White Matter Dementia: Origin, Development, Progress, and Prospects

Christopher M. Filley, M.D.

The term white matter dementia (WMD) was introduced in 1988 to highlight the role of white matter in the development of dementia. As the concept has been refined with new insights into the structure and function of normal and abnormal white matter, research has expanded to consider normal cognition, network connectivity, novel treatment ideas, and the etiopathogenesis of neurodegenerative dementia. Emerging data are also identifying new opportunities for dementia prevention by avoidance of acquired vascular and traumatic white matter insults. The idea of WMD promises to continue as a useful construct informing the study of dementia and the understanding of brain-behavior relationships.

J Neuropsychiatry Clin Neurosci 2016; 28:262–272; doi: 10.1176/appi.neuropsych.16010003

The notion that disruption of brain white matter can lead to cognitive dysfunction is not new in clinical neuroscience, and indeed the classic European neurologists of the 19th century were well aware of the importance of myelinated systems in the organization of the higher functions. White matter was seen by these pioneering neurologists as implicated in a variety of focal neurobehavioral syndromes, famously summarized in the classic paper of Norman Geschwind on disconnection syndromes in 1965.[1] Yet with respect to dementia, a strong emphasis in the 20th century on the cerebral cortex as the critical site of the higher functions has led to a "corticocentric" bias[2] that limits a complete appreciation of the organization of cognition in the context of dementing disease. The cerebral cortex accounts for only the outermost 1–4 mm of the cerebral hemispheres, and even with the inclusion of the deep nuclei and cerebellar cortex, gray matter comprises only about half of the brain volume.

In 1988, the concept of white matter dementia (WMD) was introduced to call attention to the capacity of white matter disorders to impair cognitive function to the extent that dementia results.[3] The intent of this proposal was not to diminish the importance of gray matter in the higher functions but to expand the scope of dementia research to include a consideration of myelinated tracts that link cortical regions into distributed neural networks subserving various cognitive domains. In the years since then, white matter has been increasingly appreciated as crucial for its role in normal and abnormal cognition, with a host of important clinical implications. Dementia resulting from white matter involvement has progressed from an obscure curiosity to an accepted clinical phenomenon, and the study of dementia in the context of white matter disorders has become commonplace. This review will summarize the origin and development of the concept of WMD, review recent progress, and consider the future of this unique approach to the problem of dementia.

THE BEGINNING: TOLUENE LEUKOENCEPHALOPATHY

The first and still most convincing example of WMD was encountered by my colleagues and I at the Denver General Hospital in the early 1980s. We became aware of adolescents and young adults with heavy and prolonged inhalant abuse who presented with a remarkable clinical picture of dementia, cerebellar ataxia, corticospinal dysfunction, and various brainstem and cranial nerve abnormalities.[4] This striking clinical profile was observed in otherwise healthy young people exposed to high inhaled levels of toluene, the major solvent in spray paint favored as an inhalant, for periods often lasting many years.[4] The syndrome of toluene leukoencephalopathy was found to be a chronic disorder distinct from the state of acute intoxication producing inebriation and euphoria, and care was taken to examine patients in a state of abstinence to avoid confounding the data with the acute effects of toluene. Of all the lasting neurologic deficits produced by toluene abuse, dementia proved to be the most disabling.[4] Magnetic resonance imaging (MRI), which was just beginning to be used in neurology, disclosed diffuse cerebral and cerebellar white matter damage in these patients,[5] and the extent of cerebral injury was found to correlate with the severity of dementia.[6] As autopsy brains became available, widespread cerebral myelin loss was well documented,[5,7] and the selectivity of white matter damage

compelled the conclusion that toxic white matter disease, related to the lipophilicity of toluene, was the cause of dementia.[4–8] These foundational observations, based on the tragic and still under-appreciated problem of inhalant abuse, inaugurated thinking about how dementia can arise solely from neuropathology in the half of the brain occupied by white matter.[3]

FURTHER INVESTIGATION AND CHARACTERIZATION

In addition to toxic disorders, white matter is vulnerable to a wide range of other neuropathological insults: vascular, traumatic, demyelinative, metabolic, genetic, inflammatory, infectious, neoplastic, and hydrocephalic.[9] These categories encompass a large portion of neurology, and patients with clinically significant white matter involvement can appear at any age and in many medical settings. MRI has been critical to improved understanding of the disorders within these categories, enabling detailed, noninvasive in vivo depiction of white matter lesions as never before in the history of neuroscience. As white matter disorders are typically diffuse or multifocal, the presence of dementia most likely implies the simultaneous involvement of tracts within multiple distributed neural networks. Since both white and gray matter contribute to these networks, however, and coexistent gray matter pathology is often present, it can be questioned how a dementia syndrome specific to white matter damage may be delineated. Yet a distinct profile of WMD began to be discernible as cognitive aspects of the many white matter disorders were investigated, and a generally consistent pattern of deficits and strengths became steadily more clear. As now conceptualized, the profile of WMD consists of cognitive slowing, executive dysfunction, sustained attention deficit, impaired memory retrieval, visuospatial impairment, and psychiatric dysfunction, with relatively preserved language, normal extrapyramidal function, and normal procedural memory.[9]

The WMD profile differs from that of cortical dementia,[10] and from that of subcortical dementia, which is most closely associated with pathology in deep gray matter regions.[11,12] Two key studies supported these distinctions. The first was a comparison of multiple sclerosis (MS) with the cortical dementia of Alzheimer's disease (AD) that disclosed processing speed and executive function deficits in the former, and greater impairment in memory and language in the latter.[13] The second was a comparison of MS with the subcortical dementia of Huntington's disease (HD) documenting normal procedural memory in MS and significant impairment of this domain in HD.[14] Combined with many other observations,[15–24] these studies helped establish that white matter disorders may exert a unique effect upon cognition that is reflected in the clinical profile of WMD.[9] Although many patients in clinical practice prove to have overlapping neuropathology that affects both white and gray matter structures, the accumulated evidence for a distinct profile associated with white matter involvement gains considerable strength from the combined analysis of the many white matter disorders that have been studied.

From the time of the first exploration of this topic, it was apparent that white matter disorders may produce subtle cognitive impairment that, while clinically meaningful, does not reach the level of dementia. Indeed, most patients with white matter disorders are more likely to have a cognitive syndrome that is less apparent than overt dementia. The range of impairment is well illustrated by the syndrome of toxic leukoencephalopathy, in which mild, moderate, and severe levels of leukotoxicity each have relatively consistent clinical, MRI, and neuropathological features.[8] While this wide spectrum of severity introduces more difficulty in establishing white matter-behavior correlations, the clinical importance of the early recognition of cognitive loss—before dementia sets in—is readily apparent. Thus a great deal of work in many disorders has appeared on the less obvious cognitive impact of limited white matter pathology.[9] In this context, recent advances in neuroimaging have been critical because it became possible to examine the possibility of disease within the normal-appearing white matter (NAWM), and, in a number of disorders, the NAWM was found to harbor white matter pathology that is clinically significant. Our work focused on SLE, an inflammatory cause of WMD, and indeed, magnetic resonance spectroscopy (MRS) disclosed evidence of myelin damage in the NAWM that correlated with neuropsychological deficits expected from white matter dysfunction.[25] From these and other data, the concept of mild cognitive dysfunction (MCD) was coined to operationalize what is proposed as a precursor syndrome to WMD.[26]

ADVANCES IN WHITE MATTER NEUROBIOLOGY

The importance of white matter with respect to cognition has recently been supported by evidence from the study of evolution. Since the time of Paul Broca and Charles Darwin in the 19th century, human brain size has been linked with intelligence, but data acquired with modern brain imaging have strengthened this association. Much recent evidence has led to the conclusion that brain size is correlated with general mental ability, consistent with a trend in other species that can be traced back 570 million years.[27] The number of brain neurons is a plausible explanation for this correlation, and the singular intellectual capacities of humans can be related to the greater number of brain neurons compared with any other species.[27] White matter, however, cannot be dismissed. Comparative neuroanatomy studies have revealed that white matter volume has actually enlarged more than cortical gray matter over the course of evolution by a factor of 4:3, driven by the need for thick, myelinated fibers that provide rapid communication between neuronal cell bodies increasingly separated by the expansion of the cerebral cortex.[28] Thus, white matter is highly expanded in *Homo sapiens*, supporting its importance in human cognition. Further analysis disclosed that the combination of high

neuronal numbers and well-developed white matter is unique in humans. By comparison, elephants and certain whales have larger brains than humans, almost as many cortical neurons, and greater white matter volume,[28] but their white matter tracts are thinly myelinated and therefore less adept at enhancing information transfer over intracranial distances that surpass those in the human brain.[29] These observations have prompted the conclusion that the most intelligent brains feature not only the most neurons but also the most efficient white matter.[29]

The structure of white matter has been greatly advanced by the detailed study of its neuroanatomy in the rhesus monkey using the modern technique of radioisotope tract tracing.[30] As a consequence, traditional teaching of white matter structure in standard neuroanatomy textbooks is being refined to highlight the remarkable intricacy of white matter tracts as they link cortical and deep gray matter regions throughout the brain. This information may at some point enable the integration of white matter and its role in connectivity into clinical settings where damage to white matter is presumed to be neurobehaviorally relevant. Just as clinicians now consider the cognitive impact of isolated cortical lesions, they may soon be able to include an analysis of individual tract disruption and its effects.

An old observation on the neuroanatomy of white matter receiving renewed attention is the presence of myelinated fascicles within gray matter. Small myelinated tracts are known to course through deep and cortical gray matter, as recognized by Cecile and Oskar Vogt nearly a century ago.[31] With respect to cognition, the intracortical myelin is attracting the most study, mainly in work on MS, in which the entity of "cortical MS" is being investigated. Neuropathological studies have indeed documented cortical demyelination in MS, which appears later in the disease than classic demyelinative plaques within large tracts.[32] Whereas the characterization of MS as a WMD has been challenged on the basis of cortical involvement that could explain dementia, this debate may find resolution in the realization that the primary neuropathological process in MS is demyelination, which occurs first within large white matter tracts and later in the cortex.[32] Thus the cortical features of cognitive loss in MS may plausibly be explained by cortical demyelination, whereas the profile of WMD is more appropriate for the early stages of MS.

The focus on the neuroanatomy of white matter has taken its most visible form in the genesis of the concept of the "connectome." This term, which refers to all the connections among the roughly 100 billion neurons in the brain, includes not only synaptic contacts but the linking of gray matter regions by white matter tracts.[33] Thus both the microconnectivity of gray matter and the macroconnectivity of white matter contribute to the connectome, in essence providing a structural description of the human brain.[33] Under the auspices of the publicly funded Human Connectome Project, large-scale neuroimaging studies with diffusion tensor imaging (DTI) are underway to map out the extraordinary complexity of white matter connectivity in human brains.[34] This approach promises to complement the study of cortical function with positron emission tomography and functional MRI by clarifying the structural connections between cortical regions and advancing the understanding of distributed neural networks subserving cognition.

Finally, with respect to the physiology of white matter, fascinating new work is appearing on the notion of plasticity within this region of the brain.[35] Long considered an exclusive capacity of the gray matter, where synaptic changes are widely thought to underlie learning and memory,[36] plasticity can also be observed in white matter. This idea was actually first proposed by 19th-century neuroanatomists who could see white matter but had no electrophysiology with which to study synapses, and white matter plasticity is now being observed with modern investigative techniques.[37] Structural changes in myelin are being recognized to occur in response to environmental stimulation, and the phenomenon of activity-dependent myelination appears to involve glutamatergic axo-oligodendroglial synapses that mediate axonal myelination in response to proximal volleys of action potentials.[37,38] White matter plasticity can be demonstrated in normal individuals, such as musicians whose corpus callosum connectivity increases as a consequence of years of training and experience,[39] or in left hemisphere stroke patients with Broca's aphasia, in whom melodic intonation therapy leads to expansion of the right arcuate fasciculus in parallel with improvement in language function.[40] Studies such as these not only expand our knowledge of a brain region previously thought to have a merely supportive role in brain function but also open up new vistas—to be discussed below—for considering possible treatments for a wide range of disabling neurologic disorders.

TREATMENT OPPORTUNITIES

The wide spectrum of neuropathology that can involve white matter implicates a large portion of general neurology with respect to the treatment of white matter disorders. Many standard treatments are available for these disorders,[41] and while treatment efficacy is highly variable, the clinician confronted with patients with disorders such as toluene leukoencephalopathy, MS, cobalamin deficiency, and Binswanger's disease will naturally proceed with established therapeutic measures in the hope that cognitive dysfunction or dementia can be meaningfully addressed. A focus on white matter as the site where the treatment is intended to exert its effect organizes rational treatment and follow-up, and MRI can be used as a helpful marker of treatment efficacy, much as this modality is now used in the ongoing evaluation of MS.

Regardless of neuropathology, however, heightened consideration of the white matter as a specific therapeutic target raises many new possibilities for treatment. The idea of WMD serves to focus attention squarely on the tissue in

which neuropathology takes root and invites consideration of all modalities that could potentially effect restoration of white matter as early as possible. The desirability of early treatment is underscored by the likelihood that plasticity is more robust before neuropathology becomes chronic and by much evidence that the additional burden of axonal loss worsens the outcome associated with myelin damage alone.[42,43] Emerging possibilities for the treatment of white matter disorders could therefore help reduce the burden of dementia that results from long-term consequences of myelin damage or dysfunction. This field is rapidly growing, and many new ideas are under study or being hypothesized.

To begin, a number of familiar centrally-acting drugs have been shown to have some capacity to promote myelination. Among these are the cholinesterase inhibitors,[44] atypical antipsychotic drugs,[45] selective serotonin reuptake inhibitors,[45] valproic acid[45] and lithium.[45] Anti-inflammatory drugs are capturing increasing attention as inflammation mediated by activated microglial cells appears to be involved in many white matter pathologies including traumatic brain injury (TBI)[46]. Thyroid hormones are known to be important in myelination during development, and these hormones may prove useful in adults with myelin disorders.[47] An interesting molecule found in the brain that may help repair white matter after many types of injury is neuregulin, which appears to induce *N*-methyl-D-aspartate receptor-dependent myelination by oligodendrocytes.[48] Stimulation of oligodendrocytes to enhance myelination with the neurotrophins nerve growth factor and brain-derived neurotrophic factor has also been proposed,[48,49] and oligodendrocyte stimulation after ischemia has been observed with the use of many diverse agents such as aspirin, cerebrolysin, thymosin β4, and sildenafil.[50] The area of remyelination has long been studied by neurologists seeking to repair the effects of demyelination in MS and related diseases, and among many new ideas, remyelination is being studied with fingolimod (the first approved oral medication for MS), the anticholinergic drug benztropine, and an antibody against the transmembrane protein known as leucine-rich repeat and immunoglobulin domain-containing Nogo receptor interacting protein [51]. Stem cells may also have a role in restoring white matter after pathological insult, and strategies are being considered to mobilize oligodendrocyte precursor cells as a means of stimulating endogenous repair, and to deliver myelinogenic stem cells exogenously.[52]

Exploiting the principle of white matter plasticity discussed above, a variety of stimulation paradigms can be imagined. DTI has been used to show that young adults who received training in working memory had higher fractional anisotropy in the parietal white matter and the corpus callosum.[53] A DTI study of students who took a course to prepare for the Law School Admissions Test showed that reasoning training resulted in decreased radial diffusivity in the frontoparietal white matter.[54] Music therapy has only begun to be explored,[35,37] but the potential for melodic intonation therapy to improve the integrity of the right arcuate fasciculus in Broca's aphasia[40] is promising in this regard.

Finally, neuromodulation, meaning the stimulation of the brain using devices applied internally or externally, is attracting much attention. Deep brain stimulation (DBS) has an established role in the treatment of motor dysfunction in Parkinson's disease and essential tremor, but because its greatest efficacy may be achieved with white matter stimulation sites, DBS is now being seen as a means of surgically modulating distributed neural networks via both orthodromic and antidromic stimulation of tracts connecting gray matter regions.[55] DBS has been applied to patients with AD, and preliminary studies have shown that DBS in the fornix for 12 months slowed atrophy of this tract while increasing the volume of the hippocampus, from which the fornix projects within the medial temporal declarative memory system.[56] External stimulation modalities such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation (tDCS) have been used to study cortical function, and thus far examination of white matter has been limited.[57] Structural white matter changes in descending motor tracts correlate with improvements in motor impairment after undergoing a treatment course of tDCS,[58] but cognitive function in relation to white matter changes remains to be investigated. Research into all of these areas is preliminary, but the plasticity of white matter may imply that nonpharmacological interventions of many varieties may find a place in the rehabilitation of patients with damaged white matter from any neuropathology.

WHITE MATTER IN NEURODEGENERATIVE DISEASE

A notable exception to the ten neuropathological categories that feature prominent or exclusive white matter involvement[9] is neurodegenerative disease. AD, frontotemporal dementia, and related neurodegenerative diseases are widely thought to involve primary loss of neurons in gray matter regions, and white matter changes have been regarded as secondary. Yet recent evidence has raised the provocative idea that even neurodegeneration can be triggered by white matter pathology. The still frustrating lack of disease-modifying treatment in the neurodegenerative diseases may suggest that a fresh look at etiopathogenesis is warranted, particularly in view of mounting evidence that pathology in white matter may precede the cortical changes that are routinely accepted as definitive in AD, the most common degenerative dementia.[2] Four neurodegenerativc disorders will be discussed to propose that white matter pathology merits consideration in pathogenesis.

The first disease meriting discussion in this context is Fragile X tremor-ataxia syndrome (FXTAS) [59]. This recently described inherited neurodegenerative disease is caused by a trinucleotide (CGG) repeat expansion in the premutation range [55–200] of the fragile X mental retardation 1 (*FMR1*) gene, in contrast to the Fragile X syndrome (FXS), which is caused by >200 CGG repeats.[59] Both FXTAS and FXS affect

cognition, but these diseases are clearly distinct. In addition to different age at onset and clinical phenomenology, FXTAS and FXS have unique molecular pathogenetic features; FXS is related to transcriptional silencing with reduced or absent *FMR1* protein, while FXTAS is characterized by increased *FMR1* mRNA, which is thought to cause cellular injury via a toxic gain-of-function.[59] FXTAS is more common and severe in men, in part related to the protective effect of the second X chromosome possessed by women.[59] Cognitive dysfunction often occurs along with intention tremor, gait ataxia, and other clinical manifestations in FXTAS, and dementia is a disabling feature in many patients,[59] as early executive dysfunction and slowed processing speed are accompanied by memory retrieval deficit, impaired working memory, and psychiatric dysfunction with sparing of language.[60] Autopsy of FXTAS has shown prominent white matter pathology,[61] and the middle cerebellar peduncle (MCP) is involved to the extent that conventional MRI discloses the "MCP" sign in about 60% of affected men.[59] Recent DTI and MRS studies have found that changes in NAWM correlate with slowed cognition and executive dysfunction early in the course of FXTAS,[62] suggesting that white matter pathology may be an early pathogenetic event.

Next, the neurodegenerative disease multiple systems atrophy (MSA) has recently been conceptualized as a disorder of white matter featuring primary oligodendrogliopathy,[63,64] This adult-onset disease produces mainly progressive motor and autonomic dysfunction, but cognitive decline occurs in some cases.[63] Most patients with MSA (80%) present with the parkinsonian type, formerly known as striatonigral degeneration, and a minority (20%) with the cerebellar type, formerly known as olivopontocerebellar degeneration.[63] When autonomic features dominate the clinical profile, the term Shy Drager syndrome is sometimes used. A characteristic MRI finding can often be seen in MSA—the "hot cross bun" sign, representing involvement of transverse ponto-cerebellar fibers[63]—and microscopic white matter involvement is confirmed by the presence of glial cytoplasmic inclusions within oligodendrocytes that mainly contain α-synuclein.[63] White matter is heavily damaged in MSA, with myelin loss, astrogliosis, and microgliosis, but it is noteworthy that even before α-synuclein appears, oligodendrocytes are damaged by oxidative stress as an early or even an initial pathogenetic event.[64]

A much discussed disorder in which identifiable white matter pathology may initiate the pathogenesis of dementia is chronic traumatic encephalopathy (CTE) [65]. This is a condition in which repetitive mild TBI in early life is proposed to produce a late dementia syndrome characterized by progressive cortical tau deposition. Injury sufficient to cause CTE may even involve subconcussive head blows[66] as well as concussion, but study of this issue remains in its infancy. CTE closely resembles the older entity of dementia pugilistica in boxers, but the appearance of dementia and tauopathy in former American professional football players and military combatants has expanded the range of individuals who may be at risk. CTE is presently a neuropathological diagnosis, and controversy exists about how it may be diagnosed in life, how common it may be, and who may be at risk.[67] Nevertheless, because TBI of all severity is characterized by the white matter lesion known as diffuse axonal injury (DAI) [68], and disruption of white matter connectivity is increasingly associated with neurodegeneration,[69] the putative origin of CTE in repetitive mild TBI strongly implies that injury to white matter is important in the etiopathogenesis of this disorder. Even acknowledging the uncertainty of the status of CTE, a focus on white matter, and the DAI to which it is susceptible in mild TBI, justifies consideration of whether repetitive mild TBI may in some manner eventuate in dementia years later.

Last, the most prevalent neurodegenerative disease in which white matter may be relevant is AD.[70] Although the amyloid hypothesis dominates thinking about AD pathogenesis, cortical protein deposition may be a later event that follows early white matter involvement. Neuropathological studies have detected axonopathy and transport deficits in the AD brain before amyloid deposition,[71] and degeneration of white matter has been documented in preclinical AD.[72] MRI studies have found vascular white matter lesions in up to 90% of AD patients[70] and decline in white matter integrity before the appearance of AD dementia using DTI.[73] Moreover, all of these processes take place in the aging brain, where it is likely that white matter retrogenesis is already underway.[70,74] In view of these and other similar observations, the "myelin model of AD" has been proposed, positing that early damage to white matter leads to AD through failed myelin repair mechanisms that produce cortical amyloid and its relative tau as by-products.[70] The early white matter damage—from ischemia and trauma, most prominently—is superimposed on white matter loss in aging, so that endogenous repair mechanisms of the brain are eventually overwhelmed and cortical proteins accumulate.[70] Amyloid and tau are envisioned as homeostatic response proteins that initially represent an adaptive response to white matter damage[70] but with time become toxic as continued white matter insults lead to protein deposition that no longer reflects a reparative process. After the cortical toxicity becomes established, the unchecked and steadily progressive deposition of these proteins eventually leads to synapse and neuronal cell body loss in the hippocampus and neocortex, at which time the classic amnesia, aphasia, apraxia, and agnosia of AD[10] become evident. The myelin model remains hypothetical, but early involvement of white matter in AD is well documented, and the model highlights this feature of the disease as meriting further attention in view of the persistent inability of antiamyloid agents to treat dementia.

PUBLIC HEALTH IMPLICATIONS

Of all the new directions implied by the idea of WMD, the most exciting from a clinical perspective may be the prospect of enhancing the prevention of dementia associated

with cortical pathology. That is, by considering the possibility that white matter injury occurs prior to cortical involvement in AD, CTE, and perhaps other degenerative diseases, it is conceivable that the preservation of white matter may avert the later onset of cortical dementia. Earlier sections have pointed out the remarkable plasticity of brain white matter in response to environmental stimuli, the potential of novel therapeutic modalities to repair myelin at the earliest stages of neuropathology, and the possibility that white matter damage may be a key upstream event in the pathogenesis of irreversible neurodegenerative disease. Taken together, these observations suggest that the protection of white matter in early to mid-adult life may have profound implications for the still poorly understood dementia epidemic facing our aging society. While continued efforts to treat late-life degenerative dementia are of course warranted, the WMD concept sets forth an agenda promoting the prevention of dementia as an equally compelling imperative.

To expand this discussion, the observation has been made in recent years that the burden of dementia may in fact be declining in older people, at least those living in developed countries.[75] Whereas the widely held assumption that more dementia cases will appear as the population ages is likely true for low- and middle-income countries,[76] the data from high-income countries are startling and provocative. Epidemiological findings from the United States, England, Holland, and Sweden have indicated that age-specific prevalence or incidence rates of late-life dementia have declined among people born later in the first half of the 20th century.[75] The explanation for this surprising trend is thought to derive from widespread public health benefits resulting from reduced vascular risk, greater physical activity, and improved educational opportunity enjoyed by people living in countries where these lifestyle interventions have become more common.[75] The implications of declining rates of dementia from preventive strategies are potentially transformative; a recent estimate suggested that up to one-half of all AD cases world-wide are related to modifiable risk factors.[77]

The studies documenting declining rates of late-life dementia in developed countries generally refer to unspecified dementia, and, given the fact that most dementia in older persons involves a combination of pathology that may include AD changes, vascular disease, and Lewy bodies,[78] a healthy life style may well benefit people with a wide spectrum of dementia syndromes. However, as AD remains the single most common neuropathological correlate of dementia in aging, the prospects for prevention of this disease are particularly intriguing.[79] From the perspective of the WMD concept, it is remarkable that the mechanism of dementia prevention in AD may center directly on white matter.[79] The growing body of data linking white matter pathology to AD primarily implicates vascular disease, which is the most common comorbid neuropathology in brains harboring the neuritic plaques and neurofibrillary tangles of AD.[78] While the pathophysiology of the events leading from vascular disease to AD is not well understood, one possibility is that vascular white matter disease interacts with mitochondrial dysfunction,[80] which is also known to occur early in AD pathogenesis.[81]

The public health perspective on dementia may thus revolve around the cerebral white matter as a primary site of early injury that later culminates in degenerative dementia. A number of environmental factors can be implicated in the etiopathogenesis of dementia related to AD, CTE, and by implication, other late-life dementias as well. To help prevent dementia, the protection of white matter emerges as a compelling public health objective. A wide range of risk factors predispose to white matter disease, and all may be addressed by medical or societal measures.

The first and most thoroughly studied problem in this context is cerebrovascular disease (CVD). For purposes of this review, this broad category involves the gradual appearance of atherosclerosis and the subsequent development of brain lesions including large artery territory infarction, lacunar stroke, and, most critically, white matter hyperintensities (WMH). WMH are present in the great majority of older people, and are strongly implicated in cognitive dysfunction and dementia.[9]

Heading the list of CVD risk factors is hypertension, long recognized as a major risk factor for CVD. Treatment of hypertension is widely advocated to prevent CVD, and emerging data are supporting the idea that not only stroke can be prevented, but also dementia. One particularly noteworthy study was a large European randomized controlled trial (RCT) of hypertension control lasting about four years.[82] This trial, known as the SYST-EUR study, not only reduced stroke incidence, as expected, but also lowered the incidence of dementia by 55%; of special interest is that the beneficial effect of treatment was apparent for AD as well as vascular dementia.[82] The SYST-EUR study is thus the only RCT showing that a medication of any variety can potentially reduce the incidence of AD. White matter has not been specifically examined in SYST-EUR or other similar studies as yet, but the well-publicized American Systolic Blood Pressure Intervention Trial [SPRINT] includes nested studies of cognition and MRI findings that are likely to add valuable new data to the study of this question.[83]

Diabetes mellitus, most notably type 2, is associated with cognitive dysfunction and an increased risk of dementia.[84,85] The mechanism of cognitive decline is uncertain, but it is known that patients with diabetes have an increased burden of WMH, and that these lesions are associated with deficits in processing speed, attention, and executive function,[84] closely matching the profile of WMD.[9] As diabetes nearly doubles the risk of AD,[85] an opportunity to reduce AD incidence by treatment of diabetes-related WMH may appear with further research.

Smoking has been shown to increase the burden of WMH and produce microstructural white matter changes on DTI and may increase the risk of both vascular dementia and

AD.[86] Given that more than 2 billion people around the world consume tobacco products, mostly in the form of cigarettes,[86] and that this practice may extend for many decades, the role of white matter pathology in cognitive decline associated with smoking merits more attention as a potential target of treatment intended to reduce dementia incidence.

Obesity in midlife, most evident in the abdomen and defined as a body mass index of 30 or higher, has been shown to increase the incidence of dementia and AD.[85,87] As obesity has also been associated with a higher burden of WMH[88] and microstructural white matter changes on DTI,[89] a contribution of white matter pathology to dementia mediated by obesity may offer a path to prevention by addressing this very common disorder.

Hyperlipidemia is a common condition for which many millions of people take statin drugs on a daily basis. This disorder is related to CVD, and to a heightened risk of both vascular dementia and AD.[85,90] Whereas MRI studies have not identified a higher burden of WMH in association with elevated lipids, DTI has shown that elevated cholesterol influences the microstructural integrity of white matter tracts.[91] More investigation of the role of white matter disease as a mediator of late-life dementia is warranted.

The metabolic syndrome has been introduced as a clinical construct combining multiple interrelated cerebrovascular risk factors that may be present in the same individual. Varying definitions of this syndrome have been proposed, but a typical cluster of disorders implied by this descriptor includes hypertension, type 2 diabetes mellitus, abdominal obesity, and hyperlipidemia. As can be expected from the entities subsumed under the metabolic syndrome, cognitive impairment and AD have been found to be associated in many studies.[85] Whereas an excess burden of WMH has not been detected with the metabolic syndrome, DTI has shown abnormal white matter microstructure in these patients,[92] and DTI abnormalities have been correlated with slowed processing speed.[93]

Diet is increasingly recognized to play a role in the pathogenesis of dementia. While this is a complex issue with many confounds, a Western diet with higher intake of red meat, high-fat dairy products, and refined grains has been associated with cardiovascular disease and obesity.[94] Conversely, adherence to a Mediterranean diet—one high in fish, olive oil, fruit, vegetables, and whole grains—has been tentatively shown to lower the risk of AD.[95] Interestingly, the Mediterranean diet has been shown to reduce WMH burden,[96] implying that further study of white matter as a mediator of cognitive function in relation to diet may prove revealing. A related issue is the consumption of alcohol, which may exert varying effects depending on the level of ingestion; whereas excess alcohol intake may lead to WMD via a toxic effect on myelin,[9] moderate alcohol consumption appears to be protective against AD.[97]

Physical activity is closely linked with vascular health, and has been found to improve aerobic fitness, with increased cerebral blood flow, oxygen extraction, and glucose utilization.[85] Cognitive benefits in attention and processing speed may also accrue from physical activity.[85] Physical inactivity, in contrast, increases the risk of AD,[85] and recent data suggest that physical activity may reduce the risk of dementia.[98] With respect to the possible contribution of white matter to pathogenesis, a systematic review found substantial support for a beneficial effect of physical fitness or activity on global white matter volume and burden of WMH.[99]

Depression is a very common mood disorder, particularly in older individuals, and has been recently associated with dementia and AD.[77,85,100] WMH are often found in patients with late-life depression,[101] and it may be that vascular risk factors contribute to the development of dementia by damage to white matter tracts. The fact that depression is reversible in most cases may not only lead to the restoration of normal mood in affected patients, but also to better adherence to medical regimens designed to minimize the further advance of WMH.

Sleep disorders have recently been the subject of much-needed attention in behavioral neurology and neuropsychiatry. An emerging literature is documenting a relationship between white matter disruption and sleep disturbances. Obstructive sleep apnea, for example, is associated with an increased burden of WMH,[102] and sleep-disordered breathing is linked with deficits in executive function, attention, and memory, particularly in the presence of the APOE ε4 allele.[103] An increased burden of WMH has recently been documented in subcortical ischemic vascular dementia patients with sleep disturbance.[104] Furthermore, it is of interest that shorter sleep duration and poorer sleep quality have been correlated with higher cortical amyloid as measured by Pittsburgh compound B,[105] and that, in rodent studies, sleep has been found to clear amyloid from the brain.[106] These data are consistent with a reparative function of cortical amyloid,[70] such that once the offending insult is addressed, the protein subsides as it is no longer needed.

Cognitive inactivity is being conceptualized as similar to physical inactivity in that both may be detrimental to the brain. For many years, evidence has supported a protective effect of education with respect to AD,[77,85] and recent data have indicated that occupational engagement and a socially integrated life style in adulthood may also exert some protective effect against AD.[107] These observations implicate the notion of cognitive reserve, by which is meant that people with higher education and occupational attainment can cope with incipient brain disease for a longer time.[77,85,107] In view of recent observations documenting white matter plasticity,[35–38] which may be relevant in both normal[39] and clinical populations,[30] intrinsic white matter repair mechanisms may contribute to cognitive reserve, and cognitive activity may come to be seen as a useful means of counteracting white matter pathology of many varieties.

TBI is the last item to be considered as a public health issue and deserves special consideration given the remarkably high prevalence of mild TBI and recent alarm about CTE. The recent conflicts in the Middle East and the heightened

awareness of concussion in football and other contact sports have fueled widespread concern about the long-term effects of mild TBI.[68,69,108] Efforts to prevent or lessen the severity of TBI are of course uncontroversial in general, but the specific interventions to accomplish this goal entail a host of imposing challenges involving questions of involvement in military conflict, appropriate transportation policies, safety in sport, and many others. These issues will require the collaboration of medical, public health, and societal entities, and their resolution must be seen as incremental and consistently subject to controversy. Still, a focus on white matter damage in the form of DAI[68,69,108] may provide a foundation for moving forward in the quest to reduce the burden of late-life dementia that increasingly finds its antecedents in early life injury.

SUMMARY AND FUTURE DIRECTIONS

The concept of WMD originated in clinical research on toluene leukoencephalopathy,[4–8] and emerged at a time when seminal work on disconnection syndromes[1] and subcortical dementia[11,12] had recently appeared. While not intending to question the established role of gray matter in the pathogenesis of dementia, the proposal of WMD was meant to complement thinking about how dementia arises by including white matter in the discussion. The arrival of MRI made possible the detailed and systematic study of white matter disorders, and correlations of white matter pathology with neurobehavioral and neuropsychological data revealed that gray matter pathology was not alone in producing cognitive decline.[9] Meanwhile, as behavioral neurology and neuropsychiatry advanced to the consensus that cognition is subserved by multiple distributed neural networks,[109,110] inclusion of white matter gained further credibility because all such networks include white matter connections.

In the nearly 30 years since the WMD idea was proposed, a great deal has been learned about white matter, and how damage or dysfunction sustained in this component of the brain can lead to significant neurobehavioral consequences. Based on the well-appreciated role of focal white matter lesions in disconnection syndromes,[2] clinical research proceeded to consider white matter in the pathogenesis of dementia, a task facilitated by the typically diffuse or multifocal neuropathology of white matter disorders.[9] While the concept of WMD has been both refined and expanded, the fundamental notion that white matter is relevant for the pathogenesis of dementia has been abundantly confirmed.

Many questions remain, however, and with further investigation the field appears to be poised for major new developments that will build on the WMD foundation. These advances will likely involve descriptive studies relating to the diagnosis and characterization of WMD in comparison to other forms of dementias, and the profile of WMD may be revised as further data are gathered. Similarly, the proposed precursor syndrome of MCD, which is probably relevant to many more patients than those with WMD, will be clarified by increased understanding of early white matter pathology and its neurobehavioral consequences. As is true of any pathologic condition, early diagnosis is high priority, and investigations of the MCD concept promise to help identify potentially devastating disorders years or even decades before they are destined to become symptomatic.

The conduct of these studies will depend heavily on the use of white matter neuroimaging, which has been critical from the beginning and will no doubt continue to permit ever more precise depiction of white matter wherever it is found in the brain. Longitudinal data will be most informative, as it is abundantly evident that white matter lesions, or in many cases microscopic NAWM involvement, may develop long before clinical manifestations appear. A detailed understanding of the sequence from MCD to WMD may thus be possible. With observations such as these, the study of white matter will likely yield provocative insights about the pathogenesis of many poorly understood disorders, as well as new possibilities for effective prevention and improved treatments. The consideration of white matter structure and function may inform a wide range of urgent questions, including strategies for the treatment of a host of neurologic disorders at a time when full recovery may be achievable, the maintenance of normal cognition, and the prevention of dementias including AD and CTE.

The idea that white matter is important for cognition does not represent a radical new idea,[1] but the tendency for corticocentric myopia in much of neuroscience[2] can obscure the role of myelinated fibers in considering the problem of dementia. Indeed, the fact that most dementia remains incurable—including the cortical dementia of AD that continues as such a formidable threat to medicine and society—calls out for a new paradigm that may reveal new avenues to an effective response. WMD and MCD are concepts that may stimulate such novel thinking, and they can serve in a theoretical sense to broaden the clinician's perspective in approaching dementia and its origins.

In the broadest sense, dementia must arise from dysfunction in or damage to neurons in the brain. However, the details of where, when, and how the cognitive disturbance arises are crucial. Just as neuronal cell body pathology within cortical and subcortical gray matter is important, so too is disease involving the segments of neurons within the white matter and their supporting structures. Axons, myelin, oligodendrocytes, astrocytes, microglia, and blood vessels all play vital roles in human cognition, and all need to be investigated within and between the cerebral hemispheres, in the cerebral cortex, and in the brainstem and cerebellum. Such a challenge may seem daunting, but white matter cannot be ignored, and the means of studying its macro- and microstructure are steadily more sophisticated and available. As has been true for behavioral neurology and neuropsychiatry from their inception, brain-behavior relationships in all their complexity show the way forward to a more complete understanding.

AUTHOR AND ARTICLE INFORMATION

From the Behavioral Neurology Section, University of Colorado School of Medicine, Aurora, Colo., and the Denver Veterans Affairs Medical Center.

Send correspondence to Dr. Filley; e-mail: christopher.filley@ucdenver.edu

The author reports no financial relationships with commercial interests.

Received Jan. 4, 2016; revised Feb. 28, 2016; accepted March 11, 2016; published online June 3, 2016.

REFERENCES

1. Geschwind N: Disconnexion syndromes in animals and man, I. Brain 1965; 88:237–294, 585–644
2. Parvizi J: Corticocentric myopia: old bias in new cognitive sciences. Trends Cogn Sci 2009; 13:354–359
3. Filley CM, Franklin GM, Heaton RK, et al: White matter dementia: clinical disorders and implications. Neuropsychiatry Neuropsychol Behav Neurol 1988; 1:239–254
4. Hormes JT, Filley CM, Rosenberg NL: Neurologic sequelae of chronic solvent vapor abuse. Neurology 1986; 36:698–702
5. Rosenberg NL, Kleinschmidt-DeMasters BK, Davis KA, et al: Toluene abuse causes diffuse central nervous system white matter changes. Ann Neurol 1988; 23:611–614
6. Filley CM, Heaton RK, Rosenberg NL: White matter dementia in chronic toluene abuse. Neurology 1990; 40:532–534
7. Filley CM, Halliday W, Kleinschmidt-DeMasters BK: The effects of toluene on the central nervous system. J Neuropathol Exp Neurol 2004; 63:1–12
8. Filley CM, Kleinschmidt-DeMasters BK: Toxic leukoencephalopathy. N Engl J Med 2001; 345:425–432
9. Filley CM: The Behavioral Neurology of White Matter, 2nd ed. New York, Oxford University Press, 2012
10. Geldmacher DS, Whitehouse PJ: Evaluation of dementia. N Engl J Med 1996; 335:330–336
11. Albert ML, Feldman RG, Willis AL: The 'subcortical dementia' of progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 1974; 37:121–130
12. McHugh PR, Folstein MF: Psychiatric syndromes of Huntington's Chorea, in Psychiatric Aspects of Neurologic Disease, vol 1. Edited by Benson DF, Blumer D. New York, Grune and Stratton, 1975
13. Filley CM, Heaton RK, Nelson LM, et al: A comparison of dementia in Alzheimer's disease and multiple sclerosis. Arch Neurol 1989; 46:157–161
14. Lafosse JM, Corboy JR, Leehey MA, et al: MS vs HD: can white matter and subcortical gray matter pathology be distinguished neuropsychologically? J Clin Exp Neuropsychol 2007; 29:142–154
15. Rao SM: White matter disease and dementia. Brain Cogn 1996; 31:250–268
16. Gabrieli JD, Stebbins GT, Singh J, et al: Intact mirror-tracing and impaired rotary-pursuit skill learning in patients with Huntington's disease: evidence for dissociable memory systems in skill learning. Neuropsychology 1997; 11:272–281
17. Mendez MF, Perryman KM, Bronstein YL: White matter dementias: neurobehavioral aspects and etiology. J Neuropsychiatry Clin Neurosci 2000; 12:133
18. Schmahmann JD, Smith EE, Eichler FS, et al: Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. Ann N Y Acad Sci 2008; 1142:266–309
19. Sepulcre J, Masdeu JC, Sastre-Garriga J, et al: Mapping the brain pathways of declarative verbal memory: Evidence from white matter lesions in the living human brain. Neuroimage 2008; 42:1237–1243
20. Turken A, Whitfield-Gabrieli S, Bammer R, et al: Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. Neuroimage 2008; 42:1032–1044
21. Murray ME, Senjem ML, Petersen RC, et al: Functional impact of white matter hyperintensities in cognitively normal elderly subjects. Arch Neurol 2010; 67:1379–1385
22. Bartzokis G, Lu PH, Tingus K, et al: Lifespan trajectory of myelin integrity and maximum motor speed. Neurobiol Aging 2010; 31:1554–1562
23. Debette S, Markus HS: The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2010; 341:c3666
24. Lee JH, Kim SH, Kim GH, et al: Identification of pure subcortical vascular dementia using 11C-Pittsburgh compound B. Neurology 2011; 77:18–25
25. Filley CM, Kozora E, Brown MS, et al: White matter microstructure and cognition in non-neuropsychiatric systemic lupus erythematosus. Cogn Behav Neurol 2009; 22:38–44
26. Kozora E, Filley CM: Cognitive dysfunction and white matter abnormalities in systemic lupus erythematosus. J Int Neuropsychol Soc 2011; 17:385–392
27. Rushton JP, Ankney CD: Whole brain size and general mental ability: a review. Int J Neurosci 2009; 119:691–731
28. Zhang K, Sejnowski TJ: A universal scaling law between gray matter and white matter of cerebral cortex. Proc Natl Acad Sci USA 2000; 97:5621–5626
29. Roth G, Dicke U: Evolution of the brain and intelligence. Trends Cogn Sci 2005; 9:250–257
30. Schmahmann JD, Pandya D: Fiber Pathways of the Brain. Oxford, United Kingdom, Oxford University Press, 2006
31. Nieuwenhuys R: The myeloarchitectonic studies on the human cerebral cortex of the Vogt-Vogt school, and their significance for the interpretation of functional neuroimaging data. Brain Struct Funct 2013; 218:303–352
32. Kutzelnigg A, Lucchinetti CF, Stadelmann C, et al: Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 2005; 128:2705–2712
33. Sporns O, Tononi G, Kötter R: The human connectome: a structural description of the human brain. PLOS Comput Biol 2005; 1:e42
34. Van Essen DC, Ugurbil K: The future of the human connectome. Neuroimage 2012; 62:1299–1310
35. Fields RD: White matter in learning, cognition and psychiatric disorders. Trends Neurosci 2008; 31:361–370
36. Fields RD: Imaging learning: the search for a memory trace. Neuroscientist 2011; 17:185–196
37. Fields RD: A new mechanism of nervous system plasticity: activity-dependent myelination. Nat Rev Neurosci 2015; 16:756–767
38. Alix JJ, Domingues AM: White matter synapses: form, function, and dysfunction. Neurology 2011; 76:397–404
39. Steele CJ, Bailey JA, Zatorre RJ, et al: Early musical training and white-matter plasticity in the corpus callosum: evidence for a sensitive period. J Neurosci 2013; 33:1282–1290
40. Schlaug G, Marchina S, Norton A: Evidence for plasticity in white-matter tracts of patients with chronic Broca's aphasia undergoing intense intonation-based speech therapy. Ann N Y Acad Sci 2009; 1169:385–394
41. Ropper A, Samuels M, Klein J: Adams and Victor's Principles of Neurology, 10th ed. New York, McGraw-Hill, 2014
42. Trapp BD, Peterson J, Ransohoff RM, et al: Axonal transection in the lesions of multiple sclerosis. N Engl J Med 1998; 338:278–285
43. Medana IM, Esiri MM: Axonal damage: a key predictor of outcome in human CNS diseases. Brain 2003; 126:515–530
44. Bartzokis G: Acetylcholinesterase inhibitors may improve myelin integrity. Biol Psychiatry 2007; 62:294–301
45. Bartzokis G: Neuroglialpharmacology: myelination as a shared mechanism of action of psychotropic treatments. Neuropharmacology 2012; 62:2137–2153

46. Kou Z, VandeVord PJ: Traumatic white matter injury and glial activation: from basic science to clinics. Glia 2014; 62:1831–1855
47. Calzà L, Fernandez M, Giardino L: Cellular approaches to central nervous system remyelination stimulation: thyroid hormone to promote myelin repair via endogenous stem and precursor cells. J Mol Endocrinol 2010; 44:13–23
48. Lundgaard I, Luzhynskaya A, Stockley JH, et al: Charles Ffrench-Constant: Neuregulin and BDNF induce a switch to NMDA receptor-dependent myelination by oligodendrocytes. PLoS Biol 2013; 11:e1001743
49. Acosta CM, Cortes C, MacPhee H, et al: Exploring the role of nerve growth factor in multiple sclerosis: implications in myelin repair. CNS Neurol Disord Drug Targets 2013; 12:1242–1256
50. Zhang R, Chopp M, Zhang ZG: Oligodendrogenesis after cerebral ischemia. Front Cell Neurosci 2013; 7:201
51. Kremer D, Küry P, Dutta R: Promoting remyelination in multiple sclerosis: current drugs and future prospects. Mult Scler 2015; 21: 541–549
52. Ben-Hur T, Goldman SA: Prospects of cell therapy for disorders of myelin. Ann N Y Acad Sci 2008; 1142:218–249
53. Takeuchi H, Sekiguchi A, Taki Y, et al: Training of working memory impacts structural connectivity. J Neurosci 2010; 30: 3297–3303
54. Mackey AP, Whitaker KJ, Bunge SA: Experience-dependent plasticity in white matter microstructure: reasoning training alters structural connectivity. Front Neuroanat 2012; 6:32
55. Henderson JM: "Connectomic surgery": diffusion tensor imaging (DTI) tractography as a targeting modality for surgical modulation of neural networks. Front Integr Neurosci 2012; 6:15
56. Sankar T, Chakravarty MM, Bescos A, et al: Deep brain stimulation influences brain structure in Alzheimer's Disease. Brain Stimulat 2015; 8:645–654
57. Johansson BB: Current trends in stroke rehabilitation: a review with focus on brain plasticity. Acta Neurol Scand 2011; 123:147–159
58. Zheng X, Schlaug G: Structural white matter changes in descending motor tracts correlate with improvements in motor impairment after undergoing a treatment course of tDCS and physical therapy. Front Hum Neurosci 2015; 9:229
59. Leehey MA: Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. J Investig Med 2009; 57: 830–836
60. Grigsby J, Cornish K, Hocking D, et al: The cognitive neuropsychological phenotype of carriers of the FMR1 premutation. J Neurodev Disord 2014; 6:28
61. Greco CM, Berman RF, Martin RM, et al: Neuropathology of fragile X-associated tremor/ataxia syndrome (FXTAS). Brain 2006; 129:243–255
62. Filley CM, Brown MS, Onderko K, et al: White matter disease and cognitive impairment in FMR1 premutation carriers. Neurology 2015; 84:2146–2152
63. Wenning GK, Stefanova N, Jellinger KA, et al: Multiple system atrophy: a primary oligodendrogliopathy. Ann Neurol 2008; 64: 239–246
64. Ettle B, Schlachetzki JC, Winkler J: Oligodendroglia and myelin in neurodegenerative diseases: more than just bystanders? Mol Neurobiol (Epub ahead of print, May 13, 2015)
65. McKee AC, Stern RA, Nowinski CJ, et al: The spectrum of disease in chronic traumatic encephalopathy. Brain 2013; 136:43–64
66. Bailes JE, Petraglia AL, Omalu BI, et al: Role of subconcussion in repetitive mild traumatic brain injury. J Neurosurg 2013; 119: 1235–1245
67. Wortzel HS, Brenner LA, Arciniegas DB: Traumatic brain injury and chronic traumatic encephalopathy: a forensic neuropsychiatric perspective. Behav Sci Law 2013; 31:721–738
68. Alexander MP: Mild traumatic brain injury: pathophysiology, natural history, and clinical management. Neurology 1995; 45: 1253–1260
69. Bigler ED: Traumatic brain injury, neuroimaging, and neurodegeneration. Front Hum Neurosci 2013; 7:395
70. Bartzokis G: Alzheimer's disease as homeostatic responses to age-related myelin breakdown. Neurobiol Aging 2011; 32:1341–1371
71. Stokin GB, Lillo C, Falzone TL, et al: Axonopathy and transport deficits early in the pathogenesis of Alzheimer's disease. Science 2005; 307:1282–1288
72. de la Monte SM: Quantitation of cerebral atrophy in preclinical and end-stage Alzheimer's disease. Ann Neurol 1989; 25:450–459
73. Gold BT, Johnson NF, Powell DK, et al: White matter integrity and vulnerability to Alzheimer's disease: preliminary findings and future directions. Biochim Biophys Acta 2012; 1822: 416-422
74. Brickman AM, Meier IB, Korgaonkar MS, et al: Testing the white matter retrogenesis hypothesis of cognitive aging. Neurobiol Aging 2012; 33:1699–1715
75. Larson EB, Yaffe K, Langa KM: New insights into the dementia epidemic. N Engl J Med 2013; 369:2275–2277
76. Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ: Epidemiology of dementias and Alzheimer's disease. Arch Med Res 2012; 43: 600–608
77. Barnes DE, Yaffe K: The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011; 10: 819–828
78. Schneider JA, Arvanitakis Z, Bang W, et al: Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007; 69:2197–2204
79. Filley CM: Alzheimer's disease prevention: new optimism. Neurol Clin Pract 2015; 5:193–200
80. Carvalho C, Correia SC, Perry G, et al: Cerebrovascular and mitochondrial abnormalities in Alzheimer's disease: a brief overview. J Neural Transm (Vienna) 2016; 123:107–111
81. Parker WD Jr, Parks J, Filley CM, et al: Electron transport chain defects in Alzheimer's disease brain. Neurology 1994; 44: 1090–1096
82. Forette F, Seux ML, Staessen JA, et al: Systolic Hypertension in Europe Investigators: The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med 2002; 162: 2046–2052
83. Ambrosius WT, Sink KM, Foy CG, et al: SPRINT Study Research Group: The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). Clin Trials 2014; 11:532–546
84. Biessels GJ, Reijmer YD: Brain changes underlying cognitive dysfunction in diabetes: what can we learn from MRI? Diabetes 2014; 63:2244–2252
85. Reitz C, Brayne C, Mayeux R: Epidemiology of Alzheimer disease. Nat Rev Neurol 2011; 7:137–152
86. Durazzo TC, Meyerhoff DJ, Nixon SJ: Chronic cigarette smoking: implications for neurocognition and brain neurobiology. Int J Environ Res Public Health 2010; 7:3760–3791
87. Kivipelto M, Ngandu T, Fratiglioni L, et al: Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005; 62:1556–1560
88. Jagust W, Harvey D, Mungas D, et al: Central obesity and the aging brain. Arch Neurol 2005; 62:1545–1548
89. Kullmann S, Callaghan MF, Heni M, et al: Specific white matter tissue microstructure changes associated with obesity. Neuroimage 2016; 125:36–44
90. Solomon A, Kivipelto M, Wolozin B, et al: Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dement Geriatr Cogn Disord 2009; 28:75–80
91. Williams VJ, Leritz EC, Shepel J, et al: Interindividual variation in serum cholesterol is associated with regional white matter tissue integrity in older adults. Hum Brain Mapp 2013; 34: 1826–1841

92. Segura B, Jurado MA, Freixenet N, et al: Microstructural white matter changes in metabolic syndrome: a diffusion tensor imaging study. Neurology 2009; 73:438–444
93. Segura B, Jurado MA, Freixenet N, et al: White matter fractional anisotropy is related to processing speed in metabolic syndrome patients: a case-control study. BMC Neurol 2010; 10:64
94. Fung TT, Rimm EB, Spiegelman D, et al: Association between dietary patterns and plasma biomarkers of obesity and cardiovascular disease risk. Am J Clin Nutr 2001; 73:61–67
95. Scarmeas N, Stern Y, Tang MX, et al: Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 2006; 59:912–921
96. Gardener H, Scarmeas N, Gu Y, et al: Mediterranean diet and white matter hyperintensity volume in the Northern Manhattan Study. Arch Neurol 2012; 69:251–256
97. Anstey KJ, Mack HA, Cherbuin N: Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. Am J Geriatr Psychiatry 2009; 17:542–555
98. de Bruijn RF, Schrijvers EM, de Groot KA, et al: The association between physical activity and dementia in an elderly population: the Rotterdam Study. Eur J Epidemiol 2013; 28:277–283
99. Sexton CE, Betts JF, Demnitz N, et al: A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. Neuroimage 2016; 131:81–90
100. Butters MA, Young JB, Lopez O, et al: Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialogues Clin Neurosci 2008; 10:345–357
101. Vu NQ, Aizenstein HJ: Depression in the elderly: brain correlates, neuropsychological findings, and role of vascular lesion load. Curr Opin Neurol 2013; 26:656–661
102. Kim H, Yun CH, Thomas RJ, et al: Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. Sleep 2013; 36:709–715B
103. Zimmerman ME, Aloia MS, Thomas RJ, et al: Sleep-disordered breathing and cognition in older adults. Curr Neurol Neurosci Rep 2012; 12:537–546
104. Cheng CY, Tsai CF, Wang SJ, et al: Sleep disturbance correlates with white matter hyperintensity in patients with subcortical ischemic vascular dementia. J Geriatr Psychiatry Neurol 2013; 26:158–164
105. Spira AP, Gamaldo AA, An Y, et al: Self-reported sleep and β-amyloid deposition in community-dwelling older adults. JAMA Neurol 2013; 70:1537–1543
106. Xie L, Kang H, Xu Q, et al: Sleep drives metabolite clearance from the adult brain. Science 2013; 342:373–377
107. Fratiglioni L, Wang HX: Brain reserve hypothesis in dementia. J Alzheimers Dis 2007; 12:11–22
108. DeKosky ST, Ikonomovic MD, Gandy S: Traumatic brain injury—football, warfare, and long-term effects. N Engl J Med 2010; 363:1293–1296
109. Mesulam MM: Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 1990; 28:597–613
110. Cummings JL: Frontal-subcortical circuits and human behavior. Arch Neurol 1993; 50:873–880