Brain mechanisms

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Editor's introduction: From controversy to connectivity

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> In medicine and in natural science, it is in general the rule that only the positive findings prove something, but that negative results often only state that we are not able as yet to achieve the positive.
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> From "The Problem of the Anatomy of Schizophrenia," by Spielmeyer (1930)

In the early part of this century, brain imaging and histopathologic strategies were used extensively to investigate whether there is a neuroanatomic substrate to schizophrenia. Today, it is well known to those who study schizophrenia that these investigations yielded inconsistent findings and ultimately gave rise to a controversy that has been without precedent in the field of neuroscience. In its most essential form, the dispute regarding a structural defect in schizophrenia rested on the dichotomy between the view that schizophrenia is a neurodegenerative disorder and the opposing one, that it is not due to an organic problem. The implication of the latter viewpoint was that schizophrenia is a "functional" entity in which there are no objective changes in the structural integrity of the brain. Those supporting the idea that schizophrenia is a brain disorder were consigned to an historic tomb where no respectable scientists of that era would dare to be found.

As Spielmeyer's quote at the beginning of this section implies, the belief that a structural defect is present in the brains of schizophrenics was less remarkable than the contrary belief, that there is no anatomic substrate to schizophrenia. By supporting the latter possibility, the nay-sayers proved nothing about schizophrenia. The inability of early investigators to demonstrate convincingly either positive *or* negative findings in the brains of schizophrenic subjects can now be understood in the context of the limited techniques available to ad-

dress such a complex question. From today's perspective, one cannot have confidence in data (a) not derived by quantitative techniques, (b) not acquired under blind conditions, (c) not based on the diagnosis of the schizophrenic cases using validated criteria, and (d) often not having a normal control group for comparison. Even if these design considerations had been routinely incorporated into histopathologic study designs of that period, the investigations conducted during the first half of this century would still have been futile because the analytic approaches employed were not sensitive enough to reveal subtle changes in connectivity (Benes, 1988).

Chapters 2 through 6 of this section describe sophisticated technological approaches that are now being routinely applied to the study of schizophrenia. In the field of brain imaging, magnetic resonance technology can now routinely attain a level of spatial resolution that is orders of magnitude greater than that provided by pneumoencephalography. This improved anatomic resolution, particularly when combined with functional imaging capabilities, will eventually allow investigators to establish meaningful relationships between cognitive processes and specific anatomic regions of interest, and will help to characterize the *macroanatomic circuitry* affected in schizophrenia.

In recent years, many different cortical and subcortical brain regions have been implicated in the pathophysiology of schizophrenia. By using a combination of behavioral, electrophysiological and ultrastructural analyses, basic neuroscientists are beginning to identify the intrinsic circuitry present within key corticolimbic regions of rodent and primate brain and are using such information to begin modelling different aspects of the schizophrenic syndrome. In postmortem research, recently developed molecular probes have made it possible to begin analyzing the neural circuitry involved in higher cognitive function. By using receptor binding autoradiography, immunocytochemistry, and *in situ* hybridization, investigators are comparing findings in normal and schizophrenic subjects and are attempting to solve the conundrum as to how thinking becomes disordered in schizophrenia.

Two particularly important innovations have enabled the neuroscience community to respond to the challenge posed by Spielmeyer (1930). The first came in 1972, when Ewald Weibel demonstrated that three-dimensional biological structures can be expressed and quantified using mathematical equations. With the development of stereomorphometry as a field, structural images, once evaluated subjectively, could now be analyzed with standardized approaches to both

sampling and measurement. It soon became apparent, however, that enormous amounts of primary microscopic data could be obtained with stereomorphometric approaches. In fact, the greater the amount of data collected, the more reliable would be the answer obtained. Ironically, stereomorphometry created an entirely new problem for neuroscientists, one for which the solution would require massive database management capabilities. Computer-assisted technology for quantifying, storing, and statistically analyzing neuroanatomical information has been a critical advance for the field of neuroscience in general, and for the study of schizophrenia in particular. Today, it is routinely possible for investigators studying this disorder to collect extremely large amounts of data, often from digitized images, and, using sophisticated statistical software, to "number crunch" this information so that meaningful comparisons can be made. Twenty years ago, it would have been virtually impossible for a neuroscientist to complete a morphometric analysis of regional volume or cell counts using the manual methods available prior to computerization. Today, however, computer-assisted technology is routinely applied to the study of the human brain and, together with stereomorphometric principles, it is a *sine qua non* for histopathologic studies of schizophrenia.

Even with computer assistance, stereomorphometric analysis remains a highly labor-intensive, time-consuming undertaking, one that still tries the endurance and persistence of those who use it. During Spielmeyer's period, neuroscientists were probably as hardworking and dedicated as those who study schizophrenia today. Unlike this current generation of schizophrenia researchers, Spielmeyer's colleagues had neither stereomorphometry nor computer-assisted analysis available to them, and could not have imagined the directions that studies of the central nervous system would be taking in the final decades of the twentieth century.

The chapters in this section illustrate in different ways how the technological advances of stereomorphometry and computer-assisted analysis have become common denominators in studies of schizophrenia, whether they are performed ante- or postmortem, and whether they employ *in vivo* imaging or postmortem microscopy. Thus far, the most significant advance in our understanding of the pathophysiology of schizophrenia is that it is due not to a neurodegenerative process but, rather, to subtle changes of neural circuitry in key regions of the corticolimbic system. Using computer-assisted

stereomorphometry, this field is beginning to define the discrete aspects of faulty wiring present in subjects with schizophrenia and, in so doing, is moving from uninformed controversy toward a detailed understanding of altered connectivity in schizophrenia. We can now appreciate that Spielmeyer showed not only insight, but also prescience when he recognized that the ignorance of his time could be cured only by scientific advances not available during his lifetime, perhaps advances he himself might have imagined. There is now reason to feel optimistic about our prospects for defining the alterations in neural circuitry that are present in individuals who suffer from schizophrenia.

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The functional parcellation of dorsolateral prefrontal cortex and the heterogeneous facets of schizophrenia

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Introduction

Neuropsychological evidence and clinical observations have repeatedly, directly or indirectly, implicated the prefrontal cortex as a site of dysfunction in schizophrenia – based on the similarity of impairments observed in demented patients and those with frontal lobe damage (e.g., Farkas et al., 1984; Levin, 1984a, 1984b; Weinberger et al., 1986; Goldman-Rakic, 1987, 1991). Although such findings have significantly advanced the empirical support for the "frontal-lobe" hypothesis, countless other results in the literature leave considerable room for doubt about any singular explanation for this heterogeneous disorder. Whatever the status of prefrontal involvement in schizophrenia, basic studies of its structure and function have provided support for two major conclusions: Prefrontal cortex is specialized to direct or guide behavior by internalized representations of facts, events and other memoranda (Goldman-Rakic, 1987), and prefrontal cortex carries out its functions through interactions within a complex distributed network of reciprocating pathways (Goldman-Rakic, 1988a, 1988b; Selemon and Goldman-Rakic, 1988; Goldman-Rakic et al., 1993).

It has been argued elsewhere that guiding behavior by representations – ideas and concepts – normally requires working memory and that schizophrenic thought disorder could involve a breakdown in this basic capacity for "on line" processing (Goldman-Rakic, 1987; 1991). This framework incorporates the traditional views of prefrontal association cortex as the area of the brain essential for executive (Luria, 1966; Shallice, 1982), conceptual (Goldstein, 1949) and temporal integration (Fuster, 1980; Ingvar, 1980; Milner et al., 1985) but pro-

poses a unifying theoretical foundation, cellular mechanisms and modular functional architecture out of which such complex functions as comprehension, reasoning and intentionality could emerge. If, as we have argued, the prefrontal cortex is the node in a circuit where internalized schemata, symbolic representations and ideas from long-term memory are brought to bear on ongoing events, it is not difficult to imagine that a defect in this node or in any other that feeds into it, could lead to scrambled language and disordered thinking. In our view, it is conceivable that thought disorder and behavioral disorganization may be reducible to an impairment of the operational mechanism(s) by which symbolic representations are both accessed from long-term memory and held "in mind" to guide behavior in the absence of instructive stimuli in the outside world. Basic studies of the prefrontal cortex would be central to understanding this mechanism.

This chapter reviews recent evidence from experimental research with nonhuman primates that links specific regions of prefrontal cortex to specific functions shown to be defective in schizophrenics – smooth pursuit tracking, Wisconsin Card Sort Test and delayed-response performance. Although these tasks are formally quite dissimilar, we have argued that each requires working memory to one degree or other and I believe it is this feature that makes them both vulnerable to prefrontal damage in humans and markers of prefrontal dysfunction in patients suffering from schizophrenia and/or other dementias. If the working memory demand in neuropsychological tests and in human cognition generally can be shown to be the common nexus of vulnerability in a disease such as schizophrenia, this functional thread should lead to improvement in diagnosis and possibly in treatments. Further, to the extent that specific deficits associated with schizophrenia (or any other dementia) are also associated with specific regions of the prefrontal cortex, where working memory functions are most developed, the frontally lesioned monkey may provide an important animal model of schizophrenia.

It follows that tasks designed to tap working memory will be (1) impaired in schizophrenic subjects; (2) dissociable from sensory-guided performance; and (3) correlated with their clinical symptoms. Further, prefrontal cortex of schizophrenic patients might be expected to exhibit pathophysiological changes at some stage of the illness. Nevertheless, the view that schizophrenic thought disorder is defective regulation of behavior by current internalized schemata or symbolic representations and information from long-term storage fo-

cuses attention on defective *processing* rather than on abnormal content or abnormal structure. Ultimately, we will need to address the extent to which thought disorder expressed by patients in their daily lives can be related to the variety of impairments exhibited in psychologically more delimited performance designed to test working memory processes.

The definition of working memory

Working memory is a concept developed by cognitive psychologists to refer to a distinct operation required for cognition, namely, the ability to update and/or bring information to mind from long-term memory and/or to integrate incoming information for the purpose of making an informed decision, judgment or response (Baddeley, 1986). As explained by Baddeley, the transient and active memory system referred to here as "working memory" evolved from the older concept, "short-term" memory. Working memory can be distinguished operationally from canonical or associative memory by several formal criteria: (i) its short duration; (ii) its limited capacity, and, I contend (iii), its neural substrate (Goldman-Rakic, 1987).

Most formal neuropsychological tasks have components of both associative and working memory. For present purposes, I suggest that a test can be judged as tapping working memory if its performance depends upon: (1) instructions, calculations, i.e., any information that *is not present in the environment* at the time of response choices and/or (2) requires *updating of current and/or past information on a moment-to-moment basis.* The classical delayed-response tasks used extensively in animal research are prime examples of tasks that tax a subject's ability to hold information "in mind" for a short period of time because correct performance on such tasks is memory-guided rather than sensory-guided and their correct execution requires constant updating of the relevant information; a habitual or stereotyped pattern of responding will lead to error as contingencies change from trial to trial or, in real life, moment-to-moment. The relevant memorandum in spatial delayed-response tasks is the location or direction of an object. The relevant memorandum in the Wisconsin Card Sort Test (WCST) is a categorical representation of the attributes of an object (e.g., its color or shape). Few tests are pure tests of working memory and so their effectiveness as tests of psychological dysfunction will depend on their loading upon these factors.

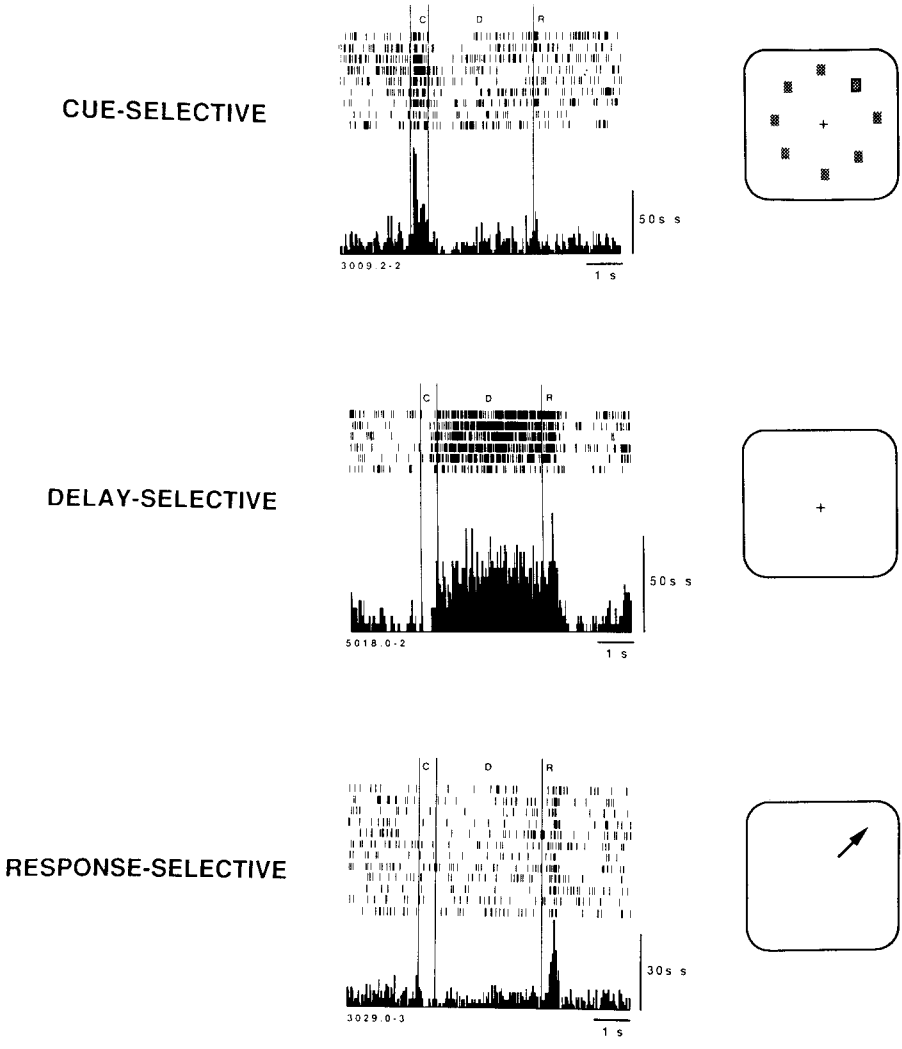

Figure 2.1. This figure displays from top to bottom the main events of an oculomotor delayed-response task and the three principal types of neurons – cue-selective, delay-selective and response-related – that can be recorded from area 46 in the dorsolateral cortex during the performance of the oculomotor delayed-response task. The cue-selective type of cell registers the incoming sensory cue (indicated by the darker square) with a brief phasic response; the delay-selective neuron is tonically activated after the cue disappears and remains activated until a response is initiated at the end of the delay; the response-related neuron displays a phasic response in relation to the eye movement either before the motion is initiated (presaccadic) or after it is completed (post-saccadic). Most neurons recorded in prefrontal cortex are directionally tuned and exhibit their most robust response only for stimuli of a particular direction. Many cells have compound

Oculomotor and manual delayed-response tasks

Studies in nonhuman primates

Delayed response. Monkeys are capable of remembering briefly presented visuospatial information over short delays – in the classical spatial delayed-response tasks (for review, see Goldman-Rakic, 1987; Fuster, 1989) as well as in the more demanding 8-item oculomotor version of that task (Funahashi et al., 1989). The ability of monkeys to retain in working memory an item of spatial information is not unlike the capacity of a human to remember a seven-digit phone number, the name of the individual just introduced, or the last hand in a bridge game. As is well established, lesions of the dorsolateral prefrontal cortex produce marked impairments on spatial delayed-response and delayed-alternation tasks and the cortical focus for these deficits is the principal sulcus (or Walker's area 46). Importantly, equally large lesions elsewhere in the parietal or temporal lobes or in other portions of prefrontal cortex fail to produce consistent or profound deficits on these tasks even though these areas of the cortex are connected with the prefrontal areas and are activated during the performance of working memory tasks (Friedman and Goldman-Rakic, 1988, 1994). Thus, many areas of the cortex contribute to performance of complex tasks but few are specialized for the *working memory component* of the performance.

Studies in this laboratory have employed an oculomotor delayed-response (ODR) paradigm to study the physiology of working memory in the rhesus monkey (Funahashi et al., 1989, 1990, 1991, 1993a). The modification of this task employed by Park and Holzman (1992; see below and elsewhere in this volume) is similar in all essential details to that used by Funahashi et al. (1989). As depicted in Figure 2.1, in the nonhuman version of the paradigm, the monkey is required to fixate a central point at the center of a TV monitor during all phases of the trial. In experiments with nonhuman primates, the

Caption to Figure 2.1. *(cont.)*
responses, i.e., show combinations of cue-, delay- and response-related activation. The three types of neurons with common directional "fields" may be interconnected within a columnar unit of cortex. The response of a given cell appears to be the same trial after trial as observed from the pattern of activation in the rasters displaying activity on the individual trials from which the cell's average response is derived.