HHS Public Access

Author manuscript

Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2016 May ; 1(3): 209–217. doi:10.1016/j.bpsc.2015.12.001.

Diffusion Imaging of White Matter In Schizophrenia: Progress and Future Directions

Katherine H. Karlsgodt

Psychiatry Research Division, Zucker Hillside Hospital and Feinstein Institute for Medical Research; Department of Psychiatry, Hofstra NorthShore LIJ School of Medicine

Abstract

Diffusion tensor imaging (DTI) is a powerful tool for the in-vivo assessment of white matter microstructure. The application of DTI methodologies to the study of schizophrenia has supported and advanced the hypothesis of schizophrenia as a disorder of disrupted connectivity. In the context of impaired structural connectivity, the extended time frame of white matter development may offer unique opportunities for treatment that can capitalize on the neural flexibility that is still present in the period leading up to and after disease onset. Therefore, it is important to gain a clear understanding of white matter deficits and how they may emerge and change across the illness. However, while there is broad consistency in the findings of white matter deficits in patients with schizophrenia, there is also a great deal of variability in specific findings across studies. In this review, the aim is to move beyond summarizing case-control analyses, to consider the many factors that may impact DTI measures, to explain variability of findings, and to explore future directions for the field. The topics explored include ways to parse DTI patterns associated with different disease subtypes, ways in which novel and established treatments might interact with or enhance white matter, ways of dissociating developmental change from the disease process itself, and understanding the role of emerging analytic methodologies.

Keywords

schizophrenia; diffusion imaging; diffusion tensor imaging; DTI; white matter; development

Since the first application of diffusion tensor imaging (DTI) to examine schizophrenia in 1998 (1), white matter (WM) investigations in psychotic disorders have become a rapidly growing area of research. Prior to the advent of DTI, our understanding of WM abnormalities in schizophrenia was necessarily limited to post mortem cellular work (2–5) and structural MRI protocols that were not easily able to differentiate individual WM tracts (6–10). With the emergence of DTI, WM could be examined with significantly enhanced

Corresponding Author: Katherine Karlsgodt, Ph.D., 75-59 263rd Street, Zucker Hillside Hospital, Glen Oaks NY 11004, kkarlsgodt@nshs.edu, Phone: 718-479-8184.

Financial Disclosures

Dr. Karlsgodt reported no biomedical financial interests or potential conflicts of interest.

detail. DTI's appeal is in part due to the growing evidence from other modalities, such as fMRI, that schizophrenia is a disorder of connectivity (11,12). In addition, there is growing awareness of schizophrenia as a developmental disorder, and WM matures up into the 4th decade of life (13, 14), later than other developmental changes such as grey matter (GM) pruning (15). This late maturation, which continues into and past the typical period of onset, may offer special opportunities for developmentally targeted intervention, but first we must be able to understand and quantify it.

Summary of Findings

Diffusion imaging is a powerful non-invasive tool for examining WM microstructure based on patterns of water diffusion in neural tissue. By observing how and in what directions diffusion is constrained, information about the surrounding tissue can be inferred. In the field of diffusion imaging, the diffusion tensor model is most commonly employed, and yields the frequently used fractional anisotropy (FA) measure, which is the ratio of the longest and shortest directions of water diffusion, and indirectly indexes "neuronal integrity", putatively reflecting both myelination and organization of the WM tracts. In addition, the secondary measures of radial (RD) and axial diffusivity (AD) are believed to more specifically index myelination and axonal organization, respectively (16–18). The majority of DTI studies in schizophrenia have shown decreased FA in long-range association tracts, including the superior longitudinal fasciculus (SLF), cingulum bundle, uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF) and arcuate fasciculus (19–21). These long connection fibers likely facilitate inter-regional communication and support a wide range of cognitive abilities. Regions connected by these tracts largely correspond to the higher order cortical regions often implicated in GM imaging studies in schizophrenia (22).

While there is a general theme of decreased FA across the DTI schizophrenia literature, there is also much variability. For instance, a subset of studies has shown no patient-control differences (20, 23–25), while others have found more global rather than regional effects (26–28). It is an open question whether this is a function of disease state (21), of developmental stage (29), or of another factor, such as medication. It is also possible that differences in scan acquisition, motion correction, and analysis may contribute. One important possibility is that over and above such technical issues, those differences exist between studies because there are different WM profiles in patients of different ages or with different patterns of cognitive deficits and symptomatology. This variability is critical to characterize, particularly since neuroimaging is an attractive candidate for use in "personalized" or "precision" medicine, which would require a deeper understanding of how imaging measures may vary at an individual level. In this review, the aim is to go beyond a simple summary of case-control analyses, to consider different factors that may impact DTI measures, and future directions for the field. These topics will include ways to parse DTI patterns associated with different disease subtypes, ways in which treatments might interact with WM, dissociating development from the disease process itself, and understanding emerging analytic methodologies.

Open Questions and Future Directions

Dissociating development and disease process

One challenge that cuts across all of the analytic and interpretive issues that may be present in psychosis research is that to some degree, the assessment of WM in schizophrenia is a moving target. Different samples include patients of different ages, and as they progress through disease stages, duration of illness and cumulative medication load become irrevocably correlated with age. Late adolescence, the period of the prodrome and often the onset of schizophrenia, is a key period for WM development. Higher order tracts, like the cingulum bundle, UF and the SLF, mature later than tracts associated with more basic functions, such as motor control (30). These later WM changes support the development of higher-order cognitive functions, which are compromised even in early phase psychotic disorders (31). It is thus important to consider that all illness related changes in young patients are occurring against the background of developmental changes that may or may not be the same as those observed in unaffected youth.

A number of studies have approached the issue of developmental vs. disease related change in schizophrenia (for more comprehensive recent reviews in this area, see Peters and Karlsgodt, 2015 (21); Kochunov and Hong, 2014 (29) and Chiapponi et al, 2013 (32)). For instance, there has been work comparing first episode (FE) and chronic patients. Some cross-sectional studies have found that WM deficits in chronic patients were either absent or less severe than in FE patients (25, 33, 34), and a meta-analysis of FE and multi-episode studies showed that longer duration of illness was associated with more severe WM abnormalities (35). Similarly, research comparing patients with either adolescent or adult onset psychosis has shown that age of onset may impact the degree of WM impairment (36–38).

Research specifically aimed at capturing lifetime development has shown disrupted early WM development in child-onset schizophrenia patients and their siblings, as well as in other young genetic and clinical risk groups (39–42). Later in life, there is potential evidence for accelerated aging, or decline after illness onset (21, 23, 43). However, this can be quite difficult to dissociate from medication effects, particularly as longitudinal studies have yielded findings of both increases and decreases in FA after antipsychotic treatment (44, 45) (46–48).

In summary, there is support for an overall pattern of disrupted WM development especially if the illness onset occurs in childhood or adolescence, and for more severe and extensive abnormalities in chronic patients than in FE patients. While we do not yet know the cause of these later changes, they may be related to abnormal or excessive aging, illness-related neurotoxicity, or medication, but possibly also confounding cohort effects. In addition, just as there may be subgroups of patients with different WM deficits in adulthood, there may be different developmental routes to each of those end points. Moving forward, our growing knowledge of the role of development presents both challenges and opportunities. First, it is important to characterize not only current age and medications, but also duration of illness as well as duration and age of onset of antipsychotic treatment. The interpretation of the results should include these factors, as well as the understanding that results from any one

sample might only represent a snapshot of a part of the larger picture across the lifespan. Furthermore, consideration of such details when designing studies will help build a more sophisticated approach to dissecting out effects of age and disease related factors. In general, work that can more clearly distinguish the roles of different factors on the development of WM deficits is very important, particularly if there may be an opportunity to target treatments by stages of illness or development.

Parsing of disease subtypes

With the growth of "big data", and steadily rising sample sizes, comes the potential to look within large groups of patients to determine whether different patterns, or subtypes, of WM deficits can be identified. The question of whether different deficit profiles exist is particularly interesting given the phenotypic variability seen in schizophrenia patients. A parsing approach is consistent with the notion of different patient sub groupings based on biological characteristics- a "biotype" approach (49), as well as NIMH Research Domain Criteria's (RDoC's) spectrum based conceptualization of psychiatric disorders. The existing literature supports the idea that phenotypic differences are reflected in WM, with findings that degree of WM impairment is correlated with cognitive impairments in schizophrenia (50–59) as well as with symptomatology (54, 60–64).

Efforts to identify subgroups of patients with different WM patterns have begun. The simplest approach is to divide patients into symptom-based groups and assess neuroanatomical differences. For example, a number of studies have shown differences between deficit and non-deficit patients, with deficit patients showing either more severe (65, 66) or different (67) WM alterations compared to controls. However, a more sophisticated approach, which relies more heavily on the existence of large data sets, is to take a large group of subjects and use data driven techniques to determine different neurobiological sub-types. Arnedo et al applied an unsupervised factorization technique to Tract Based Spatial Statistic (TBSS) skeletons and identified four different general patterns of FA changes. Each pattern was associated with different subsets of individual items from the SANS and SAPS. This interesting analysis highlights the subtlety with which both regional changes and symptom characterization must be characterized (68). Similarly, Sun et al, in a large sample of unmedicated patients, employed a cluster analysis across a series of ROIs, finding two distinct deficit patterns - one global deficit pattern and one focused in the SLF, with more severe negative symptoms observed in the global deficit group (69).

Such results may be able to elucidate the basis of the diverse findings in the schizophrenia DTI literature. They also raise the possibility that different treatments may be appropriate for patients with different neurobiological profiles, and patients in these subgroups may have different disease or developmental courses. The potential for multiple subtypes or biotypes also highlights the critical question of whether it is realistic to search for neuroimaging biomarkers or biosignatures for schizophrenia as a whole, or whether there are more likely to be a number of biomarkers, each for specific aspects or subtypes of the disorder.

Potential White Matter Interventions

Schizophrenia treatments have, up until recently, almost entirely focused on medications that alter neurotransmitter function, in particular the dopaminergic and glutamatergic systems. While much has been investigated about medication effects at a functional level, the mechanistic basis of changes in WM structure as a result of altering neurotransmitter-signaling patterns is not yet clear.

When considering which treatments might improve WM integrity and impact DTI measures, it first helps to understand the possible neural underpinnings of WM deficits. Myelin sheaths in the central nervous system are created from the lipid membranes of oligodendrocytes. First, oligodendrocyte precursor cells (OPC) settle along the tract. Once a mature oligodendrocyte develops, the cytoplasmic membrane extends out in long processes that wrap around nearby axons (70), requiring the intensive synthesis of large amounts of additional membranes. Polyunsaturated fatty acids (PUFAs) are the structural components of membrane phospholipids. EPUFAs are the essential PUFAs; they cannot be synthesized and must be consumed. Since they are limited by diet, EPUFA intake determines the rate of phosopholipid synthesis, which impacts the quantity and quality of membrane phospholipids; this is particularly important during the period of accelerated membrane growth during myelination (71, 72). If lipids are unavailable during myelin synthesis, amyelination or dysmyelination may occur (73). Interestingly, the relationship between neurons and the oligodendrocytes that myelinate them is interactive. An individual oligodendrocyte may create myelin sheaths of different thicknesses on different axons (74). For instance, level of electrical activity of neurons has been known to influence the amount of OPCs that accumulate nearby, which may encourage the myelination process to strengthen the most active networks (70, 75). A recent optogenetic study supports this notion, by showing that induced pre-motor cortex neural activity influenced not only the number of adjacent OPCs, but also increased myelin thickness and improved motor performance in the targeted region (76). Thus, the basic biology of myelination supports the consideration of two potential treatments, both of which are currently being investigated: neural stimulation techniques that might result in increased myelination of active regions, and supplementation of fatty acids to provide extra building blocks for myelination.

Stimulation Techniques—Neurostimulatory techniques such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have received increasing recent attention. ECT has a long history of use in both depression and schizophrenia (77). However, the mechanism by which ECT may have antipsychotic effects is unknown. Candidate mechanisms include effects on specific neurotransmitters, neurotrophic effects, or immunomodulatory effects, but the evidence for any of these is sparse (78). Given the evidence that neural stimulation may facilitate myelination, it is possible that myelin is one unexplored mechanism by which ECT has an effect. Accordingly, it has been shown that ECT improved FA and decreased RD in fronto-limbic tracts in depressed patients, both consistent with improved myelination (79, 80).

tDCS has somewhat more localized stimulatory effects than ECT, and may either facilitate or inhibit neuronal excitability depending on its application. While still in relatively early

stages, tDCS is thought to work via short-term modulation of membrane potential (81–83) with longer-term effects due to changes in synaptic connectivity (84). In patients with schizophrenia, there have been efforts to use tDCS to modify specific symptoms, such as auditory hallucinations (85). There may be a complex relationship between tDCS and myelination. For instance, in stroke patients, changes in FA correlated with improvements in motor impairment after treatment that included combined tDCS and behavioral modification (86). However, the directionality and strength of structural connections may either facilitate or limit the efficacy of tDCS. For instance, baseline DTI measures predicted how much stroke patients were able to benefit from tDCS, with higher FA associated with greater change (86). This raises the question of whether this treatment might be better suited to patients with relatively intact WM, for instance, older patients who are past the phase of myelination, and are without pronounced WM impairment.

Finally, cognitive remediation is being used in schizophrenia, although there are a number of different approaches, each with varying effect sizes (87, 88). While cognitive remediation is not technically stimulatory in the manner of tDCS and ECT, it does force the repeated engagement and activation of brain regions supporting cognitive function. Similar to the biological support for electrical neurostimulatory techniques as stimulators of myelination, the basic science data favors the potential of cognitive remediation to change myelination as measured by DTI. For instance, in healthy subjects, after two months of working memory training, FA increased (89). Similar effects have been seen with learning a new language (90) as well as learning physical skills in both humans (91, 92) and rats (93). However, only one study has assessed WM changes before and after cognitive remediation in schizophrenia. In a small sample Penades et al showed increases in FA in patients enrolled in a cognitive remediation course (94). This is clearly an area in need of additional research, to understand the interplay between neural changes and various treatment options.

Fatty Acid Supplementation—Administration of PUFAs as a potential supplementary treatment for psychosis has garnered a great deal of attention in recent years. A well-tolerated, low-cost, and easily accessible treatment is appealing, particularly for young populations and those at risk (95). Rationale for PUFA based treatments derives, in part, from the idea that if disrupted myelination occurs in schizophrenia, bolstering myelin formation might ameliorate these changes. In addition, patients with schizophrenia have lower blood PUFA levels than controls (96–101), potentially explaining their decreased myelination as indexed by generally lower FA. Despite the promise, clinical trials have had mixed results (102). While some reports have shown reductions in symptoms or need for medication (103–106), a meta-analysis of randomized controlled trials revealed no beneficial effect of EPUFA augmentation in established schizophrenia (107). These opposing results may be related to patient age and disease state, or as discussed earlier, to the heterogeneity of WM deficits within specific patient groups. In particular, age may be an important predictor of efficacy, as it appears that the degree of the effects of dietary lipids on myelin may be related to myelination stage (108–111), and while studies in animal models show positive effects of EPUFA supplementation on myelination, the majority of these were carried out in utero or in very early post-natal stages (112, 113). Consistent with this pattern, the early phase of schizophrenia is where some of the most favourable PUFA studies have

been conducted, particularly in at-risk populations showing prevention of transition to psychosis (114, 115). EPUFA supplementation may also provide alternative benefits, such as reduction of side effects (104, 106, 116). Thus, these putatively neuroprotective interventions may be particularly effective in prevention of psychotic disorders, but not necessarily in established schizophrenia where either the underlying neurobiological changes have already progressed too far, or the patient is past the age range of maximal myelination.

However, despite the clear role of PUFAs in myelination, there is very little data assessing WM as related to PUFA supplementation in schizophrenia. There is some evidence for an impact of fatty acid supplementation on FA and MD in normal infant development (117) and normal aging (118) and evidence that variability in PUFA related genes impacts FA across development (119). The only PUFA related DTI study in schizophrenia patients showed that in FE patients, PUFA concentration correlated positively with FA across a number of brain regions (120). This finding may support the hypothesis that lower PUFA levels in patients are directly related to the frequently observed reduction in FA in schizophrenia compared to healthy individuals. Further research may reveal whether treatments can be targeted, for instance, in an optimal age range, or in people with either low FA or low PUFA levels at baseline.

Going beyond FA

While the diffusion tensor model is the most commonly applied analysis model, particularly in clinical research, and within that model, FA is by far the most commonly used DTI measure, there has been recent movement towards employment of more sophisticated measures to assess WM, as well as movement beyond simple tensor models in general. First, in DTI studies it has become standard to report RD, AD, and MD along with FA for a deeper characterization of observed changes. Secondly, our understanding of diffusion-weighted imaging has become more sophisticated; it has become apparent that the structure of neural tissue may be too complex to be easily captured by a single diffusion tensor. One voxel may contain fibers in multiple orientations, which is a particular problem in areas where tracts intersect and there are crossing fibers. In addition, there can be intracellular and extracellular compartments within the tissue, which may have different diffusion properties as well as different biological significance. Accordingly, there has been ongoing development of alternative methods, both at the level of sequence development and at the level of analytic techniques, for better characterizing WM microstructure (see Table 1). For example, new analytic models have recently emerged such as free water imaging (FWI), diffusion kurtosis imaging (DKI), and neurite orientation distribution and density imaging (NODDI), as have new ways of acquiring data, such as high angular resolution diffusion imaging (HARDI) and diffusion spectrum imaging (DSI), that allow for new information to be gathered using the same or slightly varied scan sequences. These different methods allow for calculation of different metrics. As one example, quantitative anisotropy (QA) (121) may provide a better basis than FA for tractography and show less interference from factors like crossing fibers and has been incorporated into a number of fiber tracking algorithms.

Some of these methods have begun to be implemented in schizophrenia. DKI uses a different mathematical approach to modeling diffusion which may provide complementary information to that from FA analyses (122). A few studies have employed DKI in schizophrenia, one showing lower mean kurtosis (MK) and FA in the frontal lobe (123) and another showing decreased kurtosis measures in areas known to have complex fiber arrangements such as the corona radiata (124). DSI is another related technique aimed at clearly mapping regions of crossing fibers, and which has been able to reveal entirely new features of the organization of the WM (125–127). DSI has been only recently applied in schizophrenia, in investigations of the mirror neuron network (128), language networks (129), connectome based analyses (130), and a sibling study (128). Calculation of a permeability diffusivity index (PDI) that can putatively model more complex aspects of cellular microstructure has been used in schizophrenia, and found that membrane permeability is decreased in patients (131) and may be an important part of the accelerated aging observed in schizophrenia (132).

One alternative model that has captured the attention of schizophrenia researchers is FWI. Interest in FWI is motivated by the hypothesis that neuroinflammation plays a role in the etiology of schizophrenia (133) and that such inflammation might damage oligodendrocytes and thereby impact myelin (134, 135). FWI is sensitive to increases in extracellular water, as might be caused by edema (136, 137), and widespread changes in this measure have been shown in FE schizophrenia (138). A chronic population showed results more consistent with degeneration than active inflammation (139), which may imply that there are fundamentally different neural changes at different stages of the disorder. This technique is intriguing, as it would allow us to further understand the impact of immune factors on brain structure. Moreover, there is evidence that omega-3 fatty acids have anti-inflammatory effects (140, 141). Thus, in addition to the previously discussed role for PUFA supplementation in supporting myelination, it is also possible that the preventative effects are related to inflammation. Inflammatory markers (CRP, IL-6) have been shown to correlate with FA and RD in schizophrenia (142), and it will be of interest to explore similar markers as related to FWI.

In general, very few of these advanced techniques have been used in large-scale investigations in schizophrenia. This is in part due to the necessarily protracted time frame of studies involving recruitment of patients, as well as the increasing use of longitudinal designs, both of which can result in the use of somewhat older imaging sequences. However, moving forward, it is imperative for the field to take advantage of these methodological advances. Research using the tensor model has revealed important differences in WM in schizophrenia patients that are related to developmental change, cognitive function, and symptomatology. However while DTI has enabled a previously unprecedented look at WM microstructure, we must go still further. Initial forays into DSI, DKI, and PDI have already demonstrated that very subtle aspects of WM architecture are disrupted in schizophrenia. By revealing new microstructural details, these techniques have the potential to help not only to develop a deeper understanding of the disorder, but to identify new treatment targets that may be able to improve WM deficits.

Conclusions

After nearly two decades of diffusion imaging research in schizophrenia, our methodological approaches have made enormous strides, and a large body of evidence has accumulated to support the presence of WM deficits in schizophrenia. By carefully considering the unique biological features of WM, and gaining a better characterization of the nature of the changes seen in it in patients, DTI can help us glean important information about the biology of schizophrenia. However, there are still areas in which much more can be learned. Understanding the neuroanatomical differences in patients who may have different clusters of anatomical deficits, or in patients of different age or illness stages, is a key step towards being able to better target our interventions. Moreover, exploring the impact of novel interventions on WM can help us both better understand the treatments themselves, as well as develop new treatments. Finally, it is important to begin to include the most state-of-the-art techniques in order to best understand the connectivity changes seen in schizophrenia.

Acknowledgments

This work was funded by MH101506 (to K.H.K.). I would like to acknowledge the contributions of Drs. Kristi Clark, Maria Jalbrzikowski, and Deepak Sarpal.

References

1. Buchsbaum MS, Tang CY, Peled S, Gudbjartsson H, Lu D, Hazlett EA, et al. MRI white matter diffusion anisotropy and PET metabolic rate in schizophrenia. Neuroreport. 1998; 9:425–430. [PubMed: 9512384]
2. Akbarian S, Kim JJ, Potkin SG, Hetrick WP, Bunney WE Jr, Jones EG. Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. Archives of general psychiatry. 1996; 53:425–436. [PubMed: 8624186]
3. Kirkpatrick B, Messias NC, Conley RR, Roberts RC. Interstitial cells of the white matter in the dorsolateral prefrontal cortex in deficit and nondeficit schizophrenia. The Journal of nervous and mental disease. 2003; 191:563–567. [PubMed: 14504564]
4. Kirkpatrick B, Conley RC, Kakoyannis A, Reep RL, Roberts RC. Interstitial cells of the white matter in the inferior parietal cortex in schizophrenia: An unbiased cell-counting study. Synapse. 1999; 34:95–102. [PubMed: 10502308]
5. Highley JR, Walker MA, Esiri M, Crow TJ, Harrison PJ. Asymmetry of the Uncinate Fasciculus: A Post-mortem Study of normal Subjects and Patients with Schizophrenia. Cerebral cortex. 2002; 12:1218–1224. [PubMed: 12379610]
6. 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. Archives of general psychiatry. 1992; 49:921–926. [PubMed: 1449382]
7. Hulshoff Pol HE, Schnack HG, Bertens MG, van Haren NE, van der Tweel I, Staal WG, et al. Volume changes in gray matter in patients with schizophrenia. The American journal of psychiatry. 2002; 159:244–250. [PubMed: 11823266]
8. Okugawa G, Sedvall G, Agartz I. Reduced grey and white matter volumes in the temporal lobe of male patients with chronic schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2002; 252:120–123. [PubMed: 12192469]
9. Suzuki M, Nohara S, Hagino H, Kurokawa K, Yotsutsuji T, Kawasaki Y, et al. Regional changes in brain gray and white matter in patients with schizophrenia demonstrated with voxel-based analysis of MRI. Schizophrenia research. 2002; 55:41–54. [PubMed: 11955962]
10. Zhou SY, Suzuki M, Hagino H, Takahashi T, Kawasaki Y, Nohara S, et al. Decreased volume and increased asymmetry of the anterior limb of the internal capsule in patients with schizophrenia. Biological psychiatry. 2003; 54:427–436. [PubMed: 12915287]

11. Friston KJ, Frith CD. Schizophrenia: a disconnection syndrome? Clin Neurosci. 1995; 3:89–97. [PubMed: 7583624]
12. Bullmore ET, Frangou S, Murray RM. The dysplastic net hypothesis: an integration of developmental and dysconnectivity theories of schizophrenia. Schizophrenia research. 1997; 28:143–156. [PubMed: 9468349]
13. Yakovlev, P.; Lecours, A. Regional development of the brain in early life. Boston: Blackwell Scientific Publications; 1967.
14. Peters BD, Ikuta T, DeRosse P, John M, Burdick KE, Gruner P, et al. Age-related differences in white matter tract microstructure are associated with cognitive performance from childhood to adulthood. Biological psychiatry. 2014; 75:248–256. [PubMed: 23830668]
15. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? Journal of psychiatric research. 1982; 17:319–334. [PubMed: 7187776]
16. Wozniak JR, Lim KO. Advances in white matter imaging: a review of in vivo magnetic resonance methodologies and their applicability to the study of development and aging. Neuroscience and Biobehavioral Reviews. 2006; 30:762–774. [PubMed: 16890990]
17. 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. [PubMed: 14642481]
18. Beaulieu C, Allen PS. Determinants of anisotropic water diffusion in nerves. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 1994; 31:394–400.
19. Kyriakopoulos M, Vyas NS, Barker GJ, Chitnis XA, Frangou S. A diffusion tensor imaging study of white matter in early-onset schizophrenia. Biological psychiatry. 2008; 63:519–523. [PubMed: 17662964]
20. Wheeler AL, Voineskos AN. A review of structural neuroimaging in schizophrenia: from connectivity to connectomics. Frontiers in human neuroscience. 2014; 8:653. [PubMed: 25202257]
21. Peters BD, Karlsgodt KH. White matter development in the early stages of psychosis. Schizophrenia research. 2015; 161:61–69. [PubMed: 24893908]
22. Haijma SV, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. Schizophrenia bulletin. 2013; 39:1129–1138. [PubMed: 23042112]
23. Peters BD, Blaas J, de Haan L. Diffusion tensor imaging in the early phase of schizophrenia: what have we learned? Journal of Psychiatry Research. 2010; 44:993–1004.
24. Mulert C, Kirsch V, Whitford TJ, Alvarado J, Pelavin P, McCarley RW, et al. Hearing voices: a role of interhemispheric auditory connectivity? The world journal of biological psychiatry: the official journal of the World Federation of Societies of Biological Psychiatry. 2012; 13:153–158.
25. Kong X, Ouyang X, Tao H, Liu H, Li L, Zhao J, et al. Complementary diffusion tensor imaging study of the corpus callosum in patients with first-episode and chronic schizophrenia. J Psychiatry Neurosci. 2011; 36:120–125. [PubMed: 21138657]
26. White T, Magnotta VA, Bockholt HJ, Williams S, Wallace S, Ehrlich S, et al. Global white matter abnormalities in schizophrenia: a multisite diffusion tensor imaging study. Schizophrenia bulletin. 2011; 37:222–232. [PubMed: 19770491]
27. Reading SA, Oishi K, Redgrave GW, McEntee J, Shanahan M, Yoritomo N, et al. Diffuse abnormality of low to moderately organized white matter in schizophrenia. Brain connectivity. 2011; 1:511–519. [PubMed: 22500774]
28. 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. Archives of general psychiatry. 1999; 56:367–374. [PubMed: 10197834]
29. Kochunov P, Hong LE. Neurodevelopmental and neurodegenerative models of schizophrenia: white matter at the center stage. Schizophrenia bulletin. 2014; 40:721–728. [PubMed: 24870447]
30. Yakovlev, PI.; Lecours, AR. The myelogenetic cycles of regional maturation of the brain. In: Minkowski, A., editor. Regional Development of the Brain in Early Life. Oxford: Blackwell; 1966. p. 3-70.

31. Aas M, Dazzan P, Mondelli V, Melle I, Murray RM, Pariante CM. A systematic review of cognitive function in first-episode psychosis, including a discussion on childhood trauma, stress, and inflammation. Frontiers in psychiatry. 2014; 4:182. [PubMed: 24409157]
32. Chiapponi C, Piras F, Fagioli S, Caltagirone C, Spalletta G. Age-related brain trajectories in schizophrenia: a systematic review of structural MRI studies. Psychiatry research. 2013; 214:83–93. [PubMed: 23972726]
33. Friedman JI, Tang C, Carpenter D, Buchsbaum M, Schmeidler J, Flanagan L, et al. Diffusion tensor imaging findings in first-episode and chronic schizophrenia patients. The American journal of psychiatry. 2008; 165:1024–1032. [PubMed: 18558643]
34. Collinson SL, Gan SC, Woon PS, Kuswanto C, Sum MY, Yang GL, et al. Corpus callosum morphology in first-episode and chronic schizophrenia: combined magnetic resonance and diffusion tensor imaging study of Chinese Singaporean patients. The British journal of psychiatry: the journal of mental science. 2014; 204:55–60. [PubMed: 24202961]
35. Bora E, Fornito A, Radua J, Walterfang M, Seal M, Wood SJ, et al. Neuroanatomical abnormalities in schizophrenia: a multimodal voxelwise meta-analysis and meta-regression analysis. Schizophrenia research. 2011; 127:46–57. [PubMed: 21300524]
36. Douaud G, Mackay C, Andersson J, James S, Quested D, Ray MK, et al. Schizophrenia delays and alters maturation of the brain in adolescence. Brain: a journal of neurology. 2009; 132:2437–2448. [PubMed: 19477963]
37. Kyriakopoulos M, Frangou S. Recent diffusion tensor imaging findings in early stages of schizophrenia. Curr Opin Psychiatry. 2009; 22:168–176. [PubMed: 19553871]
38. Schneiderman JS, Buchsbaum MS, Haznedar MM, Hazlett EA, Brickman AM, Shihabuddin L, et al. Age and diffusion tensor anisotropy in adolescent and adult patients with schizophrenia. NeuroImage. 2009; 45:662–671. [PubMed: 19168139]
39. Gogtay N, Hua X, Stidd R, Boyle CP, Lee S, Weisinger B, et al. Delayed white matter growth trajectory in young nonpsychotic siblings of patients with childhood-onset schizophrenia. Archives of general psychiatry. 2012; 69:875–884. [PubMed: 22945617]
40. Karlsgodt K, Niendam TA, Bearden CE, Cannon TD. White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis. Biological psychiatry. 2009; 66:562–569. [PubMed: 19423081]
41. Carletti F, Woolley JB, Bhattacharyya S, Perez-Iglesias R, Fusar Poli P, Valmaggia L, et al. Alterations in white matter evident before the onset of psychosis. Schizophrenia bulletin. 2012; 38:1170–1179. [PubMed: 22472474]
42. Addington AM, Gornick MC, Shaw P, Seal J, Gogtay N, Greenstein D, et al. Neuregulin 1 (8p12) and childhood-onset schizophrenia: susceptibility haplotypes for diagnosis and brain developmental trajectories. Molecular psychiatry. 2007; 12:195–205. [PubMed: 17033632]
43. Kochunov P, Glahn DC, Rowland LM, Olvera RL, Winkler A, Yang YH, et al. Testing the hypothesis of accelerated cerebral white matter aging in schizophrenia and major depression. Biological psychiatry. 2013; 73:482–491. [PubMed: 23200529]
44. Reis Marques T, Taylor H, Chaddock C, Dell'acqua F, Handley R, Reinders AA, et al. White matter integrity as a predictor of response to treatment in first episode psychosis. Brain: a journal of neurology. 2014; 137:172–182. [PubMed: 24253201]
45. Ozcelik-Eroglu E, Ertugrul A, Oguz KK, Has AC, Karahan S, Yazici MK. Effect of clozapine on white matter integrity in patients with schizophrenia: a diffusion tensor imaging study. Psychiatry research. 2014; 223:226–235. [PubMed: 25012780]
46. Szeszko PR, Robinson DG, Ikuta T, Peters BD, Gallego JA, Kane J, et al. White matter changes associated with antipsychotic treatment in first-episode psychosis. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2014; 39:1324–1331. [PubMed: 24549105]
47. Wang Q, Cheung C, Deng W, Li M, Huang C, Ma X, et al. White-matter microstructure in previously drug-naive patients with schizophrenia after 6 weeks of treatment. Psychological medicine. 2013; 43:2301–2309. [PubMed: 23442742]

48. Ho BC, Andreasen NC, Ziebell S, Pierson R, Magnotta V. Long-term antipsychotic treatment and brain volumes: a longitudinal study of first-episode schizophrenia. Archives of general psychiatry. 2011; 68:128–137. [PubMed: 21300943]
49. Clementz BA, Sweeney JA, Hamm JP, Ivleva EL, Ethridge EL, Pearlson GD, et al. Identification of disting psychosis biotypes using brain-based biomarkers. Amercan Journal of Psychiatry. in press.
50. Karlsgodt K, van Erp TG, Poldrack R, Bearden CE, Nuechterlein KH, Cannon TD. Diffusion tensor imaging of the superior longitudinal fasciculus and working memory in recent-onset schizophrenia. Biological psychiatry. 2008; 63:512–518. [PubMed: 17720147]
51. Karbasforoushan H, Duffy B, Blackford JU, Woodward ND. Processing speed impairment in schizophrenia is mediated by white matter integrity. Psychological medicine. 2015; 45:109–120. [PubMed: 25066842]
52. Epstein KA, Cullen KR, Mueller BA, Robinson P, Lee S, Kumra S. White matter abnormalities and cognitive impairment in early-onset schizophrenia-spectrum disorders. Journal of the American Academy of Child and Adolescent Psychiatry. 2014; 53:362–372. e361–362. [PubMed: 24565363]
53. Hayakawa YK, Kirino E, Shimoji K, Kamagata K, Hori M, Ito K, et al. Anterior cingulate abnormality as a neural correlate of mismatch negativity in schizophrenia. Neuropsychobiology. 2013; 68:197–204. [PubMed: 24192500]
54. Szeszko PR, Robinson DG, Ashtari M, Vogel J, Betensky J, Sevy S, et al. Clinical and neuropsychological correlates of white matter abnormalities in recent onset schizophrenia. Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology. 2008; 33:976–984. [PubMed: 17581532]
55. Perez-Iglesias R, Tordesillas-Gutierrez D, McGuire PK, Barker GJ, Roiz-Santianez R, Mata I, et al. White matter integrity and cognitive impairment in first-episode psychosis. The American journal of psychiatry. 2010; 167:451–458. [PubMed: 20160006]
56. Lim KO, Ardekani BA, Nierenberg J, Butler PD, Javitt DC, Hoptman MJ. Voxelwise correlational analyses of white matter integrity in multiple cognitive domains in schizophrenia. The American journal of psychiatry. 2006; 163:2008–2010. [PubMed: 17074956]
57. Liu X, Lai Y, Wang X, Hao C, Chen L, Zhou Z, et al. Reduced white matter integrity and cognitive deficit in never-medicated chronic schizophrenia: a diffusion tensor study using TBSS. Behavioural brain research. 2013; 252:157–163. [PubMed: 23747517]
58. Mamah D, Conturo TE, Harms MP, Akbudak E, Wang L, McMichael AR, et al. Anterior thalamic radiation integrity in schizophrenia: a diffusion-tensor imaging study. Psychiatry research. 2010; 183:144–150. [PubMed: 20619618]
59. Kubicki M, Niznikiewicz M, Connor E, Ungar L, Nestor P, Bouix S, et al. Relationship Between White Matter Integrity, Attention, and Memory in Schizophrenia: A Diffusion Tensor Imaging Study. Brain imaging and behavior. 2009; 3:191–201. [PubMed: 20556231]
60. Fitzsimmons J, Schneiderman JS, Whitford TJ, Swisher T, Niznikiewicz MA, Pelavin PE, et al. Cingulum bundle diffusivity and delusions of reference in first episode and chronic schizophrenia. Psychiatry research. 2014; 224:124–132. [PubMed: 25174840]
61. Ohtani T, Bouix S, Lyall AE, Hosokawa T, Saito Y, Melonakos E, et al. Abnormal white matter connections between medial frontal regions predict symptoms in patients with first episode schizophrenia. Cortex; a journal devoted to the study of the nervous system and behavior. 2015; 71:264–276.
62. Whitford TJ, Kubicki M, Pelavin PE, Lucia D, Schneiderman JS, Pantelis C, et al. Cingulum bundle integrity associated with delusions of control in schizophrenia: Preliminary evidence from diffusion-tensor tractography. Schizophrenia research. 2015; 161:36–41. [PubMed: 25311780]
63. Ohtani T, Bouix S, Hosokawa T, Saito Y, Eckbo R, Ballinger T, et al. Abnormalities in white matter connections between orbitofrontal cortex and anterior cingulate cortex and their associations with negative symptoms in schizophrenia: a DTI study. Schizophrenia research. 2014; 157:190–197. [PubMed: 24962436]
64. Wolkin A, Choi SJ, Szilagyi S, Sanfilipo M, Rotrosen JP, Lim KO. Inferior frontal white matter anisotropy and negative symptoms of schizophrenia: a diffusion tensor imaging study. The American journal of psychiatry. 2003; 160:572–574. [PubMed: 12611842]

65. Voineskos AN, Foussias G, Lerch J, Felsky D, Remington G, Rajji TK, et al. Neuroimaging evidence for the deficit subtype of schizophrenia. JAMA psychiatry. 2013; 70:472–480. [PubMed: 23467781]

66. Kitis O, Ozalay O, Zengin EB, Haznedaroglu D, Eker MC, Yalvac D, et al. Reduced left uncinate fasciculus fractional anisotropy in deficit schizophrenia but not in non-deficit schizophrenia. Psychiatry and clinical neurosciences. 2012; 66:34–43. [PubMed: 22250608]

67. Spalletta G, De Rossi P, Piras F, Iorio M, Dacquino C, Scanu F, et al. Brain white matter microstructure in deficit and non-deficit subtypes of schizophrenia. Psychiatry research. 2015; 231:252–261. [PubMed: 25649975]

68. Arnedo J, Mamah D, Baranger DA, Harms MP, Barch DM, Svrakic DM, et al. Decomposition of brain diffusion imaging data uncovers latent schizophrenias with distinct patterns of white matter anisotropy. NeuroImage. 2015; 120:43–54. [PubMed: 26151103]

69. Sun H, Lui S, Yao L, Deng W, Xiao Y, Zhang W, et al. Two Patterns of White Matter Abnormalities in Medication-Naive Patients With First-Episode Schizophrenia Revealed by Diffusion Tensor Imaging and Cluster Analysis. JAMA psychiatry. 2015; 72:678–686. [PubMed: 25993492]

70. Baumann N, Pham-Dinh D. Biology of oligodendrocyte and myelin in the mammalian central nervous system. Physiological Reviews. 2001; 81:871–927. [PubMed: 11274346]

71. Arvindakshan M, Ghate M, Ranjekar PK, Evans DR, Mahadik SP. Supplementation with a combination of omega-3 fatty acids and antioxidants (vitamins E and C) improves the outcome of schizophrenia. Schizophrenia research. 2003; 62:195–204. [PubMed: 12837515]

72. Sastry PS. Lipids of nervous tissue: composition and metabolism. Prog Lipid Res. 1985; 24:69–176. [PubMed: 3916238]

73. Kobayashi T, Shinnoh N, Kondo A, Yamada T. Adrenoleukodystrophy protein-deficient mice represent abnormality of very long chain fatty acid metabolism. Biochemical and Biophysical Research Communications. 1997; 232:631–636. [PubMed: 9126326]

74. Waxman SG, Sims TJ. Specificity in central myelination: evidence for local regulation of myelin thickness. Brain research. 1984; 292:179–185. [PubMed: 6697207]

75. Barres BA, Raff MC. Axonal control of oligodendrocyte development. Journal of Cell Biology. 1999; 147:1123–1128. [PubMed: 10601327]

76. Gibson EM, Purger D, Mount CW, Goldstein AK, Lin GL, Wood LS, et al. Neuronal activity promotes oligodendrogenesis and adaptive myelination in the mammalian brain. Science. 2014; 344:1252304. [PubMed: 24727982]

77. Pompili M, Lester D, Dominici G, Longo L, Marconi G, Forte A, et al. Indications for electroconvulsive treatment in schizophrenia: a systematic review. Schizophrenia research. 2013; 146:1–9. [PubMed: 23499244]

78. Rosenquist PB, Miller B, Pillai A. The antipsychotic effects of ECT: a review of possible mechanisms. The journal of ECT. 2014; 30:125–131. [PubMed: 24810776]

79. Lyden H, Espinoza RT, Pirnia T, Clark K, Joshi SH, Leaver AM, et al. Electroconvulsive therapy mediates neuroplasticity of white matter microstructure in major depression. Translational psychiatry. 2014; 4:e380. [PubMed: 24713861]

80. Nobuhara K, Okugawa G, Minami T, Takase K, Yoshida T, Yagyu T, et al. Effects of electroconvulsive therapy on frontal white matter in late-life depression: a diffusion tensor imaging study. Neuropsychobiology. 2004; 50:48–53. [PubMed: 15179020]

81. Bindman LJ, Lippold OC, Redfearn JW. The Action of Brief Polarizing Currents on the Cerebral Cortex of the Rat (1) during Current Flow and (2) in the Production of Long-Lasting after-Effects. J Physiol. 1964; 172:369–382. [PubMed: 14199369]

82. Bikson M, Inoue M, Akiyama H, Deans JK, Fox JE, Miyakawa H, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. J Physiol. 2004; 557:175–190. [PubMed: 14978199]

83. Paulus W. Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. Neuropsychol Rehabil. 2011; 21:602–617. [PubMed: 21819181]

84. Tortella G, Casati R, Aparicio LV, Mantovani A, Senco N, D'Urso G, et al. Transcranial direct current stimulation in psychiatric disorders. World journal of psychiatry. 2015; 5:88–102. [PubMed: 25815258]
85. Mondino M, Haesebaert F, Poulet E, Suaud-Chagny MF, Brunelin J. Fronto-temporal transcranial Direct Current Stimulation (tDCS) reduces source-monitoring deficits and auditory hallucinations in patients with schizophrenia. Schizophrenia research. 2015; 161:515–516. [PubMed: 25468175]
86. Zheng X, Schlaug G. Structural white matter changes in descending motor tracts correlate with improvements in motor impairment after undergoing a treatment course of tDCS and physical therapy. Frontiers in human neuroscience. 2015; 9:229. [PubMed: 25983684]
87. Medalia A, Saperstein AM. Does cognitive remediation for schizophrenia improve functional outcomes? Curr Opin Psychiatry. 2013; 26:151–157. [PubMed: 23318663]
88. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. The American journal of psychiatry. 2011; 168:472–485. [PubMed: 21406461]
89. Takeuchi H, Sekiguchi A, Taki Y, Yokoyama S, Yomogida Y, Komuro N, et al. Training of working memory impacts structural connectivity. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2010; 30:3297–3303. [PubMed: 20203189]
90. Schlegel AA, Rudelson JJ, Tse PU. White matter structure changes as adults learn a second language. Journal of cognitive neuroscience. 2012; 24:1664–1670. [PubMed: 22571459]
91. Scholz J, Klein MC, Behrens TE, Johansen-Berg H. Training induces changes in white-matter architecture. Nature neuroscience. 2009; 12:1370–1371. [PubMed: 19820707]
92. Taubert M, Draganski B, Anwander A, Muller K, Horstmann A, Villringer A, et al. Dynamic properties of human brain structure: learning-related changes in cortical areas and associated fiber connections. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2010; 30:11670–11677. [PubMed: 20810887]
93. Sampaio-Baptista C, Khrapitchev AA, Foxley S, Schlagheck T, Scholz J, Jbabdi S, et al. Motor skill learning induces changes in white matter microstructure and myelination. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2013; 33:19499–19503. [PubMed: 24336716]
94. Penades R, Pujol N, Catalan R, Massana G, Rametti G, Garcia-Rizo C, et al. Brain effects of cognitive remediation therapy in schizophrenia: a structural and functional neuroimaging study. Biological psychiatry. 2013; 73:1015–1023. [PubMed: 23452665]
95. Schlogelhofer M, Amminger GP, Schaefer MR, Fusar-Poli P, Smesny S, McGorry P, et al. Polyunsaturated fatty acids in emerging psychosis: a safer alternative? Early intervention in psychiatry. 2014; 8:199–208. [PubMed: 24861004]
96. Assies J, Lieverse R, Vreken P, Wanders RJ, Dingemans PM, Linszen DH. Significantly reduced docosahexaenoic and docosapentaenoic acid concentrations in erythrocyte membranes from schizophrenic patients compared with a carefully matched control group. Biological psychiatry. 2001; 49:510–522. [PubMed: 11257236]
97. Evans DR, Parikh VV, Khan MM, Coussons C, Buckley PF, Mahadik SP. Red blood cell membrane essential fatty acid metabolism in early psychotic patients following antipsychotic drug treatment. Prostaglandins, leukotrienes, and essential fatty acids. 2003; 69:393–399.
98. Reddy RD, Keshavan MS, Yao JK. Reduced red blood cell membrane essential polyunsaturated fatty acids in first episode schizophrenia at neuroleptic-naive baseline. Schizophrenia bulletin. 2004; 30:901–911. [PubMed: 15957200]
99. Khan MM, Evans DR, Gunna V, Scheffer RE, Parikh VV, Mahadik SP. Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics. Schizophrenia research. 2002; 58:1–10. [PubMed: 12363384]
100. Arvindakshan M, Sitasawad S, Debsikdar V, Ghate M, Evans D, Horrobin DF, et al. Essential polyunsaturated fatty acid and lipid peroxide levels in never-medicated and medicated schizophrenia patients. Biological psychiatry. 2003; 53:56–64. [PubMed: 12513945]
101. Yao JK, Leonard S, Reddy RD. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. Schizophrenia research. 2000; 42:7–17. [PubMed: 10706981]

102. Fenton WS, Hibbeln J, Knable M. Essential fatty acids, lipid membrane abnormalities, and the diagnosis and treatment of schizophrenia. Biological psychiatry. 2000; 47:8–21. [PubMed: 10650444]
103. Peet M, Brind J, Ramchand CN, Shah S, Vankar GK. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. Schizophrenia research. 2001; 49:243–251. [PubMed: 11356585]
104. Emsley R, Myburgh C, Oosthuizen P, van Rensburg SJ. Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. The American journal of psychiatry. 2002; 159:1596–1598. [PubMed: 12202284]
105. Peet M, Horrobin DF. A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. Journal of psychiatric research. 2002; 36:7–18. [PubMed: 11755456]
106. Berger GE, Proffitt TM, McConchie M, Yuen H, Wood SJ, Amminger GP, et al. Ethyl-eicosapentaenoic acid in first-episode psychosis: a randomized, placebo-controlled trial. The Journal of clinical psychiatry. 2007; 68:1867–1875. [PubMed: 18162017]
107. Fusar-Poli P, Berger G. Eicosapentaenoic acid interventions in schizophrenia: meta-analysis of randomized, placebo-controlled studies. Journal of clinical psychopharmacology. 2012; 32:179–185. [PubMed: 22367656]
108. Wiggins RC. Myelin development and nutritional insufficiency. Brain research. 1982; 257:151–175. [PubMed: 7049327]
109. McKenna MC, Campagnoni AT. Effect of pre- and postnatal essential fatty acid deficiency on brain development and myelination. Journal of Nutrition. 1979; 109:1195–1204. [PubMed: 448463]
110. Berkow SE, Campagnoni AT. Essential fatty acid deficiency: effects of cross-fostering mice at birth on brain growth and myelination. Journal of Nutrition. 1981; 111:886–894. [PubMed: 7229737]
111. DeWille JW, Farmer SJ. Postnatal dietary fat influences mRNAS involved in myelination. Developmental neuroscience. 1992; 14:61–68. [PubMed: 1350977]
112. Salvati S, Attorri L, Avellino C, Di Biase A, Sanchez M. Diet, lipids and brain development. Developmental neuroscience. 2000; 22:481–487. [PubMed: 11111166]
113. Connor JR, Menzies SL. Altered cellular distribution of iron in the central nervous system of myelin deficient rats. Neuroscience. 1990; 34:265–271. [PubMed: 2325851]
114. Amminger GP, Schafer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Archives of general psychiatry. 2010; 67:146–154. [PubMed: 20124114]
115. Amminger GP, Schafer MR, Schlogelhofer M, Klier CM, McGorry PD. Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. Nature communications. 2015; 6:7934.
116. Pisano S, Gritti A, Catone G, Pascotto A. Antipsychotic-induced dyslipidemia treated with omega 3 fatty acid supplement in an 11-year-old psychotic child: a 1-year follow-up. Journal of child and adolescent psychopharmacology. 2013; 23:139–141. [PubMed: 23480323]
117. Strommen K, Blakstad EW, Moltu SJ, Almaas AN, Westerberg AC, Amlien IK, et al. Enhanced nutrient supply to very low birth weight infants is associated with improved white matter maturation and head growth. Neonatology. 2015; 107:68–75. [PubMed: 25401387]
118. Witte AV, Kerti L, Hermannstadter HM, Fiebach JB, Schreiber SJ, Schuchardt JP, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. Cerebral cortex. 2014; 24:3059–3068. [PubMed: 23796946]
119. Peters BD, Voineskos AN, Szeszko PR, Lett TA, DeRosse P, Guha S, et al. Brain white matter development is associated with a human-specific haplotype increasing the synthesis of long chain fatty acids. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2014; 34:6367–6376. [PubMed: 24790207]
120. Peters BD, Machielsen MW, Hoen WP, Caan MW, Malhotra AK, Szeszko PR, et al. Polyunsaturated fatty acid concentration predicts myelin integrity in early-phase psychosis. Schizophrenia bulletin. 2013; 39:830–838. [PubMed: 22927668]

121. Yeh FC, Verstynen TD, Wang Y, Fernandez-Miranda JC, Tseng WY. Deterministic diffusion fiber tracking improved by quantitative anisotropy. PloS one. 2013; 8:e80713. [PubMed: 24348913]
122. Jensen JH, Helpern JA. MRI quantification of non-Gaussian water diffusion by kurtosis analysis. NMR Biomed. 2010; 23:698–710. [PubMed: 20632416]
123. Ramani, A.; JHJ; Szulc, KU.; Ali, O.; Hu, C.; Lu, H., et al. Assessment of abnormalities in the cerebral microstructure of schizophrenia patients: a diffusional kurtosis imaging study. Proceedings of the 15th Annual Meeting of ISMRM; Berlin, German. 2007.
124. Zhu J, Zhuo C, Qin W, Wang D, Ma X, Zhou Y, et al. Performances of diffusion kurtosis imaging and diffusion tensor imaging in detecting white matter abnormality in schizophrenia. NeuroImage Clinical. 2015; 7:170–176. [PubMed: 25610778]
125. Wedeen VJ, Hagmann P, Tseng WY, Reese TG, Weisskoff RM. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2005; 54:1377–1386.
126. Wedeen VJ, Wang RP, Schmahmann JD, Benner T, Tseng WY, Dai G, et al. Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. NeuroImage. 2008; 41:1267–1277. [PubMed: 18495497]
127. Wedeen VJ, Rosene DL, Wang R, Dai G, Mortazavi F, Hagmann P, et al. The geometric structure of the brain fiber pathways. Science. 2012; 335:1628–1634. [PubMed: 22461612]
128. Wu CH, Hwang TJ, Chen YJ, Hsu YC, Lo YC, Liu CM, et al. Altered integrity of the right arcuate fasciculus as a trait marker of schizophrenia: a sibling study using tractography-based analysis of the whole brain. Human brain mapping. 2015; 36:1065–1076. [PubMed: 25366810]
129. Wu CH, Hwang TJ, Chen PJ, Chou TL, Hsu YC, Liu CM, et al. Reduced structural integrity and functional lateralization of the dorsal language pathway correlate with hallucinations in schizophrenia: a combined diffusion spectrum imaging and functional magnetic resonance imaging study. Psychiatry research. 2014; 224:303–310. [PubMed: 25241043]
130. Griffa A, Baumann PS, Ferrari C, Do KQ, Conus P, Thiran JP, et al. Characterizing the connectome in schizophrenia with diffusion spectrum imaging. Human brain mapping. 2015; 36:354–366. [PubMed: 25213204]
131. Kochunov P, Chiappelli J, Hong LE. Permeability-diffusivity modeling vs. fractional anisotropy on white matter integrity assessment and application in schizophrenia. NeuroImage Clinical. 2013; 3:18–26. [PubMed: 24179845]
132. Kochunov P, Chiappelli J, Wright SN, Rowland LM, Patel B, Wijtenburg SA, et al. Multimodal white matter imaging to investigate reduced fractional anisotropy and its age-related decline in schizophrenia. Psychiatry research. 2014; 223:148–156. [PubMed: 24909602]
133. Najjar S, Pearlman DM. Neuroinflammation and white matter pathology in schizophrenia: systematic review. Schizophrenia research. 2015; 161:102–112. [PubMed: 24948485]
134. Deng W. Neurobiology of injury to the developing brain. Nature reviews Neurology. 2010; 6:328–336. [PubMed: 20479779]
135. Chew LJ, Fusar-Poli P, Schmitz T. Oligodendroglial alterations and the role of microglia in white matter injury: relevance to schizophrenia. Developmental neuroscience. 2013; 35:102–129. [PubMed: 23446060]
136. Kantrowitz JT, Revheim N, Pasternak R, Silipo G, Javitt DC. It's all in the cards: effect of stimulus manipulation on Wisconsin Card Sorting Test performance in schizophrenia. Psychiatry research. 2009; 168:198–204. [PubMed: 19573928]
137. Pasternak O, Kubicki M, Shenton ME. In vivo imaging of neuroinflammation in schizophrenia. Schizophrenia research. 2015
138. Pasternak O, Westin CF, Bouix S, Seidman LJ, Goldstein JM, Woo TU, et al. Excessive extracellular volume reveals a neurodegenerative pattern in schizophrenia onset. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2012; 32:17365–17372. [PubMed: 23197727]
139. Pasternak O, Westin CF, Dahlben B, Bouix S, Kubicki M. The extent of diffusion MRI markers of neuroinflammation and white matter deterioration in chronic schizophrenia. Schizophrenia research. 2015; 161:113–118. [PubMed: 25126717]

140. Yao JK, van Kammen DP. Membrane phospholipids and cytokine interaction in schizophrenia. International review of neurobiology. 2004; 59:297–326. [PubMed: 15006493]

141. Schober ME, Requena DF, Abdullah OM, Casper TC, Beachy J, Malleske D, et al. Dietary Docosahexaenoic Acid Improves Cognitive Function, Tissue Sparing, and Magnetic Resonance Imaging Indices of Edema and White Matter Injury in the Immature Rat after Traumatic Brain Injury. Journal of neurotrauma. 2015

142. Prasad KM, Upton CH, Nimgaonkar VL, Keshavan MS. Differential susceptibility of white matter tracts to inflammatory mediators in schizophrenia: an integrated DTI study. Schizophrenia research. 2015; 161:119–125. [PubMed: 25449712]

143. Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2002; 48:577–582.

144. Lin CP, Wedeen VJ, Chen JH, Yao C, Tseng WY. Validation of diffusion spectrum magnetic resonance imaging with manganese-enhanced rat optic tracts and ex vivo phantoms. NeuroImage. 2003; 19:482–495. [PubMed: 12880782]

145. Jensen JH, Helpern JA, Ramani A, Lu H, Kaczynski K. Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2005; 53:1432–1440.

146. Sukstanskii AL, Ackerman JJ, Yablonskiy DA. Effects of barrier-induced nuclear spin magnetization inhomogeneities on diffusion-attenuated MR signal. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine. 2003; 50:735–742.

147. Sukstanskii AL, Yablonskiy DA, Ackerman JJ. Effects of permeable boundaries on the diffusion-attenuated MR signal: insights from a one-dimensional model. Journal of magnetic resonance. 2004; 170:56–66. [PubMed: 15324758]

148. Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC. NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. NeuroImage. 2012; 61:1000–1016. [PubMed: 22484410]

149. Sepehrband F, Clark KA, Ullmann JF, Kurniawan ND, Leanage G, Reutens DC, et al. Brain tissue compartment density estimated using diffusion-weighted MRI yields tissue parameters consistent with histology. Human brain mapping. 2015; 36:3687–3702. [PubMed: 26096639]

150. Yeh FC, Wedeen VJ, Tseng WY. Generalized q-sampling imaging. IEEE Trans Med Imaging. 2010; 29:1626–1635. [PubMed: 20304721]

Table 1

Advanced diffusion imaging methods and models

Acronym	Name	How it differs from the traditional diffusion tensor approach
HARDI	High Angular Resolution Diffusion Imaging	The tensor model is limited by the assumption that each voxel contains a single ellipsoid, representing one primary direction. By using very high numbers of directions and repetitions, HARDI acquisition allows the estimation of multiple directions per voxel, as would be seen in the case of crossing fibers (143)
DSI	Diffusion Spectrum Imaging	DSI sequences also were developed to address the issue of crossing fibers and complex tissue. DSI analyses can describe diffusion with a probability density function (PDF) and orientation distribution function (ODF) and thus define multiple directions of diffusivity (125, 144),
DKI	Diffusion Kurtosis Imaging	DKI models require multiple b-values (at least 3) during acquisition to quantify the degree to which the patterns of diffusion are non-Gaussian, for instance because of the presence of intracellular and extracellular compartments, or tissue barriers such as cell membranes. This index may provide additional tissue characterization, including of heterogeneity of diffusivity, a potential indicator of pathology (122, 145)
FWI	Free Water Imaging	FWI specifically models the diffusion of freely diffusing extracellular water or fluid. The free-water can be looked at as a putative measure of inflammation, or can be removed from the signal to give a more specific measure of FA within tissue (138)
PDI	Permeability Diffusivity Index	The diffusion tensor model assumes that what is measured is a single pool of diffusing water, and thus uses an overly simplistic mono-exponential function to describe signal decay due to diffusion. PDI uses a more complex bi-exponential model of the diffusion signal, which is sensitive to permeability of cellular membranes and may index aspects of tissue microstructure not captured by FA (146, 147)
NODDI	Neurite Orientation Distribution and Density Imaging	NODDI models intracellular, extracellular and CSF tissue compartments, to characterize neurite density and orientation distribution, allowing a more detailed view of WM microstructure and better estimate of myelination than FA (148, 149)
QA	Quantitative Anisotropy	QA is a metric calculated using the distribution of spins that diffuse along the fiber orientation. QA is less sensitive to partial volume effects and has been implemented in a number of fiber tracking algorithms as it may more accurately determine tract termination locations than FA (121, 150)