EDITORIAL COMMENTARY

Schizophrenia neuropathology: tortoises and hares

A decade ago, the neuropathology of schizophrenia was an aging tortoise being overtaken by the young hare of molecular genetics. The smart money was on positional cloning finding the schizophrenia gene(s), after which the pathobiology of the disorder would finally be revealed. The race, however, has taken a different turn. The hare is no longer sure what race it is in, nor where the finishing line is. Meanwhile, the tortoise has found a new turn of speed, aided by the stiffening breeze of MRI evidence for structural abnormalities, new techniques, and better methodologies. Although no findings akin to a diagnostic lesion have been identified, there is an increasingly convergent body of data that cytoarchitectural alterations in the cerebral cortex accompany the disorder. By cytoarchitectural is meant aspects of neuronal structure and distribution, such as perikaryal size, shape, density and laminar position, as well as differences at the level of the synaptic terminal.

The study by Garey et al (this issue, pp 446–453) provides another piece of the jigsaw. They found that the density of dendritic spines—the protuberances on which most excitatory synaptic contacts are made—was decreased on layer III pyramidal neurons in the frontal and temporal neocortex in 13 patients with chronic schizophrenia compared with 11 normal controls. As these neurons furnish corticocortical projections, the findings are consonant with other evidence for aberrant functional connectivity; as the neurons are excitatory, the loss of spines is also congruent with neurochemical evidence for glutamatergic deficits in schizophrenia. The method used by Garey et al, the rapid Golgi technique, remains a somewhat capricious way of impregnating neurons and their dendrites, subject to various potential confounders. For this reason, together with unavoidable limitations in the nature and documentation of material available, the authors rightly interpret their results with caution. Nevertheless, it is noteworthy that the findings are in keeping with recent immunocytochemical evidence of dendritic pathology in schizophrenia provided by protein markers such as MAP-2, suggesting that similar conclusions are being reached by complementary methods. As always in this field, replication is essential, and should be feasible given the ongoing Charing Cross prospective schizophrenia study from which some of the tissue in the present study was taken. It will also be valuable to extend the work to include other dendritic indices (for example, length, segmentation, orientation) and other neuron populations (for example, in lamina V and in hippocampal subfields).

Cytoarchitectural abnormalities are being reported in autism and bipolar disorder. Comparing and contrasting the pathological profile of various disorders is an important step in determining the correspondence between clinical syndromes and their pathological substrate(s). Such progress may finally allow the psychoses to be categorised in pathological terms, a step which would provide more electable candidate genes for schizophrenia than those currently available, and which might even prove to be an essential endophenotypic clue if the genes are to be identified. It would not be the first time the tortoise has led the hare home.

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