Cortical Pruning and the Development of Schizophrenia

To the Editors:

Hoffman and Dobscha's paper (1989) on “Cortical Pruning and the Development of Schizophrenia: A Computer Model” overlooked some earlier discussions of this possibility. I presented a similar hypothesis at the 1981 meeting of the American College of Neuropsychopharmacology (ACNP), which was later published in short form in the Psychopharmacology Bulletin (Feinberg 1982). An extended treatment of these issues, including a summary of evidence indicating that profound changes in brain physiology and function take place much later in life than had previously been thought, was published shortly afterward (Feinberg 1982/1983). A relation of cerebral metabolic rate to synaptic density, attributed by Hoffman and Dobscha to Phelps and Chugani (1988), was also suggested in these earlier papers (see also Feinberg 1988 and reply from Chugani et al. 1988).

Hoffman and Dobscha propose that if a defect in synaptic pruning causes schizophrenia, it is likely to be “overzealous” pruning that is involved. They then construct a computer model to show that, given certain assumptions, excessive pruning could cause disturbances of thinking. However, I would not yet foreclose the alternative possibilities that, “as a result of some abnormality in this [progressive] process, too many, too few or the wrong synapses are eliminated.” I believe it is still the case that “we have no basis to choose among these possibilities” (Feinberg 1982/1983, p. 331).

Although Hoffman and Dobscha’s computer simulation shows that an overpruned neural net leads to schizophrenia-type aberrations, one could write other computer programs, containing different assumptions, in which elimination of the “wrong” synapses or of an insufficient number of synapses would give rise to metabolic abnormalities and behavioral symptoms. I do not believe that low rates of frontal blood flow and metabolism (“hypofrontality”) compel the conclusion that excessive pruning has occurred. Such low rates could come about through elimination of the wrong or of too few synapses, which might lead to faulty shunting or diffusion of neural activity.

Hoffman and Dobscha note that an interesting feature of their model is that overpruned networks sometimes split off from the larger system and function in an unintegrated manner. I agree that such behavior is phenomenologically similar to some aspects of disordered thinking in schizophrenia. I would add only that an existing alternative model that invokes established neurophysiological mechanisms also explains many of these phenomena. This model considers the consequences of impaired feed-forward or corollary discharge systems (Feinberg 1978). These integrating control mechanisms play an important role in distinguishing self-generated from externally induced neural activity (e.g., thoughts from perceptions), a clinically obvious difficulty for schizophrenic patients.

Readers who are interested in late brain development and its potential implications for psychiatric illness (and normal cognition) may wish to consult a recent elaboration of these ideas (Feinberg et al. 1990). Here, we demonstrate that the ontogenetic curves for cortical metabolic rate, delta wave amplitude, and synaptic density fit the same statistical model, strengthening the argument that they are each components of a common maturational process.
This article also rectifies an important omission in our original formulation, which had considered only the potential implications of late cortical regression. But synaptic regression occurs in parallel with constructive synaptic changes (Purves 1988) that must be of equal or greater functional importance. Since all possibilities are open at this point, we must entertain the hypothesis that it is a fault in the constructive elements of late synaptic development, alone or in combination with disordered regressive processes, that causes mental illness.

Our recent article also puts forward a new model of brain maturational changes (Purves 1988), according to which neurons enter an "organizational state" after birth. They remain in this state for a finite period, which lasts seconds to years, depending on the brain system. While in the organizational state, neurons have more synapses and higher metabolic rates than when they emerge. According to this hypothesis, levels of synaptic density, cortical metabolic rate, and delta wave amplitude reflect the proportion of neurons in the organizational state at a given age.

Last, we further considered the ways in which these surprisingly late maturational changes could be involved in normal cognitive development and in psychiatric disorders, including attention-deficit syndromes and both the schizophrenic and manic-depressive psychoses. We took note of two recent findings that could open the way to noninvasive investigations of these and other potential correlates of late brain maturation. Jernigan et al. (Jernigan and Tallal 1990; Jernigan et al., submitted for publication), using automated magnetic resonance imaging (MRI), found a decline in cortical thickness over ages 10–27 years. We have found a parallel change in delta wave amplitude measured by computer over the same age range (Feinberg et al., submitted for publication). The linear slopes of the age regressions of the MRI and electroencephalographic measures in these two entirely independent studies did not differ significantly.

References


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Acknowledgments

This research was supported in part by the Department of Veterans Affairs and by NIA grant 5 R01 AG07224.

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