Published in final edited form as:
Int J Geriatr Psychiatry. 2009 February ; 24(2): 109–117. doi:10.1002/gps.2087.

Aging of Cerebral White Matter: A Review of MRI Findings

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Abstract

Background—Cerebral aging is a complex and heterogeneous process that is associated with a high degree of inter-individual variability. Structural magnetic resonance imaging (MRI) can be used to identify and quantify non-disease-related aging of the cerebral white matter.

Methods—The present article reviews the findings from several MRI techniques, including morphometric approaches, study of white matter hyperintensities, diffusion tensor imaging, and magnetization transfer imaging that have been used to examine aging of the cerebral white matter. Furthermore, the relationship of MRI indices of white matter integrity to age-related cognitive declines is reported.

Results—A general pattern of age-related preservation and decline emerges indicating that the prefrontal white matter is most susceptible to the influence of age. Studies that combine MRI with cognitive measures suggest that such age-related reductions in white matter integrity may produce a disconnection state that underlies some of the age-related performance declines in age-sensitive cognitive domains.

Conclusions—White matter aging may contribute to a disconnection state that is associated with declines in episodic memory, executive functions, and information processing speed.

Keywords

Aging; White Matter; MRI

Cerebral aging is a complex and heterogeneous process that is associated with a high degree of inter-individual variability and characterized by a pattern of selective loss and preservation. Magnetic resonance imaging (MRI) makes *in vivo* characterization of brain alterations occurring with advancing age possible. The use of MRI allows thorough characterization of non-disease-related brain aging and facilitates the study of anatomical alterations that contribute to the cognitive and affective symptoms of late-life psychiatric illnesses. This review will focus on the results of MRI studies of white matter changes that occur with normal aging and the relationship of age-associated changes in white matter to age-related declines in cognitive abilities.

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Conflict of Interest: None

Disclosures: Dr. Alexopoulos has received research grants by Forest Pharmaceuticals, Inc. and Cephalon and consults for Forest Pharmaceuticals, Sanofi-Aventis, and Novartis. He has given lectures supported by Forest, Cephalon, Bristol Meyers, Janssen, Glaxo, Pfizer and Lilly. Dr. Brickman has received compensation from ePharmaSolutions and ProPhase Training Group. Drs. Gunning-Dixon and Ms. Cheng have nothing to disclose.

Histopathological Characteristics of Cerebral White Matter Aging

Histopathological studies reveal that brain aging is marked by degradation of white matter including myelin pallor (Kemper, 1994), loss of myelinated fibers (Bartzokis, 2004; Marner *et al.*, 2003; Pakkenberg and Gundersen, 1997; Meier-Ruge *et al.*, 1992), and malformation of myelin sheaths (Peters, 2002). In elderly non-human primates, localized splitting of myelin lamellae and spherical cytoplasmic cavities or “balloons” within the myelin sheath or in the axoglial junction are commonly observed (Peters, 2002). Concomitantly, however, continued myelin production termed “redundant myelin” has been observed in older monkeys (Peters *et al.*, 2001), perhaps as a compensatory mechanism for myelin degeneration. This redundant, splitting myelin is associated with decreased conduction velocity observed in aging (Peters *et al.*, 1996; Xi *et al.*, 1999; Aston-Jones *et al.*, 1985; Peters, 2002; Peters *et al.*, 2000; Peters and Sethares, 2002). Furthermore, evidence suggests that myelination from late-differentiating oligodendrocytes is less effective and more vulnerable than myelination from oligodendrocytes present earlier in development (reviewed in (Bartzokis *et al.*, 2004).

Macrostructural Aging of the Cerebral White Matter

On MRI, there is little doubt that the brain shrinks with age. The rate of shrinkage accelerates with age and is most precipitous after about age 50 (Raz and Rodrigue, 2006). Bulk volume loss of white matter is in line with the idea that the aging brain is characterized by declining neuronal connectivity (Albert, 1993) and the question of the degree of global grey versus white matter aging has received particular attention in recent years (Peters and Rosene, 2003). Several studies have shown a relatively greater age-associated decline in white matter volume or the presence of white matter volume loss in the absence of grey matter loss (Allen et al., 2005; Bartzokis et al., 2003; Guttmann et al., 1998; Jernigan et al., 2001; Resnick et al., 2003). For example, in individuals ranging from 30 to 90 years of age, Jernigan and colleagues (2001) observed a 26% reduction in white matter tissue volume, relative to a 14% reduction in gray matter tissue volume (Greenwood, 2007). However, several other studies have shown the opposite effect, with greater age-associated grey matter loss (Blatter et al., 1995; Sullivan et al., 2004; Thompson et al., 2003). A number of factors could account for these discrepancies. First, white matter volume loss may be a feature of more advanced age (Salat et al., 1999); that is grey matter loss may begin earlier and progress gradually, whereas white matter loss may start later and progress more precipitously (Raz et al., 2005). Second, grey/white matter segmentation algorithms and intensity thresholds may differ across laboratories, producing variable results.

Most MRI studies of the regional distribution of age-related gray matter volumetric reductions, have shown the greatest effects in frontal lobe (Allen *et al.*, 2005; DeCarli *et al.*, 1994; Raz *et al.*, 1997; Raz *et al.*, 2004; Resnick *et al.*, 2003; Salat *et al.*, 1999; Tisserand *et al.*, 2002), followed by the temporal lobes (Cowell et al., 1994; Sullivan et al., 1995), with relative sparing of primary sensory areas and the occipital lobes (Bartzokis et al., 2001; Good et al., 2001; Raz et al., 1997; Raz et al., 2005). Our recent cross-sectional analysis of grey and white matter prefrontal volumes in 70 individuals across the adult lifespan indicated that grey matter volume in the lateral prefrontal cortex showed the greatest age-associated effect and appeared to decline linearly across ages, with about a 3% volume loss per decade (Brickman *et al.*, 2005). Importantly, white matter volumes appeared relatively stable, except in the oldest participants (i.e., ages 70s and 80s) who had reduced white matter volumes in dorsolateral and orbital regions, which is consistent with the idea that white matter volume changes may be most prominent among the very old (Raz et al., 2005; Salat et al., 1999).

While the presence and degree of age-related volumetric loss in cerebral white matter remains somewhat inconsistent, the frequent presence of foci of increased signal on MRI scans of older adults is a well-established phenomenon. White matter hyperintensities (WMH) (Figure 1) are areas of increased intensity appearing on T2-weighted images and are taken to indicate white matter damage. They can be discrete, or punctate, or may appear more confluent with the lateral ventricles. Until recently, WMH were considered clinically irrelevant, but a culmination of sample- and population-based research has demonstrated their functional significance (Gunning-Dixon and Raz, 2000;Malloy *et al.*, 2007). The presence of WMH is common among normal elderly adults and chronological age appears to be the strongest predictor of severity (de Leeuw *et al.*, 2001;Jernigan *et al.*, 1991;Brickman *et al.*, In press). Vascular risk factors, such as hypertension, also account for much variability in severity of WMH (de Leeuw *et al.*, 2001;Firbank *et al.*, 2007;Manolio *et al.*, 1994;Spilt *et al.*, 2005). With the exception of WMH that appear as smooth “rims” or “caps” along the surface of the lateral ventricles, WMH are thought to be ischemic in nature and often reflect rarefaction of myelin, breakdown of vessel endothelium, and microvascular disease (Fazekas *et al.*, 1995; Fernando *et al.*, 2004;Oppenheimer *et al.*, 1995;Smith *et al.*, 2000). Regarding the progression of WMH in normal aging, a study of 51 older adults (mean age 71) revealed a 43.8 and 29.7% rate increase in WMH burden for deep and perilventricular WMH, respectively. Furthermore, rate of WMH progression is greatest in anterior white matter with WMH in occipital white matter being relatively stable (Sachdev *et al.*, 2007).

The WMH studies are associated with some limitations. First, there are numerous WMH rating scales and these scales vary widely in scope, sensitivity, and reliability. Second, post-mortem studies of the histology of WMH suggest that white matter abnormalities reflect a number of pathological processes; however, the methodology prevents reliable discrimination among mechanisms. Third, analysis of WMH does not allow accurate identification of specific affected white matter tracts. Thus, one hopes the introduction of new MRI approaches (e.g., diffusion tensor, magnetization transfer) will complement the information gleaned from studies of WMH.

Aging of the White Matter Microstructure

Diffusion tensor imaging (DTI) offers a promising new technique for the identification of cerebral networks most vulnerable to the aging process. This method measures the magnitude and orientation of self-diffusion of water. When no barriers to such diffusion are present, diffusion occurs equally in all directions (i.e., it is isotropic). However, when barriers are present, diffusion tends to follow the long axis of those barriers (i.e., diffusion is anisotropic). Barriers to diffusion in the brain include cell membranes, myelin sheaths, and white matter fiber tracts. Diffusion anisotropy can be quantified by a number of different metrics, including fractional anisotropy (FA) (Figure 2), which is a measure of the strength of the directional dependence of diffusion and tissue disruption. Removal or degradation of structural barriers to the molecular motion of water (e.g., cell membrane) typically decreases FA values.

The most consistent finding from DTI studies of advancing age is a vulnerability of the prefrontal white matter to aging. Following the initial reports of greater age-related FA reductions in frontal regions of interest (ROIs) relative to more posterior ROIs (O’Sullivan et al., 2001; Sullivan et al., 2001), several studies provided converging support for an anterior-posterior gradient of age-associated decreases in FA (Ardekani *et al.*, 2007; Grieve *et al.*, 2007; Head *et al.*, 2004; Pfefferbaum and Sullivan, 2003; Salat *et al.*, 2004) as well as some evidence for age-related reductions in select striatal regions (Ardekani *et al.*, 2007; Salat *et al.*, 2004; Abe *et al.*, 2006). Furthermore, there may be differential aging effects on

FA within the frontal regions, with specific white matter areas including the ventromedial prefrontal and deep frontal white matter exhibiting the most robust relationship with age (Salat et al., 2005). Voxelwise analysis of the relationship of atrophy to age-related reductions in FA suggests that FA is a sensitive marker of aging that may precede atrophy in many regions of the brain (Hugenschmidt et al., 2007). Furthermore, FA and brain volume may be complementary indices of brain aging (Abe et al., 2006).

Abnormalities of the corpus callosum, the major commissure connecting the cerebral hemispheres, can interfere with the efficiency of interhemispheric transfer in older adults and likely contribute to specific patterns of cognitive aging (Janowsky *et al.*, 1996; Jeeves and Moes, 1996). Post mortem studies reveal subtle aging effects in the corpus callosum, with the less myelinated fibers of the genu being particularly susceptible to the deleterious effects of aging (Kemper, 1994; Aboitiz *et al*., 1992). Studies of regional FA of the corpus callosum also follow an anterior posterior gradient with the genu and rostral body exhibiting the strongest relationship with advancing age, whereas FA in the splenium is relatively stable (Ota et al., 2006; Pfefferbaum et al., 2005; Salat et al., 2005). Furthermore, application of a quantitative fiber tracking approach revealed that within the corpus callosum, there was disproportionately lower FA in anterior fiber bundles relative to posterior bundles in the older group compared to younger group (Sullivan *et al.*, 2006).

Diffusion tensor imaging indices also distinguish normal from pathological aging. For example, Head and colleagues (2004) used diffusion tensor imaging to characterize the influence of both normal and pathological (e.g., Alzheimer's disease) aging on FA. Aging effects in nondemented adults were greater in anterior compared to the posterior corpus callosum as well as greater in frontal relative to parietal, temporal, and occipital regions. In addition, demented subjects exhibited only minimal differences in anterior regions relative to their age-matched counterparts, but did show significantly reduced FA in posterior regions (Head *et al.*, 2004).

Overall, results from studies of FA suggest that microstructural white matter integrity differentiates normal from pathological aging because normal aging is associated with microstructural deterioration that generally occurs in an anterior to posterior gradient whereas dementia is associated with deterioration of more posterior regions. Some controversy exists over interpretation of DTI results. Specifically, DTI has been described as a measure of white matter integrity, but it is simply a measure of anisotropic diffusion. Furthermore, some have argued that DTI primarily measures axonal membrane integrity, with myelin playing a modulatory role (Beaulieu, 2002).

Macromolecular White Matter Changes

Magnetization transfer ratio (MTR) imaging provides information about the macromolecular structure of cerebral white matter based on the interaction of the normally observed tissue water signal with protons contained in large macromolecules (including myelin). Macromolecular semisolid structures in the brain, such as myelinated axons, are ordinarily not detectable with MRI because of their extremely short transverse relaxation times. However, protons bound to them can be selectively excited using off-resonance radio-frequency pulses. To achieve MTR contrast, two MR sequences are used. The first is a proton density (PD) weighted sequence, which reflects the total water signal. The second employs an additional pulse prior to the basic proton density sequence and serves to null the signal from water molecules that are associated with macromolecules. Thus, the second sequence reflects the signal from free water. The percent contrast difference between the two image sets is usually expressed as the magnetization transfer ratio: $MTR = (M_0 - M_{SAT})/M_0$ (Figure 3). Studies conducted in early development and multiple sclerosis

suggest that DTI and MTR may provide complementary information about white matter integrity with DTI primarily reflecting organization of fiber tracts and MTR being particularly sensitive to myelin integrity (Wozniak and Lim, 2006).

MTR in early development shows an increase during the initial years of life that coincides with brain myelination and follows the posterior to anterior temporal pattern that occurs in neurodevelopment (Wozniak and Lim, 2006). However, the relationship of MTR to age in adulthood is more controversial. For example, in 52 healthy older adults between the ages of 20 and 86 years, MTR histograms were significantly lower in the group older than 50 than those in the younger group (Ge *et al.*, 2002). The MTRs started to decline around 40 years of age. Some have suggested that if WMH are excluded, MTR remains relatively stable throughout adulthood with a trend for MTR in some regions to increase with age perhaps due to redundant myelin (Armstrong *et al.*, 2004). However, the bulk of the evidence does not support this assertion. Studies have shown that MTR values are 8 to 10% lower in WMH than in normal appearing white matter (Fazekas *et al.*, 2005; Tanabe *et al.*, 1997); but MTR is moderately negatively correlated with age both in areas of WMH and normal appearing WMH (Tanabe et al., 1997). MTR of normal appearing white matter is lower in elderly subjects related to young subjects (Fazekas *et al.*, 2005; Spilt *et al.*, 2005), but does not differ between individuals with minimal versus extensive WMH (Fazekas *et al.*, 2005). Thus, these studies support the existence of age-related reductions of MTR, which are exacerbated in areas of WMH but also occur in normal appearing white matter.

Cognition and White Matter Aging

Cognitive aging is a selective process that is marked by significant declines on tasks for which successful performance demands substantial mental effort, rely heavily on processing speed, and are characterized by complexity and novelty of the stimuli. On the other hand, performance on tasks that depend on semantic knowledge and/or overlearned skills is relatively preserved (McArdle *et al.*, 2002; Horn, 1986).

Correlations between regional brain volumes and cognitive abilities tend to be modest; however, the strength of these relationships increases with advancing age (Greenwood, 2007; Zimmerman et al., 2006) suggesting that variability in neuromorphometry among older adults at least partially accounts for age-associated variability in cognition. For example, we recently showed that relative frontal lobe white matter volume mediated the association between age and performance on tasks of memory and executive functions (Brickman et al., 2006). Furthermore, using a multivariate approach, the degree to which older adults manifested a pattern of age-associated density loss was associated with poorer performance on tasks of memory and executive abilities (Brickman *et al.*, 2007a; Brickman *et al.*, 2007b).

In addition to frontal white matter volumes, the severity of WMH is associated with poorer performance in age-sensitive domains, including executive functions, episodic memory, and slowed processing speed, among older adults (Gunning-Dixon and Raz, 2000). The contribution of WMH to age-related declines in executive skills may be independent from that of the prefrontal volume (Gunning-Dixon and Raz, 2003). Longitudinal studies also support a role of WMH in age-related declines in executive skills (Kramer *et al.*, 2007; Cook *et al.*, 2004), working memory (Raz et al., 2007), and fluid intelligence (Raz et al., 2007).

The relationship of microstructural aging to age-related cognitive decline

O'Sullivan and colleagues (2001) reported early evidence that DTI indices are related to cognitive performance in healthy older adults. In particular, lower attentional set shifting scores correlated with greater diffusivity in a frontal ROI, whereas lower verbal fluency

scores correlated with lower FA in a middle white matter ROI. The authors interpreted these relationships between DTI and attention and executive performance as evidence for cortical "disconnection" contributing to age-related cognitive declines.

Subsequent studies have provided additional evidence for the contribution of microstructural white matter reductions to select deficits in working memory and executive skills. Voxelwise analysis of FA and two measures of attention/executive skills in a sample of adults ranging in age from 20 to 73 years, detected a relationship between FA and performance on a task reliant on planning and response speed in extensive frontal, parietal, and thalamic regions, whereas no relationship was detected between performance on the attention switching task and FA (Grieve et al., 2007). In an examination of the relationship between FA in specific ROIs (anterior, middle, and posterior white matter of centrum semiovale) and executive skills, working memory, and processing speed, FA was correlated with the working memory domain only, irrespective of ROI (Charlton et al., 2006). Furthermore, in a subsample of individuals for whom MRS data were available, N-acetly-aspartate correlated with FA suggesting age-related FA reductions may be mediated by axonal loss (Charlton et al., 2006).

Regarding information processing speed, Madden and colleagues (2004) observed that higher FA in the anterior limb of the internal capsule was associated with faster response times in the older adults, whereas higher FA in the splenium of the corpus callosum was associated with faster reaction times in the younger adults only. Furthermore, results from another study suggested that age-related reductions in FA in the pericallosal frontal region and in the genu of the corpus callosum, but not in other regions, mediate the relationship between processing speed and episodic retrieval (Bucur et al., 2007). Thus, these findings provide preliminary evidence that the relationship between FA and visual attention/ information processing speed may differ between young and older adults and that white matter integrity in prefrontal regions may be one mechanism underlying the relationship between age-associated individual differences in perceptual speed and episodic memory retrieval.

Overall, results from studies examining the relationship between DTI measures and cognitive performance provide preliminary support for the idea that loss of microstuctural white matter integrity may contribute to poorer performance in age sensitive domains including executive skills, working memory, processing speed, and episodic memory.

Conclusions and Future Directions

As with most features of normal aging, observations from structural MRI aging studies are notable for increased variability and individual differences with advancing age. However, a general pattern of age-related preservation and decline has emerged with evidence that the prefrontal white matter is most susceptible to the influence of age. Studies that combine MRI with cognitive measures suggest that such age-related reductions in white matter integrity may produce a disconnection state that underlies some of the age-related performance declines on tasks of information processing speed, episodic memory, and executive functions. Furthermore, a disconnection state likely predisposes some individuals to the presentation and/or exacerbation of psychiatric illnesses (e.g., geriatric depression) that either appear or are exacerbated in late life.

We are in the early stages of understanding how genes contribute to the individual differences in white matter aging. For example, in a family-based, healthy sample from the Framingham Heart Study, heritability of WMH increased with age (Atwood *et al.*, 2004), and there is evidence showing that a gene influencing WMH is linked to chromosome 4

(DeStefano *et al.*, 2006; Seshadri *et al.*, 2007). Regarding the microstructure, DTI maps of genu FA and splenium FA show higher concordance in elderly MZ twins compared to elderly DZ twins, suggesting that there are regulated genetic effects on white matter microstructure that are quantifiable in late life (Pfefferbaum *et al.*, 2001).

While emerging evidence that use of antihypertensive medications and hormone replacement therapy appear to slow select aspects of gray matter aging, little data exist of interventions that protect against white matter aging (Erickson *et al*, 2005; Raz *et al.*, 2004; Raz *et al.*, 2006; Raz *et al.*, 2007). Preliminary findings suggest that cardiovascular fitness may have a significant influence on cerebral aging. Cardiovascular fitness has been associated with increased density in areas susceptible to aging, with the most significant effect in the anterior white matter tracts and the transverse tracts running between the frontal and posterior parietal lobes (Colcombe *et al.*, 2003). Additionally, a 6-month randomized clinical trial of older community-dwelling adults showed that significant increases in both gray matter and white matter volumes were associated with the aerobic fitness training group but not with the nonaerobic control group (Colcombe *et al.*, 2006). Future research should identify interventions that influence the course of white matter aging.

Acknowledgments

Supported by grants K23 MH074818 (FGD) K23 AG029949 (AMB) R01 NIRG-05-14586 (AMB), MH65653 (GSA), P30 MH68638 (GSA)

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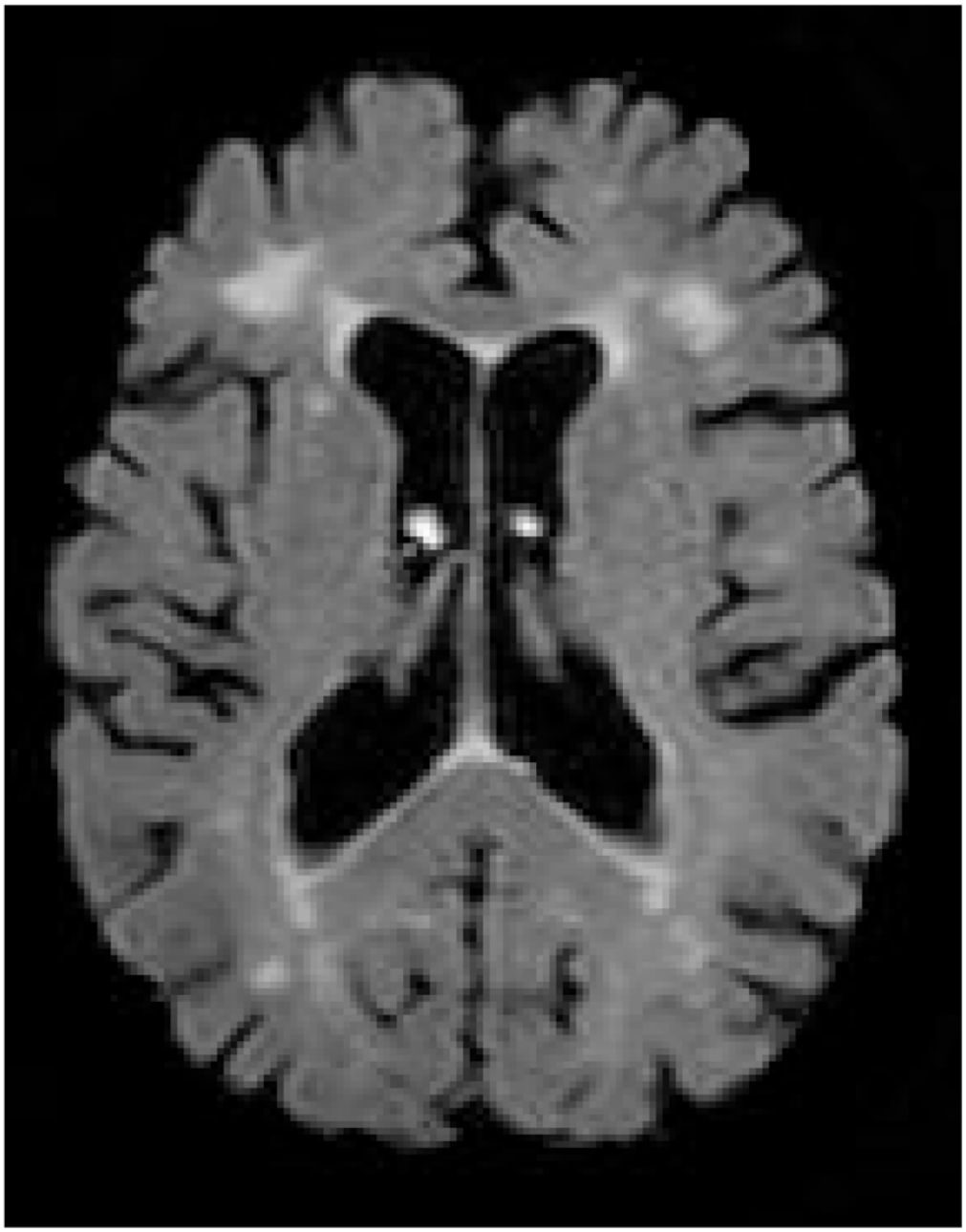

Figure 1.
White matter hyperintensities on a FLAIR image.

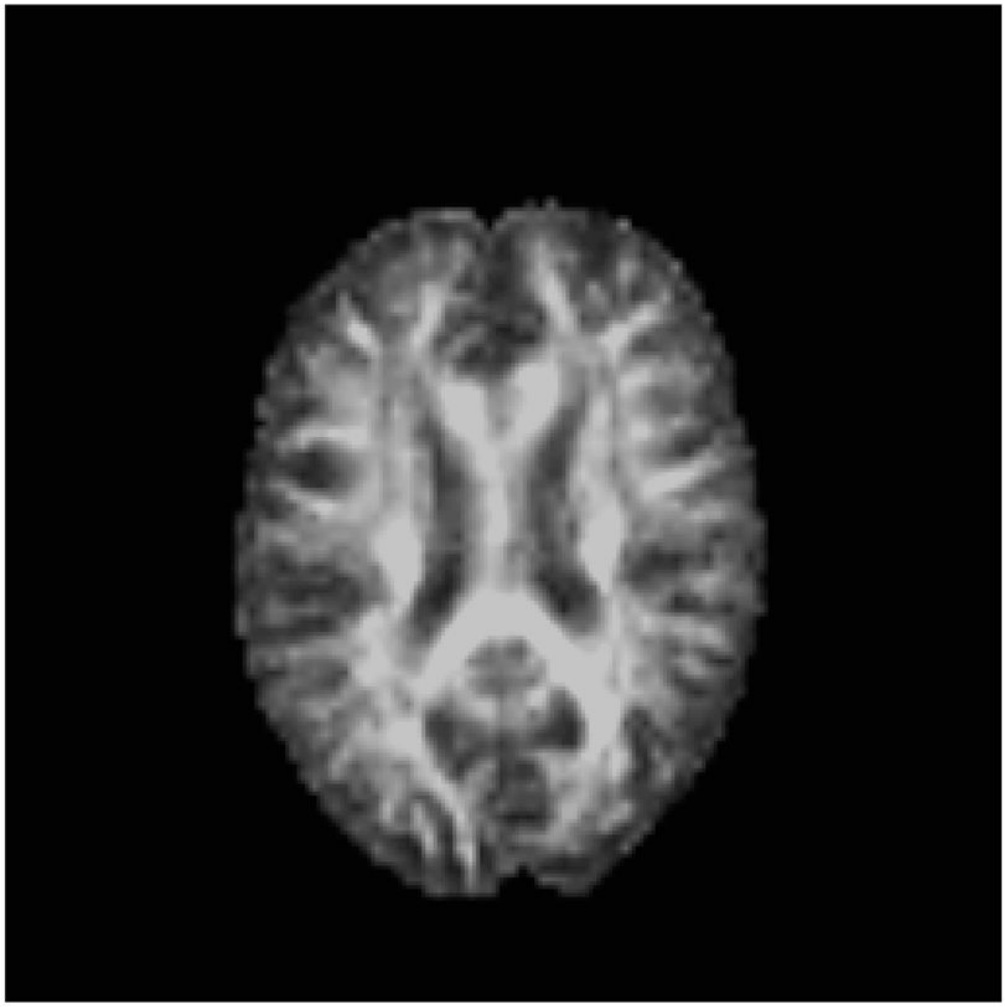

Figure 2.
Fractional anisotropy image from a diffusion tensor scan.

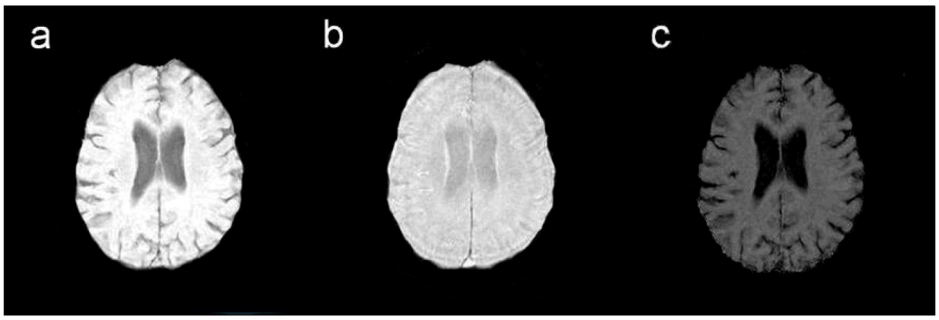

Figure 3.
a. MT_0 =Standard proton density sequence (measures bound + free protons)
b. MT_{Sat} =Saturation pulse that nulls signal due to protons bound to macromolecules including myelin (measures free protons).
c. MTR = Magnetization transfer ratio.