993; Selemon, Rjakowska, & Goldman-Rakic, 1995), but the details of how these structural abnormalities affect behavior are only beginning to be expressed. Significant volume reductions in prefrontal and limbic white matter was observed in patients with schizophrenia (Breier et al., 1992), and prefrontal volume was associated with abnormal regulation of dopamine (Breier et al., 1992). Volume is a useful index, especially because it can be assessed in vivo, but microstructural factors—such as spatial arrangements of neurones, the proportion of different types of cells in the layers of the cortex, or the extent of myelination in different regions—are much more informative. In a postmortem study, B robber and his colleagues (1991) reported that the density of the small interneurons in Layer II is reduced in the prefrontal and the cingulate cortices of patients with schizophrenia, whereas the density of pyramidal cells in Layer V of the prefrontal cortex is increased in these patients. The density of the glial cells was not different from that of normal controls. Benes et al. suggested that a reduction of interneurons in Layer II may result in a partial loss of inhibitory processing within the particular neural circuits that are crucial for schizophrenia. In addition, recent morphometric studies of the DLPFC reveal a pathologic condition in the schizophrenic brain that is characterized by an abnormal neuronal connectivity (Rjakowska, Selemon, & Goldman-Rakic, 1998; Selemon, Rjakowska, & Goldman-Rakic, 1999, 1998). With application of the direct three-dimensional counting technique, normal density in Area 9 was calculated to be 17% higher in brains of patients with schizophrenia as compared with healthy controls, yet the cortical thickness was not significantly reduced (Selemon et al., 1995). Measurements made in Area 46 revealed a 21% increase in density of schizophrenic brains (Selemon-
et al., 1986). Such observations, coupled with longitudinal neurodevelopmental studies, cast shed much light on the emergence of schizophrenic symptoms during adolescence when the changes in the corticostriatal relays and synaptic pruning are the most dramatic.

Frontal-lobe deficit in patients with schizophrenia also has been demonstrated by a variety of cognitive experiments, especially those involving oculomotor control. Patients with lesions in the frontal lobes are unable to inhibit automatic but inappropriate saccades in an antisaccade task, in which participants are required to look away from the cue (Guitton, Buechle, & Douglas, 1985). Patients with schizophrenia show the same pattern of deficit in the antisaccade task (Clementz, McDowell, & Izsook, 1994, Fukushima et al., 1988). One of the reasons for their failure may be abnormal activity of the frontal cortex. Electrophysiological studies (Evokindis, Lennios, Constantinides, & Papageorgiou, 1996) as well as clinical studies (Guitton et al., 1985; Pierrot-Deseilligny, Rivaud, Gaynard, & Agid 1991) have suggested that efficient antisaccade task performance requires intact DLPPC function. A positron emission tomography (PET) study conducted by Nakashima and his colleagues (1993, 1994) demonstrated that the left DLPPC is hypoactive in patients with schizophrenia during tasks that require memory-guided or voluntary saccades. McDowell and Clementz (1997) suggested that the observed antisaccade deficit in patients with schizophrenia is related to a neuropathologic disturbance in the corticostriatal circuitry, particularly the DLPPC. In general, patients with schizophrenia seem unable to control initiation or production of saccades in a variety of eye-movement studies in the absence of simple motor deficit in the sacadic system (e.g., Clementz et al., 1994; Hommer, Clem, Lutman, & Pickar, 1991; Mehta & Frack, 1981; Pivik, 1979; Stark, 1983), and their performance on the sacadic task is correlated with impaired performance in several attention tasks (Ross et al., 1998) and on the WCST (Karevsky, Ventre-Dominioy, Vighetto, Dalery, & d'Amato, 1998; Park, 1997).

To summarize, the frontal system is important when novel, context-relevant responses are required to override existing, automatic motor schemas, and patients with schizophrenia may show impairments under such circumstances.

Models of Human Working Memory

Working memory may be conceptualized as a system for temporary maintenance of information so that the information can be used to guide behavior or be transferred to a knowledge storage system (Baddeley, 1986, 1992a, 1992b; Roitblat, 1987). Thus, working memory is "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, p. 34). In Baddeley's (1986) model of working memory, temporary maintenance of information is achieved by an active attention control system termed the central executive, aided by modality-specific subsystems: the phonological loop and the visuospatial sketchpad. The phonological loop can hold auditory, phonological information by means of rehearsal processes. The phonological loop works together with the central executive to maintain auditory information in working memory by means of subvocal rehearsal in real time. It has been typically investigated with a variety of repetition tasks such as the digit...
span, although word repetition may be a better task for assessing the phonological loop than the digit span (Gathercole & Baddeley, 1989). The visuospatial sketchpad maintains and manipulates visuospatial images. Thus, working memory is not a single, unitary system but has separable, functional components that can be systematically probed. Deployment of attentional resources, selection of control processes or strategies, and coordination of information flow from the subsystems are thought to be mediated by the central executive system.

The concept of the central executive is similar to Shallice's (1982; 1988) model of the supervisory attentional system, which accounts for deficits shown by patients with bilateral frontal lesions. The supervisory attentional system operates when controlled processing is required to override habitual, automatic, routine processes or motor programs. A good example is the antisaccade task, which requires the suppression of one's automatic tendency to look toward a target and instead to look away from it (Guitton et al., 1985). Automatic processes arise as the result of extended practice on a task; but once a skill has been mastered (or a motor program formed), they do not make demands on the central processing capacity and hence they can be carried out in parallel (Shiffrin & Schneider, 1977). In contrast, controlled processing makes heavy demands on the central processing capacity. The supervisory attentional system monitors the internal and external context and controls the outputs of independent, schema-like subsystem modules that oversee routine responses (automatic processes). Such a system is flexible and can respond efficiently to changing environmental demands.

Frontal-lobe damage leads to behaviors that are characterized by excessive distractibility, perseveration, and a severe lack of planning. Without the central executive or the supervisory attentional system, behaviors tend to become stereotypic, perseverative, and inexcusable in the context; this is observed in a large proportion of patients with bilateral frontal lesions. Patients with frontal-lobe lesions, whether left, right, or bilateral, show deficits in tasks that require working memory (e.g., Freedman & Oscar-Berman, 1966; Levinson-Atan, Zoder, Libet, Elyberg, & Nelson, 1972). Although the extensive connectivity and the heterogeneity of the frontal system pose challenges to empirical study of the central executive, the question of capacity limit has been investigated with fruitful results, especially in relation to reading processes (see Just & Carpenter, 1992). Otherwise, most investigators have focused on either visuospatial or verbal working memory, thereby avoiding the issue of executive control to some extent. It may well be that what is thought of as the central executive is a manifestation of the general property of the neural network system that mediates working memory rather than a separate functional system within a sequential hierarchy of information processing.

Neuroanatomical correlates of working memory in healthy humans have been observed by means of PET and functional magnetic resonance imaging (fMRI), using a variety of tasks. Overall, the results point to the important role of the prefrontal cortex in working memory but, depending on the exact task (e.g., verbal or spatial), different areas within the prefrontal region are activated. Therefore, it may be useful to parse different functional components within the visuospatial working memory.

A spatial working memory task (deciding whether a probe circle marks the location of a previously presented target after a delay period) increased the activity of the right hemisphere inferior frontal (Area 47), posterior parietal, occipital, and
premotor areas in a PET study (Jonides et al., 1993). However, during a different spatial working memory task that required participants to note whether any stimuli presented in a sequence occupied the same location, the right middle frontal gyrus (including Brodmann's Area 46) was strongly activated (McCarthy et al., 1994). The disparity between the two results may be due to the different cognitive components required to perform these tasks. Jonides et al.'s (1993) task did not have intervening stimuli between the target presentation and response stage; whereas McCarthy et al.'s (1994) did. Therefore, depending on the exact structure of the task, the prefrontal system plus other cortical and subcortical areas are implicated in working memory.

Verbal or auditory working memory also increases activation of the prefrontal cortex. The mid-DLPC (including Brodmann's Areas 9 and 46) was also bilaterally activated during a nonspatial working memory task that required participants to maintain a sequence of numbers, whether self-ordered or externally generated (Petrides, Alivisatos, Meyer, & Evans, 1989). A very different verbal working memory task, which heavily taps the verbal articulatory loop, activated more posterior areas, including the supramarginal gyrus and Broca's area (Pauluss, Frith, & Frackowiak, 1993). In addition, a recent study showed a pronounced activation in the left inferior frontal gyrus (Brodmann's Areas 44, and 45) when a tone serial position task was used (Stevens, Goldman-Rakic, Gore, Pulbright, & Wexler, 1998).

The tasks used to probe spatial working memory are most often visual rather than auditory or haptic. Analogous to visual information processing, there is a dissociation between pattern-based, visual working memory and spatial working memory, both in humans (Suddley & Lusberman, 1986; Farah, 1986) and in monkeys (Bachevalier & Mishkin, 1986; Rokasaka et al., 1991; Wilson, Scalaidhe, & Goldman-Rakic, 1993). Ungerleider, Courtenay, and Hazlby (1986) showed that visual working memory, as assessed by a face-matching task, activated a region in the right inferior frontal cortex, whereas spatial working memory, as assessed by a location-matching task, activated the superior frontal region.

Maintenance of visuospatial information in working memory can be disrupted by either spatial or visual distractors and probably involves a complex network of cortical and subcortical areas (e.g., Jonides et al., 1993). Patients with schizophrenia are able to perform well in tasks involving the visuospatial sketchpad, but they show deficits if the task requires processing of semantics in addition to visuospatial imagery (David & Cutting, 1990).

Pharmacological investigations have shown that the dopamine system plays an important role in working memory. Also, it is important to note that there is a high density of D1 receptors compared with D2 receptors in the prefrontal cortex, and this density is altered in patients with schizophrenia (Goldman-Rakic, 1999). In rhesus monkeys, local injections of dopamine D1 antagonists can either disrupt working memory performance at high doses (Sawaguchi & Goldman-Rakic, 1991) or selectively facilitate the "memory fields" of prefrontal neurons at low levels (Williams & Goldman-Rakic, 1995). Castner, Williams, and Goldman-Rakic (1995) found that chronic haloperidol treatment can induce working memory impairment and that these impairments can be reversed by short-term D1 stimulation in monkeys. The effects of dopamine agonists on working memory in humans are still not clearly understood, but there have been reports of enhanced working memory following...
dopamine agoniststrate. Bromocriptin, a dopamine agonist, improved working memory performance in healthy human participants (Luria, Depe, Arbor, & Leon, 1992). Kerrase and her colleagues (2000) showed that amphetamine, which releases monoamines—particularly dopamine and norepinephrine—increases their reuptake, improved the performance on visuospatial working memory tasks as well as negative symptoms of patients with schizophrenia spectrum disorders. Further characterization of dopamine receptors in the prefrontal cortex and pharmacotherapy research should lead to additional insights on the neuropharmacology of cognition as well as the development of new antipsychotic drugs with fewer side effects (Rupnik & Iversen, 1993).

The study just discussed identify the prefrontal cortex, especially the DLPFC, as a critical element in a neural system that uses working memory to hold specific items of spatial or verbal information online. However, it is important to note that the neural system that supports working memory capacity does not reside within the prefrontal cortex but extends beyond it to involve and require interactions with other cortical and subcortical areas (Collette et al., 1999). Among these are the posterior parietal cortex, the inferotemporal cortex, the cingulate gyrus, and the hippocampal formation, which are connected with the DLPFC (Caudo & Goldman, 1982a, 1982b, Petrides & Pandya, 1984; Selemon & Goldman-Rakic, 1985; Stanton, Bruce, & Goldberg, 1990). Using fMRI, Zarahn, Aguirre, and D'Esposito (1999) showed that functional changes attributable to the retention delay of a spatial working memory task were detected in the DLPFC as well as in the right frontal eye field and in the superior parietal lobule. An fMRI study of a verbal working memory task revealed significant activations in a number of cerebral regions, including the mid-dorsolateral frontal cortex, inferior frontal gyrus, supramarginal gyrus, and cerebellum (De Zubicaray et al., 1998).

Many neuroimaging studies of patients with schizophrenia performing working memory tasks have demonstrated task-related hyperactivity (e.g., Callicott et al., 1999; Weinberger & Berman, 1996). Compared with normal controls, patients with schizophrenia show a relative physiological hyperactivity of the prefrontal cortex. Ganguli et al. (1997) reported that patients performed worse than normal controls on the verbal working memory tasks and that they had smaller increases in rCBF than controls in frontal and superior temporal cortical regions bilaterally. However, a simple hyperactivity hypothesis cannot account for more recent imaging data. In two recent studies of working memory, the activation of the right DLPFC in patients with schizophrenia was as robust as that in normal participants, and the activation in the left DLPFC was greater in patients with schizophrenia. In addition, the basal ganglia activity during working memory performance in patients with schizophrenia was greater than in controls (Manoach et al., 1999, 2000; see also chap. 13, this volume).

These contrasting results suggest that several additional factors, such as the task demand and the manipulation of task parameters, must be considered when evaluating the activation patterns in the prefrontal cortices of patients with schizophrenia versus normal controls. For example, reward or reinforcement might enhance DLPFC activation. DLPFC neurons involved in a spatial delayed-response task in monkeys show enhanced activity during delay periods when a preferred reward is anticipated than when it is not (Watanabe, 1996). To understand in depth the neuroanatomical correlates of working memory and the pathophysiology of schizophrenia.
nia, one must consider the neural network properties as well as the specific brain systems.

Neural Correlates of Working Memory in Animals

In animals, spatial working memory has been studied most often with the delayed-response paradigm. A prototypical delayed-response task involves presentations of a stimulus, followed by a short delay period and the subsequent presentation of a set of alternative choices. Much is known about the role of the DLPPC in working memory function and its regulation of higher cognitive function in rhesus monkeys (see Goldman-Rakic, 1987, 1991). The ability to perform delayed-response tasks is destroyed by lesions in the DLPPC (e.g., Blum, 1953; Funahashi, Bruce, & Goldman-Rakic, 1989, 1990, 1993; Jacobsen, 1985, Mishkin, 1977). Specifically, the principal sulcus (Area 46) is thought to mediate spatial working memory, because neurons in this area are involved in maintenance of spatial information over time (Funahashi et al., 1989, 1990, 1993; Goldman-Rakic, 1987). For example, when a stimulus to a target is delayed, the neurons in the principal sulcus increase and maintain firing during the delay period, but as soon as the response is made, the firing decreases rapidly. The spatial property of the principal sulcus neurons extends to more than one sensory modality. Lesions in principal sulcus neurons impair memory-guided manual and eye movements (Funahashi et al., 1989, 1990, 1993), in contrast to frontal eye field lesions, which impair delayed eye movements but not hand movements (Deng et al., 1984). Both the principal sulcus and the frontal eye field receive parallel projections from the posterior parietal areas (Cavada & Goldman-Rakic, 1985, 1989a, 1989b), but the frontal eye field projects to areas involved in producing eye movements, whereas the principal sulcus projects less restrictively, influencing manual responses as well as eye movements. In addition, the principal sulcus neurons are involved in the shifting of visual attention (Suzuki & Aruama, 1983), which is also an important function of the central executive.

Spatial information and nonspatial, object information seem to be processed by separate neuroanatomical systems within the frontal cortex of monkeys. dissociation of spatial and object delayed-response performances has been observed in rhesus monkeys (Oscar-Berman, 1975) and in humans (Freedman & Oscar-Berman, 1985). Spatial delayed-response performance is disrupted by lesions in the DLPPC, but object delayed response may be mediated by the orbitofrontal system. Wilson et al. (1993) demonstrated that spatial working memory is mediated by the principal sulcus region, whereas object working memory is mediated by the inferior convexity, ventrolateral to the principal sulcus. However, recordings made in monkeys during a task that required maintenance of both "what" and "where" information revealed that more than half of the neurons with delay activity showed both "what" and "where" tuning (Rao, Rainer, & Miller, 1997). This suggests that object and spatial domains of processing within the prefrontal cortex may not be strictly segregated.

To summarize, a review of the discoveries in neuropsychology, neuroanatomy, neurophysiology, and psychopathology yields a recurrent theme: The prefrontal cortex is crucial when representationally guided behavior is required. Some of the cardinal symptoms of schizophrenia have been attributed to dysfunctions in frontal systems.
Spatial Working Memory Studies in Patients With Schizophrenia

The knowledge that prefrontal lesions in humans and primates lead to behavioral deficits that closely resemble some cognitive deficits of people with schizophrenia, motivated a series of experiments that are comparable to the animal lesion studies and human neuropsychological studies of prefrontal functions. If patients with schizophrenia display behavioral deficits similar to those shown by lesioned animals and humans, then one might be able to postulate possible prefrontal areas or systems that may be dysfunctional in schizophrenia. Therefore, Park and colleagues tested the hypothesis that patients with schizophrenia are impaired on spatial working memory tasks. The specific questions addressed were as follows:

1. Is there a genuine working memory deficit that is clearly not due to any motor problems? If the problem is a basic motor deficit, then the role of the prefrontal cortex is minimized.
2. If a working memory deficit is present, how general is it? Is it confined to only one sensory modality (e.g., the oculomotor system), or is it a general spatial problem?
3. What is the relationship between the prefrontal dysfunctions and the smooth-pursuit eye tracking deficit, which has been suggested to be a possible biological marker for schizophrenia (e.g., see Holzman, 1987)?
4. Do individuals at risk for schizophrenia also show similar behavioral patterns?

Spatial Working Memory Deficits in Patients With Schizophrenia

In a study of inpatients with schizophrenia, spatial working memory function was assessed by an oculomotor delayed-response paradigm used in neuropsychological studies (Park & Holzman, 1992, 1993). The basic task consisted of flashing a target briefly in the periphery of the participant's visual field, followed by a delay period, after which participants were required to move their eyes to the remembered position of the target (see Figure 5.1 for an illustration of the procedure). To control for the possibility that patients with schizophrenia might have problems in making any eye movements, Park and Holzman also included a sensory-control task was. The sensory task required participants to move their eyes to the target itself. Through a comparison of the two tasks, the motor component may be separated from the working memory component.

Park and Holzman (1992) found that patients with schizophrenia were impaired on the working memory task but not on the sensory-control task, indicating that the patients were able to move their eyes to a visible target but not to a remembered target. Patients with schizophrenia made more errors, and their reaction times were slower, compared with bipolar patients and normal controls. Patients with schizophrenia also made more perseverative errors and hemifield errors. Matched bipolar inpatients and normal control participants were unimpaired. These results have been replicated by many groups since 1992 (e.g., Carter et al., 1996; Fleming et al., 1997; Gouding & Tallent, 2002; Karatekin & Asarnow, 1998; Koo et al., 1995, 1997; Spindler et al., 1997; Spitter, 1993).
One important question is whether the deficit shown on the oculomotor delayed-response task by patients with schizophrenia is a problem of working memory or if it is a deficit confined to the oculomotor system itself. If it is a genuine working memory deficit, then one should be able to detect it independent of the sensory modality of the task. To address this question, Park and Holzman (1992) conducted a haptic delayed-response task with the same participants. The haptic delayed-response task was essentially identical to the oculomotor delayed-response task in design and procedure, but in this case spatial working memory was tested in a nonvisual...
domain (see Figure 5.2). Blindfolded participants were required to move their hands to the remembered position of the target they had touched. In the haptic delayed-response task, all participants were accurate when no memory was required (i.e.,

**Explore with hand to find the target**

*Participant is blindfolded*

**Delay Period**

*Participant places finger at the fixation point*

**Response Stage**

*Participant moves finger to the remembered position of the target*

![Diagram](attachment:image.png)

**Figure 5.2.** Haptic delayed-response task.
they were able to move their fingers to the target position with or without vision), but patients with schizophrenia were severely impaired when they were required to make memory-guided hand movements. Patients with schizophrenia also made more perseverative errors. Bipolar and normal participants performed accurately on the haptic working memory task.

When the delayed-response task was conducted in the oculomotor domain or in the haptic domain, the sensory-control task and the memory task were identical, except for one component: the guidance of response by internal representation. The addition of the working memory component severely affected the patients with schizophrenia, but did not significantly affect the performance of the control groups. Therefore, the deficits observed in the oculomotor and the haptic delayed-response tasks are likely to be due to a working memory deficit rather than to a simple motor problem of the eye or the hand.

Is this working memory deficit a reflection of generalized cognitive deficit in all domains? It seems unlikely, because in Park and Holzman's (1992) study all participants were matched on IQ and education level. In addition, the three groups performed equally on the digit span task, which suggests that the verbal articulatory loop was intact in these schizophrenia patients. Although the digit span task is not equivalent to the oculomotor memory task in complexity and difficulty, it is commonly used to assess simple verbal working memory (Villa, Guinnot, De Bonis, & Marras, 1990). Patients with schizophrenia did not differ from bipolar patients and normal controls on the digit span task. They were able to repeat seven digits forward and five digits backward. In this study, patients with schizophrenia were able to attend to a task, and they were able to maintain simple verbal information. Thus, it is unlikely that the spatial working memory deficit in patients with schizophrenia is due to a global, generalized deficit.

There was also some evidence of frontal-limb dysfunction in patients with schizophrenia (Park, 1999). In this study, patients with schizophrenia were impaired on the WCST, which is widely used to assess prefrontal function, and the correlation between working memory and WCST performance was significant (Park, 1999). However, they were not impaired on all neuropsychological tests of frontal function. These patients performed within the normal range on the Verbal Fluency Task (see Letzkus, 1995), which taps another aspect of frontal function (Park, 1991). The Verbal Fluency Task is associated with medial frontal function and is suggested to involve more left-hemispheric function. These results are consistent with the results of a recent study (Shnit, Curtis, Zaid, Karacoc, & Lacono, 1999) in which spatial working memory impairment was related to fewer categories on the WCST but not to the measures of general cognitive functioning.

In a subsequent study, outpatients in partial remission were tested on the same oculomotor delayed response tasks, and their smooth-pursuit eye tracking was also assessed (Park & Holzman, 1993). Smooth-pursuit eye tracking performance of patients with schizophrenia has been studied extensively in the past 30 years. A majority of patients with schizophrenia, and about half of their first-degree relatives, are unable to track a smoothly moving target, such as a pendulum, with their eyes (Holzman, 1987; Holzman, Proctor, & Hughes, 1973; Holzman et al., 1974; Keefe et al., 1997; Levy et al., 1983). Normal participants can match their eye velocity to the target. Velocity is almost perfectly smooth and no tremor is present. Patients with schizophrenia tend to have poor gain (ratio of eye velocity to target velocity) and...
generate numerous saccades during smooth-pursuit tracking. This deficit has been suggested to stem from the dysfunction of the fronto-striatal system (Loevin, 1986a, 1984b) and is hypothesized to be a possible biological marker for schizophrenia (see Holz-

Outpatients with schizophrenia showed deficits in working memory, but out-
patients with bipolar disorder, and normal control participants, were unimpaired
(Park & Holzman, 1993). Thus, working memory deficits seem to be present in
patients with schizophrenia regardless of illness state, whereas bipolar patients
preserve intact working memory. In a recent study of spatial working memory in
floridly psychotic schizophrenic inpatients, Park, Puschel, Sauter, Rentech, and
Bell (1999) tracked the same patients for 4 months until they were in partial remis-
sion and functioning relatively well in the outside world. Spatial working memory
deficits were present during the acute, psychotic state and at the follow-up when
they were outpatients. These results suggest that clinical symptoms may come and
go but that the spatial working memory deficit, like the eye tracking deficit, might
always be present.

Spatial working memory deficit and smooth-pursuit eye-movement dysfunction
were associated in patients with schizophrenia (Park & Holzman, 1995; Snell et al.,
1999). Both tasks are suggested to be mediated by the prefrontal system, and eye
tracking dysfunction is present in about half of the first-degree relatives of patients
with schizophrenia.

Relatives of Patients With Schizophrenia

Park, Holzman, and Goldman-Rakic (1995) examined whether working memory is
impaired in a sample of first-degree relatives of patients with schizophrenia. They
predicted that, as a group, relatives would perform better on a working memory task
than the patients with schizophrenia but worse than the normal controls, inasmuch
as the relatives as a group presumably include not only individuals who are free of
any psychiatric dysfunctions but also a subgroup of those who do show psychological
and biological dysfunctions, as was found for eye tracking.

Park, Holzman, and Goldman-Rakic (1995) conducted two experiments to test
this hypothesis. In Experiment 1, participants completed the oculomotor delayed-
response task. For Experiment 2, the authors recruited a new group of participants,
who completed a visual-manual delayed-response task (see Figure 8.3). If the working
memory deficit is present in some of the first-degree relatives of patients with
schizophrenia, then it should be able to be detected, regardless of the response mo-
dality of the delayed response.

Relatives of patients with schizophrenia showed significant deficits in working
memory in both the oculomotor and visual-manual delayed-response tasks
compared with the normal control participants (Park, Holzman, & Goldman-Rakic,
1995). The relatives of patients with schizophrenia were not ill, and they were medica-
tion free, yet about half of them showed a working memory deficit. The results
suggest that some relatives of patients with schizophrenia are impaired on tasks
that implicate the prefrontal system, and that the delayed-response paradigm, re-
gardless of modality, may prove to be useful in detecting the schizophrenia pheno-
type. This finding has been replicated by Myles-Worsley and Park (in press) in the
Figure 5.3. Visual manual delayed-response tasks.

first-degree relatives in Palau Micronesia, where the prevalence of schizophrenia is double the worldwide rate.

The association of eye tracking dysfunction and working memory deficit observed in patients with schizophrenia were also present in the first-degree relatives of patients with schizophrenia. Relatives with normal eye tracking tended to be unimpaired on the delayed-response tasks, whereas relatives with abnormal eye tracking showed deficits in working memory (Park, Holman, & Levy, 1993). Working memory abnormalities in relatives of patients with schizophrenia reach beyond the spatial domain. Farnate et al. (1999) showed that the nonpsychotic relatives of patients with schizophrenia have deficits in object working memory as
well as spatial working memory. Verbal working memory dysfunction has also been reported in the relatives of patients with schizophrenia (Conklin, Curtis, Fattarossi, & Inoue, 2005). These results from the first-degree relatives of patients with schizophrenia suggest that spatial and other working memory dysfunction may turn out to be another behavioral marker, as an aid not only in demonstrating the pathophysiology of schizophrenia but also in characterizing the multidimensional aspects of the schizophrenia phenotype.

Spatial Working Memory in Relation to Schizotypy

Hypothetically, "psychosis-prone" individuals (Chapman & Chapman, 1985) within general population may carry a latent liability for schizophrenia, although they may never become ill (Lentenweber & Lenzenweiger, 1990a, 1990b; Mehl, 1990). Schizotypic individuals identified by various personality inventories show while deficits in sustained attention (Lenzenweiger, Cornblatt, & Paris, 1991; cognitive inhibition (Beech & Claridge, 1987; Park, Lentenweiger, Puchel, & Holzman, 1988); the WCST (Goring, Kwapi, & Talent, 1999; Lentenweiger & Korine, 1994); and oculomotor tasks, including antisaccadic and smooth-pursuit tasks (O'Tuathail, Lentenweiger, & Holzman, 1988), in the absence of any psychiatric illness. Thus, some features of schizophrenia seem to be present, albeit in a very subtle form, in the general population, and these traits may indicate a predisposition to the illness.

Park, Holzman, and Lenzenweiger (1998) examined the working memory function of undergraduate students at Cornell University. The students were assessed with a personality inventory that tapped experiences of perceptual alterations. The question was whether normally functioning young adults who score high on the Perceptual Alteration Scale (Chapman, Chapman, & Raulin, 1978) show working memory deficits. The WCST was also administered to assess perseverative tendencies and the ability to maintain conceptual set. On the WCST, the authors focused on the Failure to Maintain Set subscale, which has been shown to differentiate schizotypy individuals from normal controls (Lentenweiger & Korine, 1994; Lyvers, Merla, Young, & Kremen, 1991).

Schizotypic participants performed less accurately compared with the normal controls on the working memory task, and schizotypic participants were seven times more likely than normal controls to be impaired. There were no group differences in the number of perseverative errors or the number of categories achieved on the WCST, but schizotypic participants were less able to maintain set than were the control participants. The Failure to Maintain Set score was significantly correlated with the accuracy of working memory; participants who made more errors on the working memory task were less able to maintain set during the WCST.

However, one could argue that these schizotypic participants were recruited on the basis of perceptual alteration and that therefore they may not represent the whole range of schizotypy personality. In a later study, Park and McGee (1997) recruited healthy schizotypic participants on the basis of their scores on the Schizotypy Personality Questionnaire (Ryan, 1991), which taps the nine syndromes of schizotypy personality disorder as described in the Diagnostic and Statistical Manual of Mental Disorders (3rd ed., rev.; American Psychiatric Association, 1987). Schizotypic participants showed deficits in spatial working memory; moreover, the
subscale that tapped an absence of close social relationships correlated significantly with reduced working memory performance. Talien and Codding (1999) also showed that psychosis-prone individuals with social-interpersonal abnormalities as well as with cognitive-perceptual distortions display subtle spatial working memory impairments and that these impairments are associated with poor performance on the CST.

These results suggest that there may be subtle abnormalities in the functioning of the frontal system in a subgroup of schizotypic individuals who may carry a latent liability for schizophrenia (see Holzman et al., 1985). One important future direction of research in neurodevelopmental studies of working memory during adolescence, in relation to psychopathology in high-risk groups.

**Components of Spatial Working Memory Deficit**

Patients with schizophrenia perform less accurately than normal control participants on delayed-response tasks, regardless of the sensorimotor modality, but it is not clear why they fail on such a simple task. A componential analysis of the delayed-response performance in patients with schizophrenia indicates that there are many processes that are responsible for their poor performance (Park, Holzman, & Goldman-Rakic, 1996; Park, Holzman, & Lenzenweger, 1995; Park & O'Driscoll, 1996). Successful performance on the delayed-response task depends partly on being able to maintain target representation during the delay period as well as inhibition of irrelevant stimuli and initiation of appropriate motor responses. Failure to facilitate any of these hypothetical components may lead to an overall deficit. In monkeys, maintenance of the target position during the delay period may be disrupted by electrocortical stimulation (Stamm, 1985). If the cell activity is interrupted or discontinued in the principal sulcus, monkeys forget the target position in the oculomotor delayed-response task (Funahashi et al., 1989, 1990). In patients with schizophrenia or their relatives, it is not known what neurophysiological processes are responsible for maintaining the target representation during the delay.

Do patients with schizophrenia have problems maintaining mental representation during the delay period? Does “hypofrontality” of patients with schizophrenia (e.g., Andreasen et al., 1992; Ingvar, 1985; Ingvar & Franzen, 1974; Nakashima et al., 1994) imply inefficient or decreased activity of the frontal area? What might cause decreased activity of the neurons in the prefrontal cortex during the delay? Experimental manipulations with dopamine show that, at high concentrations, a dopamine D1 antagonist injected into the prefrontal cortex disrupts the oculomotor delayed-response performance in rhesus monkeys (Sawaguchi & Goldman-Rakic, 1991); on the other hand, however, at low concentrations D1 antagonists facilitate working memory performance (Williams & Goldman-Rakic, 1990). Neural network simulation of the frontal cortex also indicates that context-relevant processing may depend on dopamine (Cohen & Servan-Schreiber, 1991). However, the interactions of dopamine with other neurotransmitter systems (e.g., GABA, 5-HT, glutamate, acetylcholine, and norepinephrine) and hormones (e.g., estradiol, cortisol) must also be specified.

Careful examination of errors elicited during the delayed-response task shows that maintenance of representation is not the only reason for making a mistake.
What if the representation were maintained during the delay, but at the response stage one made a wrong eye movement or a hand movement? Such an error can be corrected. All errors were examined to see whether subsequent attempts to correct the mistakes were successful (Park, 1996; Park & O'Driscoll, 1996). The majority of errors made by normal and bipolar participants are such corrected errors. Patients with schizophrenia also correct more than half of their errors. Kruppmann and Everling (1998) have also reported that patients with schizophrenia generate corrective saccades in the memory-guided delayed-response task. On the other hand, patients with schizophrenia also make a significant number of errors that are never corrected, which is extremely rare in normal and bipolar participants (see Figure S.4). If the participants lost the representation of the target during the delay, and that was why they made an error, then any subsequent attempts to correct errors would result in random choices. Hence, patients with schizophrenia do seem to have problems with maintenance of representation during the delay as well as with initiating correct movements and inhibiting incorrect ones at the response stage.

Park and Holzman (1995) found an association of eye tracking performance and working memory in patients with schizophrenia. Closer examination of the patients' errors revealed that eye tracking is associated with the errors that are never corrected (Park & O'Driscoll, 1996). Patients with good eye tracking ability tend to correct their errors, whereas those with impaired eye tracking tend to make never-corrected errors. On the other hand, the number of errors that were corrected after one unsuccessful guess was not associated with eye tracking. Therefore, what may differentiate patients with schizophrenia from bipolar and normal participants, apart from the sheer number of errors, is how these errors arise. All participants

![Figure 5.4](image)

**Figure 5.4.** Frequency (freq.) of never-corrected errors per participant.
seem susceptible to making errors due to competing response tendencies at the response stage, but only patients with schizophrenia seem to lose the spatial representation. This tendency is also seen in schizotypic individuals, although the effect is small (see Figure 5.4).

Examination of the never-corrected errors also revealed a hemispheric asymmetry in the spatial working memory deficit, which is not apparent with the total number of errors. Patients with schizophrenia and schizotypic participants make a greater number of never-corrected errors when the target is presented to the right visual field (i.e., left hemisphere) than when the target is presented to the left visual field. Normal controls do not show such asymmetry (Park, 1999).

The question still remains as to why patients with schizophrenia are impaired in maintenance of representation during the delay period of the spatial working memory task, in the absence of generalized, global memory deficit. One exciting possibility for future research lies in functional-imaging techniques. Using the event-related fMRI design, it will be possible to observe activity of the network of cortical areas that are involved in mediating the maintenance of representation during the delay period of the working memory task in patients with schizophrenia. In addition, to neuroimaging studies, we are currently examining the effects of spatial and temporal distractors in working memory errors to determine when patients with schizophrenia are most vulnerable to disruptions in working memory processes.

It is likely that some of the major cognitive symptoms of patients with schizophrenia reflect a prefrontal dysfunction that manifests itself as a problem in the integrity of the working memory, but ultimately the results from working memory studies must be interpreted in relation to the actual clinical symptoms of schizophrenia. Carter et al. (1996) reported that spatial working memory deficit and negative symptoms are significantly correlated. Although our data also suggest an association of negative symptoms and working memory deficit at certain times during illness (Park et al., 1999); these results are likely to represent the very tip of the iceberg. To move beyond the realm of correlations one must also begin to specify mediating processes and mechanisms. The potential power of simple, cognitive tools, such as the delayed-response paradigm, in concert with advances in neuroimaging and neurophysiological techniques, will enable us to systematically investigate the pathophysiology of the phenotype of schizophrenia.

References


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