Functional Brain Imaging and the Neuropathology of Schizophrenia

by Christopher D. Frith

Abstract

We know much more about the anatomy of the frontal lobes than we do about their functions or how these functions go wrong in schizophrenia. Key areas for brain imaging research that will increase our understanding of frontal function concern (1) long-range functional connectivity and the mechanisms by which one brain region modulates activity in another and (2) the mechanisms underlying specific signs and symptoms associated with schizophrenia.


The principal message to emerge from these three articles (Goldman-Rakic and Selemon, Graybiel, and Haber and Fudge, all 1997, this issue) is that there is a wealth of information about the neuroanatomy of the frontal cortex and related areas—information that goes far beyond anything currently available in the way of theories about function. All the authors agree that “frontal function” depends upon an extended brain system involving circuits and loops incorporating basal ganglia and posterior brain regions as well as the frontal cortex, and that dopamine has an important regulatory role within these circuits. As discussed below, three major themes emerge to offer guiding principles for future imaging research.

The Role of Dopamine

The dopamine system is very complex and has many separable components. Haber and Fudge (1997, this issue) show how the midbrain dopamine system divides into two distinct groups of neurons and discuss the interactions of these two groups with the limbic system and other cortical areas. Goldman-Rakic and Selemon (1997, this issue) point out that there are at least three modes of dopamine modulation in the prefrontal cortex that relate in part to different types of dopamine receptors. By combining psychological activation and drug treatment, blood flow measures can be used to identify the locations at which drugs are interacting with cognitive processes (e.g., Dolan et al. 1995). It should then be possible to identify which subdivisions of the dopamine system are most relevant for our understanding of schizophrenia. The same technique could be used in conjunction with treatment trials to identify the components of the dopamine system most relevant to therapeutic effects.

Long-Range Connectivity

There is very little evidence for localized brain abnormalities associated with schizophrenia. Abnormalities seem to occur in many different areas. One common theme in these reviews is that there may be abnormalities in long-range connectivity rather than in localized lesions. Examination of connectivity in the human brain is now possible, using functional imaging techniques (Friston et al. 1992). Preliminary studies with positron emission tomography (PET) reveal evidence of frontotemporal disconnections (Friston and Frith 1995). Functional magnetic resonance imaging will provide better measures of long-range connectivity, since a great many scans can be performed on a single subject.

Long-range connectivity is not a fixed, structural property of the brain. Connectivity can be modulated to suit particular circumstances. The dopamine system (and no doubt other neurotransmitter systems) may well be involved in such modulation. Both Goldman-Rakic and Selemon (1997, this issue) and Haber and Fudge (1997, this issue) point out that dopamine neurons are in a suitable position to provide direct modulation of cortico-cortical, cortico-striatal, and cortico-thalamic projections.

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Dopamine neurons in the nucleus accumbens would also be in a position to modulate connections between the limbic and motor systems. Preliminary evidence that dopamine modulates abnormal frontotemporal connectivity in schizophrenia has been obtained using PET (Fletcher et al. 1996). Further imaging experiments could identify the site of this modulation in relation to different symptom complexes.

Brain and Cognition

It is not sufficient to show that the diagnosis of schizophrenia is associated with certain specific brain abnormalities. We also must show how these brain abnormalities can lead to the various signs and symptoms of schizophrenia. In all three reviews here, abnormalities in circumscribed neural systems are linked to specific symptoms of schizophrenia. The various circuits involving the frontal cortex and the basal ganglia are well placed in terms of their connections for regulating complex behavior. However, the detailed mechanisms by which such regulation occurs are still unknown.

In general, it is very difficult to infer function from structure. The key requirement for bridging the gap is the development of cognitive-level descriptions of relevant processes that can then be mapped onto neurophysiology. Haber and Fudge (1997, this issue) quote the work of Schultz and Romo (1987) on the role of dopamine neurons in the rewarded learning of new behaviors, but it remains to be seen how such processes link with the symptoms of schizophrenia.

Graybiel (1997, this issue) presents some very interesting speculations about the cognitive functions of the basal ganglia. In particular, she suggests that the basal ganglia may be involved in monitoring intention and its consequences. Such a function could have a major role in learning to distinguish the self from others (see also Russell 1996). A number of authors (e.g., Frith 1995) have suggested that defects of self-monitoring could be the basis of those symptoms of schizophrenia known as passivity phenomena (delusions of control, thought insertion) and also auditory hallucinations. It would be particularly exciting if a firm physiological basis for these bizarre experiences could be found through the cognitive link of a system for monitoring intention.

Goldman-Rakic and Selemon (1997, this issue) review the exciting advances in unraveling the physiological basis of working memory. I believe “working memory” is too narrow a concept to explain all the features of schizophrenia, especially key symptoms such as delusions and hallucinations. However, working memory (e.g., holding a spatial location in mind for a few seconds) can be seen as the simplest example of a class of operations that, at the other extreme, enable us to hold in mind abstract or symbolic entities such as mental states. There is preliminary evidence from brain-imaging studies that these types of ability also depend on frontal-lobe function (Fletcher et al. 1995). As Goldman-Rakic and Selemon point out, most of the symptoms of schizophrenia can be explained by failures of representation at a symbolic level. In particular, many schizophrenia delusions (e.g., persecution) reflect erroneous beliefs about the intentions of others that could arise from faults in a mechanism for representing mental states.

Before a unified account of the neuropathology of schizophrenia can be developed, it will be essential to consider individual symptoms or classes of them. On the evidence presented here, we could speculate that abnormalities in the basal ganglia are more relevant to those symptoms that reflect false beliefs about one’s own actions, while frontal damage is more relevant to false beliefs about the intentions of others. These speculations should be examined through imaging studies that identify the pattern of brain activity associated with those particular symptoms.

References


Goldman-Rakic, P.S., and Selemon, L.D. Functional and anatomical aspects of prefrontal pathology in schizophren-


The Author


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**Announcement**

The Sixth Congress of the World Association for Psychosocial Rehabilitation will be held at the Congress Centrum Hamburg, Hamburg, Germany, May 2-5, 1998. The conference is supported by the World Health Organization. Topics cover a wide variety of subjects in psychosocial rehabilitation of the mentally ill such as therapy, research, economics, social policy, relatives, and self-help.

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