What an Archaeological Dig Can Tell Us About Macro- and Microcircuitry in Brains of Schizophrenia Subjects

by Francine M. Benes

Abstract

This commentary on recent postmortem investigations suggests that schizophrenia may involve alterations of corticothalamic and temporolimbic regions of the brain. Although studies of this type are beginning to provide unique insights into the underlying pathophysiology of this disorder, all such investigations are generally hampered by the inability to differentiate between primary and secondary changes within complex macro- and microcircuitry. To overcome this basic epistemological problem, it will be necessary to develop novel strategies for determining how the communication between and within these various brain regions is decompensating, and later, compensating at different stages of the life cycle in schizophrenia.


This commentary focuses on the question of how one might empirically test the models of schizophrenia presented in the two preceding review articles: “Cortical Development and Thalamic Pathology in Schizophrenia” by Edward G. Jones (1997, this issue) and “The Temporolimbic System Theory of Positive Schizophrenic Symptoms” by Bernhard Bogerts (1997, this issue). Each of these articles uses recent postmortem evidence to propose two seemingly different neuroanatomical substrates of schizophrenia. Jones postulates that abnormal projections from the prefrontal cortex to the dorsomedial nucleus of the thalamus could alter activity-dependent gene expression in the latter. In the second review, Bogerts focuses on histopathological changes in the entorhinal cortex and hippocampal formation in the brains of schizophrenia subjects, suggesting that these changes could result in disinhibition of the amygdaloid complex. The amygdaloid complex has extensive reciprocal connections not only with the hippocampus and entorhinal cortex but also with the dorsomedial nucleus of the thalamus (Amaral et al. 1992). The prefrontal cortex (Brodmann areas 9 and 10) does not receive a significant input from the amygdaloid complex (Van Hoesen et al. 1993), but its various direct connections with the hippocampus entorhinal cortex, and dorsomedial nucleus of the thalamus make it a potential unifying factor for the two models presented by Jones and Bogerts (Benes 1995).

In either model, the respective pairs of brain areas emphasized can each be considered a macrocircuit—a unit consisting of spatially separated regions that are interconnected by projection neurons that send an efferent outflow of activity to their paired counterpart (see figure 1). Within each of the cortical regions participating in the two macrocircuits, however, there is very complex microcircuitry consisting of projection neurons and interneurons; the latter local circuit cells are responsible for fine-tuning the activity processed within the respective microcircuits and ultimately influencing the outflow of descending activity to the other subcortical regions, such as the dorsomedial nucleus of the thalamus and the amygdaloid complex. In other words, microcircuits influence the communication that occurs between two regions comprising a macrocircuit. The fact that the two model networks proposed by Jones and Bogerts have extensive reciprocal connections between their two respective cortical and subcortical components implies that the microcircuitry within each can influence that in the other, and vice versa.

Let us now consider how the models presented by Jones and Bogerts could be tested. One study design would be to examine simultaneously the two brain regions postulated to be involved in schizophrenia. By looking for covariation of the findings in one area with those of the other, it may be possible to determine whether the two regions may be subject to parallel or perhaps even similar changes. Presumably, some of the changes detected with quantitative microscopic analysis might be primarily

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Figure 1. Microcircuitry in the prefrontal cortex and in the dorsomedial nucleus of the thalamus and the larger macrocircuit that these two regions form by their interconnections

The circled numbers indicate a sequence of events beginning with gamma-aminobutyric acid (GABA)ergic inhibition in superficial (1) and then deep (2) layers of prefrontal cortex, that later influences the flow of excitatory activity to dorsomedial thalamic nucleus (3), stimulates inhibitory modulation (4) of thalamic projection neurons (5), and culminates with an outflow of excitatory activity from dorsomedial nucleus of the thalamus to the prefrontal cortex (6). (See text for details.)

The pathophysiology of schizophrenia, whereas others might be secondary in nature. Determining which set of postmortem changes occurred first, however, is challenging. On the one hand, if the prefrontal cortex plays a primary role in schizophrenia, it would be expected to show changes that are apparent in younger schizophrenia patients in the early stages of their illness. On the other hand, if the dorsomedial nucleus of the thalamus is secondarily affected by abnormalities in the prefrontal cortex, it might show a different set of alterations that are not present in the youngest cases, but only begin to appear in the later stages of the illness. For Bogerts' model, the same premises would be true, except that the earliest changes might be found in entorhinal cortex and hippocampus, whereas later-appearing ones would be found in the amygdala (i.e., if the former brain areas experienced primary involvement and the latter were secondarily affected).

Histopathological studies can be likened to an archaeological dig, in that the events leading to changes in the brain of schizophrenia subjects probably occurred many years, even decades, before detailed analyses of neural circuitry are being undertaken. At an archaeological excavation, scientists carefully remove sand, rocks, and other debris to expose key pieces of information concerning the site under investigation. Diverse pieces of data from hieroglyphics, entombed human remains, pottery fragments, and remnants of buildings are then used to devise a "story" (hypothesis) to explain how people interacted with one another and what events may have contributed to the dissolution of their society.

In postmortem studies of the brain with schizophrenia, an analogous challenge is at hand. There are several "dig" sites currently being investigated—the prefrontal and entorhinal cortex, hippocampus, amygdala, and dorsomedial nucleus of the thalamus—and careful analyses are being undertaken to characterize how specific aspects of local functioning (i.e., microcircuits) may have been altered within each region. Each small piece of postmortem information that is found within a given brain region must be gradually pieced together with all the other bits of information for that same region and with those from other interconnected regions. In this way, a hypothesis (i.e., a story) about what might have gone wrong in a macrocircuit of the brain with schizophrenia can gradually be constructed and used for empirical testing. At its best, this approach can only be considered inferential in nature because we cannot actually be there to watch what is happening when an individual with schizophrenia first becomes ill at 18 to 25 years of age, shows a deterioration in functioning during the next 5 to 10 years, develops the defect state during the mid-life period, and finally enters the senium during his final one to two decades of life (Benes 1988). Changes observed in a particular region of the brain could have appeared at any of these stages, depending on the age at which death occurred. The post-hoc reasoning typically employed in neuropathological investigations is quite limited in its
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ability to make such distinctions, and these inherent limitations must not be minimized.

Let us now return to Jones' model (Jones 1997, this issue) in which there are two relevant dig sites: the prefrontal cortex and dorsomedial nucleus of the thalamus. We must assume each of these regions has a set of microcircuitry that is uniquely different from that in the other. Even if some changes in one region of the brain with schizophrenia prove to be present in the other, each brain area must, of necessity, show alterations that are dependent on its regionally specific extrinsic and intrinsic connections. In other words, the local circuitry found within the prefrontal cortex of schizophrenia subjects could show both similarities and differences with the local circuitry observed in the dorsomedial nucleus of the thalamus. Moreover, the changes in the latter region probably depend on changes in the former because, for every change that occurs in one neuron, there will be a secondary change in another with which it is connected.

Can a distinction be made between primary and secondary changes in the prefrontal cortex-dorsomedial nucleus of the thalamus macrocircuit proposed by Jones (1997, this issue)? Let us use as an example the evolving idea that there may be a defect in gamma-aminobutyric acid (GABA)ergic neurotransmission in "frontal" cortex (Bird et al. 1977; Perry et al. 1979; Hanada et al. 1987; Simpson et al. 1989; Benes et al. 1991a, 1992b, 1996b; Akbarian et al. 1995) and hippocampal formation (Reynolds et al. 1990; Benes et al. 1996a) of brains of schizophrenia subjects. In the prefrontal cortex, such a decrease in GABAergic transmission would ultimately affect the firing of pyramidal neurons in both superficial and deep laminae (figure 1). Since layer VI of this region sends an effenter outflow to the dorsomedial nucleus of the thalamus, the activity of projection cells and GABAergic neurons within this thalamic nucleus would potentially be modified by incoming activity from the prefrontal cortex. In sending a reciprocal innervation back to the cortex, the dorsomedial nucleus will have a similar capacity to influence the firing of both projection neurons and interneurons within the prefrontal cortex. If one or both of these latter cell populations have also been primarily altered in the dorsomedial nucleus of the thalamus in schizophrenia subjects, then the outgoing activity from this nucleus could result in an additional set of secondary changes within the prefrontal cortex.

Is there any evidence to suggest that the dorsomedial nucleus of the thalamus, like the prefrontal cortex, may also show evidence of a GABA deficit in schizophrenia subjects? Unfortunately, there have been virtually no neurochemical studies of this region in postmortem brains with schizophrenia. However, two cell-counting studies conducted in different laboratories have demonstrated a reduction of neuronal numbers in the dorsomedial thalamic nucleus (Dom 1976; Pakkenberg 1990) that could possibly contribute to the volume loss observed in the thalamus of schizophrenia subjects (Andreasen et al. 1994). In one cell-counting study, a selective decrease in the density of "small" neurons that are likely local circuit cells was observed in patients with this disorder (Dom 1976). Since many of these cells are probably inhibitory interneurons, it is possible that a decrease in the activity of the GABA system may conceivably be present not only in the prefrontal cortex (Benes et al. 1991a, 1996b; Akbarian et al. 1995) but also in the dorsomedial thalamic nucleus of individuals with schizophrenia. If a decrease in GABAergic activity plays a role in an excitotoxic "lesion" in this disorder (Benes et al. 1992a; Olney and Farber 1995), then the prefrontal cortex and dorsomedial thalamic nucleus could each fall victim to the deleterious effects of abnormalities in the other because the regions have extensive reciprocal connections with each other (figure 1).

A discussion of this type rapidly becomes tautological in nature. Indeed, at this stage of analysis, we cannot rule out the possibility that both prefrontal cortex and the dorsomedial thalamic nucleus (or the hippocampus and amygdala) are the object of abnormal incoming activity generated in yet a third brain region. One possible candidate region for such a role is the anterior cingulate cortex, which has extensive connections with the dorsomedial nucleus of the thalamus (Bentoviglio et al. 1993), the amygdaldoid complex (Van Hoesen et al. 1993), the hippocampus (Finch 1993), and the prefrontal cortex (Van Hoesen et al. 1993). It has also been found to have several different abnormalities in individuals with schizophrenia (Benes and Bird 1987; Benes et al. 1987), including ones related to the GABA system (Benes et al. 1991a, 1992b), glutamate (Benes et al. 1992a), and dopamine (Benes et al. 1997) systems.

Clearly, a postmortem dig always has the disadvantage of viewing a problem retrospectively, and post-hoc analysis is therefore the best it can offer. Accordingly, it is very difficult for postmortem brain research to distinguish between primary and secondary changes, except, as noted above, by identifying ones present in young patients who have not been ill for very long and comparing them with findings in patients from the mid-life and senile periods. To accomplish this comparison in a meaningful way, large numbers of cases will be required to attain adequate statistical power. For the most part, individual studies reported to date have not had sufficiently large cohorts to permit such an approach. This problem might be overcome if each laboratory involved in this research were to


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