

## Components of working memory deficit in schizophrenia

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### Introduction

In this chapter, we focus on the working memory deficit of schizophrenic patients, as assessed by delayed-response tasks. The relevance of delayed-response performance to schizophrenia has already been extensively documented by Goldman-Rakic (1987, 1991; see also Chapter 2, this volume). A typical delayed-response task involves the presentation of a stimulus, followed by a delay period and the subsequent presentation of a small set of alternative choices. Although the delayed-response task is a simple procedure, it involves a variety of cognitive functions. In order to succeed, the target stimulus or, to be more specific, the context-relevant attribute of the stimulus, must be encoded (e.g., spatial location). This information is maintained in working memory during the delay period. Then, a motor command must be successfully executed in order to elicit a response, which may involve voluntary control over the motor system. The delayed-response task is not dependent on recognition memory because at the response stage, there is no external cue in the response environment.

Deficits in delayed-response task performance remain one of the best-documented symptoms of prefrontal damage (e.g., Jacobsen, 1935; Kojima et al., 1982). Lesions in the principal sulcus impair performance on delayed-response tasks in monkeys (e.g., Blum, 1952; Goldman and Rosvold, 1970; Gross and Weiskrantz, 1964). Humans with dorsolateral prefrontal lesions show analogous deficits on tasks that require a delayed response (e.g., Oscar-Berman, 1975; Freedman and Oscar-Berman, 1986; Lewinsohn et al., 1972).

Both animals and humans with prefrontal lesions are excessively distractible and tend to be susceptible to irrelevant stimuli. They rely heavily on external cues to guide behavior even when these cues are not reliable (Bartus and Levere, 1977; Lhermitte, 1986; Lhermitte et al., 1986). When patients with lesions in the frontal lobes are asked to perform cognitive tasks that deal with well-rehearsed information, they perform adequately, but when the task demands context-relevant modification of strategies, these patients experience enormous difficulty. They may continue to rely on previously successful but now irrelevant responses, or allow momentary external influences to override internal goals. Perseverative tendencies, distractibility, rigidity and inability to regulate behavior according to context are some of the major symptoms of frontal lobe damage (Luria, 1966; Fuster, 1980; Petrides and Milner, 1982; Shallice, 1982; Duncan, 1986) and these deficits extend to the social sphere. Similarities in neuropsychological and social profiles have led many investigators to suggest that frontal lobe deficits may be responsible for some of the most profound symptoms of schizophrenia (see, e.g., Kraepelin, 1919; Levin, 1984a, 1984b; Goldman-Rakic, 1991; also Goldman-Rakic, Chapter 3, this volume). In turn, distractibility, rigidity, loss of goal-directedness and other related dysfunctions have been explained as problems of the *central executive* system or *working memory* by neuropsychologists and cognitive psychologists.

### Cognitive models of central executive system and working memory

Our discussion of working memory will be limited to the context of a simple delayed-response problem, and therefore we will not attempt to address the question of general capacity of the *central executive system* (see Just and Carpenter, 1992). Baddeley's working memory model (1986) consists of the central executive system, which is subserved by modality-specific subsystems such as the *verbal articulatory loop* for phonological-auditory input and the *visuospatial sketchpad* for visuospatial input. The verbal articulatory loop is a phonological input store that can hold auditory information via rehearsal processes and thereby keep it temporarily. This is the process involved, for example, when one repeats a phone number in mind while searching for a pen. The visuospatial sketchpad is an input store that maintains and ma-

nipulates visuospatial images. These subsystems are closely tied to sensory systems, and a recent imaging study shows that the supra-marginal gyrus and Broca's area are implicated in the verbal articulatory loop (Paulescu et al., 1993). In Baddeley's model, the central executive deploys attentional resources, selects control processes and strategies, and coordinates information flow from the subsystems. The function of working memory is to hold information in the conscious realm until it can be used to guide behavior or be transferred to the knowledge storage system, which may be conceptualized as the long-term memory or the reference memory (Baddeley, 1986; Roitblat, 1987). The articulatory and the visuospatial sketchpad systems can hold on to information for long delays through rehearsal or visuospatial mnemonic strategies.

Similarly, Shallice (1988) postulates the existence of a *supervisory attentional system* that is needed when *controlled* processing is required to override *automatic* routine processes or motor programs. According to Shiffrin and Schneider (1977), automatic processes arise as a result of extended practice on a task. Once a skill is mastered (or a motor program formed), it becomes an automatic process gaining direct access to long-term memory and occurring outside the conscious realm. Hence, automatic processes can be carried out in parallel. In contrast, controlled processing makes heavy demands on central processing capacity and takes place in the conscious realm. The *supervisory attentional system* monitors the internal and external context in order to modulate the outputs of independent schema-like action modules that oversee routine responses (i.e., automatic processes).

A dysfunctional supervisory attentional system or central executive would result in little or no deficit when the environment is stable and only routine responses are required. However, in novel situations, where new responses are demanded of the organism, an impaired central executive would be associated with a noticeable decrement in performance, even when the sensory or the motor components required to carry out the new tasks are intact. These are the kinds of situations in which frontal and schizophrenic patients fail. Thus, studies of these populations should be able to differentiate performance deficits related to sensory or motor problems from those related to deficits in central executive or working memory. The latter deficits should be observable regardless of the input and output modalities of the paradigm.

### Working memory deficit of schizophrenic patients

Park and Holzman (1992, 1993) found that schizophrenic patients are impaired in making memory-guided eye movements and hand movements in the absence of a sensory deficit. The tasks employed were modelled after the oculomotor delayed-response tasks that were used to investigate spatial working memory function in rhesus monkeys (see Goldman-Rakic, Chapter 3, this volume). Figure 3.1 illustrates the oculomotor delayed-response tasks used in the Park and Holzman studies. Schizophrenic patients were less accurate than normal controls and bipolar patients in this task. To rule out the possibility that this deficit may have been due to a sensorimotor problem, a control task was included that was identical to the memory task except that the target never disappeared. The subject was simply required to make an eye movement to a visible target after the delay period. Schizophrenic patients performed as well as the control subjects on the sensorimotor control task. The authors interpreted these results as evidence of a deficit in working memory that was similar to the deficits displayed by monkeys with dorsolateral prefrontal (DLPFC) lesions (Funahashi et al., 1989, 1990, 1993).

On a recognition memory task, the target is present at the response stage and the subject must select the target from a number of alternatives. In a recall task, the target is not present at the response stage. Recognition memory is not involved in spatial delayed-response performance, because at the response stage of the task, there is no external cue in the response environment. Schizophrenic patients have been reported to have impaired free recall but intact recognition memory (Koh and Petersen, 1978). This pattern of deficits is similar to that observed in frontal lobe patients who are prone to "forgetting to remember" (Hecaen and Albert, 1978). Spared recognition coupled with impaired recall is also typical of patients with diseases that involve reduced dopaminergic activity – for example, Parkinson's disease (e.g., Taylor et al., 1986). Recognition memory is believed to be dependent on a neural circuit that includes the hippocampus, amygdala, medial thalamus, nucleus basalis and orbital frontal areas (Mishkin and Bachvalier, 1983), whereas free recall is thought to involve the prefrontal cortex (Taylor et al., 1986).

There is also some *indirect* evidence for the role of the frontal system in the working memory deficit of schizophrenic patients. Neuropsych-

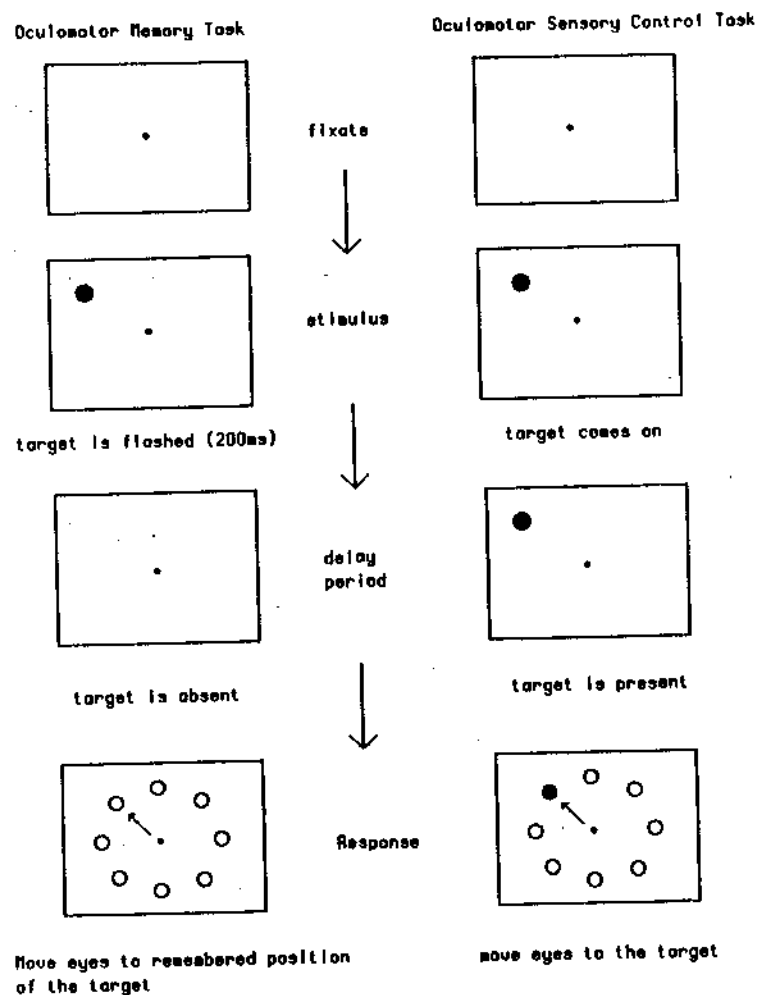


Figure 3.1. Oculomotor delayed-response tasks

chological tests of frontal lobe function were conducted in the same subjects who completed the oculomotor delayed-response task above (Park, 1991). There was a significant correlation between working memory accuracy and number of errors on the Wisconsin Card Sort Test ( $r = -.54, p < .001$ ) when all subjects were examined (Park, 1991; Park and Holzman, 1991). This is not surprising since normal subjects perform well both on the WCST and on the oculomotor delayed-response task. But the same association was also observed

within the schizophrenic group; there was a significant correlation between the accuracy of oculomotor delayed-response performance and both the total number of errors ( $r = -.82, p < .005$ ) and the number of perseverative errors ( $r = -.73, p < .02$ ) on the WCST (Park, 1991; Park and Holzman, 1991). Overall, those patients who made more errors on WCST performed less accurately on the delayed-response task. Working memory performance and failure to maintain set on the WCST are also associated in schizotypic college students (Park et al., 1995).

In contrast to their performance on the WCST, these schizophrenic patients were not impaired on the verbal fluency task (FAS), another neuropsychological test of frontal lobe function, compared with normals and bipolars ( $F(2,33) = 1.25, p > 0.25$ ), and delayed-response performance was not correlated with performance on the verbal fluency task. WCST performance may be mediated by DLPFC (e.g., Milner, 1963; Weinberger et al., 1986), whereas the verbal fluency task may involve the orbitofrontal system (Kolb and Wishaw, 1985). However, the anatomical specificity of these two neuropsychological tests is still open to debate and therefore interpretation of the localizing significance of the above results must be made with caution.\*

Another line of indirect evidence implicating possible frontal dysfunction in the delayed-response deficit of schizophrenic patients is obtained from their eye tracking data. There was an association between performance on the oculomotor delayed-response task and smooth pursuit eye tracking within the schizophrenic population (Park and Holzman, 1993) and in the healthy relatives of schizophrenic patients (Park et al., 1993). That is, subjects with smooth pursuit eye movement (SPEM) dysfunction had poorer accuracy on the delayed-response task. SPEM impairment in schizophrenic patients has been suggested to involve dysfunctional frontal eye fields (Levin, 1984a, 1984b). Indeed, SPEM dysfunction is associated with impaired performance on neuropsychological tests of frontal functions (Katsanis and Iacono, 1991), suggesting that perhaps an intact frontal system may be important for both working memory and SPEM. Again, the precise nature of this association is open to debate.

We have discussed how some cognitive features of schizophrenia and frontal lobe patients may be conceptualized as dysfunctions of the

\* On this point, see also Chapter 5, by Deborah L. Levy, this volume - Eds.

central executive system. Although the delayed-response task is a simple procedure, successful performance may depend on these functional components:

1. Mental representation of goal or sequence
2. Maintenance of target representation during the delay period
3. Inhibition of competing, irrelevant stimuli
4. Initiation and execution of an appropriate motor response

Failure to facilitate any of these hypothetical components may lead to an overall deficit in goal-directedness. Therefore, it is necessary to analyze global behavioral descriptions into cognitively and neurobiologically meaningful components in order to uncover which functional components pose difficulties for schizophrenic patients and why.

#### *Mental representation of goal or sequence*

The ability to formulate the goal of the delayed-response task does not seem to be responsible for the schizophrenic patients' deficit, since subjects were unimpaired on the sensorimotor control task, which made the same sequential demands on the patient as the memory-guided task.

#### *Maintenance of target representation during the delay period*

Maintenance of the target representation during the delay may have posed difficulties for the subjects. It is helpful to examine neurophysiological data from the primate oculomotor delayed-response studies to formulate our hypotheses on how this might occur. There are neurons in the principal sulcus (area 46) of rhesus monkeys that increase firing *only* during the delay period (e.g., Funahashi et al., 1989, 1990, 1993). Moreover, there is a correlation between cell activity and the performance of the monkey. Funahashi et al. (1989, 1990, 1993) suggest that spatial working memory in rhesus monkeys is mediated by the "memory fields" that are encoded and maintained by the neurons in the principal sulcus. Thus, spatial representation in working memory in the monkey is thought to be maintained by a significant increase in neuronal activity in specific areas in the principal sulcus. In the case of working memory failure, the interruption of cell firing for a variety of reasons probably leads to loss of information.

The working memory deficit displayed by schizophrenic patients is not likely to be the result of a specific, localized, structural lesion in the principal sulcus. Schizophrenic patients make equal numbers of errors in both visual hemifields and in all quadrants (Park, 1991; Park and Holzman, 1992), indicating that the problem is distributed over the entire visual field. This result contrasts with data from animal lesion studies. Funahashi et al. (1993) observed mnemonic "scotomas" in the visual field specific to the site of the lesion in the monkey.

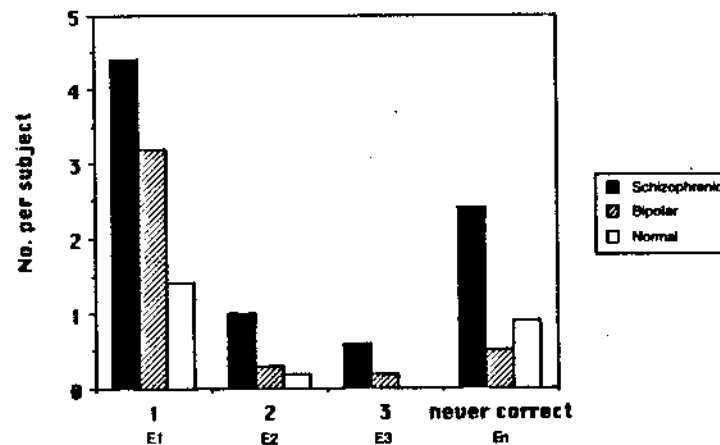
Recent theoretical and experimental work on how the dopamine system may affect working memory leads us to some interesting hypotheses. Cohen and Servan-Schreiber's neural network model (1992) of schizophrenic symptoms predicts that a decrease in dopamine gain at each unit (not necessarily neurons) may lead to a loss of context-relevant processing. Experimental manipulations with dopamine show that dopamine antagonists disrupt oculomotor delayed-response performance in rhesus monkeys (Sawaguchi and Goldman-Rakic, 1991) and dopamine agonists increase accuracy of delayed-response performance in humans (Luciana et al., 1992). Thus, one way of thinking about the working memory deficit involves the idea of reduced activity of neurons. The cells themselves may not be able to increase firing, or even if an increase in the cell activity is achieved, direct (e.g., by electrocortical stimulation) or indirect (e.g., by sudden external stimuli) interruptions may occur. Susceptibility to disruption, rather than static disruption, is possible. What kind of internal or external activity can disrupt cell firing and target representation maintenance? Introduction of concurrent tasks during the delay period has little or no effect on performance of the working memory task, as long as such tasks are not performed within the same modality; for example, a digit span task does not interfere with spatial working memory maintenance (see Baddeley, 1986). Even if the tasks are performed within the same sensory modality, they do not interfere if they are sufficiently separated in levels of processing; for example, neither caloric or rotatory-induced nystagmus (involuntary smooth eye movement) disrupts spatial working memory, whereas tracking a moving target (voluntary smooth eye movement) results in a marked decrement in spatial working memory performance (see Baddeley, 1986).

In a pilot study of the delayed-response task, it was found that most subjects (both controls and patients) performed the task by developing idiosyncratic mnemonic strategies – for example by assigning

numbers to each target position or using fingers to record the target position (Yesutis, 1990). In other words, working memory was not utilized because the answer was coded externally, in much the same way as if the target position had been written down on a piece of paper. The results from the pilot study of working memory showed that schizophrenic patients were less accurate than the normal controls. However, the difference observed could have been the result of more efficient use of external mnemonic strategies by normal controls. For this reason, a concurrent but noninterfering task was introduced during the delay period, obliging all subjects to engage in the same mental activity (Park and Holzman, 1992, 1993). These concurrent tasks had the additional benefit of ensuring that all subjects fixated on the center of the screen during the delay. The concurrent tasks, number subtraction and category switching did not disrupt delayed-response performance but they prevented subjects from engaging in external mnemonic strategies in a pilot study (Park, 1991). Thus, schizophrenic patients' deficits in delayed response cannot be ascribed to the superior mnemonic strategies of normals, or to interference by the concurrent tasks themselves.

#### *Inhibition of competing, irrelevant stimuli*

Although schizophrenic patients performed less accurately than the control groups, it was not clear whether the problem lay in the maintenance of spatial information in working memory or with failed inhibition of competing responses. Konorski and Lawicka (1964) reported that prefrontal-lesioned dogs made numerous perseverative errors in a 3-choice delayed-response task, but these dogs always corrected their errors by subsequently choosing the correct position. This pattern of results suggests that in these animals, maintenance of spatial representation during the delay was not the main problem. They seemed unable to inhibit competing, previously reinforced responses. In the delayed-response task, schizophrenic patients made perseverative errors, whereas normals and bipolars rarely did. In order to disentangle the errors due to a failure to maintain spatial representation and those due to disinhibition of competing responses, we analyzed the types of errors made by subjects in a previous study by Park and Holzman (1993). That is, all errors were examined to see if subsequent attempts to move eyes to the remembered position of the target were successful. In addition to the subjects reported, two more



No. of incorrect guesses before reaching the correct position

Figure 3.2. Frequency of corrected errors per subject. The X-axis represents the number of incorrect guesses made by subjects before they chose the correct position. E1 means there was 1 error before the correct choice was made. E2 means there were 2 errors before the correct choice was made. E3 means there were 3 incorrect guesses before the correct choice was made. En means the subject never got to the correct position within the time limit of 10 seconds. The Y-axis represents the mean number of errors made per subject.

schizophrenic patients who met the recruiting criteria were tested. Figure 3.2 shows the frequency of errors made per subject before the correct position was finally chosen. It can be seen that schizophrenic patients *do* correct errors, after the first unsuccessful attempt, usually on the second try. Sometimes schizophrenic patients make errors apparently because they are unable to inhibit irrelevant responses, but when they are given another chance, often they are then able to choose the correct target. Therefore, the initial errors seem to be caused by temporary disinhibition. However, it can also be seen that there are some errors which are *never* corrected, suggesting a possible failure to maintain spatial representation of the target. Thus, schizophrenic patients seem to be susceptible both to interference from competing response tendencies, leading to a faulty initiated choice, and to a maintenance failure of the target representation, as evidenced by the presence of *never-corrected* errors.

We examined the group differences in the number of errors that

were corrected after one unsuccessful attempt ( $E_1$ ) and those that are never corrected ( $E_n$ ). Schizophrenic patients made significantly more  $E_1$  errors per subject than normal controls ( $F(1,59) = 22.0, p < 0.0001$ ) and bipolars ( $F(1,27) = 5.3, p < 0.03$ ). They also made more  $E_n$  errors than normals ( $F(1,59) = 8.0, p < 0.007$ ) and bipolars ( $F(1,27) = 7.8, p < 0.01$ ). Figure 2 illustrates the error analysis.

Interference from competing response tendencies is commonly observed in animals and humans with lesions in the frontal lobes (see, e.g., Goldberg and Bilder, 1985; Stamm, 1985). Indeed, there seems to be an association between delayed-response performance and some neuropsychological tests of frontal lobe functions. Performance on the oculomotor and haptic delayed-response tasks correlated significantly with perseverative errors on the WCST (Park, 1991; Park and Holzman, 1991). In addition, Park and Holzman (1993) found an association between eye tracking performance and accuracy on the oculomotor working memory task in schizophrenic patients. The smooth pursuit eye tracking dysfunction in schizophrenic patients has been suggested to involve deficits in the frontal eye fields (Levin, 1984a,b).

We now examine whether there is a difference between those patients with normal SPEM and those with impaired eye tracking in the types of delayed-response task errors made. In the normal control group, eye tracking was not associated with error types. We did not compute the correlation for the bipolar patients because they were all receiving lithium, which impairs smooth pursuit eye tracking (Levy et al., 1985). Within the schizophrenic group (lithium-free), the number of never-corrected errors per subject (i.e., those errors that probably arise from maintenance failure) was significantly correlated with smooth pursuit eye tracking performance ( $r = -.49, p < .05$ ). Thus, schizophrenic patients with impaired SPEM tend to make more of these *never-corrected* errors than do the schizophrenic patients with normal eye tracking. On the other hand, the number of errors that was corrected after one unsuccessful attempt (i.e., those errors that probably arise from interference due to competing response tendencies) was not correlated with eye tracking ( $r = .32, p > .10$ ), suggesting that schizophrenic patients with both good eye tracking and bad eye tracking were susceptible to interference from irrelevant stimuli. Therefore, in schizophrenic patients, a disruption in the process responsible for maintaining information during the delay period of the

oculomotor delayed-response task seems to be associated with impaired eye tracking performance, but inhibition of competing, irrelevant stimuli is unrelated to eye tracking performance.

#### *Initiation and execution of motor response*

In our experiments, delays in initiating responses can be observed in the response times. Schizophrenic patients were significantly slower than bipolar patients and normal controls on the memory-guided eye movement task, although they were not slower than the bipolar patients on the sensory control task (Park and Holzman, 1992, 1993). The execution of appropriate motor responses was often impeded by incorrect eye movements, which were later corrected, as discussed in the preceding section.

#### *Future directions*

It is important to note that we still do not know what disrupts the maintenance of information during the delay. Although we can rule out concurrent tasks during the delay, we cannot rule out the possibility that other distracting influences may interfere with maintenance. Stamm (1985) summarized electrocortical stimulation studies, in which the principal sulcus was stimulated during the delayed-response task. Correct performance in the monkey was disrupted *only* if the electrocortical stimulation to principal sulcus occurred during the early period of the delay (less than 2 seconds) or at the end of the cue presentation. This finding remained stable with different delay periods and with changing the hand of response. At present, Park and colleagues in Zurich are investigating the temporal parameters of working memory in schizophrenic patients. It is already known that schizophrenic patients make more errors than normals overall, but their susceptibility to distracting stimuli may also differ from normals across the delay period. Such a difference may lead us to understand more about how performance on working memory tasks can be disrupted.

In addition to the temporal parameter, the spatial properties of distracting stimuli are being studied in schizophrenic patients, patients with focal cerebral lesions and normal controls. Since the target position is thought to be spatially coded and maintained by specific

cells in the principal sulcus in rhesus monkeys (e.g., Funahashi et al. 1989, 1990, 1993), the spatial relation between the target stimulus and the distracting stimulus may be an important factor in determining susceptibility to working memory deficits. In the oculomotor delayed-response paradigm, the distracting stimulus is introduced unexpectedly during the delay period and the distance, intensity and similarity to the target stimulus are varied systematically. A parallel neurophysiological study in animals that can document cell activities during the interrupted delay period as a function of different properties of the distractor is much needed. Information on the differing efficacy of various parameters of the distractor may provide clues as to how maintenance of representation in working memory may be disrupted.

In this chapter, we have attempted to unravel what processes underlie the working memory deficit in schizophrenic patients. Judging from their pattern of errors, it seems unlikely that any one process alone is responsible for the observed delayed-response deficit. We find that there are at least two different types of errors and that only the *never-corrected* errors are associated with the SPEM deficit in schizophrenic patients. On the other hand, those errors generated by interference from competing stimuli seem to be independent of eye tracking dysfunction. It is possible that separate neuroanatomical systems are mediating these different types of errors (for example, the dorsolateral system versus the orbitofrontal system), but future studies are necessary to address this issue. Finally, we need to clarify what these errors mean in the context of specific schizophrenic symptoms.

Animal models of schizophrenia have been extremely enlightening and influential in guiding us toward formulating more lucid hypotheses. Now we need to be able to go one step further in order to integrate our findings with the clinical realities of schizophrenia. Systematic studies of working memory may help elucidate neurophysiological mechanisms and psychological processes involved in some of the cardinal symptoms of schizophrenia.

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#### References

- Baddeley, A. (1986) *Working memory*. New York: Oxford University Press.
- Bartus, R. T., and Levere, T. E. (1977) Frontal decortication in rhesus monkeys: A test of interference hypothesis. *Brain Res.* 119:133-148.
- Berman, K. F., Gold, J., Randolph, C., Jones, D. W., Berg, G. W., Goldberg, T. E., Carlson, R. E., and Weinberger, D. R. (1990) Studies of frontal lobe functions with positron emission tomography and regional cerebral blood flow. *J. of Nuclear Medicine. Proceedings of the 37th Annual Meeting*, 750.
- Blum, R. A. (1952) Effects of subtotal lesions of frontal granular cortex on delayed reaction in monkeys. *AMA Arch. Neurol. Psychiatry* 67:375-386.
- Cohen, J. D., and Servan-Schreiber, D. (1992). Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychological Review* 99(1): 45-77.
- Duncan, J. (1986) Disorganization of behaviour after frontal lobe damage. *Cognitive Neuropsychology* 3:271-290.
- Freedman, M., and Oscar-Berman, M. (1986) Bilateral frontal lobe disease and selective delayed-response deficits in humans. *Behav Neurosci.* 100:337-342.
- Funahashi, S., Bruce, C. J., and Goldman-Rakic, P. S. (1989) Mnemonic coding of visual cortex in the monkey's dorsolateral prefrontal cortex. *Journal of Neurophysiology*, 61(2): 331-348.
- Funahashi, S., Bruce, C. J., and 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., and Goldman-Rakic, P. S. (1993) Dorsolateral prefrontal lesion and oculomotor delayed response performance: Evidence for mnemonic "scotomas." *J. Neuroscience* 13(4): 1479-1497.
- Fuster, J. M. (1980) *The prefrontal cortex: Anatomy, physiology and neuropsychology of the frontal lobes*. New York: Raven Press.
- Goldberg, E., and Bilder, R. (1985) The frontal lobes and hierarchical organization of cognitive control. In E. Perecman, ed., *The frontal lobes revisited*. Hillsdale, NJ: LEA.
- Goldman, P. S., and Rosvold, H. E. (1970) Localization of function within the dorsolateral prefrontal cortex of the rhesus monkey. *Exp. Neurol.* 27:291-304.
- Goldman-Rakic, P. S. (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational knowledge. In F. Plum and

- V. Mountcastle, eds., *Handbook of physiology - The nervous system V*. 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*. New York: Raven Press.
- Gross, C. G., and Weiskrantz, L. (1964) Some changes in behaviour produced by lateral frontal lesion in the macaque. In J. M. Warren and K. Akert, eds., *Frontal granular cortex and behavior*. New York: McGraw-Hill.
- Hecaen, H., and Albert, M. (1978) *Human Neuropsychology*. New York: Wiley.
- Jacobsen, C. F. (1936) Studies of cerebral functions in primates: I. The functions of the frontal association areas in monkeys. *Comparative Psychology Monographs* 13:3-60.
- Just, M. A., and Carpenter, P. A. (1992) A capacity theory of comprehension: Individual differences in working memory. *Psychological Review* 99(1): 122-149.
- Katsanis, J., and Iacono, W. G. (1991) Clinical, neuropsychological and brain structural correlates of smooth pursuit eye tracking performance in chronic schizophrenia. *J. Abnormal Psychology* 100(4): 526-534.
- Koh, C., and Petersen, A. R. (1978) Recognition memory of schizophrenic patients. *J. Abnormal Psychology* 87:303-313.
- Kojima, S., Kojima, M., and Goldman-Rakic (1982) Operant behavioral analysis of memory loss in monkeys with prefrontal lesions. *Brain Res.* 248:51-59.
- Kolb, B., and Wishaw, I. Q. (1985) *Fundamentals of human neuropsychology* 2nd ed. New York: Freeman.
- Konorski, J., and Lawicka, W. (1964) Analyses of errors by prefrontal animals on the delayed-response test. In J. M. Warren and K. Akert, eds., *The frontal granular cortex and behavior*. New York: McGraw-Hill.
- Kraepelin, E. (1919) *Dementia Praecox*, translated by R. M. Barclay (1971). Edinburgh: Livingstone.
- Levin, S. (1984a) Frontal lobe dysfunctions in schizophrenia - I. Eye movement impairments. *Journal of Psychiatric Research* 18(1): 27-55.
- Levin, S. (1984b) Frontal lobe dysfunctions in schizophrenia - II. Impairments of psychological brain functions. *Journal of Psychiatric Research* 18(1): 57-72.
- Levy, D. L., Dorus, E., Shaughnessy, R., Yasillo, N. J., Pandey, G. N., Janicak, P. G., Gibbons, R. D., Gaviria, M., and Davis, J. M. (1985) Pharmacological evidence for specific pursuit dysfunction to schizophrenia: Lithium carbonate associated abnormal pursuit. *Archives of General Psychiatry* 42: 335-341.
- Lewinsohn, P. M., Zieler, J. L., Libet, L., Eyeberg, S., and Nielson, G. (1972) Short-term memory; a comparison between frontal and non-

- frontal right and left hemisphere brain-damaged patients. *J. Comp. Physiol. Psy* 81:248-255.
- Lhermitte, F. (1986) Human autonomy and the frontal lobes. II. Patient behavior in complex and social situations. "The environmental dependency syndrome." *Ann. Neurol.* 19:335-343.
- Lhermitte, F., Pillon, B., and Serdaru, M. (1986) Human autonomy and the frontal lobes. I. Imitation and utilization behavior: A neuropsychological study of 75 patients. *Ann. Neurol.* 19: 326-334.
- Luciana, M., Depue, R. A., Arbisi, P., and Leon, A. (1992) Facilitation of working memory in humans by a D2 dopamine receptor agonist. *Journal of Cognitive Neuroscience* 4(1): 58-68.
- Luria, A. R. (1966) *Higher cortical function in man*. New York: Basic Books.
- Luria, A. R. (1973) The frontal lobes and regulation of behavior. In K. Pribram and A. R. Luria, eds., *Psychophysiology of the frontal lobes*. New York: Academic Press.
- Milner, B. (1963) Effects of different brain lesions on card sorting. *Archives of Neurology* 9:100-110.
- Mishkin, M., and Bachevalier, J. (1983) Object recognition impaired by ventromedial but not dorsolateral prefrontal cortical lesions in monkeys. *Soc. Neurosci. Abstr.* 9:29.
- 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.
- Park, S. (1991) The role of prefrontal cortex in spatial working memory deficits of schizophrenic patients. Doctoral Dissertation. Harvard University.
- Park, S., and Holzman, P. S. (1991) The role of prefrontal cortex in spatial working memory deficits of schizophrenic patients. *Schizophrenia Research*, 4(3), abstracts supp.
- Park, S., and Holzman, P. S. (1992) Schizophrenics show working memory deficits. *Arch. Gen. Psychiatry* 49:975-982.
- Park, S., and 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., and Lenzenweger, M. L. (1995) Individual difference in spatial working memory in relation to schizotypy. *Journal of Abnormal Psychology* 104(2): 355-364.
- Park, S., Holzman, P. S., and 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(2): 184.
- Paulescu, E., Frith, C. D., and Frackowiak, R.S.J. (1993) The neural components of working memory. *Nature* 362: 342-345.



- Petrides, M., and Milner, B. (1982) Deficits on subject-ordered tasks after frontal and temporal lobe lesions in man. *Neuropsychologia* 20:249-262.
- Roitblat, H. L. (1987). *Introduction to comparative cognition*. New York: Freeman.
- Sawaguchi, T., and Goldman-Rakic, P. S. (1991) D<sub>1</sub> Dopamine receptors in prefrontal cortex: Involvement in working memory. *Science* 251: 947-950.
- Shallice, T. (1982) Specific impairments of planning. *Phil. Trans. Royal Soc. Lon: B.*, 199-209.
- Shallice, T. (1988) *From neuropsychology to mental structures*. Cambridge University Press.
- Shiffrin, R. M., and Schneider, W. (1977) Controlled and automatic human information processing II. *Psychological Review* 84:127-190.
- Stamm, J. S. (1985) The riddle of the monkey's delayed response deficit has been solved. In E. Perecman, ed., *The frontal lobes revisited*. Hillsdale, NJ: LEA.
- Taylor, A. E., Saint-Cyr, J. A., and Lang, A. E. (1986) Parkinson's disease, cognitive changes in relations to treatment response. *Brain* 110:35-51.
- Weinberger, D. R., Berman, K. F., and Zec, R. F. (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. regional cerebral blood flow evidence. *Arch. Gen. Psychiatry* 43:114-124.
- Yesutis, J. (1990) Spatial memory and schizophrenia. Unpublished senior thesis, Harvard University.

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## Temporal lobe structural abnormalities in schizophrenia: A selective review and presentation of new magnetic resonance findings

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It seemed not improbable that cortical centres which are last organized, which are the most highly evolved and voluntary and which are supposed to be localized in the left side of the brain, might suffer first in insanity.

Crichton-Browne (1879), p. 42

### I. Introduction

Schizophrenia is a major mental illness that affects 1% of the general population and is extremely costly to the patient, family, and larger community. Unfortunately, its etiology is as yet unknown, and for this reason it is categorized as a "functional" psychosis rather than an "organic" psychosis, a category which implies that it arises from no known structural or pathological alteration of the brain. The role of brain dysfunction, however, in the etiology of schizophrenia seems likely in light of recent brain structural and functional studies, and has been suspected since Kraepelin (1919/1971) and Bleuler (1911/1950) first delineated the syndrome(s). Kraepelin, in fact, believed that the symptoms of schizophrenia, which he called Dementia Praecox, would ultimately be linked to abnormalities in both the frontal and temporal lobes. He believed that the frontal lobes were responsible for the disruption in reasoning so clearly evident in schizophrenia, while the temporal lobes were responsible for auditory hallucinations and delusions. Other workers at the close of the nineteenth century, such as Crichton-Browne, quoted above, as well as Alzheimer (1897), Kahlbaum (1874), and Hecker (1871) also believed that to understand the etiology of severe mental illnesses, such as schizophrenia, an understanding of the brain was necessary. Consequently, this peri-