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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 intangible 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; the more interesting questions are *how* their patterns of behavior diverge 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 Macbeth would have been wiser had he 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

This chapter focuses on a subset of cognitive deficits displayed by patients with schizophrenia that closely resembles dysfunctions of the prefrontal cortex. Deficits of executive functions, such as distractibility, perseveration, and an inability to

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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, 1991). 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, looseness of associations and auditory hallucinations presented to a tertiary care hospital. . . . The patient received a diagnosis of schizophreniform disorder and treatment with haloperidol was started. . . . Examination led to detection 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 recall 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; Kolb & Wishaw, 1983; Pantelis 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 mnestic 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, Pliskin, Berman, & Podd, 1989).

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 hypoactive at resting state. In addition, hypofrontality seems to be specifically related to negative symptoms (Andreasen et al., 1992; Wolkin et al., 1992). Hypofrontality and specific cognitive deficits are often associated. During the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtis, 1993), 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, & Illowsky, 1988; Weinberger, Berman, & Zec, 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; Wenberger et al., 1986). During the Tower of Hanoi task (Lezak, 1995), 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, Illowsky, & Weinberger, 1988).

Structural abnormalities in the frontal cortex of patients with schizophrenia have also been observed (e.g., Benes, McSparren, Bird, SanGiovanni, & Vincent, 1991; Breier et al., 1992; Breier, Davis, Buchanan, Moricle, & Munson, 1993; Selemon, Rajkowska, & Goldman-Rakic, 1995), but the details of how these structural abnormalities affect behavior are only beginning to be expressed. Significant volume reduction 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., 1993). Volume is a useful index, especially because it can be assessed *in vivo*, but microstructural factors—such as spatial arrangements of neurons, 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, Benes and her 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 (Rajkowska, Selemon, & Goldman-Rakic, 1998; Selemon, Rajkowska, & Goldman-Rakic, 1995, 1998). With application of the direct three-dimensional counting technique, neuronal 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., 1998). Such observations, coupled with longitudinal neurodevelopmental studies, could shed much light on the emergence of schizophrenic symptoms during adolescence when the changes in the corticolimbic 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, Buchtel, & Douglas, 1985). Patients with schizophrenia show the same pattern of deficit in the antisaccade task (Clementz, McDowell, & Zisook, 1994; Fukushima et al., 1988). One of the reasons for their failure may be abnormal activity of the frontal cortex. Electrophysiological studies (Evdokimidis, Liakopoulos, Constantinidis, & Papageorgiou, 1996) as well as clinical studies (Guitton et al., 1985; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991) have suggested that efficient antisaccade task performance requires intact DLPFC function. A positron emission tomography (PET) study conducted by Nakashima and his colleagues (1993, 1994) demonstrated that the left DLPFC is hypoactive in patients with schizophrenia during tasks that require memory-guided or volitional 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 DLPFC. 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 saccadic system (e.g., Clementz et al., 1994; Hommer, Clem, Litman, & Pickar, 1991; Mialat & Pichot, 1981; Pivik, 1979; Stark, 1983), and their performance on the saccade task is correlated with impaired performance in several attention tasks (Ross et al., 1998) and on the WCST (Karoumi, Ventre-Dominey, 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 nonword 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 action 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 insensitive to 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, 1986; Lewinsohn, Zieler, Libet, Eyeberg, & Nielson, 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-DLPFC (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, 1993). 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 (Paulesu, Frith, & Frackowiak, 1993). In addition, a recent study showed a pronounced activation in the left inferior frontal gyrus (Brodmann's Areas 4, 44, and 45) when a tone serial position task was used (Stevens, Goldman-Rakic, Gore, Fulbright, & 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 (Baddeley & Lieberman, 1980; Farah, 1988) and in monkeys (Bachevalier & Mishkin, 1986; Kowalska et al., 1991; Wilson, Scalaidhe, & Goldman-Rakic, 1993). Ungerleider, Courtney, and Haxby (1998) 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, 1992).

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 (2000) 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 agonist intake. Bromocriptin, a dopamine agonist, improved working memory performance in healthy human participants (Luciana, Depue, Arbisi, & Leon, 1992). Kirrane and her colleagues (2000) showed that amphetamine, which releases monoamines—particularly dopamine and norepinephrine—and blocks 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 (Rupniak & Iversen, 1993).

The studies 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 on-line. 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 (Cavada & Goldman-Rakic, 1989a, 1989b; Petrides & Pandya, 1984; Selemon & Goldman-Rakic, 1985; Stanton, Bruce, & Goldberg, 1995). 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 hypofrontality* (e.g., Callicott et al., 1998; Weinberger & Berman, 1996). Compared with normal controls, patients with schizophrenia show a relative physiological hypoactivity 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 hypofrontality 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 in 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 schizophre-

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 presentation 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 DLPFC 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 DLPFC (e.g., Blum, 1952; Funahashi, Bruce, & Goldman-Rakic, 1989, 1990, 1993; Jacobsen, 1935; Mishkin, 1957). 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 saccade 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 & Azuma, 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, 1986). Spatial delayed-response performance is disrupted by lesions in the DLPFC, 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 convexivity, 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 dysfunctional 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 neurophysiological 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; Gooding & Tallent, 2002; Karatekin & Asarnow, 1998; Keefe et al., 1995, 1997; Spindler et al., 1997; Spitzer, 1993).

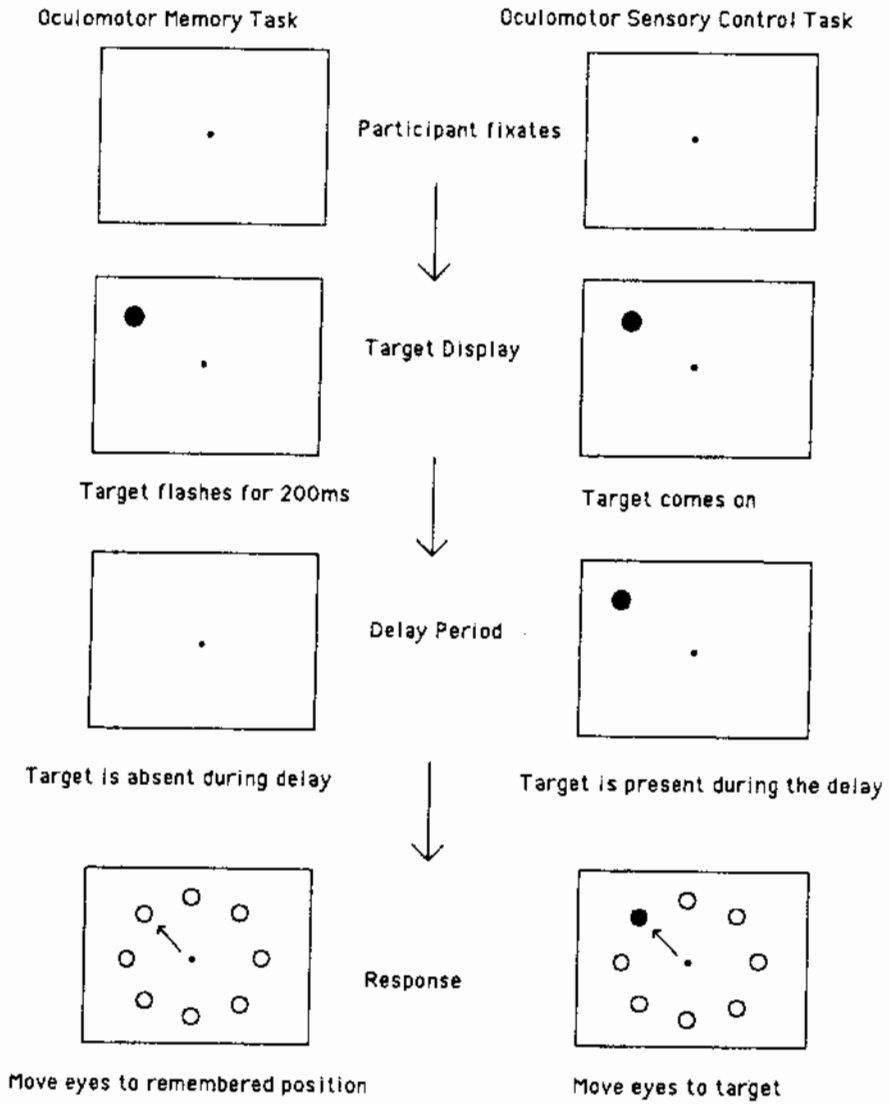

Figure 5.1. Schematic diagram of oculomotor delayed-response tasks.

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 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.,

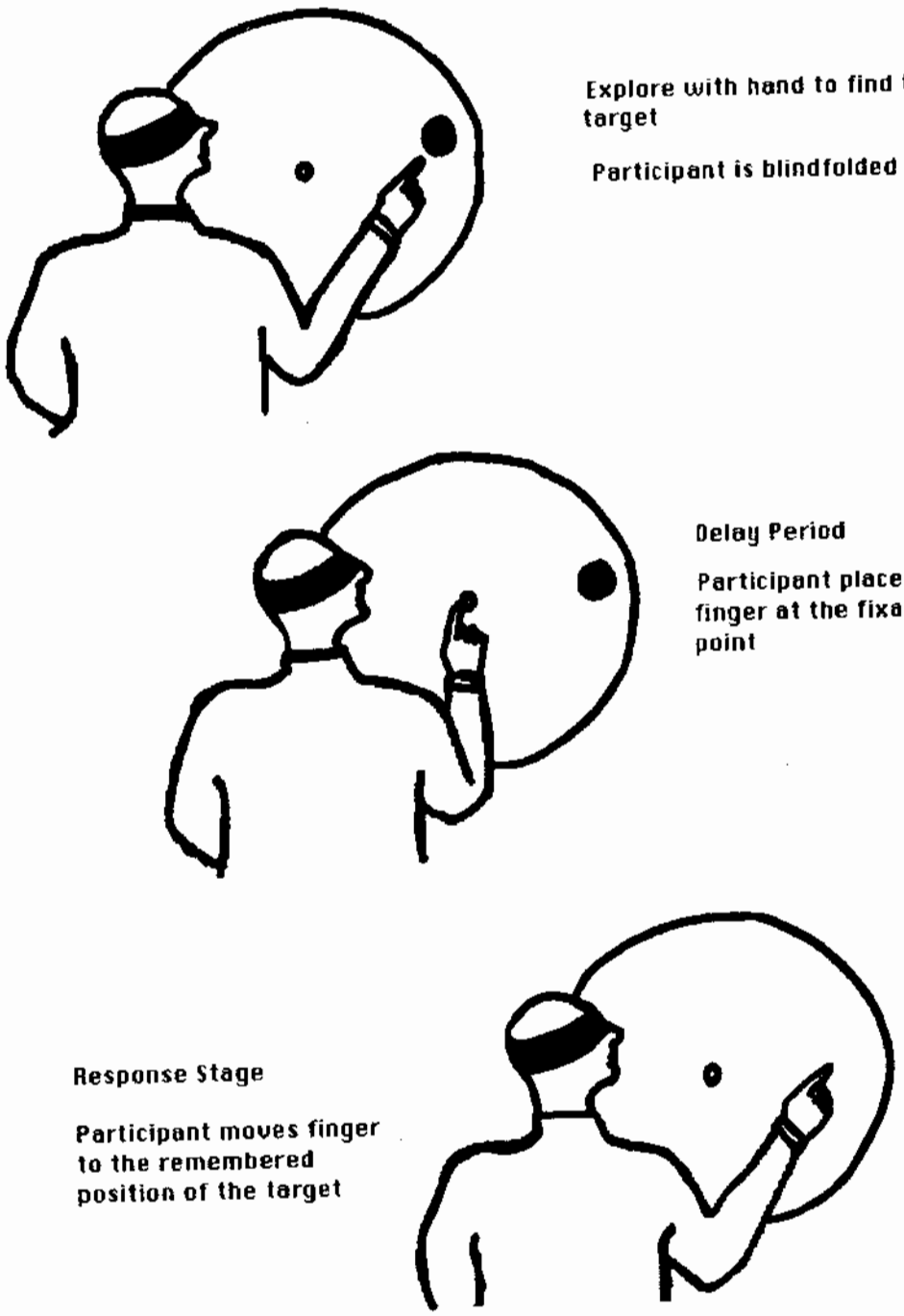

Figure 5.2. Haptic delayed-response task.

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.

Whether 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, Gainotti, De Bonis, & Marra, 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-lobe 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 test of frontal function. These patients performed within the normal range on the Verbal Fluency Task (see Lezak, 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 (Snitz, Curtis, Zald, Karsanis, & Iacono, 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 almost instantaneously and continue to pursuit smoothly. Schizophrenic patients 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 frontal system (Levin, 1984a, 1984b) and is hypothesized to be a possible biological marker for schizophrenia (see Holzman, 1987; Holzman & Matthysse, 1990).

Outpatients with schizophrenia showed deficits in working memory, but outpatients 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 schizophrenia inpatients, Park, Püschel, Sauter, Rentsch, and Hell (1999) tracked the same patients for 4 months until they were in partial remission 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, 1993; Snitz 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 5.3). 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 modality 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 medication 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, regardless of modality, may prove to be useful in broadening the schizophrenic phenotype. This finding has been replicated by Myles-Worsley and Park (in press) in the

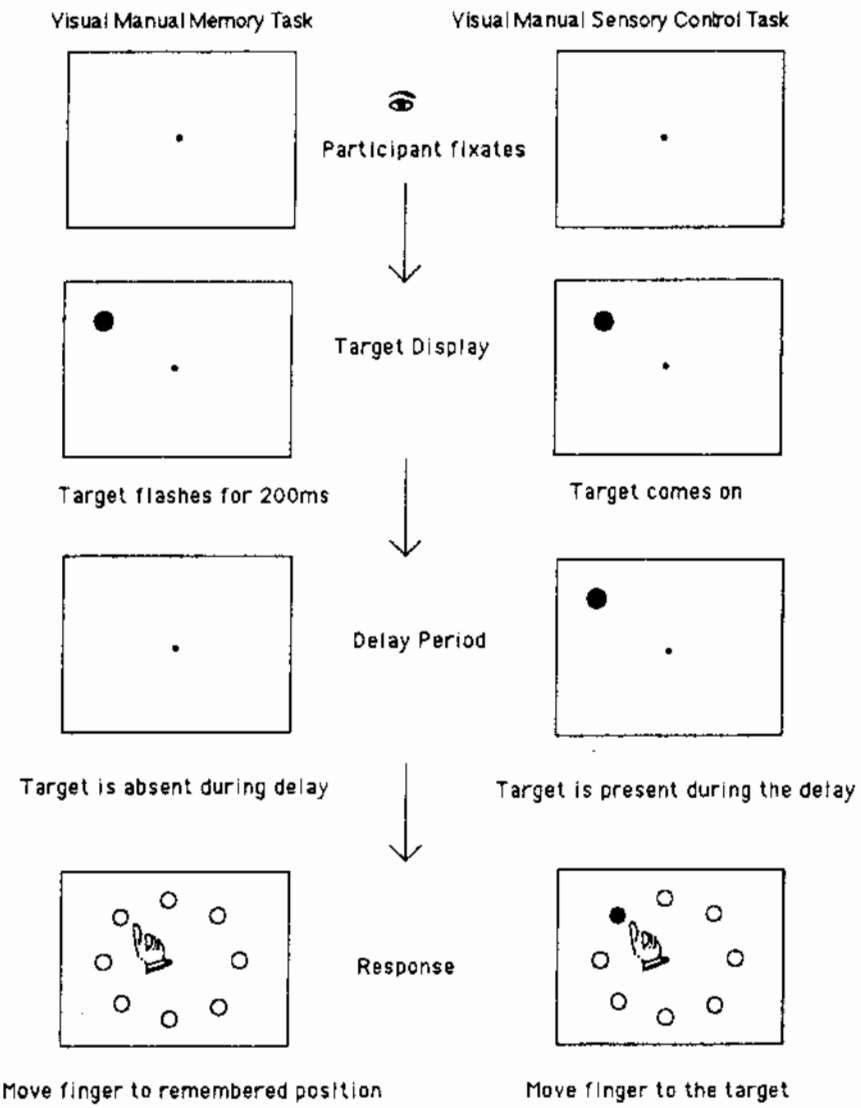

Figure 5.3. Visual manual delayed-response tasks.

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, Holzman, & Levy, 1993).

Working memory abnormalities in relatives of patients with schizophrenia reach beyond the spatial domain. Faraone 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, Katsanis, & Iacono, 2000). 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 schizophrenic 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 (Lenzenweger & Loranger, 1989a, 1989b; Meehl, 1990). Schizotypic individuals identified by various personality inventories show subtle deficits in sustained attention (Lenzenweger, Cornblatt, & Putnick, 1991); cognitive inhibition (Beech & Claridge, 1987; Park, Lenzenweger, Puschel, & Holzman, 1996); the WCST (Gooding, Kwapil, & Tallent, 1999; Lenzenweger & Korfine, 1994); and oculomotor tasks, including antisaccadic and smooth-pursuit tasks (O'Driscoll, Lenzenweger, & Holzman, 1998), in the absence of any psychiatric illness. Thus, some features of schizophrenia seem to be present, albeit in a very diluted form, in the general population, and these traits may indicate a predisposition to the illness.

Park, Holzman, and Lenzenweger (1995) examined the working memory function of undergraduate students at Cornell University. The students were assessed with a personality inventory that tapped experiences of perceptual aberrations. The question was whether normally functioning young adults who score high on the Perceptual Aberration 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 schizotypic individuals from normal controls (Lenzenweger & Korfine, 1994; Lyons, 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 aberration and that therefore they may not represent the whole range of schizotypal personality. In a later study, Park and McTigue (1997) recruited healthy schizotypic participants on the basis of their scores on the Schizotypal Personality Questionnaire (Raine, 1991), which taps the nine syndromes of schizotypal 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. Tallent and Gooding (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 WCST.

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., 1995). One important future direction lies 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, 1995; 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, 1993). 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, 1980; 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 (Willams & Goldman-Rakic, 1995). Neural network simulation of the frontal cortex also indicates that context-relevant processing may depend on dopamine (Cohen & Servan-Schreiber, 1992). 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, 1999; 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. Krappmann 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 5.4). 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 (1993) 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

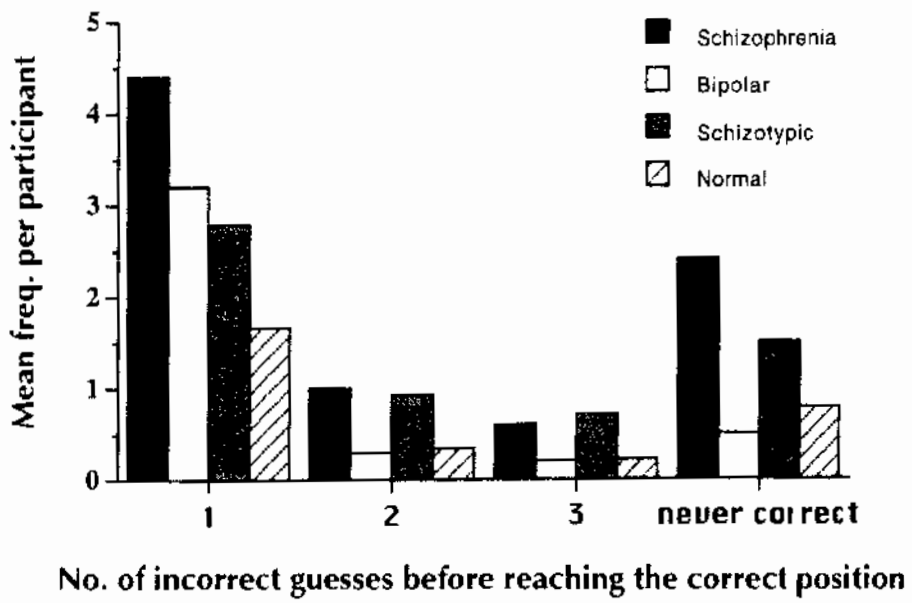

Figure 5.4. Frequency (freq.) of corrected errors per participant.

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 on 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

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.

Andreasen, N. C., Rezai, K., Alliger, R., Swayze, V. W., Flaum, M., Kirchner, P., et al. (1992). Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. *Archives of General Psychiatry, 49*, 943–958.

Bachevalier, J., & Mishkin, M. (1986). Visual recognition impairment follows ventromedial but not dorsolateral prefrontal lesions in monkeys. *Behavioural Brain Research, 20*, 249–261.

Baddeley, A. D. (1986). *Working memory*. New York: Oxford University Press.

Baddeley, A. D. (1992a). Working memory. *Science, 255*, 556–559.

Baddeley, A. D. (1992b). Working memory: The interface between memory and cognition. *Journal of Cognitive Neuroscience, 4*, 281–288.

Baddeley, A. D., & Lieberman, K. (1980). Spatial working memory. In R. S. Nickerson (Ed.), *Attention and performance* (pp. 521–539). Hillsdale, NJ: Erlbaum.

Beech, A., & Claridge, G. (1987). Individual differences in negative priming: Relations with schizotypal personality traits. *British Journal of Psychology, 78*, 349–356.

Benes, F. M., McSparren, J., Bird, E. D., SanGiovanni, J. P., & Vincent, S. L. (1991). Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients. *Archives of General Psychiatry, 48*, 996–1001.

Berman, K. F., Illowsky, B. P., & Weinberger, D. R. (1988). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: IV. Further evidence for regional and behavioral specificity. *Archives of General Psychiatry, 45*, 616–623.

Blum, R. A. (1952). Effects of subtotal lesions of frontal granular cortex on delayed reaction in monkeys. *American Medical Association Archives of Neurology and Psychiatry, 67*, 375–386.

Breier, A., Buchanan, R. W., Elkashef, A., Munson, R. C., Kirkpatrick, B., & Gellad, F. (1992). Brain morphology and schizophrenia: An MRI study of limbic, prefrontal cortex and caudate structures. *Archives of General Psychiatry, 49*, 921–926.

Breier, A., Davis, O. R., Buchanan, R. W., Moricle, L. A., & Munson, R. C. (1993). Effects of metabolic perturbation on plasma homovanillic acid in schizophrenia. *Archives of General Psychiatry, 50*, 541–550.

Calev, A. (1984). Recall and recognition in mildly disturbed schizophrenics: Use of matched tests. *Psychological Medicine, 14*, 425–429.

Callicott, J. H., Ramsey, J. H., Tallent, K., Bertolino, A., Knable, M. B., Coppola, R., et al. (1998). Functional magnetic resonance imaging brain mapping in psychiatry: Methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology, 18*, 186–196.

Carter, C. S., Robertson, L. C., Nordahl, T., Chadderjian, M., Kraft, L., & O'Shora-Celaya, L. (1996). Spatial working memory deficits and their relationship to negative symptoms in unmedicated schizophrenia patients. *Biological Psychiatry, 40*, 930–932.

Castner, S. A., Williams, G. V., & Goldman-Rakic, P. S. (2000). Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. *Science, 287*, 2020–2022.

Cavada, C., & Goldman-Rakic, P. S. (1985). Parieto–prefrontal connections in the monkey: Topographical distribution within the prefrontal cortex of sectors connected with the lateral and medial posterior parietal cortex. *Society of Neuroscience Abstracts, 11*, 323.

Cavada, C., & Goldman-Rakic, P. S. (1989a). Posterior parietal cortex in rhesus monkeys: I. Parcellation of areas based on distinctive limbic and sensory cortico–cortical connections. *Journal of Comparative Neurology, 287*, 393–421.

Cavada, C., & Goldman-Rakic, P. S. (1989b). Posterior parietal cortex in rhesus monkeys: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *Journal of Comparative Neurology, 287*, 422–445.

Chapman, L. J., & Chapman, J. P. (1985). Psychosis proneness. In M. Alpert (Ed.), *Controversies in schizophrenia: Changes and constancies* (pp. 157–172). New York: Guilford Press.

Chapman, L. J., Chapman, J. P., & Raulin, M. L. (1978). Body-image aberration in schizophrenia. *Journal of Abnormal Psychology, 87*, 399–407.

Clementz, B. A., McDowell, J. E., & Zisook, S. (1994). Saccadic system functioning among schizophrenia patients and their first degree relatives. *Journal of Abnormal Psychology, 103*, 277–287.

Cohen, J. D., & Servan-Schreiber, D. (1992). Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychological Review, 99*, 45–77.

Collette, F., Salmon, E., Van der Linden, M., Chicherio, C., Belleville, S., Degueldre, C., et al. (1999). Regional brain activity during tasks devoted to the central executive of working memory. *Cognitive Brain Research, 7*, 411–417.

Conklin, H. M., Curtis, C. E., Katsanis, J., & Iacono, W. G. (2000). Verbal working memory impairment in schizophrenia patients and their first-degree relatives: Evidence from the digit span task. *American Journal of Psychiatry, 157*. 275–277.

David, A. S., & Cutting, J. C. (1992). Visual imagery and visual semantics in the cerebral hemispheres in schizophrenia. *Schizophrenia Research, 8*, 263–271.

Deng, S.-Y., Segraves, M. A., Ungerleider, L. G., Mishkin, M., & Goldberg, M. E. (1984). Unilateral frontal eye field lesions degrade saccadic performance in the rhesus monkey. *Society of Neuroscience Abstracts, 10*, 59.

de Zubicaray, G. I., Williams, S. C. R., Wilson, S. J., Rose, S. E., Brammer, M. J., Bullmore, E. T., et al. (1998). Prefrontal cortex involvement in selective letter generation: A functional magnetic resonance imaging study. *Cortex, 34*, 389–401.

Evdokimidis, I., Liakopoulos, D., Constantinidis, T. S., & Papageorgiou, C. (1996). Cortical potentials with antisaccades. *Electron Clinical Neurophysiology, 98*, 377–384.

Farah, M. J. (1988). Is visual imagery really visual? *Psychological Review, 95*, 307–317.

Faraone, S. V., Seidman, L. J., Kerene, W. S., Toomey, R., Pepple, J. R., & Tsuang, M. T. (1999). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: A 4-year follow-up study. *Journal of Abnormal Psychology, 108*, 176–187.

Fleming, K., Goldberg, T. E., Binks, S., Randolph, C., Gold, J. M., & Weinberger, D. R. (1997). Visuospatial working memory in patients with schizophrenia. *Biological Psychiatry, 41*, 43–49.

Freedman, M., & Oscar-Berman, M. (1986). Bilateral frontal lobe disease and selective delayed-response deficits in humans. *Behavioral Neuroscience, 100*, 337–342.

Fukushima, J., Fukushima, K., Chiba, T., Tanaka, S., Yamashita, I., & Masamichi, K. (1988). Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. *Biological Psychiatry, 23*, 670–677.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1989). Mnemonic coding of visual cortex in the monkey's dorsolateral prefrontal cortex. *Journal of Neurophysiology, 61*, 331–348.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1990). Visuospatial coding in primate prefrontal neurons revealed by oculomotor paradigms. *Journal of Neurophysiology, 63*, 814–831.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1993). Dorsolateral prefrontal lesion and oculomotor delayed response performance: Evidence for mnemonic "scotomas." *Journal of Neuroscience, 13*, 1479–1497.

Ganguli, R., Carter, C., Mintun, M., Brar, J., Becker, J., Sarma, R., et al. (1997). PET brain mapping study of auditory verbal supraspan memory versus visual fixation in schizophrenia. *Biological Psychiatry, 41*, 33–42.

Gathercole, S., & Baddeley, A. D. (1989). Evaluation of the role of phonological STM in the development of vocabulary in children: A longitudinal study. *Journal of Memory and Language, 28*, 200–213.

Goldberg, T. E., Weinberger, D. R., Pliskin, N. H., Berman, K. F., & Podd, M. H. (1989). Recall memory deficit in schizophrenia: A possible manifestation of prefrontal dysfunction. *Schizophrenia Research, 2*, 251–257.

Goldman-Rakic, P. S. (1987). Circuitry of primate prefrontal cortex and regulation of behavior by representational knowledge. In F. Plum & V. Mountcastle (Eds.), *Handbook of physiology—The nervous system V* (pp. 373–417). Bethesda, MD: American Physiological Society.

Goldman-Rakic, P. S. (1991). Prefrontal cortical dysfunction in schizophrenia: The relevance of working memory. In B. Carroll (Ed.), *Psychopathology and the brain* (pp. 1–22). New York: Raven Press.

Goldman-Rakic, P. S. (1999). The relevance of the Dopamine-D1 receptor in the cognitive symptoms of schizophrenia. *Neuropsychopharmacology, 21*, S170–S180.

Gooding, D. C., Kwapil, T. R., & Tallent, K. A. (1999). Wisconsin Card Sorting Test deficits in schizotypic individuals. *Schizophrenia Research, 40*, 201–209.

Gooding, D. C., & Tallent, K. A. (2002). Spatial working memory performance in patients with schizoaffective psychosis versus schizophrenia: A tale of two disorders? *Schizophrenia Research, 53*, 209–218.

Guitton, D., Buchtel, H. A., & Douglas, R. M. (1985). Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Experimental Brain Research, 58*, 455–472.

Gur, R. C., Saykin, A. J., & Gur, R. E. (1991). Neuropsychological study of schizophrenia. In C. A. Tamminga & S. C. Schultz (Eds.), *Advances in neuropsychiatry and psychopharmacology: Vol. 1. Schizophrenia research* (pp. 153–162). New York: Raven Press.

Hall, D. P., & Young, S. A. (1992). Frontal lobe aneurysm rupture presenting as psychosis. *Journal of Neurology, Neurosurgery and Psychiatry, 55*, 1207–1208.

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtis, G. (1993). *Wisconsin Card Sorting Test manual: Revised and expanded*. Odessa, FL: Psychological Assessment Resources.

Holzman, P. S. (1987). Recent studies of psychophysiology in schizophrenia. *Schizophrenia Bulletin, 13*, 49–75.

Holzman, P. S., Coleman, M., Lenzenweger, M. F., Levy, D. L., Matthysse, S., O'Driscoll, G. A., et al. (1995). Working memory, anti-saccade and thought disorder in relation to schizotypy. In A. Raine, T. Lencz, & S. Mednick (Eds.), *Schizotypal personality* (pp. 353–381). Cambridge, England: Cambridge University Press.

Holzman, P. S., & Matthysse, S. (1990). The genetics of schizophrenia: A review. *Psychological Science, 1*, 279–286.

Holzman, P. S., Proctor, L. R., & Hughes, D. W. (1973). Eye tracking patterns in schizophrenia. *Science, 181*, 179–181.

Holzman, P. S., Proctor, L. R., Levy, D. L., Yasillo, N. J., Meltzer, H. Y., & Hurt, S.W. (1974). Eye tracking dysfunctions in schizophrenic patients and their relatives. *Archives of General Psychiatry, 31*, 143–151.

Hommer, D. W., Clem, T., Litman, R., & Pickar, D. (1991). Maladaptive anticipatory saccades in schizophrenia. *Biological Psychiatry, 30*, 779–794.

Ingvar, D. H. (1980). Abnormal distribution of cerebral activity in chronic schizophrenia: A neurophysiological interpretation. In C. Baxter & T. Melnechuk (Eds.), *Perspectives in schizophrenia* (pp. 107–125). New York: Raven Press.

Ingvar, D. H., & Franzen, I. (1974). Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatrica Scandinavica, 50*, 425–462.

Jacobsen, C. F. (1935). Studies of cerebral functions in primates: I. The functions of the frontal association areas in monkeys. *Comparative Psychology Monographs, 13*, 3–60.

Jonides, J., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S., & Mintun, M. (1993). Spatial working memory in humans as revealed by PET. *Nature, 363*, 623–625.

Just, M. A., & Carpenter, P. A. (1992). A capacity theory of comprehension: Individual differences in working memory. *Psychological Review, 99*, 122–149.

Karatekin, C., & Asarnow, R. F. (1998). Working memory in childhood-onset schizophrenia and attention-deficit/hyperactivity disorder. *Psychiatry Research, 80*, 165–176.

Karoumi, B., Ventre-Dominey, J., Vighetto, A., Dalery, J., & d'Amato, T. (1998). Saccadic eye movements in schizophrenic patients. *Psychiatry Research, 17*, 9–19.

Keefe, R. S. E., Roitman, S. E. L., Harvey, P. D., Blum, C. S., DuPre, R. L., Davidson, M., & Davis, K. L. (1995). A pen-and-paper human analogue of a monkey prefrontal cortex activation task: spatial working memory in patients with schizophrenia. *Schizophrenia Research, 17*, 25–33.

Keefe, R. S. E., Silverman, J. M., Mohs, R. C., Siever, L. J., Harvey, P. D., Friedman, L., et al. (1997). Eye tracking, attention, and schizotypal symptoms in nonpsychotic relatives of patients with schizophrenia. *Archives of General Psychiatry, 54*, 169–176.

Kirrane, R. M., Mitropoulou, V., Nunn, M., New, A. S., Harvey, P. D., Schopick, F., et al. (2000). Effects of amphetamine on visuospatial working memory performance in schizophrenia spectrum personality disorder. *Neuropsychopharmacology, 22*, 14–18.

Koh, C., & Petersen, A. R.(1978). Recognition memory of schizophrenic patients. *Journal of Abnormal Psychology, 87*, 303–313.

Kolb, B., & Wishaw, I. Q. (1983). Performances of schizophrenic patients on tests sensitive to left or right frontal, temporal, or parietal function in neurological patients. *Journal of Nervous and Mental Disease, 171*, 435–443.

Kowalska, D. M., Bachevalier, J., & Mishkin, M. (1991). The role of the inferior prefrontal convexity in performance of delayed nonmatching-to-sample. *Neuropsychologia, 29*, 583–600.

Krappmann, P., & Everling, S. (1998). Spatial accuracy of primary and secondary memory-guided saccades in schizophrenic patients. *Schizophrenia Research, 30*, 183–185.

Lenzenweger, M. F., Cornblatt, B. A., & Putnick, M. (1991). Schizotypy and sustained attention. *Journal of Abnormal Psychology, 100*, 84–89.

Lenzenweger, M. F., & Korfine, L. (1994). Perceptual aberrations, schizotypy, and Wisconsin Card Sorting Test performance. *Schizophrenia Bulletin, 20*, 345–357.

Lenzenweger, M. F., & Loranger, A. W. (1989a). Detection of familial schizophrenia using a psychometric measure of schizotypy. *Archives of General Psychiatry, 46*, 902–907.

Lenzenweger, M. F., & Loranger, A. W. (1989b). Psychosis-proneness and clinical psychopathology: Examination of the correlates of schizotypy. *Journal of Abnormal Psychology, 98*, 3–8.

Levin, S. (1984a). Frontal lobe dysfunctions in schizophrenia: I. Eye movement impairments. *Journal of Psychiatric Research, 18*, 27–55.

Levin, S. (1984b). Frontal lobe dysfunctions in schizophrenia: II. Impairments of psychological brain functions. *Journal of Psychiatric Research, 18*, 57–72.

Levy, D. L., Yasillo, N. J., Dorus, E., Shaughnessy, R., Gibbons, R. D., Peterson, J., et al. (1983). Relatives of unipolar and bipolar patients have normal pursuit. *Psychiatry Research, 10*, 285–293.

Lewinsohn, P. M., Zieler, J. L., Libet, L., Eyeberg, S., & Nielson, G. (1972). Short-term memory: A comparison between frontal and non-frontal right and left hemisphere brain-damaged patients. *Journal of Comparative Physiological Psychology, 81*, 248–255.

Lezak, M. D. (1995). *Neuropsychological assessment* (3rd ed.). New York: Oxford University Press.

Luciana, M., Depue, R. A., Arbisi, P., & Leon, A. (1992). Facilitation of working memory in humans by a D2 dopamine receptor agonist. *Journal of Cognitive Neuroscience, 4*, 58–68.

Lyons, M. J., Merla, M. E., Young, L., & Kremen, W. S. (1991). Impaired neuropsychological functioning in symptomatic volunteers with schiztotypy: Preliminary findings. *Biological Psychiatry, 30*, 424–426.

Manoach, D. S., Gollub, R. L., Benson, E. S., Searl, M. M., Goff, D. C., Halpern, E., et al. (2000). Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biological Psychiatry, 48*, 99–109.

Manoach, D. S., Press, D. Z., Thangaraj, V., Searl, M. M., Goff, D. C., Halpern, E., et al. (1999). Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biological Psychiatry, 45*, 1128–1137.

McCarthy, G., Blamire, A. M., Puce, A., Nobre, A. C., Bloch, G., Hyder, F., et al. (1994). Functional magnetic resonance imaging of the human prefrontal cortex activation during a spatial working memory task. *Proceedings of the National Academy of Sciences, USA, 91*, 8690–8694.

McDowell, J. E., & Clementz, B. A. (1997). The effect of fixation condition manipulations on antisaccade performance in schizophrenia: Studies of diagnostic specificity. *Experimental Brain Research, 115*, 333–344.

Meehl, P. E. (1990). Towards an integrated theory of schizotaxia, schizotypy and schizophrenia. *Journal of Personality Disorders, 4*, 1–99.

Mialat, J. P, & Pichot, P. (1981). Eye tracking patterns in schizophrenia: An analysis based on the incidence of saccades. *Archives of General Psychiatry, 38*, 183–186.

Mishkin, M. (1957). Effects of small frontal lesions on delayed alternation in monkeys. *Journal of Neurophysiology, 20*, 615–622.

Myles-Worsley, M., & Park, S. (in press). Working memory deficits in schizophrenia patients and their first-degree relatives in Palau, Micronesia. *American Journal of Medical Genetics.*

Nakashima, Y., Momose, T., Sano, I., Katayama, S., Niwa, S., & Matsushita, M. (1993). Left dorsolateral prefrontal cortex role in the control of saccade and its dysfunction in schizophrenia. *Journal of Cerebral Blood Flow and Metabolism, 13*(Suppl. 1), 507.

Nakashima, Y., Momose, T., Sano, I., Katayama, S., Niwa, S., & Matsushita, M. (1994). Cortical control of saccade in normal and schizophrenic subjects: A PET study using task-evoked rCBF paradigm. *Schizophrenia Research, 12*, 259–264.

O'Driscoll, G. A., Lenzenweger, M. F., & Holzman, P. S. (1998). Antisaccades and smooth pursuit eye tracking and schizotypy. *Archives of General Psychiatry, 55*, 837–843.

Oscar-Berman, M. (1975). The effects of dorsolateral–frontal and ventrolateral–orbitofrontal lesions on spatial discrimination learning and delayed response in two modalities. *Neuropsychologia, 13*, 237–246.

Pantelis, C., Barnes, T. R. E., Nelson, H. E., Tanner, S., Weatherley, L., Owen, D. R., & Ronnins, T. W. (1997). Frontal–striatal cognitive deficits in patients with chronic schizophrenia. *Brain, 120*, 1823–1843.

Park, S. (1991). *The role of prefrontal cortex in spatial working memory deficits of schizophrenic patients.* Unpublished doctoral dissertation, Harvard University.

Park, S. (1997). Association of an oculomotor delayed response task and the Wisconsin Card Sort Test in schizophrenic patients. *International Journal of Psychophysiology, 27*, 147–151.

Park, S. (1999). Hemispheric asymmetry of spatial working memory deficit in schizophrenia. *International Journal of Psychophysiology, 34*, 313–322.

Park, S., & Holzman, P. S. (1992). Schizophrenics show working memory deficits. *Archives of General Psychiatry, 49*, 975–982.

Park, S., & Holzman, P. S. (1993). Association of working memory deficit and eye tracking dysfunction in schizophrenia. *Schizophrenia Research, 11*, 55–61.

Park, S., Holzman, P. S., & Goldman-Rakic, P. S. (1995). Spatial working memory deficits in the relatives of schizophrenic patients. *Archives of General Psychiatry, 52*, 821–828.

Park, S., Holzman, P. S., & Lenzenweger, M. F. (1995). Individual difference in spatial working memory in relation to schizotypy. *Journal of Abnormal Psychology, 105*, 355–364.

Park, S., Holzman, P. S., & Levy, D. L. (1993). Spatial working memory deficit in the relatives of schizophrenic patients is associated with their smooth pursuit eye tracking performance. *Schizophrenia Research, 9*, 184.

Park, S., Lenzenweger, M. F., Puschel, J., & Holzman, P. S. (1996). Attentional inhibition in schizophrenia and schizotypy: A spatial negative priming study. *Cognitive Neuropsychiatry, 1*, 125–149.

Park, S., & McTigue, K. (1997). Spatial working memory and the syndrome of schizotypal personality. *Schizophrenia Research, 26*, 213–220.

Park, S., & O'Driscoll, G. A. (1996). Components of working memory deficit in schizophrenia. In S. Matthysse, D. L. Levy, J. Kagan, & F. Benes (Eds.), *Psychopathology: The evolving science of mental disorder* (pp. 34–50). Cambridge, England: Cambridge University Press.

Park, S., Püschel, J., Sauter, B., Rentsch, M., & Hell, D. (1999). Spatial working memory deficits and clinical symptoms in schizophrenia: A 4-month follow-up study. *Biological Psychiatry, 46*, 392–400.

Paulesu, E., Frith, C. D., & Frackowiak, R. S. J. (1993). The neural components of the verbal working memory. *Nature, 362*, 342–345.

Petrides, M., Alivisatos, B., Evans, A. C., & Meyer, E. (1993). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Sciences, 90*, 873–877.

Petrides, M., Alivisatos, B., Meyer, E., & Evans, A. C. (1993). Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Sciences, 90*, 878–882.

Petrides, M., & Pandya, D. N. (1984). Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *Journal of Comparative Neurology, 228*, 105–116.

Pierrot-Deseilligny, C., Rivaud, S., Gaymard, B., & Agid, Y. (1991). Cortical control of memory-guided saccades in man. *Experimental Brain Research, 83*, 607–617.

Pivik, R. T. (1979). Smooth pursuit eye movements and attention in psychiatric patients. *Biological Psychiatry, 14*, 859–879.

Raine, A. (1991). The SPQ: A scale for the assessment of schizotypal personality based on *DSM-III-R* criteria. *Schizophrenia Bulletin, 17*, 555–564.

Rajkowska, G., Selemon, L. D., & Goldman-Rakic, P. S. (1998). Neuronal and glial somal size in the prefrontal cortex: A postmortem study of schizophrenia and Huntington's disease. *Archives of General Psychiatry, 55*, 215–224.

Rao, S. C., Rainer, G., & Miller, E. K. (1997). Integration of what and where in the primate prefrontal cortex. *Science, 276*, 821–824.

Roitblat, H. L. (1987). *Introduction to comparative cognition*. New York: Freeman.

Ross, R. G., Harris, J. G., Olincy, A., Radant, A., Adler, L. E., & Freedman, R. (1998). Familial transmission of two independent saccadic abnormalities in schizophrenia. *Schizophrenia Research, 30*, 59–70.

Rupniak, N. M. J., & Iversen, S. D. (1993). Cognitive impairment in schizophrenia: How experimental models using non-human primates may assist improved drug therapy for negative symptoms. *Neuropsychologia, 31*, 1133–1146.

Sagawa, K., Kawakatsu, S., Shibuya, I., Arata, O., Morinobu, S., Komatani, A., et al. (1990). Correlation of regional cerebral blood flow with performance on neuropsychological tests in schizophrenic patients. *Schizophrenia Research, 3*, 241–246.

Sawaguchi, T., & Goldman-Rakic, P. S. (1991). D1 dopamine receptors in prefrontal cortex: Involvement in working memory. *Science, 251*, 947–950.

Selemon, L. D., & Goldman-Rakic, P. S. (1985). Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *Journal of Neuroscience, 5*, 776–794.

Selemon, L. D., Rajkowska, G., & Goldman-Rakic, P. S. (1995). Abnormally high neuronal density in the schizophrenic cortex: A morphometric analysis of prefrontal area 9 and occipital area 17. *Archives of General Psychiatry, 52*, 805–818.

Selemon, L. D., Rajkowska, G., & Goldman-Rakic, P. S. (1998). Elevated neuronal density in prefrontal area 46 in brains from schizophrenic patients: Application of a three dimensional, stereologic counting method. *Journal of Comparative Neurology, 392*, 402–412.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London, B*, 199–209.

Shallice, T. (1988). *From neuropsychology to mental structures*. Cambridge, England: Cambridge University Press.

Shiffrin, R. M., & Schneider, W. (1977). Controlled and automatic human information processing II. *Psychological Review, 84*, 127–190.

Snitz, B. E., Curtis, C. E., Zald, D. H., Karsanis, J., & Iacono, W. G. (1999). Neuropsychological and oculomotor correlates of spatial working memory performance in schizophrenia patients and controls. *Schizophrenia Research, 38*, 37–50.

Spindler, K. A., Sullivan, E. V., Menon, V., Lim, K. O., & Pfefferbaum, A. (1997). Deficits in multiple systems of working memory in schizophrenia. *Schizophrenia Research, 27*, 1–10.

Spitzer, M. (1993). The psychopathology, neuropsychology and neurobiology of associative and working memory in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience, 243*, 57–70.

Stamm, J. S. (1985). The riddle of the monkey's delayed response deficit has been solved. In E. Perecman (Ed.), *The frontal lobes revisited* (pp. 73–90). Hillsdale, NJ: Erlbaum.

Stanton, G. B., Bruce, C. J., & Goldberg, M. E. (1995). Topography of projections to posterior cortical areas from the macaque frontal eye fields. *Journal of Comparative Neurology, 353*, 291–305.

Stark, L. (1983). Abnormal patterns of normal eye movements in schizophrenia. *Schizophrenia Bulletin, 9*, 55–72.

Stevens, A. A., Goldman-Rakic, P. S., Gore, J. C., Fulbright, R. K., & Wexler, B. E. (1998). Cortical dysfunction in schizophrenia during auditory word and tone working memory demonstrated by functional magnetic resonance imaging. *Archives of General Psychiatry, 55*, 1097–1103.

Stuss, D. T., & Benson, D. F. (1984). Neuropsychological studies of the frontal lobes. *Psychological Bulletin, 95*, 3–28.

Stuss, D. T., & Benson, D. F. (1985). The frontal lobes and control of cognition and memory. In E. Perecman (Ed.), *The frontal lobes revisited* (pp. 141–158). Hillsdale, NJ: Erlbaum.

Suzuki, H., & Azuma, M. (1983). Topographic studies on visual neurons in the dorsolateral prefrontal cortex of the monkey. *Experimental Brain Research, 53*, 47–58.

Tallent, K. A., & Gooding, D. C. (1999). Working memory and Wisconsin Card Sorting Test performance in schizotypic individuals: A replication and extension. *Psychiatry Research, 89*, 161–170.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1986). Parkinson's disease: Cognitive changes in response to treatment response. *Brain, 110*, 35–51.

Ungerleider, L. G., Courtney, S. M., & Haxby, J. V. (1998). A neural system for human visual working memory. *Proceedings of the National Academy of Sciences USA, 95*, 883–890.

Villa, G., Gainotti, G., De Bonis, C., & Marra, C. (1990). Double dissociation between temporal and spatial pattern processing in patients with frontal and parietal damage. *Cortex, 26*, 399–407.

Watanabe, M. (1996). Reward expectancy in primate prefrontal neurons. *Nature, 382*, 629–632.

Weinberger, D. R., & Berman, K. F. (1996). Prefrontal function in schizophrenia: Confounds and controversies. *Philosophical Transactions of the Royal Society in London, 351*, 1495–1503.

Weinberger, D. R., Berman, K. F., & Illowsky, B. P. (1988). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: III. A new cohort and evidence for monoaminergic mechanism. *Archives of General Psychiatry, 45*, 609–615.

Weinberger, D. R., Berman, K. F., & Zec, R. F. (1986). Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. *Archives of General Psychiatry, 43*, 114–124.

Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine D1 receptor in prefrontal cortex. *Nature, 376*, 572–575.

Wilson, F. A. W., Scalaidhe, S. P. O., & Goldman-Rakic, P. S. (1993). Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science, 260*, 1955–1957.

Wolkin, A., Sanfilipo, M., Wolf, A. P., Angrist, B., Brodie, J. D., & Rotrosen, J. (1992). Negative symptoms and hypofrontality in chronic schizophrenia. *Archives of General Psychiatry, 49*, 959–966.

Zarahn, E., Aguirre, G. K., & D'Esposito, M. (1999). Temporal isolation of the neural correlates of spatial mnemonic processing with fMRI. *Cognitive Brain Research, 7*, 255–268.

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