NMDA-receptor hypofunction versus excessive synaptic elimination as models of schizophrenia

Ralph E. Hoffman and Thomas H. McGlashan

Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06520. **ralph.hoffman@yale.edu** **thomas.mcglashan@yale.edu**

Abstract: We propose that the primary cause of schizophrenia is a pathological extension of synaptic pruning involving local connectivity that unfolds ordinarily during adolescence. Computer simulations suggest that this pathology provides reasonable accounts of a range of symptoms in schizophrenia, and is consistent with recent postmortem and genetic studies. NMDA-receptors play a regulatory role in maintaining and/or eliminating cortical synapses, and therefore may play a pathophysiological role.

The target article by Phillips & Silverstein (P&S) proposes that the primary lesion producing disorganization symptoms in schizophrenia is dysfunction of the NMDA-receptor. They postulate that a primary consequence of this pathophysiology is a breakdown of local coordination of cortical processes, expressed behaviorally as a disruption in contextual sensitivity of information processing.

It would be surprising to us if NMDA-receptors were not somehow involved in the pathophysiology of schizophrenia. Alterations in learning and adaptation are hallmarks of this disorder. These processes rely, at least in part, on neuroplastic alterations mediated by NMDA-receptors (Contestabile 2000). However, we have some concerns.

The authors disclaim that their hypothesis about NMDA-hypofunction and context disorganization can explain the different symptoms associated with schizophrenia. This is a familiar caveat among schizophrenia researchers and scholars, the conundrum of heterogeneity. However, the authors also appear uncomfortable with this disclaimer when they mention Jansen and Faull's (1991) quip to the effect that it is "impossible to propose a model of schizophrenia without ignoring most of the data" (target article, sect. 7, para. 1). We agree that schizophrenia *seems* maddeningly heterogeneous, but we also feel that to model the disorder successfully, a large number of findings need be accounted for, including the nature and course of a relatively full range symptoms, plus epidemiological, genetic, and neurobiological findings.

The theory of NMDA-hypofunction and context disorganization proposed by the authors explains some phenomenology of persons with schizophrenia. We have argued, however, that more than NMDA-hypofunction must be involved; and, specifically, that cortical connectivity is reduced neuroanatomically in schizophrenia (Hoffman & Dobscha 1989; Hoffman & McGlashan 1997; McGlashan & Hoffman 2000; see also Feinberg 1982/1983). The most parsimonious explanation for such connectivity reductions, we propose, is that schizophrenia arises from an extension of synaptic pruning in association cortex that ordinarily unfolds during adolescence. These arguments have been based on computer simulations of neural networks showing how this neurodevelopmental abnormality produces a range of schizophrenic-like abnormalities – including disruptions of context-based information processing such as described by P&S – and spurious attractor states that could produce hallucinations, delusions, and thought disorder (Hoffman & Dobscha 1989; Hoffman & McGlashan 1997; Siekmeier & Hoffman 2002). We have also shown how synaptic pruning based on neural competition, when turned off just below the psychotogenic threshold, produces robust cognitive advantages (Hoffman & McGlashan 1997; 2001; McGlashan & Hoffman 2000). Therefore, genetic factors are predicted to push to the limit synaptic pruning in higher-level association cortex, to maximize these advantages in human populations. Schizophrenia, we postulate, will represent the small percentage of the population where genetically programmed synaptic pruning is pushed too far. The genetic predisposition to schizophrenia will be maintained across generations – even though reproductive success for persons with this disorder is greatly reduced (Kendler et al. 1993) – given the cognitive benefits afforded to the larger population.

Persons with schizophrenia are predicted to be especially vulnerable to NMDA-antagonists because these drugs may function as temporary disconnection agents in a condition where disconnection is already excessive. We do agree with the authors that the main locus of disconnection in schizophrenia is within cortical regions rather than involving distant connections between regions. Our reasoning is based on a recent monkey study demonstrating that "late" (i.e., peripubescent) neurodevelopment is characterized by a loss of local, within-module connectivity while distant connections remain unchanged (Woo et al. 1997). If schizophrenia is an extension of normal adolescent cortical pruning, then local connectivity would be most vulnerable to loss in this disorder (Lewis & Gonzales-Burgos 2000). This prediction is consistent with our more recent neural network models of this disorder (Hoffman & McGlashan 1997; Siekmeier & Hoffman 2002).

Are NMDA-receptor hypofunction and excessive cortical pruning really the same thing? We think not. First, only the latter perspective readily accounts for a range of post mortem findings. One such study demonstrated increased packing density of prefrontal neurons in the postmortem tissue of persons with schizophrenia compared with controls (Selemon et al. 1995). Since there is little evidence of significant loss of neurons in the cerebral cortex in schizophrenia (Selemon & Goldman-Rakic 1999), the most likely explanation is a loss of neuropil volume, that is, the dense entanglement of dendrites and axons surrounding neurons. Other postmortem studies more consistent with an anatomic pruning model of schizophrenia include those demonstrating reduced dendritic spines on pyramidal neurons (Garey et al. 1998; Glantz & Lewis 2000), and reduced phosphoproteins utilized by synaptic terminals (Eastwood & Harrison 1995; Glantz & Lewis 1997; Karson et al. 1999). Second, a pruning model predicts that the molecular basis of schizophrenia will be found in processes that maintain the corresponding microanatomy, namely, synapses and neuropil, rather than reflecting disturbed function of a particular receptor.

At the time of this writing, only two genes have been specifically linked to schizophrenia in the published literature as far as we know – one coding for dysbindin and the other coding for neuroregulin I (Stefansson et al. 2002; Straub et al. 2002). Both proteins appear to be concentrated in synapses rather than being directly referable to a particular receptor. However, the second protein has been shown to alter expression and activation of glutamate receptors. Mutant mice heterozygous for this gene have fewer functional NMDA-receptors than wild-type mice, and show behavior overlapping with mouse models for schizophrenia that is partially reversible with clozapine, a drug used to treat schizophrenia. Moreover, there is now a growing body of literature indicating that NMDA-receptors play an important role in maintaining and/or eliminating synaptic connections (Bock & Braun 1999; Hasbani et al. 2001). Thus, bets are on that NMDA-receptors are involved in the pathophysiology of schizophrenia, but where and how these receptors fit into the causal chain of antecedents and consequences of this enigmatic illness remains uncertain.

ACKNOWLEDGMENT

Simulation studies cited above were supported in part by NIMH grant RO1-MH50557.

https://doi.org/10.1017/S0140525X03320023 Published online by Cambridge University Press