The lifetime trajectory of schizophrenia and the concept of neurodevelopment

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Defining the lifetime trajectory of schizophrenia and the mechanisms that drive it is one of the major challenges of schizophrenia research. Kraepelin assumed that the mechanisms were neurodegenerative ("dementia praecox"), and the early imaging work using computerized tomography seemed to support this model. Prominent ventricular enlargement and increased cerebrospinal fluid on the brain surface suggested that the brain had atrophied. In the 1980s, however, both neuropathological findings and evidence from magnetic resonance imaging (MRI) provided evidence suggesting that neurodevelopmental mechanisms might be a better explanation. This model is supported by both clinical and MRI evidence, particularly the fact that brain abnormalities are already present in first-episode patients. However, longitudinal studies of these patients have found evidence that brain tissue is also lost during the years after onset. The most parsimonious explanation of these findings is that neurodevelopment is a process that is ongoing throughout life, and that schizophrenia occurs as a consequence of aberrations in neurodevelopmental processes that could occur at various stages of life.

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Identifying the mechanisms and lifetime trajectory of schizophrenia is one of the major challenges of schizophrenia research. Kraepelin's original delineation of its lifetime trajectory prevailed for nearly a century. His description of schizophrenia emphasized that this disorder caused a deterioration in cognitive function that began at an early age ("dementia praecox"") and that it was an early-onset neurodegenerative disorder similar to the late-onset neurodegenerative disorder discovered by his colleague Alois Alzheimer.[1] He believed that dementia praecox was a brain disease that could be localized in frontal and temporal regions. He and his colleagues searched in vain for a neuropathological signature that was comparable to the plaques and tangles of Alzheimer's disease. Despite the lack of an identified neuropathology, for most of the 20th century schizophrenia was assumed to be a dementia-like disease that was characterized by a deteriorating course. Among biologically oriented psychiatrists, it was assumed that this course reflected an underlying deterioration in the brain.

The advent of neuroimaging technologies offered the possibility that they might provide a noninvasive way for tracking neurodegenerative processes in schizophrenia in vivo. Computerized tomography (CT) scanning was

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the first modality to be applied to in vivo studies of the brain in schizophrenia, and it seemed to provide confirmation for the Kraepelinian view. Beginning with the Northwick Park study in 1975, a steady series of reports appeared, describing"brain atrophy" in schizophrenia.[2-4] Although CT provided images of the brain that were striking in the 1970s and early 1980s, because the human brain could be directly visualized and measured in vivo for the first time, its limitations may in fact have been misleading. The early CT scans only permitted visualization of brain parenchyma and cerebrospinal fluid (CSF). The inherent limitations of CT scanning contributed to the belief that the brain had atrophied. The main finding was that patients had enlargement of the ventricular system and an increase in CSF on the brain surface, in a pattern that was quite similar to Alzheimer's disease. By inference, as in Alzheimer's disease, patients with schizophrenia had lost brain tissue that was once present.

Early forerunners of the neurodevelopmental hypothesis

During this time, however, a modest minority view was being presented by individuals who looked primarily at the developmental trajectory of the illness and generated hypotheses based on its age of onset and other early characteristics. In the 1970s Barbara Fish suggested that schizophrenia might be a consequence of a congentital inherited neurointegrative defect that she referred to as "pandysmaturation" or "pandevelopmental retardation."[5] She based her argument on her observations of premorbid indicators of pathology in children who developed schizophrenia, particularly when they were from affected families and carried a genetic vulnerability. She noted that many children who later develop schizophrenia have a variety of motor, cognitive, language, and social impairments. Her discussion of pandysmaturation presages much of the work that is considered to be *au courant* today: the use of the concept of "biomarkers," an emphasis on early identification and treatment prior to the emergence of psychosis, use of epidemiological data such as IQ tests administered to military inductees prior to onset to identify "at-risk" individuals, and a discussion of how pregnancy complications and birth injuries might contribute to the development of schizophrenia. Her work epitomizes one perspective on the developmental trajectory of schizophrenia; as a child psychiatrist, she emphasizes the role of maturational processes occurring early in development, a view that has sometimes been called "doomed from the womb."

Another remarkably prescient hypothesis concerning neurodevelopmental factors and schizophrenia was advanced by Irwin Feinberg, who in 1983 proposed that schizophrenia might be "caused by a fault in programmed synaptic elimination during adolescence."[6] While Fish emphasized the importance of genetic vulnerability and markers that appeared during early childhood, Feinberg argued that the crucial period for the development of schizophrenia occurred during the teens and 20s, when brain maturation is occurring rapidly and when the disorder has its most characteristic age of onset. Working as a sleep researcher, he had noted that normal adolescents exhibit striking changes in sleep architecture and event-related potentials, as measured by electroencephalography (EEG). He also drew on early observations that brain metabolic rate, measured using the nitrous oxide method, declines during adolescence and inferred that this might reflect the occurrence of a major change in brain organization.[7] Drawing on Huttenlocher's studies showing that synaptic density decreases during adolescence,[8] presumably due to pruning back of gray matter (GM), he inferred that the brain's decreased metabolic needs during normal adolescence were due to a paradoxical process that eliminated synapses and yet also increased efficiency of cognitive processing. He then proceeded to suggest that schizophrenia occurs as a consequence of a defect in a gene/protein that regulates neurodevelopmental processes such as synaptic pruning, and nerve growth factor (NGF) is cited as a possible example:

> The control [over synaptic elimination] may be exercised by determining the availability of, or the requirements for, the trophic factor that maintains synaptic connections.... As a result of some abnormality in this process, too many, too few or the wrong synapses are eliminated. (Regrettably, we have no basis to choose among these possibilities.) As a consequence of this "bug" in the genetic program, defects of neuronal integration develop, producing the symptomatology of schizophrenia. (p 331)

This seminal paper thus laid the groundwork for an alternative view: schizophrenia is a neurodevelopmental disorder that arises during adolescence or young adulthood because of an aberration in the genetic regulation of brain maturation.

The emergence of magnetic resonance imaging and the re-emergence of neuropathology

When magnetic resonance imaging (MRI) emerged as a new imaging modality in the early to mid-1980s, a powerful tool became available to study the human brain in health and disease. Unlike CT, MRI provided exquisite anatomic detail, with clear differentiation of tissues such as GM, WM, and CSF. Subcortical structures were also clearly visible, such as caudate, putamen, globus pallidus, thalamus, and hippocampus. Visualization of cerebral sulci permitted the delineation of lobes and Brodmann areas. Because MRI did not entail any exposure to ionizing radiation (unlike CT), new research options were available, such as the study of children or the use of repeated scans to track brain development or brain aging.

MRI studies of schizophrenia quickly provided evidence to support the primacy of the neurodevelopmental hypothesis. The first quantitative case-control MRI study of schizophrenia appeared in 1986.[9] It used the superior anatomic resolution of MR to measure frontal lobe size in addition to cerebral and cranial size; it found that all of these structures were significantly smaller in patients than in controls, and that these decreases were related to negative symptoms and cognitive impairment. Because cranial expansion occurs secondary to cerebral growth, the study suggested that patients with schizophrenia may have some type of early developmental abnormality.

> ...the present findings suggest that patients suffering from schizophrenia may have had some type of early developmental abnormality that led to impaired capacity of the brain to grow, thereby causing a correspondingly small cranial area. This could, of course, be due to a variety of factors, such as genetics, maternal nutrition, maternal alcohol consumption, difficulties during delivery, or environmental factors (eg, nutrition and infections) during the first year of life. (p 142-143)

The findings were not consistent with an atrophic process, through which brain tissue was lost over time. The findings of decreased frontal, cerebral, and cranial size were subsequently repeatedly confirmed, as were the relevance of the various potential causes of early neurodevelopmental abnormalities.[10-22]

At the same time (and in the same issue of *Archives of General Psychiatry*) new neuropathology data also emerged that provided indirect support for the neurodevelopmental hypothesis. Benes et al conducted quantitative analyses of glial density, neuron-glia ratios, and neuronal size in the prefrontal, anterior cingulate, and primary motor cortex.[23] Their findings did not meet neuropathological criteria for evidence of a neurodegenerative/atrophic process: neuronal loss, gliosis, a decrease in the neuron:glia ratio, and neuronal shrinkage. Instead they observed reduced numbers of neurons per unit volume of tissue and a decrease in glia. They concluded that their findings did not support the presence of a neurodegenerative process in schizophrenia. These findings have also been repeatedly confirmed.[24-27] There is now a consensus that the neuropathology of schizophrenia is defined by increased neuronal density, a reduction in the dendritic arbor, and cortical thinning. Following these reports in 1986, schizophrenia researchers on both sides of the Atlantic put forth additional arguments in support of the neurodevelopmental model, which became increasingly widely accepted.[28-30] In general, most articulations of this model have emphasized the importance of very early developmental processes, which occurred either prior to birth or shortly afterward. The model assumes that a genetic vulnerability may be present, and that this vulnerability is expressed if a sufficient number of releasing factors converge in the vulnerable individual early in life. Some of these may occur prior to birth, such as viral infections, maternal malnutrition, or exposure to toxins in utero; some may occur shortly after, such as obstetrical complications and birth injuries, or viral infections. These factors are presumed to injure the developing brain, to express themselves in the type of neuropathology that was described in the 1986 Benes study and later ones, and to create impairments in structural or functional connectivity that will be the substrate upon which schizophrenia will develop at a later age. Clinical findings in support of an early developmental abnormality include a variety of premorbid indicators or markers, such as decreased cranial size, motor impairments and neurological soft signs, and cognitive and social impairments. These findings have been repeatedly replicated in high-risk samples or studies of children who later developed schizophrenia using a variety of ingenious designs.[10-18]

During the ensuing years, MR studies also continued to add to the evidence in support of the neurodevelopmental hypothesis. Many of the early MR studies examined samples of convenience, such as institutionalized patients

or patients with established chronicity. Determining if brain abnormalities are present in individuals with schizophrenia at the time of onset ("first-episode patients," FEP) provides a crucial test of the hypothesis, since any abnormalities noted would have presumably antedated the clinical presentation. Investigators conducting studies of FEP began to study patients at the time of onset of illness and to find that many types of brain abnormalities are present early in the illness. These include decreased cerebral size, decreased frontal and temporal lobe size, decreased thalamic size, decreases in GM and WM volume, and increased CSF on the brain surface and in the ventricles.[22,31]

Does tissue loss continue after onset?

Another critical question about the lifetime trajectory of schizophrenia and the related concept of neurodevelopment is whether the brain abnormalities that are present at onset continue to worsen over time. If patients with schizophrenia lose tissue at a greater rate than healthy normals, this could suggest that the disorder also has a neuroprogressive or neurodegenerative component. The optimal way to address this question is to conduct longitudinal studies of brain changes over time, beginning at the time of onset, and to obtain repeated scans spaced several years apart. Since the brain loses tissue over time as a consequence of the normal aging process, a cohort of longitudinally studied normal controls is a mandatory component of this type of study. Several recent overviews have summarized progress in the area to date.[31,32] There have been only seven MR studies that use a prospective longitudinal design.[33-47] The majority of these provide evidence for progression, using a variety of measures, such as ventricular size, cerebral volume, grey matter volume, or white matter volume. All of these studies have had significant limitations, however. For example, patient sample sizes are typically very small, usually in the 20s or 30s, and control groups are even smaller, usually in the 10s to 20s. Surveillance periods are relatively short, often as small as 1 year. Therefore, the validity of the conclusions drawn from these sMR studies has been called into question, and the magnitude of the changes reported has been considered implausible; it has been pointed out that if the magnitude of changes reported are actually true, patients with schizophrenia would have very little brain tissue left by the time that they reach their 50s or 60s.[48]

In order to determine whether brain abnormalities present at onset continue to progress over time and to delineate their pattern, a research design that implements a prospective longitudinal study is necessary. Optimally such a study should meet several criteria: (i) a large first episode sample; (ii) a large normal control sample; (iii) a low attrition rate in both samples in order to ensure that they are representative; (iv) surveillance over a sufficiently long time period to determine the pattern and degree of change (ie, a minimum of 5 years, and preferably 10 to 20); (v) sampling with multiple time points in order to determine the pattern of change (ie, linear, nonlinear) and its relation to the time of onset; (vi) use of multimodal scanning sequences that permit reliable quantitative measurement of GM, WM, CSF, lobes, and cortical and subcortical regions. Almost none of the currently published studies meets these criteria. Perhaps the strongest is one that has examined 119 patients at 3-year intervals for a period of up to 12 years; patients were genotyped for the BDNF val/met polymorphism (rs6265) in order to examine the impact of a well-understood neurodevelopmental gene on neuroprogression; the met allele carriers displayed significantly more brain tissue loss on the frontal cortex than did the val homozygotes.[47]

The meaning of "neurodevelopmental" and "neuroprogressive"

Some findings about schizophrenia are sufficiently well-replicated that they can be treated as reasonably well-established facts. These include the following: (i) schizophrenia has a genetic component; (ii) some individuals who later develop schizophrenia manifest premorbid indicators; (iii) the age of onset is typically in the teens and twenties; (iv) brain abnormalities are present at the time of onset; (v) brain abnormalities (probably) continue to progress after onset; (vi) none of these generalizations applies to all individuals with schizophrenia, and therefore they are not really "facts" in the sense of being universally true. However, if we accept these as guides to our thinking, what conclusions can we draw?
Discussions about the lifetime trajectory of schizophrenia may have been hampered by a tendency to ask questions that oversimplify and polarize. For example, is the process neurodevelopmental or neuroprogressive (neurodegenerative)? If neurodevelopmental, does it occur early or late?

The optimal way to integrate our existing information is to remind ourselves that brain development is an ongoing process that occurs throughout life. Brain development is comprised of some processes that typically or only occur early, such as neuron formation, neuronal migration, and formation of cortical lamina. Other processes such as increased myelination and synaptic pruning occur primarily during adolescence. Yet other processes such as synaptic plasticity (formation or maintenance of dendrites, spines, and synapses) are ongoing throughout life, even on into old age. All of these are cellular and molecular processes that are regulated by genes, and probably a very large number of genes that interact epistatically and that respond to changes in their environment. Some genes, such as *BDNF* or *NRG1* or *NGF* or *RELN*, have known neurodevelopment functions that make them obvious candidates, but many relevant genes are probably as yet undiscovered. We are still a very long way from understanding how these processes and neuroregulatory genes, or an aberration in them, may lead the development of schizophrenia or to the measurable brain changes that have been observed. But that is the path on which we should be travelling.

Conclusion

In this context the polarities being used to discuss the lifetime trajectory of schizophrenia seem to be unhelpful. The term "neurodegeneration" is probably not an appropriate one for referring to ongoing changes in the brain after onset, since it carries too much heavy baggage by suggesting a similarity between schizophrenia and classic neurodegenerative disorders such as Alzheimer's disease or Huntington's disease. It should probably be replaced with the term "neuroprogression." Explaining how the "early developmental" damage could lie fallow until the teens and twenties has always been a problem for the "doomed from the womb" formulation, but that problem disappears when we recognize that neurodevelopment is ongoing. Combining a recognition that abnormalities are present at onset (further evidence for neurodevelopment) with a recognition that changes also occur or continue after onset (neuroprogression) also ceases to present problems. There could be a continuation of the same developmental process (eg, pruning) or a different one (eg, impaired synaptic plasticity), but in either case the process that shapes the lifetime trajectory of schizophrenia is fundamentally a neurodevelopmental one. ❑

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REFERENCES

1. Kraepelin E, Barclay RM, Robertson GM. *Dementia Praecox and Paraphrenia*. Edinburgh, Scotland: E&S Livingstone; 1919.
2. Johnstone EC, Frith CD, Crow TJ, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet*. 1976;2:924-926.
3. Weinberger DR, Torrey EF, Neophytide AN, Wyatt RJ. Lateral cerebral ventricular enlargement in chronic schizophrenia. *Arch Gen Psychiatry*. 1979;36:735-739.
4. Andreasen NC, Olsen S. Negative v positive schizophrenia: definition and validation. *Arch Gen Psychiatry*. 1982;39:789-794.
5. Fish B, Marcus J, Hans SL, Auerbach JG, Perdue S. Infants at risk for schizophrenia: sequelae of a genetic neurointegrative defect. A review and replication analysis of pandysmaturation in the Jerusalem Infant Development Study. *Arch Gen Psychiatry*. 1992;49:221-235.
6. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res*. 1982;17:319-334.
7. Kety SS, Woodford RB, Harmel MH, Freyhan FA, Appel KE, Schmidt CF. Cerebral blood flow and metabolism in schizophrenia: the effects of barbiturate semi-narcosis, insulin coma and electroshock. *Am J Psychiatry*. 1948;104:765-770.
8. Huttenlocher PR. Synaptic density in human frontal cortex--developmental changes and effects of aging. *Brain Res*. 1979;163:195-205.
9. Andreasen N, Nasrallah HA, Dunn V, et al. Structural abnormalities in the frontal system in schizophrenia. A magnetic resonance imaging study. *Arch Gen Psychiatry*. 1986;43:136-144.
10. Walker E, Lewine RJ. Prediction of adult-onset schizophrenia from childhood home movies of patients. *Am J Psychiatry*. 1990;147:1052-1056.
11. 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.
12. Jones P, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet*. 1994;344:1398-1402.
13. McNeil TF, Cantor-Grae E, Nordstrom LG, Rosenlund T. Head circumference in 'preschizophrenic' and control neonates. *Br J Psychiatry*. 1993;162:517-523.
14. McNeil TF, Cantor-Graae E, Weinberger DR. Relationship of obstetric complications and differences in size of brain structures in monozygotic twin pairs discordant for schizophenia. *Am J Psychiatry* 2000;157:203-212.
15. Hulshoff Pol HE, Hoek HW, Susser E, et al. Prenatal exposure to famine and brain morphology in schizophrenia. *Am J Psychiatry*. 2000;157:1170-1172.
16. Ward KE, Friedman L, Wise A, Schulz SC. Meta-analysis of brain and cranial size in schizophrenia. *Schiz Res*. 1996;22:197-213.
17. Gupta S, Andreasen NC, Arndt S, et al. Neurological soft signs in neuroleptic-naive and neuroleptic-treated schizophrenic patients and in normal comparison subjects. *Am J Psychiatry*. 1995;152:191-196.

El curso vital de la esquizofrenia y el concepto de neurodesarrollo

Uno de los principales desafíos en la investigación de la esquizofrenia es la definición de su trayectoria a lo largo de la vida y los mecanismos que la dirigen. Kraepelin asumió que los mecanismos eran neurodegenerativos ("demencia precoz") y los primeros trabajos con neuroimágenes empleando tomografía computarizada dieron soporte a este modelo. El marcado agrandamiento ventricular y el aumento del líquido céfalo raquídeo en la superficie del cerebro hicieron suponer una atrofia cerebral. Sin embargo, en la década de 1980, ambos hallazgos neuropatológicos y la evidencia proveniente de las imágenes de resonancia magnética (IRM) aportaron evidencias que sugerían que los mecanismos del neurodesarrollo constituirían una mejor explicación. Este modelo se sustenta en evidencias clínicas y de IRM, principalmente por el hecho que las anormalidades cerebrales ya están presentes en los pacientes con el primer episodio. Sin embargo, estudios longitudinales de estos pacientes han aportado evidencia que el tejido cerebral también se pierde durante los años que siguen a la aparición del cuadro. La explicación más restringida de estos hallazgos es que el neurodesarrollo sería un proceso que se produciría a lo largo de la vida y que la esquizofrenia occurriría a consecuencia de alteraciones en los procesos de neurodesarrollo que podrían presentarse en varias etapas de la vida.

La schizophrénie au cours de la vie : concept du neurodéveloppement

L'un des principaux défis de la recherche sur la schizophrénie est de définir son parcours durant la vie et les mécanismes qui le sous-tendent. D'après Kraepelin, les mécanismes seraient neurodégénératifs (démence précoce) comme semblaient le confirmer les premières études d'imagerie réalisées à l'aide de scanner (tomodensitométrie numérisée). L'augmentation importante du volume ventriculaire et l'augmentation de liquide céphalorachidien extracérébral suggéraient une atrophie cérébrale. Cependant, dans les années 80, les résultats de la neuropathologie et les images d'IRM (imagerie par résonance magnétique) ont prouvé que les mécanismes neurodéveloppementaux seraient une meilleure explication, en particulier par la présence d'anomalies cérébrales dès les premiers épisodes symptomatiques. Des études longitudinales effectuées sur les patients présentant une schizophrénie débutante ont néanmoins montré une perte de tissu cérébral au cours des années suivant le début de la maladie. L'explication la plus simple en serait que, le neurodéveloppement étant un processus évolutif au cours de la vie, la schizophrénie surviendrait comme une conséquence d'aberrations de ce processus pouvant intervenir à des stades différents de la vie.

18. Ho BC, Andreasen NC, Nopoulos P, Fuller R, Arndt S, Cadoret RJ. Secondary prevention of schizophrenia: utility of standardized scholastic tests in early identification. *Ann Clin Psychiatry*. 2005;17:11-18.

19. Nopoulos P, Torres I, Flaum M, Andreasen NC. Brain morphology in first episode schizophrenia. *Am J Psychiatry*. 1995;152:1721-1724.

20. Andreasen NC, Flashman L, Flaum M, et al. Regional brain abnormalities in schizophrenia measured with magnetic resonance imaging. *JAMA*. 1994;272:1763-1769.

21. Gur RE, Cowell PE, Latshaw A, et al. Reduced dorsal and orbital frontal gray matter volumes in schizophrenia. *Arch Gen Psychiatry*. 2000; 57:761-768.

22. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr Res*. 2001;49:1-52.

23. Benes FM, Davidson J, Bird ED. Quantitative cytoarchitectural studies of the cerebral cortex of schizophrenics. *Arch Gen Psychiatry*. 1986;43:31-35.

24. Benes FM, McSparren J, Bird ED, SanGiovanni JP, Vincent SL. Deficits in small interneurons in prefrontal and cingulate cortices of schizophrenic and schizoaffective patients. *Arch Gen Psychiatry*. 1991;48:996-1001.

25. 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; discussion 819-820.

26. Selemon LD, Mrzljak J, Kleinman JE, Herman MM, Goldman-Rakic PS. Regional specificity in the neuropathological substrates of schizophrenia: a morphometric analysis of Broca's area 44 and area 9. *Arch Gen Psychiatry*. 2003;60:69-77.

27. Selemon LD, Kleinman JE, Herman MM, Goldman-Rakic PS. Smaller frontal gray matter volume in postmortem schizophrenic brains. *Am J Psychiatry*. 2002;159:1983-1991.

28. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *BMJ*. 1987;295:681-682.

29. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987;44:660-669.

30. Castle DJ, Murray RM. The neurodevelopmental basis of sex differences in schizophrenia. *Psychol Med*. 1991;21:565-575.

31. Giedd JN, Jeffries NO, Blumenthal J, et al. Childhood-onset schizophrenia: progressive brain changes during adolescence. *Biol Psychiatry*. 1999;46:892-898.

32. Thompson PM, Vidal C, Giedd JN, et al. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proc Natl Acad Sci U S A*. 2001;98:11650-11655.

33. Arango C, Moreno C, Martinez S, et al. Longitudinal brain changes in early-onset psychosis. *Schizophr Bull*. 2008;34:341-353.

34. DeLisi LE. The concept of progressive brain change in schizophrenia: implications for understanding schizophrenia. *Schizophr Bull*. 2008;34:312-321.
35. Cahn W, Hulshoff Pol HE, Lems EB, et al. Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. *Arch Gen Psychiatry*. 2002;59:1002-1010.
36. Degreef G, Ashtari M, Wu HW, Borenstein M, Geisler S, Lieberman J. Follow up MRI study in first episode schizophrenia. *Schizophr Res*. 1991;5:204-206.
37. DeLisi LE, Sakuma M, Maurizio AM, Relja M, Hoff AL. Cerebral ventricular change over the first 10 years after the onset of schizophrenia. *Psychiatry Res*. 2004;130:57-70.
38. 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.
39. DeLisi LE, Stritzke P, Riordan H, et al. The timing of brain morphological changes in schizophrenia and their relationship to clinical outcome. *Biol Psychiatry*. 1992;31:241-254.
40. DeLisi LE, Tew W, Xie S, et al. A prospective follow-up study of brain morphology and cognition in first-episode schizophrenic patients: preliminary findings. *Biol Psychiatry*. 1995;38:349-360.
41. Gur RE, Cowell P, Turetsky BI, et al. 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.
42. Lieberman J, Chakos M, Wu H, et al. Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry*. 2001;49:487-499.
43. Whitford TJ, Grieve SM, Farrow TF, et al. Progressive grey matter atrophy over the first 2-3 years of illness in first-episode schizophrenia: a tensor-based morphometry study. *Neuroimage*. 2006;32:511-519.
44. Wood SJ, Velakoulis D, Smith DJ, et al. A longitudinal study of hippocampal volume in first episode psychosis and chronic schizophrenia. *Schizophr Res*. 2001;52:37-46.
45. Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M. Progressive structural brain abnormalities and their relationship to clinical outcome. *Arch Gen Psychiatry*. 2003;50:585-594.
46. Milev P, Ho BC, Arndt S, Nopoulos P, Andreasen NC. Initial magnetic resonance imaging volumetric brain measurments and outcome in schizophrenia: a prospective longitudinal study with 5-year follow-up. *Biol Psychiatry*. 2005;54:608-615.
47. Ho BC, Andreasen NC, Dawson JD, Wassink TH: Association between brain-derived neurotrophic factor Val66Met gene polymorphism and progressive brain volume changes in schizophrenia. *Am J Psychiatry*. 2007;164:1890-1899.
48. Weinberger DR, McClure RK. Neurotoxicity, neuroplasticity, and magnetic resonance imaging morphometry: what is happening in the schizophrenic brain? *Arch Gen Psychiatry*. 2002;59:553-558.