Schizophrenia Bulletin vol. 40 no. 4 pp. 721–728, 2014
doi:10.1093/schbul/sbu070
Advance Access publication May 27, 2014

Neurodevelopmental and Neurodegenerative Models of Schizophrenia: White Matter at the Center Stage

Peter Kochunov* and L. Elliot Hong

Department of Psychiatry, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD.

*To whom correspondence should be addressed; Department of Psychiatry, Maryland Psychiatric Research Center, University of Maryland, School of Medicine, Baltimore, MD 21043, US; tel: 410-402-6110, fax: 410-402-6077, e-mail: pkochunov@mprc.umaryland.edu

Schizophrenia is a disorder of cerebral disconnectivity whose lifetime course is modeled as both neurodevelopmental and neurodegenerative. The neurodevelopmental models attribute schizophrenia to alterations in the prenatal-to-early adolescent development. The neurodegenerative models identify progressive neurodegeneration as its core attribute. Historically, the physiology, pharmacology, and treatment targets in schizophrenia were conceptualized in terms of neurons, neurotransmitter levels, and synaptic receptors. Much of the evidence for both models was derived from studies of cortical and subcortical gray matter. We argue that the dynamics of the lifetime trajectory of white matter, and the consistency of connectivity deficits in schizophrenia, support white matter integrity as a promising phenotype to evaluate the competing evidence for and against neurodevelopmental and neurodegenerative heuristics. We develop this perspective by reviewing normal lifetime trajectories of white and gray matter changes. We highlighted the overlap between the age of peak of white matter development and the age of onset of schizophrenia and reviewed findings of white matter abnormalities prior to, at the onset, and at chronic stages of schizophrenia. We emphasized the findings of reduced white matter integrity at the onset and findings of accelerated decline in chronic stages, but the developmental trajectory that precedes the onset is largely unknown. We propose 4 probable lifetime white matter trajectory models that can be used as the basis for separation between the neurodevelopmental and neurodegenerative etiologies. We argue that a combination of the cross-sectional and longitudinal studies of white matter integrity in patients may be used to bridge the neurodevelopment and degeneration heuristics to advance schizophrenia research

Key words: white matter integrity/etiology of schizophrenia/diffusion tensor imaging

Overview

The neurodevelopmental and neurodegenerative models of schizophrenia are 2 competing heuristics on the etiology and clinical course of this disorder. The neurodevelopmental models posit that genetic and environmental risk factors act during prenatal, perinatal, and early adolescence periods, thus altering the developmental trajectory and leading to the onset during adolescence and young adulthood.[1–5] The neurodegenerative models describe schizophrenia as a disease of progressively unfavorable neurodegenerative trajectory.[6,7] The primary evidence supporting these heuristic models came from observations of progressive changes, or the lack thereof, in gray matter (GM) and lateral ventricles, as well as measurements of morphological, neuronal, synaptic, and neurotransmitter differences in postmortem samples.

Schizophrenia is often described as a disorder of altered cerebral connectivity.[8–11] Yet historically, the research on the etiology, progress, and treatment of schizophrenia regarded the GM as the "primary" tissue of interest, often overlooking the importance of intact cerebral white matter (WM) in maintaining normal cerebral connectivity. In this perspective opinion, we propose that the improved understanding of the role that WM plays in schizophrenia may help to clarify the neurodevelopmental or neurodegenerative course of schizophrenia. Importantly, placing WM at the frontline of schizophrenia research may be particularly relevant for bridging the powerful heuristics neurodevelopmental and degenerative models into concrete discoveries. We will first summarize the neurodevelopmental and the neurodegenerative models and their underlying evidence and arguments. We will then present evidence supporting the role of WM in schizophrenia, by placing a particular attention to the normative differences of the life span trajectories between WM vs GM. Last, we develop an argument that the knowledge

of the WM life span trajectory is necessary for bridging the neurodevelopmental and neurodegenerative models to advance schizophrenia research.

Neurodevelopment Models of Schizophrenia

The neurodevelopment models postulate that schizophrenia is caused by environmental and/or genetic insults that occur during prenatal, perinatal, or early childhood/adolescence, leading to alteration of brain structure and function and setting the stage for schizophrenia.[1–5] These heuristics are supported by findings of reduced cortical volume, altered gyrification patterns, and ventricular enlargement at the onset of schizophrenia. This argues that the damage to the brain from the altered early development occurs before the onset of psychosis, and further worsening is not expected.[1] Alternatively, the late neurodevelopment model suggested that the risk factors for schizophrenia may act during the synaptic reorganization and pruning stages that occur during early adolescence.[12] It argues that the disruption of this important cortical maturation step underlines the emergence of schizophrenia.[12] This model is supported by imaging studies that report that cerebral cortical GM structures undergo significant change prior to the onset of psychosis in individuals at high risk for developing schizophrenia.[13,14]

The "second hit' theory combines the early and late developmental risks to suggest that schizophrenia is caused by a sequence of unfavorable events that occur during early (eg, prenatal or perinatal) and late (adolescent) development. For example, Rappoport and colleagues argue that risk genes for schizophrenia are differentially expressed in the early vs late development and that their effects are additive. The "first hit" occurs at early developments stages, setting the stage for the second hit, which occurs at or near the onset of psychosis. This model was conceived to explain the variable age of onset and behavioral and cognitive heterogeneity in the clinical course of schizophrenia.[4,15] Nonetheless, the neurodevelopmental models have limitations. Chief among them is the difficulty to explain the young adulthood (18–28 years) age of onset that occurs a decade after the cortex has reached the peak of cortical thickness and long after the cortical reorganization has began. The neurodevelopment models also fail to address progressive brain deterioration observed in chronic schizophrenia patients.[14,16–22]

Neurodegenerative Models of Schizophrenia

The role of progressive neurodegeneration in schizophrenia has been an active research topic since Kraepelin's observation of mental decline in schizophrenia patients.[6,7,23,24] Unlike affective disorders, patients with schizophrenia may follow a progressive, neurodegenerative clinical course, an observation that has been repeatedly been upheld.[7] The Chestnut Lodge Longitudinal study reported striking, longitudinal differences between patients with schizophrenia and those with affective disorders, consonant with Kraepelin's original observations.[25,26] Over 60% of schizophrenia patients experienced a deteriorative clinical course, compared with only 30% of patients with affective disorders.[25,26] Patients included in that study came from the upper socioeconomic bracket and were receiving the best available care.[25,26] Schizophrenia is also associated with earlier age of onset and increased rate of many chronic cardiovascular and metabolic illnesses commonly associated with aging.[27–29]

Using Neuroimaging to Quantify Normal Lifetime trajectories of WM and GM

Cerebral WM and GM compartments undergo continuous change over the life span,[30–33] each with own characteristic age-related trajectory, which can be measured using modern, noninvasive imaging. Changes in cerebral WM are commonly assessed using fractional anisotropy (FA) of water diffusion, while changes in cortical GM are ascertained using cortical GM volume or thickness. FA, calculated from diffusion tensor imaging (DTI) data, describes the directional selectivity of the random diffusion of water molecules.[34] Absolute WM FA values are sensitive to many parameters,[34] but the changes in regional FA values during normal life span trajectory are believed to be mainly due to changes in cerebral myelin levels and myelin packing density.[35–37] Cortical thickness is calculated as the distance from the outer cortical surface to the inner cortical WM-GM boundary[38,39] and serves as an indirect measure of underlying cortical architecture, including cortical myelination level, cell density, and synaptic pruning.[40] Both cerebral FA and cortical GM thickness follow inverse-U trajectories with age, but the age when they reach their peaks is separated by a decade (figure 1).[31,33,41–43] Importantly, there is a significant regional heterochronicity—the differences in the age of peak for maturation of different WM tracts. Specifically, WM tracts that carry higher level, associative cognitive functions follow a more protracted developmental trajectory and mature much later, late adolescence to early adulthood, than the sensory and motor tracts that mature in the first and second decades of life.[31,33,44–46] Another important consideration is that the time by which the average cerebral FA reaches its maximum overlaps with the average age of the onset of schizophrenia,[31,47] while the peak in the cortical GM thickness occurs a decade before (figure 1A).

Abnormal WM Neurobiology in Schizophrenia

In one of the first reviews on the importance of WM in schizophrenia, Davis and colleagues pointed the role that oligodendroglial abnormalities play in schizophrenia.[51] The postmortem studies in schizophrenia report

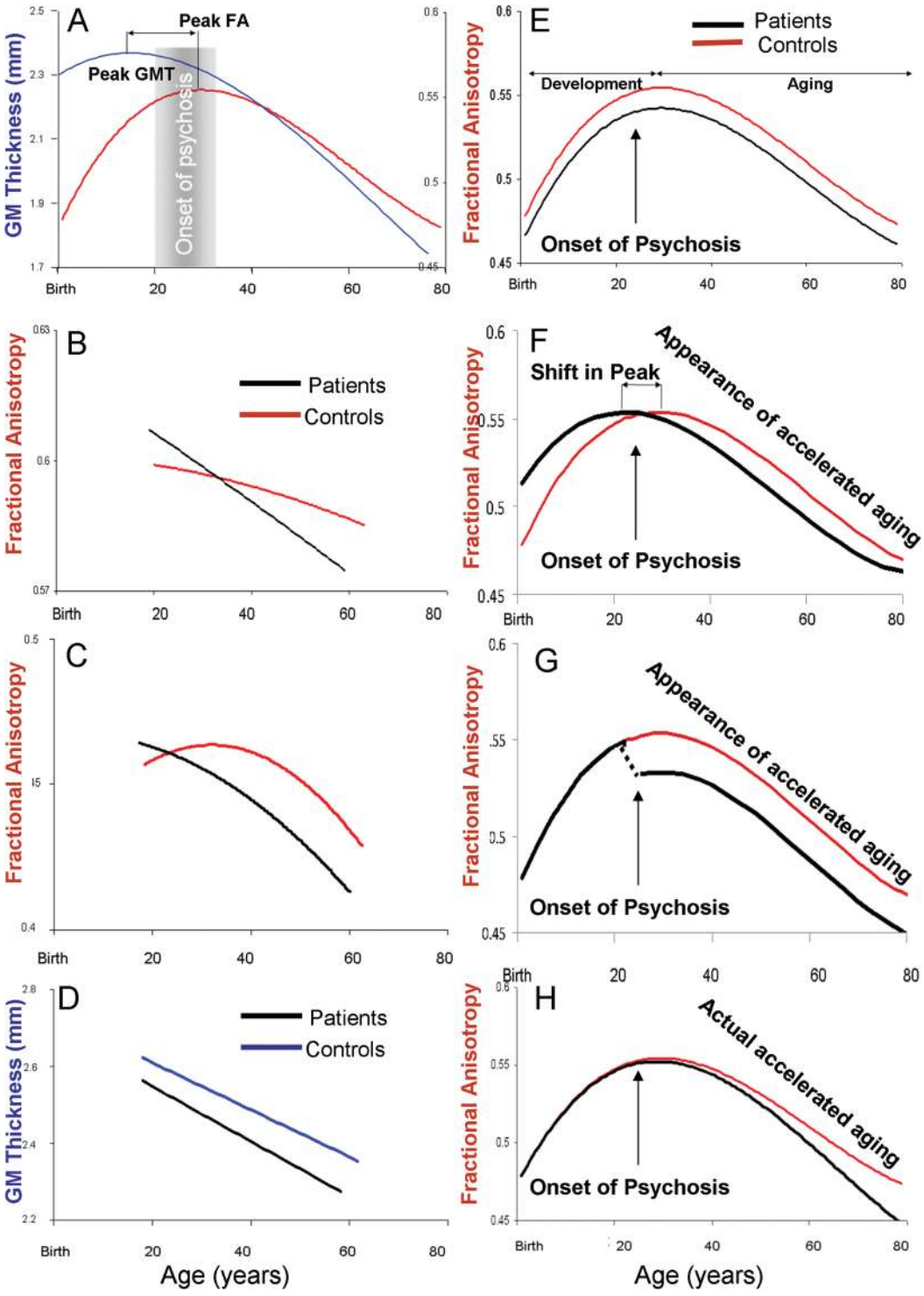

Fig. 1. Experimental (left column) and simulated (right column) life-long trajectories of fractional anisotropy (FA) and gray matter thickness (GMT) were evaluated to clarify neurodevelopmental and neurodegenerative etiologies of schizophrenia. Section (A) Normal, life-trajectories of the whole-brain average GMT (blue curve) and FA (red curve) calculated from a large cross-sectional data set of healthy subjects[47,48] demonstrate that the peak GMT and FA values are separated by about a decade. In addition, the peak FA values overlap with the average age of the onset of psychosis. (B) Whole-brain average FA values for schizophrenia patients demonstrated significant diagnosis-by-age interaction, suggesting presence of accelerated aging in schizophrenia patients.[49] (C) The finding of significant diagnosis-by-age interaction was replicated in an independent cohort.[50] (D) No evidence for accelerated aging in whole-brain average GM thickness were observed in the subjects from the replication (1C) cohort[50] (unpublished data). (E) Systematic differences in FA values across the life span would suggest the early neurodevelopmental causes of schizophrenia. (F) A shift in the age of peak in FA by 5 years in patient would also suggest an early developmental etiology and may account of finding of accelerated aging in cross-sectional samples. (H) Finally, pure neurodegenerative etiology would lead to a progressive aging-related difference in FA values.

significantly reduced cellular density and integrity of oligodendrocytes in patients, especially in the associative fiber tracts that connect prefrontal cortices.[52,53] The findings of reduced expressions of key oligodendrocyte/myelination genes also support the key role that altered WM integrity plays in this disorder.[51,54] Moreover, postmortem examinations also reveal that the damage, degeneration, and loss of oligodendrocyte density are also present in the associative cortical GM layers in schizophrenia patients.[52,55–57] This suggests that findings of reduced cortical GM thickness and reduced WM integrity may have a common culprit.[47] Alterations in oligodendrocyte density are also hypothesized to be responsible for age-dependent abnormality in myelinated fibers in schizophrenia.[58]

Developments in neuroimaging had greatly expanded ability for in vivo research on WM structure and function. Early studies in schizophrenia reported reduced WM volume, especially in the frontal areas.[59–61] A longitudinal 3-year follow-up study of early stage of schizophrenia identified that the decline in the frontal lobe volume was driven by WM and reported no differences in the frontal GM volumes between patients and controls.[62] Improvements in magnetic resonance imaging technology led to development of quantitative imaging methods with DTI-FA emerging as a particularly sensitive phenotype.[63] DTI-FA measurements proved to be sensitive to the progression of various degenerative WM disorders that result in axonal loss and/or destruction of myelin sheath.[64] Schizophrenia was one of the first clinical application of DTI-FA methods in psychiatry, and Lim and colleagues demonstrated that patients with schizophrenia have significant disturbances in the regional FA values, implicating impaired WM integrity.[63] Henceforth, DTI-FA methods became widely used neuroimaging biomarkers for schizophrenia.[49,65–70]

WM Imaging Findings in Support of Neurodevelopmental Model

Presently, there is a shortage of data that describe the trajectory of WM development in patients prior to the onset of schizophrenia. Nonetheless, some inferences can be made from the studies in the high-risk individuals and patients at the onset of psychosis. These studies provide initial evidence that WM changes may precede and potentially predict the severity of this disorder. Karlsgodt and colleagues were first to report that WM development may be altered in adolescents at high clinical risk for psychosis.[71] Moreover, they observed that lower FA values were predictive of negative changes in functional and cognitive status, supporting the developmental nature of the WM deficit in this disorder.[71] Follow-up studies in high-risk cohorts provided support for a 2-hit developmental model.[72,73] The high-risk individuals had reduced FA values prior to onset, and the onset of psychosis was mirrored with an additional reduction of WM integrity, the second hit.[72,73]

WM Imaging Findings in Support of Neurodegenerative Model

The finding of reduced FA at the onset and during chronic states of schizophrenia is remarkably consistent across most reports although there are some inconsistencies with regard to the regions affected by this decline and the size of this effect.[66,74–77] Kubicki and colleagues summarized that significant abnormalities are most consistently reported in the WM tracts that connect prefrontal and temporal lobes including uncinate fasciculus, cingulum bundle, and arcuate fasciculus.[78] The studies that report higher FA values[79] or no difference[80] are typically underpowered due to a small number of subjects[78] (N = 13 and 14 patients for studies by Hubl[79] and Jones,[80] respectively). Moreover, the difference between patients and controls may increase with age, supporting the neurodegenerative model. Schizophrenia patients show twice the rate of the aging-related decline in FA values, compared with controls.[49,65,66] Our group examined the rates of age-related decline in whole-brain FA in patients with schizophrenia and contrasted them with aging trends in patients of major depression and normal controls.[49] Schizophrenia patients demonstrated an accelerated age-related decline (figure 1B), but the accelerated aging was not present in patients suffering from depression.[49] The finding of accelerated FA reduction with age in schizophrenia was later replicated in an independent sample using a more advanced DTI sequences[50] (figure 1C). The accelerated decline in FA is occurring in patients with a normal rate of age-related decline in the WM perfusion,[50] suggesting that cerebrovascular-related disorders are unlikely the driving forces behind the accelerated FA decline.[50] Moreover, the accelerated WM aging is occurring in patients with no apparent accelerated aging trends in cortical GM thickness (figure 1D) or accelerated rise in the hyperintensive WM lesions volume.[81] The biological basis of the accelerated decline in FA values in schizophrenia, therefore likely reflects unique WM neuropathology and other than that of vascular nature.

Linking Neurodevelopmental and Neurodegenerative Models of Schizophrenia

A notable attribute of the lifetime WM trajectory is the overlap between the average age of peak development and the average age of onset of schizophrenia (figure 1A). Intriguingly, the age of onset of schizophrenia overlaps with the age of peak for WM tracts that carry higher order associative function, rather than these carrying motor and sensory information.[48] These frontal and temporal WM tracks, eg, the genu of corpus callosum that connects the bilateral frontal lobes, are also most

consistently reported as the regions of significant FA deficits[82] and accelerated aging in patients.[49] In comparison, cortical GM volume and thickness development peaks a decade before the onset of schizophrenia and normally is already in decline at the average age of onset of schizophrenia (figure 1A). The patient-control GM differences are present at the onset of the disease, and further decline in GM in schizophrenia follows the same rate decline afterward (figure D). This argues that changes in WM integrity can be more sensitive to neuropathology associated with disease onset and its subsequent trajectory (figure C). Confirming this, neurodegeneration trajectory requires an imaging epidemiological study with a longitudinal follow-up. This is a significant challenge to the field. The limited evidence that report altered WM integrity at or before the onset of psychosis can be used to support the developmental etiologies. Resolving schizophrenia-specific neurodevelopmental deficits would require longitudinal data collected several years prior to the onset. Resolving schizophrenia-specific neurodegenerative deficits would require longitudinal follow-up in subjects across the broad range of age. Once these data become available, we may attempt to interpret them using the following 4 hypothesized lifetime trajectories. We contrived them based on existing evidence to bridge the neurodevelopmental and neurodegenerative theories with WM as the key component:

1. WM maturation in schizophrenia may follow the same temporal trajectory as normal controls but at the reduced integrity throughout the life span (figure 1E). This scenario would support the early developmental origins of the disorder. This trajectory is supported by findings of lower FA values prior to and at the onset of disorder. However, this model will not explain accelerated aging in chronic patients (figure 1B and C).
2. WM may reach the peak maturity earlier in schizophrenia compared with healthy subjects. As the consequence of this shift in development, the subsequent age-related decline may be interpreted as "accelerated" although the "neurodegeneration" of WM is only an artifact of the precocious WM development and plateau. Finding of this trajectory would also argue for the neurodevelopmental etiology of schizophrenia (figure 1F).
3. A stall in WM maturation may be the trigger of psychosis. This would be detectable as an onset-related decline in FA that has been observed[72,73] (figure 1G). In this scenario, the WM development is halted or drastically altered at the onset of psychosis, leading to the appearance of a neurodegenerative course, while in fact it is neither neurodevelopmental nor neurodegenerative (figure 1G)
4. Finally, the life-long trajectory may include a period of normal development until the onset of disorder, followed by a true accelerated decline with age. This scenario would argue for a neurodegenerative rather than neurodevelopmental course of the disorder (figure 1H)

These 4 hypotheses are illustrated in figure 1E–H. Clearly, it is also possible that these scenarios are not isolated. What is also likely is that individual patients may follow different lifetime trajectories. It is likely that not 1 model is appropriate for the disorder as heterogeneous as schizophrenia, and the heterogeneity of this syndrome may be due to the variable schizophrenia × development and/or schizophrenia × aging course in the individual clinical histories.

Conclusion

Schizophrenia is regarded as a disorder of cerebral connectivity although its neurobiology has historically been explained by changes in neurons, neurotransmitters, and synaptic receptors rather than integrity of the axonal fibers that make up and support the cerebral networks. This bias toward GM-based etiology is evident across physiology, pharmacology, and treatment research in schizophrenia. However, imaging, postmortem, and genetic research have increasingly suggested that compromised WM structure and function may be at the core of this disorder.[65–68] Indeed, our understanding of the role that cerebral WM is playing in schizophrenia is changing. Recent reports of normalization of WM physiology following the successful treatments[83,84] suggest that WM may potentially be the target to direct pharmacological interventions.[4] We hypothesized 4 possible lifetime WM trajectories that incorporate the neurodevelopmental and neurodegenerative findings reported in this disorder. We argue that an epidemiological study of WM integrity that incorporates longitudinal data prior to, at, and following the onset may facilitate the bridging of neurodevelopmental and degenerative heuristics and translation of these models into tangible etiology and treatment targets.

Funding

National Institute of Health (R01EB015611 to P.K., R01DA027680, R01MH085646 to L.E.H.).

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Weinberger DR, Lipska BK. Cortical maldevelopment, antipsychotic drugs, and schizophrenia: a search for common ground. *Schizophr Res*. 1995;16:87–110.
2. Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. *Annu Rev Neurosci*. 2002;25:409–432.

3. Rapoport JL, Giedd JN, Gogtay N. Neurodevelopmental model of schizophrenia: update 2012. *Mol Psychiatry*. 2012;17:1228–1238.
4. Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. *Mol Psychiatry*. 2005;10:434–449.
5. Murray RM, O'Callaghan E, Castle DJ, Lewis SW. A neurodevelopmental approach to the classification of schizophrenia. *Schizophr Bull*. 1992;18:319–332.
6. Knoll JLt, 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.
7. Anderson JE, O'Donnell BF, McCarley RW, Shenton ME. Progressive changes in schizophrenia: do they exist and what do they mean? *Restor Neurol Neurosci*. 1998;12:175–184.
8. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? *Clin Neurosci*. 1995;3:89–97.
9. Repovs G, Csernansky JG, Barch DM. Brain network connectivity in individuals with schizophrenia and their siblings. *Biol Psychiatry*. 2011;69:967–973.
10. Weinberger DR. On the plausibility of "the neurodevelopmental hypothesis" of schizophrenia. *Neuropsychopharmacology*. 1996;14(suppl 3):1S–11S.
11. Lillrank SM, Lipska BK, Weinberger DR. Neurodevelopmental animal models of schizophrenia. *Clin Neurosci*. 1995;3:98–104.
12. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res*. 1982;17:319–334.
13. Pantelis C, Yücel M, Wood SJ, et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull*. 2005;31:672–696.
14. Sun D, Phillips L, Velakoulis D, et al. Progressive brain structural changes mapped as psychosis develops in 'at risk' individuals. *Schizophr Res*. 2009;108:85–92.
15. Rapoport JL, Addington A, Frangou S. The neurodevelopmental model of schizophrenia: what can very early onset cases tell us? *Curr Psychiatry Rep*. 2005;7:81–82.
16. 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.
17. Woods BT. Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism. *Am J Psychiatry*. 1998;155:1661–1670.
18. Lieberman JA. Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. *Biol Psychiatry*. 1999;46:729–739.
19. Lieberman J, Chakos M, Wu H, et al. Longitudinal study of brain morphology in first episode schizophrenia. *Biol Psychiatry*. 2001;49:487–499.
20. McCarley RW, Wible CG, Frumin M, et al. MRI anatomy of schizophrenia. *Biol Psychiatry*. 1999;45:1099–1119.
21. Pantelis C, Stuart GW, Nelson HE, Robbins TW, Barnes TR. Spatial working memory deficits in schizophrenia: relationship with tardive dyskinesia and negative symptoms. *Am J Psychiatry*. 2001;158:1276–1285.
22. Rimol LM, Nesvåg R, Hagler DJ Jr, et al. Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. *Biol Psychiatry*. 2012;71:552–560.
23. Andreasen NC. The lifetime trajectory of schizophrenia and the concept of neurodevelopment. *Dialogues Clin Neurosci*. 2010;12:409–415.
24. Jeste DV, Wolkowitz OM, Palmer BW. Divergent trajectories of physical, cognitive, and psychosocial aging in schizophrenia. *Schizophr Bull*. 2011;37:451–455.
25. McGlashan TH. The Chestnut Lodge follow-up study. II. Long-term outcome of schizophrenia and the affective disorders. *Arch Gen Psychiatry*. 1984;41:586–601.
26. McGlashan TH. The Chestnut Lodge follow-up study. I. Follow-up methodology and study sample. *Arch Gen Psychiatry*. 1984;41:573–585.
27. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J*. 2005;150:1115–1121.
28. Kirkpatrick B. Schizophrenia as a systemic disease. *Schizophr Bull*. 2009;35:381–382.
29. Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR. Is schizophrenia a syndrome of accelerated aging? *Schizophr Bull*. 2008;34:1024–1032.
30. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci*. 2003;6:309–315.
31. Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A*. 2004;101:8174–8179.
32. Yakovlev PI, Lecours AR. *Regional Development of the Brain in Early Life*. Boston, MA: Blackwell Scientific Publications; 1967.
33. Kochunov P, Williamson DE, Lancaster J, et al. Fractional anisotropy of water diffusion in cerebral white matter across the lifespan. *Neurobiol Aging*. 2012;33:9–20.
34. Beaulieu C. The basis of anisotropic water diffusion in the nervous system—a technical review. *NMR Biomed*. 2002;15:435–455.
35. Mädler B, Drabycz SA, Kolind SH, Whittall KP, MacKay AL. Is diffusion anisotropy an accurate monitor of myelination? Correlation of multicomponent T2 relaxation and diffusion tensor anisotropy in human brain. *Magn Reson Imaging*. 2008;26:874–888.
36. Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage*. 2003;20:1714–1722.
37. Song SK, Yoshino J, Le TQ, et al. Demyelination increases radial diffusivity in corpus callosum of mouse brain. *Neuroimage*. 2005;26:132–140.
38. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000;97:11050–11055.
39. Lerch JP, Evans AC. Cortical thickness analysis examined through power analysis and a population simulation. *Neuroimage*. 2005;24:163–173.
40. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol*. 1997;387:167–178.
41. Salthouse TA. When does age-related cognitive decline begin? *Neurobiol Aging*. 2009;30:507–514.
42. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci*. 2003;6:309–315.
43. Cancelliere A, Mangano FT, Air EL, et al. DTI values in key white matter tracts from infancy through adolescence. *AJNR Am J Neuroradiol*. 2013;34:1443–1449.
44. Flechsig P. Developmental (myelogenetic) localisation of the cerebral cortex in the human. *Lancet*. 1901;158:1027–1030.

45. Kochunov P, Glahn DC, Lancaster J, et al. Blood pressure and cerebral white matter share common genetic factors in Mexican Americans. *Hypertension*. 2011;57:330–335.
46. Westlye LT, Walhovd KB, Dale AM, et al. Differentiating maturational and aging-related changes of the cerebral cortex by use of thickness and signal intensity. *Neuroimage*. 2010;52:172–185.
47. Kochunov P, Glahn DC, Lancaster J, et al. Fractional anisotropy of cerebral white matter and thickness of cortical gray matter across the lifespan. *Neuroimage*. 2011;58:41–49.
48. Kochunov P, Williamson DE, Lancaster J, et al. Fractional anisotropy of water diffusion in cerebral white matter across the lifespan. *Neurobiol Aging*. 2012;33:9–20.
49. Kochunov P, Glahn DC, Rowland LM, et al. Testing the hypothesis of accelerated cerebral white matter aging in schizophrenia and major depression. *Biol Psychiatry*. 2013;73:482–491. doi:10.1016/j.biopsych.2012.10.002.
50. Wright S, Kochunov P, Chiappelli J, et al. Accelerated white matter aging in schizophrenia: role of white matter blood perfusion. *Neurobiol Aging*. 2014. doi:10.1016/j.neurobiolaging.2014.02.016.
51. Davis KL, Stewart DG, Friedman JI, et al. White matter changes in schizophrenia: evidence for myelin-related dysfunction. *Arch Gen Psychiatry*. 2003;60:443–456.
52. Hof PR, Haroutunian V, Friedrich VL Jr, et al. Loss and altered spatial distribution of oligodendrocytes in the superior frontal gyrus in schizophrenia. *Biol Psychiatry*. 2003;53:1075–1085.
53. Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. *Schizophr Res*. 2004;67:269–275.
54. Mitkus SN, Hyde TM, Vakkalanka R, et al. Expression of oligodendrocyte-associated genes in dorsolateral prefrontal cortex of patients with schizophrenia. *Schizophr Res*. 2008;98:129–138.
55. Uranova N, Orlovskaya D, Vikhreva O, et al. Electron microscopy of oligodendroglia in severe mental illness. *Brain Res Bull*. 2001;55:597–610.
56. Hof PR, Haroutunian V, Copland C, Davis KL, Buxbaum JD. Molecular and cellular evidence for an oligodendrocyte abnormality in schizophrenia. *Neurochem Res*. 2002;27:1193–1200.
57. Vostrikov V, Uranova N. Age-related increase in the number of oligodendrocytes is dysregulated in schizophrenia and mood disorders. *Schizophr Res Treatment*. 2011;2011:174689.
58. Uranova NA, Vikhreva OV, Rachmanova VI, Orlovskaya DD. Ultrastructural alterations of myelinated fibers and oligodendrocytes in the prefrontal cortex in schizophrenia: a postmortem morphometric study. *Schizophr Res Treatment*. 2011;2011:325789.
59. Woods BT, Yurgelun-Todd D, Goldstein JM, Seidman LJ, Tsuang MT. MRI brain abnormalities in chronic schizophrenia: one process or more? *Biol Psychiatry*. 1996;40:585–596.
60. Turetsky B, Cowell PE, Gur RC, Grossman RI, Shtasel DL, Gur RE. Frontal and temporal lobe brain volumes in schizophrenia. Relationship to symptoms and clinical subtype. *Arch Gen Psychiatry*. 1995;52:1061–1070.
61. 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.
62. Ho BC, Andreasen NC, Nopoulos P, Arndt S, Magnotta V, Flaum M. Progressive structural brain abnormalities and their relationship to clinical outcome: a longitudinal magnetic resonance imaging study early in schizophrenia. *Arch Gen Psychiatry*. 2003;60:585–594.
63. 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.
64. Horsfield MA, Jones DK. Applications of diffusion-weighted and diffusion tensor MRI to white matter diseases - a review. *NMR Biomed*. 2002;15:570–577.
65. Mori T, Ohnishi T, Hashimoto R, et al. Progressive changes of white matter integrity in schizophrenia revealed by diffusion tensor imaging. *Psychiatry Res*. 2007;154:133–145.
66. Friedman JI, Tang C, Carpenter D, et al. Diffusion tensor imaging findings in first-episode and chronic schizophrenia patients. *Am J Psychiatry*. 2008;165:1024–1032.
67. Glahn DC, Curran JE, Winkler AM, et al. High dimensional endophenotype ranking in the search for major depression risk genes. *Biol Psychiatry*. 2012;71:6–14.
68. Nazeri A, Chakravarty MM, Felsky D, et al. Alterations of superficial white matter in schizophrenia and relationship to cognitive performance. *Neuropsychopharmacology*. 2013;38:1954–1962. doi:10.1038/npp.2013.93.
69. Alba-Ferrara LM, de Erausquin GA. What does anisotropy measure? Insights from increased and decreased anisotropy in selective fiber tracts in schizophrenia. *Front Integr Neurosci*. 2013;7:9.
70. Perez-Iglesias R, Tordesillas-Gutierrez D, McGuire PK, et al. White matter integrity and cognitive impairment in first-episode psychosis. *Am J Psychiatry*. 2011;167:451–458.
71. Karlsgodt KH, Niendam TA, Bearden CE, Cannon TD. White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis. *Biol Psychiatry*. 2009;66:562–569.
72. Carletti F, Woolley JB, Bhattacharyya S, et al. Alterations in white matter evident before the onset of psychosis. *Schizophr Bull*. 2012;38:1170–1179.
73. Bloemen OJ, de Koning MB, Schmitz N, et al. White-matter markers for psychosis in a prospective ultra-high-risk cohort. *Psychol Med*. 2010;40:1297–1304.
74. Szeszko PR, Ardekani BA, Ashtari M, et al. White matter abnormalities in first-episode schizophrenia or schizoaffective disorder: a diffusion tensor imaging study. *Am J Psychiatry*. 2005;162:602–605.
75. Perez-Iglesias R, Tordesillas-Gutierrez D, Barker GJ, et al. White matter defects in first episode psychosis patients: a voxelwise analysis of diffusion tensor imaging. *Neuroimage*. 2013;49:199–204.
76. Peters BD, Blaas J, de Haan L. Diffusion tensor imaging in the early phase of schizophrenia: what have we learned? *J Psychiatr Res*. 2013;44:993–1004.
77. Nazeri A, Chakravarty MM, Felsky D, et al. Alterations of superficial white matter in schizophrenia and relationship to cognitive performance. *Neuropsychopharmacology*. 2013;38:1954–1962.
78. Kubicki M, McCarley R, Westin CF, et al. A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res*. 2007;41:15–30.
79. Hubl D, Koenig T, Strik W, et al. Pathways that make voices: white matter changes in auditory hallucinations. *Arch Gen Psychiatry*. 2004;61:658–668.
80. Jones DK, Catani M, Pierpaoli C, et al. Age effects on diffusion tensor magnetic resonance imaging tractography measures of frontal cortex connections in schizophrenia. *Hum Brain Mapp*. 2006;27:230–238.

81. Kochunov P, Chiappelli J, Wright S, et al. Multimodal white matter imaging to investigate reduced fractional anisotropy and its age-related decline in schizophrenia. *Psychiatry Res Neuroimag*. In press.
82. Kubicki M, Styner M, Bouix S, et al. Reduced interhemispheric connectivity in schizophrenia-tractography based segmentation of the corpus callosum. *Schizophr Res*. 2008;106:125–131.
83. Reis Marques T, Taylor H, Chaddock C, et al. White matter integrity as a predictor of response to treatment in first episode psychosis. *Brain*. 2014;137:172–182.
84. Hadley JA, Nenert R, Kraguljac NV, et al. Ventral tegmental area/midbrain functional connectivity and response to antipsychotic medication in schizophrenia. *Neuropsychopharmacology*. 2014;39:1020–1030.