On Localizing Schizophrenic Neuropathology

by Daniel R. Weinberger

Abstract

Many brain regions and circuits have been implicated in the neuropathology of schizophrenia. Drs. Bogerts and Jones have reviewed the evidence that links the disorder to temporal limbic structures and to frontal-thalamic circuits, respectively. Each article is an important update on what we know about the relevance of these brain regions to schizophrenia. In addition, each article, in summarizing the accumulation of relevant research data, is a testament to the likelihood that these structures play a role in the disease. In light of their compelling arguments, this commentary emphasizes incompleteness in the data and inconsistencies in published findings. The principal weaknesses of the temporal limbic findings are that most have been reported in chronically ill patients and that the only qualitative finding of cytoarchitectural disorganization has not been replicated convincingly. Problems of replication also compromise the interpretation of neuropathological findings in prefrontal cortex and thalamus. Despite the loose ends, I agree with the conclusions of Drs. Bogerts and Jones that brain circuits involving thalamus, prefrontal, and temporolimbic cortices are involved in the basic biology of schizophrenia.


The excellent reviews and thought-provoking proposals of Bogerts (1997, this issue) and Jones (1997, this issue) follow a time-honored tradition of clinical-pathological correlations in neurology and neuropathology. This tradition has its modern origins in the second half of the 18th century, as scientists began to localize complex brain functions such as language to relatively discrete regions of the brain. The notion that perceptual, cognitive, and psychological phenomena, such as those associated with schizophrenia, might be localized in the same way has since challenged clinicians and basic scientists. Bogerts confidently presents the case for the temporolimbic structures of the mesial-temporal lobe; Jones, somewhat more reluctantly, makes the argument for the thalamus. Each study is an important update on what we know about the relevance of these brain regions to schizophrenia. In summarizing the accumulation of relevant research data, each is a testament to the likelihood that these structures play a role in the disease. Each study also—although less affirmatively—acknowledges that there are important missing pieces of the puzzle and that some of the existing pieces do not quite fit. Because the authors have taken on the greater challenge of assembling the puzzle, I will highlight some of its missing pieces.

As Bogerts (1997, this issue) emphasizes, there is abundant evidence implicating the temporolimbic cortex, including indirect clues (e.g., psychosis in patients with neurological lesions) and some direct evidence (e.g., neuropathological findings in patients with schizophrenia). This region has the “right connections” to be important in processing sensory information in the context of past experience; it also has felt “right” to neuroscientists for at least half a century (e.g., MacLean 1952). The data, however, could use some strengthening. Too many of the findings are based on patients with chronic illness, where the potential artifacts associated with long-standing ill health (both physical and mental) cannot be excluded. This is especially problematic in postmortem studies, as it complicates the interpretation of morphometric and cell-density data (Kleinman et al. 1995). This limitation also casts a shadow on quantitative neurochemical findings, including the latest gene-expression data.

For these reasons, qualitative findings that cannot be explained by the epiphenomena of having chronic schizophrenia generate a great deal of excitement. An example is the report by Jakob and Beckmann (1986) of cytoarchi-
tectural disarray in the entorhinal cortex, presumably an indication of cortical maldevelopment. Unfortunately, this potentially profound finding has not been independently replicated. In a comprehensive cytoarchitectural mapping study of the entorhinal cortex, our group could not replicate it and attributed the original finding to imprecise anatomical matching of samples (Krimer et al., in press). Nevertheless, a neuropathological fingerprint of a premorbid abnormality is arguably the most important result that could emerge from the next decade of schizophrenia research.

Imaging studies, which allow us to examine acute patients, have produced an incomplete data base with respect to temporolimbic cortical anatomy in patients near the onset of illness, and the results have been inconsistent (as has the methodological precision). As Bogerts (1997, this issue) implies, this may reflect the small effect size of the finding and the relatively small samples studied. Our group has been exploring in vivo neurochemical pathology using a magnetic resonance imaging (MRI) proton spectroscopic technique that generates neurochemical maps of multiple brain slices with relatively high resolution (approximately 1 ml voxel size). We have found—in both chronic and never-medicated acute patients—a pattern of relatively reduced concentrations of N-acetyl aspartate (NAA), an intraneuronal marker, exclusively in mesial temporolimbic and dorsolateral prefrontal cortices, bilaterally (Bertolino et al. 1996a, 1996b). The neuropathological implications of this finding are uncertain (it does not correlate with hippocampal volume), but the finding does point to the temporolimbic cortex as a pathological site, and it appears to exclude chronicity as a factor. A finding of reduced NAA concentrations in the rostral temporal cortex in first-episode patients has also been reported by another group using a single-voxel proton spectroscopy approach (Renshaw et al. 1995), so the temporal cortex result appears to be replicable. More work is needed to decipher its clinical and neurobiological implications.

The data from functional neuroimaging studies also support the role of the temporolimbic cortex, as noted by Bogerts (1997, this issue), but important pieces of this part of the puzzle seem to be squeezed into spaces where they do not quite fit. For example, the study by Liddle et al. (1992), which involved chronic, medicated patients, found positive correlations between parahippocampal cortex regional cerebral blood flow acquired at rest and clinical ratings primarily of hallucinations and delusions (the so-called reality distortion syndrome). This finding implies that schizophrenia, at least in patients with prominent "positive" symptoms, is associated with overactivity of this region. However, no absolute differences in activity between patients and controls was reported.

In contrast, in the only analogous study of unmedicated patients, Kaplan et al. (1993) found no correlation between reality distortion ratings and parahippocampal glucose use. In medication-free patients, Tamminga et al. (1992) found reduced glucose use in the parahippocampal region of their subjects (especially those with "positive" symptoms), compared with controls. Clearly, it is a bit of a stretch to conclude that too much and too little physiological activity have the same implications for temporolimbic function. Thus, a consistent functional neuroimaging finding in the temporolimbic cortex of patients with schizophrenia has yet to emerge.

Jones (1997, this issue) offers a sober and circumspect view of localizing interpretations, favoring the notion of distributed neural circuits and connections between regions. In this context, he notes that the thalamus is an important point of intersection of many circuits implicated in schizophrenia; thus, it would be hard to imagine the thalamus not being involved. Direct neuropathological evidence of thalamic involvement is, however, relatively limited. The principal recent finding is from the methodologically impressive work of Pakkenberg (1990, 1992). However, her dramatic results of a 40 percent reduction of cell number and a 25 percent reduction in volume of mediodorsal thalamus seem inconsistent with some negative postmortem (e.g., Lesch and Bogerts 1984) and in vivo imaging studies (e.g., Jernigan et al. 1991). We have surveyed the thalamus using our MRI proton spectroscopic imaging method, which is sensitive to neuronal loss, and found no differences between patients and controls (Bertolino et al. 1996a, 1996b).

The study by Andreassen et al. (1994) is often cited as showing reduced thalamic volume; however, in this comparison of "averaged" brains of a group of patients and a group of controls, only differences in signal intensity were reported and those differences were primarily in the right dorsolateral thalamus, an area not particularly noteworthy in other studies. The meaning of this finding in terms of structural anatomy is unclear. Another ill-fitting piece with respect to the thalamus is the finding that neurological lesions of this structure rarely are associated with psychosis (Lewis 1995).

Perhaps the strongest argument implicating the thalamus has to do with its role in integrating neuronal populations of the prefrontal cortex, which Jones (1997, this issue) refers to as the thalamic component of prefrontal "collectives." The evidence of prefrontal pathology, both functional and structural, is considerable, making an associated failure (primary or secondary) of coordinated thalamic activity a rational possibility. Here too, however, the puzzle has holes. For example, some of the postmortem
data cited by Jones would appear to suggest that gamma-aminobutyric acid (GABA)ergic function is "severely compromised," but the remarkable ineffectiveness of GABAmimetic drugs challenges this conclusion.

The landmark finding from Jones' laboratory of shifted distributions of nicotinamide adenine dinucleotide phosphate-diaphorase positive neurons in the schizophrenic prefrontal cortex—a finding that appears to implicate an abnormality in cortical development—has yet to be independently replicated. Indeed, it is not entirely clear that Jones and his coworkers can themselves replicate the finding. In their original report, they described at least some measure of a laminar distributional abnormality in all five of their patients (Akbarian et al. 1993). In their subsequent report (Akbarian et al. 1996), which included the first 5 patients but used an entirely different statistical analysis, only 7 of the total sample of 20 subjects apparently had an abnormality. Jones cautions that there is no conclusive evidence of a developmental defect in the schizophrenia brain.

I have highlighted some of the missing and ill-fitting evidence to complement the persuasive arguments presented by Bogerts (1997, this issue) and Jones (1997, this issue). In spite of the loose ends, I agree with their assertions that brain circuits involving the thalamus and the prefrontal and temporolimbic cortices are involved in the basic biology of schizophrenia. I believe the scientific evidence consistent with this conclusion far outweighs the inconsistent evidence. Nevertheless, we lack an anatomical "smoking gun" to finger a particular site as a primary focus. As Jones and Bogerts recognize, localization in terms of schizophrenia may ultimately turn out to be more relative than absolute. Indeed, recent positron emission tomography studies (e.g., Silbersweig et al. 1995) and case studies of patients with metachromatic leukodystrophy who present with a schizophrenia-like psychosis (Hyde et al. 1991) illustrate that the condition may depend on abnormal patterns of interregional cross-talk. While the regions and structures that make up this pattern include those emphasized by Bogerts and Jones, it may be their relationships with other regions that are critical. The hypothesis that developmental miswiring is responsible for such abnormal patterns of intracortical connectivity is currently in vogue; Jones and Bogerts wisely caution us that we need a lot more data to confirm that hypothesis.

References


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The Author

Daniel R. Weinberger, M.D., is Chief, Clinical Brain Disorders Branch, Intramural Research Program, National Institute of Mental Health Neuroscience Center, National Institutes of Health at St. Elizabeths Hospital, Washington, DC.