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# NEUROIMAGING OF WHITE MATTER IN AGING AND DEMENTIA

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Clinical neuroscientists have focused increasing attention on white matter connections in the brain and on the effects of aging and disease on these connections. Recent advances in magnetic resonance imaging (MRI) analysis have given researchers new tools for quantifying and visualizing white matter to better relate white matter structure and function. The goals of this article are (a) to acquaint the reader with both established and newer methods for imaging and quantifying white matter anatomy and pathology; and (b) to review recent findings on white matter pathology in aging and dementia. Computer-assisted quantification appears to offer better statistical power than visual rating scales for detecting these relationships. New MR modalities such as diffusion imaging can detect white matter abnormalities not shown with conventional acquisition sequences. These newer techniques hold promise for early detection of disease and for delineating functional connections between brain areas.

# INTRODUCTION

The goals of this article are (a) to acquaint the reader with both established and newer methods for imaging white matter anatomy and pathology; and (b) to review recent findings on the etiology of white matter changes in the elderly and their neuropsychological and behavioral sequelae. We briefly review white matter anatomy and the basics of MRI image acquisition. This will set the stage for a review of imaging methods for quantifying white matter pathology, including newer techniques such as diffusion tensor imaging. Finally, we will review application of these methods to the study of white matter changes in the elderly including common forms of dementia. We have limited our discussion to MRI techniques because they are the preferred modality for most current imaging research. Although our discussion focuses on aging and dementia, the neuroimaging techniques covered in this review apply to a wide range of other disorders affecting white matter, including multiple sclerosis, HIV-related neuropathology, and the leukodystrophies.

Neuronal tissue in the brain can be divided on gross inspection into gray and white matter. The gray matter is comprised primarily of neuronal cell bodies and includes the cerebral cortex, the deep brain nuclei of the thalamus, and the basal ganglia. White

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matter lies below the cortical surface and comprises approximately 40–50% of total volume of the healthy young adult human brain (Guttmann et al., 1998). The white matter is composed of bundles of myelin-coated axons, often called *tracts* that conduct neural information between gray matter regions thereby permitting the brain to work in a coordinated fashion. Terms other than "tract" used to describe white matter pathways include *bundle*, *capsule*, *fasciculus*, *funiculus*, *lemniscus*, and *peduncle* (Filley, 2001a). The gray vs. white matter distinction is somewhat incomplete, in that myelinated fibers are present throughout the gray matter mantel, and many axons are not myelinated in the human brain. Still, this distinction of gray matter within the cortical ribbon and deep nuclei with connecting white matter networks has heuristic value.

Cortical gray matter areas have been the focus of much research and conceptual work in the history of neuropsychology and behavioral neurology. In studying language systems, for example, early researchers concentrated on the effects of lesions to Broca's and Wernicke's areas in the production of receptive and expressive aphasias. However, it quickly became clear that certain language disorders such as conduction aphasia resulted from lesions in white matter connections among cortical language zones. The essential role of white matter connections in language disorders was cemented by Geschwind's classic work on disconnection syndromes (Geschwind, 1965a, 1965b), which showed that some syndromes like alexia without agraphia could be explained only by reference to lesions in specific white matter tracts. It is now widely recognized that cortical areas cannot fulfill their functions without white matter connections. Increased interest in these white matter brain connections has developed from a desire to understand the pathogenesis and clinical impact of certain disease processes that have a predilection for white matter (e.g., multiple sclerosis, leukodystrophies, and small vessel cerebrovascular disease). Neuroimaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) provide in vivo visualization of the white matter lesions (WML) associated with these and other disease processes. MRI is generally superior to CT for detecting and visualizing WML and is the preferred imaging modality for WML research.

WML appearing as punctate foci or confluent areas of signal abnormality on MRI are common in the elderly and are usually thought to reflect underlying small artery disease (Ho & Garcia, 2000; Udaka, Sawada, & Kameyama, 2002). WML in the elderly have been shown to adversely impact cognition and behavior (Breteler et al., 1994; de Groot et al., 2000; de Leeuw, de Groot, & Breteler, 2000; Inzitari, 2000; Junque et al., 1990) but the strength of this association has varied across studies due to differences in study populations, imaging modalities (i.e., CT vs. MRI), analysis techniques (i.e., qualitative vs. quantitative measurements), and cognitive test batteries. Newer MRI techniques such as diffusion tensor imaging (DTI) offer improved detection of white matter changes and may enhance understanding of the pathogenesis of WML and their impact on cognition and behavior.

# **NEUROANATOMY OF WHITE MATTER**

# White Matter Tracts

The three major groups of white matter pathways include projection, commissural, and association fibers (see Figure 1). *Projection* fibers are long ascending



Figure 1 Selected association (a), commissural (b), and projection (c) white matter tracts shown in brain dissection. Adapted with permission from Terence H. Williams et al., the University of Iowa Virtual Hospital, *The Human Brain*, Chapter 5, The Cerebral Hemispheres. http://www.vh.org/adult/provider/anatomy/BrainAnatomy/Ch5Text/Section15.html

and descending fibers that connect the spinal cord, diencephalic, and mesencephalic structures with the cortex. Projection pathways include *ascending pathways* from the thalamus and basal ganglia to the cortex (e.g., corona radiata, anterior internal capsule), and *descending pathways* (e.g., pyramidal tracts) from cortex to subcortical structures. Some of these ascending and descending tracts form reciprocal connections, providing the basis for feedback loops. For example, cortical attentional systems can affect input from sensory systems via thalamic gating; pyramidal and extrapyramidal motor systems can interact to produce coordinated movement. *Commisural* fibers connect the two cerebral hemispheres and the largest bundle of such fibers is the corpus callosum. *Association* fibers connect cortical regions within a hemisphere and are comprised of two subtypes: short association fibers (called

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U-fibers or arcuate fibers) that connect adjacent cortical gyri, and long association fibers (e.g., the superior longitudinal fasciculus) that connect more disparate cortical regions (Carpenter, 1991; Filley, 2001a). Long association tracts are usually more susceptible than U-fibers to injury from small vessel cerebrovascular disease, which is typically most pronounced in the periventricular and deep white matter regions that these fibers traverse. Most long association fibers project to the frontal lobes, suggesting that they facilitate interaction of the frontal lobes with all other cerebral regions. The frontal cortex also has numerous connections with subcortical gray matter structures including the striatum, thalamus, and limbic structures. These frontal-cortical and frontal-subcortical circuits subserve executive function and behavioral regulation (Mega & Cummings, 1994). A number of additional smaller white matter tracts lie deep within the brain (e.g., extreme capsule, medial forebrain bundle) and presumably link subcortical gray structures with one another and with cortical regions (Carpenter, 1991; Filley, 2001a).

Certain white matter tracts, such as the corpus callosum, anterior and posterior commissures, cingulum bundle, and internal and external capsules are readily identified on conventional neuroimaging, particularly MRI. However, much of the white matter appears homogeneous without distinct tracts. Different regions are therefore anatomically designated by broad, somewhat imprecise terms. For example, *periventricular white matter* is contiguous to the lateral ventricles. *Deep white matter* typically refers to white matter not directly adjacent to the ventricles but usually excludes U-fibers. The term *subcortical white matter* is sometimes used to refer to periventricular and deep white matter collectively, and may or may not include U-fibers.

# White Matter Pathology in the Elderly

There are generally two types of WML visible on MRI in the elderly. The appearance of these lesions depends on the contrast characteristics specified in the MRI acquisition (e.g., T1- vs. T2-weighted); this will be discussed in the next section. One type of WML is a region that appears more *hyperintense* (bright) than the surrounding tissue on T2-weighted MRI. These WML can appear in periventricular and deep white matter regions, as well as in basal ganglia or other subcortical gray nuclei. These hyperintense lesions begin as small punctate areas that, over time, can expand and coalesce into larger confluent regions with disease progression. These hyperintensities are thought to reflect regions of incomplete infarction due to hypoperfusion associated with underlying small vessel disease (see below). The second type of WML are *lacunar infarcts*, which typically appear as small, circular, circumscribed *hypoin*tense (dark) holes on T1-weighted MRI. These hypointensities represent areas of completed infarction. However, they may be confused with dilated perivascular spaces, which also occur with aging and have a similar appearance. The earliest white matter changes seen on MRI in the elderly are typically hyperintensities seen in the areas surrounding the frontal horns and the trigone of the lateral ventricles. As discussed in more detail below, some mild degree of white matter hyperintensities occurs in normal aging without demonstrable changes in cognition or behavior. However, more severe changes in deep white matter and in subcortical deep gray matter structures (e.g., basal ganglia) can result in neuropsychological deficits ranging from mild problems to dementia. The range of white matter hyperintensities



Figure 2 Subcortical hyperintensities on MRI, ranging in severity from none (left), through mild and moderate, to severe (right).

is illustrated in Figure 2. Although most white matter changes in the elderly are vascular in origin, there are many other disorders that can cause white matter hyperintensities (Yamamoto & Bogousslavsky, 2000).

There is some ambiguity in the terms used in the literature to describe these white matter abnormalities. Leukoaraiosis (literally, "rarified white matter") is a term introduced by Hachinski and colleagues (Hachinski, Potter, & Merskey, 1986, 1987) to describe the appearance of white matter hypodense regions on CT scan without reference to the underlying pathology or their clinical significance. Current usage of the term also includes MRI hyperintensities. However, the term is also commonly used to imply the presence of a variety of pathologies, risk factors, and clinical associations for which it was not intended (Merino & Hachinski, 2000). Radiologically, hyperintense lesions are sometimes referred to as subcortical hyperintensities (SH) or T2-hyperintensities, although these terms may fail to distinguish between hyperintensities occurring in white matter and those seen in subcortical nuclei such as the basal ganglia. The term white matter changes (WMC) is also sometimes used to refer to WMH. Particularly confusing is the acronym WML which may mean white matter lesions or white matter lucencies, both of which generally refer to hyperintensities but retain some ambiguity. For consistency, we will use white matter hyperintensities (WMH) when referring specifically to hyperintensities in white matter distinct from basal ganglia or thalamic hyperintensities and lacunar infarcts. We will use the term *white matter lesions (WML)* to refer collectively to hyperintense and lacunar lesions in white matter.

Age is the strongest predictor of WML (de Leeuw et al., 2001). Additional risk factors include hypertension, atherosclerosis, diabetes, smoking, hypercholesterolemia (de Leeuw et al., 2000), elevated homocysteine (Vermeer et al., 2002), and hypotension (Raiha et al., 1993). Of these additional risk factors, hypertension has shown the most consistent association with WML (de Leeuw et al., 2000). Incidence estimates of WML range from 10% to 100% of non-demented elderly, depending on the severity criteria used for defining lesions, particularly WMH (de Leeuw et al., 2000; Hunt et al., 1989; Jernigan, Press, & Hesselink, 1990).

The basic neuropathological correlates of vascular WMH in the elderly include loss of axons, demyelination, increased numbers of astrocytes and microglia (i.e., *gliosis*), and necrotic changes that produce scarring or cavitation (Englund, 2000). These changes can arise generally from complete and incomplete infarction and hypoperfusion-hypoxic injury due to blood vessel pathology including lipid

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deposition, hyalinization of the vessel wall with increased rigidity, breakdown of vessel endothelial function, and microaneurysms (Englund, 2000; Fazekas et al., 1993; Fazekas, Schmidt, & Scheltens, 1998; Ho & Garcia, 2000). These vascular changes result in lowered permeability and decreased tissue perfusion. The severity and extent of these vascular changes increases in correspondence with the extent of hyperintensities on MRI, from discrete punctate lesions through beginning confluence to large confluent regions (Fazekas et al., 1993, 1998a; Scheltens et al., 1995). One notable exception to the vascular origin of WMH are periventricular hyperintensities, including capping frontal horns and a smooth, band-like halo along the ventricle body. These have been linked to disruption of the ependymal lining of the ventricle, causing transudation of cerebrospinal fluid with resultant gliosis and concomitant loss of myelin (Fazekas et al., 1993; Thomas, O'Brien, Barber, McMeekin, & Perry, 2003).

Many of these pathological processes result in increased tissue water content and it is this increase in interstitial water that produces the hyper- or hypointense appearance of WML on MRI. This is because MRI is based on excitation and relaxation of hydrogen atoms, and so the interstitial fluid increase alters MRI signal. To better understand how these alterations in tissue water concentration affect MRI signal, and how newer technologies exploit these effects, it is important to understand the basic principles of MRI physics. Toward this end we will provide a brief discussion of the basics of the physics and technical aspects of MRI. A thorough treatment is well beyond the scope of this review article, and of necessity many important aspects of MRI technology are omitted or considerably simplified.

# **BASICS OF MR IMAGE ACQUISITION**

MRI uses a strong magnetic field and radio waves to produce images of human tissue. MR imaging is based on a natural electromagnetic property of hydrogen atoms called *nuclear magnetic resonance* (NMR). Hydrogen atoms are abundant in fat and water in biological tissues. The protons of hydrogen atoms have spin and a positive charge that together produce a small magnetic field. These spinning protons cause the hydrogen atom to *precess* around its axis, much like a spinning toy top wobbles on its axis. Normally, hydrogen atoms in fat and water precess independently and their magnetic fields are aligned randomly. Exposing the atoms to a strong magnetic field (i.e., the bore of an MRI scanner) causes most of them to align with the main magnetic field, and they begin to precess in phase at the *resonance frequency*, which is proportional to the strength of the magnetic field. Higher field magnets cause a greater proportion of atoms to align with the field, potentially producing a superior image. The net alignment and precessional phasing are the starting point for MR imaging.

The next step in MRI is to generate a signal that can be detected by the scanner. To accomplish this, the tissue is bombarded with a brief radiofrequency (RF) pulse corresponding to the resonant frequency of the precessing hydrogen atoms (*Larmor frequency*). These RF pulses cause the atoms to absorb energy, flipping their alignment away from the main magnetic field, and producing a more complete locking of the precessional phases. When the RF pulse is turned off, the absorbed RF energy is released by two simultaneous processes, *relaxation* and *dephasing*. In relaxation, there is loss of energy that causes the spinning atoms to realign with the main



Figure 3 T1 and T2 relaxation.

magnetic field. In dephasing, energy is lost due to loss of precessional phase across atoms. The time required for the re-alignment is called T1 and the time required for dephasing is called T2. The energy given off during the T1 and T2 relaxation process is the signal that is measured by the MRI scanner to produce an image (see Figures 3a and 3b).

MRI image contrast between tissue types occurs because fat and water have different T1 and T2 relaxation times. Knowing these values, the timing of RF pulses and signal measurement can be varied, with signal dominated by either T1- or T2-weighting to produce images with different contrast effects. *T1-weighted images* produce good anatomic resolution, but are relatively insensitive to pathology. Most pathology appears hypointense (dark areas) on T1. *T2-weighted images* produce poor anatomic resolution, but most pathology can be readily seen as hyperintense. The T2 signal is higher in pathological tissue because most pathology is associated with increased water content (see Figure 3c). One limitation of T2-weighted images is that both cerebrospinal fluid (CSF) and pathological tissue can be equally

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**Figure 4** Large vessel stroke of the left middle cerebral artery resulting in Wernicke's aphasia. Note that pathology is dark on T1-weighted image (a), bright on T2-weighted image (b), and that the FLAIR image (c) allows discrimination of cerebrospinal fluid from lesion.

hyperintense making it difficult to delineate boundaries between CSF spaces such as the ventricles or subarachnoid space and adjacent pathology. *Proton density images* were previously used to make this discrimination, because it provided for gradations of hyperintensity between free water (e.g., ventricles) and bound water (i.e., pathology). Currently, *FLAIR* (fluid attenuated inversion recovery) sequences are more commonly used. FLAIR images produce superior anatomic resolution and better discrimination of pathology from normal tissue. An example of lesion appearance in these various pulse sequences is presented in Figure 4.

#### **General Technical Issues in MRI**

The standard MRI scanner consists of a main magnet; gradient coils to produce magnetic gradients in the *x*, *y*, and *z* directions for signal localization, slice thickness adjustments, and other important functions; RF transmitter and receiver coils (in some scanners one set of coils serves both functions); an RF receiver that detects, deconvolves, and amplifies the raw signal coming from the tissue; a pulse programmer that controls the timing of RF pulse sequences and signal acquisition; a computer with a console interface with specialized software that controls the pulse programmer and reconstructs the raw data into images; and a film printer (Wolbarst, 1993a, 1993b).

Most standard MRI systems in use today are superconducting magnets with field strength of 1.5 Tesla (1.5 T), which is approximately 25,000 times the strength of the Earth's magnetic field (Reyfman, 1997). Higher field systems (3 T and above) are becoming more common. Pulse sequences typically used in clinical imaging are pre-programmed on most systems and are adjustable within certain safety limits to fine-tune different contrast effects. Research agreements between manufacturers and institutions can be negotiated to allow the research centers to develop new software, imaging sequences, and hardware.

A variety of free and commercial image analysis software programs are available for quantitative imaging analysis. Such programs permit morphometric analysis of specific anatomical structures or lesions, segmentation of white matter from gray matter and CSF, region-of-interest analysis, and numerous other procedures. Frequently, MRI research centers develop their own "in-house" software to achieve specific analyses.

#### **IMAGING WHITE MATTER LESIONS USING CONVENTIONAL MRI**

#### **Ratings of WML**

Much of the research on WML in the elderly has focused on determining the presence or absence of WML and correlating WML severity with putative risk factors and with measures of cognition, behavior, and function (Mantyla et al., 1997). Two approaches have been used for quantitating WML severity: visual rating scales and computerized methods.

Visual rating scales are convenient, especially for clinical and epidemiological studies, because they are based on the MRI (or CT) films and can be performed relatively quickly without specialized computer software. Visual ratings of lacunar infarctions typically involves determining their number and location. Visual ratings of WMH are more complicated. Large lesions can be difficult to localize as falling in periventricular or deep white matter. Another key limitation of visual WMH rating scales is that they tend to take a continuous variable (i.e., severity of WMH) and map it to an ordinal, categorical scale (e.g., absence, mild, moderate, severe) with discrete scores and qualitative anchor points. This invariably constrains the range of WMH severity, which in turn limits the available variance for correlational analysis with cognitive test scores or other measures. Another limitation of some visual rating scales is that raters must often make decisions about how to score WMH severity that falls between the categories. Variability in the application of decision rules can lead to unacceptably low levels of inter- and intra-rater reliability. This can be improved with adequate rater training with a set of training images, establishment of appropriate image exemplars for anchoring ratings, and deferring to consensus ratings on particularly problematic cases.

Three key variables should be considered in a visual rating scale: location, size, and number of lesions (de Leeuw et al., 2000). Initially, most researchers developed their own rating scales. An early study (Mantyla et al., 1997) showed that use of different rating scales grouped individuals similarly in terms of their "grade" of WMH severity. However, there was poor agreement about the severity of hyperintensities in periventricular and deep white matter regions. Two methods have nonetheless gained relatively wide acceptance: the Fazekas scale (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987; Schmidt, 1992) and the Schelten's scale (Scheltens et al., 1993). Others include those of Victoroff (Victoroff, Mack, Grafton, Schreibear, & Chui, 1994), Erkinjuntti (Vataja et al., 2003) and Manolio (Manolio et al., 1994). The Fazekas scale was developed to assess periventricular and deep white matter hyperintensities on a 0 (none) to 3 (severe) scale. The Scheltens scale (Scheltens et al., 1993) attempted to improve upon the Fazekas scale. They designed a new rating scale in which periventricular and deep white matter signal hyperintensities as well as basal ganglia and infratentorial signal hyperintensities were rated separately in a semiquantitative way. They compared the inter- and intra-observer agreements of this scale to the widely used rating scale of Fazekas. The new scale provided better inter-rater agreement with respect to the white matter, basal ganglia, and infratentorial signal hyperintensities; but it yielded no advantages in rating periventricular hyperintensities. Comparative studies of inter-rater reliability among the different scales have revealed two significant contributors to acceptable levels rater agreement: number of hyperintensities and experience. Wardlaw, Ferguson, and Graham (2004)

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examined inter-rater agreement (Kappa coefficient) between two raters completing multiple white matter hyperintensity MRI ratings scales on a large sample (n = 494) with mixed pathologies. They found the rater agreement was highest when the number of hyperintensity was greatest and agreement fell when rating MR images with fewer hyperintensities. A more recent study (Kapeller et al., 2003) examined the interrater reliability of three raters trained at different sites and having different levels of experience on three established visual rating scales (Fazekas, Scheltens, & Manolio) on baseline and follow-up scans (1.5 to 4 years) of 74 elderly individuals. Interrater reliability for the baseline scans was better between the Fazekas and Scheltens scale than between those two and the Manolio scale. Interrater reliability was poor for detecting progression of WML on the follow-up scans. There was no difference in rating scores among the three raters despite their differing training and levels of experience. This suggests that providing clear scoring instructions and visual exemplars of the different severity ratings promoted consistency in the ratings.

### **Computerized Measures of WML**

These methods are based on the digital MRI data and require specialized computer software. Key advantages to these methods are that they can be automated or semi-automated to increase inter- and intra-rater reliability, and they can provide a more accurate volumetric measure of WMH and lacunar infarction burden corrected for brain size. Limitations include the requirement for digital data (rather than just the MRI film) and the increased time needed to perform the measurements. One approach is to use a *thresholding* technique that segments tissue types (i.e., CSF, white matter, WML, gray matter). This can be achieved by having the software program display a histogram of pixel intensity values for the tissue to be segmented, selecting an intensity threshold that has a high probability of including only that tissue type, and then use the software to count all pixels within the specified intensity range (Salloway et al., 1996). In seed-growing techniques, an algorithm detects regions of interest grown from a seed inserted interactively by a user. The regions consist of contiguous areas or volumes having similar pixel intensity values. Parameters for controlling the growth of the seed can be set interactively, or may be determined automatically from a sample region. Regions of interest can be successively extended into adjacent slices, building up a three-dimensional (3D) volume (Sivewright & Elliott, 1994). Usually, some form of user intervention is required to exclude extraneous or missed voxels to finalize the volume determination. Lastly, manual tracing of lesion boundaries has been used. In all of these approaches, WMH volume can be calculated by multiplying the number of selected pixels by the slice thickness and number of slices sampled. WMH volume can then be adjusted for brain volume also measured with computer methods. One study comparing the manual tracing method with two different visual rating scales found no clear superiority for the computerized method in terms of improving inter-rater reliability or in the correlation between ratings (Sachdev, Cathcart, Shnier, Wen, & Brodaty, 1999). However, quantitative measurements may be superior to visual rating scales for detecting progression of WMH (Prins et al., 2004) and may have higher correlations with cognitive deficits thought to be disrupted by WMH (i.e., psychomotor processing speed, executive functions, visuoconstructional ability) (Davis Garrett et al.,



Figure 5 Semi-automated thresholding of white matter hyperintensities and whole brain volume on MRI.

2004). A meta-analysis also showed that quantitative measurements of WMH severity were more strongly correlated with psychomotor processing speed than were visual ratings (Gunning-Dixon & Raz, 2000). Taken together, these results suggest that while inter-rater reliability might be similar between visual and computerized measurements of WMH severity, the computerized measurements may be preferred because of they have greater power to correlate with cognitive functions. Examples of WMH and whole brain thresholding are shown in Figure 5.

# NEW MRI TECHNIQUES FOR IMAGING WHITE MATTER

# **Magnetic Transfer Imaging**

Magnetic transfer imaging (MTI) measures the exchange of magnetization between the mobile and bound water (i.e., water bound to macromolecules) in tissues. The key value of interest is the magnetic transfer ratio (MTR), a ratio of the signal strengths with and without a special off-resonance RF pulse that suppresses signal from both bound, and to a lesser extent, mobile water. The MTR is calculated for each image voxel and these values are used to generate an image. MTI is highly sensitive to demyelination and axonal loss (Bognato & Frank, 2003; Gavra, Voumvourakis, Gouliamos, Sfagos, & Vlahos, 2004; Henkelman, Stanisz, & Graham, 2001).

MTI has found its greatest brain research application in the study of multiple sclerosis (Bognato & Frank, 2003; Gavra et al., 2004; Henkelman et al., 2001; Mezzapesa, Rocca, Pagani, Comi, & Filippi, 2003), in which it has been shown to be capable of detecting alterations in white matter regions that appear normal on conventional MR images (Filippi et al., 1995; Goodkin et al., 1998; Hiehle et al., 1995). MTR decreases at the time of MS lesion development and then subsequently increase with lesion recovery, but do not return to normal levels (Bognato & Frank, 2003; Goodkin et al., 1998). Also, differences in MTR values within the center vs. periphery of MS lesions have been demonstrated suggesting that MTI is capable of detecting gradations of demyelination within lesions (Hiehle, Grossman, Ramer, Gonzalez-Scarano, & Cohen, 1995). The alterations in MTR have been shown to correlate with pathological changes in myelination (Schmierer, Scaravilli, Altmann, Barker, & Miller, 2004).

MTI may also be a useful tool for quantifying white matter changes in aging and in diseases other than MS. For example, MTRs start to decline in both gray and white matter after the age of approximately 40 years in both men and women (Ge et al., 2002). Specific findings related to aging and dementia will be discussed below.

#### **Diffusion-Weighted Imaging (DWI)**

DWI is an important clinical MRI method for detecting acute stroke. DWI works by measuring the characteristics of water diffusion in the brain. In biological tissue, diffusion of water molecules is restricted by microstructural barriers such as cell membranes, organelles, and microtubules. Ischemia and other pathological processes destroy or damage these microstructural barriers and this permits water molecules to diffuse more freely.

In DWI, just as in conventional MRI, an RF pulse is used to excite the hydrogen atoms and bring them into precessional phase. DWI modifies this basic MRI acquisition by applying two brief, strong, and opposing magnetic gradient pulses in rapid succession. These *diffusion-encoding* gradients are applied in the time interval between initial RF pulse but before signal readout (Stejskal & Tanner, 1965). Diffusion-encoding gradients can be applied in any direction and combinations are also possible (Bammer, 2003). In clinical DWI for stroke detection, diffusionencoding gradients are typically applied in the three principle axes of the scanner (x, y, z). These gradients consist of a linearly increasing magnetic field superimposed on the main magnetic field and are controlled by switching on and off the electric current to the scanner's gradient coils. Gradients can be applied sequentially or simultaneously, depending on the specifics of the image acquisition protocol (Bammer). Protons at spatially different locations along the gradient experience a slightly different magnetic field strength causing a slight shift in precessional phase from their proton neighbors. This shift in the phases of the protons would effectively cancel all the signal. However, after turning off the first gradient pulse, a second pulse of equal strength is turned on in the opposite direction. For protons that were stationary (i.e., part of macromolecules), the second gradient unwinds the phase shift caused by the first and there is no net phase change or signal loss. For mobile protons in water molecules, the phase shift caused by the first gradient pulse is not entirely unwound by the second gradient because the proton has diffused to a different location along the gradient. This loss of precessional phase within a voxel results in signal attenuation that is proportional to how far the proton has moved (Bammer; Buxton, 2002; Reinges, Schoth, Coenen, & Krings, 2004). It should be noted that multiple methods have been developed for acquiring DWI data that differ in terms of the timing and application of RF pulses and diffusion-encoding gradients and other parameters. Each method has its own advantages and disadvantages in terms of the time taken to acquire the data, hardware considerations, and susceptibility to different kinds of artifact (Bammer).

In DWI, signal is acquired with and without diffusion encoding and a diffusion coefficient (D) is calculated for each voxel. The values of this ratio can mapped to an image called the *apparent diffusion coefficient* (ADC) map in which areas with the largest D (greatest diffusion) are brightest. Alternatively, a *diffusion-weighted* map



Figure 6 Diffusion weighted image three hours after acute onset of aphasia in an elderly woman. Adapted from http://rabi.nmr.mgh.harvard.edu/fMRI/new/QTV.com/DWI+PWI.html.

can be created directly from the diffusion-encoded signal values. In these images, regions of high diffusion appear dark because of signal attenuation (Bammer, 2003; Buxton, 2002).

Figure 6 presents an example of DWI in acute stroke. Note that the conventional T2-weighted image (left) does not display the infarction, but the initial DWI image (center) shows a small area of abnormality in the vicinity of Broca's area. The DWI acquired later (right) shows a larger area of infarction.

Despite its advantages for imaging acute ischemia, DWI used alone is limited for describing the three-dimensional characteristics of water diffusion in white matter. In pure liquid, water molecules diffuse constantly and randomly, their speed being dependent on temperature. This type of diffusion is *isotropic*; that is, water molecules may diffuse at equal rates in all directions. In white matter, or other highly organized tissue that restricts diffusion in one or more directions, water diffusion becomes *anisotropic*, with the diffusion greater in some directions than others, i.e., greater along the axons than perpendicular to them (Beaulieu, 2002; Chabriat et al., 1999). In most clinical applications of DWI, diffusion-encoding gradients are typically applied along the three main scanner axes (x, y, and z) (Buxton, 2002). This is generally sufficient for characterizing diffusion in gray matter where cellular barriers are not highly directionally aligned, and as a result, diffusion approaches isotropy. However, the three x, y, and z diffusion-encoding directions are insufficient for characterizing three dimensional anisotropic diffusion such as that found in white matter or other directionally aligned tissues (e.g., muscle). Anisotropy measures obtained from DWI may be spuriously low and may inaccurately suggest the presence of pathology particularly in regions where white matter pathways are oriented obliquely to the scanner axes. For this reason, anisotropy estimates derived from DWI are considered to be *rotationally variant*; that is, they are dependent on the orientation of the tissue relative to the axes of the diffusion-encoding gradients (Basser, Mattiello, & LeBihan, 1994; Basser & Pierpaoli, 1996; Pierpaoli & Basser, 1996). Accurate three-dimensional characterization of diffusion in anisotropic tissues requires a method capable of producing rotationally invariant data. A technique for achieving this is called *diffusion-tensor imaging*. (Basser & Jones, 2002; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996.)

#### **Diffusion Tensor Imaging (DTI)**

DTI is an extension of DWI that provides information about the microstructural integrity of white matter in vivoby measuring the *magnitude and direction* of water diffusion (Basser & Pierpaoli, 1996; Pierpaoli & Basser, 1996; Zhang, Kindlmann, & Laidlaw, 2004). In DTI at least six diffusion weighted images are acquired, each with different diffusion encoding gradients, from a set of noncollinear directions (e.g., x, y, z, xy, xz, yz), instead of only three (Basser & Pierpaoli, 1996; Buxton, 2002; Pierpaoli & Basser, 1996; Reinges et al., 2004). An additional image is typically acquired with no diffusion encoding. It is important to stress that six diffusion-encoding gradients is the minimum for describing three-dimensional anisotropy. More directions will improve the quality of the data and minimize errors, particularly in regions where white matter fibers interdigitate.

DTI is mathematically complex and several steps are needed to summarize the data and produce images. The first step in data processing is to summarize the data from each of the multiple diffusion-encoded images for each voxel as a numerical matrix or *tensor* (Ahrens, Laidlaw, Readhead, Brosnan, & Fraser, 1998; Reinges et al., 2004). The tensor can then be mathematically reduced (diagonalized) to its three principal *eigenvalues* and corresponding *eigenvectors*, which contain information about the magnitude of the diffusion in various orienations. The eigenvalues and eigenvectors are used to produce images of the DTI data.

At its most basic level, the diffusion tensor for each image voxel can be visualized as an ellipsoid (see Figure 7). The shape of the ellipsoid is determined by the relative magnitudes of the three eigenvalues, its size is determined by the product of the eigenvalues, and its orientation is determined by the primary eigenvector of the diffusion tensor (Laidlaw et al., 1998; Reinges et al., 2004; Westin et al., 2002; Zhang, Kindlmann, et al., 2004).

The ellipsoid reflects the underlying tissue microstructure. Purely isotropic diffusion is represented as a sphere showing that diffusion is equal in all directions. Anisotropic diffusion is represented either as linear (cigar shaped) or planar (plate shaped). Linear ellipsoids represent diffusion that is greatest in one direction and restricted in the other two as might occur in a white matter fiber bundle. Planar ellipsoids occur when diffusion is restricted in only one direction and may occur in regions where fiber pathways cross (Westin et al., 2002; Zhang, Bastin, et al.,



**Figure 7** Linear, planar, and spherical ellipsoids in DTI. Ellipsoids are an idealized representation that are convenient as a conceptual heuristic; in actuality the shape of the diffusion ellipsoids are more complex. Courtesy of Dr. Gordon Kindlmann, Harvard University.

2004; Zhang, Demiralp, & Laidlaw, 2003). Brain maps of the spherical (isotropy), linear, and planar diffusion can be produced based on these ellipsoids and their underlying eigenvalues.

A more commonly used method of visualizing and analyzing DTI data is to produce scalar parameter maps. These are 2D images based on scalar values calculated from the principal eigenvalues in each image voxel. Scalars are quantities that have only magnitude (e.g., speed; 30 mph). Scalars contrast with vectors, which have magnitude and direction (e.g., velocity; 30 mph, east). Among the many possibilities for these values are diffusivity (i.e., the magnitude of diffusion) and anisotropy (i.e., the extent to which diffusion is directionally restricted). These variables serve as indirect markers of the underlying tissue microstructure without reference to the directional orientation of diffusion. For example, tissue damage often results in increased interstitial fluid content with concomitant increased diffusivity. Damage occurring to highly organized tissues such as white matter results not only in increased diffusivity, but also to decreased anisotropy due to loss of axonal elements that directionally restrict diffusion.

The most commonly reported DTI scalar parameters of diffusivity are the *trace* of the tensor (i.e., the sum of the three principle eigenvalues) and *mean diffusivity* (MD) (i.e., the directionally averaged diffusion; i.e., trace/3). MD and trace have units of mm<sup>2</sup>/s and have values ranging from 0 to 1 with higher values representing greater diffusion. The most commonly reported anisotropy scalars are *relative anisotropy* (RA) (i.e., the ratio of the anisotropic to isotropic part of the diffusion tensor) and *fractional anisotropy* (FA) (i.e., the fraction of diffusion that can be ascribed to anisotropic diffusion) (Le Bihan et al., 2001). Like diffusivity measures, FA and RA can take on any value from 0 to 1, with 0 representing random diffusion and 1 representing completely directional diffusion. However, unlike diffusivity measures, FA and RA are unitless. In intact and highly organized white matter RA and FA measures tend to be fairly robust, measuring above 0.35. In damaged white matter, these values fall below 0.3, and in gray matter, with relative few organized barriers to random diffusion, measures of anisotropic diffusion fall below 0.2.

In addition to these intravoxel scalar parameters of RA and FA, intervoxel measures such as *lattice index (LI)* and *coherence (C)* have been used to describe the coherence of anisotropy across neighboring voxels. The majority of published clinical studies of white matter using DTI have compared patient and control groups on these intra- and intervoxel scalar parameters. The expectation in these studies is typically that white matter integrity will be poorer in the patient vs. control groups as evidenced by increased diffusion and decreased anisotropy. Several studies using these scalar parameters have now shown that DTI can detect changes in white matter microstructural integrity in regions that appear normal on conventional MRI sequences (Chabriat et al., 1999; O'Sullivan, Summers, et al., 2001).

Researchers have adopted two main approaches to analyzing DTI scalar data: region-of-interest (ROI) and voxel-wise comparisons. The strength of an ROI approach is that it allows researchers to examine discrete brain regions based on *a priori* hypotheses. For example, a researcher might examine the hypothesis that DTI values in frontal white matter ROIs might be more strongly related to executive dysfunction than posterior regions. The ROIs are typically placed on one image volume at a time and then pooled across subjects and compared in statistical analyses. The potential disadvantage of the ROI approach is that it may overlook important differences occurring outside of the chosen ROI (Type II error). In voxel-wise or "whole brain white matter" analyses, individual image volumes are spatially normalized to a standard template. Then a segmented mask of the white matter is created and composite maps of each group are compared statistically on a voxel-by-voxel basis. The result is a statistical probability map of white matter differences among groups. This approach provides an atheoretical method that may uncover unexpected relationships between white matter changes and function. The potential disadvantages of the voxel-wise approach are that it is highly dependent on the thresholds used to determine statistical significance between voxels, and it may identify spurious differences (Type I error).

Another important method for visualizing DTI data is *tractography* (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000). Tractography incorporates both scalar and vector parameters to generate computerized representations of the topology of white matter fiber pathways as they course through the brain—information that is lost when scalar indices are used to compare differences in local brain structure. The most basic approach to visualizing fiber directions is to produce color anisotropy maps in which color represents the primary orientation of anisotropy and intensity represents the degree of anisotropy (Reinges et al., 2004). These maps are typically based on FA and the most common color scheme is to use red for left-right fibers, green for anterior-posterior, and blue for superior-inferior.

In true tractography methods, mathematical algorithms are used to produce colorized white matter fiber maps (see Figure 8) based on coherence of linear anisotropy across voxels (Basser et al., 2000; Reinges et al., 2004; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004; Westin et al., 2002; Zhang et al., 2003). In the simplest terms, these algorithms work by propagating a continuous track from an initial seed-point in the direction of the principal eigenvector of a set of voxels whose linear anisotropy is above a certain empirically pre-determined threshold.



**Figure 8** Three-dimensional DTI reconstruction of white matter tracts using streamtubes. All tracts are shown on the right; on the left thresholding and color coding has been used to display specific tracts, based on coherence of linear anisotropy across voxels.

If, over a certain specified distance, the track breaks (i.e., linear anisotropy falls below the predetermined threshold) or its curvature becomes too great, it is terminated. A number of labs have developed fiber-tracking methods, each with unique strengths and weaknesses, and each using different digital glyphs to visualize fiber tracts including lines (Westin et al.) and streamtubes and streamsurfaces (Zhang et al., 2003). Results can vary depending on the formulas used to determine the main direction of diffusion, and computational decision rules governing when to terminate a tract due to directional changes or loss of anisotropy.

DTI tractography is still an evolving technique and limitations exist. Comparisons of fiber pathways are difficult to make across populations. Trial and error may be needed to set the algorithm properly to minimize generation of spurious pathways that have no anatomic correlate, and methods are needed for culling out numerous small pathways that may obscure visualization of major fiber bundles of interest (Zhang, Bastin, et al., 2004). Significant computational errors in trajectories can occur in regions where the white matter structures cross, diverge, or are adjacent to other tissues, resulting in the plotting of spurious pathways (Pierpaoli & Basser, 1996). Such errors can occur because the algorithm may follow a pathway of linear anisotropy that is not real but rather arises from the amalgam of tensor vectors in these regions of complex tissue microstructure. Tractography is also sensitive to image noise from motion, or artifact and a small amount of noise can lead to significantly different results.

DTI holds promise for understanding the impact of disease on white matter health and for understanding functional brain connectivity. However, many caveats need to be considered. First, post-processing of raw DTI data and generation of scalar maps and tractography is computationally complex and can be time consuming, depending on the algorithms used for estimating and fitting the tensors. At least one scanner manufacturer now has software for producing scalar maps including colorcoded directional maps directly on the scanner console in real time. This holds promise for utilizing DTI data for clinical purposes, but many neuroradiologists are not yet versed in interpreting these images. Second, the most commonly employed DTI acquisition protocols rely on echo-planar imaging (EPI)—a very rapid method of acquiring data. However, EPI is very susceptible to image distortion, especially in orbitofrontal regions due to the differences in magnetic susceptibility of different tissues. Third, DTI can be acquired very quickly when using EPI, but if the goal is to perform tractography, small isotropic voxels (cube-shaped) and a high number of gradient directions are preferred, and this can greatly increase scan time. This can be a problem for studying certain populations such as elderly demented patients who may not be able to tolerate a long acquisition. Fourth, DTI is highly sensitive to movement. Movement during the application of one diffusion-encoding gradient but not others can cause inaccuracies in the tensor. Some centers, especially those performing tractography, use cardiac gating in which image acquisition is linked to the cardiac cycle to reduce physiological movement. Fifth, because some degree of image distortion is common, particularly in EPI-acquired images, registration with high-resolution anatomic images can be difficult. A variety of acquisition sequences and hardware have been developed to address many of these problems (Bammer, 2003) but the improvements are often achieved at the expense of increased scan time.

#### CLINICAL APPLICATIONS OF NEW WHITE MATTER IMAGING TECHNIQUES

#### **Age-Related Changes**

Neuroimaging and neuropathological studies have consistently demonstrated loss of white matter with age that exceeds cortical gray matter loss (Double et al., 1996; Filley, 2001b; Jernigan et al., 2001; Meier-Ruge, Ulrich, Bruhlmann, & Meier, 1992). Adjusting for WMH does not alter the age-related white matter volume loss (Guttmann et al., 1998).

In addition to white matter volume loss, WMH and lacunar infarcts are common in the elderly. In clinically asymptomatic individuals the reported prevalence ranges from 20 to 60% for deep and subcortical white matter hyperintensities and from 15 to 94% for periventricular changes. In general, studies have shown that WMH increase with age (de Leeuw et al., 2000, 2001) and are correlated with cognitive dysfunction (Barber et al., 1999; Boone et al., 1992; Breteler et al., 1994; de Groot et al., 2000; Matsubayashi, Shimada, Kawamoto, & Ozawa, 1992). For example, in the large scale Cardiovascular Health Study (Longstreth, 1998; Longstreth et al., 1996), correlates of white matter findings were examined among 3301 participants who denied a history of stroke or transient ischemic attack. Neuroradiologists graded white matter findings on MRI from 0 (none) to 9 (maximal) without clinical information. White matter grade was associated with greater age, impaired cognitive function, and a number of risk factors.

A recent meta-analysis showed that the association between WMH and cognitive function in *non-demented* elderly were generally modest and were strongest for psychomotor processing speed and executive function; significant correlations were also noted for global cognitive ability and for immediate and delayed memory (Gunning-Dixon & Raz, 2000). Controlling for age in the analysis did not significantly impact these relationships, and associations with general intelligence were not significant.

The relationship between WMH and cognitive function in the elderly has been a matter of some dispute, however, with some studies failing to show an association (Hershey, Modic, Greenough, & Jaffe, 1987; Mirsen et al., 1991). Some researchers have suggested that there might be a threshold of WMH burden that must be exceeded for the expression of cognitive deficit. In a sample of subjects with no WMH, mild to moderate WMH, and large areas of WMH, substantial disturbances in basic attention and selected frontal lobe skills were detected only in the six subjects with the large WMH areas (Boone et al., 1992). However, in a large population study, de Groot and colleagues (2001) showed that WMH were related to subjective cognitive decline both in patients with and without objective cognitive impairment. Differences across studies in the prevalence of WHM and pattern and strength of correlations with cognitive function likely reflect methodological differences (Moser, Kanz, & Garret, 2005; Fazekas, Schmidt, Kleinert, et al., 1998). These include visual rating vs. quantitative measurement SH, inconsistencies in the threshold specified for defining the presence or absence of SH, differences in cognitive test batteries and the methods used to reduce the number of cognitive variables (e.g., composite standard scores vs. derived factor scores), and inconsistent inclusion/exclusion criteria (Moser et al.).

The presumed mechanism whereby WMH are associated with cognitive dysfunction is disconnection due to disruption in white matter circuits. The disruption can range from degraded white matter transmission of information between critically connected gray matter regions due to damaged myelin to frank disconnection due to axonal loss. WMH are most prevalent in frontal regions, although WMH in any region is associated with decreased frontal metabolism (Tullberg et al., 2004). The precise mechanism whereby frontally-mediated functions appear to be preferentially impacted by WMH is uncertain, but it may be due to a convergence of white matter pathways on the frontal lobes (Kramer, Reed, Mungas, Weiner, & Chui, 2002; Tullberg et al.).

There has also been considerable debate in the literature about the impact of lacunes vs. WMH on cognition. A recent study (Mungas, 2005) found that total lacune volume accounted for a small amount of independent variance (5%) in executive function after accounting for WMH volume and cortical gray matter and hippocampal volumes. Lacunes were not, however, associated with memory function. This study did not localize lacunes in specific functional circuits (e.g., thalamo-frontal tracts), so the role of strategic infarct in producing cognitive impairment or dementia remained unclear.

Studies using magnetization transfer imaging (MTI) to study white matter changes in aging have yielded mixed results. Some studies have found small but significant age-related changes in MTR in normal individuals, which were thought to reflect increase in white matter water content with aging (Armstrong et al., 2004; Hofman, Kemerink, Jolles, & Wilmink, 1999; Silver, Barker, MacManus, Tofts, & Miller, 1997). However, in a somewhat larger sample, Rovaris et al. (2003) found no association between MTR and age in a sample of 89 individuals divided into seven 10-year age groups.

Studies using DWI have generally found age-related increases in ADC with age. For example, Lovblad et al. (2004) found an age-associated increase in ADC in frontal white matter in patients referred for assessment of minor cognitive deficits. This effect was noted in patients with and without WMH. Engelter, Provenzale, Petrella, DeLong, and MacFall (2000) used DWI to study age effects on white matter ACD values in 38 subjects with normal MRI. Subjects were selected from a larger sample of individuals referred for clinical MRI. They found a small but statistically significant increase in ADC in the white matter of individuals age 60 and older compared to those under 60. A similar but not statistically significant trend was noted in the thalamus. In contrast, Helenius, Soinne, Perkio et al. (2002) found no association between white matter ADC values and age in 40 men and 40 women in four age groups: 20–34, 35–49, 50–64, and 65 and older.

Studies using DTI scalar parameters have demonstrated age-related reductions in white matter anisotropy, increases in diffusivity, and decreased intravoxel coherence with a tendency toward greater effects in anterior vs. posterior regions (Abe et al., 2002; Head et al., 2004; Madden et al., 2004; Moseley, 2002; Pfefferbaum et al., 2000; Shimony et al., 1999; Sullivan et al., 2001). Figure 9 gives an example of age-related changes in FA demonstrated using DTI.

Some DTI studies have demonstrated a relationship between region-of-interest (ROI)-defined age-related white matter changes and cognitive functioning. Madden et al. (2004) found evidence of an anterior shift in attentional control with age. Specifically, the best predictor of reaction time performance on a visual odd-ball task was FA in the splenium in young adults, but in older adults the best predictor was FA in the anterior limb of the internal capsule. O'Sullivan, Jones, et al. (2001) studied 10 younger and 20 older healthy controls and found that performance on an executive measure (Trail Making Test part B minus part A) was significantly



**Figure 9** Age-related changes in anterior white matter FA in normal subjects: age = 49 and FA = 0.47 on left, age = 79 and FA = 0.30 on right. Note the differences in the thickness of the genu and splenium on representative slices through the lateral ventricles. FA was measured in the genu and white matter anterior to the frontal horns of the lateral ventricles.

correlated with mean diffusivity in anterior ROI defined regions and verbal fluency was correlated with FA in middle ROI-defined white matter. This correlation remained significant after accounting for age, sex, white matter volume, premorbid IQ estimate, and general cognitive functioning.

# **Degenerative Dementia**

Quantitative MRI studies have found that patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) display more atrophy in entrorhinal cortex and hippocampus than age-matched controls (Du et al., 2001). Although there have been some negative findings (Kozachuk et al., 1990; Leys et al., 1990), patients with AD are also more likely to have evidence of abnormal WMH than age-matched controls (Hunt et al., 1989; McDonald et al., 1991). This has led to an ongoing debate regarding the nature of these WMH in AD—Do they represent vascular pathology associated with AD (e.g., amyloid angiopathy) or a separate disease process (e.g., mixed vascular and AD dementia) (Barber et al., 1999)?

Prevalence estimates of WMH in patients with AD range from 21 to 100% in periventricular regions and from 32 to 100% in deep white matter regions depending on the rating scale used and the severity of AD in the sample (Vermeulen & Scheltens, 2000). The volume of WMH in patients with AD and mixed dementia is more closely associated with cortical gray matter atrophy than with hippocampal or entorhinal cortex volume (Capizzano et al., 2004; Du et al., 2005).

WMH may contribute to the conversion from MCI to dementia. One longitudinal study using CT found that patients with MCI who converted to dementia after 29 months had higher level white matter hypodensities, smaller left medial temporal lobes, and a trend toward smaller right medial temporal lobes at baseline (Wolf, Ecke, Bettin, Dietrich, & Gertz, 2000). WMH may also contribute to the conversion from normal aging to MCI. In the Cardiovascular Health Study (Lopez et al., 2003), patients who developed MCI had a higher burden of WMH, larger ventricles, more lacunes, and greater atrophy on baseline MRI performed approximately 6 years earlier. However, only lacunes and atrophy remained associated with MCI in a logistic regression analysis that included the MRI variables along with several demographic, genetic, and medical risk variables.

Vascular white matter injury may increase the risk of AD and its clinical severity. Van der Flier et al. (2004) found a synergistic interaction between high WMH volume and medial temporal lobe volume, with the presence of both abnormalities markedly increasing the risk of AD. Among subjects in the Nun Study (Snowdon et al., 1997) who met pathological criteria for AD at autopsy, a clinical diagnosis of dementia was more common in those who also had subcortical lacunar infarction. Moreover, a lower burden or AD pathology was needed to produce clinical dementia in the presence of lacunar infarcts. In contrast, lacunar infarcts were only weakly associated with cognitive impairment and dementia diagnosis among subjects who did not meet pathological criteria for dementia. A major multi-site study (Alzheimer's Disease Neuroimaging Initiative) sponsored by the National Institute of Aging is currently underway to identify neuroimaging markers of conversion from normal aging to MCI and from MCI to AD.

In contrast to the relationship between lacunar infarcts and dementia severity in the Nun study, results of studies on the specific cognitive and behavioral correlates of WMH in AD have generally failed to find robust relationships. Bigler, Kerr, Victoroff, Tate, & Breitner (2002) found that WMH severity was not associated with performance on the Mini-Mental State Exam (Folstein, et al., 2001) (MMSE) after controlling for global cortical atrophy. It should be noted, however, that the MMSE provides limited assessment of executive functioning and no assessment of processing speed, the cognitive functions most strongly associated with WMH. Hirono, Kitagaki, Kazui, Hashimoto, and Mori (2000) reported that WMH volume was not associated with performance on a cognitive test battery, but was positively correlated with incontinence, the presence of a grasp reflex, and aberrant motor behavior. This suggests that WMH can contribute to frontally-mediated neurological and neurobehavioral symptoms. Using a more comprehensive battery in a sample of patients with both AD, subcortical vascular cognitive impairment, and mixed dementia, Mungas et al. (2001) reported that cognitive impairment in the context of subcortical vascular injury (with or without AD) was more strongly related to cortical atrophy and hippocampal volume loss than to lacunar infarction or WMH volume. In contrast to the previous studies, Capizzano et al. (2004) reported that in a sample of 81 patients with AD, WMH volume was associated with poorer total recall on the Buschke Selective Reminding Task.

Overall, studies using conventional imaging and neuropathology suggest that vascular white matter injury may work synergistically with AD pathology to worsen dementia symptoms and increase the risk of dementia diagnosis. WMH appear to be associated with loss of cortical gray matter in AD and may advance disability in AD by impacting psychomotor speed and motor functions. Debate continues as to whether the pathogenesis of microvascular injury shares common mechanism with the development of AD (Berzin et al., 2000; Salloway, Gur, et al., 2002).

Studies using MTI in AD have demonstrated significant reductions in MTR in patients vs. controls in whole brain, cortical gray matter, and temporal lobes

(Bozzali et al., 2001) and in the hippocampus (Hanyu et al., 2000, 2001). MTI may be sensitive to early brain changes in MCI. One study reported that the peak height of the MTR histogram (corrected for brain parenchymal volume) was lower in the whole brain and in the temporal and frontal lobes of patients with MCI and AD compared to controls. (van der Flier et al., 2002). The authors hypothesized that the differences might be attributable to Wallerian degeneration and neuronal loss as well as demyelination and gliosis. Lower MTR has even been found in the hippocampus of patients with MCI vs. controls (Hanyu et al., 2001), and patients with MCI have reductions in bilateral temporal MTR vs. controls without significant reductions in temporal lobe volume (Kabani, Sled, Shuper, & Chertkow, 2002). Hence, MTR values may be useful for detecting MCI related changes prior to the lobar volumetric changes seen in AD.

A small number of studies have used DWI to examine white matter integrity in AD. Hanyu et al. (1997) reported increased diffusivity (ADC values) in normalappearing anterior and posterior periventricular white matter and loss of anisotropy in posterior periventricular white matter in patients with mild-to-moderate AD vs. controls. Kantarci et al. (2001) examined diffusivity (ADC) and an anisotropy index in patients with MCI, AD, and controls. Region of interest analysis revealed significantly higher ADC in the hippocampus of MCI patients vs. controls, but no other regional ADC differences were found between these groups. In contrast, the AD group displayed significantly lower ADC values than the controls in the hippocampus and in white matter in parietal, occipital, temporal stem, and posterior cingulate regions. For the anisotropy analysis, the only significant group difference was lower anisotropy in the occipital white matter of MCI patients vs. controls. One consideration of these studies is that a full tensor model was not developed for the diffusion weighted imaging, thus slight variations in head position within the scanner could affect the resulting measures of anisotropic diffusion. Kantarci et al. (2005) recently reported a subsequent longitudinal study of 21 patients with amnestic MCI and 54 controls who had DWI at baseline and who received annual follow-up clinical evaluations. At baseline, the MCI group had higher hippocampal ADC values and lower hippocampal volumes and these were negatively correlated. Hippocampal ACD significantly predicted conversion to dementia 29.5 months later. The addition of hippocampal volume to the Cox proportional hazards model did not improve prediction suggesting that hippocampal DWI predicts conversion to dementia at least as well as hippocampal atrophy. Taken together, these studies demonstrate the ability of DWI-derived ADC values to detect changes in white matter and hippocampal regions that appear normal on conventional MRI sequences in patients with AD and MCI. Higher ADC values in the hippocampus of patients with MCI may predict conversion to dementia.

Studies using DTI have detected white matter changes in small samples of patients with mild to moderate AD who were screened for the presence of significant vascular-related white matter changes on T2-weighted images. There is some indication that posterior white matter fibers are more severely affected in AD than anterior white matter, but this has not been a consistent finding (Bozzali et al., 2001, 2002; Head et al., 2004; Rose et al., 2000; Takahashi et al., 2002). Some studies have also demonstrated DTI parameters to be associated with global cognitive functioning (Bozzali et al., 2002; Rose et al.). The source of white matter DTI

abnormalities in AD is unclear, but a recent study suggests that it may be related to over-expression of amyloid  $\beta$  (A $\beta$ ). Song, Kim, Lin, Brendza, and Holtzman (2004) measured relative anisotropy and trace in several white matter structures in transgenic mice that develop age-dependent A $\beta$  deposits and neurofibrillary tangles, the pathological hallmarks of AD. Relative anisotropy was decreased and trace was increased in several white matter structures in the older transgenic mice relative to age-matched control mice. The authors also examined directional anisotropy and concluded the results implied that the DTI parameter changes reflected loss of myelin without significant axonal injury. They noted that this was consistent with the report of Bozzali et al. (2002) who found increased diffusivity and decreased fractional anisotropy in the corpus callosum and in the frontal, temporal, and parietal lobes of patients with AD vs. controls but that a measure of intervoxel coherence of anisotropy did not differ significantly between groups.

Head et al. (2004) used DTI to study young controls, elderly controls, patients with very mild AD (clinical dementia rating = 0.5) and mild AD (clinical dementia rating = 1.0). There were significant age effects of diffusivity and anisotropy in anterior and posterior corpus callosum and in frontal, temporal, and occipital white matter, and these effects were greater for anterior vs. posterior regions. However, there was little additional acceleration of DTI changes in anterior white matter regions, whereas there were slight but statistically significant reductions in diffusivity in temporal, parietal, and occipital regions in the AD vs. old control groups. The authors concluded that AD likely imparts a mechanism of white matter change in posterior regions that is distinct from the anterior changes seen in normal aging. Fellgiebel et al. (2004) also used DTI to study patients with MCI. They showed that relative to controls patients with MCI had reductions in diffusivity but not FA in the left centrum semiovale, the right and left temporal lobes, and the right hippocampus.

#### **Cerebrovascular Disease**

Extensive WMH or lacunes may be sufficient to produce vascular dementia, independent of any cortical neurodegenerative disorder such as Alzheimer's disease. This is thought to occur by degrading of cortico-cortical and cortico-subcortical white matter pathways. WML tend to be more severe in anterior than posterior regions, and this may explain the preponderance of executive, processing speed, and behavioral abnormalities in this disorder (Ishii, Nishihara, & Imamura, 1986; Tanabe et al., 1999; Tullberg et al., 2004). However, a single strategic infarct in critical pathways (e.g., thalamus, basal forebrain) can produce dementia (Auchus, Chen, Sodagar, Thong, & Sng, 2002; Tatemichi, Desmond, & Prohovnik, 1995; Van der Werf et al., 2003).

Small vessel disease (revealed as WMH) shares risk factors with lacunar and cortical stroke (e.g., hypertension, diabetes mellitus, cardiac disease). WMH may be an earlier expression of the same disease that leads to large vessel stroke and may increase the risk of intracerebral hemorrhage (Inzitari, 2003). Stroke patients with WMH are at greater risk for subsequent stroke and for post-stroke (vascular) dementia (Inzitari, 2000; Leys & Pasquier, 2000).

In addition to the aforementioned associations with cognitive functions of executive functioning, processing speed, and memory, WMH is also associated with gait impairment in patients with early vascular dementia and in community-dwelling

elderly. Computerized measures of periventricular WMH have been shown to be associated with computerized assessment of impaired gait in patients thought to be in the early stages of vascular dementia (Hennerici et al., 1994). The authors theorized that the association reflected disruption of thalamo-cortico-mediocapsular circuits. More recently, Starr et al. (2003) demonstrated an association between gait and WMH in a group of 97 community-dwelling elderly. Visual ratings were performed of deep and periventricular white matter (Fazekas scale) and brain stem lesions. Brain stem lesions were associated with decreased walking speed and poorer balance. Structural equation modeling produced two latent traits: one that incorporated deep and periventricular white matter and brain stem lesions and one that incorporated walking speed, balance, anxiety and depression, and a measure of non-verbal abstract reasoning. The two latent variables were moderately correlated (p = .47).

MTI may be more sensitive to conventional MRI for detecting subtle vascular white matter injury. Wong, Grossman, Boorstein, Lexa, and McGowan (1995) found that MTR was decreased in lesioned and in normal-appearing white matter in patients with WMH compared to normal elderly. Tanabe et al. (1999) demonstrated that MTR may detect differences in the severity of lesions with similar appearance on T2-weighted images. They studied MTR values in patients with subcortical ischemic vascular disease (SIVD) and controls. The SIVD group had a higher volume of WMH and larger ventricles. MTR values in periventricular WHM were lower in patients than in controls and there was a trend toward MTR being lower in periventricular vs. non-periventricular WMH in both groups. MTR values were not related to the size of the lesions nor did they appear to be due to measurement error from partial volume effects. MTR values were not associated with scores on the MMSE.

High sensitivity (94%) and specificity (100%) have been reported in the diagnosis of acute cerebral infarction with DWI (Stadnik et al., 2003). DWI has been shown to detect stroke earlier than conventional MRI (Huisman, 2003). DWI can be useful in monitoring stroke evolution (Davis & Donnan, 2004), and can help to discriminate stroke from other brain diseases which may manifest with sudden neurological deficits mimicking acute ischemic stroke (Romano et al., 2003). The combination of DWI with perfusion-weighted imaging (an MRI technique that provides information about cerebral blood flow) within the first few hours of a stroke may be helpful in determining what affected tissue is capable of recovery, and hence whether to employ thrombolytic therapy (Schellinger, Fiebach, & Hacke, 2003). DWI may be sensitive for detecting new silent lacunar infarctions in patients who already have ischemic leukoariosis (O'Sullivan, Rich, Barrick, Clark, & Markus, 2003) or vascular dementia (Choi et al., 2000). In addition to its ability to detect new lesions, results of one study raise the possibility that DWI may be useful for staging the severity of WMH since ADC values within lesions have been shown to decline as the overall severity of WMH increased (Helenius, Soinne, & Salonen, 2002).

Diffusion-tensor imaging (DTI) studies of both experimental and human stroke suggest that DTI may provide more information about the evolution of acute ischemia than available from DWI (Sotak et al., 2002). Acute reductions in the average diffusivity following the onset of cerebral ischemia are often accompanied by increases in diffusion anisotropy. In the transition from acute to sub-acute and chronic stroke, average diffusivity normalizes and subsequently increases, whereas diffusion anisotropy measures (e.g., FA) decline and remain reduced in chronic

infarcts. ADC information has been combined with that of other MR parameters (including DTI) to unambiguously stage and predict ischemic brain injury over its entire temporal evolution.

Studies using DTI in patients with SIVD have demonstrated changes in scalar parameters of diffusion and anisotropy in white matter regions that appear normal on conventional MR sequences. O'Sullivan and colleagues (2004) reported significant correlations between DTI changes in normal appearing white matter (NAWM) and performance on executive measures in patients with SIVD vs. normal elderly controls. These correlations remained significant after controlling for age and T1 and T2 lesion volumes. DTI abnormalities were reported in abnormal-appearing white matter in patients with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), a genetic form of SIVD, vs. normal controls (Chabriat et al., 1999). The DTI abnormalities were correlated with global cognitive impairment, measured by the MMSE, and with greater functional impairment. A similar but less robust pattern of results was observed in NAWM. Molko et al. (2001) showed DTI changes in non-infarcted regions of the putamen and thalamus in patients with CADASIL vs. normal controls, and the thalamic DTI changes were correlated with MMSE score. In a subsequent study, Molko et al. (2002) also demonstrated that whole-brain diffusivity was related to MMSE and functional capacity at baseline in patients with CADASIL and was sensitive to progression of white matter changes at 21-month follow-up.

#### Late-Life Depression and Apathy

It has long been recognized that depression is common after large vessel cortical stroke (Robinson & Price, 1982). However, it is becoming increasingly clear that depression can also result from subcortical vascular disease, particularly in the elderly (Alexopoulos et al., 1997; Krishnan, 1991; Krishnan, Hays, & Blazer, 1997; Kumar, Lavretsky, & Haroon, 2005). MRI studies have demonstrated that patients with late-onset depression have more severe and frequent patchy lesions in the frontal deep white matter and basal ganglia than do controls or patients with early-onset depression (Krishnan, 1991, 2002; Krishnan et al., 2004; O'Brien, Perry, Barber, Gholkar, & Thomas, 2000; Salloway et al., 1996). Figiel et al. (1991) found a higher occurrence of caudate (60% vs. 11%) hyperintensities in elderly subjects with lateonset depression compared with early onset elderly depressed subjects. These findings indicate that late-onset depression may be mediated by disruption of frontal cortical circuits due to vascular white matter injury.

Some research on small groups of patients also suggests that white matter lesion burden may be related to treatment response in late-life depression. Levretsky (1999) conducted a 6-year follow-up of 16 patients with late-life depression to evaluate the relationships between clinical and neuroradiologic variables and disease outcome. Patients had a comprehensive neuropsychiatric evaluation and magnetic resonance imaging (MRI) at baseline and follow-up. Six of eight patients with a chronic course had WMH on MRI at baseline. Four patients whose WMH increased in size over time developed a chronic unremitting course of depression. No patients with non-chronic depression had large areas of WMH at baseline or exhibited increased WMH size over time. In contrast, Salloway and colleagues (Salloway, Correia, et al., 2002) found no difference in antidepressant treatment response between elderly depressed subjects with high vs. low levels of visually-rated WMH severity. Alexopoulos, Kiosses, Choi, Murphy, and Lim (2002) used diffusion tensor imaging to study remission of depression in a small number of geriatric patients in an open treatment trial of citalopram at a target daily dose of 40 mg for 12 weeks. Lower FA of the right and the left frontal white matter regions 15 mm above the anterior commissure-posterior commissure plane was associated with a low remission rate after age was considered. Remission was not significantly associated with FA of lower frontal regions or a temporal region.

Many elderly patients who are diagnosed with "depression" actually display little disturbance of mood and no dramatic sadness. Rather, they lack energy, initiative, and drive (Lampe & Heeren, 2004). This has led some researchers to suggest that there is a distinct syndrome of apathy, with different phenomenology, etiology, and response to treatment (Marin, 1991; Marin, Fogel, Hawkins, Duffy, & Krupp, 1995; Watanabe et al., 1995). A number of scales have been developed recently to assess apathy (for review see Malloy & Grace, 2005). Disruption of medial frontal circuits in a variety of diseases has been associated with apathetic syndromes, ranging from reduced motivation to akinetic mutism (Cummings, 1995; Mega & Cummings, 1994). Apathy is the most common neuropsychiatric problem in AD (Boyle & Malloy, 2004), and reduced frontal perfusion in AD is associated with greater apathy (Craig et al., 1996). Apathy is more common in the frontal than the temporal variant of fronto-temporal dementia (Liu et al., 2004). Apathy is also present in up to 45% of patients with Parkinson's disease (Isella et al., 2002), which is known to affect fronto-subcortical circuits. Both large vessel stroke and small vessel cerebrovascular disease are pathologic processes that can affect frontal circuits (Bogucki, Janczewska, Koszewska, Chmielowski, & Szymanska, 1991; Okada, Kobayashi, Yamagata, Takahashi, & Yamaguchi, 1997), and apathy and abulia are common after stroke involving these circuits (Bhatia & Marsden, 1994; Engelborghs, Marien, Pickut, Verstraeten, & De Deyn, 2000; Piamarta et al., 2004).

There have been few studies relating WMH and apathy. Nebes et al. (2001) studied ninety-two community-dwelling elderly individuals. Hyperintensities in the deep white matter, but not in the periventricular white matter, were associated with impaired motivation, concentration, and decision-making. This relationship was especially strong in individuals carrying the APOE-4 allele. Starkstein et al. (1997) reported higher levels of apathy and extrapyramidal motor signs in patients with AD who had moderate WMH compared with those with low levels of WMH. The two groups did not differ in terms of their performance on an extensive neuro-psychological test battery. Thomas et al. (2004) found that the presence white matter disease on CT, particularly in frontal areas, was associated with higher levels of apathy and poorer performance on frontal cognitive testing.

# **SUMMARY**

Clinical neuroscientists have focused increasing attention on white matter connections in the brain, and on the effects of aging and disease on them. The development of magnetic resonance imaging has allowed clinicians to correlate white matter lesions with behavior change. Recent advances in image acquisition techniques and computerized analysis tools provide researchers with powerful techniques to better relate white matter structure and function. Computer-assisted quantification of white matter lesion load appears to offer better statistical power than visual rating scales in detecting these relationships. New imaging modalities such as MTR, DWI, and DTI can detect white matter abnormalities not shown with conventional acquisition sequences. These newer techniques hold promise for early detection of disease, characterizing disease course, and for delineating functional connections between brain areas.

### REFERENCES

- Abe, O., Aoki, S., Hayashi, N., Yamada, H., Kunimatsu, A., Mori, H., et al. (2002). Normal aging in the central nervous system: Quantitative MR diffusion-tensor analysis. *Neurobiology of Aging*, 23(3), 433–441.
- Ahrens, E., Laidlaw, D., Readhead, C., Brosnan, C., & Fraser, S. (1998). MR microscopy of transgenic mice that spontaneously aquire experimental allergic encephalomyelitis. *Magnetic Resonance Imaging*, 40(1), 119–132.
- Alexopoulos, G. S., Kiosses, D. N., Choi, S. J., Murphy, C. F., & Lim, K. O. (2002). Frontal white matter microstructure and treatment response of late-life depression: A preliminary study. *American Journal of Psychiatry*, 159(11), 1929–1932.
- Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). "Vascular depression" hypothesis. Archives of General Psychiatry, 54, 915–922.
- Armstrong, C. L., Traipe, E., Hunter, J. V., Haselgrove, J. C., Ledakis, G. E., Tallent, E. M., et al. (2004). Age-related, regional, hemispheric, and medial-lateral differences in myelin integrity in vivo in the normal adult brain. *AJNR American Journal of Neuroradiology*, 25(6), 977–984.
- Auchus, A. P., Chen, C. P., Sodagar, S. N., Thong, M., & Sng, E. C. (2002). Single stroke dementia: Insights from 12 cases in Singapore. *Journal of Neurologic Science*, 203–204, 85–89.
- Bammer, R. (2003). Basic principles of diffusion-weighted imaging. *European Journal of Radiology*, 45(3), 169–184.
- Barber, R., Scheltens, P., Gholkar, A., Ballard, C., McKeith, I., Ince, P., et al. (1999). White matter lesions on magnetic resonance imaging in dementia with Lewy bodies, Alzheimer's disease, vascular dementia, and normal aging. *Journal of Neurology, Neurosurgery, and Psychiatry*, 67(1), 66–72.
- Basser, P. J. & Jones, D. K. (2002). Diffusion-tensor MRI: Theory, experimental design and data analysis—A technical review. NMR in Biomedicine, 15(7–8), 456–467.
- Basser, P. J., Mattiello, J., & LeBihan, D. (1994). Estimation of the effective self-diffusion tensor from the NMR spin echo. *Journal of Magnetic Resonance. Series B*, 103(3), 247–254.
- Basser, P. J., Pajevic, S., Pierpaoli, C., Duda, J., & Aldroubi, A. (2000). In vivo fiber tractography using DT-MRI data. *Magnetic Resonance in Medicine*, 44(4), 625–632.
- Basser, P. J. & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance. Series B*, 111(3), 209–219.
- Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system—A technical review. NMR in Biomedicine, 15(7–8), 435–455.
- Berzin, T. M., Zipser, B. D., Rafii, M. S., Kuo-Leblanc, V., Yancopoulos, G. D., Glass, D. J., et al. (2000). Agrin and microvascular damage in Alzheimer's disease. *Neurobiology of Aging*, 21(2), 349–355.

- Bhatia, K. P. & Marsden, C. D. (1994). The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain*, 117(Pt 4), 859–876.
- Bigler, E. D., Kerr, B., Victoroff, J., Tate, D. F., & Breitner, J. C. (2002). White matter lesions, quantitative magnetic resonance imaging, and dementia. *Alzheimer Disease and Associated Disorders*, 16(3), 161–170.
- Bognato, F. & Frank, J. (2003). The role of nonconventional magnetic resonance imaging techniques in demyelinating disorders. *Current Neurology and Neuroscience Reports*, 3(3), 238–245.
- Bogucki, A., Janczewska, E., Koszewska, I., Chmielowski, M., & Szymanska, R. (1991). Evaluation of dementia in subcortical arteriosclerotic encephalopathy (Binswanger's disease). European Archives of Psychiatry and Clinical Neuroscience, 241(2), 91–97.
- Boone, K. B., Miller, B. L., Lesser, I. M., Mehringer, C. M., Hill-Gutierrez, E., Goldberg, M. A., et al. (1992). Neuropsychological correlates of white-matter lesions in healthy elderly subjects. A threshold effect. *Archives of Neurology*, 49(5), 549–554.
- Boyle, P. A. & Malloy, P. F. (2004). Treating apathy in Alzheimer's disease. Dementia and Geriatric Cognitive Disorders, 17(1–2), 91–99.
- Bozzali, M., Falini, A., Franceschi, M., Cercignani, M., Zuffi, M., Scotti, G., et al. (2002). White matter damage in Alzheimer's disease assessed in vivo using diffusion tensor magnetic resonance imaging. *Journal of Neurology, Neurosurgery, and Psychiatry*, 72, 742–746.
- Bozzali, M., Franceschi, M., Falini, A., Pontesilli, S., Cercignani, M., Magnani, G., et al. (2001). Quantification of tissue damage in ad using diffusion tensor and magnetization transfer MRI. *Neurology*, 57(6), 1135–1137.
- Breteler, M. M., van Swieten, J. C., Bots, M. L., Grobbee, D. E., Claus, J. J., van den Hout, J. H., et al. (1994). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam study. *Neurology*, 44(7), 1246–1252.
- Buxton, R. (2002). Diffusion and the MR signal. In *Introduction to functional magnetic* resonance imaging (pp. 185–216). New York: Cambridge University.
- Capizzano, A. A., Acion, L., Bekinschtein, T., Furman, M., Gomila, H., Martinez, A., et al. (2004). White matter hyperintensities are significantly associated with cortical atrophy in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 75(6), 822–827.

Carpenter, M. (1991). Core text of neuroanatomy (4th ed.). Baltimore: Williams & Wilkins.

- Chabriat, H., Pappata, S., Poupon, C., Clark, C. A., Vahedi, K., Poupon, F., et al. (1999). Clinical severity in CADASIL related to ultrastructural damage in white matter: In vivo study with diffusion tensor MRI. *Stroke*, 30(12), 2637–2643.
- Choi, S. H., Na, D. L., Chung, C. S., Lee, K. H., Na, D. G., & Adair, J. C. (2000). Diffusionweighted MRI in vascular dementia. *Neurology*, 54(1), 83–89.
- Craig, A. H., Cummings, J. L., Fairbanks, L., Itti, L., Miller, B. L., Li, J., et al. (1996). Cerebral blood flow correlates of apathy in Alzheimer disease. *Archives of Neurology*, 53(11), 1116–1120.
- Cummings, J. L. (1995). Anatomic and behavioral aspects of frontal-subcortical circuits. Annals of the New York Academy of Science, 769, 1–13.
- Davis Garrett, K., Cohen, R. A., Paul, R. H., Moser, D. J., Malloy, P. F., Shah, P., et al. (2004). Computer-mediated measurement and subjective ratings of white matter hyperintensities in vascular dementia: Relationships to neuropsychological performance. *The Clinical Neuropsychologist*, 18(1), 50–62.
- Davis, S. M. & Donnan, G. A. (2004). Advances in penumbra imaging with MR. Cerebrovascular Disease, 17(Suppl 3), 23–27.
- de Groot, J. C., de Leeuw, F. E., Oudkerk, M., Hofman, A., Jolles, J., & Breteler, M. M. (2001). Cerebral white matter lesions and subjective cognitive dysfunction: The Rotterdam scan study. *Neurology*, 56(11), 1539–1545.

- de Groot, J. C., de Leeuw, F. E., Oudkerk, M., van Gijn, J., Hofman, A., Jolles, J., et al. (2000). Cerebral white matter lesions and cognitive function: The Rotterdam scan study. *Annals of Neurology*, 47(2), 145–151.
- de Leeuw, F. E., de Groot, J. C., Achten, E., Oudkerk, M., Ramos, L. M., Heijboer, R., et al. (2001). Prevalence of cerebral white matter lesions in elderly people: A population based magnetic resonance imaging study. The Rotterdam scan study. *Journal of Neurology*, *Neurosurgery, and Psychiatry*, 70(1), 9–14.
- de Leeuw, F. E., de Groot, J. C., & Breteler, M. M. B. (2000). White matter changes: Frequency and risk factors. In L. Pantoni, D. Intzitari & A. Wallin (Eds.), *The matter* of white matter: Clinical and pathophysiological aspects of white matter disease related to cognitive decline and vascular dementia (Vol. 10, pp. 19–33). Utrecht, Netherlands: Academic Pharmaceutical Productions.
- Double, K. L., Halliday, G. M., Kril, J. J., Harasty, J. A., Cullen, K., Brooks, W. S., et al. (1996). Topography of brain atrophy during normal aging and Alzheimer's disease. *Neurobiology of Aging*, 17(4), 513–521.
- Du, A. T., Schuff, N., Amend, D., Laakso, M. P., Hsu, Y. Y., Jagust, W. J., et al. (2001). Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 71(4), 441–447.
- Du, A. T., Schuff, N., Chao, L. L., Kornak, J., Ezekiel, F., Jagust, W. J., et al. (2005). White matter lesions are associated with cortical atrophy more than entorhinal and hippocampal atrophy. *Neurobiology of Aging*, 26(4), 553–559.
- Engelborghs, S., Marien, P., Pickut, B. A., Verstraeten, S., & De Deyn, P. P. (2000). Loss of psychic self-activation after paramedian bithalamic infarction. *Stroke*, 31(7), 1762–1765.
- Engelter, S. T., Provenzale, J. M., Petrella, J. R., DeLong, D. M., & MacFall, J. R. (2000). The effect of aging on the apparent diffusion coefficient of normal-appearing white matter. *AJR American Journal of Roentgenology*, *175*(2), 425–430.
- Englund, E. (2000). Neuropathology of white matter disease: Parenchymal changes. In L. Pantoni, D. Inzitari & A. Wallin (Eds.), *The matter of white matter: Clinical and pathophysiological aspects of white matter disease related to cognitive decline and vascular dementia* (Vol. 10, pp. 223–246). Utrecht, The Netherlands: Academic Pharmaceutical Productions.
- Fazekas, F., Chawluk, J. B., Alavi, A., Hurtig, H. I., & Zimmerman, R. A. (1987). MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR American Journal* of Roentgenology, 149(2), 351–356.
- Fazekas, F., Kleinert, R., Offenbacher, H., Schmidt, R., Kleinert, G., Payer, F., et al. (1993). Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*, 43(9), 1683–1689.
- Fazekas, F., Schmidt, R., Kleinert, R., Kapeller, P., Roob, G., & Flooh, E. (1998a). The spectrum of age-associated brain abnormalities: Their measurement and histopathological correlates. *Journal of Neural Transmission Supplementum*, 53, 31–39.
- Fazekas, F., Schmidt, R., & Scheltens, P. (1998b). Pathophysiologic mechanisms in the development of age-related white matter changes of the brain. *Dementia and Geriatric Cognitive Disorders*, 9(Suppl 1), 2–5.
- Fellgiebel, A., Wille, P., Muller, M. J., Winterer, G., Scheurich, A., Vucurevic, G., et al. (2004). Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: A diffusion tensor imaging study. *Dementia and Geriatric Cognitive Disorders*, 18(1), 101–108.
- Figiel, G. S., Krishnan, K. R., Doraiswamy, P. M., Rao, V. P., Nemeroff, C. B., & Boyko, O. B. (1991). Subcortical hyperintensities on brain magnetic resonance imaging:

A comparison between late age onset and early onset elderly depressed subjects. *Neurobiology of Aging*, *12*(3), 245–247.

- Filippi, M., Campi, A., Dousset, V., Baratti, C., Martinelli, V., Canal, N., et al. (1995). A magnetization transfer imaging study of normal-appearing white matter in multiple sclerosis. *Neurology*, 45(3 Pt 1), 478–482.
- Filley, C. M. (2001). The behavioral neurology of white matter. New York: Oxford.
- Folstein, M., Folstein, S., McHugh, P., & Fanjian, G. (2001). *MMSE: User's guide*. Odessa, FL: Psychological Assessment Resources, Inc.
- Gavra, M. M., Voumvourakis, C., Gouliamos, A. D., Sfagos, C., & Vlahos, L. J. (2004). Brain MR post-gadolinium contrast in multiple sclerosis: The role of magnetization transfer and image subtraction in detecting more enhancing lesions. *Neuroradiology*, 46(3), 205–210.
- Ge, Y., Grossman, R. I., Babb, J. S., Rabin, M. L., Mannon, L. J., & Kolson, D. L. (2002). Agerelated total gray matter and white matter changes in normal adult brain. Part I: Volumetric MR imaging analysis. AJNR American Journal of Neuroradiology, 23(8), 1327–1333.
- Geschwind, N. (1965a). Disconnexion syndromes in animals and man. I. *Brain*, 88(2), 237–294.
- Geschwind, N. (1965b). Disconnexion syndromes in animals and man. II. Brain, 88(3), 585-644.
- Goodkin, D. E., Rooney, W. D., Sloan, R., Bacchetti, P., Gee, L., Vermathen, M., et al. (1998). A serial study of new MS lesions and the white matter from which they arise. *Neurology*, 51(6), 1689–1697.
- Gunning-Dixon, F. M. & Raz, N. (2000). The cognitive correlates of white matter abnormalities in normal aging: A quantitative review. *Neuropsychology*, 14(2), 224–232.
- Gunning-Dixon, F. M. & Raz, N. (2003). Neuroanatomical correlates of selected executive functions in middle-aged and older adults: A prospective MRI study. *Neuropsychologia*, 41(14), 1929–1941.
- Guttmann, C. R., Jolesz, F. A., Kikinis, R., Killiany, R. J., Moss, M. B., Sandor, T., et al. (1998). White matter changes with normal aging. *Neurology*, 50(4), 972–978.
- Hachinski, V. C., Potter, P., & Merskey, H. (1986). Leuko-araiosis: An ancient term for a new problem. *Canadian Journal of Neurological Sciences*, 13(4 Suppl), 533–534.
- Hachinski, V. C., Potter, P., & Merskey, H. (1987). Leuko-araiosis. Archives of Neurology, 44(1), 21–23.
- Hanyu, H., Asano, T., Iwamoto, T., Takasaki, M., Shindo, H., & Abe, K. (2000). Magnetization transfer measurements of the hippocampus in patients with Alzheimer's disease, vascular dementia, and other types of dementia. *AJNR American Journal of Neuroradiology*, 21(7), 1235–1242.
- Hanyu, H., Asano, T., Sakurai, H., Takasaki, M., Shindo, H., & Abe, K. (2001). Magnetization transfer measurements of the hippocampus in the early diagnosis of Alzheimer's disease. *Journal of Neurological Sciences*, 188(1–2), 79–84.
- Hanyu, H., Shindo, H., Kakizaki, D., Abe, K., Iwamoto, T., & Takasaki, M. (1997). Increased water diffusion in cerebral white matter in Alzheimer's disease. *Gerontology*, 43(6), 343–351.
- Head, D., Buckner, R. L., Shimony, J. S., Williams, L. E., Akbudak, E., Conturo, T. E., et al. (2004). Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: Evidence from diffusion tensor imaging. *Cerebral Cortex*, 14(4), 410–423.
- Helenius, J., Soinne, L., Perkio, J., Salonen, O., Kangasmaki, A., Kaste, M., et al. (2002a). Diffusion-weighted MR imaging in normal human brains in various age groups. AJNR American Journal of Neuroradiology, 23(2), 194–199.
- Helenius, J., Soinne, L., Salonen, O., Kaste, M., & Tatlisumak, T. (2002b). Leukoaraiosis, ischemic stroke, and normal white matter on diffusion-weighted MRI. *Stroke*, 33(1), 45–50.
- Henkelman, R. M., Stanisz, G. J., & Graham, S. J. (2001). Magnetization transfer in MRI: A review. *NMR in Biomedicine*, *14*(2), 57–64.

- Hennerici, M. G., Oster, M., Cohen, S., Schwartz, A., Motsch, L., & Daffertshofer, M. (1994). Are gait disturbances and white matter degeneration early indicators of vascular dementia? *Dementia*, 5(3–4), 197–202.
- Hershey, L. A., Modic, M. T., Greenough, P. G., & Jaffe, D. F. (1987). Magnetic resonance imaging in vascular dementia. *Neurology*, *37*(1), 29–36.
- Hiehle, J. F., Jr., Grossman, R. I., Ramer, K. N., Gonzalez-Scarano, F., & Cohen, J. A. (1995). Magnetization transfer effects in MR-detected multiple sclerosis lesions: Comparison with gadolinium-enhanced spin-echo images and nonenhanced T1-weighted images. *AJNR American Journal of Neuroradiology*, 16(1), 69–77.
- Hirono, N., Kitagaki, H., Kazui, H., Hashimoto, M., & Mori, E. (2000). Impact of white matter changes on clinical manifestation of Alzheimer's disease: A quantitative study. *Stroke*, 31(9), 2182–2188.
- Ho, K.-L., & Garcia, J. (2000). Neuropathology of the small blood vessels in selected diseases of the cerebral white matter. In L. Pantoni, D. Inzitari, & A. Wallin (Eds.), *The matter of white matter: Clinical and pathophysiological aspects of white matter disease related to cognitive decline and vascular dementia* (Vol. 10, pp. 247–274). Utrect, The Netherlands: Academic Pharmaceutical Productions.
- Hofman, P. A., Kemerink, G. J., Jolles, J., & Wilmink, J. T. (1999). Quantitative analysis of magnetization transfer images of the brain: Effect of closed head injury, age and sex on white matter. *Magnetic Resonance in Medicine*, 42(4), 803–806.
- Huisman, T. A. (2003). Diffusion-weighted imaging: Basic concepts and application in cerebral stroke and head trauma. *European Radiology*, 13(10), 2283–2297.
- Hunt, A. L., Orrison, W. W., Yeo, R. A., Haaland, K. Y., Rhyne, R. L., Garry, P. J., et al. (1989). Clinical significance of MRI white matter lesions in the elderly. *Neurology*, 39(11), 1470–1474.
- Inzitari, D. (2000). Age-related white matter changes and cognitive impairment. Annals of Neurology, 47(2), 141–143.
- Inzitari, D. (2003). Leukoaraiosis: An independent risk factor for stroke? *Stroke*, 34(8), 2067–2071.
- Inzitari, D., Carlucci, G., & Pantoni, L. (2000). White matter changes: The clinical consequences in the aging population. *Journal of Neural Transmission Supplementum*, 59, 1–8.
- Isella, V., Melzi, P., Grimaldi, M., Iurlaro, S., Piolti, R., Ferrarese, C., et al. (2002). Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. *Movement Disorders*, 17(2), 366–371.
- Ishii, N., Nishihara, Y., & Imamura, T. (1986). Why do frontal lobe symptoms predominate in vascular dementia with lacunes? *Neurology*, *36*(3), 340–345.
- Jernigan, T. L., Archibald, S. L., Fennema-Notestine, C., Gamst, A. C., Stout, J. C., Bonner, J., et al. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiology of Aging*, 22(4), 581–594.
- Jernigan, T. L., Press, G. A., & Hesselink, J. R. (1990). Methods for measuring brain morphologic features on magnetic resonance images. Validation and normal aging. Archives of Neurology, 47(1), 27–32.
- Junque, C., Pujol, J., Vendrell, P., Bruna, O., Jodar, M., Ribas, J. C., et al. (1990). Leukoaraiosis on magnetic resonance imaging and speed of mental processing. *Archives of Neurology*, 47(2), 151–156.
- Kabani, N. J., Sled, J. G., Shuper, A., & Chertkow, H. (2002). Regional magnetization transfer ratio changes in mild cognitive impairment. *Magnetic Resonance in Medicine*, 47(1), 143–148.
- Kantarci, K., Jack, C. R., Jr., Xu, Y. C., Campeau, N. G., O'Brien, P. C., Smith, G. E., et al. (2001). Mild cognitive impairment and Alzheimer disease: Regional diffusivity of water. *Radiology*, 219(1), 101–107.

- Kantarci, K., Petersen, R. C., Boeve, B. F., Knopman, D. S., Weigand, S. D., O'Brien, P. C., et al. (2005). DWI predicts future progression to Alzheimer disease in amnestic mild cognitive impairment. *Neurology*, 64(5), 902–904.
- Kapeller, P., Barber, R., Vermeulen, R. J., Ader, H., Scheltens, P., Freidl, W., et al. (2003). Visual rating of age-related white matter changes on magnetic resonance imaging: Scale comparison, interrater agreement, and correlations with quantitative measurements. *Stroke*, 34(2), 441–445.
- Kozachuk, W. E., DeCarli, C., Schapiro, M. B., Wagner, E. E., Rapoport, S. I., & Horwitz, B. (1990). White matter hyperintensities in dementia of Alzheimer's type and in healthy subjects without cerebrovascular risk factors. A magnetic resonance imaging study. *Archives* of Neurology, 47(12), 1306–1310.
- Kramer, J. H., Reed, B. R., Mungas, D., Weiner, M. W., & Chui, H. C. (2002). Executive dysfunction in subcortical ischaemic vascular disease. *Journal of Neurology, Neurosurgery,* and Psychiatry, 72(2), 217–220.
- Krishnan, K. R. (1991). Organic bases of depression in the elderly. Annual Review of Medicine, 42, 261–266.
- Krishnan, K. R. (2002). Biological risk factors in late life depression. *Biological Psychiatry*, 52(3), 185–192.
- Krishnan, K. R., Hays, J. C., & Blazer, D. G. (1997). MRI-defined vascular depression. American Journal of Psychiatry, 154(4), 497–501.
- Krishnan, K. R., Taylor, W. D., McQuoid, D. R., MacFall, J. R., Payne, M. E., Provenzale, J. M., et al. (2004). Clinical characteristics of magnetic resonance imagingdefined subcortical ischemic depression. *Biological Psychiatry*, 55(4), 390–397.
- Kumar, A., Lavretsky, H., & Haroon, E. (2005). Neuropsychiatric correlates of vascular injury: Vascular dementia and related neurobehavioral syndromes. In R. Paul, R. Cohen, B. Ott & S. Salloway (Eds.), *Vascular dementia: Cerebrovascular mechanisms and clinical management* (pp. 157–169). Totowa, NJ: Humana.
- Laidlaw, D., Ahrens, E., Kremers, D., Avalos, M., Readhead, C., & Jacobs, R. (1998). Visualizing diffusion tensor images of the mouse spinal cord. Proceedings of IEEE Visualization, IEEE Computer Society Press, pp. 127–134.
- Lampe, I. K. & Heeren, T. J. (2004). Is apathy in late-life depressive illness related to age-atonset, cognitive function or vascular risk? *International Psychogeriatrics*, 16(4), 481–486.
- Lavretsky, H., Lesser, I. M., Wohl, M., Miller, B. L., & Mehringer, C. M. (1999). Clinical and neuroradiologic features associated with chronicity in late-life depression. *American Jour*nal of Geriatric Psychiatry, 7(4), 309–316.
- Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., et al. (2001). Diffusion tensor imaging: Concepts and applications. *Journal of Magnetic Resonance Imaging*, 13(4), 534–546.
- Leys, D. & Pasquier, F. (2000). Relevance of white matter changes to post-stroke dementia. In L. Pantoni, D. Inzitari & A. Wallin (Eds.), *The matter of white matter: Clinical and pathophysiological aspects of white matter disease related to cognitive decline and vascular dementia* (Vol. 10, pp. 97–108). Utrecht, The Netherlands: Academic Pharmaceutical Productions.
- Leys, D., Soetaert, G., Petit, H., Fauquette, A., Pruvo, J. P., & Steinling, M. (1990). Periventricular and white matter magnetic resonance imaging hyperintensities do not differ between Alzheimer's disease and normal aging. *Archives of Neurology*, 47(5), 524–527.
- Liu, W., Miller, B. L., Kramer, J. H., Rankin, K., Wyss-Coray, C., Gearhart, R., et al. (2004). Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. *Neurology*, 62(5), 742–748.

- Longstreth, W. T., Jr. (1998). Brain abnormalities in the elderly: Frequency and predictors in the United States (the cardiovascular health study). Cardiovascular health study collaborative research group. *Journal of Neural Transmission Supplementum*, 53, 9–16.
- Longstreth, W. T., Jr., Manolio, T. A., Arnold, A., Burke, G. L., Bryan, N., Jungreis, C. A., et al. (1996). Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The cardiovascular health study. *Stroke*, 27(8), 1274–1282.
- Lopez, O. L., Jagust, W. J., Dulberg, C., Becker, J. T., DeKosky, S. T., Fitzpatrick, A., et al. (2003). Risk factors for mild cognitive impairment in the cardiovascular health study cognition study: Part 2. Archives of Neurology, 60(10), 1394–1399.
- Lovblad, K. O., Delavelle, J., Wetzel, S., Kelekis, A. D., Assal, F., Palmesino, M., et al. (2004). ADC mapping of the aging frontal lobes in mild cognitive impairment. *Neuroradiology*, 46(4), 282–286.
- Madden, D. J., Whiting, W. L., Huettel, S. A., White, L. E., MacFall, J. R., & Provenzale, J. M. (2004). Diffusion tensor imaging of adult age differences in cerebral white matter: Relation to response time. *Neuroimage*, 21(3), 1174–1181.
- Malloy, P. & Grace, J. (2005). A review of rating scales for measuring behavior change due to frontal systems damage. *Cognitive and Behavioural Neurology*, *18*(1), 18–27.
- Manolio, T. A., Kronmal, R. A., Burke, G. L., Poirier, V., O'Leary, D. H., Gardin, J. M., et al. (1994). Magnetic resonance abnormalities and cardiovascular disease in older adults. The cardiovascular health study. *Stroke*, 25(2), 318–327.
- Mantyla, R., Erkinjuntti, T., Salonen, O., Aronen, H. J., Peltonen, T., Pohjasvaara, T., et al. (1997). Variable agreement between visual rating scales for white matter hyperintensities on MRI. Comparison of 13 rating scales in a poststroke cohort. *Stroke*, 28(8), 1614–1623.
- Marin, R. S. (1991). Apathy: A neuropsychiatric syndrome. Journal of Neuropsychiatry and Clinical Neuroscience, 3(3), 243–254.
- Marin, R. S., Fogel, B. S., Hawkins, J., Duffy, J., & Krupp, B. (1995). Apathy: A treatable syndrome. *Journal of Neuropsychiatry and Clinical Neuroscience*, 7(1), 23–30.
- Matsubayashi, K., Shimada, K., Kawamoto, A., & Ozawa, T. (1992). Incidental brain lesions on magnetic resonance imaging and neurobehavioral functions in the apparently healthy elderly. *Stroke*, 23(2), 175–180.
- McDonald, W. M., Krishnan, K. R., Doraiswamy, P. M., Figiel, G. S., Husain, M. M., Boyko, O. B., et al. (1991). Magnetic resonance findings in patients with early-onset Alzheimer's disease. *Biological Psychiatry*, 29(8), 799–810.
- Mega, M. S. & Cummings, J. L. (1994). Frontal-subcortical circuits and neuropsychiatric disorders. Journal of Neuropsychiatry and Clinical Neuroscience, 6(4), 358–370.
- Meier-Ruge, W., Ulrich, J., Bruhlmann, M., & Meier, E. (1992). Age-related white matter atrophy in the human brain. *Annals of the New York Academy of Science*, 673, 260–269.
- Merino, J. G. & Hachinski, V. (2000). Leukoaraiosis: Reifying rarefaction. Archives of Neurology, 57(7), 925–926.
- Mirsen, T. R., Lee, D. H., Wong, C. J., Diaz, J. F., Fox, A. J., Hachinski, V. C., et al. (1991). Clinical correlates of white-matter changes on magnetic resonance imaging scans of the brain. Archives of Neurology, 48(10), 1015–1021.
- Molko, N., Pappata, S., Mangin, J. F., Poupon, C., Vahedi, K., Jobert, A., et al. (2001). Diffusion tensor imaging study of subcortical gray matter in CADASIL. *Stroke*, 32(9), 2049–2054.
- Molko, N., Pappata, S., Mangin, J. F., Poupon, F., LeBihan, D., Bousser, M. G., et al. (2002). Monitoring disease progression in CADASIL with diffusion magnetic resonance imaging: A study with whole brain histogram analysis. *Stroke*, 33(12), 2902–2908.
- Moseley, M. (2002). Diffusion tensor imaging and aging—A review. *NMR in Biomedicine*, 15(7-8), 553–560.

- Moser, D., Kanz, J. E., & Garret, K. (2005). White matter hyperintensities and cognition. In R. Paul, R. Cohen, B. Ott, & S. Salloway (Eds.), *Vascular dementia: Cerebrovascular mechanisms and clinical management* (pp. 223–230). Totowa, NJ: Humana.
- Mungas, D. (2005). Contributions of subcortical lacunar infarcts to cognitive impairment in older persons. In R. Paul, R. Cohen, B. Ott, & S. Salloway (Eds.), *Vascular dementia: Cerebrovascular mechanisms and clinical management* (pp. 211–222). Totowa, NJ: Humana.
- Mungas, D., Jagust, W. J., Reed, B. R., Kramer, J. H., Weiner, M. W., Schuff, N., et al. (2001). MRI predictors of cognition in subcortical ischemic vascular disease and Alzheimer's disease. *Neurology*, 57(12), 2229–2235.
- Nebes, R. D., Vora, I. J., Meltzer, C. C., Fukui, M. B., Williams, R. L., Kamboh, M. I., et al. (2001). Relationship of deep white matter hyperintensities and apolipoprotein e genotype to depressive symptoms in older adults without clinical depression. *American Journal of Psychiatry*, 158(6), 878–884.
- O'Brien, J., Perry, R., Barber, R., Gholkar, A., & Thomas, A. (2000). The association between white matter lesions on magnetic resonance imaging and noncognitive symptoms. *Annals* of the New York Academy of Science, 903, 482–489.
- O'Sullivan, M., Jones, D. K., Summers, P. E., Morris, R. G., Williams, S. C., & Markus, H. S. (2001a). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology*, 57(4), 632–638.
- O'Sullivan, M., Morris, R. G., Huckstep, B., Jones, D. K., Williams, S. C., & Markus, H. S. (2004). Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. *Journal of Neurology, Neurosurgery, and Psychiatry*, 75(3), 441–447.
- O'Sullivan, M., Rich, P. M., Barrick, T. R., Clark, C. A., & Markus, H. S. (2003). Frequency of subclinical lacunar infarcts in ischemic leukoaraiosis and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *AJNR American Journal* of Neuroradiology, 24(7), 1348–1354.
- O'Sullivan, M., Summers, P. E., Jones, D. K., Jarosz, J. M., Williams, S. C., & Markus, H. S. (2001b). Normal-appearing white matter in ischemic leukoaraiosis: A diffusion tensor MRI study. *Neurology*, 57(12), 2307–2310.
- Okada, K., Kobayashi, S., Yamagata, S., Takahashi, K., & Yamaguchi, S. (1997). Poststroke apathy and regional cerebral blood flow. *Stroke*, 28(12), 2437–2441.
- Pfefferbaum, A., Sullivan, E. V., Hedehus, M., Lim, K. O., Adalsteinsson, E., & Moseley, M. (2000). Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magnetic Resonance in Medicine*, 44(2), 259–268.
- Piamarta, F., Iurlaro, S., Isella, V., Atzeni, L., Grimaldi, M., Russo, A., et al. (2004). Unconventional affective symptoms and executive functions after stroke in the elderly. *Archives* of Gerontology and Geriatrics Supplement, 9(9), 315–323.
- Pierpaoli, C. & Basser, P. J. (1996). Toward a quantitative assessment of diffusion anisotropy. Magnetic Resonance in Medicine, 36(6), 893–906.
- Pierpaoli, C., Jezzard, P., Basser, P. J., Barnett, A., & Di Chiro, G. (1996). Diffusion tensor MR imaging of the human brain. *Radiology*, 201(3), 637–648.
- Prins, N. D., van Straaten, E. C., van Dijk, E. J., Simoni, M., van Schijndel, R. A., Vrooman, H. A., et al. (2004). Measuring progression of cerebral white matter lesions on MRI: Visual rating and volumetrics. *Neurology*, 62(9), 1533–1539.
- Raiha, I., Tarvonen, S., Kurki, T., Rajala, T., & Sourander, L. (1993). Relationship between vascular factors and white matter low attenuation of the brain. *Acta Neurologica Scandinavica*, 87(4), 286–289.
- Reinges, M. H., Schoth, F., Coenen, V. A., & Krings, T. (2004). Imaging of postthalamic visual fiber tracts by anisotropic diffusion weighted MRI and diffusion tensor imaging: Principles and applications. *European Journal of Radiology*, 49(2), 91–104.

- Reyfman, A. (1997). *The physics hypertextbook*. Retrieved March 21, 2005, from http:// hypertextbook.com/facts/1997/AllaReyfman.shtml
- Robinson, R. G. & Price, T. R. (1982). Post-stroke depressive disorders: A follow-up study of 103 patients. *Stroke*, 13(5), 635–641.
- Romano, A., Bozzao, A., Bonamini, M., Fasoli, F., Ferrante, M., Floris, R., et al. (2003). Diffusion-weighted MR imaging: Clinical applications in neuroradiology. *La Radiologia Medica*, 106(5–6), 521–548.
- Rose, S. E., Chen, F., Chalk, J. B., Zelaya, F. O., Strugnell, W. E., Benson, M., et al. (2000). Loss of connectivity in Alzheimer's disease: An evaluation of white matter tract integrity with colour coded MR diffusion tensor imaging. *Journal of Neurology, Neurosurgery, and Psychiatry*, 69(4), 528–530.
- Rovaris, M., Iannucci, G., Cercignani, M., Sormani, M. P., De Stefano, N., Gerevini, S., et al. (2003). Age-related changes in conventional, magnetization transfer, and diffusion-tensor MR imaging findings: Study with whole-brain tissue histogram analysis. *Radiology*, 227(3), 731–738.
- Sachdev, P., Cathcart, S., Shnier, R., Wen, W., & Brodaty, H. (1999). Reliability and validity of ratings of signal hyperintensities on MRI by visual inspection and computerised measurement. *Psychiatry Research*, 92(2–3), 103–115.
- Salloway, S., Correia, S., Boyle, P., Malloy, P., Schneider, L., Lavretsky, H., et al. (2002a). Mri subcortical hyperintensities in old and very old depressed outpatients: The important role of age in late-life depression. *Journal of Neurological Sciences*, 203–204, 227–233.
- Salloway, S., Gur, T., Berzin, T., Tavares, R., Zipser, B., Correia, S., et al. (2002b). Effect of APOE genotype on microvascular basement membrane in Alzheimer's disease. *Journal of Neurological Sciences*, 203–204, 183–187.
- Salloway, S., Malloy, P., Kohn, R., Gillard, E., Duffy, J., Rogg, J., et al. (1996). MRI and neuropsychological differences in early- and late-life-onset geriatric depression. *Neurol*ogy, 46(6), 1567–1574.
- Schellinger, P. D., Fiebach, J. B., & Hacke, W. (2003). Imaging-based decision making in thrombolytic therapy for ischemic stroke: Present status. *Stroke*, 34(2), 575–583.
- Scheltens, P., Barkhof, F., Leys, D., Pruvo, J. P., Nauta, J. J., Vermersch, P., et al. (1993). A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *Journal of Neurological Sciences*, 114(1), 7–12.
- Scheltens, P., Barkhof, F., Leys, D., Wolters, E. C., Ravid, R., & Kamphorst, W. (1995). Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. *Neurology*, 45(5), 883–888.
- Schmidt, R. (1992). Comparison of magnetic resonance imaging in Alzheimer's disease, vascular dementia and normal aging. *European Neurology*, *32*(3), 164–169.
- Schmierer, K., Scaravilli, F., Altmann, D. R., Barker, G. J., & Miller, D. H. (2004). Magnetization transfer ratio and myelin in postmortem multiple sclerosis brain. *Annals of Neurology*, 56(3), 407–415.
- Shimony, J. S., McKinstry, R. C., Akbudak, E., Aronovitz, J. A., Snyder, A. Z., Lori, N. F., et al. (1999). Quantitative diffusion-tensor anisotropy brain MR imaging: Normative human data and anatomic analysis. *Radiology*, 212(3), 770–784.
- Silver, N. C., Barker, G. J., MacManus, D. G., Tofts, P. S., & Miller, D. H. (1997). Magnetisation transfer ratio of normal brain white matter: A normative database spanning four decades of life. *Journal of Neurology, Neurosurgery, and Psychiatry*, 62(3), 223–228.
- Sivewright, G. J. & Elliott, P. J. (1994). Interactive region and volume growing for segmenting volumes in MR and CT images. *Medical Informatics*, 19(1), 71–80.
- Snowdon, D. A., Greiner, L. H., Mortimer, J. A., Riley, K. P., Greiner, P. A., & Markesbery,
  W. R. (1997). Brain infarction and the clinical expression of Alzheimer disease. The Nun
  Study. JAMA: The Journal of the American Medical Association, 277(10), 813–817.

- Song, S. K., Kim, J. H., Lin, S. J., Brendza, R. P., & Holtzman, D. M. (2004). Diffusion tensor imaging detects age-dependent white matter changes in a transgenic mouse model with amyloid deposition. *Neurobiology of Disease*, 15(3), 640–647.
- Sotak, C. H. (2002). The role of diffusion tensor imaging in the evaluation of ischemic brain injury-a review. *NMR in Biomedicine*, *15*(7–8), 561–569.
- Stadnik, T. W., Demaerel, P., Luypaert, R. R., Chaskis, C., Van Rompaey, K. L., Michotte, A., et al. (2003). Imaging tutorial: Differential diagnosis of bright lesions on diffusionweighted MR images. *Radiographics*, 23(1), e7.
- Starkstein, S. E., Sabe, L., Vazquez, S., Di Lorenzo, G., Martinez, A., Petracca, G., et al. (1997). Neuropsychological, psychiatric, and cerebral perfusion correlates of leukoaraiosis in Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 63(1), 66–73.
- Starr, J. M., Leaper, S. A., Murray, A. D., Lemmon, H. A., Staff, R. T., Deary, I. J., et al. (2003). Brain white matter lesions detected by magnetic resonance imaging are associated with balance and gait speed. *Journal of Neurology, Neurosurgery, and Psychiatry*, 74(1), 94–98.
- Stejskal, E. & Tanner, J. (1965). Spin diffusion measurements: Spin echoes in the presence of a time-dependent field gradient. *Journal of Chemical Physics*, 42, 288–292.
- Sullivan, E. V., Adalsteinsson, E., Hedehus, M., Ju, C., Moseley, M., Lim, K. O., et al. (2001). Equivalent disruption of regional white matter microstructure in ageing healthy men and women. *Neuroreport*, 12(1), 99–104.
- Takahashi, S., Yonezawa, H., Takahashi, J., Kudo, M., Inoue, T., & Tohgi, H. (2002). Selective reduction of diffusion anisotropy in white matter of Alzheimer disease brains measured by 3.0 Tesla magnetic resonance imaging. *Neuroscience Letters*, 332(1), 45.
- Tanabe, J. L., Ezekiel, F., Jagust, W. J., Reed, B. R., Norman, D., Schuff, N., et al. (1999). Magnetization transfer ratio of white matter hyperintensities in subcortical ischemic vascular dementia. AJNR American Journal of Neuroradiology, 20(5), 839–844.
- Tatemichi, T. K., Desmond, D. W., & Prohovnik, I. (1995). Strategic infarcts in vascular dementia. A clinical and brain imaging experience. *Arzneimittelforschung*, 45(3A), 371–385.
- Thomas, A. J., O'Brien, J. T., Barber, R., McMeekin, W., & Perry, R. (2003). A neuropathological study of periventricular white matter hyperintensities in major depression. *Journal* of Affective Disorders, 76(1–3), 49–54.
- Thomas, P., Hazif-Thomas, C., Saccardy, F., & Vandermarq, P. (2004). Loss of motivation and frontal dysfunction. Role of the white matter change. *Encephale*, *30*(1), 52–59.
- Tullberg, M., Fletcher, E., DeCarli, C., Mungas, D., Reed, B. R., Harvey, D. J., et al. (2004). White matter lesions impair frontal lobe function regardless of their location. *Neurology*, 63(2), 246–253.
- Udaka, F., Sawada, H., & Kameyama, M. (2002). White matter lesions and dementia: MRIpathological correlation. Annals of the New York Academy of Science, 977, 411–415.
- van der Flier, W. M., Middelkoop, H. A., Weverling-Rijnsburger, A. W., Admiraal-Behloul, F., Spilt, A., Bollen, E. L., et al. (2004). Interaction of medial temporal lobe atrophy and white matter hyperintensities in AD. *Neurology*, 62(10), 1862–1864.
- van der Flier, W. M., van den Heuvel, D. M., Weverling-Rijnsburger, A. W., Bollen, E. L., Westendorp, R. G., van Buchem, M. A., et al. (2002). Magnetization transfer imaging in normal aging, mild cognitive impairment, and Alzheimer's disease. *Annals of Neurol*ogy, 52(1), 62–67.
- Van der Werf, Y. D., Scheltens, P., Lindeboom, J., Witter, M. P., Uylings, H. B., & Jolles, J. (2003). Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. *Neuropsychologia*, 41(10), 1330–1344.
- Vataja, R., Pohjasvaara, T., Mantyla, R., Ylikoski, R., Leppavuori, A., Leskela, M., et al. (2003). MRI correlates of executive dysfunction in patients with ischaemic stroke. *European Journal of Neurology*, 10(6), 625–631.

- Vermeer, S. E., van Dijk, E. J., Koudstaal, P. J., Oudkerk, M., Hofman, A., Clarke, R., et al. (2002). Homocysteine, silent brain infarcts, and white matter lesions: The Rotterdam scan study. *Annals of Neurology*, 51(3), 285–289.
- Vermeulen, R. & Scheltens, P. (2000). Heterogeneity in Alzheimer's disease: The role of white matter changes. In L. Pantoni, D. Inzitari, & A. Wallin (Eds.), *The matter of white matter: Clinical and pathophysiological aspects of white matter disease related to cognitive decline and vascular dementia.* (Vol. 10, pp. 109–122). Utrecht, The Netherlands: Academic Pharmaceutical Productions.
- Victoroff, J., Mack, W. J., Grafton, S. T., Schreiber, S. S., & Chui, H. C. (1994). A method to improve interrater reliability of visual inspection of brain MRI scans in dementia. *Neurology*, 44(12), 2267–2276.
- Wakana, S., Jiang, H., Nagae-Poetscher, L. M., van Zijl, P. C., & Mori, S. (2004). Fiber tractbased atlas of human white matter anatomy. *Radiology*, 230(1), 77–87.
- Wardlaw, J. M., Ferguson, K. J., & Graham, C. (2004). White matter hyperintensities and rating scales-observer reliability varies with lesion load. *Journal of Neurology*, 251(5), 584–590.
- Watanabe, M. D., Martin, E. M., DeLeon, O. A., Gaviria, M., Pavel, D. G., & Trepashko, D. W. (1995). Successful methylphenidate treatment of apathy after subcortical infarcts. *Journal of Neuropsychiatry and Clinical Neuroscience*, 7(4), 502–504.
- Westin, C. F., Maier, S. E., Mamata, H., Nabavi, A., Jolesz, F. A., & Kikinis, R. (2002). Processing and visualization for diffusion tensor MRI. *Medical Image Analysis*, 6(2), 93–108.
- Wolbarst, A. (1993a). Magnetic resonance III: Relaxation times (T1 and T2), pulse sequences, and image contrast. In *Physics of radiology* (pp. 91–101). Norwalk, CT: Appleton & Lange.
- Wolbarst, A. (1993b). Magnetic resonance IV: Imaging. In *Physics of radiology* (pp. 102–117). Norwalk, CT: Appleton & Lange.
- Wolf, H., Ecke, G. M., Bettin, S., Dietrich, J., & Gertz, H. J. (2000). Do white matter changes contribute to the subsequent development of dementia in patients with mild cognitive impairment? A longitudinal study. *International Journal of Geriatric Psychiatry*, 15(9), 803–812.
- Wong, K. T., Grossman, R. I., Boorstein, J. M., Lexa, F. J., & McGowan, J. C. (1995). Magnetization transfer imaging of periventricular hyperintense white matter in the elderly. AJNR American Journal of Neuroradiology, 16(2), 253–258.
- Yamamoto, H. & Bogousslavsky, J. (2000). Cerebral white matter changes: Differential diagnosis. In L. Pantoni, D. Inzitari, & A. Wallin (Eds.), *The matter of white matter: Clinical* and pathophysiological aspects of white matter disease related to cognitive decline and vascular dementia (Vol. 10, pp. 189–205). Utrect, The Netherlands: Academic Pharmaceutical Productions.
- Zhang, S., Bastin, M. E., Laidlaw, D. H., Sinha, S., Armitage, P. A., & Deisboeck, T. S. (2004a). Visualization and analysis of white matter structural asymmetry in diffusion tensor MRI data. *Magnetic Resonance in Medicine*, 51(1), 140–147.
- Zhang, S., Demiralp, C., & Laidlaw, D. (2003). Visualizing diffusion tensor MR images using streamtubes and streamsurfaces. *IEEE Transactions on Visualization and Computer Graphics*, 9(4), 454–462.
- Zhang, S., Kindlmann, G., & Laidlaw, D. (2004b). Diffusion tensor MRI visualization. In C. D. Hanson & C. R. Johnson (Eds.), *Visualization handbook*. St. Louis, MO: Academic Press.