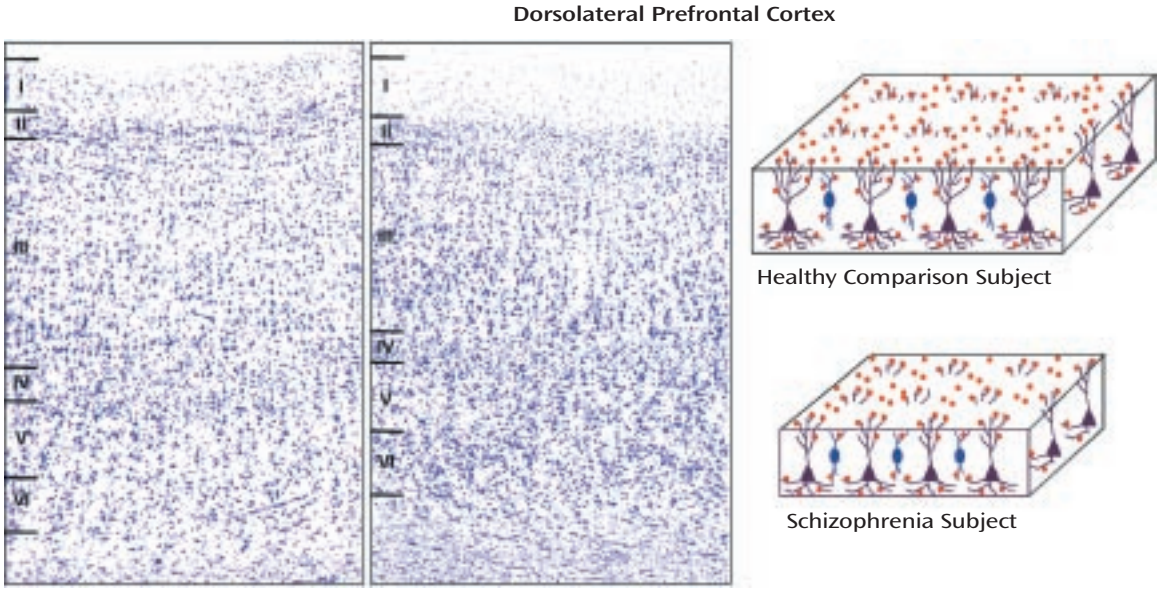
Carol A. Tamminga, M.D., Editor

Increased Cortical Neuronal Density in Schizophrenia



The most notable observation about the brain of a schizophrenia subject, including the prefrontal cortex, is its normal appearance. This absence of any discernible morphologic abnormality led to extreme skepticism among many early anatomists about a structural basis for the disorder. However, over the last two decades, quantitative approaches have been applied to the study of brain diseases and have spawned a new era in schizophrenia neuropathology. These techniques reveal anomalies in brain structure that are not at all obvious to the naked eye or even with light microscopy. For example, a direct, three-dimensional cell counting method has been applied to postmortem human tissue from persons with schizophrenia. In Brodmann's areas 9 and 46 of the prefrontal cortex and Brodmann's area 17 of the occipital cortex, increased neuronal densities of 17%, 21%, and 10%, respectively, were detected using this quantitative, analytic approach. The increase was evident in Brodmann's area 9 in layers III-IV and in Brodmann's area 46 in layers II-IV and VI. The densities of both pyramidal and nonpyramidal neurons were elevated. The figure illustrates the tissues used to make these quantitative measures. As you can see, the nature of the structural change, while significant upon quantitative analysis, is still subtle to visual inspection. This increase in neuronal density could be a reflection of an overall increase in the number of neurons in the tissue under study. But it could also result from a reduction in the overall volume of tissue, with no loss of neurons, due to a reduction in the interneuronal spaces (as depicted in the schematic diagram). In light of evidence of volume reduction in schizophrenia cortex of 3%–13%, derived from various sources (including in vivo imaging), this latter interpretation has been favored. The interneuronal spaces contain neuronal processes and synaptic contacts between neurons that are collectively referred to as neuropil. The loss of volume in the neocortex of schizophrenia subjects likely represents a reduction of synaptic elements and neuronal connections without a decrease in total neuronal number. The reduction of neuropil could underlie abnormalities of information processing and produce cognitive dysfunction in the illness. The complexity of the cerebral cortex requires high-resolution quantitative analysis to develop meaningful data in order to understand disease mechanisms.

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