# 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.

*Arch Gen Psychiatry. 2000;57:637-648*

Kraepelin[1] 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.

*From Yale University School of Medicine, New Haven, Conn.*

## 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-

cipital cortex but is not complete until midadolescence in prefrontal and association areas.[2] Early in development, synaptogenesis likely creates connections more or less randomly, with subsequent selective elimination of weaker connections based on experience,[4] as well as endogenous factors.[5-7] In adulthood, production of new synapses is matched by a similar rate of synaptic elimination.

Prospective repeated neuroimaging of normal children and adolescents,[8-13] nonpatient controls,[14,15] or nonschizophrenic, treatment-seeking patients[16] provides a cumulative picture of normal gray matter volumetric development. Gray matter loss starts around age 5 years and becomes more robust through later childhood and adolescence before tailing off to lower adult rates in the third decade of life. These changes are concentrated in the frontal and parietal but not in the temporal and occipital cortical areas.[14]

## RECENT EVIDENCE FOR REDUCED CONNECTEDNESS IN SCHIZOPHRENIA

The most compelling data supporting reduced synaptic connectivity in schizophrenia comes from postmortem and neuroimaging studies. Huttenlocher[2] and Huttenlocher and Dabholkar[3] reported that cortical synaptic density normally diminishes developmentally, especially during adolescence. This triggered the first suggestion that schizophrenia was a disorder of neuritic pruning,[17] a suggestion supported by subsequent postmortem histopathologic studies demonstrating reduced spine densities and smaller dendritic arbors on the pyramidal cells of the prefrontal cortex in schizophrenia.[18-21] Other findings relate to changes in synaptic "products," including reduced glutamate and γ-aminobutyric acid synaptosome release in schizophrenia,[22,23] decreased synaptic protein messenger RNA expression in schizophrenic temporal cortex,[24] and reduced synaptophysin in the dorsolateral prefrontal cortex[25-28] and thalamus[29] in schizophrenia. The most replicated postmortem finding has been increased cortical neuronal density seen on histological examination as reduced neuropil[30-34] without neuronal loss.[35] This has been interpreted as neurodevelopmental failure and/or neurodegeneration insofar as the decreased neuropil represents a loss of connections between neurons. Retained neuronal numbers and lack of gliosis have been interpreted as evidence against neuronal loss per se.

Structural magnetic resonance imaging (MRI) studies indicate that patients with established schizophrenia demonstrate reduced brain volume,[36-40] reduced gray matter volume,[9,36,41-50] and increased extracerebral (sulcal) cerebrospinal fluid[9,42,49-54] compared with normal controls. Woods[55] reviews data supporting that such changes can occur only from diffuse brain loss after brain and intracranial (skull) growth cease in early childhood. As such, these changes argue strongly against schizophrenia being determined solely by a prenatally or perinatally determined static neurodevelopmental deficit. Rather, they argue for the induction of a later neurobiological degenerative process in the pathophysiology of schizophrenia.

Rapoport et al[14,56] studied MRI ventricular and gray matter volumes through adolescence in normal controls and neuroleptic-treated patients with childhood-onset schizophrenia. The patients demonstrated a higher rate of ventricular enlargement and a greater loss of frontal, parietal, and temporal gray matter through 4 years of midadolescence. Therefore, if these changes stem from synaptic pruning and are minimally influenced by neuroleptics, the process is more aggressive in childhood-onset schizophrenia and, perhaps by extension, in vulnerable prepsychotic individuals.

Premortem and neuroimaging evidence supporting reduced connectedness comes from observations that schizophrenialike symptoms can arise from disruptions of cortical-cortical synaptic communication through functional glutamate receptor blockade by phencyclidine,[57,58] or from anatomical disruption of white matter axonal connections in metachromatic leukodystrophy.[59]

## A COMPUTER SIMULATION OF SYNAPTIC PRUNING AND ITS CONSEQUENCES

In this section we review a neural network computer simulation of auditory hallucinations reported previously.[60] Studies suggest that this highly prevalent schizophrenic symptom arises from neurocircuitry underlying perceptual processing of speech.[61-64] We developed a simulation of continuous, narrative speech perception to investigate pathophysiological mechanisms.[60]

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.[65]

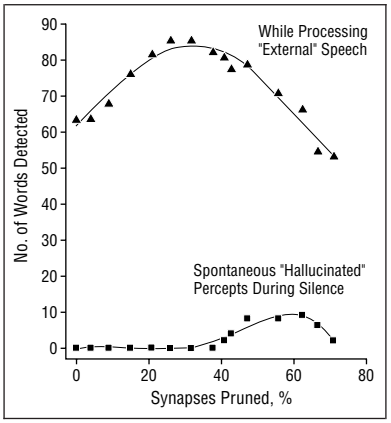


**Figure 1.** *Data generated from computer model described by Hoffman and McGlashan.[60] Network performance from 5 different trials using different sets of random numbers to phonetically degrade inputs were averaged together. Connections are pruned according to a "darwinian rule"; ie, weaker connections (both excitatory and inhibitory) are eliminated. Net reduction in synapses was estimated by assuming that connection strength between 2 neurons generated by the computer model has a linear correlation with the number of "synapses" required to sustain that connection. The top tracing corresponds to words correctly generated (identified) from degraded inputs. The lower tracing shows emergence of perceptual outputs in the absence of inputs corresponding to "hallucinations."*

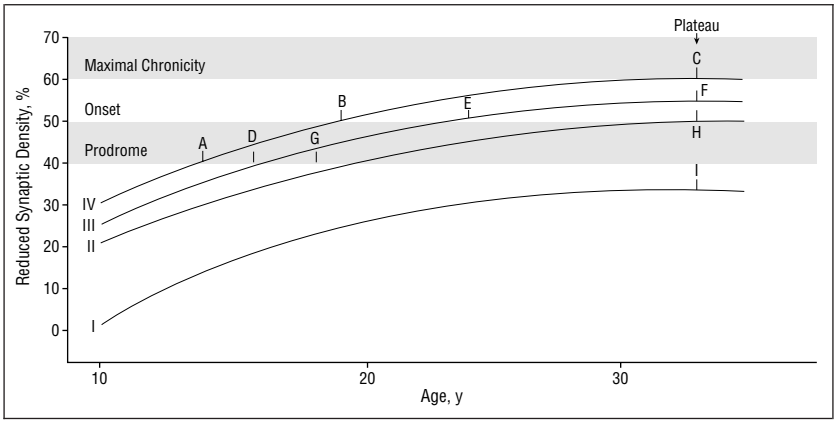


**Figure 2.** *Model of reduced synaptic density over time and the development of schizophrenia with constant pruning rate but variable level of synaptic density at baseline. I indicates normal; II, mild schizophrenia; III, moderate schizophrenia; and IV, severe schizophrenia. A, D, and G indicate prodromal onset points; B, E, H, psychosis onset points; and C, F, H, and I, plateau or point of maximal degeneration from pruning.*

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.[60,66] 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[55] 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.[67] This has subsequently been articulated as a combined early neurodevelopmental and later neurodegenerative model of schizophrenia,[55,68,69] although many models suggest the neurodegenerative element is neurotoxic rather than developmental.[69,70-75] Variations of this model have also been articulated as a "disconnection"[76,77] or a "misconnection"[78] 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,[2,3] 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

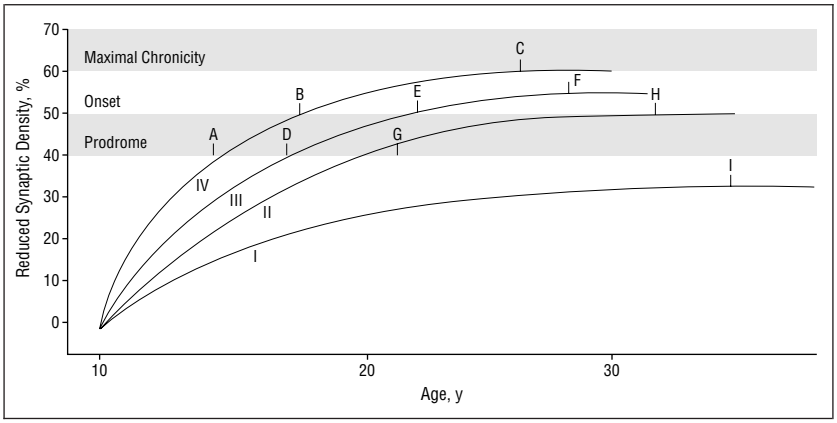


**Figure 3.** *Model of reduced synaptic density over time and the development of schizophrenia with constant baseline synaptic density but variable pruning rate. I indicates normal; II, mild schizophrenia; III, moderate schizophrenia; and IV, severe schizophrenia. A, D, and G indicate prodromal onset points; B, E, H, psychosis onset points; and C, F, H, and I, plateau or point of maximal degeneration from pruning.*

plateau in pruning (and disorder). 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.[67] 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.[79]

### 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[80,81] and the P300 evoked potential latency prolongation to the oddball paradigm.[82] 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.[83]

### Neurodevelopmental Deficits

Neurodevelopmental theories postulate that early neurobiological lesions interact later with normal development to generate schizophrenia.[84-88] The central nervous system defect(s) is determined in as yet unknown ways by genetics[89-92] and by any of a variety of perinatal insults or stressors,[92] including prenatal viral infections,[93-96] famine and malnutrition,[97,98] Rh incompatibility,[99] severe environmental stress,[100,101] obstetrical complications,[92,102-105] and signs of general fetal distress as reflected in hypoxia at birth.[106-110] The epidemiologic risk factors of urban and winter birth[111] are likely related to perinatal perturbations, especially infection. These and other aspects of neurodevelopmental pathogenesis have been reviewed extensively.[112-115]

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,[116] passivity, social maladjustments, anxiety, withdrawal, and poor peer relationships.[90-92,117-120] Neuromotor abnormalities in the form of poor coordination, poor perceptual-motor integration, or abnormal speech are seen,[90,91,121-128] as well as minor physical anomalies,[129,130] neurocognitive deficits,[92,131] poor attention and concentration,[90,91,132] and lower IQ and poor educational achievements.[133-146] Vulnerability is occasionally expressed as disruptive and aggressive behavior, most often in males.[92,117,123,147-149]

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.[150] 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,[151-158] 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.[159,160]

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.[161-163]

Davidson et al[164] 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[165] 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 (sulcal) cerebrospinal fluid seen by MRI in established schizophrenia (reviewed earlier) are already present in first-episode schizophrenia, strongly suggesting they predate characteristic symptom formation.[49,174-180]

### 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.[194-196] 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 nonprogression,[176,201-205] 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.[216,217] 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 of 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.[220-223] 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 neuritic 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.[237,238] 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.[158] 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.[158] 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.[239] Among patients selected for ongoing postonset deterioration, the degree of increase in serial VBRs was also correlated with a younger age.[218]

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[158] 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,[240] 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[241-247] at the expense of loss of flexibility.[248] 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.[249-252] This could also account for the persistence of the schizophrenia genotype in the world's population and its uniform[253] and uniformly persistent[158] incidence despite the obvious fertility disadvantage of its clinical phenotype.[254-257] IQ appears to be increasing at a rate of 3 points per decade since measures of intelligence have been developed.[258] 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, gray 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[259,260] and/or transcranial magnetic stimulation,[261,262] 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[164] comes the 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-

sity.[263,264] 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.

*Accepted for publication March 7, 2000.*

*This research was supported by grants K05MH01654 (Dr McGlashan) and MH-50557 (Dr Hoffman) from the National Institute of Mental Health, Bethesda, Md, and by the National Alliance for Research in Schizophrenia and Depression (Great Neck, NY) Senior Investigator's Award (Dr McGlashan).*

*Presented at the Second Conference of the International Early Psychosis Association, New York, NY, April 1, 2000.*

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

## REFERENCES

1. Kraepelin E. *Dementia Praecox and Paraphrenia*. Translated by RM Barclay. Huntington, NY: Robert E Krieger Publishing Co; 1971.
2. Huttenlocher PR. Synaptic density in the human frontal cortex: developmental changes and effects of aging. *Brain Res*. 1979;163:195-205.
3. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol*. 1997;387:167-178.
4. Murphy KJ, Regan CM. Contributions of cell adhesion molecules to altered synaptic weightings during memory consolidation. *Neurobiol Learn Mem*. 1998;70:73-81.
5. Bock J, Braun K. Blockade of N-methyl-D-aspartate receptor activation suppresses learning-induced synaptic elimination. *Proc Natl Acad Sci U S A*. 1999;96:2485-2490.
6. Etienne P, Baudry M. Role of excitatory amino acid neurotransmission in synaptic plasticity and pathology: an integrative hypothesis concerning the pathogenesis and evolutionary advantages of schizophrenia-related genes. *J Neural Transm*. 1990;29(suppl):39-48.
7. Sestan N, Artevanis-Tsakonas S, Rakic P. Contact-dependent inhibition of cortical neurite growth mediated notch signaling. *Science*. 1999; 286:741-746.
8. Jernigan T, Tallal P. Late childhood changes in brain morphology observable with MRI. *Dev Med Child Neurol*. 1990;32:379-385.
9. Jernigan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of human cerebrum observed in vivo during adolescence. *Brain*. 1991;114:2037-2049.
10. Reiss A, Abrams M, Singer H, Ross J, Denckla M. Brain development, gender, and IQ in children: a volumetric imaging study. *Brain*. 1996; 119:1763-1774.
11. Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Vaituzis AC, Vauss YC, Hamburger SD, Kaysen D, Rapoport JL. Quantitative magnetic resonance imaging of human brain development: ages 4-18. *Cereb Cortex*. 1996;6: 551-560.
12. Sowell E, Thompson P, Holmes C, Jernigan TR, Barth R, Naravan S, Toga A. Statistical parametric mapping of structural brain changes between childhood and adolescence. Presented as poster 123.4 at: 28th Annual Meeting of the Society for Neurosciences; November 7-12, 1998; Los Angeles, Calif.
13. Sowell E, Jernigan T. Further MRI evidence of late brain maturation: limbic volume increases and changing asymmetries during childhood and adolescence. *Dev Neuropsychol*. In press.
14. Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicolson R, Bedwell J, Lenane M, Zijdenbos A, Paus T, Evans A. Progressive cortical change during adolescence in childhood-onset schizophrenia: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry*. 1999;56:649-654.
15. Giedd J, Jeffries N, Nicolson R, Hamburger SD, Nelson J, Vaituzis AC, Lenane M, Rapoport JL. Differential progression of MRI ventricular and temporal lobe structure during adolescence for childhood onset schizophrenics. *Biol Psychiatry*. In press.
16. Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Kim KO. A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch Neurol*. 1994;51:874-887.
17. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res*. 1983;17:319-334.
18. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry*. 2000; 57:65-73.
19. Garey LJ, Ong WY, Patel TS, Kanani M, Davis A, Mortimer AM, Barnes TR, Hirsch SR. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. *J Neurol Neurosurg Psychiatry*. 1998;65:446-453.
20. Lewis DA, Pierri JN, Volk DW, Melchitzky DS, Woo TW. Altered GABA neurotransmission and prefrontal cortical dysfunction in schizophrenia. *Biol Psychiatry*. 1999;46:616-626.
21. Black JE, Klintsova AY, Laddu A, Grossman A, Uranova NA, Kodish I, Greenough WT. Smaller, pathological layer V pyramidal neurons in prefrontal cortex with schizophrenia. Presented at: American Psychiatric Association Annual Meeting; May 19, 1999; Washington, DC.
22. Deakin JFW, Slater P, Simpson MDC, et al. Frontal cortical and left temporal glutaminergic deficiency in schizophrenia. *J Neurochem*. 1989; 52:1781-1786.
23. Sherman AD, Davidson AT, Baruah S, Hegwood TS, Waziri R. Evidences of glutamatergic deficiency in schizophrenia. *Neurosci Lett*. 1991; 121:77-90.
24. Sokolov BP, Tcherepanov A, Haroutunian V, Davis KL. Synaptic protein mRNA expression in schizophrenia. Presented at: American Psychiatric Association Annual Meeting; May 19, 1999; Washington, DC.
25. Karson CN, Mrak RE, Schluterman KO, Sturner WQ, Sheng JG, Griffin WS. Alterations in synaptic proteins and their encoding mRNAs in prefrontal cortex in schizophrenia: a possible neurochemical basis for "hypofrontality." *Mol Psychiatry*. 1999;4:39-45.
26. Perrone-Bizzozero NI, Sower AC, Bird ED, Benowitz LI, Ivins KJ, Neve RL. Levels of the growth-associated protein GAP-43 are selectively increased in association cortices in schizophrenia. *Proc Natl Acad Sci U S A*. 1996;93:14182-14187.
27. Glantz LA, Lewis DA. Reduction of synaptophysin immunoreactivity in the prefrontal cortex of subjects with schizophrenia. *Arch Gen Psychiatry*. 1997;54:943-952.
28. Honer WG, Falkai P, Chen C, Arango V, Mann JJ, Dwork AJ. Synaptic and plasticity-associated proteins in anterior frontal cortex in severe mental illness. *Neuroscience*. 1999;91:1247-1255.
29. Landen M, Davidsson P, Gottfries C, Grenfeldt B, Stridsberg M, Blennow K. Reduction of the small synaptic vesicle protein synaptophysin but not the large dense core chromogranins in the left thalamus of subjects with schizophrenia. *Biol Psychiatry*. 1999;46:1698-1702.
30. Pakkenberg B. Post-mortem study of chronic schizophrenic brains. *Br J Psychiatry*. 1987;151: 744-752.
31. Daviss SR, Lewis DA. Local circuit neurons of the prefrontal cortex in schizophrenia: selective increase in the density of calbindin-immunoreactive neurons. *Psychiatr Res*. 1995;59:81-96.
32. Selemon LD, Rajkowska G, Goldman-Rakic PS. Abnormally high neuronal density in the schizophrenic cortex: a morphometric analysis of prefrontal area 9 and occipital area 17. *Arch Gen Psychiatry*. 1995;52:805-818.
33. Rajkowska G, Selemon LD, Goldman-Rakic PS. Neuronal and glial somal size in the prefrontal cortex: a postmortem morphometric study of schizophrenia and Huntington disease. *Arch Gen Psychiatry*. 1998;55:215-224.
34. Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol Psychiatry*. 1999;45:17-25.
35. Harrison PJ. The neuropathology of schizophrenia: a critical review of the data and their interpretation. *Brain*. 1999;122:593-624.
36. Andreasen NC, Flashman L, Flaum M, Arndt S, Swayze V II, O'Leary DS, Ehrhardt JC, Yuh WTC. Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. *JAMA*. 1994;272:1763-1769.
37. Gur RE, Mozley PD, Shtasel DL, Cannon TD, Gallacher F, Turetsky B, Grossman R, Gur RC. Clinical subtypes of schizophrenia: differences in brain and CSF volume. *Am J Psychiatry*. 1994;151: 343-350.
38. Baare WFC, van Oel CJ, Hulshof Pol HE, Schnack H, Sitskoorn MM, Kahn RS. Genetics and intrauterine environment in schizophrenia: a twin study. *Schizophr Res*. 1999;36:189.
39. Ward K, Woods BT. The confounding effect of covariance for intracranial volume (ICV) on measurement of progressive brain volume (BV) loss in schizophrenia [abstract]. *Schizophr Res*. 1999; 36:214.
40. Wright IC, Rabe-Hesketh S, Woodruff PWR, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry*. 2000;157:16-25.
41. Shelton RC, Karson CN, Doran AR, Pickar D, Bigelow LB, Weinberger DR. Cerebral structural pathology in schizophrenia: evidence for a selective prefrontal cortical defect. *Am J Psychiatry*. 1988;145:154-163.
42. Woods BT, Yurgelun-Todd D. Brain volume loss

in schizophrenia: when does it occur and is it progressive? *Schizophr Res*. 1991;5:202-204.
43. DeLisi LE, Hoff AL, Schwartz JE, Shields GW, Halthore SN, Gupta SM, Henn FA, Anand AK. Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. *Biol Psychiatry*. 1991;29: 159-175.
44. Zipursky RB, Lim KO, Sullivan EV, Brown BW, Pfefferbaum A. Widespread cerebral gray matter volume deficits in schizophrenia. *Arch Gen Psychiatry*. 1992;49:195-205.
45. Breier A, Buchanan RW, Elkashef A, Munson RC, Kirkpatrick B, Gellad F. Brain morphology and schizophrenia: a magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. *Arch Gen Psychiatry*. 1992;49:921-926.
46. Harvey I, Ron MA, Du Boulay G, Wicks D, Lewis SW, Murray RM. Reduction of cortical volume in schizophrenia on magnetic resonance imaging. *Psychol Med*. 1993;23:591-604.
47. Schlaepfer TE, Harris GJ, Tien AY, Peng LW, Lee S, Federman EB, Chase GA, Barta PE, Pearlson GD. Decreased regional cortical gray matter volume in schizophrenia. *Am J Psychiatry*. 1994; 151:842-848.
48. Lim KO, Harris D, Beal M, Hoff AL, Minn K, Csernansky JG, Faustman WO, Marsh L, Sullivan EV, Pfefferbaum A. Gray matter deficits in young onset schizophrenia are independent of age of onset. *Biol Psychiatry*. 1996;40:4-13.
49. Lim KO, Tew W, Kushner M, Chow K, Matsumoto R, DeLisi LE. Cortical gray matter volume deficit in patients with first episode schizophrenia. *Am J Psychiatry*. 1996;153:1548-1553.
50. Gur RE, Turetsky BI, Bilker WB, Gur RC. Reduced gray matter volume in schizophrenia. *Arch Gen Psychiatry*. 1999;56:905-911.
51. Gur RE, Mozley D, Resnick SM, Shtasel D, Kohn M, Zimmerman R, Herman G, Atlas S, Grossman R, Erwin R, Gur RC. Magnetic resonance imaging in schizophrenia. *Arch Gen Psychiatry*. 1991;48:407-412.
52. Arango C, Vladar K, Bartko JJ, Buchanan RW. Brain abnormalities in schizophrenia: when do the changes take place? *Schizophr Res*. 1999; 36:189.
53. McCarley RW, Wible CG, Frumin M, Hirayasu Y, Levitt JJ, Fischer A, Sheton ME. MRI anatomy of schizophrenia. *Biol Psychiatry*. 1999;45:1099-1119.
54. Pearlson GD, Marsh L. Structual brain imaging schizophrenia: a selective review. *Biol Psychiatry*. 1999;46:627-649.
55. Woods BT. Is schizophrenia a progressive neurodevelopmental disorder? toward a unitary pathogenetic mechanism. *Am J Psychiatry*. 1998; 155:1661-1670.
56. Rapoport JL, Giedd J, Kumra S, Jacobsen L, Smith A, Lee P, Nelson J, Hamburger S. Childhood-onset schizophrenia: progressive ventricular change during adolescence. *Arch Gen Psychiatry*. 1997;54:897-903.
57. Allen RM, Young SJ. Phencyclidine-induced psychosis. *Am J Psychiatry*. 1978;135:1081-1084.
58. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry*. 1991;148:1301-1308.
59. Hyde TM, Ziegler JC, Weinberger DR. Psychiatric disturbance in metachromatic leukodystrophy: insight into the neurobiology of psychosis. *Arch Neurology*. 1992;49:401-406.
60. Hoffman RE, McGlashan TH. Synaptic elimination, neurodevelopment and the mechanism of hallucinated "voices" in schizophrenia. *Am J Psychiatry*. 1997;154:1683-1689.
61. Hoffman RE. Verbal hallucinations and language production processes in schizophrenia. *Behav Brain Sci*. 1986;9:503-548.
62. Silbersweig DA, Stern E, Frith C, Cahill C, Holmes A, Grootoonk S, Seaward J, McKenna P, Chua SE, Schnorr L, Jones T, Frackowiak RSJ. A functional neuroanatomy of hallucinations in schizophrenia. *Nature*. 1995;378:176-179.
63. David AS, Woodruff PW, Howard R, Mellers JD, Brammer M, Bullmore E, Wright I, Andrew C, Williams SC. Auditory hallucinations inhibit exogenous activation of auditory association cortex. *Neuroreport*. 1996;7:932-936.
64. Hoffman RE, Boutros NN, Berman RM, Roessler E, Krystal JH, Charney DS. Transcranial magnetic stimulation of left temporoparietal cortex in three patients reporting hallucinated "voices." *Biol Psychiatry*. 1999;46:130-132.
65. Hoffman RE, Rapoport J, Mazure CM, Quinlan DM. Schizophrenic patients reporting hallucinated "voices" demonstrate selective speech perception alterations. *Am J Psychiatry*. 1999;156: 393-399.
66. Hoffman RE, McGlashan TM. Using speech perception neural network simulations to explore normal neurodevelopment and hallucinated "voices" in schizophrenia. In: Reggia J, Ruppin E, Glanzman D, eds. *Disorders of Brain, Behavior and Cognition: The Neurocomputational Perspective*. Amsterdam, the Netherlands: Elsevier; 1999:18:311-325.
67. Hoffman RE, McGlashan TH. Parallel distributed processing and the emergence of schizophrenia symptoms. *Schizophr Bull*. 1993;19: 119-139.
68. Keshavan MS, Anderson S, Pettegrew J. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? the Feinberg hypothesis revisited. *J Psychiatr Res*. 1994;28: 239-265.
69. Anderson JE, O'Donnell BF, McCarley RW, Sheton ME. Progressive changes in schizophrenia: do they exist and what do they mean? *Restor Neurol Neurosci*. 1998;12:175-184.
70. Lieberman JA, Sheitman BB, Kinon BJ. Neurochemical sensitization in the pathophysiology of schizophrenia: deficits and dysfunction in neuronal regulation and plasticity. *Neuropsychopharmacology*. 1997;17:205-229.
71. Kraus J, Perkins DO, Lieberman JA. Pathophysiology of schizophrenia: neurodevelopmental and neurodegenerative processes. In: Miller TJ, Mednick SA, McGlashan TH, Libiger J, Johannessen JO, eds. *Early Intervention in Psychotic Disorders*. Amsterdam, the Netherlands: Kluwer Academic Publishers. In press.
72. Olney JW. Excitatory amino acids and neuropsychiatric disorders. *Biol Psychiatry*. 1989;26: 505-525.
73. Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry*. 1995;52:998-1007.
74. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vöckler J, Dikranian K, Tenkova TI, Stefovska V, Turski L, Olney JW. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. *Science*. 1999;283:70-74.
75. Coyle JT. The glutamatergic dysfunction hypothesis for schizophrenia. *Harvard Rev Psychiatry*. 1996;3:241-253.
76. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? *Neuroscience*. 1995;3:89-97.
77. Friston KJ. Theoretical neurobiology and schizophrenia. *Br Med Bull*. 1996;52:644-655.
78. Andreasen NC. A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. *Arch Gen Psychiatry*. 1999;56:781-787.
79. McGlashan TH, Fention WS. The positive/negative distinction in schizophrenia: review of natural history validators. *Arch Gen Psychiatry*. 1992;49:63-72.
80. Seeman P. Human brain dopamine receptors in children and aging adults. *Synapse*. 1987;1:399-404.
81. Seeman P. Pruning during development. *Am J Psychiatry*. 1999;156:168.
82. O'Donnel BF, Faux SF, McCarley RW, Kimble MO, Salisbury DF, Nestor PG, Kikinis R, Ferenc JA, Jolesz FA, Shenton ME. Increased rate of P300 latency prolongation with age in schizophrenia. *Arch Gen Psychiatry*. 1995;52:544-549.
83. Sachdev P, Brodaty H. Quantitative study of signal hyperintensities on T2-weighted magnetic resonance imaging in late-onset schizophrenia. *Am J Psychiatry*. 1999;156:1958-1967.
84. Jakob H, Beckmann H. Prenatal developmental disturbances in the limbic allocortex in schizophrenics. *J Neural Transm*. 1986;65:303-326.
85. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *BMJ*. 1987;295: 681-682.
86. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987;44:660-667.
87. Jones GH, Lewis JE. Head size in dementia [letter]. *Br J Psychiatry*. 1992;160:565.
88. Keshavan MS. Neurodevelopment and schizophrenia: quo vadis? In: Keshavan MS, Murry RM, eds. *Neurodevelopment and Adult Psychopathology*. Cambridge, England: Cambridge University Press; 1997:267-278.
89. Erlenmeyer-Kimling L, Squires-Wheeler E, Adamo U, Bassett AS, Cornblatt BA, Kestenbaum CJ, Rock D, Roberts SA, Gottesman II. The New York High-Risk Project: psychosis and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. *Arch Gen Psychiatry*. 1995;52:857-865.
90. Ingraham LJ, Kugelmass S, Frenkel MN, Mirsky AF. Twenty-five-year follow-up of the Israeli High Risk Study: current and lifetime psychopathology. *Schizophr Bull*. 1995;21:183-192.
91. Mirsky AF, Kugelmass S, Ingraham LJ, Frenkel E, Nathan M. Overview and summary: twenty-five-year follow-up of high-risk children. *Schizophr Bull*. 1996; 2:227-239.
92. Olin SS, Mednick SA. Risk factors of psychosis: identifying vulnerable populations premorbidity. *Schizophr Bull*. 1996;22:223-240.
93. Mednick SA, Machon RA, Hutunen MO, Bonnet D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry*. 1988;45:189-192.
94. O'Callaghan E, Sham PC, Takei N, Murray G, Glover G, Hare EH, Murray RM. The relationship of schizophrenic births to 16 infectious diseases. *Br J Psychiatry*. 1994;164:353-356.
95. Jones P, Pang D, Piriach S, Fine P. Prenatal viral infection and subsequent mental illness: a long term cohort study of 6152 subjects [abstract]. *Schizophr Res*. 1999;36:45.
96. Izumoto Y, Inoue S, Yasuda N. Schizophrenia and the influenza epidemics of 1957 in Japan. *Biol Psychiatry*. 1999;46:119-124.
97. Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D, Gorman JM. Schizophrenia after prenatal famine. *Arch Gen Psychiatry*. 1996; 53:25-31.
98. Hoek HW, Brown AS, Dingemans A, Hulshoff-Pol, Kahn RS, Susser E. Prenatal famine and schizophrenia spectrum disorders [abstract]. *Schizophr Res*. 1999;36:42.
99. Hollister JM, Laing P, Mednick SA. Rhesus incompatibility as a risk factor for schizophrenia in male adults. *Arch Gen Psychiatry*. 1996;53: 19-23.
100. van OS J, Selten JP. Prenatal exposure to maternal stress and subsequent schizophrenia: the May 1940 invasion of the Netherlands. *Br J Psychiatry*. 1998;172:324-326.
101. Selten JP, van der Graaf Y, van Duursen R, Gispen-de Wied CC, Kahn RS. Psychotic illness after prenatal exposure to the 1953 Dutch flood disaster. *Schizophr Res*. 1999;35:243-245.
102. McNeil TF. Obstetric complications in schizophrenic patients. *Schizophr Res*. 1991;5:89-101.
103. Rosso IM, Cannon TD, Huttunen T, Huttnunen M, Lonnqvist J, Gasperoni TL. Obstetric risk factors for early onset schizophrenia in a Finnish birth cohort [abstract]. *Schizophr Res*. 1999;36:53.
104. McNeil TF, Cantor-Graae E. Does preexisiting abnormality cause labor-delivery complications in fetuses who will develop schizophrenia? *Schizophr Bull*. 1999;25:425-435.

105. McNeil TF, Cantor-Graae E, Weinberger DR. The relationship of obstetric complications to brain structure size differences in monozygotic twin pairs discordant for schizophrenia [abstract]. *Schizophr Res*. 1999;36:51.
106. Cannon TD, vanErp TGM, Huttunen J, Lonnqvist SO, Valanne L, Poutanen VP, Standertskjold-Nordenstam CG. Perinatal hypoxia and regional brain morphology in schizophrenic patients, their siblings, and controls [abstract]. *Schizophr Res*. 1999;36:192.
107. Buka SL, Goldstein JM, Zornberg GL, Seidman LJ, Donatelli J, Denny LR, Tsuang MT. Interactive effects of parental schizophrenia and perinatal hypoxia on abnormal neurobehavioral development in childhood [abstract]. *Schizophr Res*. 1999;36:37.
108. Seidman LJ, Goldstein JM, Buka SL, Zornberg GL, Denny L, Donatelli J, Burbridge J, Tsuang MT. Effects of genetic vulnerability and obstetric complications on cognitive functioning in offspring at high risk for psychosis [abstract]. *Schizophr Res*. 1999;36:54.
109. Zornberg GL, Buka SL, Tsuang MT. Fetal and neonatal complications and risk of schizophrenia and other nonaffective psychoses: a 19-year population-based follow-up study [abstract]. *Schizophr Res*. 1999;36:59.
110. Geddes JR, Verdoux H, Takei N, Lawrie M, Bovet P, Eagles JM, Heun R, McCreadie RG, McNeil TF, O'Callaghan E, Sötber G, Willinger U, Murray R. Schizophrenia and complications of pregnancy and labor: an individual patient data meta-analysis. *Schizophr Bull*. 1999;25:413-423.
111. Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, Mors O, Andersen PK, Melbye M. Effects of family history and place and season of birth on the risk of schizophrenia. *N Engl J Med*. 1999;340:603-608.
112. Arnold SE, Trojanowski JQ. Recent advances in defining the neuropathology of schizophrenia. *Acta Neuropathol*. 1996;92:217-231.
113. Roberts GW. Schizophrenia: a neuropathological perspective. *Br J Psychiatry*. 1991;158:8-17.
114. Jones P, Murray RM. The genetics of schizophrenia is the genetics of neurodevelopment. *Br J Psychiatry*. 1991;158:615-623.
115. Weinberger DR. From neuropathology to neurodevelopment. *Lancet*. 1995;346:552-557.
116. Grimes K, Walker EF. Childhood emotional expressions, educational attainment, and age at onset of illness in schizophrenia. *J Abnorm Psychol*. 1994;103:784-790.
117. Done D, Crow TJ, Johnstone EC, Sacker A. Childhood antecedents of schizophrenia and affective illness: social adjustment at ages 7 and 11. *BMJ*. 1994;309:699-703.
118. Watt NF. Patterns of childhood social development in adult schizophrenics. *Arch Gen Psychiatry*. 1978;35:160-165.
119. Lewine RR, Watt NF, Prentky RA, Fryer JH. Childhood social competence in functionally disordered psychiatric patients and in normals. *J Abnorm Psychol*. 1980;89:132-138.
120. Olin SS, John RS, Mednick SA. Assessing the predictive value of teacher reports in a high risk sample for schizophrenia: an ROC analysis. *Schizophr Res*. 1995;16:53-66.
121. Walker EF, Savoie T, Davis D. Neuromotor precursors of schizophrenia. *Schizophr Bull*. 1994;20:441-451.
122. Hans SL, Marcus J, Nuechterlein KH, Asarnow RF, Styr B, Auerbach JG. Neurobehavioral deficits at adolescence in children at risk for schizophrenia: The Jerusalem Infant Development Study. *Arch Gen Psychiatry*. 1999;56:741-748.
123. Bearden CE, Cannon TD, Hollister JM, Gasperoni TL, Hadley T. A prospective cohort study of childhood behavioral deviance and language abnormalities as predictors of adult schizophrenia [abstract]. *Schizophr Res*. 1999;36:37.
124. Gasperoni TL, Cannon TD, Bearden CE, Hollister JM, Rosso IM, Hadley T. Neuromotor abnormalities as precursors of schizophrenia: a prospective cohort study [abstract]. *Schizophr Res*. 1999;36:40.
125. Cannon M, Jones P, Huttunen MO, Tanskanen A, Huttunen T, Rabe-Hesketh S, Murray R. School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. *Arch Gen Psychiatry*. 1999;56:457-463.
126. Fish B. Neurobiological antecedents of schizophrenia in children. *Arch Gen Psychiatry*. 1997;34:1297-1313.
127. Griffith JJ, Mednick SA, Schulsinger F, Diderichsen B. Verbal associative disturbances in children at high risk for schizophrenia. *J Abnorm Psychol*. 1980;89:125-131.
128. Marcus J, Hans SL, Auerbach JG, Auerbach AG. Children at risk for schizophrenia: The Jerusalem Infant Development Study, II: neurobehavioral deficits at school-age. *Arch Gen Psychiatry*. 1993;50:797-809.
129. Waddington JL, Lane A, Larkin C, O'Callaghan EO. The neurodevelopmental basis of schizophrenia: clinical clues from cerebro-craniofacial dysmorphogenesis, and the roots of a lifetime trajectory of disease. *Biol Psychiatry*. 1999;46:31-39.
130. Buckley PF. The clinical stigmata of aberrant neurodevelopment in schizophrenia. *J Nerv Ment Dis*. 1998;186:79-86.
131. David AS, Malmberg A, Lewis G, Brandt L, Allebeck B. Premorbid neuropsychological performance as a risk factor for schizophrenia: 13 year follow-up of 50,000 conscripts [abstract]. *Schizophr Res*. 1995;15:114.
132. Cornblatt B. Attention deficits as a marker of risk to schizophrenia. Presented at: International Congress on Schizophrenia Research; April 22, 1999; Santa Fe, NM.
133. Bower EM, Shellhamer TA. School characteristics of male adolescents who later became schizophrenics. *Am J Orthopsychiatry*. 1960;30:712-729.
134. Offord DR. School performance of adult schizophrenics, their siblings and age mates. *Br J Psychiatry*. 1974;125:12-19.
135. Aylward E, Walker E, Battes B. Intelligence in schizophrenia: meta-analysis of the research. *Schizophr Bull*. 1984;10:430-459.
136. Crawford JR, Besson JAO, Bremner M, Ebmeier KP, Cochrane RHB, Kirkwood K. Estimation of premorbid intelligence in schizophrenia. *Br J Psychiatry*. 1992;161:69-74.
137. Kremen WS, Buka SL, Seidman LJ. IQ decline during childhood and adult psychotic symptoms in a community sample: a 19-year longitudinal study. *Am J Psychiatry*. 1998;155:672-677.
138. Keith SJ, Regier DA, Rae RS. Schizophrenic disorders. In: Robins LN, Raegier DA, eds. *Psychiatric Disorders in America: The Epidemiologic Catchment Area Study*. New York, NY: The Free Press; 1991:33-52.
139. Jones P, Rodgers B, Murray R, Marmot M. Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*. 1994;344:1398-1402.
140. Lane EA, Albee GW. On childhood intellectual decline of adult schizophrenics: a reassessment of an earlier study. *J Abnorm Psychol*. 1968;35:747-753.
141. Offord DR, Cross LA. Adult schizophrenia with scholastic failure or low IQ in childhood. *Arch Gen Psychiatry*. 1971;24:431-436.
142. Kremen WS, Buka LJ, Seidman LJ, Goldstain JM, Koren D, Tsuang MT. Childhood IQ decline and adult psychotic symptoms in a community sample: a 19-year longitudinal study [abstract]. *Schizophr Res*. 1995;15:124.
143. Russel AJ, Munro JC, Jones PB, Hemsley DR, Murray RM. Schizophrenia and the myth of intellectual decline. *Am J Psychiatry*. 1997;154:635-639.
144. David AS, Malmberg A, Brandt L, Allebeck P, Lewis G. IQ and risk for schizophrenia: a population-based cohort study. *Psychol Med*. 1997;27:1311-1323.
145. Isohanni I, Jarvelin MR, Nieminen P, Jones P, Rantakallio P, Jokelainen J, Isohanni M. School performance as a predictor of psychiatric hospitalization in adult life: a 28-year follow-up in the Northern Finland 1966 Birth Cohort. *Psychol Med*. 1998;28:967-974.
146. Cannon M, Jones P, Huttunen M, Tanskanen A, Huttunen T, Rabe-Hesketh S, Murray RM. School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. *Arch Gen Psychiatry*. 1999;56:457-463.
147. Andreasen NC, Hoenk PR. The predictive value of adjustment disorder: a follow-up study. *Am J Psychiatry*. 1982;139:584-590.
148. Erlenmeyer-Kimling L, Cornblatt B. Behavioral risk factors in children of schizophrenic parents. *J Autism Dev Disord*. 1984;14:357-374.
149. Malmberg A, David A, Allebeck P, Lewis G. Premorbid adjustment and personality in schizophrenia: a review and historical cohort study. *Br J Psychiatry*. 1998;172:308-312.
150. Jones PB, van Os JJ. Predicting schizophrenia in teenagers: pessimistic results from the British 1946 birth cohort [abstract]. *Schizophr Res*. 1998;29:11.
151. Huber G, Gross G, Schuttler R, Linz M. Longitudinal studies of schizophrenic patients. *Schizophr Bull*. 1980;6:592-605.
152. Gross G. The "basic" symptoms of schizophrenia. *Br J Psychiatry*. 1989;155(suppl 7):21-25.
153. Klosterkotter J, Ebel H, Schultze-Lutter F, Steinmeyer EM. Diagnostic validity of basic symptoms. *Eur Arch Psychiatry Clin Neurosci*. 1996;246:147-154.
154. Hafner H, Riecher-Rossler A, Maurer K, Fatkenheuer B, Loffler W. First onset and early symptomatology of schizophrenia: a chapter of epidemiological and neurobiological research into age and sex differences. *Eur Arch Psychiatry Clin Neurosci*. 1992;242:109-118.
155. Hafner H, Maurer K, Loffler W, Fatkenheur B, an der Heiden A, Riecher-Rossler A, Behrens S, Gattaz WF. The epidemiology of early schizophrenia: influence of age and gender on onset and early course. *Br J Psychiatry*. 1994;164 (suppl 23):29-38.
156. Hafner H, Nowotny B, Loffler W, an der Heiden W, Maurer K. When and how does schizophrenia produce social deficits? *Eur Arch Psychiatry Clin Neurosci*. 1995;246:17-28.
157. Hambrecht M, Hafner H, Loffler W. Beginning schizophrenia observed by significant others. *Soc Psychiatry Psychiatry Epidemiol*. 1994;29:53-60.
158. Hafner H, an der Heiden W. Epidemiology of schizophrenia. *Can J Psychiatry*. 1997;42:139-151.
159. Yung AR, McGorry PD. The prodromal phase of first episode psychosis: past and current conceptualizations. *Schizophr Bull*. 1996;22:353-370.
160. Yung AR, McGorry PD, McFarlane CA, Jackson HJ, Patton GC, Rakkar A. Monitoring and care of young people at incipient risk of psychosis. *Schizophr Bull*. 1996;22:283-303.
161. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull*. 1982;8:470-484.
162. Haas GL, Sweeney JA. Premorbid and onset features of first episode schizophrenia. *Schizophr Bull*. 1992;18:373-386.
163. Larsen TK, McGlashan TH, Johannessen JO, Vibe-Hansen L. First-episode schizophrenia, II: premorbid patterns by gender. *Schizophr Bull*. 1996;22:257-269.
164. Davidson M, Reichenberg MA, Rabinowitz J, Weiser M, Kaplan Z, Mark M. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. *Am J Psychiatry*. 1999;156:1328-1335.

165. Davidson M. Markers for schizophrenia in male adolescents. Presented at: World Psychiatry Association Meeting; August 8, 1999; Hamburg, Germany.
166. Goldberg TE, Hyde TM, Kleinman JE, Weinberger DR. Course of schizophrenia: neuropsychological evidence for a static encephalopathy. *Schizophr Bull*. 1993;19:797-804.
167. Goldstein G, Allen DN, van Kammen DP. Individual differences in cognitive decline schizophrenia. *Am J Psychiatry*. 1998;155:1117-1118.
168. Rund BR. A review of longitudinal studies of cognitive functions in schizophrenia patients. *Schizophr Bull*. 1998;24:425-435.
169. Mohamed S, Paulsen JS, O'Leary D, Arndt S, Andresen N. Generalized cognitive deficits in schizophrenia: a study of first-episode patients. *Arch Gen Psychiatry*. 1999;56:749-754.
170. Gold S, Arndt S, Nopoulos P, O'Leary DS, Andreasen NC. Longitudinal study of cognitive function in first-episode and recent-onset schizophrenia. *Am J Psychiatry*. 1999;156:1342-1348.
171. Hoff AL, Sakuma M, Wieneke M, Horon R, Kushner M, DeLisi LE. Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. *Am J Psychiatry*. 1999;156:1336-1341.
172. Hyde TM, Nawroz S, Goldberg T, Bigelow LB, Strong D, Ostrem JL, Weinberger DR, Kleinman JE. Is there cognitive decline in schizophrenia? a cross-sectional study. *Br J Psychiatry*. 1994;164:494-500.
173. Aleman A, Hijman, deHaan EHF, Kahn RS. Memory impairment in schizophrenia: a meta-analysis. *Am J Psychiatry*. 1999;156:1358-1366.
174. DeGreef G, Bogerts B, Ashtari M, Lieberman J. Ventricular system morphology in first episode schizophrenia: a volumetric study of ventricular subdivisions on MRI [abstract]. *Schizophr Res*. 1990;3:18.
175. DeLisi LE, Hoff AL, Schwartz JE, Shield GW, Halthore SN, Gupta SM, Henn FA, Anand AK. Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. *Biol Psychiatry*. 1991;29:159-175.
176. DeLisi LE, Stritzke P, Riordan H, Holan V, Boccio A, Kushner M, McClelland J, Van Eyl O, Anand A. The timing of brain morphology changes in schizophrenia and their relationship to clinical outcome. *Biol Psychiatry*. 1992;31:241-254.
177. Hemmingsen R, Madsen A, Karle A, Rubin P. Progressive cortical atrophy in first-episode schizophrenia [abstract]. *Schizophr Res*. 1999;36:200.
178. Zipursky RB, Lambe E, Kapur S, Mikulis DJ. Cerebral gray matter volume deficits in first episode psychosis. *Arch Gen Psychiatry*. 1998;55:540-546.
179. Nopoulos P, Torres I, Flaum M, Andreasen NC, Ehrardt JC, Yum WTC. Brain morphology in first episode schizophrenia. *Am J Psychiatry*. 1995;152:1721-1729.
180. Hirayasu Y, Sheton ME, Salisbury DR, Dickey CD, Fischer IA, Mazzoni P. Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. *Am J Psychiatry*. 1998a;155:1384-1391.
181. McGlashan TH. Schizophrenia: psychosocial therapies and the role of psychosocial factors in its etiology and pathogenesis. In: Frances AJ, Hales RE, eds. *The American Psychiatric Association Annual Review*. Washington, DC: American Psychiatric Press; 1986:96-111.
182. McGlashan TH. A selective review of recent North American long-term follow-up studies of schizophrenia. *Schizophr Bull*. 1988;14:515-542.
183. Harding CM, Brooks GW, Ashikaga T, Strauss JS, Breier A. The Vermont longitudinal study of persons with mental illness, I: methodology, study sample, and overall status 32 years later. *Am J Psychiatry*. 1987;144:718-726.
184. Harding CM, Brooks GW, Ashikaga T, Strauss JS, Breier A. The Vermont longitudinal study of persons with mental illness, II: long-term outcome of subjects who retrospectively met *DSM-III* criteria for schizophrenia. *Am J Psychiatry*. 1987;144:727-735.
185. Carone BJ, Harrow M, Westermeyer JF. Posthospital course and outcome in schizophrenia. *Arch Gen Psychiatry*. 1991;48:247-253.
186. Carpenter WT, Strauss JS. The prediction of outcome in schizophrenia, IV: eleven-year follow-up of the Washington IPSS cohort. *J Nerv Ment Dis*. 1991;179:517-525.
187. DeSisto MJ, Harding CM, McCormick RV, Ashikaga T, Brooks GW. The Maine and Vermont three-decade studies of serious mental illness, I: matched comparison of cross-sectional outcome. *Br J Psychiatry*. 1995;167:331-338.
188. DeSisto MJ, Harding CM, McCormick RV, Ashikaga T, Brooks GW. The Maine and Vermont three-decade studies of serious mental illness, II: longitudinal course comparisons. *Br J Psychiatry*. 1995;167:338-342.
189. Davidson L, McGlashan TH. The varied outcomes of schizophrenia. *Can J Psychiatry*. 1997;42:34-43.
190. Harvey PD, Silverman JM, Mohs RC, Parrella M, White L, Powchik P, Davidson M, Davis KL. Cognitive decline in late-life schizophrenia: a longitudinal study of geriatric chronically hospitalized patients. *Biol Psychiatry*. 1999;45:32-40.
191. Barak Y, Swartz M, Davidson M. Dementia in elderly schizophrenic patients: reviewing the reviews. *Int Rev Psychiatry*. 1997;9:459-463.
192. Purohit DP, Davidson M, Perl DP, Powchik P, Haroutunian VH, Bierer LM. Severe cognitive impairment in elderly schizophrenic patients: a clinicopathological study. *Biol Psychiatry*. 1993;33:255-260.
193. Friedman JI, Harvey PD, Kemether E, Byne W, Davis KL. Cognitive and functional changes with aging in schizophrenia. *Biol Psychiatry*. 1999;46:921-928.
194. Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes, I: longitudinal study of paranoid, hebephrenic, and undifferentiated schizophrenia. *Arch Gen Psychiatry*. 1991;48:969-977.
195. Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes, II: positive and negative symptoms and long-term course. *Arch Gen Psychiatry*. 1991;48:978-986.
196. McGlashan TH, Fenton WS. Subtype progression and pathophysiologic deterioration in early schizophrenia. *Schizophr Bull*. 1993;19:71-84.
197. Leiberman JA, Alvir JM, Koreen A, Geisler S, Chakos M, Sheitman B, Woerner M. Psychobiologic correlates of treatment response in schizophrenia. *Neuropsychopharmacology*. 1996;14(suppl):13S-21S.
198. Eaton WW, Mortensen PB, Herrman H, Freeman H, Bilker W, Burgess P. Long-term course of hospitalization for schizophrenia, part I: risk for hospitalization. *Schizophr Bull*. 1992;18:217-228.
199. Eaton WW, Bilker W, Haro JM, Herrman H, Mortensen PB, Freeman H. Long-term course of hospitalization for schizophrenia, part II: change with passage of time. *Schizophr Bull*. 1992;18:229-241.
200. Madsen AL, Vorstrup S, Rubin P, Larsen JK, Hemmingsen R. Neurological abnormalities in schizophrenic patients: a prospective follow-up study 5 years after first admission. *Acta Psychiatr Scand*. 1999;100:119-125.
201. DeGreef G, Ashtari M, Wu H, Borenstein M, Geisler S, Lieberman J. Follow-up MRI study in first episode schizophrenia. *Schizophr Res*. 1991;5:204-206.
202. Sponheim SR, Iocono WG, Beiser M. Stability of ventricular size after the onset of psychosis in schizophrenia. *Psychiatry Res Neuroimaging*. 1991;40:21-29.
203. DeGreef G, Ashtari M, Bogerts B, Bilder RM, Jody DN, Alvir JMJ, Lieberman JA. Volumes of ventricular system subdivisions measured from magnetic resonance images in first-episode schizophrenic patients. *Arch Gen Psychiatry*. 1992;49:531-537.
204. Jaskiw GE, Juliano DM, Goldberg TE, Hertzman M, Urowhamell E, Weinberger DR. Cerebral ventricular enlargement in schizophreniform disorder does not progress: a seven-year follow-up study. *Schizophr Res*. 1994;14:23-28.
205. Vita A, Giobbio GM, Dieci M, Garbarini M, Morganti C, Comazzi M, Inverniizzi G. Stability of cerebroventricular size from the appearance of the first psychotic symptoms to the later diagnosis of schizophrenia. *Biol Psychiatry*. 1994;35:960-962.
206. Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A. Longitudinal analysis of MRI brain volumes in schizophrenia. *Schizophr Res*. 1997;24:152.
207. DeLisi LE, Tew W, Xie S, Hoff AL, Sakuma M, Kushner M, Lee G, Shadlock K, Smith AM, Grimson R. A prospective follow-up study of brain morphology and cognitive in first-episode schizophrenic patients: preliminary findings. *Biol Psychiatry*. 1995;38:349-360.
208. DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Res*. 1997;74:129-140.
209. Davis KL, Buchsbaum MS, Shihabuddin L, Spiegel-Cohen J, Metzger M, Frecska E, Keefe RS, Powchik P. Ventricular enlargement in poor-outcome schizophrenia. *Biol Psychiatry*. 1998;43:783-793.
210. Kemali D, Maj M, Galderisi S, Milici N, Salvati A. Ventricle to brain ratio in schizophrenia: a controlled follow-up study. *Biol Psychiatry*. 1989;26:753-756.
211. Woods BT, Yurgelun-Todd D, Berres FM, Frankenburg FR, Pope HG, McSparren J. Progressive ventricular enlargement in schizophrenia: comparison to bipolar affective disorder and correlation with clinical course. *Biol Psychiatry*. 1990;27:341-352.
212. Hirayasu Y, Sheton ME, Salisbury DR, Dickey CD, Fischer IA, Kisler T, Kwon JS. Superior temporal gyrus changes over time in first-episode schizophrenia [abstract]. *Biol Psychiatry*. 1998;43:116S.
213. Nair TR, Christensen JD, Kingsbury SJ, Kumar NG, Terry WM, Garver DL. Progression of cerebroventricular enlargement and the subtyping of schizophrenia. *Psychiatry Res*. 1997;74:141-150.
214. Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, Gur RC. A follow-up magnetic resonance imaging study of schizophrenia: relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry*. 1998;55:145-152.
215. Garver DL. The etiologic heterogeneity of schizophrenia. *Harvard Rev Psychiatry*. 1997;4:317-327.
216. Pettegrew JW, Keshevan MS, Panchalingam K, Strychor S, Kaplan DB, Tretta MG, Allen M. Alterations in brain high-energy phosphate and membrane phospholipid metabolism in first-episode, drug naive schizophrenics. *Arch Gen Psychiatry*. 1991;48:563-568.
217. Stanley JA, Williamson PC, Drost DJ, Carr TJ, Rylett J, Malla A, Thompson RT. An in vivo study of the prefrontal cortex of schizophrenic patients at different stages of illness via phosphorus magnetic resonance spectroscopy. *Arch Gen Psychiatry*. 1995;52:399-406.
218. Knoll JL, Garver DL, Ramberg JE, Kingsbury SJ, Croissant D, McDermott B. Heterogeneity of the psychoses: is there a neurodegenerative psychosis? *Schizophr Bull*. 1998;24:365-379.
219. Bedwell JS, Keller B, Smith AK, Hamburger S, Kumra S, Rapoport JL. Why does postpsy-

chotic IQ decline in childhood-onset schizophrenia? *Am J Psychiatry*. 1999;156:1996-1997.
220. Bardenstein KK, McGlashan TH. Gender differences in affective, schizoaffective and schizophrenic disorders: a review. *Schizophr Res*. 1990; 3:159-172.
221. McGlashan TH, Bardenstein KK. Gender differences in affective, schizoaffective and schizophrenic disorders. *Schizophr Bull*. 1990;16:319-329.
222. Goldstein JM, Tsuang MT. Gender and schizophrenia. *Schizophr Bull*. 1990;16:179-194.
223. Loranger AW. Sex differences in age of onset of schizophrenia. *Arch Gen Psychiatry*. 1984;41: 157-161.
224. Hafner H, Behrens S, DeVry J, Gattaz WF. Oestradiol enhances the vulnerability threshold for schizophrenia in women by an early effect on dopaminergic transmission: evidence from an epidemiological study and from animal experiments. *Eur Arch Psychiatry Clin Neurosci*. 1991; 241:65-68.
225. Riecher-Rossler A, Hafner H, Dutsch-Trobel A, Oster M, Stumbaum M, van Gülick-Bailer M. Further evidence for a specific role of estradiol in schizophrenia. *Biol Psychiatry*. 1994;36:492-495.
226. Seeman MV. Interaction of sex, age, and neuroleptic dose. *Compr Psychiatry*. 1983:24:125-128.
227. Seeman MV, Lang M. The role of estrogens in schizophrenia gender differences. *Schizophr Bull*. 1990;16:185-194.
228. MacLusky NJ, Naftolin F. Sexual differentiation of the central nervous system. *Science*. 1981; 211:1294-1302.
229. MacLusky NJ, Clark AS, Naftolin F, Goldman-Rakic PS. Estrogen formation in the mammalian brain: possible role of aromatase in sexual differentiation of the hippocampus and neocortex. *Steroids*. 1987;50:459-474.
230. McEwen BS. Neural gonadal steroid actions. *Science*. 1981;211:1303-1311.
231. McGlone J. Sex differences in human brain asymmetry: a critical survey. In: *The Behavioral and Brain Sciences*. Cambridge, England: Cambridge Univeristy Press; 1980:215-263.
232. Puzzo-Miller LD, Inoue T, Murphy DD. Estradiol increases spine density and NMDA-dependent Ca2+ transients in spines of CA1 pyramidal neurons from hippocampal slices. *J Neurophysiol*. 1999;81:1404-1411.
233. Desmond NL, Levy WB. Ovarian steroidal control of connectivity in the female hippocampus: an overview of recent experimental findings and speculations on its functional consequences. *Hippocampus*. 1997;7:239-245.
234. Naftolin F, Garcia-Segura LM, Keefe D, Leranth C, Maclusky NJ, Brawer JR. Estrogen effects on the synaptology and neural membranes of the rat hypothalamic arcuate nucleus. *Biol Reprod*. 1990;42:21-28.
235. Munoz-Cueto A, Garcia-Segura M, Ruiz-Marcos A. Developmental sex differences and effect of ovariectomy on the number of cortical pyramidal cell dendritic spines. *Brain Res*. 1990; 515:64-68.
236. Woolley CS, Wenzel HJ, Schwartzkroin PA. Estradiol increases the frequency of multiple synapse boutons in the hippocampal CA1 region of the adult female rat. *J Comp Neurol*. 1996;373: 108-117.
237. Asarnow J. Annotation: childhood onset schizophrenia. *J Child Psychol Psychiatry*. 1994;35: 1345-1371.
238. Remschmid HE, Schulz E, Martin M, Warnke A, Trott GE. Childhood-onset schizophrenia: history of the concept and recent studies. *Schizophr Bull*. 1994;20:727-745.
239. Stefanis N, Frangou S, Yakeley J, Sharma T, O'Connell P, Morgan K, Sigmudsson T, Taylor M, Murray R. Hippocampal volume reduction in schizophrenia: effects of genetic risk and pregnancy and birth complications. *Biol Psychiatry*. 1999;46:697-702.
240. McGlashan TH. Duration of untreated psychosis in first-episode schizophrenia: marker or determinant of course? *Biol Psychiatry*. 1999;46: 899-907.
241. Hoffman RE, McGlashan TH. Reduced corticocortical connectivity can induce speech perception pathology and hallucinated "voices." *Schizophr Res*. 1998;30:137-141.
242. Casey BJ. Maturation in brain activation. *Am J Psychiatry*. 1999;156:504.
243. Chechik C, Meilijson I, Ruppin E. Synaptic pruning in development: a computational account. *Neural Comput*. 1998;10:1759-1777.
244. Changuex JP, Danchin A. Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. *Nature*. 1976; 264:705-712.
245. Bock J, Braun K. Filial imprinting in domestic chicks is associated with spine pruning in the associative area, dorsocaudal neostriatum. *Eur J Neurosci*. 1999;11:2566-2570.
246. Buchel C, Coull JT, Friston KJ. The predictive value of changes in effective connectivity for human learning. *Science*. 1999;283:1538-1541.
247. Bock J, Braun K. Differential emotional experience leads to pruning of dendritic spines in the forebrain of domestic chicks. *Neural Plast*. 1998; 6:17-27.
248. Carlson M, Earls F, Todd RD. The importance of regressive changes in the development of the nervous system: towards a neurobiological theory of child development. *Psychiatr Dev*. 1988;1:1-22.
249. Karlsson J. *Inheritance and Creative Intelligence*. Chicago, Ill: Nelson-Hall; 1978.
250. Karlsson J. Family transmission of schizophrenia: a review and synopsis. *Br J Psychiatry*. 1982; 140:600-606.
251. Lange-Eichbaum W. Genius and insanity. In: Lange-Eichbaum W, ed. *The Problem of Genius*. New York, NY: MacMillan; 1932:102-141.
252. Anthony EJ, Cohler BJ, eds. *The Invulnerable Child*. New York, NY: The Guilford Press; 1987.
253. Jablensky A, Sartorius N, Ernberg G, Anker M, Kortn A, Cooper JE, Day R, Bertelsen A. Schizophrenia: manifestations, incidence and course in different cultures: a World Health Organization ten-country study. *Psychol Med*, Monograph Suppl 20. Cambridge, England: Cambridge University Press; 1992.
254. Book JA. Schizophrenia as a gene mutation. *Acta Genet*. 1953;4:133-139.
255. MacSorley K. An investigation into the fertility rates of mentally ill patients. *Ann Hum Genet Lond*. 1964;27:247-256.
256. Haverkamp F, Propping P, Hilger T. Is there an increase of reproductive rates in schizophrenics? I: critical review of the literature. *Arch Psychiatr Nevernkr*. 1982;232:439-450.
257. Crow TJ. A Darwinian approach to the origins of psychosis. *Br J Psychiatry*. 1995;167:12-25.
258. Neissen U, ed. *The Rising Curve: Long-Term Gains in IQ and Related Measures*. Washington, DC: American Psychological Association; 1998.
259. Pearlson GD, Marsh L. Structural brain imaging in schizophrenia: a selective review. *Biol Psychiatry*. 1999;46:627-649.
260. Lim KO, Hedehus M, Moseley M, de Crespigny A, Sullivan EV, Pfefferbaum A. Compromised white matter tract integrity in schizophrenia inferred from diffusion tensor imaging. *Arch Gen Psychiatry*. 1999;56:367-374.
261. Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Naatanen R, Katila T. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *Neuroreport*. 1997; 8:3537-3540.
262. Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *J Neurosci*. 1997;17:3178-3184.
263. Sugarhara M, Shiraishi H. Synaptic density of the prefrontal cortex regulated by dopamine instead of serotonin in rats. *Brain Res*. 1998;814: 143-156.
264. Sugarhara M, Shiraishi H. Dopamine D1 and D2 receptor agents and their interaction influence the synaptic density of the rat prefrontal cortex. *Neurosci Lett*. 1999;259:141-144.