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*in vivo q*uantification of white matter microstructure for use in aging: A focus on two emerging techniques

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Abstract

Human brain imaging has seen many advances in the quantification of white matter *in vivo*. For example, these advances have revealed the association between white matter damage and vascular disease as well as their impact on risk for and development of dementia and depression in an aging population. Current neuroimaging methods to quantify white matter damage provide a foundation for understanding such age-related neuropathology; however, these methods are not as adept at determining the underlying microstructural abnormalities signaling at risk tissue or driving white matter damage in the aging brain. This review will begin with a brief overview of the use of diffusion tensor imaging (DTI) in understanding white matter alterations in aging before focusing in more detail on select advances in both diffusion-based methods and multi-component relaxometry techniques for imaging white matter microstructural integrity within myelin sheaths and the axons they encase. While DTI greatly extended the field of white matter interrogation, these more recent technological advances will add clarity to the underlying microstructural mechanisms that contribute to white matter damage. More specifically, the methods highlighted in this review may prove more sensitive (and specific) for determining the contribution of myelin versus axonal integrity to the aging of white matter in brain.

Keywords

multi-component relaxometry; diffusion tensor imaging; myelin; axons; aging

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White matter damage, detectable on T2-weighted magnetic resonance imaging (MRI) as white matter hyperintensities, becomes increasingly common with advancing age (1). Present in over 40% of non-demented healthy controls at autopsy, such white matter damage is associated with increased risk for cognitive and affective declines. Though the microstructural basis for age-associated white matter damage is not fully known, MRI-based neuropathology studies have shown that when confluent, white matter hyperintensities usually represent cerebral small vessel disease (CSVD) (2). Vascular risk factors for CSVD include hypertension, diabetes and hypercholesterolemia (3,4) and 'vascular risk-factor-related' CSVD has been cited as a distinct pathological feature of white matter damage in the aging brain (5). In conjunction or isolation, vascular risk factors promote white matter damage that negatively impact cognition in normal (6) and pathological aging (7). This combination of white matter damage and cognitive impairment associated with vascular risk increases the risk for and development of dementia (8,9) as well as depression (10,11).

The extent of white matter damage associated with vascular risk in aging is difficult to determine since the T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) MRI sequences used for white matter hyperintensity quantification are unable to detect subtle, but potentially critical structural alterations in otherwise normal appearing white matter. For example, in patients with hypertension normal appearing white matter as seen on conventional MRI shows reductions in cerebral blood flow when compared to normal controls (12) and white matter biochemical changes akin to individuals with dementia (13) suggesting at risk tissue can be identified before T2-detectable white matter damage occur. Thus, by the time white matter neuropathology is detected via traditional structural imaging, the opportunity for preventative measures such as aggressive vascular risk factor control may have passed. Early detection of subtle changes in white matter combined with an increased understanding of the underlying microstructural damage driving these changes may make it possible to devise interventions that will slow or even stop the progression of white matter neuropathology in at-risk older adults.

This review begins with a brief overview of the use of diffusion tensor imaging (DTI) to understand white matter alterations in aging and quickly moves to a more targeted discussion of select advances in both diffusion imaging and multi-component relaxometry (MCR) for visualizing white matter microstructure including myelin sheaths and the axons they encase. We begin with DTI because it revealed that normal appearing white matter as seen on conventional T2-weighted MRI has diffusion-specific changes that allow for a more detailed measure of tissue structure and organization (14). While DTI-derived metrics of fractional anisotropy, axial and radial diffusivity greatly extended the field of white matter interrogation; more recent technological advances including MCR may add more sensitive and specific information to the underlying microstructural mechanisms contributing to white matter damage in aging not hitherto obtainable *in vivo*.

DTI of White Matter: Initial metrics of white matter damage

DTI is one technique to determine subtle alterations in white matter *in vivo*. Water diffusion in normal white matter is predominantly along the direction of white matter fiber tracts. If these tracts are disrupted, directional diffusion is impaired resulting in a reduction of fractional anisotropy (FA), a primary measure extracted from DTI data. Of the diffusion tensor eigenvalues that make up FA, the largest (or eigenvalue 1; Table 1) that corresponds to the principal eigenvector represents water movement parallel to the axonal fibers or axial diffusivity (AD). The average of the remaining eigenvalues 2 and 3 (Table 1) represent radial diffusivity (RD) or water movement perpendicular to the axonal fibers (15,16). In mice, axonal damage results in significant decreases in AD (and little to no alteration in RD) while demyelination significantly increases radial but not axial diffusivity (15,16).

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Increasingly these mouse model indices of white matter microstructure have been applied to human neuroimaging studies.

Neuroimaging studies using these DTI-derived metrics support the general hypothesis that white matter damage negatively impacts cognitive and affective functioning in the aging brain (17). Focusing briefly on FA, alterations in this metric have been linked with alterations in such abilities as working memory (e.g., 18), attention switching (19), episodic memory (20) and elevations in depressive symptomatology (21). Region of interest analyses reveal that reductions in prefrontal FA may be accounting for the more ‘executive’ correlations (22) as well as those related to depression, particularly in older adults with late life depression (23,24,25). Tractography studies based on DTI show an anterior to posterior gradient of FA results among neural pathways intimately connected to the prefrontal cortex (26,27). Other studies incorporating tractography reveal the importance of posterior white matter involvement in age-related executive dysfunction (28,29) and dementia (30). Patterns of these results support the retrogenesis hypothesis of aging (28) while others also support theories of white matter (dis-)connectivity in age-related cognitive and affective impairment (31) long advocated by the likes of Norman Geschwind (32,33) and Alexander Luria (34).

Thus, the DTI-derived metric of FA provided greater specificity than T2-FLAIR in white matter associated cognitive and affective functioning in aging (see 17 for a directed review); however, the DTI-derived metrics of axial and radial diffusivity have not provided a clearer understanding of the underlying microstructure driving age-related white matter damage and its behavioral associations. Using prefrontal structure and function as an example, initial studies suggested greater age-related alterations in radial compared to axial diffusivity within this region (35) that correlated with executive dysfunction (27). Although this finding is still reported in the literature (36), it is not without caveats (28). For example, AD results are highly variable in aging with reported increases and/or decreases paired with more consistent age-related increases in RD (26,37,38). Other studies report alterations in both radial and axial diffusivity (e.g., 39) and associations of both indices to executive tasks (40). In fact, there are over five distinct permutations relating FA, radial and axial diffusivity in the aging literature (26,37,39). While some investigators interpret the various combinations of results as indicative of diversity in neurodegeneration across brain regions including the prefrontal cortex (e.g., 37), there is a lack of longitudinal data empirically testing this assumption.

Other investigators cite problems with the microstructure metrics derived from DTI that may explain the varying results and restrict the interpretations one can make using axial and radial diffusivity data (41). From a practical standpoint, the initial AD and RD metrics were derived from a rodent species known for loosely packed, very thin or absent myelin sheaths and lacking inflammation or axonal loss in brain (15) with the implication being water displacement is much less restricted. Such an environment cannot be so well isolated in the aging brain and may not accurately reflect the microstructural changes that occur in aging. For example, normal age-related neuropathology includes inflammation as well as lacunar infarctions and general atrophy. Furthermore, such age-related neuropathology may negatively impact not only the shape of the calculated cell ellipsoid but also the magnitude of individual eigenvectors and associated eigenvalues (42,43). Age-related cerebral atrophy may also introduce additional fluid/tissue interface issues that further corrupt axial and radial diffusion.

Some critics argue that the only way to ensure DTI-derived eigenvalues of axial and radial diffusion are measuring axonal and myelin integrity respectively is to check the alignment of the corresponding eigenvectors to the underlying tissue structure (44). Evidence exists documenting that AD and RD values may be unrelated to actual tissue organization and that the primary eigenvectors of comparison may even measure (i.e., point to) different directions (44). Such issues are particularly important when comparing healthy to diseased tissue either within- or between- groups.

Furthermore, DTI-based RD may be altered by more than demyelination, making it more a composite index of white matter microstructure than a specific myelin marker. For example, decreased axonal diameter and reduction in axons or axonal density may contribute to this variable (17). All of these aforementioned confounds may i) contribute to variations in previous results, ii) explain the high degree of collinearity between measures and iii) explain the limited divergent information relating axial and radial diffusivity to behavior seen in aging studies. In addition, these metrics, like many other MRI techniques, vary based on scanner platform and lack a standardized metric to address these differences and allow for better comparison across studies.

Thus, critical barriers remain to understanding the contribution of axonal loss and demyelination to white matter alterations as measured by axial and radial diffusivity; barriers that necessitate the development of more specific neuroimaging techniques to visualize white matter microstructure *in vivo*. For example, age-related white matter damage may be related to a variety of microstructural changes including axonal density and size, neurofibril degeneration and/or demyelination; the imaging of which may be negatively impacted by a variety of macrostructural alterations including microbleeds and infarcts. It is key to have sensitive imaging methods that quantify specific aspects of white matter alterations if we are to fully understand the processes involved in risk for and development of cognitive decline, dementia and depression in aging.

Developing Methods for White Matter Microstructural Imaging *in vivo*

Recent and developing neuroimaging techniques attempt to quantify white matter microstructure with increased accuracy by addressing many of the limitations inherent in DTI. Brain white matter is heterogeneous at a microscopic level with key constituents being glia (subtypes including astrocytes, oligodendrocytes and resulting myelination of axons), axonal projections and blood vessels. There is also accumulating evidence for an additional glial subtype, oligodendrocyte pre-cursor cells (45). While DTI is sensitive to overall alterations in white matter, increasingly investigators are calling for caution when attempting to use this method beyond a ‘first port of call in investigations of white matter’ (41). Thus, advanced neuroimaging techniques have emerged for the quantification of white matter microstructure including myelin (e.g., by interrogating the water trapped within the lipid bilayers of the myelin sheath) and even the diameter of the encapsulated axons surrounded by the myelin sheath (i.e., axonal integrity). Given the increasing support for the notion that declines in either myelin or axonal integrity signal alterations may be the harbinger of risk for the development of dementia and/or depression in older adults, we will focus on two emerging techniques to quantify these underlying neuropathologies, i.e., advanced DTI techniques for quantifying axonal diameter distribution (AxCaliber) and multi-component relaxometry imaging for quantifying myelin water volume fraction within the myelin sheath.

While these techniques are in various stages of development for *in vivo* work in humans, they are already proving to be more accurate assessments of white matter microstructure based on head-to-head neuroimaging and histological comparisons. It should be noted that although glial cells contribute to overall myelin volume, protons within these cells are typically believed to be ‘invisible’ to magnetic resonance given their rapid transverse relaxivity (i.e., relaxation properties T2 < 10us) (46). As a result, this review will be restricted to MRI methodological advances to visualize the myelination of axons resulting from oligodendrocyte activity and axonal integrity *in vivo*.

Axonal Integrity

It is possible that white matter vulnerability in aging may be investigated with novel techniques to reveal the contribution of reductions in axonal integrity and associated neuronal transmission. Axonal diameter, one of the major MRI metrics of axonal integrity being quantified to date (47,48), may be thought of as a proxy measure of neuronal transmission. Large axonal diameters, like those found in the axons of the body of the corpus callosum and the corticospinal tract, allow for the *fast* transfer of information – an asset for motor and visual processing. In contrast, small axonal diameters allow for a higher quantity of higher-level information transfer like those found within regions such as the genu of the corpus callosum (49). Thus, axonal diameter differs across brain regions and information processing streams; when quantified, it may serve as a proxy for age-related degradation in neural transmission for vulnerable brain regions (e.g., prefrontal cortices) and/or types of behavior (e.g., higher-order executive functions).

Diffusion MRI is a primary tool for measuring axonal integrity (50). Standard DTI methods for determining axonal integrity within white matter regions assume that water molecules diffuse predominantly in parallel to the axonal axis. Disruption of this process is thought to be an indication of disrupted axonal integrity (i.e., AD) and perhaps even an indication of increased axonal diameter. Such an assumption, however, does not account for the fact that some axons fan, bend or cross within an image voxel resulting in disrupted water diffusion for no other reason than changes in axonal flow or direction (51). If left unaccounted for, mere changes in axonal direction may lead to overestimation of axonal loss and inflation in presumed axonal diameter. Several methods with improved ability to reveal complicated fiber structures including q-ball (52) and diffusion spectrum imaging (53) as well as spherical deconvolusion (54,55) have been developed to take this altered dispersion secondary to fanning, bending or crossing fibers into account. These methodological advances are especially useful when determining the contribution of axonal diameter to white matter microstructural integrity.

Diffusion MRI can quantify more than a global measure of water dispersion. By considering water trapped within the axon as showing restricted diffusion based on axonal diameter and water outside of the axon as showing hindered diffusion based on axonal flow and number (e.g., a tightly packed bundle of axons will hinder water more so than a loosely packed bundle of axons) one can separate these two types of diffusion for a more accurate assessment of axonal flow and hence, a more accurate quantification of the axonal compartment (56). Combining this two-pool concept with the knowledge that a range of small and large axonal diameters exist in cerebral white matter led investigators to develop a technique known as AxCaliber (47) that samples white matter across multiple diffusion times. Given that the diffusion of restricted intra-axonal water is dependent on axonal diameter, i.e., smaller axons experiencing diffusion at shorter diffusion times while larger axons experiencing diffusion at longer diffusion times, the probability function and displacement associated with water diffusion can be obtained and an axonal diameter distribution determined with sub-micrometer accuracy (47).

Unlike conventional DTI, AxCaliber does not assume a Gaussian diffusion process and can directly infer the tissue microstructures through which water molecules diffuse. Animal as well as computer modeling experiments of axonal diameter have confirmed the accuracy of this non-invasive MRI technique (49) with correspondence across histological measurement of sciatic and optic nerve fibers nearing 1 in some instances (47). This suggests the axonal diameter distribution detected on MRI is highly correlated to the actual axon diameter as seen in histological stains of the same material (47). While this method appears extremely powerful, restrictions including the relatively long scan time, the limited diffusion-weighting gradient amplitudes available on commercial clinical MRI scanners and floor effects in the ability to image axonal diameters smaller than 0.4 μm may limit its applicability.

In addition to AxCaliber, many other diffusion imaging techniques are emerging together with associated models to relate the diffusion MRI signals with tissue microstructures for axonal integrity quantification. For example, recent developments enable estimation of axonal diameter as well as axonal density *in vivo* (57–59) by combining several approaches to diffusion imaging including, but not limited to aspects of AxCaliber, orientational invariance and/or diffusion kurtosis analysis (57,58). These methods take advantage of known fiber orientation of major white matter pathways to maximize the assumptions made about axonal orientation for determination of axonal characteristics using diffusion imaging (60). Other high b-value diffusion imaging techniques to model underlying white matter microstructure exist (61,62) including the fractional order calculus model (63,64) which may provide a method for delineating white matter tissue structure such as tightly packed axons. While more work is needed on determining axonal integrity metrics within a clinically acceptable time frame, it is clear the addition of such indices holds great promise toward uncovering the contributions of key aspects of white matter microstructural degradation in the aging brain.

Myelin Integrity

Increasing evidence exists from neuropathology, histology and neuroimaging studies of the role of demyelination in normal (65) and pathological (66) aging. For example, animal studies suggest that age-related white matter damage is primarily driven by alterations in myelin integrity (67). Human imaging points toward the role of demyelination in aging and decreased motor functioning (66); however, this work was conducted using the DTI-derived radial diffusivity metric and hence subject to all the limitations of myelin quantification as previously discussed. Given that myelin breakdown begins as early as the fourth decade of life (68,69) and accelerates with aging (38,68), exploring measures of myelin that overcome the limits of conventional imaging techniques holds great promise in identifying a more subtle biomarker for future white matter research.

A novel MRI technique based in multi-component relaxometry provides quantitative assessment of myelin content with high spatial resolution throughout the brain in clinically acceptable scan times for use across aging populations. Briefly, the MCR technique (70–72) aims to decompose the measured MR signal into contributions from discrete microanatomical tissue environments based on their unique T1 and T2 relaxation characteristics. In brain tissue, two such environments are detectable, one corresponding to the 'free' intra and extra-cellular water and one attributed to the 'restricted' water trapped within the lipid bilayers of the myelin sheath (70). By quantifying this latter environment's contribution through such techniques as multicomponent-driven equilibrium single-pulse observation of T1 and T2 (mcDESPOT), a surrogate marker of myelin volume, which some investigators call the myelin water volume fraction (MWF) (71,72) may be calculated that corresponds strongly with gold standard histological assessments (73–76). Additionally, MWF is insensitive to edema and inflammation as well as to tissue geometry and architecture (e.g., crossing fibers) known to pose problems for DTI research (75,76). Further, by promoting the use of study-specific templates (77), proponents of this technique address problems in comparisons based on age-related atrophy.

Research to date using mcDESPOT and other MCR-based technology has shown it to be more sensitive compared to other imaging modalities like T2/FLAIR or DTI and more specific to myelin growth and degeneration. Thus, prior studies have shown the MWF derived from myelin mapping techniques to be a superior marker of myelin content and integrity than DTI or magnetization transfer metrics (76,78). In a study of over 150 infants and toddlers, Deoni and colleagues (77) have mapped myelin maturation across the first 5 years of life. The progression delineated from this neuroimaging technique is almost identical to that documented using post-mortem histological studies of a similar age cohort (79). In addition to growth, myelin decline or degradation has been documented in mid-life demyelination disorders such as multiple sclerosis using MCR techniques (80). Additionally, researchers are addressing the role of demyelination in risk for and development of dementia (81).

Additional Considerations

Rightly, novel methods of imaging brain including white matter microstructure increasingly require extensive validation to post-mortem human tissue; users of these techniques should be aware of the assumptions made about human *in vivo* white matter imaging and the degree to which these assumptions are validated by such confirmatory evidence. Across the key neuroimaging methods discussed in this review (i.e., DTI, AxCaliber, MCR), all owe some degree of validation to direct comparisons of animal and/or human MRI to histopathology; the key is knowing the extent of these validation. DTI-derived metrics of axonal and myelin integrity showed remarkable accuracy when compared to post-mortem staining of axonal and myelin integrity in mice (15,16). To our knowledge, little to no confirmatory evidence exists in humans regarding the accuracy of these metrics. Computer modeling as well as animal neuroimaging/histological comparisons have confirmed the accuracy of both AxCaliber (47,49) and MCR (73,75,76). Comparisons of recorded histology on pediatric myelin maturation and *in vivo* MWF maps in a similar age cohort (77) as well as a direct comparison of myelin content in post-mortem brains of individuals with multiple sclerosis imaged for MWF and also stained for myelin content (74) further confirm the accuracy of MCR.

Some of the white matter microstructural techniques discussed above have the additional benefit of standardized output metrics that show good consistency and reliability across time and across scanner platforms and scanner sites. For example, the standardized MWF z-map allows for highly reproducible values longitudinally (82) and may allow for comparisons of results across research sites as well as research scanners making multi-center studies on varying scanner platforms possible. While empirical testing of such repeatability and multi-center reliability has yet to be conducted for axonal diameter imaging in humans, many investigators using these techniques feel their applicability across longitudinal and multi-center studies would be robust (47).

Conclusion and Future Directions

The techniques of AxCaliber and MCR discussed in this review represent state-of-the-art methods for visualizing white matter microstructure *in vivo*. While not all metrics are fully optimized, the groundwork has been laid and optimization continues in such areas as decreasing scan time and increasing water compartment conceptualization. For example, acquisition of MWF via mcDESPOT includes a series of sequences across multiple flip angles within as little as 10–12 minutes of total scan time for whole brain coverage. Further, increases in the number of compartments available to water diffusion and image capture for the accurate quantification of white matter microstructure have begun to include such environments as cerebrospinal fluid filled regions and the extra-cellular matrix (83,84). Initial work incorporating these compartments suggests that expanding the number of water compartments captured beyond the traditional two or three significantly increases the accuracy of the final metrics of white matter microstructure (84). Although the modeling needed to extract the relaxation rates for this increasing number of compartments is complex, the end result will be a more accurate depiction of the underlying microstructural components driving white matter damage in the aging brain.

Although we have focused our review on advancing our understanding of white matter hyperintensities and CSVD in aging, it is important to remain considerate of the contribution of alternative forms of white matter damage including lacunar infarctions and microbleeds – not only as they negatively impact the acquisition of DTI-based imaging data as discussed above – but also on how they negatively impact the aging process more generally. Techniques like susceptibility weighted imaging (SWI) (85) exist to quantify infarctions and microbleeds; however few move beyond visual inspection and volumetric quantification for a more robust measure of resulting white matter disruption via disconnectivity or overall vasculature *in vivo*. Thus, more work is needed to quantify and merge information about lacunar infarctions and microbleeds into metrics of white matter damage in an aging population. A brief summary of ways to image infarctions and microbleeds – as well as the microstructural integrity of axons and myelin – may be found in Table 2.

Additional work is also needed to put these techniques into a larger ‘multimodal’ context. For example, the means by which white matter microstructural damage negatively impacts functional connectivity as determined through functional MRI remains to be fully investigated; as does the ability of the brain to compensate or adapt to white matter damage by altering not only structural but functional connectivity networks to increase successful performance. Determining thresholds of damage beyond which such compensation is no longer feasible, using more sensitive measures of white matter microstructure like those outlined in this review, will also ensure early identification of risk. Early identification of risk provides the potential to implement interventions to stave off development of dementia and/or depression, a primary aim for aging research. Methods such as diffusional kurtosis imaging and anomalous diffusion imaging are using the diffusion signal to better characterize tissue architecture (86,87). The aim of these methods is to increase our ability to detect changes in tissue and thus monitor disease progression and perhaps even treatment efficacy.

Despite the work that remains, findings across the two main imaging techniques reviewed are promising for the highly sensitive delineation of white matter microstructural damage not only in aging but for use across the lifespan. Although DTI greatly expanded on earlier methods including T2-weighted/FLAIR to visualize subtle alterations in white matter not hitherto seen with MRI *in vivo*, now, as was then, the field is pushing forward. Novel methods to image white matter microstructure will add clarity to the mechanisms that contribute to the DTI signals and the commonly used DTI-derived metrics of axial and radial diffusivity. Further, these newer methods may provide, as some have already (76,78), a more sensitive and specific technique for determining the contribution of axonal and myelin integrity (or lack thereof) to the ever changing aging brain.

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References

1. Bots ML, van Swieten JC, Breteler MM, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. Lancet. 1993; 341(8855):1232–7. [PubMed: 8098390]

2. Fazekas F, Kleinert R, Offenbacher H, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. Neurology. 1993; 43(9):1683–9. [PubMed: 8414012]
3. Arvanitakis Z, Schneider JA, Wilson RS, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. Neurology. 2006; 67(11):1960–5. [PubMed: 17159101]
4. Roman GC. Vascular dementia. Advances in nosology, diagnosis, treatment and prevention. 2004; 46(4):207–15.
5. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010; 9(7):689–701. [PubMed: 20610345]
6. Au R, Massaro JM, Wolf PA, et al. Association of white matter hyperintensity volume with decreased cognitive functioning: the Framingham Heart Study. Arch Neurol. 2006; 63(2):246–50. [PubMed: 16476813]
7. Breteler MM. Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. Neurobiol Aging. 2000; 21(2):153–60. [PubMed: 10867200]
8. Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. Jama. 1997; 277(10):813–7. [PubMed: 9052711]
9. Schneider JA, Boyle PA, Arvanitakis Z, et al. Subcortical infarcts, Alzheimer's disease pathology, and memory function in older persons. Ann Neurol. 2007; 62(1):59–66. [PubMed: 17503514]
10. Alexopoulos GS, Kiosses DN, Klimstra S, et al. Clinical presentation of the "depression-executive dysfunction syndrome" of late life. Am J Geriatr Psychiatry. 2002; 10(1):98–106. [PubMed: 11790640]
11. Alexopoulos GS, Meyers BS, Young RC, et al. 'Vascular depression' hypothesis. Archives of General Psychiatry. 1997; 54(10):915–22. [PubMed: 9337771]
12. O'Sullivan M, Lythgoe DJ, Pereira AC, et al. Patterns of cerebral blood flow reduction in patients with ischemic leukoaraiosis. Neurology. 2002; 59(3):321–6. [PubMed: 12177363]
13. Catani M, Mecocci P, Tarducci R, et al. Proton magnetic resonance spectroscopy reveals similar white matter biochemical changes in patients with chronic hypertension and early. Alzheimer's disease. 2002; 50(10):1707–10.
14. O'Sullivan M, Summers PE, Jones DK, et al. Normal-appearing white matter in ischemic leukoaraiosis: a diffusion tensor MRI study. Neurology. 2001; 57(12):2307–10. [PubMed: 11756617]
15. Song SK, Sun SW, Ramsbottom MJ, et al. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. Neuroimage. 2002; 17(3):1429–36. [PubMed: 12414282]
16. Song SK, Sun SW, Ju WK, et al. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage. 2003; 20(3):1714–22. [PubMed: 14642481]
17. Madden DJ, Bennett IJ, Song AW. Cerebral white matter integrity and cognitive aging: contributions from diffusion tensor imaging. Neuropsychol Rev. 2009; 19(4):415–35. [PubMed: 19705281]
18. Charlton RA, Landau S, Schiavone F, et al. A structural equation modeling investigation of age-related variance in executive function and DTI measured white matter damage. Neurobiol Aging. 2008; 29(10):1547–55. [PubMed: 17451845]
19. Grieve SM, Williams LM, Paul RH, et al. Cognitive aging, executive function, and fractional anisotropy: a diffusion tensor MR imaging study. AJNR Am J Neuroradiol. 2007; 28(2):226–35. [PubMed: 17296985]
20. Kennedy KM, Raz N. Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. Neuropsychologia. 2009; 47(3):916–27. [PubMed: 19166865]
21. Lamar M, Charlton RA, Morris RG, et al. The impact of subcortical white matter disease on mood in euthymic older adults: a diffusion tensor imaging study. Am J Geriatr Psychiatry. 2010; 18(7): 634–42. [PubMed: 20220594]
22. Sasson E, Doniger GM, Pasternak O, et al. Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. Brain Struct Funct. 2012; 217(2):503–15. [PubMed: 21909706]

23. Taylor WD, Macfall JR, Boyd B, et al. One-year change in anterior cingulate cortex white matter microstructure: relationship with late-life depression outcomes. Am J Geriatr Psychiatry. 2011; 19(1):43–52. [PubMed: 20808126]
24. Colloby SJ, Firbank MJ, Thomas AJ, et al. White matter changes in late-life depression: a diffusion tensor imaging study. J Affect Disord. 2011; 135(1–3):216–20. [PubMed: 21862137]
25. Taylor WD, MacFall JR, Payne ME, et al. Late-life depression and microstructural abnormalities in dorsolateral prefrontal cortex white matter. Am J Psychiatry. 2004; 161(7):1293–6. [PubMed: 15229065]
26. Bennett IJ, Madden DJ, Vaidya CJ, et al. Age-related differences in multiple measures of white matter integrity: A diffusion tensor imaging study of healthy aging. Hum Brain Mapp. 2010; 31(3):378–90. [PubMed: 19662658]
27. Davis SW, Dennis NA, Buchler NG, et al. Assessing the effects of age on long white matter tracts using diffusion tensor tractography. Neuroimage. 2009; 46(2):530–41. [PubMed: 19385018]
28. Brickman AM, Meier IB, Korgaonkar MS, et al. Testing the white matter retrogenesis hypothesis of cognitive aging. Neurobiol Aging. 2012; 33(8):1699–715. [PubMed: 21783280]
29. Lamar M, Charlton RA, Ajilore O, et al. Prefrontal vulnerabilities and whole brain connectivity in aging and depression. Neuropsychologia. in press.
30. Lamar M, Catani M, Price CC, et al. The impact of region-specific leukoaraiosis on working memory deficits in dementia. Neuropsychologia. 2008; 46(10):2597–601. [PubMed: 18501390]
31. Catani M, ffytche DH. The rises and falls of disconnection syndromes. Brain. 2005; 128(Pt 10): 2224–39. [PubMed: 16141282]
32. Geschwind N. Disconnexion syndromes in animals and man. I Brain. 1965; 88:237–94.
33. Geschwind N. Disconnexion syndromes in animals and man. II Brain. 1965; 88:585–644.
34. Luria, AR. Higher cortical functions. New York: Basic Books; 1980. p. 246-360.
35. Sullivan EV, Pfefferbaum A. Diffusion tensor imaging and aging. Neurosci Biobehav Rev. 2006; 30(6):749–61. [PubMed: 16887187]
36. Zhong WJ, Guo DJ, Zhao JN, et al. Changes of axial and radial diffusivities in cerebral white matter led by normal aging. Diagn Interv Imaging. 2012; 93(1):47–52. [PubMed: 22277710]
37. Burzynska AZ, Preuschhof C, Backman L, et al. Age-related differences in white matter microstructure: region-specific patterns of diffusivity. Neuroimage. 2010; 49(3):2104–12. [PubMed: 19782758]
38. Inano S, Takao H, Hayashi N, et al. Effects of age and gender on white matter integrity. AJNR Am J Neuroradiol. 2011; 32(11):2103–9. [PubMed: 21998104]
39. Zahr NM, Rohlfing T, Pfefferbaum A, et al. Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study. Neuroimage. 2009; 44(3):1050–62. [PubMed: 18977450]
40. Sullivan EV, Rohlfing T, Pfefferbaum A. Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: relations to timed performance. Neurobiol Aging. 2010; 31(3):464–81. [PubMed: 18495300]
41. Jones DK, Knosche TR, Turner R. White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. Neuroimage. 2012
42. Field AS, Alexander AL, Wu YC, et al. Diffusion tensor eigenvector directional color imaging patterns in the evaluation of cerebral white matter tracts altered by tumor. J Magn Reson Imaging. 2004; 20(4):555–62. [PubMed: 15390227]
43. Basser PJ, Pajevic S. Statistical artifacts in diffusion tensor MRI (DT-MRI) caused by background noise. Magn Reson Med. 2000; 44(1):41–50. [PubMed: 10893520]
44. Wheeler-Kingshott CA, Cercignani M. About "axial" and "radial" diffusivities. Magn Reson Med. 2009; 61(5):1255–60. [PubMed: 19253405]
45. Kremer D, Aktas O, Hartung HP, et al. The complex world of oligodendroglial differentiation inhibitors. Ann Neurol. 2011; 69(4):602–18. [PubMed: 21520230]
46. Levesque IR, Sled JG, Narayanan S, et al. Reproducibility of quantitative magnetization-transfer imaging parameters from repeated measures. Magn Reson Med. 2010; 64:391–400. [PubMed: 20665783]

47. Assaf Y, Blumenfeld-Katzir T, Yovel Y, et al. AxCaliber: a method for measuring axon diameter distribution from diffusion MRI. Magn Reson Med. 2008; 59(6):1347–54. [PubMed: 18506799]
48. Dyrby TB, Sogaard LV, Hall MG, et al. Contrast and stability of the axon diameter index from microstructure imaging with diffusion MRI. Magn Reson Med. 2012
49. Barazany D, Basser PJ, Assaf Y. In vivo measurement of axon diameter distribution in the corpus callosum of rat brain. Brain. 2009; 132(Pt 5):1210–20. [PubMed: 19403788]
50. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B. 1996; 111(3):209–19. [PubMed: 8661285]
51. Wedeen VJ, Rosene DL, Wang R, et al. The geometric structure of the brain fiber pathways. Science. 2012; 335(6076):1628–34. [PubMed: 22461612]
52. Tuch DS. Q-ball imaging. Magn Reson Med. 2004; 52(6):1358–72. [PubMed: 15562495]
53. Wedeen VJ, Wang RP, Schmahmann JD, et al. Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. Neuroimage. 2008; 41(4):1267–77. [PubMed: 18495497]
54. Tournier JD, Yeh CH, Calamante F, et al. Resolving crossing fibres using constrained spherical deconvolution: validation using diffusion-weighted imaging phantom data. Neuroimage. 2008; 42(2):617–25. [PubMed: 18583153]
55. Alexander DC. Maximum entropy spherical deconvolution for diffusion MRI. Inf Process Med Imaging. 2005; 19:76–87. [PubMed: 17354686]
56. Assaf Y, Freidlin RZ, Rohde GK, et al. New modeling and experimental framework to characterize hindered and restricted water diffusion in brain white matter. Magn Reson Med. 2004; 52(5):965–78. [PubMed: 15508168]
57. Alexander DC, Hubbard PL, Hall MG, et al. Orientationally invariant indices of axon diameter and density from diffusion MRI. Neuroimage. 2010; 52(4):1374–89. [PubMed: 20580932]
58. De Santis S, Assaf Y, Jones DK. Using the biophysical CHARMED model to elucidate the underpinnings of contrast in diffusional kurtosis analysis of diffusion-weighted MRI. MAGMA. 2012; 25(4):267–76. [PubMed: 22113517]
59. Avram AV, Ozarslan E, Sarlls JE, et al. In vivo detection of microscopic anisotropy using quadruple pulsed-field gradient (qPFG) diffusion MRI on a clinical scanner. Neuroimage. 2013; 64:229–39. [PubMed: 22939872]
60. Schneider T, Wheeler-Kingshott CA, Alexander DC. In-vivo estimates of axonal characteristics using optimized diffusion MRI protocols for single fibre orientation. Med Image Comput Comput Assist Interv. 2010; 13(Pt 1):623–30. [PubMed: 20879283]
61. Yablonskiy DA, Bretthorst GL, Ackerman JJ. Statistical model for diffusion attenuated MR signal. Magn Reson Med. 2003; 50(4):664–9. [PubMed: 14523949]
62. Ozarslan E, Basser PJ, Shepherd TM, et al. Characterization of anomalous diffusion from mr signal may be a new probe to tissue microstructure. Conf Proc IEEE Eng Med Biol Soc. 2006; 1:2256–9. [PubMed: 17946947]
63. Zhou XJ, Gao Q, Abdullah O, et al. Studies of anomalous diffusion in the human brain using fractional order calculus. Magn Reson Med. 2010; 63(3):562–9. [PubMed: 20187164]
64. Magin RL, Abdullah O, Baleanu D, et al. Anomalous Diffusion in the Bloch-Torrey Equation Expressed Through Fractional Order Differential Operators. Journal of Magnetic Resonance. 2008; 190:255–70. [PubMed: 18065249]
65. Hinman JD, Abraham CR. What's behind the decline? The role of white matter in brain aging. Neurochem Res. 2007; 32(12):2023–31. [PubMed: 17447140]
66. Bartzokis G. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. Neurobiol Aging. 2004; 25(1):5–18. author reply 49–62. [PubMed: 14675724]
67. Peters A. The effects of normal aging on myelinated nerve fibers in monkey central nervous system. Front Neuroanat. 2009; 3:11. [PubMed: 19636385]
68. Bartzokis G, Lu PH, Tingus K, et al. Lifespan trajectory of myelin integrity and maximum motor speed. Neurobiol Aging. 2010; 31(9):1554–62. [PubMed: 18926601]

69. Kochunov P, Williamson DE, Lancaster J, et al. Fractional anisotropy of water diffusion in cerebral white matter across the lifespan. Neurobiol Aging. 2012; 33(1):9–20. [PubMed: 20122755]
70. Whittall KP, MacKay AL, Graeb DA, et al. In Vivo Measurement of T2 Distributions and Water Contents in Normal Human Brain. Magnetic Resonance Medicine. 1997; 37:34–43.
71. Deoni SC, Rutt BK, Arun T, et al. Gleaning multicomponent T1 and T2 information from steady-state imaging data. Magn Reson Med. 2008; 60(6):1372–87. [PubMed: 19025904]
72. Deoni SC. Correction of main and transmit magnetic field (B0 and B1) inhomogeneity effects in multicomponent-driven equilibrium single-pulse observation of T1 and T2. Magn Reson Med. 2011; 65(4):1021–35. [PubMed: 21413066]
73. Webb S, Munro CA, Midha R, et al. Is multicomponent T2 a good measure of myelin content in peripheral nerve? Magn Reson Imaging. 2003; 49:638–45.
74. Laule C, Leung E, Li DK, et al. Myelin water imaging in multiple sclerosis: Quantitative correlations with histopathology. Multiple Sclerosis. 2006; 12:747–53. [PubMed: 17263002]
75. Stanisz GJ, Webb S, Munro CA, et al. MR properties of excised neural tissue following experimentally induced inflammation. Magn Reson Imaging. 2004; 51:473–79.
76. Gareau PJ, Rutt BK, Karlik SJ, et al. Magnetization transfer and multicomponent T2 relaxation measurements with histopathologic correlation in an experimental model of MS. J Magn Reson Imaging. 2000; 11:586–595. [PubMed: 10862056]
77. Deoni SC, Dean DC 3rd, O'Muircheartaigh J, et al. Investigating white matter development in infancy and early childhood using myelin water faction and relaxation time mapping. Neuroimage. 2012; 63(3):1038–53. [PubMed: 22884937]
78. Madler B, Drabycz SA, Kolind SH, et 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; 26:874–78. [PubMed: 18524521]
79. Yakovlev, PI.; Lecours, AR. The myelogenetic cycles of regional maturation of the brain. In: Yakovlev, PI.; Lecours, AR.; Mankowski, A., editors. Regional development of the brain in early life. Philadelphia: David; 1967. p. 3-69.
80. Kitzler HH, Su J, Zeineh M, et al. Deficient MWF mapping in multiple sclerosis using 3D whole-brain multi-component relaxation MRI. NeuroImage. 2012; 59(3):2670–77. [PubMed: 21920444]
81. Lamar, M.; Walker, L. In: Lamar, M., editor. Alternative techniques for quantifying white matter in aging and late life depression; The 12th annual International College of Geriatric Psychoneuropharmacology; Sevilla, Spain. 2012.
82. Kolind SH, Deoni SC. Rapid three-dimensional multicomponent relaxation imaging of the cervical spinal cord. Magn Reson Med. 2011; 65(2):551–6. [PubMed: 20882672]
83. Deoni SC, Matthews L, Kolind SH. One component? Two components? Three? The effect of including a nonexchanging "free" water component in multicomponent driven equilibrium single pulse observation of T(1) and T(2). Magn Reson Med. 2012
84. Panagiotaki E, Schneider T, Siow B, et al. Compartment models of the diffusion MR signal in brain white matter: a taxonomy and comparison. Neuroimage. 2012; 59(3):2241–54. [PubMed: 22001791]
85. Barth M, Nobauer-Huhmann IM, Reichenbach JR, et al. High-resolution three-dimensional contrast-enhanced blood oxygenation level-dependent magnetic resonance venography of brain tumors at 3 Tesla: first clinical experience and comparison with 1. 5 Tesla. Invest Radiol. 2003; 38(7):409–14. [PubMed: 12821854]
86. Bar-Shir A, Duncan ID, Cohen Y. QSI and DTI of excised brains of the myelin-deficient rat. Neuroimage. 2009; 48(1):109–16. [PubMed: 19539038]
87. Hall MG, Barrick TR. From diffusion-weighted MRI to anomalous diffusion imaging. Magn Reson Med. 2008; 59(3):447–55. [PubMed: 18224695]
88. Haacke EM, Miao Y, Liu M, et al. Correlation of putative iron content as represented by changes in R2* and phase with age in deep gray matter of healthy adults. J Magn Reson Imaging. 2010; 32(3):561–76. [PubMed: 20815053]

Table 1

DTI-derived variables of interest

Fractional Anisotrophy (FA)	$FA=\frac{\sqrt{3}}{\sqrt{2}}\frac{\sqrt{(\lambda_1-\lambda)^2+(\lambda_2-\lambda)^2+(\lambda_3-\lambda)^2}}{\sqrt{\lambda_1^2+\lambda_2^2+\lambda_3^2}}$
Axial Diffusivity (AD)	λ_1 denoted as $\lambda_{\parallel}$
Radial Diffusivity (RD)	$(\lambda_2+\lambda_3)/2$ denoted as $\lambda_{\perp}$

NOTE: λ_1, λ_2, & λ_3 represents the eigenvalues from the diffusion tensor & λ represents mean diffusivity

Table 2

Methods comparison for *in vivo* brain imaging

LEVEL OF INQUIRY	METHOD	METRIC	OVERVIEW	PROS	CONS	KEY REFS
Microstructural integrity of White Matter & White Matter Hyperintensities						
axonal	DTI	Axial diffusivity (AD)	Of the diffusion tensor eigenvalues that make up FA, the largest (eigenvalue 1) represents water movement parallel to the axonal fibers	• Validated in mouse models of white matter microstructure • Can be obtained from conventional DTI scanning	• Varying results using this metric in aging • The orientation of the principal eigenvector at the time of data acquisition may influence the microstructure represented • Highly correlated with radial diffusivity	(15,16)
	AxCaliber	Axonal diameter distribution (ADD)	Separates hindered and restricted water pools for a better assessment of axonal flow combined with multiple diffusion times that take into account a range of axonal diameters	• Takes altered dispersion secondary to fanning, bending or crossing fibers into account • Does not assume a Gaussian diffusion process • Validated across histological measurement of sciatic and optic nerve fibers	• Long scan time • Limited by commercially available scanner capacities • Capturing small axonal diameters(< 0.4 µm) difficult	(56,47)
myelin	DTI	Radial diffusivity (RD)	Of the diffusion tensor eigenvalues that make up FA, the average of eigenvalues 2 and 3 represent water movement perpendicular to the axonal fibers	• Validated in mouse models of white matter microstructure • Can be obtained from conventional DTI scanning	• See axial diffusivity cons listed above • May be altered by more than demyelination	(15,16)
	MCR with mcDESPOT as one technique used to calculate the metric	Myelin water volume fraction (MWF)	• Decomposes the measured MR signal into contributions from discrete tissue environments based on their unique relaxation characteristics and	• High spatial resolution • Clinically acceptable scan times • Corresponds strongly with gold standard	• Separate sequences must be acquired • Not commercially available	(70–72)

LEVEL OF INQUIRY	METHOD	METRIC	OVERVIEW	PROS	CONS	KEY REFS
	described at right		measures restricted water trapped within the lipid bilayers of the myelin sheath	histological assessment • Insensitive to edema, inflammation, tissue geometry and axonal architecture • Standardized z-map may be obtained		
Alternate Forms of White Matter Damage						
infarcts	T2/FLAIR	Total number; Total volume	Counting or volume quantification of visible infarcts	• Allows for a gross measure of the contribution of infarcts	• Must be visible for quantification • No at risk tissue easily identifiable	
microbleeds	SWI	brain vasculature	Imaging of venous blood and iron storage	• Sensitive to both iron and blood for a detailed picture of brain vasculature	• Quantification of information still ongoing	(88)

Note: DTI=diffusion tensor imaging; FA=fractional anisotropy; MCR=multi-component relaxometry; mcDESPOT= multicomponent-driven equilibrium single-pulse observation of T1 and T2; T2/FLAIR=T2-weighted/Fluid attenuated inversion recovery; SWI=susceptibility weighted imaging.