Functional and Anatomical Aspects of Prefrontal Pathology in Schizophrenia

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Abstract

Clinical and experimental research have provided anatomical, pharmacological, and behavioral evidence for a prominent prefrontal dysfunction in schizophrenia. Negative symptoms and behavioral disorganization in the disorder can be understood as a failure in the working memory functions of the prefrontal cortex by which information is updated on a moment-to-moment basis or retrieved from long-term stores, held in mind, and used to guide behavior by ideas, concepts, and stored knowledge. This article recounts efforts to dissect the cellular and circuit basis of working memory with the goal of extending the insights gained from the study of normal brain organization in animal models to an understanding of the clinical disorder; it includes recent neuropathological findings that indicate that neural dystrophy rather than cell loss predominates in schizophrenia. Evidence from a variety of studies is accumulating to indicate that dopamine has a major role in regulating the excitability of the cortical neurons upon which the working memory function of the prefrontal cortex depends. Interactions between monoamines and a compromised cortical circuitry may hold the key to the salience of frontal lobe symptoms in schizophrenia, in spite of widespread pathological changes. We outline several direct and indirect intercellular mechanisms for modulating working memory function in the prefrontal cortex based on the localization of dopamine receptors on the distal dendrites and spines of glutamatergic pyramidal cells and on gamma-aminobutyric acid (GABA)ergic interneurons in the prefrontal cortex. Understanding the interactions between the major cellular constituents of cortical circuits—pyramidal and nonpyramidal cells—is a necessary step in unraveling the receptor mechanisms, which could lead to an effective pharmacological treatment of negative and cognitive symptoms, as well as improved insight into the pathophysiological basis of the disorder.

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Schizophrenia is commonly considered to be among the most intractable of mental illnesses and among the least comprehensible in terms of neurobiological mechanisms. Heterogeneity marks its phenotypic expression among different individuals, its multiple etiological paths, its fluctuations in different stages of the illness, and its responsiveness to treatment. It is unremarkable then that no one system of the brain nor singular dysfunction has been accepted as central to the pathophysiology of the disease. Yet, as more is learned about the brain and its integrative systems, there is every reason to seek unifying hypotheses that explicate the common threads among sufferers that classify them as having schizophrenia. It seems reasonable to proceed on the assumption that the major symptoms arise from disturbances in different brain areas and that explicit linkages exist between cellular changes in these areas and the information-processing failures that result in psychopathological signs and symptoms. Any full account of schizophrenia should meet the test of comportment with convergent evidence from neurophysiology, neuropsychology, and neuroanatomy.

Previously, it has been argued that dysfunction in working memory is a fundamental deficit underlying the cognitive features of schizophrenia and, as such, invokes cellular mechanisms intrinsic to the prefrontal cortex (Goldman-Rakic 1987, 1991, 1995*a*, 1995*b*). The disorganized thought process in schizophrenia patients that manifests itself in idiosyncratic content may be reducible to an impairment of the neural mechanisms by which symbolic representations are both retrieved from long-term memory

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and held "in mind" to guide behavior in the absence of instructive stimuli in the outside world. It is now becoming possible to further specify the cellular mechanisms that underlie working memory, the breakdown of which could lead to psychopathology. In particular, evidence is accumulating to suggest that the modulation of pyramidal cell firing, particularly in prefrontal cortex, may hold the key to an understanding of cognitive dysfunction. The purpose of this article is (1) to review briefly and selectively the association of working memory with prefrontal cortex and outline its relevance to schizophrenia, (2) to examine the neuropathological evidence for involvement of prefrontal cortex in the disorder, and (3) to elaborate on the neurobiological framework that we believe to be essential for further progress in understanding the breakdown of prefrontal circuits that may underlie diseases such as schizophrenia.

A few caveats are in order, however, to dispel misconceptions about the working memory/frontal lobe hypothesis. First, cognitive neuroscience and neuropsychology have advanced to the stage where it is possible to be quite specific as to the areal and often the cellular level of analysis. When discussing the frontal lobe involvement in schizophrenia, it is important to designate which portion of this large territory and which of its ascribed functions is under consideration. Since the prefrontal cortex comprises several different areas, each defined by distinct anatomical connections, the range of affective and cognitive symptoms associated with schizophrenia may reflect the involvement to different degrees of one or more subsystems of the medial and posterior orbitofrontal as well as the dorsolateral regions that have recently received more attention. Although in this article we focus on the dorsolateral prefrontal cortex, the cellular findings reviewed below may apply to these other areas as well. Second, neither the working memory hypothesis nor the frontal lobe hypothesis generally requires an obvious or specific type of lesion in the prefrontal cortex, nor does each presume the basic cellular, pharmacological, developmental, or genetic defect in the disease. Finally, it should be very clear that a major role for the prefrontal cortex in schizophrenia necessarily implicates the basal ganglia, thalamus, brainstem, hippocampal formation, and other neocortical areas in the pathophysiology of the disorder. Indeed, volume losses that have been observed in medial and lateral temporal lobe structures have been correlated with frontal lobe impairment (Shenton et al. 1992; Bilder et al. 1995). We have consistently emphasized that the prefrontal cortex carries out its functions through interactions within a complex distributed array of anatomically and functionally related areas (Goldman-Rakic 1987, 1988*a*, 1988*b*; Selemon and Goldman-Rakic 1988; Goldman-Rakic et al. 1993). Moreover, our recent postmortem study of prefrontal cortex in schizophrenia patients has revealed changes in regions as widespread and functionally diverse as the primary visual and prefrontal cortices (Selemon et al. 1995); these findings add to the considerable evidence for pathological changes in other regions of the schizophrenic brain (see below) and lead us to conclude that the pathological process in this disease does not respect regional boundaries. Thus, a major issue for the field and for advocates of a frontal lobe focus of psychopathology is to examine if and how "frontal" symptoms come to predominate in a condition that may involve widespread pathological changes. Obviously, this is the burden for any pathophysiological theory that assigns predominance to one basic function (e.g., sensory gating or attentional deficits) or brain area (e.g., anterior cingulate, posterior cingulate, superior temporal, hippocampal areas). In the face of such complexity, we turn to the basic anatomy, physiology, and functions of normal model systems as a starting point for approaching the neurobiology of mental disease and for pursuing a rational approach toward its diagnosis and treatments.

Prefrontal Cortex, Working Memory, and Schizophrenia

There are considerable grounds on which to conceptualize the disorganization in thought and behavior of schizophrenia patients in terms of profound information-processing deficits (Goldman-Rakic 1987, 1991, 1995*a*, 1995*b*; Goldman-Rakic and Chafee 1994). Among these, a working memory deficiency compels consideration as one explanation of the behavioral disorganization, features of negative symptoms, and perhaps even some features of positive symptomatology that typify schizophrenia. This section provides a brief review of working memory as a psychological concept and of its linkage to the basic functional and anatomical organization of the prefrontal cortex.

Definition and Functional Architecture of Working Memory. The conception of working memory in this and previous articles follows, in most respects, that based on studies of normal human cognition; it encompasses both storage and processing functions that together support the distinctively human capacities of comprehension, computation, and planning (Atkinson and Shiffrin 1968; Baddeley 1986; Newell and Simon 1972; Carpenter and Just 1988). In its barest form, working memory serves as a computational arena or workspace for holding items of information in mind as they are recalled, manipulated, and associated to other ideas and incoming information.

Individuals with working memory problems are not amnestic, agnostic, or aphasic, and their sensory and gross motor capacities can be within the normal range. Rather, their problem lies in retrieving and processing information from past experience or keeping in mind a concept, idea, or schema to guide current behavior. Baddeley's (1986) metaphor of a mental "sketchpad" is appropriate for its implication both of limited capacity and of erasability. It is not difficult to imagine how a failure in the retrieval component, the transient storage component, or the erasure mechanism of working memory could result in either impoverished thought processes on the one hand or repetitive or perseverative thought processes on the other.

Modular Architecture of Working Memory. Experimental studies in nonhuman primates indicate that there may be multiple working memory domains within the prefrontal cortex, each with its own specialized "central processor" and content-specific storage mechanisms that are organized in distinctly parallel anatomical networks (Goldman-Rakic 1987, 1988*a*; Selemon and Goldman-Rakic 1988; Cavada and Goldman-Rakic 1989*a*, 1989*b*; Wilson et al. 1993). Visuospatial processing as studied by delayed response tasks relies on the dorsolateral prefrontal convexity both in monkeys (Fuster and Alexander 1971; Kubota and Niki 1971; Friedman and Goldman-Rakic 1988, 1994; Funahashi et al. 1989; MacAvoy et al. 1991) and in humans (Freedman and Oscar-Berman 1986; Verin et al. 1993), and these same areas are consistently activated as human subjects retrieve visuospatial information from long-term storage or immediate experience through representation-based action (McCarthy et al. 1994; Nichelli et al. 1994; Baker et al. 1996; Gold et al. 1996; Goldberg et al. 1996; Owen et al. 1996; Smith et al. 1996; Sweeney et al. 1996). In contrast, working memory for the features of objects or faces engages anatomically different, more lateral and inferior prefrontal regions in both species (Wilson et al. 1993; Cohen et al. 1994; Adcock et al. 1996; Courtney et al. 1996; McCarthy et al. 1996), and semantic encoding and retrieval as well as other verbal processes engage still more inferior, insular, and anterior prefrontal regions (Paulesu et al. 1993; Raichle et al. 1994; Demb et al. 1995; Fiez et al. 1996; Price et al. 1996). To date, noninvasive imaging of subjects performing working memory tasks has failed to identify one common locus of a central "executive processor" (Baddeley 1986) or contention scheduler (Shallice 1982) that would mediate any and all informational systems. On the contrary, it is now possible to reference specific neuropsychological deficits associated with schizophrenia to specific areas of the prefrontal cortex (for review, see Goldman-Rakic 1996). Nevertheless, one might not expect to find a circumscribed lesion in one and only one area of the prefrontal cortex in psychiatric disease (or any other endemic condition) that would result in a region-specific profile of impairment on the one hand or across-the-board processing deficits on the other.

Prefrontal Dysfunction in Schizophrenia. The evidence for the direct dependence of intact cognitive function upon the integrity of the prefrontal cortex in schizophrenia is overwhelming and takes several forms. A persuasive line of support comes from positron emission tomography (PET) of deficient blood flow or metabolism in the prefrontal cortex of schizophrenia subjects, particularly during behavioral performance (Franzen and Ingvar 1975; Buchsbaum and Ingvar 1982; Ariel et al. 1983; Buchsbaum et al. 1984; Farkas et al. 1984; Kurachi et al. 1985; Berman et al. 1986; Chabrol et al. 1986; Guenther et al. 1986; Volkow et al. 1987; Mathew et al. 1988; Wolkin et al. 1988; Paulman et al. 1990; Sagawa et al. 1990; Andreasen et al. 1992; Cohen and O'Leary 1992; Liddle et al. 1992; Goldberg et al. 1996; Weinberger et al. 1996). An equally strong line of evidence derives from neuropsychological and neurophysiological observations that have repeatedly highlighted similarities of impairments observed in patients with schizophrenia and in those with frontal lobe damage (Morihisa et al. 1983; Knight 1984, 1992; Levin 1984; Frith and Done 1988; Williamson et al. 1989; Merriam et al. 1990; Goldman-Rakic 1991, 1995*a*, 1995*b*; Liddle and Morris 1991; Park and Holzman 1992, 1993; Goldberg et al. 1993; Javitt et al. 1993). Patients compromised by frontal lobe lesions and schizophrenia patients are similarly impaired on the Continuous Performance Task (Rosvold 1956; Buchsbaum et al. 1990); on tests of categorization and flexibility, such as the Wisconsin Card Sort Test (Milner 1964; Kolb and Whishaw 1983; Weinberger et al. 1986; Seidman et al. 1991; Franke et al. 1992; Heaton et al. 1993), the Stroop Test (Stroop 1935; Abramczyk et al. 1983; Everett et al. 1989; Schooler et al. 1997), and the Tower of London task (Perret 1974; Shallice 1982; Andreasen et al. 1992); and on oculomotor delayed-response paradigms (Guitton et al. 1985; Fukushima et al. 1988; Hommer et al. 1991; Park and Holzman 1992; Currie et al. 1993; Pierrot-Deseilligny et al. 1993). Although these tasks are formally quite dissimilar, each requires working memory (e.g., keeping a running record of recent events or instructions), and it is this feature that makes them both vulnerable to prefrontal damage in humans and markers of prefrontal dysfunction in patients suffering from schizophrenia or other dementias.

Questions for Future Research on Working Memory Dysfunction and Schizophrenia. At least three lines of

research have been opened up by the findings described above. First is the interest in applying PET or functional magnetic resonance imaging (fMRI) to determine the full range of prefrontal areas and prefrontal functions in which blood flow and metabolism may be abnormal. A useful approach would be to determine whether the several working memory domains (spatial, object, and verbal) are differentially vulnerable in schizophrenia and whether patients show diverse patterns of activation that are related to the expression of clinical symptoms. Although visuospatial working memory has been shown to be impaired in schizophrenia subjects, other working memory domains could also be compromised, possibly more severely. Strous et al. (1995) have recently shown that schizophrenia patients are impaired in the ability to match two tones after a 300-ms delay, but are unimpaired when there is no delay, thus providing evidence that schizophrenia patients have deficits in auditory processing when it involves memory guidance and therefore frontal lobe function. Such deficits may be causal for language disturbance. Context-dependent verbal working memory in schizophrenia patients has been correlated with volume loss in dorsolateral prefrontal cortex (Maher et al. 1995). Disturbance in echoic memory (Strous et al. 1995), semantic priming (Spitzer et al. 1993), and sentence completion (Salzinger et al. 1970) may also derive from an underlying deficit in auditory/linguistic working memory and prefrontal dysfunction, but these associations are still mainly conjectural. The use of verbal working memory, dual task paradigms, and other means of examining the temporal parameters of working memory within and across information-processing domains in patients and controls would be particularly illuminating. The recent studies of Currie et al. (1993) and Schooler et al. (1997) exemplify the departure from pure demonstration experiments to an analytic focus on the temporal dynamics, memory spans, and other indices of transient storage capacity in patients versus control populations.

Second, research is needed on the relationship between the clinical symptoms expressed by patients in their daily lives and the variety of impairments exhibited in psychologically more delimited performance designed to test working memory processes. If, as has been argued, the prefrontal cortical areas are the places where internalized schema, 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 one of these domains or in any other of the nodes that feed into it could lead to loose associations, scrambled language, disorder thinking, and erratic or apathetic behavior; such a defect could also be highly correlated with formal thought disorder. At present, the evidence on this point is all too limited. The Tower of London task has been correlated with high scores for negative symptoms (Andreasen et al. 1992). Correlations between negative symptoms and MRI spectroscopic evidence of prefrontal pathology have also been reported (Williamson et al. 1991). 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 to behavioral modification procedures that recognize the loss of "on line" processing ability.

Finally, research is needed on the extent to which the cortical areas that are anatomically and functionally interconnected with the prefrontal cortex are functionally disconnected, as described by Liddle et al. (1992), Weinberger et al. (1992), and Friston et al. (1996). Studies on nonhuman primates have provided both anatomical (Goldman-Rakic et al. 1984; Cavada and Goldman-Rakic 1989*b*) and functional (Friedman and Goldman-Rakic 1994; Goldman-Rakic and Chafee 1994) evidence for powerful prefrontal regulation of posterior cortical areas.

Prefrontal Cortex and Neuropathology

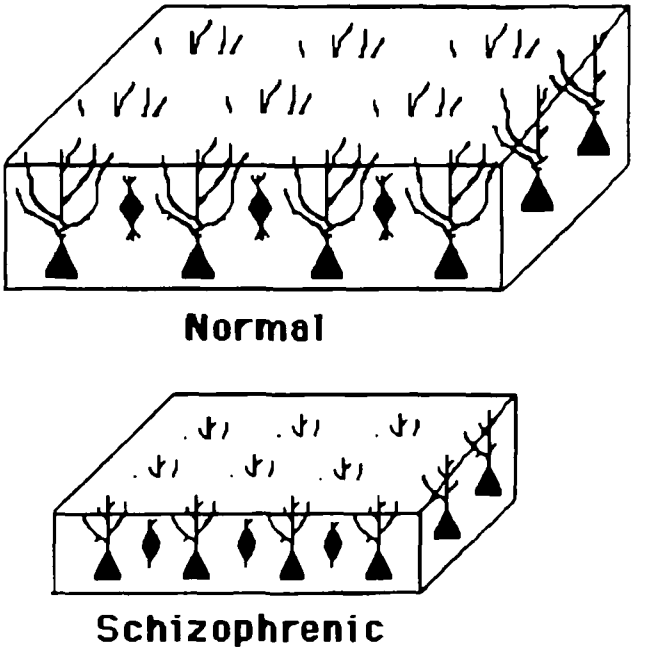
Because of the role of the prefrontal cortex in working memory functions and the evidence that working memory deficits are prominent in schizophrenia patients, some sign of compromise of the structural integrity of prefrontal cortex could be expected in this disorder. However, postmortem examination of brains of schizophrenia subjects has generally not revealed gross morphometric alteration in most neocortical areas examined, including the prefrontal cortex. The recent application of quantitative immunocytochemical and histochemical methods to well-documented case material has occasioned a resurgence of interest in postmortem studies, and many differences in cellular pathology between schizophrenic and normal prefrontal cortices have emerged (for recent reviews see Bogerts 1993; Shapiro 1993; Benes 1995). Additionally, modern methods of brain imaging, particularly MRI for analysis of volumetric changes, are providing a rich and invaluable complementary source of data in the brains of living subjects.

Postmortem Studies of Prefrontal Cortex Reveal Subtle Pathological Changes. We have recently completed a detailed morphometric analysis of Brodmann's area 9 in the prefrontal cortex in schizophrenia patients and controls using a three-dimensional counting method (Selemon et al. 1995). The stereological method we used is one of several that avoid the counting errors to which

traditional methods are prone (Williams and Rakic 1988). Brodmann's area 9 was selected in this initial study because its location is particularly easy to track in different brains. With this new and more sensitive methodology, we observed an abnormally high neuronal density in conjunction with reduced cortical thickness. Layer V is the site of the largest increase in area 9, but neuronal density is also elevated in layers III through VI (Selemon et al. 1995). Similar increases in neuronal density have also been found in prefrontal area 46 (Selemon et al., unpublished observations) and in the primary visual cortex (Selemon et al. 1995). Thus, the morphometric abnormality we have uncovered is widespread and not confined to those regions of the cerebral mantle that have classically been labeled dysfunctional in schizophrenia. Further, the cells that appear most vulnerable in the disease are the larger pyramidal neurons of layer III (Rajkowska et al. 1995), rather than the smaller cells associated with nonpyramidal morphologies that are compromised in the cingulate cortex (Benes et al. 1991). Neurons in layers III and V project to other cortical areas, whereas those in layer V project, in addition, to the caudate nucleus and superior colliculus. These findings point to a prominence of cortico-cortical circuitry in schizophrenia and are in agreement with structural findings obtained with MRI that report either a frontal lobe volume reduction (e.g., Andreasen et al. 1990*a*; Breier et al. 1992; Raine et al. 1992; Zipursky et al. 1992; Nopoulis et al. 1995) or a widespread cortical volume reduction that is relatively greater in the prefrontal cortex (Lim et al. 1995; Sullivan et al., in press). An increase in neuronal density in layer V of Brodmann's area 10 was also reported by Benes et al. (1991), and in agreement with our results, Daviss and Lewis (1995) have observed an increased density of calbindin-stained neurons in areas 9 and 46. Enlargement of the cerebral ventricles and of the anterior horns in particular (Brown et al. 1986; Andreasen et al. 1990*b*; Shiraishi et al. 1990), and increased sulcal width (Weinberger et al. 1979; Shelton et al. 1988; Friedman et al. 1993) are all supportive of prefrontal volume reduction and indicative of possible cellular atrophy.

On the basis of our findings of increased neuronal density and decreased cortical thickness, we have hypothesized that the intraneuronal neuropil—the space between cells—is reduced in the cortex of subjects with schizophrenia (figure 1) (Selemon et al. 1995). This space is packed with the dendritic processes of pyramidal and nonpyramidal neurons and the axonal processes of both intrinsic and extrinsic neurons; this denser cell packing indicates that the meshwork of connectivity in which cortical neurons are embedded may be underrepresented in the brain of schizophrenia subjects. Other constituents

Figure 1. Higher cell-packing density as observed in postmortem prefrontal cortex of schizophrenia patients in the study of Selemon et al. (1995)



of the neuropil, such as blood vessels and glial cells, may also be affected. The interpretation of increased neuronal density as a neuropil deficit is compatible with magnetic resonance spectroscopy data indicating a shift from anabolic to catabolic membrane phospholipids in the dorsolateral prefrontal cortex of neuroleptic-naive, as well as chronic-treated schizophrenia subjects (Keshavan et al. 1991; Pettegrew et al. 1991; Williamson et al. 1991). Indeed, Fujimoto et al. (1992) and Pettegrew et al. (1993) have speculated that the excess of catabolic phosphorus compounds might be due to regressive processes in the neuropil, including possibly apical and basal dendrites. A report of decreased synaptophysin protein (Glantz and Lewis 1993) and spine density on layer III pyramidal cells in the prefrontal cortex (Garey et al. 1995; Glantz and Lewis 1995) and of a reduction in messenger ribonucleic acid (mRNA) in medial temporal cortex (Eastwood et al. 1995) also fits well with the idea that dendritic and axonal processes are reduced in the cortex of subjects with schizophrenia. Further, Akbarian et al. (1996) have recently reported an increased expression of the NR2D subunit of the *N*-methyl-D-aspartate (NMDA) receptor that could be considered a possible compensatory response to hypoactivity caused by deficits in NMDA neurotransmission. This finding is of particular interest in

that it was selective to the prefrontal cortex and was not evident in the parietotemporal or cerebellar cortices (Akbarian et al. 1996). It is also consistent with the abnormality in circuitry suggested by our cytometric findings. Our view is that certain neurons are dystrophic and undergo atrophy of their neuronal processes, rather than degeneration or apoptosis, consistent with evidence of normal neuron number in the brain of schizophrenia subjects (Pakkenberg 1993).

The Distributed Circuitry of Schizophrenia. No one area of the brain has been found to be consistently compromised in schizophrenia patients. It is interesting nevertheless that pathological findings have been obtained in several subcortical and cortical areas that are linked in important ways to the prefrontal cortex. The list includes (among cortical areas) the anterior and posterior cingulate cortex, the superior temporal gyrus, and the medial temporal areas and (among subcortical nuclei) the neostriatum, the nucleus accumbens, and the medial dorsal nucleus of the thalamus. A challenge for the future is to determine whether pathological findings in any of these areas could arise from either hyperactivation or hypoactivity in prefrontal projection neurons as a result of the dystrophic changes described above or, alternatively, whether changes in anatomically related areas are primary and produce pathological signs in prefrontal areas (e.g., Carlsson and Carlsson 1990; Grace 1991). Since the connectional relationship between areas and nuclei is invariably topographic, it should be possible, using volumetric, cytometric, and immunocytochemical measures, to determine which specific pathways may be preferentially compromised in postmortem tissues and in living patients with noninvasive imaging techniques.

For example, the mediodorsal (MD) nucleus is the major thalamic relay to the prefrontal areas, and studies of nonhuman primates with MD lesions reveal that their deficits resemble those associated with the prefrontal cortex (Isseroff et al. 1982). Pakkenberg (1993) has reported both volume reduction and a 40 percent decrease in the number of neurons in this nucleus in postmortem brains of schizophrenia subjects. Recent MRI studies have indicated volume loss in the thalamus as a whole (Andreasen et al. 1994; Bloom et al. 1995), which is indicative of its nonselective shrinkage. Studies are needed to determine whether the changes in overall thalamic volume are specific to those thalamo-cortico-thalamic pathways presumed to play a role in prefrontal pathophysiology. Based on the fact that each major subdivision of the MD nucleus preferentially targets one and only one cytoarchitectonic subdivision of the prefrontal cortex (Goldman-Rakic and Porrino 1985), the following hypotheses could be tested. Patients with eye-tracking deficits could be expected to suffer changes in the lateralmost part of this nucleus, whereas this region may be spared in patients in whom such deficits are not observed. Patients with prominent thought disorder might be expected to have more severe pathology in the middle portion of the MD nucleus, and affective signs would be associated with medial MD loss. As the ventral anterior and medial pulvinar also provide important inputs to the prefrontal cortex (Goldman-Rakic and Porrino 1985; Giguere and Goldman-Rakic 1988), they should not be overlooked in future studies.

Unresolved Questions Regarding the Anatomical Basis of Schizophrenia. Evidence of increased neuronal density and the consequent shrinkage of neuropil opens a host of questions for future research. The hypothesis examined in this essay is that schizophrenia, like other dementias, involves to some degree a breakdown in prefrontal cortical function. However, we do not yet know which intrinsic and extrinsic elements that comprise the particular circuits of prefrontal cortex are implicated in dysfunction. Analysis of other prefrontal areas as well as nonfrontal cortical regions in both schizophrenia subjects and relevant control populations is clearly warranted. Do specific classes of neurons (cortico-striatal, cortico-thalamic, or cortico-cortical) or specific portions (dendrites, dendritic spines, or soma) of neurons express selective vulnerabilities, as indicated above? Whether nonpyramidal GABAergic cells or any other class of neuron or glia is missing from the circuit in schizophrenia is still open to investigation. The evidence from our morphometric study of the integrity of prefrontal and visual cortices challenges the idea that cell loss occurs, even of a subset of cortical neurons or glia. If degenerative processes are occurring in other areas of the brain, such as the cingulate cortex, are these related in any way to the neuropil reduction in prefrontal cortex, as suggested by Benes et al. (1991)? If a loss of the axonal and dendritic processes is the major factor in neuropil reduction, which specific elements are compromised: local circuits or long-tract connections? It is possible that synaptic contacts are lost between neuronal classes as in normal aging, or in contrast, they may be more concentrated on shrunken dendritic arbors with consequent imbalances in the interaction of multiple inputs that hyperpolarize or depolarize the cells. Is there a substantial reduction in the large number of nonsynaptic contacts that have been encountered in ultrastructural studies? Or alternatively could an atrophied neuron have a normal or excessive afferent input that it cannot integrate? In both human and nonhuman primates, an overproduction of synapses after birth is followed by gradual elimination of synapses as maturation proceeds (Huttenlocher

1979; Rakic et al. 1986; Huttenlocher and de Courten 1987; Bourgeois et al. 1994). Is failure to prune or excess synaptic pruning a cause of an imbalance in afferent connections, as has been speculated on the basis of the normal developmental progression of synapse formation (Feinberg 1982; Hoffman and Dobsha 1989)? If so, is altered synaptogenesis a cause or a consequence of a cellular deficit; for example, an enzymatic deficiency or defect in signaling pathways unrelated to synapse elimination? Jacobsen et al. (1996) have recently shown that, when corrected for smaller cerebral volume, the corpus callosum of patients with childhood-onset schizophrenia is larger than that in controls, suggesting a relative sparing of white matter tracts in the context of decreased cortical volume. Are there similar neuropil changes in every part of the prefrontal cortex, or are there regional differences? Finally, the effects of reduced synaptic architecture on cell metabolism, on the density and distribution of neurotransmitter receptors, and on neural transmission are major unknowns. We certainly suspect but have no direct evidence in the brain of schizophrenia subjects that cortical circuits are modulated by monoaminergic neurotransmitters, particularly dopamine. These are some of the questions that now need to be addressed by direct analysis of the postmortem cortex, and many can only be answered at the cellular and molecular level of analysis. Anything short of a comprehensive analysis in optimally preserved tissues with reasonable postmortem intervals or *in situ* hybridization of mRNAs directly in schizophrenic cortices will not be convincing. Thus, determination of specific neuronal subtypes, their synaptic inputs and density, the volumetric proportion of neuropil, and dendritic morphology in brains of schizophrenia subjects will be necessary before we have a full picture of the specific neural components that are targeted by the disease.

Direct and Indirect Regulation of Pyramidal Cell Firing by Monoamines: Anatomy and Anatomical and Functional Properties of Neurotransmitters and Neurotransmitter Receptors in the Prefrontal Cortex

Although gross morphological anomalies have been reported in the brains of some schizophrenia subjects (Arnold et al. 1991; Jacob and Beckmann 1991), overall the neuropathological findings point to more subtle cellular abnormalities. This raises the issue of how relatively inconspicuous morphological alterations can result in impaired interactions sufficient to produce the most profound cognitive disturbances. As discussed in further detail below, neurobiological techniques now allow analysis to be focused on the cell as the unit of cortical pathology in schizophrenia. In this section, we explore the possibility that selective prefrontal involvement in schizophrenia may occur through an interaction between a compromised neural substrate, the prefrontal neuron, and its modulation by a variety of neurotransmitter systems. Although it has been known for several decades that the frontal lobe receives a major dopamine innervation, researchers have only recently been able to link dopamine afferents to specific cellular targets and neuronal circuits. Understanding the details of this linkage in prefrontal circuits may be important not only in resolving the various quandaries concerning the mechanisms of dopamine action and the validity of the dopamine hypothesis of schizophrenia but also in extending to other areas of the cortex, such as the cingulate and anterior temporal lobe, which also have a rich dopamine innervation. A particular challenge is finding an explanation for the failure of most neuroleptic medications to significantly improve the negative and cognitive symptoms of schizophrenia. An important development in the field that may provide some insight into these issues is the recognition that dopamine's actions must be viewed within a wider context of interaction with other neurotransmitter systems, notably the excitatory amino acid neurotransmitter glutamate (e.g., Carlsson and Carlsson 1990; Olney and Farber 1995) and the inhibitory neurotransmitter gamma-aminobutyric acid, (GABA; Benes et al. 1991; Bourdelais and Deutch 1994; Vincent et al. 1994). Accordingly, the last section of this review describes selected recent advances in the functional and chemical architecture of the prefrontal cortex, with particular emphasis on the dopaminergic modulatory influences affecting pyramidal cell firing in the prefrontal cortex. As the dorsolateral prefrontal cortex in nonhuman primates is among the several areas of the primate brain that both receive a substantial dopamine innervation (Brown et al. 1979; Williams and Goldman-Rakic 1993) and are linked at the circuit and cellular levels to working memory functions, it represents an excellent model system for examining these interactions and may provide a clue to the dominance of prefrontal psychopathology in schizophrenia. Advances in this area are opening new directions for study of the basic cortical operations that underlie working memory and related cognitive processes.

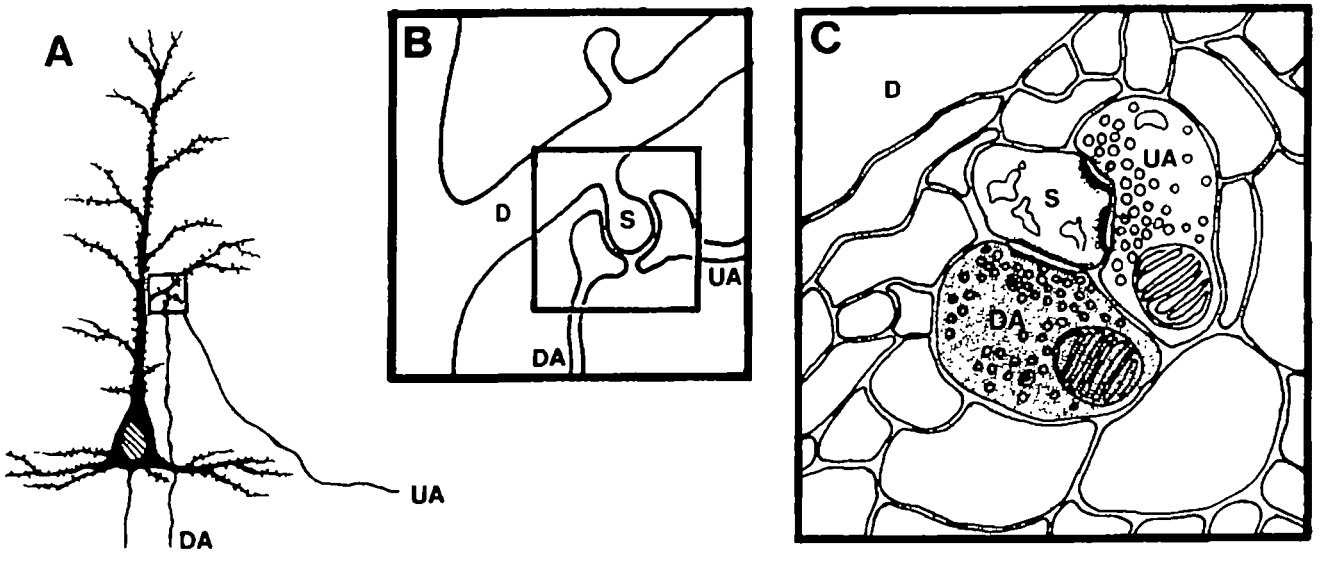
Three Modes of Dopamine Modulation in the Prefrontal Cortex. Physiological studies have consistently indicated that dopamine has inhibitory actions on prefrontal cortical neurons (e.g., Bunney and Aghajanian

1976; Ferron et al. 1984; Fitzgerald et al. 1995; Williams and Goldman-Rakic 1995) and have provided powerful evidence of dopamine modulation of pyramidal cell excitability (e.g., Cepeda et al. 1992; Gellman and Aghajanian 1993; Law-Tho et al. 1994; Williams and Goldman-Rakic 1995; Yang and Seamans 1996). Recent anatomical studies have elucidated at least three distinct substrates that could underlie this interaction. One mode of action appears to be via direct synapses on cortical neurons in both monkey (Goldman-Rakic et al. 1989) and rodent (Van Eden et al. 1987; Seguela et al. 1989) prefrontal cortice. Further, in primate prefrontal cortices, synaptic complexes termed "triads" have been observed in which spines of pyramidal neurons are frequently postsynaptic to both a dopamine terminal and an excitatory terminal as shown in figure 2 (Goldman-Rakic et al. 1989). As the majority of the dopamine synapses appear to be formed on pyramidal neurons, dopamine axons are placed in direct contact with the major projection neurons of the prefrontal cortex—the cortico-thalamic, cortico-striatal, and cortico-cortical projections—and presumably can modulate their activity directly. There is thus a surprising degree of targeting in the dopaminergic projections to the dorsolateral prefrontal cortex, different from that of the proverbial "sprinkler system" that has characterized dopamine traditionally.

However, a second mode of action in prefrontal cortex is undoubtedly nonsynaptic. Nonsynaptic neurotransmission may be a pervasive means of altering pyramidal cell activity as numerous dopamine varicosities are observed in nonsynaptic relationship to cortical elements (Smiley and Goldman-Rakic 1993; Smiley et al. 1994). Additionally, D_1 receptors have been localized to spines of pyramidal cells that appear to lack a dopamine synaptic terminal, but these receptors are invariably apposed to glutamatergic synapses on the same spine (Smiley et al. 1994). Members of the D_1 family of dopamine receptors have been found to be particularly prominent in the prefrontal cortex of primates (Lidow et al. 1989, 1991; Goldman-Rakic et al. 1990), and both D_1 and D_5 receptor proteins have been localized to the distal dendrites and spines of pyramidal cells (Bergson et al. 1995). Recent studies in this laboratory indicate that the D_1 receptor may be importantly involved in regulating neurons that subserve specific working memory functions (Williams and Goldman-Rakic 1995; see below).

Finally, dopamine may have its most powerful effects on pyramidal cell firing *indirectly* via feed-forward inhibition from nonpyramidal neurons in local circuits. We have recently shown that pyramidal and nonpyramidal neurons interact physiologically as monkeys hold a particular item of information in working memory (Wilson et al. 1993).

Figure 2. Synaptic triad observed at the light microscopic (A) and electronmicroscopic (B and C) levels



A synaptic triad is formed by a dopamine terminal (DA) onto a spine (S) of a pyramidal cell; the same spine receives an excitatory terminal from an axon of unidentified origin (UA). This arrangement provides one mechanism by which dopamine can directly modulate the spine's response to its excitatory (perhaps sensory) input. If a given pyramidal neuron receives a number of dopamine inputs onto its many spines, as anatomical data suggest, then fluctuations in dopamine would affect the cell's ability to integrate its informational input. D = dendrite.

The indirect action of dopamine on this circuit derives from two recent discoveries. The first is the identification of dopamine synaptic contacts on nonpyramidal GABAergic neurons in the prefrontal cortex, although these contacts appear to be less common than those on pyramidal neurons (Goldman-Rakic et al. 1989; Smiley et al. 1992; Smiley and Goldman-Rakic 1993; Sesack et al. 1995). The second finding is that the D_4 member of the D_2 family of dopamine receptors is localized postsynaptically on a subset of GABA interneurons (Mrzljak et al. 1996). D_4 receptors are also observed in pyramidal cell spines, although possibly not as densely as D_1 receptors are. The localization to interneurons is noteworthy since it suggests that D_2 receptor family sites may preferentially inhabit interneurons, whereas the D_1 and D_5 receptors appear to be preferentially localized to pyramidal neurons (Smiley and Goldman-Rakic 1993; Bergson et al. 1995). These new results raise the interesting possibility that D_4 antagonists may have both direct and indirect effects on pyramidal cell firing. The direct effects could be mediated by blocking D_4 receptors directly on cortical pyramidal cells, where, as mentioned, dopamine's action is primarily inhibitory. The same end result—decreased threshold of pyramidal cell excitability—may also be achieved via disinhibition (i.e., by blocking nonpyramidal cell firing). Physiological studies have shown that dopamine may inhibit pyramidal cell firing, in part by activation of GABA inhibitory neurons (Pirot et al. 1992; Gellman and Aghajanian 1993). Further, GABA release in the cerebral cortex is known to be modulated by D_2-like receptors (Retaux et al. 1991).

The soma and dendrites of nonpyramidal neurons in the cortex are a primary postsynaptic target of serotoninergic axons, although pyramidal neurons also receive some serotoninergic afferents (Jakab and Goldman-Rakic 1996; Jakab et al. 1996; Smiley and Goldman-Rakic 1996). Serotonin 5-HT_2 receptors have been reported in cortical interneurons by Morilak et al. (1993). The presumed colocalization of D_4 and serotonin receptors in nonpyramidal neurons could provide a basis for a synergistic action of these monoamines on cognitive function. Given that the atypical neuroleptic clozapine has a high affinity for the 5-HT_2 as well as the D_4 receptor (Meltzer et al. 1989; Leysen et al. 1995), the new D_4 localization data focus attention on the nonpyramidal cell as a major target of pharmacological intervention and offer a possible neural explanation for the reported improvements in negative symptoms by atypical neuroleptics (Lee et al. 1994). Serotonin induces inhibitory postsynaptic potentials (IPSPs) in pyramidal neurons and excitatory responses in a subset of nonpyramidal neurons, and both effects are blocked by the 5-HT_{2A}/5-HT_{1C} antagonist ritanserin (Sheldon and Aghajanian 1990) and by atypical neuroleptics (Gellman and Aghajanian 1994). Presumably systemic elevation of serotonin could inhibit cell discharge in some pyramidal neurons via a feed-forward inhibition, whereas neuroleptic medication would disinhibit the pyramidal cells, causing them to become more excitable. In line with this possibility is the recent experimental evidence that chronic treatment with clozapine can produce myoclonic jerks in a dose-dependent manner in a small proportion of rats subjected to this treatment (Denny and Stevens 1995). A paroxsymal electroencephalogram and myoclonus are indicative of cortical excitability. A major question for future research is whether blockage of the dopamine D_4 receptor alone may have analogous disinhibitory actions in prefrontal cortical circuits mediating the working memory functions of prefrontal cortex (see below).

The effectiveness of clozapine in improving cognitive processes and in reducing primary negative symptoms (as opposed to those associated with diminution of extrapyramidal side effects) is still very much in question. Buchanan et al. (1994) found evidence of improvement in verbal fluency and visuospatial ability, but impairment on Trail Making Test, Trails B (The Adjutant General's Office 1944) after 1 year of clozapine treatment. Likewise, in a more recent study by Hoff et al. (in press), 12 weeks of clozapine treatment of chronically hospitalized schizophrenia patients improved their Brief Psychiatric Rating Scale scores (Overall and Gorham 1962), clinical course, verbal fluency, and graphomotor speed, but produced impairment on measures of visual memory, Trails B, and the Wisconsin Card Sort Test. Thus, the effects of clozapine treatment on measures of various cognitive functions appear to be mixed. However, as both dopamine and serotonin have complex effects—modulating pyramidal cell firing directly and indirectly through control of nonpyramidal cell firing—understanding the relative impact of direct and indirect actions of these neurotransmitters on pyramidal cell firing in vivo may hold the key to effective pharmacotherapy of all classes of symptoms in schizophrenia.

Functional-Anatomical Correlations. Dopamine regulation of excitatory neurotransmission in cortical circuits is supported by electrophysiological studies not only in slices of rodent prefrontal cortex (e.g., Gellman and Aghajanian 1993; Law-Tho et al. 1994; Yang and Seamans 1996) but also in human cortical "slices" (Cepeda et al. 1992) and in studies of nonhuman primates in which the neurons studied are functionally characterized while the monkeys perform a working memory task (Williams and Goldman-Rakic 1995). Our study in pri-

mates took advantage of the remarkable fact that the process of mental representation can be captured as a sequence of electrophysiological events in prefrontal neurons (Fuster and Alexander 1971; Kubota and Niki 1971; Funahashi et al. 1989). Analogous to visual receptive fields recorded in primary visual cortex, the "memory field" of a prefrontal neuron is defined as maximal firing of a neuron during recall or transient storage of a specific item of information; for example, the location of an object in one or a few locations of the visual field (e.g., Fuster and Alexander 1971; Kubota and Niki 1971; Funahashi et al. 1989) or the memory of a particular face or object (Wilson et al. 1993). Williams and Goldman-Rakic (1995) reported that iontophoretic application of a D_1 receptor antagonist enhanced the memory field of the neurons; it increased cell firing only for the cell's "best direction," whereas the cell's responses during behavioral baseline or when nonpreferred targets were recalled were unaltered (Williams and Goldman-Rakic 1995). This pattern of selective enhancement of a cell's mnemonic responses can be accounted for by a juxtaposition in the recorded cell of an excitatory input, as from a parietal afferent, and a dopamine modulatory input, such as exists in the triadic synaptic complex described above. The effect we observed was biphasic—both excess stimulation and excess blockade of the D_1 receptor inhibited cell firing. Recent in vitro studies by Yang and Seamans (1996) are enlarging our understanding of the ionic mechanisms by which D_1 stimulation regulates pyramidal cell firing, and such studies together with the findings described above could provide a cellular basis for the commonly observed deficits in working memory consequent to dopamine depletion (Brozoski et al. 1979; Schneider and Kovelowski 1990) or, as recently demonstrated, to conditions that result in hyperdopaminergia (Murphy et al. 1996; Verma and Moghaddam 1996). It is tempting to speculate that fluctuations in dopamine release and dopamine receptor occupancy, and the consequent effects on excitatory transmission in information-processing pathways, may account for fluctuations in symptom expression during the course of schizophrenia both before and during drug treatment.

If both too little or too much dopamine D_1 stimulation is detrimental to prefrontal function, as the aforementioned studies suggest, then different treatment strategies may be useful at different stages of the disease. Baruch et al. (1988) have shown that acute schizophrenia subjects are impaired on a test of latent inhibition, whereas those with chronic schizophrenia performed as well as controls. The authors hypothesized that the subjects with acute schizophrenia were hyperdopaminergic and that neuroleptic treatment normalized dopaminergic response in the chronic patients. The evidence in animals that chronic neuroleptic treatments can both increase dopamine release (Youngren et al. 1994) and downregulate dopamine D_1 receptors (Lidow and Goldman-Rakic 1994) in the prefrontal cortex raises the question of whether these changes are associated with the reduction of positive symptoms or with the lack of improvement in negative symptoms or with both. An additional question is whether these changes are stable throughout the long course of the disease and drug treatment. Thus, among the major unresolved functional issues in the pathophysiology of schizophrenia are determination of the status of dopamine response at different stages of the disease; the effect of drug treatment itself on dopamine release and uptake mechanisms in prefrontal cortex; and the correlation of dopamine response with positive, negative, and disorganizational symptoms. Noninvasive imaging of receptor-ligand interactions in vivo may provide the necessary tools for addressing such questions in animal models and in humans. A recent study using single photon emission computer tomography has provided evidence that schizophrenia patients whose positive symptoms worsened in response to amphetamine challenge also demonstrated higher dopamine release than patients whose symptoms were not exacerbated (Laruelle et al. 1996). Similar methods may soon be available for evaluation of prefrontal cortical receptors in schizophrenia.

Further Issues for Pharmacotherapy. It is not known at present whether D_1 or D_2 receptors are implicated in the primary pathophysiology of schizophrenia, and in the case of D_2, the mechanism of its therapeutic effectiveness is also unknown. Recent reports indicate that pyramidal neurons in the cortex of schizophrenia subjects suffer a loss of spines (Garey et al. 1995) or synaptic proteins that are markers of dendritic spines (Glantz and Lewis 1993, 1995; Eastwood et al. 1995) and a selective increase in expression of the mRNA for a subunit of the glutamate receptor (Akbarian et al. 1996). To the extent that several dopamine receptors are preferentially localized in spines, we might expect some loss of these receptors in the cortex of subjects with schizophrenia. Further reduction of D_1 receptors and upregulation of D_2 receptors in cortical areas may be expected with chronic neuroleptic drug treatment, assuming similar effects of these drugs in human and nonhuman primates (Lidow and Goldman-Rakic 1994). Meltzer (1991) and Wadenberg et al. (1993) have considered a role of D_1 antagonism in the effects of clozapine. Given the evidence that D_1 stimulation can modulate excitatory transmission in pyramidal neurons both in vitro and in vivo, the latter on neurons specifically engaged in working memory, it will be important to study

the potential functional significance of D_1 receptors in the pathophysiology and treatment of schizophrenia. The study on the working memory-enhancing potential of low doses of D_1 receptor antagonists administered systemically in our laboratory indicates that D_1 occupancy optimal for cognitive performance is achieved at low doses (Williams et al., unpublished observations). To date, there have been few clinical trials with D_1 antagonists, and those that have been conducted with high doses of D_1 antagonists have not had encouraging results. It would therefore be of interest for clinical trials to be conducted with appropriately low doses of D_1 antagonists or alternatively, with low doses of D_1 agonists, depending upon the individual patient's state of dopamine response (to amphetamine challenge, for example).

However, understanding the role of the D_1 site will provide only a partial view of neuroleptic action in prefrontal cortex. The role of the D_4 receptor in cortical function is very intriguing, given the high affinity of this receptor protein for clozapine (Seeman 1992). Looking to the future, it will be important to determine dopamine action at D_4 sites on both nonpyramidal and pyramidal neurons in prefrontal circuits, whether these effects are synergistic or antagonistic, and the in vivo cellular responses of prefrontal neurons recorded in monkeys during working memory performance. We need to learn more about the functional consequences of depolarization block (Chiodo and Bunney 1983; Grace 1991) caused by chronic drug treatments, as well as the increased dopamine release that has been reported to occur under chronic treatment conditions. It will also be of value to examine the effects of drug therapies on working memory and to learn whether cognitive performance can be related to cellular operations altered by drugs.

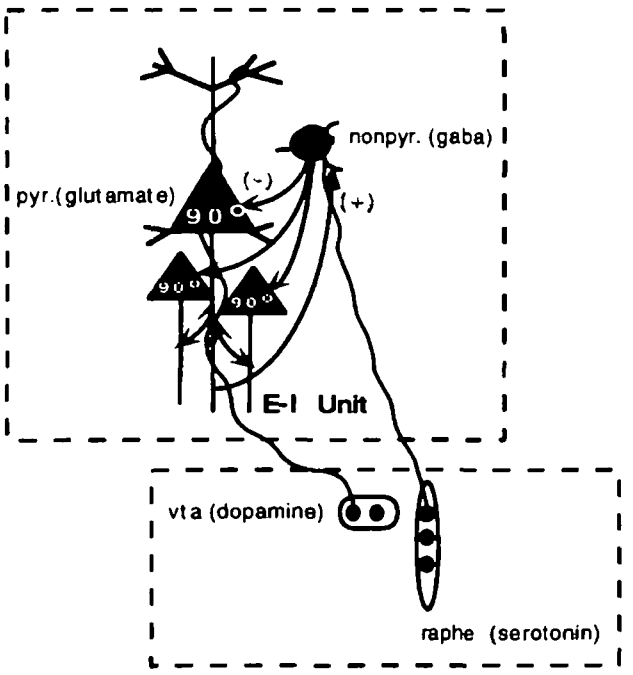
The Multidimensionality of Schizophrenia: A Variety of Signaling Pathways Can Cause Trouble in Information-Processing Circuits in the Prefrontal Cortex

Postmortem and in vivo anatomical findings have spawned a number of hypotheses regarding the site, genesis, and nature of neuropathological changes in cortexes of schizophrenia subjects. Meltzer has reviewed the considerable potential of serotonin receptors, particularly the $5\text{-}HT_{2A/2C}$ receptor in subcortical structures, as targets of clozapine and other atypical neuroleptics (Meltzer et al. 1996). Based on findings in postmortem cingulate cortex, Benes has proposed a loss of GABA neurons accompanied by an excess number of dopamine contacts on the remaining inhibitory neurons as a critical "lesion" in schizophrenia (Benes et al. 1991, 1995; Vincent et al. 1994). As many nonpyramidal neurons form inhibitory synapses on the distal dendrites of pyramidal neurons, a reduction in the number of GABAergic cells might be expected to lead to increased firing of pyramidal cells in schizophrenia patients, at least in the cingulate cortex. Diminished inhibition figures prominently in the model developed by Olney (Olney and Farber 1995). The excitotoxic potential of glutamate in the central nervous system has led Olney to propose that NMDA receptor hypofunction (NRH) represents the underlying pathological process in schizophrenia in combination with dopamine system dysfunction, particularly engaging D_2 receptors. The mechanism of pathogenesis is that diminished NMDA function removes an important and critical source of stimulation of interneurons, causing a failure of feedback inhibition in cortical circuits that results in "unmodulated stimulatory activity to flood corticolimbic brain regions" (Olney and Farber 1995, p. 1002). As stated by these authors, the loss of GABAergic interneurons represents an equivalent NRH condition, and the reduction of nonpyramidal neurons in the cingulate gyrus of some patients with schizophrenia is supportive of this view (Benes et al. 1991). Both the NRH hypothesis and Benes et al.'s GABA hypothesis lead to the expectation of degenerative changes and neuronal loss in the cortex of schizophrenia patients. As mentioned above, this expectation was not supported in our examination of prefrontal areas (Selemon et al. 1995). However, we did not examine the cingulate areas studied by Benes et al. and Olney and Farber and have not offered a specific etiological hypothesis. Instead, we have noted that disturbed nonpyramidal-pyramidal cell interactions need not involve loss of inhibitory interneurons but rather some loss of their effectiveness and, in the case of prefrontal neurons, with consequences for cognitive processing.

Knowledge to the cortical architecture should provide new insights into the action of neuroleptics and by inverse reasoning to the underlying pathophysiology of the disease. As mentioned earlier, the local circuit formed by pyramidal and nonpyramidal neurons constitutes the elements of an information-processing architecture that underlies the capacity to hold a particular item of information in working memory (Wilson et al. 1993). Differential innervation of the two principal components of a functional unit of cortex by dopamine and serotonin, respectively, opens the possibility for an integrated view of cortical dysfunction in schizophrenia—namely, that glutamate, GABA, serotonin, or dopamine, singly or in combination, could disturb the prefrontal circuitry essen-

tial for working memory (figure 3). The same net effect could be produced by alterations in other neurotransmitters; for example, cholinergic and adrenergic neurotransmission that are as much a part of the cortical circuitry as the neurotransmitters highlighted in this article. Thus, dysfunction in any one of these neurotransmitter systems, their signaling mechanisms, and biosynthetic pathways could produce the same phenotypic end result. Each is an integral part of an elemental functional circuit, the output of which has consequences for information processing. These consequences could take the form of inadequate maintenance of a representation or even inadequate cessation of a mental representation (in the absence of the triggering stimulus) that might qualify as a hallucination. It is possible to imagine how either dopamine excess or deficiency or a pyramidal cell deficiency or both could alter pyramidal cell modulation in a profound way, with the net effect being that the pyramidal cell can no longer integrate its myriad informational inputs and no longer maintain information "on line." Timing of information will be off kilter, fragmentation of the thought process could result, and the neural systems needed for guiding behavior could be thrown into default mode (i.e., reliance on automatic responses, prepotent responses, stereotypical responses, and absence of forethought).

Figure 3. A basic excitatory-inhibitory (E-I) functional unit in the cerebral cortex



The assignment of a "memory field" to the cluster of pyramidal neurons is conjectural. Pyramidal neurons (pyr.), which are glutamatergic, are innervated by nonpyramidal (nonpyr.) neurons, which are gamma-aminobutyric acid (GABA)ergic. Dopamine axons preferentially target pyramidal neurons; serotonin preferentially targets a subset of nonpyramidal neurons. Disturbances in dopamine, serotonin, glutamate, or GABA can presumably alter the function of this basic unit of circuitry. If this circuit is part of the necessary substrate of a memory field, working memory for a particular memorandum (e.g., 90°) will be compromised or fail. vta = ventral tegmental areas.

Kirkpatrick and Carpenter (1995) have recently commented that the failure of neuroleptic drugs to completely relieve the negative and cognitive symptoms of schizophrenia may be due to insufficient targeting of the relevant circuits involved in cognitive behavior. The localization of neurotransmitter receptors in functionally defined cortical circuits, particularly those underlying such cognitive processes as working memory, may offer a new cortical model for drug development. To fully understand the functional ramifications and details of structural changes in schizophrenia, it will obviously be critical to determine which cortical pyramidal and nonpyramidal neurons are particular targets of dopamine synapses and which receive serotonergic, cholinergic, and adrenergic terminals. The constellation of receptor sites on each type of neuron must also be known. Most GABA neurons are sources of feedforward inhibition to pyramidal neurons, and different subtypes of the inhibitory interneuronal pool have different local effects depending on whether they establish synapses on the soma, dendritic shafts, or spines of their postsynaptic targets. Some GABA neurons project to other GABA cells (Kisvardy et al. 1993). Either pathway will have a powerful influence on pyramidal cell firing. Depending on the effects of dopamine (or serotonin) on GABA interneurons, pyramidal neurons will be excessively inhibited or excited. If neuroleptic drugs disinhibit pyramidal cell firing, as some findings reviewed above suggest, then it is possible that schizophrenia could represent a condition of excessive inhibition of information-processing circuits in certain portions of prefrontal cortex, among other deficits.

Among the many avenues of exploration now before us, elucidation of the nature of disrupted modulation on cortical pyramidal cells will be a high priority for future studies. New opportunities with in situ hybridization of riboprobes for mRNAs of specific receptors will allow determination of precisely which cells are the bearers of specific receptors in the different cortical layers and which cells and which proteins are most compromised in dementias such as schizophrenia. If neuroleptic drugs achieve some of their positive results either by direct or indirect effects on pyramidal cell firing as reviewed above, further analysis of the functional interactions

between nonpyramidal and pyramidal neurons and localization of neurotransmitter receptors within these local circuits may bring insight into the modulation of cognitive function by dopamine and other modulatory neurotransmitters. Insights into pathophysiological mechanisms underlying hypofrontality and prefrontal deficit symptoms in schizophrenia, on the one hand, and postmortem anatomical findings in brains of schizophrenia subjects, on the other, compel analysis at the cellular level in animal models. If working memory is an essential functional deficit in schizophrenia, which depends in large measure on the integrity of prefrontal cortex, then understanding the cellular elements and physiological properties of prefrontal neurons is essential for a rational and detailed understanding of the pathophysiological mechanisms in the disease.

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Announcement

The Rochester Psychiatric Center, the New York State Office of Mental Health, and the Department of Psychiatry of the University of Rochester will sponsor a conference entitled **Psychiatric Rehabilitation of Schizophrenia: Current Trends and Future Directions** to be held in Rochester, New York, September 12-14, 1997. This conference will focus on a wide range of issues, including social-learning based treatment approaches, models of intermediate and long-term inpatient care, outpatient care strategies, assertive community treatment, reducing stigmatization, the impact of cognitive deficits on treatment outcome, approaches to cognitive rehabilitation, aggression, staff training, and assessment.

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