EDITORIAL

The functional architecture of the prefrontal cortex and schizophrenia

Findings from a number of studies have implicated the prefrontal cortex (PFC), especially the dorsolateral region, as a site of dysfunction in schizophrenia (Goldberg et al. 1989). For example, in contrast to controls, schizophrenics fail to activate the dorsolateral PFC while engaged in the Wisconsin Card Sort Task (Weinberger et al. 1986), and they exhibit an inability to learn how to perform this task (Goldberg et al. 1987). Schizophrenic subjects also demonstrate significant impairments on oculomotor delayed-response tasks (Park & Holzman, 1992), a behavioural paradigm that in nonhuman primates appears to be a selective and reliable measure of dorsolateral PFC function (Fuster, 1989; Funahashi et al. 1991, 1993). Despite these clear deficits in PFC functioning in schizophrenia, the apparent lack of gross structural abnormalities in the PFC of schizophrenic subjects suggests that this dysfunction may be a consequence of more subtle alterations in the intrinsic neural circuitry of this region. Understanding how such disturbances in connectivity might occur in schizophrenia requires knowledge of the normal functional architecture of the PFC. In addition, the PFC is functionally coupled with multiple other brain regions, some of which may also be impaired in schizophrenia. Consequently, it is important to understand how information processing within the PFC influences, and is influenced by, the activity of these regions.

Any hypothesis of PFC dysfunction in schizophrenia also needs to account for the typical onset of the symptoms of this disorder, including impairments in cognitive processes (Heaton et al. 1994), during late adolescence or young adulthood (Carpenter & Buchanan, 1994). In addition, hypotheses of PFC dysfunction in schizophrenia should consider the possible role of dopamine, which has long been considered to play a part in the pathophysiology of this disorder. Although our knowledge of these factors remains limited in many respects, recent advances in understanding the normal functional architecture of the primate PFC, in concert with post-mortem studies of schizophrenic patients, have provided a basis for the generation of novel, testable hypotheses regarding the pathophysiology of PFC dysfunction in this illness.

FUNCTIONAL ARCHITECTURE OF THE PRIMATE PREFRONTAL CORTEX

Many of the PFC-mediated tasks on which schizophrenic subjects perform poorly share as a common feature the involvement of working memory (Goldman-Rakic, 1987) or the temporal integration of information (Fuster, 1985); that is, the experimental subject has to retain knowledge of the information provided by an environmental cue in order to perform the appropriate behavioural response after the cue has been removed. In spatial delayed-response tasks in monkeys, animals are required to hold ‘on line’, or in working memory, the location of an environmental cue in space during a delay period following the removal of the cue. By recording from micro-electrodes in the dorsolateral PFC of monkeys as they perform such tasks, it has been possible to correlate neuronal activity with cognitive processes. Separate populations of PFC neurons have been identified whose activity is temporally linked to specific components of the delayed-response task.
These clustered horizontal connections appear to link columns of cells with preferences for specific clusters of terminal fields that are distributed as patches (Rockland & Lund, 1983; Livingstone & Hubel, 1984; DeFelipe et al. 1986; Matsubara et al. 1987; King et al. 1989; Juliano et al. 1990). These clustered horizontal connections appear to link columns of cells with preferences for specific types of stimuli (T'so et al. 1986; Matsubara & Phillips, 1988; T'so & Gilbert, 1988; Wallace et al. 1991). In monkey PFC, the axon collaterals of a subpopulation of pyramidal neurons also extend for considerable distances horizontally. However, these intrinsic axon collaterals give rise to clusters of axon terminals in the superficial layers (see Fig. 1) which form a distinctive lattice-like structure organized as a series of stripes (LeVitt et al. 1993). Although the results of direct physiological investigations of these lattice connections are not yet available, by analogy to sensory regions, this lattice structure of interconnected stripes may link the activity of spatially segregated populations of PFC neurons. For example, combined retrograde and anterograde tracing studies have demonstrated that reciprocal divergent and convergent projections are present among lattice stripes of monkey PFC (Pucak et al. 1994). These findings raise the possibility that intrinsic lattice connections could be the substrate for a reverberating cortical circuit that maintains and coordinates the activity of specific populations of PFC neurons during the delay phase of delayed-response tasks. Pyramidal neurons in layer 3 are major contributors of the axon collaterals that form the intrinsic lattice, and consequently these neurons may play a particularly vital role in the integrated activity of specific groups of PFC neurons. It is interesting in this regard that when monkeys were engaged in a spatial delayed-response task, glucose utilization was found to be greatest in layer 3 of the dorsolateral PFC (Friedman & Goldman-Rakic, 1994).

In addition to pyramidal neurons in layer 3, pyramidal cells in layers 2 and 5 contribute axon collaterals to the lattice structure of intrinsic excitatory connections (LeVitt et al. 1993). The main axonal trunks of some pyramidal neurons in layers 2, 3 and 5 enter the white matter and provide the principal source of PFC connections to other cortical regions and some subcortical structures such as the striatum. Thus, the axons of these neurons are equipped not only to participate in the coordination of activity among groups of PFC neurons, but also to convey that information to more broadly distributed networks of neurons. Indeed, recent studies have shown that individual
PFC pyramidal neurons provide both intrinsic axon collaterals to lattice stripes and axonal projections to other cortical regions (Melchitzky et al. 1994).

Thus, the patterns of intra- and inter-areal connectivity subserved by these populations of PFC neurons suggest that they may be critical components of the neural circuitry underlying the distinctive behavioural tasks mediated by the PFC. Consequently, these connections must be strongly considered as possible suspects for the disrupted or altered circuitry that is manifest as PFC dysfunction in schizophrenia.
DEVELOPMENT OF PFC CIRCUITRY AND THE ONSET OF SCHIZOPHRENIC SYMPTOMS

A critical test of any explanation of PFC dysfunction in schizophrenia is its ability to account for the typical onset of the symptoms of this disorder, including cognitive impairment (Heaton et al. 1994), during late adolescence and early adulthood. Studies in both monkeys and humans have demonstrated that the period of adolescence is associated with a marked reduction in the density of PFC synapses (Huttenlocher, 1979; Bourgeois et al. 1994). In monkeys, the greatest degree of change appears to involve asymmetric (excitatory) axospinous synapses in the supragranular layers (Bourgeois et al. 1994). Consistent with these observations, the density of dendritic spines on layer 3 pyramidal neurons in monkey PFC has been observed to decline by 50% between the ages of 2 and 4 years (Anderson et al. 1995), the period of adolescence in this species (Plant, 1988). Because dendritic spines are the primary site of excitatory inputs to these neurons (Colonnier, 1968; LeVay, 1973; Mates & Lund, 1983), these findings suggest that layer 3 pyramidal neurons lose a substantial portion of their excitatory input during the late functional maturation of the PFC. Given that the majority of cortical synapses are derived from intrinsic sources (White, 1989), the synapses formed by axon collaterals of pyramidal neurons are likely candidates for this loss. In contrast, the other major source of excitatory inputs to the superficial cortical layers, associational and callosal corticocortical afferents, would have to be pruned to a very high extent to produce a total decrease of 50% in synaptic density. In addition, the number of axons in the corpus callosum of monkeys decreases from a peak at birth to reach stable levels by 6 months of age (LaMantia & Rakic, 1990), suggesting that these axons may be less likely to be involved in the peripubertal attrition of PFC excitatory synapses. Consequently, the loss during the peripubertal period of a large proportion of synapses furnished by axon collaterals of lattice neurons could refine the pattern of discontinuities in the intrinsic connections furnished by each pyramidal neuron, and give rise, during late adolescence, to the mature form of the intrinsic lattice structure.

Disturbances in this developmental process could produce abnormalities in intrinsic PFC circuitry that might underlie the PFC dysfunction present in schizophrenia (Feinberg, 1982; Hoffman & Dobscha, 1989). For example, if the speculations discussed above about the role of lattice connectivity in PFC function are correct, then a deficient number of lattice connections could impair the sustained activity of specific networks of PFC neurons required for tasks involving working memory (Goldman-Rakic, 1987) or the integration of cross-temporal contingencies (Fuster, 1985). Thus, abnormalities in lattice connections might produce the types of PFC dysfunction that are characteristic of schizophrenia. Alternatively, the maturation of the intrinsic lattice structure might unmask the functional consequences of abnormalities in PFC circuitry that occurred earlier in development (Weinberger, 1987; Benes et al. 1991, 1992; Akbarian et al. 1993).

Hypotheses of PFC dysfunction in schizophrenia should also consider the possible role of dopaminergic (DA) systems in this disorder. Although the data are quite limited, both clinical studies (Doran et al. 1987; Weinberger et al. 1988; Breier et al. 1993) and theoretical modelling (Cohen & Servan-Schreiber, 1992) have suggested that PFC dysfunction in schizophrenia may be associated with abnormalities in the DA innervation of this region. In addition, animal studies have clearly demonstrated that an intact DA innervation of PFC is critical for the functional integrity of this region on delayed-response tasks (Brozoski et al. 1979; Sawaguchi & Goldman-Rakic, 1991; Roberts et al. 1994). Interestingly, the available data indicate that DA afferents to PFC innervate pyramidal neurons (Goldman-Rakic et al. 1989; Sesack et al. 1995; Smiley & Goldman-Rakic, 1993), at least some of which may participate in lattice connectivity (see Fig. 1). In addition, some dendritic spines receive convergent input from a Type 1 (asymmetric) excitatory synapse and a Type 2 (symmetric) DA synapse (Goldman-Rakic et al. 1989). Although the source of these asymmetric synapses has not been determined, this arrangement raises the possibility that DA afferents may directly modulate, at the level of dendritic spines, activity within the intrinsic lattice structure of excitatory connections.

In addition, the DA innervation of PFC also undergoes substantial changes during adolescence.
that may be temporally linked to the developmental refinements in lattice connectivity described above. For example, the density of DA varicosities in layer 3 of monkey dorsolateral PFC reaches a peak in animals 2–3 years-of-age, before declining to stable adult levels (Rosenberg & Lewis, 1995). The possible relationship of these changes to the maturation of lattice connectivity is further strengthened by the fact that the developmental changes in DA innervation appear to be specific to layer 3 in that such developmental changes do not occur in the more superficial or deep cortical layers (Rosenberg & Lewis, 1995). Consequently, alterations in the intrinsic lattice structure of PFC connectivity in schizophrenia may be reflected in altered DA function of this region.

IMPLICATIONS FOR PFC DYSFUNCTION IN SCHIZOPHRENIA

As suggested above, the typical late adolescent/early adult onset of schizophrenia may represent the behavioural manifestation of an abnormality in the maturation of the intrinsic lattice organization during this period of development. Indeed, several lines of evidence from studies of the brains of schizophrenic subjects are consistent with the hypothesis that schizophrenia is characterized by a decrease in the intrinsic connectivity of dorsolateral PFC. For example, although the total number of cortical neurons does not appear to be altered in schizophrenia (Pakkenberg, 1993; Akbarian et al. 1995), cell packing density is increased in the PFC in schizophrenic subjects (Pakkenberg, 1993; Selemon et al. 1993; Daviss & Lewis, 1995), suggesting that the amount of cortical neuropil is decreased. In addition, a decreased density of dendritic spines on layer 3 pyramidal neurons (Garey et al. 1994), lower measures of synaptic markers (Glantz & Lewis, 1994) and loss of synaptic building blocks (Pettegrew et al. 1991) have recently been reported in the PFC of schizophrenic subjects. These observations could all be attributable to a common process that reduced the number of intrinsic connections, which account for over two-thirds of all cortical synapses (White, 1989). In addition, at least some recent findings with brain imaging techniques, such as decreased PFC activation as measured by PET (Buchsbaum et al. 1992) and decreased cortical grey matter thickness as measured by MRI (Zipursky et al. 1992; Schlaepfer et al. 1994; Seidman et al. 1994), may also be consistent with a defect in PFC connectivity in schizophrenic subjects. In these imaging studies, and those involving MRI spectroscopy (Pettegrew et al. 1991), the reported differences between schizophrenics and controls are in the same direction as those changes found to occur normally over the adolescent age range (for review, see Keshavan et al. 1994).

How might the failure to develop the normal lattice organization of intrinsic connections in the PFC result in the symptoms of schizophrenia? One possibility is that, without an intact lattice structure, the recruitment of the networks of neurons necessary for the temporal organization of thought processes is impaired. For example, disrupted lattice connections could limit the coordinated activity of the components of the neural network responsible for holding ‘on line’ a specific set of stimulus characteristics. Moreover, such a disturbance of connectivity could also impair the flow of information between the groups of neurons responsible for remembering these characteristics, and those involved in preparing an appropriate response. The failure to maintain properly the relevant bits of information in working memory and the subsequent impairment of the preparation of an appropriate response might be reflected in a disorder of the temporal organization of thought and language, producing symptoms such as loose associations (Fuster, 1993). Finally, because of its role in the temporal organization of thought processes that involve other cortical regions, a deficit in the intrinsic connectivity of the PFC may also contribute to the production of symptoms that have been generally related to the dysfunction of these regions.

This view posits that the dysfunction of the PFC is due to a ‘fixed’ lesion of intrinsic excitatory connections that does not vary with time after the mature pattern of those connections is achieved in early adulthood. However, it must be kept in mind that the severity of the symptoms attributed to this deficit could vary with changes in other dynamic aspects of PFC circuitry. For example, one class of GABAergic local circuit neuron in monkey PFC, the wide arbor neuron (Lund & Lewis, 1993), has an axon arbor that may be specialized for establishing zones of inhibition between the
stripes of the intrinsic lattice structure (Levitt et al. 1993; see Fig. 1). Activity-dependent changes in the functional properties of these inhibitory neurons (Jones, 1993) could have, in turn, an impact on the fidelity of information processing in the remaining lattice connections by either sharpening or distorting the boundaries of the interconnected lattice stripes. In this regard, it is interesting to note that several recent studies of local circuit neurons in the PFC of schizophrenic subjects have revealed the altered expression of functionally important proteins in GABAergic neurons, in the absence of any apparent changes in the number of these neurons (Akbarian et al. 1995; Daviss & Lewis, 1995).

CONCLUSION

The recent increases in knowledge about the functional architecture of the primate PFC, combined with imaging and post-mortem studies of the brains of schizophrenic subjects, make it possible to generate new hypotheses regarding the neurobiological substrates of PFC dysfunction in this illness. In this essay we suggest the hypothesis that PFC dysfunction in schizophrenia results from alterations in the intrinsic lattice structure of excitatory connectivity in the PFC. However, significant gaps in our understanding remain. For example, what are the physiological properties of lattice connections in the PFC? What is the precise time course of the functional maturation of the lattice structure and what factors are important in the regulation of its development? What are the anatomical and functional relationships between lattice connections and dopaminergic afferents to the PFC? How accurately do studies in non-human primates predict the organization of the intrinsic circuitry of human PFC? What role do lattice connections actually play in the temporal organization of thought processes? The integration of basic and clinical studies of the functional architecture and development of the PFC may provide answers to these questions, as well as clearer insights into the mechanisms that underlie PFC dysfunction in schizophrenia.

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REFERENCES


collateralisation of axons arising from corticocortical cells in
monkey sensory motor cortex. Journal of Neuroscience 6, 3749–
3766.

Doran, A. R., Boronow, J. D., Weinberger, D. R., Wolkowitz, O. M.,
schizophrenia revisited: prefrontal cortex pathology is inversely
associated with cerebrospinal fluid levels of homovanillic acid.
Neuropsychopharmacology 1, 25–32.

synaptic elimination during adolescence? Journal of Psychiatric
Research 17, 319–334.

neuron. In Cerebral Cortex. Cellular Components of the Cerebral

Friedman, H. R. & Goldman-Rakic, P. S. (1994). Coactivation of
prefrontal cortex and inferior parietal cortex in working memory
tasks revealed by 2DG functional mapping in the rhesus monkey.
Journal of Neuroscience 14, 2775–2788.

Funahashi, S., Bruce, C. J. & Goldman-Rakic, P. S. (1989). Mnemonic
coding of visual space in the monkey’s dorsolateral prefrontal
cortex. Journal of Neurophysiology 61, 331–349.

activity related to saccadic eye movements in the monkey’s
dorsolateral prefrontal cortex. Journal of Neurophysiology 65,
1464–1483.

Funahashi, S., Bruce, C. J. & Goldman-Rakic, P. S. (1993). Dorsolateral prefrontal lesions and olivoculomotor delayed-response
performance: evidence for mnemonic ‘scotomas’. Journal of
Neuroscience 13, 1479–1497.

Fuster, J. M. (1985). The prefrontal cortex, mediator of cross-


3, 160–165.

in the dorsolateral prefrontal cortex of the monkey in cognitive

from cortical pyramidal cells in schizophrenia. Schizophrenia
Research 11, 137.

Glantz, L. A. & Lewis, D. A. Synaptophysin and not RABA3 is
specifically reduced in the prefrontal cortex of schizophrenic
subjects. Society for Neuroscience Abstracts 20, 622.

Goldberg, T. E., Weinberger, D. R., Berman, K. F., Plisnin, N. H.
& Podd, M. H. (1987). Further evidence for dementia of the
prefrontal type in schizophrenia? Archives of General Psychiatry
44, 1008–1014.

orientation to work on the prefrontal cortex in schizophrenia. In

Goldman-Rakic, P. S. (1987). Cerebellar output to prefrontal cortex
and V. Mountcastle), pp. 373–417. American Physiological
Society: Bethesda, MD.

Goldman-Rakic, P. S., Lerauni, C., Williams, S. M., Mons, N.
& Geffard, M. (1989). Dopamine synaptic complex with pyramidal
neurons in primary cerebral cortex. Proceedings of the National
Academy of Sciences USA 86, 9015–9019.

Heaton, R., Paulsen, J. S., McAdams, L. A., Kuck, J., Zisook, S.,
deficits in schizophrenics: relationship to age, chronicity, and
dementia. Archives of General Psychiatry 51, 469–476.

development of schizophrenia: a computer model. Schizophrenia
Bulitett 15, 477–490.

Huttenlocher, P. R. (1979). Synaptic density in human frontal
cortex—developmental changes and effects of aging. Brain
Research 163, 195–205.

Jones, E. G. (1993). GABAergic neurons and their role in cortical
plasticity in primates. Cerebral Cortex 3, 361–372.

connections predict patches of stimulus-evoked metabolic activity
in monkey somatosensory cortex. Journal of Comparative Neuro-
physiology 298, 23–39.

schizophrenia due to excessive synaptic pruning in the prefrontal
Research 28, 239–265.

Biocytin: a versatile anterograde neuroanatomical tract-tracing

LaMania, A. S. & Rakic, P. (1990). Axon overproduction and
elimination in the corpus callosum of the developing rhesus

LeVay, S. (1973). Synaptic patterns in the visual cortex of the cat and
monkey. Electron microscopy of Golgi preparations. Journal of
Comparative Neurology 150, 53–86.

18, of the cat: morphological and immunocytochemical evidence
for an excitatory function. Journal of Comparative Neurology 269,
265–275.

Topography of pyramidal neuron intrinsic connections in macaque
monkey prefrontal cortex (areas 9 & 46). Journal of Comparative
Neurology 338, 360–376.

18, of the cat: morphological and immunocytochemical evidence
for an excitatory function. Journal of Comparative Neurology 269,
283–285.

and mature macaque prefrontal cortex: Golgi and immunocyto-
chemical characteristics. Journal of Comparative Neurology 328,
282–312.

Targets of horizontal connections in macaque primary visual

type I synapses on spiny stellate neurons in primate visual cortex.
Journal of Comparative Neurology 211, 91–97.

Anatomical properties and physiological correlates of the intrinsic

and their physiological correlates in the primary auditory cortex

Melchitzky, D. S., Pucak, M. L., Dammerman, R. S. & Lewis, D.
(1994). Morphology and extrinsic targets of pyramidal neurons
furnishing intra-areal connections in monkey prefrontal cortex.
Society for Neuroscience Abstracts 20, 1416.

Pakkonen, B. (1993). Total nerve cell number in neocortex in
chronic schizophrenics and controls estimated using optical
 directive. Biological Psychiatry 34, 768–772.

working memory deficits. Archives of General Psychiatry 49,
975–982.

Petegrew, J. W., Keshavan, M. S., Panchalingam, K., Strychor, S.
brain high-energy phosphate and membrane phospholipid metab-
olism in first-episode, drug-naive schizophrenics. Archives of
General Psychiatry 48, 563–568.

Plant, T. M. (1988). Neuroendocrine basis of puberty in the rhesus
monkey (Macaca mulatta). In Frontiers in Neuroendocrinology, vol.
New York.

Roth, M. L. Levitt, J. B., Clasey, J. D., Lund, J. S. & Lewis, D.
A. (1994). Comparison of intra- and inter-areal patterns of con-
ectivity in monkey prefrontal cortex. Society for Neuroscience
Abstracts 20, 1416.
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