Schizophrenia as a Disorder of Developmentally Reduced Synaptic Connectivity

Thomas H. McGlashan, MD; Ralph E. Hoffman, MD

Recent postmortem and neuroimaging studies of schizophrenia delineate changes in brain structure and volume that appear to arise from a reduction of neuritic processes (such as dendrites and synapses) rather than loss of neuronal or glial cell bodies. To account for these findings, we propose a pathophysiological model of reduced synaptic connectivity arising from disturbances of brain development active during perinatal and adolescent periods. We review a computer simulation of the elimination of the synaptic connections that models normal cognitive development and psychotic symptom formation. We describe the model's key parameters and discuss how they can account for important aspects of schizophrenia, including its unique symptoms, short- and long-term course, typical age of onset, neurodevelopmental deficits, limited neurodegenerative progression, sex differences, and more. We discuss some of the model's predictions and questions raised for basic research, early detection, and preventive intervention.

Kraepelin1 described schizophrenia as a severe organic brain disease resulting in deterioration and chronic disability. Many explanatory models have been proposed for the disorder, but none have accounted for more than a few of the disorder's features. Most puzzling was the lack of clear postmortem differences in the brains of patients with schizophrenia. Sophisticated histopathologic and neuroimaging techniques, however, are now demonstrating subtle but distinct neurobiological variances that offer more clues to the disorder's pathophysiology.

In this article we review recent postmortem and neuroimaging findings and formulate a pathophysiological model of schizophrenia referred to as developmentally reduced synaptic connectivity (DRSC) to account for them. This model posits that schizophrenia arises from critically reduced synaptic connectedness as a result of developmental disturbances of synaptogenesis during gestation and early childhood and/or synaptic pruning during adolescence. We review a computer simulation of the elimination (pruning) of synaptic connections that models normal cognitive development as well as symptom formation in schizophrenia. The model's implications are elaborated into parameters that may account for the disorder's phenomenology, waxing and waning symptomatic states, onset epidemiology, neurodevelopmental deficits, window of deterioration, sex differences, differences in clinical presentation and course determined by age of onset, and preservation of the schizophrenic genotype in the population despite diminished phenotypic fecundity.

CORTICAL CONNECTEDNESS AND NORMAL PRUNING: WHAT DO WE KNOW?

Postnatal mammalian brain development is characterized by synaptogenic overelaboration of neuritic processes, ie, axons and dendrites, in the cortex followed by a gradual reduction of synaptic density to about 60% of maximum levels.2,3 In humans this process is largely complete by age 2 years in sensory areas such as the oc-
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A COMPUTER SIMULATION OF SYNAPTIC PRUNING AND ITS CONSEQUENCES

In this section we review a neural network computer simulation of auditory hallucinations reported previously. Studies suggest that this highly prevalent schizophrenic symptom arises from neurocircuitry underlying perceptual processing of speech. We developed a simulation of continuous, narrative speech perception to investigate pathophysiological mechanisms.

Normal human speech perception, as effortless as it seems, is a complex task given the high level of acoustic ambiguity of everyday speech produced at normal rates in “noisy” environments. The process involves verbal working memory capacity that uses expectations based on prior words and phrases to disambiguate new verbal noises or phonemes and transform them into meaningful words. Our neural network computer simulation featured a verbal working memory component with linguistic expectations built up from prior exposure to a training set of grammatical sentences. In this way it was programmed to process degraded input signals into identifiable words. The number of words correctly generated (identified) from input was counted as well as the number of words incorrectly generated (misidentified). “Voices” or hallucinations were scored when words were generated during periods of input silence.

The effects of pruning connections in the memory component are illustrated in Figure 1. Initial detection rates of phonetically degraded words improved when up to 30% of “synapses” were eliminated. Pruning above 35%, however, produced progressive impairment in network word detection. At still higher levels (>40% pruning), hallucinations were simulated (as “speech percepts” occurring in the absence of inputs) with further speech processing impairment. A later study with human subjects demonstrated a similar pattern of speech processing impairments highly specific to schizophrenic patients reporting auditory hallucinations.
Our model also simulated neuromodulation (not shown in Figure 1). By altering the “bias” or “excitability” of the memory “neuronal” elements, hallucinations could be eliminated, although cognitive impairments remained unchanged. These alterations are suggestive of receptor-mediated neuromodulatory drug treatment that reverses positive symptoms, but effects little change in cognitive deficits—a simulation, perhaps, of the treated “residual” state of schizophrenia.

Our model essentially simulates 2 neurobiological processes that are potentially pathogenic. The first consists of structural (neuroanatomical) reductions of connectivity in a large, complex, self-organizing system of neuronal elements. The interactive system, rather than the individual neurons and synapses, becomes pathogenic. The second is neuromodulatory and involves altering the excitability of all neuronal elements in a continuous fashion. Our model incorporates both processes in symptom formation. Reduced connectivity is always necessary, sometimes sufficient. Neuromodulation varies the functional impact of reduced connectedness over a limited range, often around the critical threshold of symptom formation. The model predicts that the focus of psychotogenic synaptic reductions lies in the working memory systems. For language processing, these systems are likely to involve interactions among the frontal, temporal, and parietal cortices, especially in the dominant hemisphere.

Our computer simulation is a model of pathophysiology, not etiology. It suggests that symptom formation occurs late in the process of loss of connectivity. Woods asserts that schizophrenia, like Parkinson disease, is a disorder that develops late relative to neurobiological loss. In our model, neurodegeneration means loss of neuronal connectivity through developmental processes, not loss of neuronal cells through neurotoxic processes. The key pathogenic process is a reduction of synaptic connectivity (density) below a critical level. We postulated that this arises from 2 processes, both related to development: (1) limited synaptic density to start with in early childhood from genetic/perinatal factors and/or (2) pruning of synaptic connections in adolescence and young adulthood. This has subsequently been articulated as a combined early neurodevelopmental and later neurodegenerative model of schizophrenia, although many models suggest the neurodegenerative element is neurotoxic rather than developmental. Variations of this model have also been articulated as a “disconnection” or a “misconnection” syndrome.

THE DRSC MODEL: KEY PARAMETERS

The DRSC model identifies reduced synaptic density in prefrontal and other areas of association cortex as the “final common pathway” to the symptoms and course of schizophrenia and, perhaps, to other psychotic disorders. As suggested by our computer model and the heterogeneity of schizophrenia, the degree of reduced synaptic density may determine the severity of phenomenology and course. If normal adult levels of synaptic density are 40% of maximal levels, let us assume for heuristic purposes that specific reductions beyond 40% may trigger prodromal symptoms, a reduction of 50% may precipitate psychotic symptoms, and a reduction of 60% may lead to chronic active psychosis requiring institutionalization.

We propose 2 pathophysiological determinants of such reductions, the richness of baseline childhood synaptic connections and the subsequent rate of neuritic pruning in later childhood and adolescence. These parameters are depicted in Figure 2 and Figure 3, respectively.

Figure 2 illustrates reduced synaptic connectedness and the developing course of disorder across 4 “individuals” through onset to a...
Because pruning rate is held constant, this model highlights neurodevelopmental pathophysiology; ie, what happens when early latent deficits interact with later neurodegeneration. The variability of baseline synaptic densities is determined by genetics, perinatal stress, and other processes (discussed below). In the interest of simplicity, this model does not illustrate neuritic proliferation. Individual I represents normal development with elimination of synaptic connections through childhood and adolescence to levels necessary for adult functioning. Individual II represents mild schizophrenia. The threshold for psychosis coincides with the point of maximal loss of synaptic connectedness. The patient’s disorder is treatment responsive and relatively mild. Because pruning has plateaued at onset, the clinical picture, neurocognitive deficits, and neuroanatomical changes remain static without further deterioration. Individuals III and IV start with thinner synaptic densities at baseline that lead to more severe disorders with further developmental pruning. Because neuritic pruning has not plateaued by onset, continuing deterioration of symptom picture, treatment response, functional capacity, neurocognition, and neuroanatomy are likely to be seen.

Figure 2 predicts that, pruning rates being equal, reduced childhood or “baseline” synaptic richness is likely to correlate with a briefer prodromal phase, an earlier onset, a longer postonset window of deterioration, and a more severe disorder by the time the pruning plateau has been reached.

Figure 3 illustrates the neurodegenerative model; ie, reduced synaptic connectedness from variable rates of pruning with baseline synaptic density held constant. Here, higher rates of pruning are associated with an earlier onset, a shorter prodrome, more rapid deterioration after onset, and a more severe disorder by the pruning plateau. With individual IV, for example, we are likely to see the rapid development of treatment resistance, not because of “toxic” active psychosis but because of the continuing pruning process.

These models are representations and undoubtedly oversimplified. Borderline synaptic density and the rate and depth of synaptic pruning vary across individuals. Many relevant variables are not modeled, such as degree of neuritic proliferation and topographical differential localization of pruning among the frontal, parietal, temporal, and occipital cortices. Nevertheless these models illustrate how a limited number of parameters may account for some of the heterogeneity in schizophrenia.

**THE DRSC MODEL: VALIDATIONS AND PREDICTIONS**

The validity of any model rests on its ability to account for multiple observations about schizophrenia. Those we regard as essential are elaborated below.

**Symptoms**

Our simulation specifically models hallucinations in which words are perceived in the absence of acoustic input. The link to other schizophrenic symptoms involves extrapolations from this program. For example, a generic consequence of excessively reduced synaptic connectivity is the generation of localized cerebral activity spontaneously and autonomously. If activity is generated in the speech perception area independently of sensory input, the result is hallucination. If cerebral activity generates thoughts independently of a sense of will or agency, the result is delusion or first-rank phenomenology. If linguistic activity is generated independently of prefrontal executive integration, the result is disorganization of speech. A parallel consequence of reduced synaptic connectivity is diminished overall cerebral cross-communication expressed as pervasive negative symptoms. Continued pruning in our computer model resulted in diminished hallucinatory “output,” modeling the regression of positive symptoms and progression of negative symptoms with time and chronicity in schizophrenia.

**Waxing and Waning Symptomatic Course**

The relatively abrupt appearance of hallucinations in our simulation at around 40% reduction in synapses suggests that the symptom-generating threshold is relatively discrete where small changes in the percentage of working synaptic connections determine state differences between no symptoms and active symptoms. In the simulation, these small changes could be manipulated by modulating the overall excitability of the neural units, thus modeling how neuroleptics raise the threshold for symptom formation and stress lowers the threshold, both (in part) through perturbations in dopamine drive. In this way the model simulates the remissions and relapses...
common to the schizophrenic disorder depending on drug status and stress level.

Age of Onset

The DRSC model accounts for the onset epidemiology of schizophrenia; ie, the emergence of disorder throughout the lifespan starting after age 5 years with the highest frequency of new cases in adolescence and young adulthood. Onset occurs when a critically low synaptic connection threshold is reached. Between the ages of 16 and 30 years (when roughly 75% of cases happen) this may be reached as illustrated in Figures 2 and 3. Childhood-onset schizophrenia arises when a dangerously thin neurodevelopmentally determined network is subjected to an abnormally aggressive pruning process. Adult onset after age 30 years results from normal annual loss of synaptic density in a person whose synaptic network is already very close to the critical threshold. In adult networks not close to the threshold, critical levels can still be reached if genotypic vulnerability determines an accelerated annual loss of connectivity. That this occurs is suggested by 2 putative markers of synaptic density, D2 receptor density and the P300 evoked potential latency prolongation to the oddball paradigm. Persons who develop schizophrenia have higher rates of D2 receptor density attrition and P300 latency prolongation compared with normal controls. Late-onset schizophrenia (paraphrenia) emerges in someone near threshold undergoing normal age-related pruning or in someone distant from threshold whose annual loss of connections increases secondary to some other age-related neurodegenerative process.

Neurodevelopmental Deficits

Neurodevelopmental theories postulate that early neurobiological lesions interact later with normal development to generate schizophrenia. The central nervous system defect(s) is determined in as yet unknown ways by genetics and by any of a variety of perinatal insults or stressors, including prenatal viral infections, famine and malnutrition, Rh incompatibility, severe environmental stress, obstetrical complications, and signs of general fetal distress as reflected in hypoxia at birth. The epidemiologic risk factors of urban and winter birth are likely related to perinatal perturbations, especially infection. These and other aspects of neurodevelopmental pathogenesis have been reviewed extensively.

The mild dysfunctions associated with these early neurobiological lesions occasionally emerge in childhood and early adolescence as vulnerability factors or risk markers of psychosis. They include diminished expression of positive and negative emotions, passivity, social maladjustments, anxiety, withdrawal, and poor peer relationships. Neuromotor abnormalities in the form of poor coordination, poor perceptual-motor integration, or abnormal speech are seen, as well as minor physical anomalies, neurocognitive deficits, poor attention and concentration, and lower IQ and poor educational achievements. Vulnerability is occasionally expressed as disruptive and aggressive behavior, most often in males.

Evidence of neurodevelopmental deficits in a subset of persons who develop schizophrenia is extensive and convincing, yet such deficits do not appear necessary or sufficient to produce schizophrenia. They are present in a minority of preschizophrenic persons, are mild, seldom score outside ranges of normal, and are not strongly predictive of later schizophrenia. The most convincing evidence against a singular neurodevelopmental pathophysiology, however, is the typical and often dramatic deterioration in functioning in young adulthood originally described by Kraepelin, which has been the clinical landmark of schizophrenia for a century.

The DRSC model regards genetic and perinatal perturbations as major determinants of childhood ("baseline") synaptic density and vulnerability to psychosis, the pathophysiological contribution of which is depicted in Figure 2. While the role of neurodevelopmental deficits may be substantial, they are seldom (if ever) sufficient to account for the disorder. A second "hit" is also necessary. This hit is developmentally driven synaptic pruning, both normal (Figure 2) and abnormal (Figure 3). It ushers in a limited period or “window” of neurobiological deterioration in which the full-blown disorder becomes manifest. This window has preonset and postonset phases, each with its own phenotypic expressions of reduced synaptic connectivity.

The Window of Deterioration: Preonset Expressions

The clearest preonset signal of deterioration is the appearance of “prodromal” symptoms. As outlined by German psychiatry, the first symptoms are gradually developing, nonspecific negative symptoms starting 3 to 5 years before onset, followed by positive symptoms around 1 year before onset that in the final months crescendo in severity to meet official diagnostic criteria. This development and phenomenology has been thoroughly reviewed.

Other frequent nonsymptomatic preonset expressions include functional decline in work capacity and social and sexual functioning. The most careful studies of “premorbid” adjustment reveal on average a slow, steady pattern of degeneration with acceleration closer to onset.

Davidson et al used Israeli Draft Board Register assessment scores gathered from all Israeli 16- to 17-year-old males to characterize those who ultimately went on to develop schizophrenia during the subsequent decade. Those later hospitalized for schizophrenia (on average 5 years from testing) displayed deficits at age 16 or 17 years on IQ (0.5 SD below normal), social functioning (1.0 SD below normal), and autonomy (0.5 SD below normal). Together these behavioral and cognitive measures held a positive predictive power of 72%, a prediction rate distinctly better than rates associated with neurodevelopmental risk markers from high-risk and birth cohort studies.

Longitudinal cross-sectional analysis of these deficits across yearly Israeli draft cohorts provides a cohort-reconstructed picture of these
deficits during successive time intervals between assessment and onset. Social functioning was below normal to start with, but became progressively worse up to onset, and continued to deteriorate after onset. The IQ in those developing schizophrenia was below normal but stable until approximately 2 years prior to onset. The IQ then declined up until onset at which time it plateaued. Interestingly, our computer model found that cognitive performance declined prior to symptom formation, a finding in keeping with the Israeli data. These levels then stabilize as demonstrated by numerous studies of neurocognition in the early phases of schizophrenia. 166-173 Additionally, many changes in brain volume, gray matter volume, and extracerebral (subcortical) cerebrospinal fluid seen by MRI in established schizophrenia (reviewed earlier) are already present in first-episode schizophrenia, strongly suggesting they predate characteristic symptom formation. 169,174-180

The Window of Deterioration: Postonset Expressions

Following first treatment, positive symptoms usually diminish to “residual” levels and functional capacity recovers somewhat to preonset levels. Changes in symptoms and functioning continue in many cases for a limited time but eventually a pattern sets and remains stable for many years, the so-called middle phase or plateau. Symptom relapses occur if treatment is interrupted and/or stress amplifies, 181 but overall function and disability change little. The evidence for a plateau without further deterioration is substantial, both for clinical symptoms 182-189 and for neurocognitive functioning. 167,168,172,173

The late phase of disorder is usually an indistinguishable extension of the plateau. Recent studies, however, suggest that subgroups aged 65 years and older may undergo an accelerated decline in cognitive and functional capacities. 190-193

In many cases of schizophrenia, often the majority, the active symptom profile is stable from onset onward. When early postonset clinical deterioration occurs, it is usually in a subset. 194-196 This deterioration has various phenotypic expressions such as increasing treatment resistance over sequential relapses, 197 a high frequency of hospitalizations within the first 3 years of manifest illness, 198,199 early symptom progression from organized delusions and strong affects to thought disorder, disorganized behavior, and negative symptoms, and subtype progression from paranoid to disorganized/undifferentiated or from nondeficit to deficit. 194-198 This deterioration can also be seen on standard neurological examination. 200 Variable deterioration is also seen in MRI gray matter loss, which provides a mixed picture of non-progression, 176,201-203 progression that is often subtle, 197,206-212 or progression that is restricted to subgroups, 209,213-215 All of these findings are consistent with our model. In Figures 2 and 3, for example, individual II, in contrast to individual IV, is likely to present a static clinical, neurological, neuroanatomical, and neurophysiological profile over time. In one MRI study, first-episode patients with good 3-year outcome (remission and no relapses) had no change in ventricular volume compared with patients with poor 3-year outcome (no remissions or remissions with relapses) who had increasing ventricular volume over time. 197 Again, the first group could be comparable to individual II, the latter group to individual IV.

When postonset deterioration is occurring, as in individuals III and IV of Figures 2 and 3, our model predicts that the rate of deterioration will be greatest in the immediate postonset period. Consistent with this, one study of serial ventricle-brain ratios (VBRs) in first-episode patients distinguished 2 groups, one with static VBR and one in which VBR increased over time. 213 When VBR was expanding, the rate of expansion was greatest early in the illness. Phosphorus magnetic resonance spectroscopy can measure brain substances that are putative markers of synaptogenesis vs synaptic pruning. 216,227 Stanley et al 217 found that markers of synaptogenesis were lower than normal in schizophrenia at all stages of illness, but that markers of synaptic pruning were highest in the early postonset period of active disorder.

When postonset deterioration is occurring, our model also predicts that the rate of deterioration will be greater the younger the age at onset. Consistent with this, Knoll et al 218 studied a sample of patients selected for a deteriorating course and found that increasing VBR over time correlated significantly with younger age and, by inference, younger age of onset. Also consistent with this, postonset IQ decreased strikingly in a group with childhood-onset schizophrenia in contrast to many studies in adult-onset schizophrenia. 219

Sex Differences in Onset and Course

This model may also account for the repeated finding that males have a more severe form of schizophrenia that emerges 3 to 4 years earlier. 220-222 This sex difference may relate to the protective effect of estrogens via their attenuated dopamine blocking effect at D2 receptors. 158,224-227

However, recent studies suggest estrogens also influence neurodevelopmental processes, including neural growth, synaptogenesis, and synaptic pruning. 228-232 Animal studies have found higher female hormones associated with delayed developmental pruning of cortical connections 233 and with higher levels of connectivity and neurtitic proliferation. 234-236 By our model, delayed onset and reduced rate of pruning in puberty could also determine the epidemiologic differences in onset between men and women (in Figure 3, for example, the difference is illustrated if individual II is female and individual IV is male).

Age of Onset and Degree of Postonset Deterioration

If the parameters of baseline network synaptic density and rate of pruning vary as illustrated in Figures 2 and 3, our model predicts that earlier onset will be associated with an ultimately more severe, disorganizing, and deteriorated form of schizophrenia. The earlier the onset, the farther the person is (at onset) from their final pruning end point, and the greater will be the postonset destruction of neural net-
work connectedness. This appears to be the case for childhood-onset schizophrenia. It may also be the case for adolescent- and young adult-onset schizophrenia. A reanalysis of a large adult, first-episode cohort found that earlier-onset patients had significantly higher syndromal symptom scores by structured interview. The same authors applied a symptom checklist similar to the structured interview to an even larger sample (N=1109) of schizophrenic patients first admitted to the hospital in the years 1978 to 1992. An interaction emerged between predominant symptom pattern at first admission and age of onset with the earliest-onset cases characterized by more disorganization (incoherence of thought and disordered sense of self) and later-onset cases by more organized systematic and paranoid delusions. Neuroanatomical changes consistent with greater severity would also be expected from this model. In a study of nonfamilial schizophrenic patients with histories of severe pregnancy and birth complications, smaller than normal hippocampal volumes were found and the degree of volume reduction correlated significantly with younger age of onset. Among patients selected for ongoing postonset deterioration, the degree of increase in serial VBRs was also correlated with a younger age.

We regard this prediction as more speculative than the others because we do not know if our postulated parameters of baseline synaptic density and rate of pruning vary as illustrated in Figures 2 and 3 and whether they vary independently. Furthermore, the findings of the Hafner and an der Heiden studies are consistent with our model only if the duration of untreated psychosis in these “first-episode” patients is substantial, because we otherwise would expect few differences in clinical presentation at the actual point of onset. Duration of untreated psychosis in most first-episode samples is substantial, but we do not know whether this was the case for these samples.

Maintenance of the Schizophrenia Genotype

We believe our computer simulation not only provides a model for schizophrenic symptom formation but also provides an understanding of the adaptive utility of neuritic pruning. It seems to serve learning by increasing cognitive capacity, accuracy, efficiency, and speed of learning at the expense of loss of flexibility. As such, it is both a natural and necessary neurobiological process subserving human social, linguistic, and intellectual functioning. More speculatively, “optimal” neuritic pruning may subserve adaptation and competitive advantage. Survival may select naturally toward maximal neuritic pruning with its attendant risk of overpruning and psychosis. This could account for the occasionally documented familial association between creativity, genius, and psychosis. This could also account for the persistence of the schizophrenia genotype in the world’s population and its uniform incidence despite the obvious fertility disadvantage of its clinical phenotype. Incidence appears to be increasing at a rate of 3 points per decade since measures of intelligence have been developed. Such change may be necessary for optimal adaptation to an increasingly complex, industrialized world. It may be that schizophrenia is the risk or negative by-product of this evolutionary pressure toward increasing intelligence, and that it is mediated by a persistent adaptive advantage conferred by more robust neuritic pruning.

TESTS OF THE MODEL

The DRSC model can be tested in several ways. At the clinical level, we have predicted that younger age of onset will be associated with more postonset deterioration and ultimate disability and that postonset deterioration, when it occurs, will progress most rapidly closer to onset. Our computer model also predicts that hallucinations will diminish in frequency and/or severity with further pruning. Clinically, this translates into a prediction that in adolescent-onset cases vs adult-onset cases, hallucinations (or other positive symptoms) are likely to be less persistent than negative and disorganized symptoms. Similar predictions can be made for cognitive functioning and for brain structural parameters such as brain volume, grey matter volume, and ventricular volume. Most compelling would be prospective longitudinal demonstrations of deteriorative changes in these measures in late premorbid and/or prodromally symptomatic persons who go on to develop schizophrenia.

The ultimate tests of this model would be postmortem measures of synaptic density and/or premortem measures of synaptic connectivity applied prospectively as above, whenever such a measure is developed. Several technologies are emerging as candidates, such as diffusion tensor imaging and/or transcranial magnetic stimulation so the wait may not be prolonged.

IMPLICATIONS OF THE DRSC MODEL

The DRSC model has implications for early detection, preventive intervention, and future research. The aims of early detection are to identify the onset of the window of deterioration in vulnerable individuals with high predictive validity. The work of Davidson et al comes closest so far and demonstrates that predictability takes a quantum leap in adolescence (even prior to the prodrome). As such, we need to focus preonset early detection efforts not just on those who are prodromally symptomatic but also on premorbid individuals who are at high risk by genetic and perinatal history and who present with progressive social deficits in adolescence.

The major question regarding preventive intervention is whether existing treatments can affect the loss of synaptic connectivity. If the answer is yes, secondary prevention in schizophrenia will be possible. Early interventions that reduce duration of untreated psychosis will improve lifetime prognosis, and interventions in the prodrome will delay or prevent onset. If the answer is no and deterioration proceeds despite early intervention, then we must focus on understanding what determines neuritic arborization and pruning. Existing treatments should be tested in appropriate patients; this should include medications which, albeit neuromodulatory in nature, may influence synaptic den-
Finally, our model predicts that even if deterioration continues, its consequences may be ameliorated with early intervention in some cases. For example, antipsychotic treatment in the prodromal phase of individuals at risk for milder forms of schizophrenia (such as individual II in Figures 2 and 3) will raise the threshold for psychosis and theoretically prevent the person from ever manifesting schizophrenia, providing, of course, that the treatment is continuous.

Finally, to the extent that it proves to be valid, the DRSC model orients neurobiological research in 3 directions. The first is to develop measures of synaptic density that can be used safely in the clinical context for vulnerability assessment. The second is to understand better the neurobiology of neuritic proliferation and pruning. The third is to understand better the neurodevelopmental determinants of reduced baseline synaptic density.

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Reprints: Thomas H. McGlashan, MD, Yale Psychiatric Institute, PO Box 208038, New Haven, CT 06520 (e-mail: thomas.mcglashan@yale.edu).

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