

White Matter: Organization and Functional Relevance

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Received: 19 January 2010 / Accepted: 16 March 2010 / Published online: 31 March 2010
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Abstract Norman Geschwind's landmark paper in 1965, "Disconnexion Syndromes in Animals and Man," inspired a generation of investigators to consider the effects of focal brain lesions disrupting higher brain functions. Although Geschwind viewed disconnection as resulting from either white or gray matter lesions, his signature article drew upon the insights of 19th century neurologists and firmly established white matter within the vocabulary of behavioral neurology, neuropsychology, and cognitive neuroscience. This influence, and the advent of sensitive neuroimaging techniques later in the 20th century, led to white matter gradually gaining more attention as an essential component of distributed neural networks subserving cognition and emotion. Today, whereas focal white matter lesions remain central to the pathogenesis of classic neurobehavioral syndromes, diffuse white matter involvement is regarded as increasingly relevant to a wide variety of dementia syndromes and a host of neuropsychiatric disorders as well. In parallel, better understanding of the neurobiology of brain white matter at all ages has been achieved. While much remains to be explored, a general conceptual formulation is that white matter supports

information transfer to complement the information processing carried out by gray matter. As knowledge of the organization and functional relevance of white matter continues to advance, improved understanding of the role of myelinated tracts in higher function can be anticipated, and with it many clinical benefits.

Keywords White matter · Geschwind · Disconnection · Distributed neural networks · White matter dementia

White matter occupies about half the brain, but its role in the mediation of higher functions is less securely recognized than that of gray matter. In the last several decades, however, substantial progress has been made in the understanding of white matter as an essential component of brain systems subserving cognition and emotion. Much of the credit for this development goes to a landmark paper of 1965 in which Norman Geschwind resurrected long neglected insights of 19th century neurologists and reintroduced white matter into the discourse of behavioral neurology (Geschwind 1965). This contribution was but one of many in this well-known article, "Disconnexion Syndromes in Animals and Man" (Geschwind 1965), a remarkable work that inspired a generation of investigators studying the brain and behavior.

Geschwind's major goal was to conceptualize higher brain functions as the result of interconnected brain regions that operate in synchrony to enable specific cognitive functions. Discrete brain regions were seen as anatomically linked to permit a given mental operation, and clinical deficits such as aphasia, apraxia, and agnosia were interpreted as resulting from disconnections in these circuits. Whereas the implication that white matter lesions could produce these disconnections is obvious, Geschwind

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also believed gray matter lesions to be capable of disconnecting brain areas and leading to specific neuro-behavioral syndromes. Thus his approach was intended to highlight overall connectivity, and not as much the details of specific white matter tracts and lesions. Nevertheless, his work set the stage for many subsequent advances as methods for studying white matter become more sophisticated and the clinical correlates of focal and diffuse lesions could be better established (Filley et al. 1988; Mesulam 1990; Absher and Benson 1993; Filley 1998; Sullivan and Pfefferbaum 2003; Catani and Ffytche 2005; Aralasmak et al. 2006; Schmahmann and Pandya 2006; Fields 2008).

In this review, I will aim to provide a clinically relevant survey of the organization and functional relevance of white matter for the study of cognition and emotion. This task has special meaning since I had the opportunity, as a fellow in behavioral neurology at the Boston VA Hospital, to work with Geschwind in the last year of his life. His erudition, enthusiasm, and insights into brain-behavior relationships continue to be influential today as they were then, and it is a privilege to extend the thinking he presented 45 years ago that has had such a lasting impact.

Organization

White matter makes up about 50% of human brain volume (Filley 1998), and an estimated 135,000 km of myelinated fibers course within the forebrain (Saver 2006). These facts alone argue strongly for the notion that myelinated tracts are important for higher functions, and evidence supporting this concept steadily mounts. Yet the relationships of white matter structure and function to cognition and emotion are not easily understood. To clinicians accustomed to seeing standard brain imaging studies, the white matter appears to be an undifferentiated mass of tissue lying between the cortex and the ventricles, and the enormous complexity of its connectivity is not readily apparent. No maps of the white matter exist that compare to the Brodmann areas of the cerebral cortex, and indeed, many finer details of white matter neuroanatomy remain to be fully described. Less metabolically active than gray matter, white matter cannot be usefully approached with functional neuroimaging. However, important work is rapidly proceeding, largely propelled by advances in structural neuroimaging, and more detailed understanding of the organization of white matter is now emerging.

Neuroanatomy

As neuroanatomy is a vast discipline (Nolte 2002), only selected aspects of white matter can be reviewed here. White matter is found throughout the central nervous system, and that within the brain is pertinent to higher

function. The descriptor “cerebral” is often used to refer to the white matter of the brain, although tracts in the brain stem and cerebellum should also be included in a complete account, and indeed, evidence supports the importance of all white matter above the spinal cord in the organization of cognition and emotion (Schmahmann and Pandya 2008). A convenient distinction can then be made between the macrostructure and microstructure of brain white matter, as both features have implications for brain-behavior relationships.

The traditional understanding of brain white matter macrostructure designates three categories of tracts—projection, commissural, and association—and for most purposes these distinctions are still useful (Nolte 2002). However, as Table 1 illustrates, the understanding of white matter anatomy is quickly evolving with the advances of modern neuroimaging (Aralasmak et al. 2006; Schmahmann and Pandya 2006). Association and commissural tracts are most crucial for cognition and emotion, as projection fiber systems are devoted mainly to elemental sensory and motor functions. Association tracts are either long (serving to connect distant regions) or short (linking adjacent gyri), and interconnect intrahemispheric gray matter structures. The major, but not only, commissural tract is the corpus callosum, a massive collection of myelinated axons that connects the two cerebral hemispheres; this tract is considered in detail elsewhere in this issue. Together, the association and commissural tracts comprise the essential foundation of brain connectivity that occurs in intricate patterns to integrate gray matter regions into functional neuronal ensembles. The various classifications presented in Table 1 (Aralasmak et al. 2006; Schmahmann and Pandya 2006; Nolte 2002) should be seen as indicating ongoing refinement in our knowledge of white matter macrostructure that will significantly influence future studies of behavioral neuroanatomy.

A less often recognized feature of white matter is that it is also found within the gray matter of both the cortical mantle and subcortical nuclei (Nolte 2002). In the cerebral cortex, for example, horizontal white matter fascicles—the outer and inner bands of Baillarger—travel in layers IV and V (Nolte 2002). These fibers are currently attracting increased attention because intracortical myelin is affected in multiple sclerosis (MS; Stadelmann et al. 2008), and the neurobehavioral consequences of this demyelination may be considerable. Adjacent to the hippocampus, the alveus carries efferent fibers that combine to form the fimbria and then fornix, and white matter fascicles also course through the thalamus and basal ganglia (Nolte 2002).

The microstructure of brain white matter plays a complementary, and equally important, role in the organization of cognition and emotion. The key neuroanatomical feature is myelin, the fatty insulation that coats most axons in the brain and dramatically increases neuronal conduction

Table 1 Evolving formulations of cerebral white matter tracts

Methods: Gross dissection, myelin staining of human brain, lesion degeneration (Nolte 2002)	Method: Diffusion tensor imaging of human brain (Aralasmak et al. 2006)	Methods: Autoradiography and diffusion spectrum imaging of rhesus monkey brain (Schmahmann and Pandya 2006)
<i>Association</i>	<i>Association</i>	<i>Association</i>
Short association (U) fibers	Short association (U) fibers	Local (U) fiber system Neighborhood fiber system
Arcuate Fasciculus	Superior Longitudinal (Arcuate) Fasciculus	Arcuate Fasciculus Superior Longitudinal Fasciculus 1 Superior Longitudinal Fasciculus 2 Superior Longitudinal Fasciculus 3 Middle Longitudinal Fasciculus Extreme Capsule
Superior Occipitofrontal Fasciculus	Superior Fronto-occipital (Subcallosal) Fasciculus	Fronto-occipital Fasciculus
Inferior Occipitofrontal Fasciculus	Inferior Fronto-occipital Fasciculus	
Uncinate Fasciculus	Inferior Longitudinal Fasciculus	Inferior Longitudinal Fasciculus
Cingulum	Uncinate Fasciculus	Uncinate Fasciculus
	Cingulum	Cingulum Bundle <i>Striatal</i> External Capsule Subcallosal Fasciculus of Muratoff (Muratoff Bundle)
<i>Commissural</i>	<i>Commissural</i>	<i>Commissural</i>
Corpus Callosum	Corpus Callosum	Corpus Callosum
Anterior Commissure	Anterior Commissure	Anterior Commissure
Hippocampal Commissure	Hippocampal Commissure	Hippocampal Commissure
	Habenular Commissure	
	Posterior Commissure	
	Tectal Commissure	
<i>Projection</i>	<i>Projection</i>	<i>Projection (Subcortical)</i>
Internal Capsule	Internal Capsule	Internal Capsule
Optic Radiation	Optic Radiation	Optic Radiation (within the Sagittal Stratum)
Thalamocortical Radiation	Acoustic Radiation	Thalamic Peduncles
	Fornix	

velocity (Baumann and Pham-Dinh 2001). Myelin, a complex mixture of about 70% lipid and 30% protein, encircles axons in a circumferential manner after being laid down by oligodendrocytes, one of the abundant glial cell types in the brain (Bennarroch 2009). The glistening white hue of the cut brain at autopsy in fact derives from myelin. At the neuronal level, myelin forms a concentric sheath along the length of the axon, leaving small unmyelinated segments called nodes of Ranvier (Baumann and Pham-Dinh 2001). These nodes permit the extraordinary phenomenon of saltatory conduction, by which the action potential “jumps” from one node to the next as it rapidly traverses the length of the axon to the terminal dendrites and synapses (Baumann and Pham-Dinh 2001). Thus the

white matter remarkably accelerates the transfer of information in the brain.

Neurophysiology

The crucial physiologic aspect of white matter is its vastly enhanced speed of electrical conduction compared to that seen in unmyelinated axons. By means of saltatory conduction, action potentials or “spikes” in myelinated axons jump from one node of Ranvier to the next, increasing the cell’s conduction velocity by as much as 100 times (Filley 2001a). The brain contains some 100 billion neurons, many of which are far removed from each other, and the capacity of the brain to “talk” to itself is

essential for the seamless and efficient operations of evolved complex behavior (Filley 2001a). White matter provides this essential function, enabling rapid communication between gray matter regions that combine to subservise cognition and emotion. Whereas it may seem disarmingly simple that slower electrical conduction of brain neurons means slowed mentation, much evidence now demonstrates exactly this; it appears that the more myelin is engaged in a given function, the faster the speed with which the operations supporting that function are performed (Turken et al. 2008; Bartzokis et al. 2008; Kochunov et al. 2010).

The faster electrical conduction enabled by white matter appears to have evolutionary importance. Myelin is a recent development in phylogeny, and is almost exclusively confined to the nervous systems of vertebrate species (Baumann and Pham-Dinh 2001). Recent data also indicate a selective increase in prefrontal white matter volume in humans compared to nonhuman primates, whereas gray matter volume is not significantly different (Schoenemann et al. 2005). From these observations, it can be concluded that the myelin within white matter has a special role not only in enhancing neuronal conduction velocity generally within the brain, but specifically within frontal networks devoted to the most highly evolved human behaviors.

Development and Aging

The processes of brain development and aging show markedly different trajectories for white and gray matter. With the exception of neurons that are now known to differentiate after neurologic damage (Martí-Fàbregas et al. 2010), the brain complement of neurons, the cell bodies of which are the central constituent of gray matter, is formed during the first half of gestation; in contrast, white matter is only beginning to develop at birth, and myelination occurs mainly in postnatal life (Baumann and Pham-Dinh 2001). Myelin is in fact laid down steadily for many years, particularly in childhood and adolescence but even into the sixth decade (Benes et al. 1994), and reaches its maximal volume in midlife (Filley 2001a). Recent evidence has confirmed a “quadratic” or inverted *U* pattern of brain white matter development whereby myelination proceeds to expand white matter until about the age of 50, after which this volume slowly declines (Bartzokis et al. 2001). In early life, the association tracts and cerebral commissures are the latest to develop, and myelination as a delayed maturational event in ontogeny corresponds with the appearance of the mature adult brain and its associated behaviors (Filley 2001a). In late life, loss of white matter has been associated with age-related changes in cognition (Filley 2001a), and considerable neuroimaging evidence has identified an anterior–posterior gradient whereby frontal–temporal tracts

and the anterior corpus callosum are preferentially affected in normal aging (Davatzikos and Resnick 2002; Sullivan and Pfefferbaum 2010; Zahr et al. 2009; Madden et al. 2009). This temporal profile suggests that, perhaps even more than gray matter, the cerebral white matter may influence the most highly evolved human behaviors over the entire lifespan (Bartzokis 2005). Moreover, it has been theorized that a wide range of neurobehavioral disorders of early and late life—from autism to Alzheimer’s Disease (AD)—may relate in some manner to the incomplete formation of myelin before maturity, or the attrition of white matter with senescence (Filley 2001a; Bartzokis 2005). While parallel developments in gray matter, such as synaptic pruning in development and neuronal cell body loss in aging, cannot be overlooked, white matter likely exerts its own unique effects on normal mentation throughout life.

Structural and Functional Neuroimaging

Despite its distinction from gray matter by Andreas Vesalius as long ago as 1543 (Filley 2001a), white matter has proved neuroanatomically challenging to this day. The study of brain-behavior relationships requires a method whereby brain regions can be reliably identified as a basis for understanding their functional affiliations. For most of the history of neuroscience, including the 19th century when the classic neurologists discussed in Geschwind’s paper were active, this method was the autopsy. Many problems with this approach, however, confound correlations of brain and behavior, and although still useful, autopsy studies of localization have been largely supplanted by elegant neuroimaging methods that can be safely and repeatedly employed during life (Bandettini 2009). These advances have revolutionized clinical neuroscience, enabling the detailed investigation of brain structure and function in health and disease. Much attention has been devoted to the functional imaging of cortical regions, but nowhere has structural imaging been more profoundly influential than in the depiction of white matter.

The study of brain white matter entered a new era in the early 1980s when magnetic resonance imaging (MRI) appeared. For the first time, the *in vivo* demonstration of white matter became possible, and in particular, disorders of white matter could be routinely seen by clinicians and investigators (Filley 2001a). Figure 1, for example, shows the MRI scan of an older adult with ischemic white matter disease. Geschwind witnessed only the beginning of this era, and now the technology has advanced much further to permit greater understanding of the white matter connections he could only discuss in general terms (Geschwind 1965). In the ensuing years, functional MRI (fMRI) appeared as a means of imaging brain metabolism

(Bandettini 2009), and together with positron emission tomography (PET) scanning, important advances have been made in understanding the localization of cognition and emotion (Bandettini 2009). fMRI and PET, however, are capable of investigating only cortical regions, where neuronal function produces relatively high metabolic activity, and white matter remained inaccessible to these methods.

The most important new technique for the study of white matter-behavior relationships is diffusion tensor imaging (DTI; Basser and Jones 2002; Catani 2006; Catani et al. 2005; Mori et al. 2009). Figure 2 is a DTI scan of the brain of a normal young adult selectively depicting white matter tracts. Using the concepts of anisotropy, the directional (non-random) diffusion of water along a normal tract, and isotropy, the random diffusion of water in the area of a damaged tract, DTI is capable of identifying both normal white matter pathways and lesions within these tracts (Basser and Jones 2002). Normal connective neuroanatomy can be estimated by tractography, which is in essence a “virtual dissection” of the living brain (Catani 2006). Novel observations are rapidly appearing with DTI, such as, for one example, more complex connectivity of the perisylvian language network (Catani et al. 2005), and white matter atlases are thus being compiled that will help enrich and standardize neuroanatomical understanding of these tracts (Mori et al. 2009).

The combined use of structural white matter imaging and functional gray matter imaging promises to define and characterize the distributed neural networks dedicated to cognition and emotion (Mesulam 1990). Clinicians and

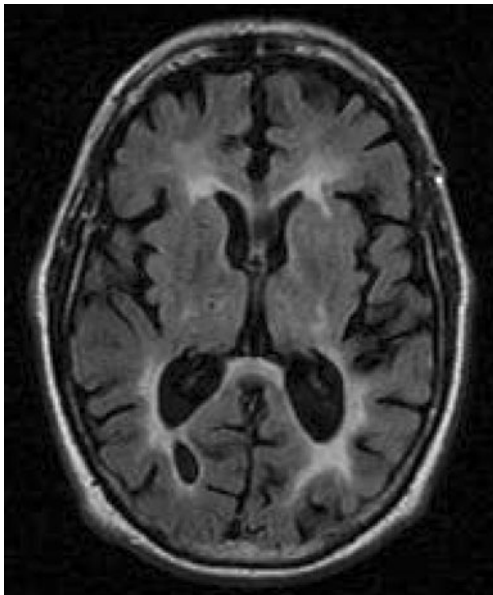


Fig. 1 Brain magnetic resonance imaging (MRI) of an older adult showing ischemic white matter disease

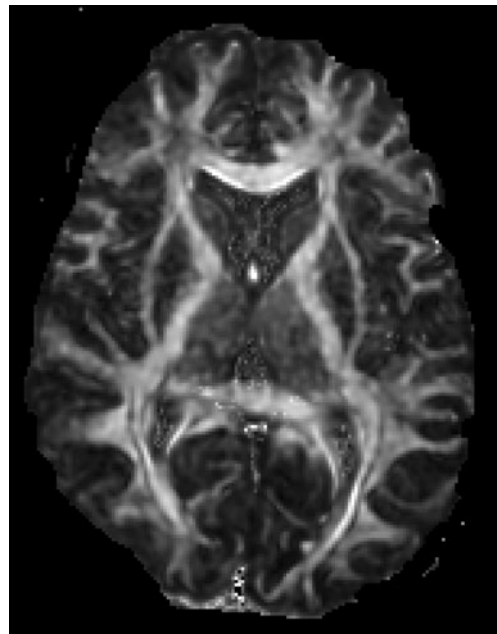


Fig. 2 Diffusion tensor imaging (DTI) scan demonstrating white matter tracts in the brain of a normal young adult

investigators alike are now able to view the details of neural networks engaged in specific behaviors, gaining unprecedented insights into the interactions between white and gray matter (Filley 2001a).

Functional Relevance

Surprisingly, contemporary neurology has only gradually recognized that white matter in the brain contributes significantly to cognition and emotion. Geschwind's paper was accepted as describing cerebral disconnection (Geschwind 1965), but cortical regions were still seen as the primary repository of higher functions, and indeed, in Luria's terminology (Luria 1966), the phrase “higher cortical function” endures today to denote for many the interests of behavioral neurologists. Clinical experience guided prevailing opinion: because cognition was assumed to be unaffected in MS and other white matter diseases, many neurologists concluded that white matter involvement did not notably impact higher functions, whereas cortical diseases, most notably AD, clearly did. With further study, however, the effects of white matter pathology on cognition and emotion became inescapable. Today, stimulated by advanced neuroimaging techniques, myelinated systems are receiving far more attention in the study of behavior, and the complex interplay of white and gray matter involvement is the focus of much investigation.

It is now clear that a wide range of white matter disorders disturb behavior to produce a variety of neurobehavioral

syndromes (Filley 2001a). These syndromes include not only the focal disconnections of Geschwind, but also dementia from the diffuse involvement of white matter—which is in fact far more common neuropathologically. In addition, a number of intriguing hypotheses have been generated about the possible role of white matter dysfunction in a number of neuropsychiatric conditions that have long puzzled clinicians and investigators. This section will use the lesion method of behavioral neurology to consider the functional relevance of white matter (Filley 1998; Aralasmak et al. 2006; Filley 2001a; Schmahmann et al. 2008).

White Matter Disorders

Well over 100 disorders exist in which brain white matter is prominently or exclusively involved (Filley 2001a; Schmahmann et al. 2008). These disorders can occur at all ages, appear in any clinical setting, and result from disease, injury, or intoxication of myelinated tracts in the brain (Filley 2001a; Schmahmann et al. 2008). Table 2 lists the 10 categories of white matter disorder and examples of each. Although the prevalence of neurobehavioral dysfunction in these disorders cannot be precisely stated, close inspection of clinical reports indicates that cognitive or emotional impairment can appear in all; and because elemental motor and sensory deficits may be more readily elicited, neurobehavioral syndromes may be underdiagnosed (Filley 2001a).

Genetic Diseases White matter can be affected by a wide range of genetic diseases. These diseases are rare and incompletely understood; many, such as the recently described vanishing white matter disease (van der Knaap et al. 2006), are being regularly discovered by the combination of MRI and genetic analyses. Patients with these diseases typically come to the attention of child neurologists, but occasional individuals may develop initial clinical features as adults. Metachromatic leukodystrophy (MLD) is a useful example of this category because its etiology has been defined and its clinical features relatively well characterized. MLD is one of the leukodystrophies, diseases characterized by dysmyelination, the abnormal formation of myelin. A deficiency of aryl sulfatase A causes lysosomal sulfatide accumulation and progressive neurologic and neurobehavioral decline (Austin et al. 1968). Usually a disease of infancy, MLD can present in adulthood, and a consistent pattern has been noted of psychiatric dysfunction resembling schizophrenia that progresses to dementia as the disease advances (Filley and Gross 1992; Hyde et al. 1992). Peripheral neuropathy is the major elemental neurologic finding of MLD, but dementia is its most prominent feature, with a range of deficits primarily signifying frontal lobe disturbance: disinhibi-

tion, executive dysfunction, impaired sustained attention, relatively intact language, and visuospatial impairment (Filley 2001a). MRI shows white matter hyperintensities throughout the cerebrum, and, once these changes appear, dementia inexorably progresses.

Demyelinative Diseases This category includes MS and many related but less common inflammatory diseases of myelin. In contrast to the dysmyelinative diseases such as MLD, MS involves inflammatory demyelination in the central nervous system, with many consequent forms of neurologic dysfunction. The disease may damage axons as well as myelin, which is now known to confer a worse prognosis (Medana and Esiri 2003). The elemental neurologic deficits of MS are well recognized, and include hemiparesis, visual loss, diplopia, nystagmus, ataxia, spasticity, gait disorder, and incontinence. In terms of higher function, MS has recently been better appreciated as a source of cognitive and emotional impairment, recalling the initial insights of the great French neurologist Jean-Martin Charcot in the 1870s (Charcot 1877). As recently as 1970, cognitive impairment of any degree in MS was thought to occur about 5% of patients (Kurtzke 1970), but more recent community-based neuropsychological studies have put this figure at 43% (Rao et al. 1991). Dementia may also occur, and its prevalence has been estimated to be as high as 23% (Boerner and Kapfhammer 1999). The profile of cognitive impairment in MS has been reported to include deficits in executive function, sustained attention, memory retrieval, and visuospatial function, with relative sparing of language (Filley 2001a); some evidence has also been presented for impaired memory encoding (Filley 2001a), which could relate to demyelination of the alveus. A host of other syndromes can also be seen in MS, including a wide range of focal neurobehavioral syndromes such as aphasia and callosal disconnection, and neuropsychiatric disturbances including euphoria and pathological laughter and crying (Fields 2008; Filley 2001a). The source of cognitive impairment and dementia is likely damage to white matter, as many studies have found at least modest correlations between extent of MRI white matter damage and the degree of cognitive loss (Filley 2001a). More sophisticated MRI techniques have also documented abnormalities in the normal-appearing white matter, indicating that subtle white matter pathology may be missed by conventional MRI. Recent studies have also identified cerebral cortical involvement, and “cortical MS” has been invoked to explain cognitive decline (Stadelmann et al. 2008). While intracortical myelin is affected in MS, and cortical lesions can now be assessed neuroradiologically, demyelination of large white matter tracts remains the MS neuropathology most directly implicated in cognitive impairment and dementia (Penny et al. 2010). MS damages

Table 2 Cerebral white matter disorders

Genetic	Leukodystrophies (e.g. Metachromatic Leukodystrophy)
	Aminoacidurias (e.g. Phenylketonuria)
	Phakomatoses (e.g. Neurofibromatosis)
	Mucopolysaccharidoses
	Muscular Dystrophy
Demyelinative	Callosal Agenesis
	Multiple Sclerosis
	Acute Disseminated Encephalomyelitis
	Acute Hemorrhagic Encephalomyelitis
	Schilder's Disease
Infectious	Marburg's Disease
	Balo's Concentric Sclerosis
	HIV-Associated Dementia
	Progressive Multifocal Leukoencephalopathy
	Subacute Sclerosing Panencephalitis
Inflammatory	Progressive Rubella Panencephalitis
	Varicella Zoster Encephalitis
	Cytomegalovirus Encephalitis
	Lyme Encephalopathy
	Systemic Lupus Erythematosus
Toxic	Behcet's Disease
	Sjogren's Syndrome
	Wegener's Granulomatosis
	Temporal Arteritis
	Polyarteritis Nodosa
Metabolic	Scleroderma
	Isolated Angiitis of the CNS
	Sarcoidosis
	Cranial Irradiation
	Therapeutic Drugs
Vascular	Drugs of Abuse (e.g. Toluene)
	Environmental Toxins (e.g. Carbon Monoxide)
	Cobalamin Deficiency
	Folate Deficiency
	Central Pontine Myelinolysis
Traumatic	Hypoxia
	Hypertensive Encephalopathy
	Eclampsia
	High Altitude Cerebral Edema
	Binswanger's Disease
Neoplastic	CADASIL
	Leukoaraiosis
	Cerebral Amyloid Angiopathy
	White Matter Disease of Prematurity
	Migraine
Neoplastic	Traumatic Brain Injury
	Shaken Baby Syndrome
	Corpus Callosotomy
	Gliomatosis Cerebri
	Diffusely Infiltrative Gliomas

Table 2 (continued)

Hydrocephalic	Lymphomatosis Cerebri
	Focal White Matter Tumors
	Early Hydrocephalus
	Normal Pressure Hydrocephalus

a higher volume of white matter in large fiber tracts than in the cortex, and the neuropsychological profile of cognitive loss in MS (Filley 2001a) suggests that demyelination in these tracts is likely to be the main determinant of neurobehavioral dysfunction.

Infectious Diseases Infections of the brain cannot be exclusively characterized as confined to the cortical, subcortical gray, or white matter. However, certain brain infections, in many cases at least, display a predilection for white matter, and this tendency may have important neurobehavioral implications. The prototype disorder of this type is the dementia associated with human immunodeficiency virus (HIV) infection, which was first termed the acquired immunodeficiency syndrome (AIDS) dementia complex (ADC; Navia et al. 1986a) and later called HIV-associated dementia (HAD; Boissé et al. 2008). The propensity for HAD to involve white matter is evident both in the high frequency of MRI white matter hyperintensities in HIV and HAD patients, and the presence of white matter pallor as an early neuropathological finding of HAD (Filley 2001a). Fulminant and fatal leukoencephalopathy can be seen as the only manifestation of HIV infection (Jones et al. 1988). It must be acknowledged that the basal ganglia are also involved (Navia et al. 1986b), and indeed the initial reports of dementia in AIDS stressed the subcortical profile of the dementia (Navia et al. 1986a), with cognitive slowing, impaired attention, memory loss, and personality change, similar to the clinical features of patients with traditional subcortical dementias such as Huntington's Disease (HD) and Parkinson's Disease (PD). However, the role of white matter dysfunction is not easily dismissed in HIV infection, as MRI white matter changes improve in parallel with cognitive decline in patients successfully treated for ADC (Thurnher et al. 2000). Advanced neuroimaging is clarifying this issue, and most recently, DTI has shown that white matter injury in association tracts and the corpus callosum is related to cognitive impairment in HIV-infected individuals (Gongvatana et al. 2009). HIV patients without dementia have also been shown to have white matter tract injury with DTI (Pfefferbaum et al. 2009). While the complex neuropathology of HAD is still being elucidated, evidence to date supports further consideration of the role of white matter dysfunction in neurobehavioral impairment.

Inflammatory Diseases Inflammatory, autoimmune brain diseases are similar to the infections described above in that their pathology cannot be assigned to the cerebral white matter alone. The neuropathology of these diseases is multifaceted, involving many brain regions and different pathogenic processes. Still, growing evidence implicates a role for white matter involvement in neurobehavioral dysfunction. Systemic lupus erythematosus (SLE) is well studied example and proves illustrative. SLE, often known simply as lupus, is an idiopathic autoimmune disease with protean systemic effects that may involve the skin, joints, heart, kidneys, and other organs in addition to the nervous system. Neuropsychiatric lupus refers to a diverse collection of syndromes in SLE that includes cognitive dysfunction (West 1994), a problem that can be noted in SLE patients both with and without neurologic disease such as a stroke or seizure disorder (Kozora et al. 1996). Considerable evidence supports an association between cognitive dysfunction, which includes deficits in attention, concentration, visuospatial skills, and processing speed, and leukoencephalopathy, a general term for cerebral white matter pathology (Filley 2001a). Progression of cognitive impairment to a more severe state can also occur, and a relationship has been postulated between dementia and widespread leukoencephalopathy in SLE (Kirk et al. 1991). MRI white matter hyperintensities are common (Kozora et al. 1996), putatively related to the underlying vasculopathy of SLE that compromises the blood supply of the white matter. Magnetic resonance spectroscopy (MRS) studies have shown that, even in SLE patients with normal white matter on conventional MRI and no neuropsychiatric features, subtle cognitive impairment correlates with increased frontal white matter choline, but not with the neuronal marker N-acetyl aspartate (NAA) or hippocampal atrophy (Filley et al. 2009). Support for a contribution of cerebral myelin damage to cognitive impairment in SLE is thus accumulating.

Toxic Leukoencephalopathy Many toxic disorders of the brain display a predilection to affect the cerebral white matter, and a spectrum of severity exists from mild, reversible confusion to coma and death, with concomitant MRI and neuropathological white matter changes (Filley and Kleinschmidt-DeMasters 2001). Cranial irradiation and several cancer chemotherapeutic drugs are well recognized leukotoxins that can lead to such neurobehavioral complications in the treatment of many malignancies. One of the more intriguing discoveries made possible by the application of MRI is toluene leukoencephalopathy (TL), which convincingly illustrates the capacity for pure white matter damage to produce dementia (Hormes et al. 1986; Rosenberg et al. 1988a, b; Filley et al. 1990, 2004). Toluene (methylbenzene) is a widely used household and industrial solvent that is also

popular as a drug of abuse among millions of people in the U.S. and elsewhere. Inhalant abuse is a common but underappreciated form of drug abuse, with a lifetime prevalence in the U.S. estimated at 18% (Filley et al. 2004). Toluene, the major solvent in spray paint, is inhaled as a euphorogenic agent, often for years without respite, and the result of long-term toluene abuse is a devastating syndrome of dementia, ataxia, corticospinal dysfunction, and cranial nerve deficits that has readily detectable MRI characteristics (Rosenberg et al. 1988a). MRI scans of toluene abusers display diffuse T2 hyperintensity in the cerebral and cerebellar white matter, and the degree of cerebral involvement strongly correlates with the severity of dementia, the most prominent clinical manifestation (Filley et al. 1990). Dementia is striking, with a pattern of cognitive slowing, apathy, impaired vigilance, poor memory, and visuospatial dysfunction with intact language (Filley 2001a; Hormes et al. 1986; Filley et al. 1990). Autopsy studies of TL confirm the MRI findings by revealing selective myelin loss with sparing of the cerebral cortex, neuronal cell bodies, and even axons in all but the most severe cases (Rosenberg et al. 1988b; Filley et al. 2004). A recent review of 30 empirical studies of toluene misuse concluded that white matter is indeed the likely target of toluene, and that observed cognitive deficits are consistent with white matter damage (Yücel et al. 2008). TL thus serves to illustrate the toxic white matter disorders, but also stands out as the most convincing example of white matter dementia (Filley et al. 1988; Filley 1998, 2001a; see below).

Metabolic Disorders In this diverse group, metabolic disturbances produce white matter neuropathology and a variety of associated neurobehavioral syndromes. In clinical practice, metabolic disturbances often co-exist with toxic disorders to produce a complex clinical and MRI picture known as reversible posterior leukoencephalopathy syndrome (Hinchey et al. 1996), but for our purposes a useful example of this category is dementia related to cobalamin (vitamin B₁₂) deficiency. Cobalamin, routinely assessed in the evaluation of neurologic patients, is important in the maintenance of normal myelin, and its deficiency results in the familiar subacute combined degeneration (SCD) of the spinal cord. Less well recognized is that cobalamin deficiency may also cause perivascular degeneration of myelinated fibers in the cerebrum that is identical to the spinal cord pathology of SCD, and these brain lesions have been postulated to account for neurobehavioral dysfunction (Adams and Kubik 1944). The myelin lesions are scattered irregularly throughout the white matter, resembling the distribution of MS plaques, and patients may present with diverse clinical features including apathy, irritability, fatigue, depression, confusion, and dementia (Pennypacker et al. 1992). Because cobalamin deficiency may produce dementia

that can be easily corrected with treatment, vitamin B₁₂ screening has become a regular component of the reversible dementia work-up. Cobalamin levels below 100 pg/ml represent significant tissue deficiency of B₁₂, and levels between 100 and 300 pg/ml justify testing for the metabolites homocysteine and methylmalonic acid, elevations of which also signify clinically relevant B₁₂ deficiency (Miller et al. 2005). Well documented cases of dementia with MRI white matter lesions have demonstrated that treatment using parenteral vitamin B₁₂ improve both the dementia and the white matter changes (Chatterjee et al. 1996; Stojsavljević et al. 1997).

Vascular Diseases Whereas it is clear that most of the lesions on which Geschwind based his thinking were focal cerebral infarctions, this category has recently proven one of the more confusing areas of neurobehavioral research. Much of this confusion stems from lingering uncertainty about the classification of patients with presumed cerebrovascular disease and cognitive impairment or dementia. One contentious area concerns the seemingly ubiquitous focal white matter changes on computed tomography (CT) and MRI scans of older people, for which the term leukoaraiosis (LA) has been introduced to describe the “rarefaction” of white matter (Hachinski et al. 1987). Figure 1 illustrates a marked degree of LA as shown on MRI. These neuroimaging findings resurrected a century-old debate surrounding the entity of Binswanger’s Disease (BD; Babikian and Ropper 1987; Caplan 1995). BD, or subcortical arteriosclerotic encephalopathy, describes a dementia syndrome attributed to widespread white matter infarction and ischemia, but the disease has sparked debate because of incomplete data in the original case descriptions (Hachinski 1991). Nevertheless, the concept of BD has persisted as a pathologic diagnosis that is arguably one of the most frequent causes of vascular dementia (VaD). Although it has long been clear that LA and BD are not synonymous, a consensus view holds that LA is a vascular disorder (Pantoni and Garcia 1997), and many believe that a continuum of severity exists from LA to BD (Román 1996). Because of uneasiness still engendered by the term BD, the less controversial descriptor subcortical ischemic vascular dementia (SIVD) has been proposed to include both BD and a close relative called the lacunar state (Chui 2007). Whatever terminology is preferred, considerable evidence favors the existence of a type of VaD primarily characterized by white matter infarction and ischemic demyelination (Román et al. 1993). VaD of this type is typically characterized by confusion, apathy, and poor memory in the absence of aphasia; concomitantly, motor signs including weakness, spasticity, hyperreflexia, extensor plantar responses, and gait disorder are common neurologic findings (Filley 2001a). An important reason to

focus on this entity is that primary care efforts to prevent or minimize VaD are feasible by close attention to cerebrovascular risk factors earlier in life (van Gijn 1998). In this regard, a syndrome called vascular cognitive impairment (VCI; Selnes and Vinters 2006) has been introduced in an attempt to identify people at risk for VaD, just as those with mild cognitive impairment (MCI) are identified as being at risk for AD (Petersen et al. 1999); white matter pathology may be present in many, if not all people with VCI. An interesting parallel development that has evolved with this thinking has been the discovery of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a genetic white matter disorder with clinical and neurobehavioral features reminiscent of BD (or SIVD) except for the absence of cerebrovascular risk factors (Harris and Filley 2001).

Traumatic Disorders Traumatic brain injury (TBI) is an important source of neurobehavioral disability, estimated to affect 1.4 million Americans per year (Langlois et al. 2004), and will serve as the primary example of traumatic white matter damage. TBI is especially problematic because of its dramatic peak incidence in young adulthood, often leaving patients with decades of disability and lost productivity. Among the many lesions head trauma may produce, including cortical contusion, intracerebral hemorrhage, subdural hematoma, epidural hematoma, penetrating injury, and hypoxic-ischemic damage, arguably the most important TBI lesion is diffuse axonal injury (DAI), sometimes called traumatic axonal injury, within the white matter (Adams et al. 2000; Smith et al. 2003). DAI indicates that traumatic shearing injury has damaged white matter tracts, and those in the brainstem, cerebral hemispheres, and corpus callosum are most vulnerable (Filley 2001b); evidence suggests that DAI is probably a ubiquitous white matter injury in TBI (Filley 2001b; Kraus et al. 2007). DAI has been linked with the acute loss of consciousness, and with chronic sequelae including persistent attentional, executive, compartmental, and memory disturbances (Filley 2001b); neurobehavioral deficits are thus associated with DAI in all degrees of TBI severity, from concussion to the vegetative state (Adams et al. 2000; Alexander 1995). Damage to frontal lobe white matter is particularly detrimental, compromising long-term outcome by interfering with restoration of normal personality, occupational function, and community reintegration (Filley 2001a, b).

Neoplasms Brain tumors have been considered less than optimal for investigating brain-behavior relationships because they are often not clearly localizable; complicating factors such as their wide extent, mass effect, and associated edema hinder precise tumor localization. However, with the assistance of improved neuroimaging and

traditional neuropathology, the neurobehavioral effects of many cerebral neoplasms can be better defined (Filley and Kleinschmidt-DeMasters 1995). Tumors can be particularly illustrative in terms of their important effects on white matter tracts. Gliomas, for example, are now recognized to originate primarily from glial progenitor cells in the white matter (Canoll and Goldman 2008), and they disseminate via white matter tracts to other brain regions (Giese and Westphal 1996; Geer and Grossman 1997). An outstanding example of a white matter neoplasm producing neurobehavioral dysfunction is gliomatosis cerebri, a diffusely infiltrative astrocytic malignancy with a marked predilection for cerebral white matter (Filley et al. 2003). Neurobehavioral deficits such as apathy, fatigue, memory retrieval impairment, and executive dysfunction are the most common presenting and persistent clinical manifestations of this rare tumor, which can be documented by MRI to spread via inter- and interhemispheric white matter pathways and produce progressive dementia (Filley et al. 2003). Gliomatosis cerebri illustrates once again that selective white matter neuropathology results in clinically significant cognitive and emotional dysfunction (Filley et al. 2003). Cerebral lymphoma demonstrates a similar clinical course when it takes the diffusely infiltrative form of lymphomatosis cerebri (Rollins et al. 2005). Study of brain tumors as the agents of neurobehavioral deficits related to white matter dysfunction deserves more attention, especially as more sensitive neuroimaging techniques offer the opportunity to view the location and spread of these tumors throughout their clinical course.

Hydrocephalus The final category of cerebral white matter disorder in Table 2 is hydrocephalus. Whether originating early or late in life, hydrocephalus has been shown to exert its most prominent neuropathological effects on cerebral white matter (Del Bigio 1993; Del Bigio et al. 1994). Cortical damage is uncommon, occurring only late in the disease course, and injury to the deep gray matter is also less marked than white matter injury, indicating that the cognitive effects of hydrocephalus are mainly related to tract damage, at least when diagnostic and treatment issues are most critical. The periventricular white matter is most compromised, and neurosurgical shunting procedures can be effective in alleviating this damage by reducing intraventricular cerebrospinal fluid volume and pressure. In older patients with normal pressure hydrocephalus (NPH; Adams et al. 1965), the often sought but rarely found reversible dementia, shunting can lead to clinical improvement in some cases. In this disease, gait disorder and incontinence characteristically accompany the dementia, which has deficits consistent with frontal lobe dysfunction: cognitive slowing, apathy, and inattention (Filley 2001a). Shunt procedures, however, may be less effective in NPH

than in younger hydrocephalus patients because of coexistent ischemic damage in the white matter (Earnest et al. 1974) or concomitant AD (Bech et al. 1997). As a general rule, however, white matter injury associated with hydrocephalus has a relatively favorable prognosis because, at least early in the course, widespread gray matter injury has not occurred.

Neurobehavioral Syndromes

The neurobehavioral syndromes implicating white matter involvement can be divided into three categories. As Geschwind discussed (Geschwind 1965), a host of focal neurobehavioral syndromes represent classic disconnection of cortical areas. Next, it is now clear that diffuse white matter involvement may lead to the syndrome of white matter dementia, in which a profile of deficits tends to cluster together (Filley et al. 1988; Filley 1998, 2001a). Last, a wide range of neuropsychiatric conditions merit discussion as putatively implicating white matter dysfunction.

Focal Neurobehavioral Syndromes Little need be added to the rich literature on these syndromes, listed in Table 3, except to point out that all of them have been documented in the modern era to be associated with white matter lesions in areas predicted by the disconnection model put forth by Geschwind (Geschwind 1965; Aralasmak et al. 2006; Filley 2001a; Schmahmann et al. 2008). These syndromes form much of the core knowledge of behavioral neurology and neuropsychology, and the fact that they were discovered in the pre-neuroimaging era stands as a monument to the elegance of clinical-pathological correlations that were painstakingly conducted using autopsy alone.

White Matter Dementia This term refers to a dementia syndrome resulting from the effects of diffuse or multifocal white matter involvement in the brain (Filley et al. 1988; Filley 1998, 2001a; Schmahmann et al. 2008). Such a syndrome can be predicted by the prominence of disconnection syndromes with focal white matter lesions and the observation that most white matter disorders feature diffuse or multifocal pathology, and in fact the literature does support the existence of white matter dementia in all the categories discussed above (Filley 2001a; Schmahmann et al. 2008). Early recognition of the syndrome was apparent when the white matter disorders were combined with the subcortical gray matter diseases such as PD and HD into the single category of subcortical dementia (Cummings and Benson 1984; Cummings 1990). Yet the white matter disorders causing dementia can be distinguished from the subcortical gray matter dementias neuroradiologically, neuropathologically, and in neurobehavioral terms, and

Table 3 Focal neurobehavioral syndromes of white matter

Amnesia	Alexia
Aphasia	Pure Alexia
Broca's	Alexia with Agraphia
Wernicke's	Developmental Dyslexia
Conduction	Gerstmann's Syndrome
Global	Agnosia
Transcortical Motor	Visual
Transcortical Sensory	Auditory
Anomic	Neglect
Mixed Transcortical	Visuospatial Dysfunction
Apraxia	Akinetic Mutism
Ideomotor	Executive Dysfunction
Callosal	Callosal Disconnection

white matter dementia is likely common and under-recognized (Filley 1998, 2001a). The syndrome can range in severity from mild to severe (Filley 1998, 2001a; Filley and Kleinschmidt-DeMasters 2001), and recent findings suggest that white matter neuropathology also underlies the profound impairments associated with the vegetative and minimally conscious states (Adams et al. 2000; Graham et al. 2005), in which patients with severely impaired consciousness can be shown by functional neuroimaging to have some preservation of cortical activity (Schiff et al. 2005; Owen et al. 2005). White matter dementia thus not only provides an interesting theoretical model for considering the cognitive and emotional effects of widespread white matter damage, but also generates a host of clinically relevant implications.

Table 4 displays the profile of deficits that characterize white matter dementia. Evidence suggests that this syndrome differs from both cortical dementia (Filley 2001a; Filley et al. 1989), and from subcortical gray matter dementia with which it has much in common (Filley 2001a; Lafosse et al. 2007). Recent findings using advanced white matter imaging has highlighted the prominence of cognitive slowing as a central feature of cerebral white matter involvement (Turken et al. 2008; Bartzokis et al. 2008; Kochunov et al. 2010; Sullivan and Pfefferbaum 2010; Zahr et al. 2009; Madden et al. 2009; Rabbitt et al. 2007), and this slowing of cognitive processing is indeed typical of white matter dementia (Filley 1998, 2001a; Schmahmann et al. 2008). This pervasive deficit in turn contributes to impaired executive function and sustained attention, deficits that are often described in terms of the closely related concept of working memory (Filley 2001b). Simultaneously, memory retrieval deficits in declarative memory are seen, while memory encoding is largely spared. Language is relatively unaffected while visuospatial skills are compromised. Psychiatric dysfunction is common

and may take many forms (Filley 2001a; Schmahmann et al. 2008). So far, this profile is quite similar to that of typical subcortical dementia (Cummings and Benson 1984; Cummings 1990), but the key differences distinguishing white matter dementia are the sparing of procedural memory and extrapyramidal function, both of which are consistently affected in subcortical dementia (Filley 2001a; Cummings and Benson 1984; Cummings 1990; Lafosse et al. 2007). The collection of deficits and relative strengths shown in Table 4 offers a useful framework for considering the role of white matter in the pathogenesis of dementia, and, for general medical purposes, white matter dementia highlights the substantial burden of white matter disorders as leading to neurobehavioral impairment that may go unnoticed. In short, invoking the concept of white matter dementia can guide both cognitive research and clinical care.

A final issue pertinent to white matter dementia is the potential role of white matter dysfunction in the pathogenesis of AD, the most common dementia of older persons and an increasingly ominous threat to medicine and society. Whereas the clinical profile of the two entities differs markedly, and degenerative disease is not one of the categories causing white matter dementia (Filley et al. 1988; Filley 1998, 2001a), it is possible that the cortical pathology of AD—amyloid plaques, neurofibrillary tangles, and neuronal and synaptic loss—may be initiated by breakdown of the cerebral white matter. Bartzokis has presented a provocative hypothesis—the “myelin model”—proposing that the cortical dementia of AD is superimposed on normal aging as a result of selective white matter vulnerability (Bartzokis 2009). According to this model, myelin and oligodendrocytes are highly susceptible to aging and associated factors such as ischemia and TBI, and normal repair processes are insufficient to cope with these insults; as a result, neuronal and synaptic loss develop in cortical regions, and the neuropathological hallmarks of AD—plaques and tangles—are byproducts of homeostatic myelin repair processes (Bartzokis 2009). Persistent problems with the amyloid hypothesis of AD, including most

Table 4 The profile of white matter dementia

Cognitive Slowing
Executive Dysfunction
Sustained Attention Deficit
Memory Retrieval Deficit
Visuospatial Impairment
Psychiatric Disorder
Relatively Preserved Language
Normal Extrapyramidal Function
Normal Procedural Memory

recently the apparent failure of amyloid-clearing therapy to significantly improve cognition in the disease (Hardy 2009), add credence to this idea, which is amenable to study with existing *in vivo* methods (Bartzokis 2009).

Neuropsychiatric Conditions This category is intriguing in that it involves innovative thinking about the potential of white matter dysfunction as a basis of neuropsychiatric dysfunction (Fields 2008; Filley 2001a). Our discussion of this area must be brief, but the field can be considered first in terms of the putative emotional syndromes related to known neurologic white matter disorders, and then by the known psychiatric diseases in which white matter is now being examined (Table 5). Neurologists are familiar with many of the behavioral changes seen in patients with MS and other white matter disorders, including depression, mania, psychosis, disinhibition, euphoria, pathological laughter and crying, and apathy (Filley 2001a). How much and in what manner these disturbances result from white matter damage remain open but important questions. Turning to known psychiatric diseases, white matter abnormalities have been associated with schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, autism, and attention deficit-hyperactivity disorder (Fields 2008). The precise role of white matter changes in these diseases remains uncertain, but modern investigative techniques promise to assist as never before.

What is the Role of White Matter in Higher Function?

The singular feature of white matter is the impressive enhancement of axonal conduction velocity conferred by myelin. Myelinated tracts in the brain not only connect gray matter areas, but, in addition, enhance this connectivity by increasing the speed of impulse conduction in the axons joining them. Because white matter is always conjoined with gray matter neuroanatomically, it follows that all mental function is faster as a result of myelination. Thus the *information processing* of gray matter, manifested by such synaptic events as neurotransmitter release and long-term

potentiation (Mesulam 2000), is complemented by the *information transfer* of white matter, which enables the fast and efficient operation of a distributed neural network (Mesulam 1990; Filley 2001a). Both are essential for the highly evolved behaviors of the human brain. Thus, for example, successful executive function requires not only the dorsolateral prefrontal cortices that enable working memory and problem-solving, but also frontal white matter tracts subserving rapid information transfer and the synchronous activation of all cortical regions necessary for task completion. Important behavioral changes likely also involve brain white matter over the lifespan, including both the maturation of adult behavior with early life myelination (Fields 2008; Filley 2001a; Bartzokis et al. 2001, 2008; Bartzokis 2005), and the decline in cognitive speed and related functions in normal aging associated with white matter loss (Filley 2001a; Bartzokis et al. 2001; Davatzikos and Resnick 2002; Sullivan and Pfefferbaum 2010; Zahr et al. 2009; Madden et al. 2009; Miller 1994; Birren and Fisher 1995; Garde et al. 2005).

Whereas Geschwind and his predecessors rightly emphasized that ablation of a single white matter tract can produce a disconnection syndrome, it is now clear that many more dimensions of white matter structure and function merit consideration, including the combined effects of diffuse white matter involvement, the subtler neurobehavioral impact of incomplete tract damage, the role of intracortical myelin disease, the common commingling of white and gray matter neuropathology, and the interaction of white matter with cortical and subcortical gray matter in the operations of distributed neural networks. As a guiding principle to address these issues, white matter can be usefully envisioned as the component of the brain that renders more efficient the function of gray matter regions responsible for the specific tasks of cognition and emotion.

Clinical Implications

The recognition that brain white matter makes a crucial contribution to neurobehavioral function opens the door to many clinical advances. Identifying focal or diffuse white

Table 5 Neuropsychiatric conditions

Psychiatric Syndromes in White Matter Disorders	Psychiatric Diseases with White Matter Abnormalities
Depression	Schizophrenia
Mania	Depression
Psychosis	Bipolar disorder
Disinhibition	Obsessive–compulsive disorder
Euphoria	Post-traumatic stress disorder
Pathological laughter and crying	Autism
Apathy	Attention deficit-hyperactivity disorder

matter lesions or dysfunction with clinical methods, including neurobehavioral evaluation, neuropsychological testing, and modern neuroimaging testing, enables a degree of clinical sophistication that surely would have impressed Geschwind.

Diagnosis The diagnosis of white matter disorders affecting cognition and emotion has already benefited from many advances, as discussed above (Filley 1998, 2001a; Schmahmann et al. 2008), and one of the major reasons for introducing the concept of white matter dementia is to raise clinical awareness of this area of neurology (Filley et al. 1988; Filley 1998, 2001a; Schmahmann et al. 2008). Central to this field is the role of neuropsychology, which brings the expertise of cognitive testing to patients with what may be subtle yet still important neuropsychological deficits. The opportunity to follow patients through the course of treatment is another advantage, as the pattern and severity of neuropsychological deficits are crucial not only for specific diagnosis but also all aspects of subsequent care. Allied with clinical evaluation is the ever-expanding array of neuroimaging techniques to assess the integrity of white matter (Sullivan and Pfefferbaum 2003; Bandettini 2009; Basser and Jones 2002; Catani 2006; Catani et al. 2005; Mori et al. 2009), which will soon include MRI techniques at high field strength (7.0 T and 9.4 T) to enable visualization of very thin fascicles—such as the lines of Baillarger and the alveus—in health and disease (Laule et al. 2008; Fatterpekar et al. 2002).

Prognosis The outcome for white matter disorders and neurobehavioral syndromes is highly variable, depending on the specific disorder, its severity, patient age, and coexisting conditions (Filley 2001a). A useful generalization is that white matter disorders that involve only loss of myelin and leave axons intact carry a better prognosis for many patients (Filley 2001a). In such cases, remyelination or other mechanisms may serve to restore function (Franklin and Ffrench-Constant 2008). If the axons are also destroyed, as may occur in many neuropathological states including MS, stroke, and intoxication, the possibilities for recovery diminish (Medana and Esiri 2003). Future developments in the study of white matter can be expected to clarify and expand our understanding.

Treatment The treatment of white matter disorders falls to general neurology and will not be specifically discussed; standard textbooks describe the details. However, as understanding of white matter and its disorders increases, specific interventions for neurobehavioral syndromes such as stimulant drugs, cholinesterase inhibitors, selective serotonin reuptake inhibitors, and cognitive rehabilitation may find widespread utility. Interest also continues in the

neurobiology of remyelination, which is well studied in experimental models but often inadequate to effect recovery in patients (Franklin and Ffrench-Constant 2008). In this context, much excitement now attends the emergence of stem cell therapeutics, which may involve either exogenous stem cell implantation or stimulation of endogenous stem cells in the brain (Zhao et al. 2008). Ethical issues will continue to influence this work, but prospects exist for substantial clinical benefit. Perhaps most intriguing is the recent discovery of endogenous stem cells that can potentially be induced to differentiate into functional neurons and glial cells (Martí-Fàbregas et al. 2010; Zhao et al. 2008). The presence of stem cells in the hippocampus, for example, has provoked interest in the possible treatment of memory dysfunction in AD by stimulating the replacement of dying neurons (Zhao et al. 2008). With respect to white matter pathology, the proliferation of stem cells in the subventricular zone after ischemic stroke (Martí-Fàbregas et al. 2010) raises the exciting possibility that novel strategies could be devised to stimulate the differentiation of oligodendrocytes; these cells, in turn, could theoretically restore the structure of white matter tracts within and between the cerebral hemispheres by remyelination (Franklin and Ffrench-Constant 2008).

Plasticity Generations of neuroscientists have been fascinated by the plasticity of the brain, and the focus has traditionally been on cortical function, most prominently at the level of the synapse. Recent findings have shown that white matter also manifests plasticity (Fields 2008). In animal studies, enriched environments produce not only increased synaptic density in the brain, but also greater numbers of oligodendrocytes and more myelination (Markham and Greenough 2004). Fascinating human studies have shown that piano players demonstrate experience-dependent plasticity in white matter, as more highly organized myelination can be demonstrated in the corticospinal tracts and corpus callosum that is proportional to the number of hours practiced (Bengtsson et al. 2005). Rehabilitation based on these observations can presumably be implemented and evaluated with neuroimaging techniques, although how much remyelination and functional improvement can occur after white matter damage are key unanswered questions. Nevertheless, the white matter can now be seen as a legitimate target of efforts to improve brain function through exploiting the phenomenon of plasticity.

Summary

The white matter about which Geschwind wrote in 1965 has steadily, if somewhat tenuously, become more firmly estab-

lished in the study of brain-behavior relationships. Largely through the advances enabled by MRI and its successor DTI, the investigation of white matter has evolved to include not only the focal neurobehavioral syndromes he famously discussed, but a host of other disorders with diffuse involvement producing white matter dementia, and potentially a variety of neuropsychiatric syndromes. It is even possible that AD may itself be explained by primary white matter pathology, although much remains unknown. A recurring theme throughout is that white matter can be conceptualized as subserving information transfer as a complement to the information processing of gray matter. Both processes are vital to the operations of distributed neural networks that underlie evolved cognitive and emotional behaviors. As the 21st century proceeds, it can be anticipated that the often-criticized “diagram-making” of the classic neurologists, on which Geschwind based so much of his thinking, will be to a large extent vindicated and rendered more sophisticated by advances that he could only briefly observe. A gratifying range of clinical benefits will also likely appear as the full contribution of white matter to human behavior is increasingly revealed.

Acknowledgements Preparation of this article was supported by National Institutes of Health research grants R01 AR049152-02S1 and R01 AR049152-01A2.

Disclosures The author declares that no conflicts of interest are associated with the preparation of this article.

References

- Absher, J. R., & Benson, D. F. (1993). Disconnection syndromes: as overview of Geschwind's contributions. *Neurology*, *43*, 862–867.
- Adams, R. D., & Kubik, C. S. (1944). Subacute degeneration of the brain in pernicious anemia. *N Engl J Med*, *231*, 1–9.
- Adams, R. D., Fisher, C. M., Hakim, S., et al. (1965). Symptomatic occult hydrocephalus with “normal” cerebrospinal-fluid pressure. *N Engl J Med*, *273*, 117–126.
- Adams, J. H., Graham, D. I., & Jennett, B. (2000). The neuropathology of the vegetative state after an acute brain insult. *Brain*, *123*, 1327–1338.
- Alexander, M. P. (1995). Mild traumatic brain injury: pathophysiology, natural history, and clinical management. *Neurology*, *45*, 1252–1260.
- Aralasmak, A., Ulmer, J. L., Kocak, M., et al. (2006). Association, commissural, and projection pathways and their functional deficit reported in literature. *J Comput Assist Tomogr*, *30*, 695–715.
- Austin, J., Armstrong, D., Fouch, S., et al. (1968). Metachromatic leukodystrophy (MLD). VIII. MLD in adults: diagnosis and pathogenesis. *Arch Neurol*, *18*, 225–240.
- Babikian, V., & Ropper, A. H. (1987). Binswanger's disease: a review. *Stroke*, *18*, 2–12.
- Bandettini, P. (2009). What's new in neuroimaging methods? *Ann NY Acad Sci*, *1156*, 260–293.
- Bartzokis, G. (2005). Brain myelination in prevalent neuropsychiatric developmental disorders: primary and comorbid addiction. *Adolesc Psychiatry*, *29*, 55–96.
- Bartzokis, G. (2009). Alzheimer's Disease as homeostatic responses to age-related myelin breakdown. *Neurobiol Aging*, Sep 21 [Epub ahead of print].
- Bartzokis, G., Beckson, M., Lu, P. H., et al. (2001). Age-related changes in frontal and temporal lobe volumes in men. *Arch Gen Psychiatry*, *58*, 461–465.
- Bartzokis, G., Lu, P. H., Tingus, K., et al. (2008). Lifespan trajectory of myelin integrity and maximum motor speed. *Neurobiol Aging*, Oct 15 [Epub ahead of print].
- Basser, P. J., & Jones, D. K. (2002). Diffusion-tensor MRI: theory, experimental design and data analysis-technical review. *NMR Biomed*, *15*, 457–467.
- Baumann, N., & Pham-Dinh, D. (2001). Biology of oligodendrocyte and myelin in the mammalian nervous system. *Physiol Rev*, *81*, 871–927.
- Bech, R. A., Juhler, M., Waldemar, G., et al. (1997). Frontal brain and leptomeningeal biopsy specimens correlated with cerebrospinal fluid outflow resistance and B-wave activity in patients suspected of normal-pressure hydrocephalus. *Neurosurgery*, *40*, 497–502.
- Benes, F. M., Turtle, M., Khan, Y., & Farol, P. (1994). Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. *Arch Gen Psychiatry*, *51*, 477–484.
- Bengtsson, S. I., Nagy, Z., Skare, S., et al. (2005). Extensive piano practicing has regionally specific effects on white matter development. *Nat Neurosci*, *8*, 1148–1150.
- Bennarroch, E. F. (2009). Oligodendrocytes. Susceptibility to injury and involvement in neurologic disease. *Neurology*, *72*, 1779–1785.
- Birren, J. E., & Fisher, L. M. (1995). Aging and speed of behavior: possible consequences for psychological functioning. *Annu Rev Psychol*, *46*, 329–353.
- Boerner, R. J., & Kapfhammer, H. P. (1999). Psychopathological changes and cognitive impairment in encephalomyelitis disseminata. *Eur Arch Clin Neurosci*, *249*, 96–102.
- Boissé, L., Gill, J., & Power, C. (2008). HIV infection of the central nervous system: clinical features and neuropathogenesis. *Neurol Clin*, *26*, 739–819.
- Canoll, P., & Goldman, J. E. (2008). The interface between glial progenitors and gliomas. *Acta Neuropathol*, *116*, 465–477.
- Caplan, L. R. (1995). Binswanger's disease—revisited. *Neurology*, *45*, 626–633.
- Catani, M. (2006). Diffusion tensor magnetic resonance imaging tractography in cognitive disorders. *Curr Opin Neurol*, *19*, 599–606.
- Catani, M., & Ffytche, D. H. (2005). The rises and falls of disconnection syndromes. *Brain*, *128*, 2224–2239.
- Catani, M., Jones, D. K., & Ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Ann Neurol*, *57*, 8–16.
- Charcot, J. M. (1877). *Lectures on the diseases of the nervous system delivered at La Salpêtrière*. London: New Sydenham Society.
- Chatterjee, A., Yapundich, R., Palmer, C. A., et al. (1996). Leukoencephalopathy associated with cobalamin deficiency. *Neurology*, *46*, 832–834.
- Chui, H. (2007). Subcortical ischemic vascular dementia. *Neurol Clin*, *25*, 717–740.
- Cummings, J. L. (Ed.). (1990). *Subcortical dementia*. New York: Oxford University Press.
- Cummings, J. L., & Benson, D. F. (1984). Subcortical dementia. Review of an emerging concept. *Arch Neurol*, *41*, 874–9.
- Davatzikos, C., & Resnick, S. M. (2002). Degenerative age changes in white matter connectivity visualized in vivo using magnetic resonance imaging. *Cerebral Cortex*, *12*, 767–771.
- Del Bigio, M. R. (1993). Neuropathological changes caused by hydrocephalus. *Acta Neuropathol*, *85*, 573–585.

- Del Bigio, M. R., da Silva, M. C., Drake, J. M., & Tuor, U. I. (1994). Acute and chronic cerebral white matter damage in neonatal hydrocephalus. *Can J Neurol Sci*, *21*, 299–305.
- Earnest, M. P., Fahn, S., Karp, J. H., & Rowland, L. P. (1974). Normal pressure hydrocephalus and hypertensive cerebrovascular disease. *Arch Neurol*, *31*, 262–266.
- Fatterpekar, G. M., Naidich, T. P., Delma, B. N., et al. (2002). Cytoarchitecture of the human cerebral cortex: MR spectroscopy of excised specimens at 9.4 T. *AJNR*, *23*, 1313–1321.
- Fields, R. D. (2008). White matter in learning, cognition and psychiatric disorders. *Trends Neurosci*, *31*, 361–370.
- Filley, C. M. (1998). The behavioral neurology of cerebral white matter. *Neurology*, *50*, 1535–1540.
- Filley, C. M. (2001a). *The behavioral neurology of white matter*. New York: Oxford University Press.
- Filley, C. M. (2001b). *Neurobehavioral anatomy* (2nd ed.). Boulder: University Press of Colorado.
- Filley, C. M., & Gross, K. F. (1992). Psychosis with cerebral white matter disease. *Neuropsychiatry Neuropsychol Behav Neurol*, *5*, 119–125.
- Filley, C. M., & Kleinschmidt-DeMasters, B. K. (1995). Neurobehavioral presentations of brain neoplasms. *West J Med*, *163*, 19–25.
- Filley, C. M., & Kleinschmidt-DeMasters, B. K. (2001). Toxic leukoencephalopathy. *N Engl J Med*, *345*, 425–432.
- Filley, C. M., Franklin, G. M., Heaton, R. K., & Rosenberg, N. L. (1988). White matter dementia: clinical disorders and implications. *Neuropsychiatry Neuropsychol Behav Neurol*, *1*, 239–254.
- Filley, C. M., Heaton, R. K., Nelson, L. M., Burks, J. S., & Franklin, G. M. (1989). A comparison of dementia in Alzheimer's Disease and multiple sclerosis. *Arch Neurol*, *46*, 157–161.
- Filley, C. M., Heaton, R. K., & Rosenberg, N. L. (1990). White matter dementia in chronic toluene abuse. *Neurology*, *40*, 532–534.
- Filley, C. M., Kleinschmidt-DeMasters, B. K., Lillehei, K. O., Damek, D. M., & Harris, J. G. (2003). Gliomatosis cerebri: neurobehavioral and neuropathological observations. *Cogn Behav Neurol*, *16*, 149–159.
- Filley, C. M., Halliday, W., & Kleinschmidt-DeMasters, B. K. (2004). The effects of toluene on the central nervous system. *J Neuropathol Exp Neurol*, *63*, 1–12.
- Filley, C. M., Kozora, E., Brown, M. S., et al. (2009). White matter microstructure and cognition in non-neuropsychiatric systemic lupus erythematosus. *Cogn Behav Neurol*, *22*, 38–44.
- Franklin, R. J. M., & Ffrench-Constant, C. (2008). Remyelination in the CNS: from biology to therapy. *Nat Rev Neurosci*, *9*, 839–855.
- Garde, E., Lykke Martensen, E., Rostrup, E., & Paulson, O. B. (2005). Decline in intelligence is associated with progression in white matter hyperintensity volume. *J Neurol Neurosurg Psychiatry*, *76*, 1289–1291.
- Geer, C. P., & Grossman, S. A. (1997). Interstitial flow along white matter tracts: a potentially important mechanism for the dissemination of primary brain tumors. *J Neurooncol*, *32*, 193–201.
- Geschwind, N. (1965). Disconnexion syndromes in animals and man. *Brain*, *88*(237–294), 585–644.
- Giese, A., & Westphal, M. (1996). Glioma invasion in the central nervous system. *Neurosurgery*, *39*, 235–250.
- Gongvatana, A., Schweinsburg, B. C., Taylor, M. J., et al. (2009). White matter tract injury and cognitive impairment in human immunodeficiency virus-infected individuals. *J Neurovirol*, *15*, 187–195.
- Graham, D. I., Adams, J. H., Murray, L. S., & Jennett, B. (2005). Neuropathology of the vegetative state after head injury. *Neuropsychol Rehab*, *15*, 198–213.
- Hachinski, V. C. (1991). Binswanger's disease: neither Binswanger's nor a disease. *J Neurol Sci*, *103*, 1.
- Hachinski, V. C., Potter, P., & Merskey, H. (1987). Leuko-araiosis. *Arch Neurol*, *44*, 21–23.
- Hardy, J. (2009). The amyloid hypothesis for Alzheimer's Disease: a critical reappraisal. *J Neurochem*, *110*, 1129–1134.
- Harris, J. G., & Filley, C. M. (2001). CADASIL: Neuropsychological findings in three generations of an affected family. *J Int Neuropsychol Soc*, *7*, 768–774.
- Hinchey, J., Chaves, C., Appignani, B., et al. (1996). A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*, *334*, 494–500.
- Hornes, J. T., Filley, C. M., & Rosenberg, N. L. (1986). Neurologic sequelae of chronic solvent vapor abuse. *Neurology*, *36*, 698–702.
- Hyde, T. M., Ziegler, J. C., & Weinberger, D. R. (1992). Psychiatric disturbances in metachromatic leukodystrophy. Insights into the neurobiology of psychosis. *Arch Neurol*, *49*, 401–406.
- Jones, H. R., Ho, D. D., Forgacs, P., et al. (1988). Acute fulminating fatal leukoencephalopathy as the only manifestation of human immunodeficiency virus infection. *Ann Neurol*, *23*, 519–522.
- Kirk, A., Kertesz, A., & Polk, M. J. (1991). Dementia with leukoencephalopathy in systemic lupus erythematosus. *Can J Neurol Sci*, *18*, 344–348.
- Kochunov, P., Coyle, T., Lancaster, J., et al. (2010). Processing speed is correlated with cerebral health markers in the frontal lobes quantified by neuroimaging. *Neuroimage*, *49*, 1190–1199.
- Kozora, E., Thompson, L. L., West, S. G., & Kotzin, B. L. (1996). Analysis of cognitive and psychological deficits in systemic lupus erythematosus patients without overt central nervous system disease. *Arthritis Rheum*, *39*, 2035–2045.
- Kraus, M., Susmaras, T., Caughlin, B. P., et al. (2007). White matter injury and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. *Brain*, *130*, 2508–2519.
- Kurtzke, J. F. (1970). Neurologic impairment in multiple sclerosis and the disability status scale. *Acta Neurol Scand*, *46*, 493–512.
- Lafosse, J. M., Corboy, J. R., Leehey, M. A., Seeberger, L. C., & Filley, C. M. (2007). MS vs. HD: Can white matter and subcortical gray matter pathology be distinguished neuropsychologically? *J Clin Exp Neuropsychol*, *29*, 142–54.
- Langlois, J., Rutland-Brown, W., & Thomas, K. (2004). *Traumatic brain injury in the United States: Emergency department visits, hospitalizations and deaths*. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention.
- Laule, C., Koslowski, P., Leung, E., et al. (2008). Myelin water imaging of multiple sclerosis at 7 T: correlations with histopathology. *Neuroimage*, *40*, 1575–1580.
- Luria, A. R. (1966). *Higher cortical functions in man*. New York: Consultants Bureau.
- Madden, D. J., Bennett, I. J., & Song, A. W. (2009). Cerebral white matter integrity and cognitive aging: contributions from diffusion tensor imaging. *Neuropsychol Rev*, *19*, 415–35.
- Markham, J. A., & Greenough, W. T. (2004). Experience-driven brain plasticity: beyond the synapse. *Neuron Glia Biol*, *1*, 351–363.
- Martí-Fàbregas, J., Romaguera-Ros, M., Gómez-Pinedo, U., et al. (2010). Proliferation in the human ipsilateral subventricular zone after ischemic stroke. *Neurology*, *74*, 357–365.
- Medana, I. M., & Esiri, M. M. (2003). Axonal damage: a key predictor of outcome in human CNS diseases. *Brain*, *126*, 515–530.
- Mesulam, M.-M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol*, *28*, 597–613.
- Mesulam, M.-M. (2000). Behavioral neuroanatomy. Large-scale neural networks, association cortex, frontal systems, the limbic system, and hemispheric specializations. In M.-M. Mesulam (Ed.), *Principles of behavioral and cognitive neurology* (2nd ed., pp. 1–120). New York: Oxford University Press.

- Miller, E. M. (1994). Intelligence and brain myelination: a hypothesis. *Person Individ Diff*, *17*, 803–832.
- Miller, A., Korem, M., Almog, R., & Galboiz, Y. (2005). Vitamin B12, demyelination, remyelination and repair in multiple sclerosis. *J Neurol Sci*, *233*, 93–97.
- Mori, S., Oishi, K., & Faria, A. V. (2009). White matter atlases based on diffusion tensor imaging. *Curr opin neurol*, *22*, 362–369.
- Navia, B. A., Jordan, B. D., & Price, R. W. (1986a). The AIDS dementia complex: I. Clinical features. *Ann Neurol*, *19*, 517–524.
- Navia, B. A., Cho, E.-S., Petito, C. K., & Price, R. W. (1986b). The AIDS dementia complex: II. Neuropathology. *Ann Neurol*, *19*, 525–535.
- Nolte, J. (2002). *The human brain* (5th ed.). St. Louis: Mosby.
- Owen, A. M., Coleman, M. R., Boly, M., et al. (2005). Detecting awareness in the vegetative state. *Science*, *313*, 1402.
- Pantoni, L., & Garcia, J. H. (1997). Pathogenesis of leukoarosis. A review. *Stroke*, *28*, 652–659.
- Penny, S., Khaleeli, Z., Cipolotti, L., Thompson, A., & Ron, M. (2010). Early imaging predicts later cognitive impairment in primary progressive multiple sclerosis. *Neurology*, *74*, 545–552.
- Pennypacker, L. C., Allen, R. H., Kelly, J. P., et al. (1992). High prevalence of cobalamin deficiency in elderly outpatients. *J Am Geriatr Soc*, *40*, 1197–1204.
- Petersen, R. C., Smith, G. E., Waring, S. C., et al. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*, *56*, 303–308.
- Pfefferbaum, A., Rosenbloom, M. J., Rohlfing, T., et al. (2009). Frontostriatal fiber bundle compromise in HIV infection without dementia. *AIDS*, *23*, 1977–1985.
- Rabbitt, P., Scott, M., Lunn, M., Thacker, N., Lowe, C., Pendleton, N., et al. (2007). White matter lesions account for all age-related declines in speed but not in intelligence. *Neuropsychology*, *21*, 363–370.
- Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology*, *41*, 685–691.
- Rollins, K. E., Kleinschmidt-DeMasters, B. K., Corboy, J. R., Damek, D. M., & Filley, C. M. (2005). Lymphomatosis cerebri as a cause of white matter dementia. *Hum Pathol*, *36*, 282–290.
- Román, G. C. (1996). From UBOs to Binswanger's disease. Impact of magnetic resonance imaging on vascular dementia research. *Stroke*, *27*, 1269–1273.
- Román, G. C., Tatemichi, T. K., Erkinjuntti, T., et al. (1993). Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*, *43*, 250–60.
- Rosenberg, N. L., Spitz, M. C., Filley, C. M., et al. (1988a). Central nervous system effects of chronic toluene abuse—clinical, brainstem evoked response and magnetic resonance imaging studies. *Neurotoxicol Teratol*, *10*, 489–495.
- Rosenberg, N. K., Kleinschmidt-DeMasters, B. K., Davis, K. A., et al. (1988b). Toluene abuse causes diffuse central nervous system white matter changes. *Ann Neurol*, *23*, 611–614.
- Saver, J. L. (2006). Time is brain—quantified. *Stroke*, *37*, 263–266.
- Schiff, N. D., Rodriguez-Moreno, D., Kamal, A., et al. (2005). fMRI reveals large-scale network activation in minimally conscious patients. *Neurology*, *64*, 514–523.
- Schmahmann, J. D., & Pandya, D. N. (2006). *Fiber pathways of the brain*. New York: Oxford University Press.
- Schmahmann, J. D., & Pandya, D. N. (2008). Disconnection syndromes of basal ganglia, thalamus, and cerebrotocerebellar systems. *Cortex*, *44*, 1037–1066.
- Schmahmann, J. D., Smith, E. D., Eichler, F. S., & Filley, C. M. (2008). Cerebral white matter. Neuroanatomy, clinical neurology, and neurobehavioral correlates. *Ann NY Acad Sci*, *1142*, 266–309.
- Schoenemann, P. T., Sheehan, M. J., & Glotzer, L. D. (2005). Prefrontal white matter is disproportionately larger in humans than in other primates. *Nat Neurosci*, *8*, 242–252.
- Selnes, O. A., & Vinters, H. V. (2006). Vascular cognitive impairment. *Nat Clin Prac Neurol*, *2*, 538–547.
- Smith, D. H., Meaney, D. F., & Shull, W. H. (2003). Diffuse axonal injury in head trauma. *J Head Trauma Rehabil*, *18*, 307–316.
- Stadelmann, C., Albert, M., Wegner, C., & Brück, W. (2008). Cortical pathology in multiple sclerosis. *Curr Opin Neurol*, *21*, 239–234.
- Stojasavljević, N., Lević, Z., Drulović, J., & Dragutinović, G. (1997). A 44-month clinical-brain MRI follow-up in a patient with B₁₂ deficiency. *Neurology*, *49*, 878–881.
- Sullivan, E. V., & Pfefferbaum, A. (2003). Diffusion tensor imaging in normal aging and neuropsychiatric disorders. *Eur J Radiol*, *45*, 24–255.
- Sullivan, E. V., & Pfefferbaum, A. (2010). Diffusion in ageing and age-related neurodegenerative disorders. In D. K. Jones (Ed.), *Diffusion MRI: Theory, methods and applications*. New York: Oxford University Press.
- Thurnher, M. M., Schindler, E. G., Thurnher, S. A., et al. (2000). Highly active antiretroviral therapy for patients with AIDS dementia complex: effect on MR imaging findings and clinical course. *AJNR*, *21*, 670–678.
- Turken, A. U., Whitfield-Gabrieli, S., Bammer, R., et al. (2008). Cognitive speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. *Neuroimage*, *42*, 1032–1044.
- van der Knaap, M., Prank, J. C., & Scheper, G. C. (2006). Vanishing white matter disease. *Lancet Neurol*, *5*, 413–423.
- van Gijn, J. (1998). Leukaraiosis and vascular dementia. *Neurology*, *51*(Suppl 3), S3–S8.
- West, S. G. (1994). Neuropsychiatric lupus. *Rheum Dis Clin N Am*, *20*, 129–158.
- Yücel, M., Takagi, M., Walterfang, M., & Lubman, D. I. (2008). Toluene misuse and long-term harms: a systematic review of the neuropsychological and neuroimaging literature. *Neurosci Bio-behav Rev*, *32*, 910–926.
- Zahr, N. M., Rohlfing, T., Pfefferbaum, A., & Sullivan, E. V. (2009). Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study. *Neuroimage*, *44*, 1050–62.
- Zhao, C., Deng, W., & Gage, F. H. (2008). Mechanisms and functional implications of adult neurogenesis. *Cell*, *132*, 645–660.