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Imaging Small Vessel-Associated White Matter Changes in Aging

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Abstract

Alterations in cerebrovascular structure and function may underlie the most common age-associated cognitive, psychiatric, and neurological conditions presented by older adults. Although much remains to understand, existing research suggests several age-associated detrimental conditions may be mediated through sometimes subtle small vessel-induced damage to the cerebral white matter. Here we review a selected portion of the vast work that demonstrates links between changes in vascular and neural health as a function of advancing age, and how even changes in low-to-moderate risk individuals, potentially beginning early in the adult age-span, may have an important impact on functional status in late life.

Introduction

It has been long understood that severe disruption of the cerebral vasculature is a major cause of functional decline in older adults resulting in an appreciable scourge on society. Proceedings from a panel discussion on ‘Problems of Aging’ at The New York Academy of Medicine in 1955 highlight the urgency at the time to better understand overt forms of cerebrovascular disease (Adams et al., 1956). The Moderator, Irving S. Wright (Figure 1), founder of the American Federation for Aging Research and the first physician to use heparin to treat blood clots (Wright, 1959, Mueller, 1995), opened the session as follows:

“This major problem has been sadly neglected in the past but in the last year or two has come more to the forefront of medicine. In 1952 approximately 170,000 people died with cerebrovascular diseases in this country. It is true that many of them were elderly. However, more than 44,000 of them were in the productive age group under 65 years of age. This represents an enormous loss of productivity to the country. In addition it is estimated that approximately 1,800,000 people alive today in the United States have suffered from some manifestations of cerebral vascular disease. Many of them are not only incapacitated themselves but in addition they require the aid, often full time, of from one to three or four additional people, which again represents an enormous loss to our community life in this country.

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There are many thousands confined for long periods in various private, municipal, state and veterans hospitals unable to care for themselves as the result of these diseases. Many more thousands are in nursing homes or the homes of their families where they constitute a heavy burden. It is not necessary for me to go into this in greater detail since I am sure that this audience fully recognizes the gravity of the problem. The question is, what are we going to do about it?"

Although it is clear that major cerebrovascular injury has a profoundly destructive influence on brain tissue and subsequently on society, the full extent of vascular influences is still unknown. This lack of knowledge is particularly evident with regard to the subtle variation in microvascular health that begins to decline almost ubiquitously as part of the aging process and may begin to exert influence on the brain and clinical course much earlier in adulthood than previously suspected (Swan et al., 1998, Launer et al., 2000, Kivipelto et al., 2001a, Kivipelto et al., 2001b, Korf et al., 2004, Debette et al., 2011, Gorelick et al., 2011, Tolppanen et al., 2012). A range of systemic vascular conditions elevate with increasing age. For example, hypertension alone has an age-adjusted prevalence of approximately 40% in Americans aged 45-64 and this pervasiveness jumps to approximately 70% in individuals >65 years of age (Keenan et al., 2011)(see also ranging estimates of hypertension prevalence across varying samples and assessment methods, e.g. (Egan et al., 2010, Kaplan et al., 2010, Mujahid et al., 2011, Guo et al., 2012, Joffres et al., 2013)). Hypertension contributes to detrimental remodeling of large and small cerebral and peripheral vessels (Lammie, 2000, Feihl et al., 2008, Lemarie et al., 2010, Schiffrin, 2012), and these deviations from optimal health diminish routine cerebrovascular function (Paulson et al., 1990, Iadecola and Davisson, 2008, Toth et al., 2013). In more advanced stages vascular alterations are hypothesized to create a state of chronic hypoperfusion to brain tissue (Fernando et al., 2006, Iadecola and Davisson, 2008). With similar timing in the age-span as these vascular changes, cerebral white matter exhibits several forms of deterioration including substantial volume loss (Guttmann et al., 1998, Salat et al., 1999, Bartzokis et al., 2001, Ge et al., 2002a, Raz et al., 2005, Walhovd et al., 2005, Salat et al., 2009, Westlye et al., 2010), increased lesion volume (Fazekas, 1989, Jernigan et al., 1991a, DeCarli et al., 1995), and accelerated alterations in tissue microstructure (Ge et al., 2002b, Bartzokis et al., 2003, Westlye et al., 2010).

There is an immense literature describing the broad topic of cerebrovascular contributions to neural aging. We review here neuroimaging studies linking vascular and white matter health with a focus on how subtle variation in small vessel vascular function, even within a relatively low risk range, may have cognitive, behavioral and psychiatric consequences. We focus selectively on a small portion of this work contributing to the idea that subtle changes may in fact be a primary mechanism of decline with advancing age; contributing to reduction in quality of life, and in more extreme forms, heralding significant disability. A full review of vascular contributions to psychiatric symptoms is beyond the scope of this summary however readers are referred to several existing resources on this topic (O'Brien and Ames, 1996, Thomas et al., 2002, Fields, 2008, Herrmann et al., 2008).

We refer here to 'white matter lesions' generically as either signal abnormalities within the white matter on neuroimaging or tissue changes measured histologically without a reference

to a specific pathophysiology. It is important to recognize that a range of pathologies contribute to lesioned tissue, and the type of damage may differ depending on various factors associated with the population under study (e.g. (Tomimoto et al., 1996, Gouw et al., 2008, Gouw et al., 2011, Schmidt et al., 2011)). It is also essential to consider that much of the literature reviewed here is cross-sectional and associational. Although substantial data have accumulated to support the notions presented, and while certain concepts seem intuitive (e.g. white matter damage is a *result* of poor vascular health), any assumed directionality from association is inferential and should be considered cautiously. In fact, little is known about the precise mechanisms by which vascular dysfunction contributes to observed changes in neural tissue (Pantoni, 2010). Aside from a small number of existing interventional studies, much work remains to demonstrate a direct causal mechanistic link between small vessel pathology and the common white matter changes associated with vascular risk. Finally, much of the literature reviewed used classical imaging markers of white matter damage (e.g. 'white matter hyperintensities') as a proxy for vascular associated tissue damage. However, the volume of overt white matter lesions is strongly correlated with the microstructural integrity of normal appearing white matter (NAWM)(Vernooij et al., 2008, Leritz et al., 2013) and the integrity of the NAWM is reduced in individuals with white matter lesions (O'Sullivan et al., 2001). These findings are not surprising given the fact that there is a global decrease in vascular density throughout the brain in individuals with vascular-associated white matter damage as opposed to vessel changes being limited to lesioned tissue (although not necessarily accompanied by parenchymal damage)(Brown et al., 2007). Vascular-associated influence to the white matter therefore expands beyond the classically examined 'hyperintensities' to the microstructural properties of NAWM. In fact, statistical control for the degree of white matter lesions removes a substantial portion of the variance shared between age and microstructural changes in NAWM (Vernooij et al., 2008, Leritz et al., 2013). Thus, although overt lesions seem to intuitively be an appropriate target for investigation and therapeutics, this damage is strongly linked to the overall connective integrity of the brain. Selected studies demonstrating associations between white matter microstructural properties in NAWM and vascular parameters are therefore additionally reviewed here. The current data suggest that subtle inter-individual variations in health parameters associated with vascular structure and function contribute to degenerative changes in cerebral white matter. These degenerative changes in the tissue supporting neural connectivity in turn contribute to functional decline in older adults. This influence potentially begins in midlife and occurs even within the range of variation considered normal to moderate risk for cerebrovascular disease; yet has an appreciable effect on cognition and other functional parameters and may progress substantially across time. These data highlight the need to consider an additional category of vascular health which is characterized by subtle deviation from the optimal state for maintenance of brain tissue and cognition, and may provide a target for therapeutics to maintain peak neural and functional health in late life (Gorelick et al., 2011).

Imaging white matter integrity and damage

Early imaging work using computed tomography (CT) noted the prevalence and extent of incidental white matter damage in older adults. It was through this work that the term 'leukoaraiosis', referring to a hypodensity on CT, was coined as an image-associated

occurrence without claim to a specific pathology (Hachinski et al., 1986, 1987, Pantoni and Garcia, 1997, O'Sullivan, 2008). Routine access to MRI provided the ability to better visualize the morphology of the lesions and subsequent procedures for the quantitative measurement of lesion in the form of hyperintense signal within white matter, typically measured on T2 or fluid attenuated inversion recovery (FLAIR) imaging. Initially, white matter lesions were assessed by semi-quantitative rating scales of the degree of total damage (e.g. (Fazekas et al., 1987, Scheltens et al., 1993)), and such scales continue to provide a reasonable and simple means for clinical and research assessment (King et al., 2013). Subsequent development of computer-based image segmentation routines (Jernigan et al., 1991a, Jernigan et al., 1991b) led to the more routine quantitative volumetric measurement and regional mapping of white matter lesions in patient populations (Tanabe et al., 1997). These procedures also facilitated the volumetric measurement of the 'normal appearing white matter' (NAWM), typically referring to tissue that is not hyperintense on T2 or FLAIR MRI. In addition to the macrostructural procedures for calculating total lesion volume, current assessment often additionally includes procedures for measurement of tissue 'microstructure', referring to certain biophysical properties of the tissue *within* the unit of resolution (e.g. within an MRI voxel; Figure 2). Such procedures produce varying measures thought to be linked to the 'integrity' of tissue (measured within and outside of the lesion). For example, measures extracted from diffusion tensor imaging (DTI) show strong associations with age (Pfefferbaum et al., 2000, Abe et al., 2002, Moseley, 2002, Salat et al., 2005a, Salat et al., 2005b, Sullivan and Pfefferbaum, 2006, Davis et al., 2009), are related to cognitive and behavioral performance (Madden et al., 2004, O'Sullivan et al., 2004, Charlton et al., 2006, Grieve et al., 2007, Madden et al., 2009), are predictive of subsequent white matter atrophy (Ly et al., 2013), and can provide information about the degree of signal abnormality within a lesion (e.g. see (Jones et al., 1999))(see also review in (Salat, 2011)). Diffusion measures loosely reflect a mix of the degree of myelination, fiber density, and fiber organization within tissue (Beaulieu, 2002); however, it's important to emphasize that imaging provides an indirect marker of histological phenomena and the use of these procedures to robustly quantitate specific pathologies remains to be developed and validated. With these potential caveats in mind, neuroimaging procedures provide several means by which the white matter anatomy and integrity can be understood in the context of healthy and diseased individuals as well as monitored for progressive changes across time.

Systemic, demographic, and disease factors associated with white matter damage in older adults

Several factors related to systemic physiology have been associated with severity of white matter damage. It was recognized early on that lesioned tissue was more often found in older individuals with vascular disease, however, tissue damage is also apparent incidentally in older adults without symptomatic disease (Roman, 1987). An early imaging study by Fazekas and colleagues examined the relationship between white matter lesions and a range of parameters linked to vascular health in individuals 51-70 years of age with no evidence of cerebrovascular, neurologic, or psychiatric disease on history or neurologic examination. Individuals with white matter lesions (T2 hyperintensities) had greater extracranial carotid artery disease, lower mean gray matter blood flow, a significant reduction in blood flow of the 'slow-flowing' compartment (an estimate of white matter flow), hypertension, and

diabetes (Fazekas et al., 1988). The lesions were attributed to general microcirculatory disturbance. The link between white matter lesions and metrics of vascular health is now fairly well established in diseased and non-diseased populations. Findings include elevated lesion volume in individuals with hypertension (Breteler et al., 1994, Longstreth et al., 1996, Dufouil et al., 2001, de Leeuw et al., 2002, Raz et al., 2007), individuals with elevated plasma homocysteine (Hogervorst et al., 2002, Wright et al., 2005), smokers (Hogervorst et al., 2002), and individuals with elevated composite risk scores such as the Framingham Stroke Risk Profile (Jeerakathil et al., 2004). The association between multiple cerebrovascular risk factors and white matter lesions may be greater than additive. Lechner and colleagues demonstrated that, in older adults without cerebrovascular symptoms, 92% had white matter lesions when two risk factors were present, and 100% when three risk factors were present (Lechner et al., 1988). It is not clear exactly when in the lifespan adverse vascular health may influence brain tissue. Adults with high midlife systolic blood pressure have greater white matter lesion volumes in later life compared to individuals with lower blood pressure suggesting a long-term impact (Swan et al., 1998). White matter lesions are progressive, and can approximately double in volume across a five year period in a vascular risk population (Raz et al., 2007). Additionally, white matter lesions have > 70% heritability in twin studies (Carmelli et al., 1998, Atwood et al., 2004), however, it is not clear whether this heritability is directly related to vascular risk *per se*, or some other aspect of lesion formation. Although often found incidentally, in contrast to normative populations, the prevalence of white matter lesions may be low and show reduced longitudinal increase in older adult populations selected for good vascular health (Kozachuk et al., 1990, Raz et al., 2007). These studies and supporting work are suggestive of a multifactorial condition by which changes in vascular health, potentially across a span of decades, subtly erodes the integrity of the tissue that functions to provide optimized information transmission throughout the central nervous system.

Imaging/pathologic correlations

Studies linking imaging findings to tissue pathology add support to the connection between microvascular changes and lesion formation. Awald and colleagues used MRI to identify lesions for pathologic analysis in older adults dying of non-neurologic causes and found that subcortical lesions were associated with arteriosclerosis, dilated perivascular spaces, and dilation of vessels accompanied occasionally by gliosis and infarction (Awad et al., 1986). The authors noted the nonspecific nature of the MRI signal and attributed signal changes to aging, hypertension, and vascular factors. Related studies found lesions to be associated with wide-ranging phenomena including perivascular demyelination, small vascular malformations, deformations of the lateral ventricle extending into the white matter, infarction, fiber loss, cavitation, and arteriolosclerosis (Kirkpatrick and Hayman, 1987, Yamanouchi et al., 1989, van Swieten et al., 1991, Fazekas et al., 1993, Brown et al., 2000). Although much of the imaging/pathologic correlations suggest that age-associated white matter lesions have a vascular etiology, it is important to note that these should not be equated in all cases as other disease processes can result in similar appearing findings. Detailed characterization of damage with regard to location, size, morphology, and clinical presentation is necessary to distinguish vascular contributions from lesions due to non-vascular origins. For example, the more common periventricular ‘caps’ (typically observed

as MR signal abnormality in the frontal horns of the ventricles) often do not reflect ischemic damage but occur with subependymal gliotic demyelination with alterations in the ependymal lining (Fazekas et al., 1993, Takao et al., 1999). It is also important to consider that certain prior concepts of differentiating lesions based on localization, such as deep versus periventricular, may not actually reflect distinct categories of damage given their high correlation across a broad clinical sample (DeCarli et al., 2005), although certain categorical differentiation may provide important etiological and prognostic information (Kim et al., 2008, Schmidt et al., 2011).

Brain changes associated with small vessel damage such as white matter lesions are often linked to other types of neural damage. For example, in a sample of 51 healthy adults across a broad age-span (ages 19-91), DeCarli and colleagues demonstrated that white matter lesion volume was associated with increased ventricular volume, reduced total brain volume, and reduced cerebral metabolism measured by flurodeoxyglucose (FDG) positron emission tomography (PET) (DeCarli et al., 1995). Given these findings, and the greater degree of hypertension and reduced cognition in individuals with white matter lesions, this work provided an important demonstration of a potentially broad syndrome accompanying this type of damage and the authors concluded that such lesions be considered pathologic (DeCarli et al., 1995). It is currently unclear, however, whether such neural changes represent a coherent cascade of events, or if each form of neural deterioration is an independent manifestation of microvascular dysfunction. Associations between measures of cortical integrity and vascular risk profile exist even when limiting the analysis to individuals in the low-to-moderate risk range of inter-individual variation (Leritz et al., 2011). It is therefore uncertain at present the degree to which white matter damage mediates cognitive, behavioral, and neurological decline relative to other types of tissue damage that may also be present in individuals with poor vascular health. Future work should aim to employ multimodal neural assessment to determine the *specific* contributions of white matter damage to cognitive and behavioral profiles while controlling for the influence of other neural markers vulnerable to small vessel changes.

Cognitive, behavioral, and psychiatric consequences of vascular associated white matter damage

The clinical significance of white matter lesions was unclear for some time (Pantoni and Garcia, 1995, O'Sullivan, 2008) and remains somewhat unresolved. In part, this based on the somewhat anecdotal and qualitative fact that certain individuals have appreciable lesion volume yet demonstrate general function relatively on par with others in their demographic, likely due to heterogeneity in the pathology contributing to the imaging result. Multiple large-sample studies have accumulated demonstrating that these lesions, or conditions tied to lesion formation, are in fact associated with detrimental conditions and phenomena that are of great importance to better characterize. Impairment across several major functional domains is related to the existence of microvascular associated white matter damage (Pantoni, 2008, Brickman et al., 2009a). Cognitively, individuals with greater white matter lesion volumes perform worse on tests of frontal and executive and speeded function with lesions having more minimal impact on domains supported by medial temporal lobe (de Groot et al., 2000, Gunning-Dixon and Raz, 2000, Au et al., 2006, Jacobs et al., 2013). The

partial cognitive selectivity is potentially due to a preferential disruption of frontal circuitry (Nordahl et al., 2006) and/or to disruption of cholinergic pathways (Swartz et al., 2003). Although lesions tend to be similarly spatially distributed in specific hemodynamic risk zones across various clinical populations (Holland et al., 2008), lesion location is to some degree related to the cognitive deficits observed (Smith et al., 2011), and lesions are independently associated with cognition relative to other measures of brain structure such as prefrontal volume (Gunning-Dixon and Raz, 2003). Associations between executive cognition and white matter microstructure may be substantially mediated by the degree of white matter lesions (Jacobs et al., 2013), potentially suggesting that vulnerability to vascular-associated tissue damage accounts for much of age-associated variation in cognition. Behaviorally, altered gait (Whitman et al., 2001, Baloh et al., 2003, Baezner et al., 2008) and balance (Starr et al., 2003) are conditions often reported in individuals with white matter damage. Psychiatrically, hyperintensities on MRI have been associated with geriatric depression (Hickie et al., 1997, Gunning-Dixon and Raz, 2003, Sheline et al., 2010) and an association between blood pressure and white matter microstructure has been demonstrated in individuals with geriatric depression (Hoptman et al., 2009). White matter lesions are associated with other clinical manifestations that impact quality of life including urinary incontinence and urgency (Poggesi et al., 2008, Kuchel et al., 2009). These findings alone demonstrate that although once considered 'silent', white matter lesions may in fact influence a range of cognitive, behavioral, and neurological domains and have a cumulative effect on functional independence.

Prognosis for disability

Microvascular changes in white matter may indicate future conditions with severe consequences including disability and death. The population based Leukoariosis and Disability (LADIS) study found that the severity of white matter damage was strongly related to time to convert to a dependent state measured by the Instrumental Activities of Daily Living (IADL), a scale of an individuals' independent functioning in a community (Inzitari et al., 2007, Inzitari et al., 2009). The investigators found that the risk of transition to disability or death was more than twice as high in older adults with severe compared to mild white matter lesions across an approximate period of 2.5-3 years with decline apparent in some in as early as one year (Inzitari et al., 2007, Inzitari et al., 2009). Findings from The Rotterdam Scan Study and The Framingham Offspring Study and others demonstrate the independent predictive nature of white matter lesions for risk of stroke (Vermeer et al., 2003, Kuller et al., 2004), cognitive impairment, and death relative to vascular risk factors (Debette et al., 2010). Thus, neuroimaging measures of white matter lesion index vascular risk that is not detectable by standard clinical measures.

A recent meta-analysis on prognosis of individuals with white matter lesions measured on MRI supported these conclusions finding that this tissue damage was associated with increased stroke risk (hazard ratio 3.3, 95% confidence interval 2.6 to 4.4), dementia (1.9, 1.3 to 2.8), and death (2.0, 1.6 to 2.7) (Debette and Markus, 2010). The authors suggested that, given the independent association of white matter hyperintensities with stroke after adjustment for vascular risk factors in prior work, white matter lesions reflect an important marker of uncontrolled vascular risk that may be more valuable than any individual risk

factor. These studies demonstrate the critical need for novel sensitive markers of cerebral vascular sufficiency, as well as quantitative metrics of cumulative burden to brain tissue that may be important to consider with regard to clinical intervention.

Cerebral amyloid angiopathy (CAA; (Vanley et al., 1981, Gilbert and Vinters, 1983, Vinters and Gilbert, 1983, Cosgrove et al., 1985, Biffi and Greenberg, 2011) (Cosgrove et al., 1985, Itoh et al., 1993, Biffi and Greenberg, 2011)), is condition in which excessive aggregations of beta-amyloid protein fibrils accumulate in the walls of small to medium-sized cerebral vessels, initially disrupting overall vascular function and ultimately resulting in lobar hemorrhage in a portion of affected individuals. The sporadic prevalence of this condition is high in adults over 60 years of age and even greater in patients with AD (Attems et al., 2008). As might be expected, individuals with probable CAA have impaired vascular reactivity (Dumas et al., 2012), increased prevalence of white matter lesions (Greenberg et al., 2004, Holland et al., 2008), and accelerated progression of lesions over time (Chen et al., 2006). Individuals with CAA additionally have reduced tissue integrity in the normal appearing white matter (Salat et al., 2006). Therefore, it is possible the substantial changes in white matter microstructure consistently observed in older adults may, in certain cases, reflect subclinical CAA and may indicate risk for future CAA-associated hemorrhage. Procedures for identifying probable CAA based in part on imaging findings have been described (Knudsen et al., 2001, Smith and Greenberg, 2003) and more information about early subtle effects of CAA to white matter damage may improve this in vivo detection in future work.

Vascular damage and white matter lesions are elevated in patients with AD (Steingart et al., 1987, Hogervorst et al., 2002, Makedonov et al., 2013)(for review see (Brickman et al., 2009a)). Whether this finding is related to a simple comorbid condition with an additive influence on clinical presentation, reflects an interaction between an independent classical AD and vascular pathology, or is related to a primary mechanism of AD is yet to be determined. Although there is a high prevalence of CAA in AD, at least a portion of the tissue changes in AD reflect similar types of microvascular pathology that accompanies non-amyloid based vascular conditions (Brun and Englund, 1986). White matter lesions seem to play a more prominent role modifying clinical presentation in the early stages of AD, or with mild cognitive impairment, but are less predictive of clinical status with greater disease severity (Chui et al., 2006, DeBette and Markus, 2010). Regionally, individuals with AD and mild cognitive impairment are more likely to have lesions in posterior periventricular and posterior callosal regions compared to cognitively healthy older adults (Yoshita et al., 2006). Cognitive abilities may be less associated with the severity of white matter lesions in patients with AD without cerebrovascular risk factors (Kozachuk et al., 1990) suggesting that vascular risk may contribute to lesion formation with unique variance when vascular health is poor and when degenerative changes of later stage AD do not dominate clinical presentation. Recent data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) highlight the fact that even in a sample selected to mirror a clinical trial for AD and screening and statistically controlling for several factors, white matter disease at baseline still remained an important predictor of short-term (1 year) changes in global cognition (Carmichael et al., 2010) highlighting the necessity to consider vascular risk and white matter lesions in clinical trials of age-associated disease, even in relatively low-risk

populations. Additional data from ADNI suggests that white matter damage may be a 'second hit' necessary for the clinical expression of AD (Provenzano et al., 2013). Evidence has been presented suggesting that cerebrovascular dysfunction, deterioration of the neurovascular unit, and homeostatic responses to myelin deterioration may contribute to pathologic cascades that promote or exacerbate classically recognized pathologies of AD (Wardlaw et al., 2003, de la Torre, 2004, Bell and Zlokovic, 2009, de la Torre, 2010, Bartzokis, 2011). These ideas provide valuable mechanisms to explore with regard to AD therapeutics in addition to the more commonly considered pathologic targets.

Vascular health

The literature reviewed suggests that in addition to the common consideration of vascular-linked clinical categories such as 'cerebrovascular disease' and 'vascular dementia', a more subtle class of cerebral phenomena is governed by variation in the degree of overall 'vascular health' and that there are functional consequences to this variation. That is, in addition to the focus on extreme deviation that contributes to explicit disease and disability, a secondary goal is to understand the optimal physiological state for peak neural health and the variations from this optimal state that occur yet are not deviant enough to be classified as overt disease. Age alone, independent of vascular risk is considered one of the primary factors contributing to the increase in white matter lesions (Longstreth et al., 1996, Brickman et al., 2008, Debette and Markus, 2010). Chronological age is an arbitrary marker of health that may instead represent, in part, a proxy for deviation in the optimal vascular state beyond what is detected with standardized values for vascular disease (e.g. hypertensive/normotensive). In fact, it has been suggested that any individual category of vascular risk is not particularly informative in the context of treatment (Jackson et al., 2005). In support of this, prior work has demonstrated that white matter lesions are elevated in individuals with higher blood pressure within the normal range (DeCarli et al., 1995). We and others have found cross-sectional associations between blood pressure (Kennedy and Raz, 2009, Leritz et al., 2010, Salat et al., 2012) as well as serum lipids (Williams et al., 2012) and integrity of NAWM in relatively low-risk populations of older adults. Systemic measures are indirect markers of cerebral vascular risk but do not provide direct information about cerebral vascular function. A limited set of studies have examined the association between white matter lesions and more direct measures of vascular activity in brain tissue as opposed to systemic measures. Individuals with white matter lesions have reduced cerebral blood flow (CBF) (Fazekas et al., 1988) as well as reduced flow and reactivity within the lesions (Marstrand et al., 2002, Brickman et al., 2009b, Makedonov et al., 2013). O'Sullivan demonstrated reduced CBF in the NAWM in individuals with ischemic white matter lesions which was interpreted to potentially demonstrate hypoperfusion as a precursor to periventricular lesions (O'Sullivan et al., 2002). We have recently demonstrated that cortical blood flow, which is reduced with advancing age (Chen et al., 2011), is strongly associated with white matter integrity measured by DTI in a sample of generally healthy adults with some mild vascular risk (Chen et al., 2013). This association was only minimally mediated by age and vascular risk. These cross-sectional associations may suggest that subtle variation in vascular parameters have neural consequences in even low-risk populations. However, alternative interpretations of these data, namely a reduction in metabolic demands resulting in a reduction in CBF are also valid and therefore these relationships must be

explored more directly. The data at least argue for the need to perform additional work in this domain and may suggest that normative considerations of vascular contributions to white matter damage are different from those for overt cardio/cerebrovascular disease. These studies also highlight the importance of direct measures of vascular compliance and regulation in monitoring parameters that contribute to common neural changes in older adults as a range of systemic conditions likely combine to determine an individual's unique vascular-functional state. Development of sensitive procedures for the measurement of specific aspects of vascular structure (e.g. vessel density and caliber) and function (e.g. endothelial activity and white matter perfusion regulation) could provide optimal screening and endpoint targets to advance clinical trials evaluating therapies to reduce vascular-associated disability in older adults.

Potential therapeutic routes for the reduction of microvascular associated white matter damage

It is an unfortunate fact that the microvascular system is detrimentally susceptible to a range of biological and environmental influences. However, the malleability of this system also provides a entry into therapeutic interventions that may either attenuate or reverse associated neural damage. Frameworks based in existing medicine have been presented providing valuable guidance for clinical trials (e.g. see discussions in (Zieman et al., 2005, Alagiakrishnan et al., 2006, Gorelick et al., 2011)). The effective application of such therapeutics specific to microvascular-associated white matter damage in the 'preclinical' stages is however yet to be demonstrated. A primary purported mechanism of white matter damage is due to hypoperfusion and ischemic tissue damage that results from a number of factors including age-associated increase in systemic vascular risk, alterations in cardiovascular function, and damage to or loss of deep penetrating vessels. Novel neuroimaging procedures for hemodynamic monitoring could provide sensitive information about the degree and quality of the blood supply throughout the brain and therefore can be used as a screening tool to determine individuals who are most likely to develop future damage. Once identified, several procedures exist for enhancing vascular health, which could be tailored to the individual. These include dietary (Esposito et al., 2004, Barcelo et al., 2009, Esposito et al., 2011, Scarmeas et al., 2011, Anton and Leeuwenburgh, 2013), lifestyle (Higashi et al., 1999, DeSouza et al., 2000, Kozakova et al., 2007, Seals et al., 2008, Erickson et al., 2013), and pharmaceutical (Takami and Shigemasa, 2003, Jackson et al., 2005, Rizos et al., 2010) intervention, which all may mechanistically ameliorate limitations in cerebral blood flow and enhance blood flow regulation. In the more distant future, experimental procedures for angiogenesis therapy (e.g. (Kusaka et al., 2005, Xiong et al., 2010, Ergul et al., 2012)) may one day be applicable to chronic cerebral hypoperfusion.

In addition to the plasticity of the vascular system, there is a natural myelin restoration process within white matter (Franklin and Ffrench-Constant, 2008). White matter lesions in demyelinating conditions such as multiple sclerosis demonstrate dynamic patterns of deterioration and some repair (Meier et al., 2007), and experimental therapeutics targeting myelin signaling pathways may enhance this repair ability (Taveggia et al., 2010). It is therefore possible that future therapies may promote repair of damaged tissue on top of enhancing the vascular environment promoting neural health. Monitoring for vulnerability

and therapeutic intervention would likely need to begin early in life, at least by midlife, for greatest potential preventative efficacy.

Given the range of conditions contributing to vascular dysfunction, it has been suggested that a therapeutic focus on small vessel cognitive impairment would be a beneficial first step in understanding therapeutic possibilities because of the high prevalence and relatively homogenous, and moderately progressive nature of this condition (Pantoni, 2010). As discussed in prior sections, such trials would greatly benefit from advances in the noninvasive measurement of tissue pathology and vascular structure and function. Thus, these concepts provide an initial framework to address the most ubiquitous forms of cognitive-altering conditions in seniors.

Future directions

Our understanding of cerebrovascular contributions to white matter damage and resultant clinical course has been greatly enhanced over decades of study via neuroimaging, however, much remains to elucidate. Specifically, understanding the optimal physiological state for neural health, the causes of deviations from this optimal state, and procedures for re-attaining this state could result in significant advances towards preservation of functional independence and improved quality of life of seniors. Advances in technology since initial studies using computed tomography and visual rating scales have opened several novel doors. Neuroimaging has provided us with tools to explore vascular phenomena across multiple populations, matched to in vivo physiology and simultaneous cognitive and clinical scales in large population samples. More work is necessary to better describe the full biological milieu that ultimately determines the vascular influence of neural health. Multispectral imaging procedures must be developed to better differentiate among pathologies given the heterogeneous nature of vascular-associated tissue damage (Gouw et al., 2008, Schmidt et al., 2011, Wardlaw et al., 2013). It is promising that vascular targeted therapies may reduce white matter lesion progression across time (Dufouil et al., 2005, Richard et al., 2010) advancing possibilities for early and aggressive targeted interventions in the future. Such work to date is limited but is effective at least in individuals with clinically expressed cerebrovascular disease (Dufouil et al., 2005). Given the modifiable nature of the cerebral vasculature across dietary, lifestyle, pharmacological and surgical manipulation, it is hopeful that a combined therapeutic approach would be effective in the reduction in the highly prevalent condition of vascular-associated deterioration and impairment in the foreseeable future.

Conclusions

The cerebral white matter is vulnerable to damage associated with suboptimal vascular health. It is possible that even subtle variation in normal vascular function beginning in middle age may contribute to the degradation of the connectivity of the brain and in turn promote a range of detrimental conditions. More extreme cases of dysfunction contribute to appreciable tissue damage as well as the clinical expression of dementing illness including AD, and alterations in vascular integrity and white matter deterioration may even contribute to the initiation of AD pathologic cascades. Given the high prevalence of vascular risk and

disease in older adults, a focus on therapeutics to optimize vascular health across the lifespan may have considerable implications in ameliorating late-life disability.

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Figure 1.

Irvine H. Page's group to discuss the formation of a National Academy of Medicine met for the first time on January 17, 1967, at the Cleveland Clinic Foundation. Although Page never realized his ambition to create such an academy, this group supplied the impetus that eventually led to the founding of the Institute of Medicine. Top, left to right: Fay H. Lefevre, M.D.; J. Englebert Dunphy, M.D.; Carleton B. Chapman, M.D.; Francis D. Moore, M.D.; William B. Bean, M.D.; John B. Hickam, M.D.; E. Cowles Andrus, M.D.; Robert A. Aldrich, M.D.; Ivan L. Bennett, Jr., M.D.; and Stuart M. Sessoms, M.D.; Bottom, left to right: James A. Shannon, M.D.; Frederick C. Robbins, M.D. (who would later become the institute's fourth president, in 1980); Irving S. Wright, M.D.; Irvine H. Page, M.D.; Douglas D. Bond, M.D.; and Robert H. Williams. Photograph courtesy of The Cleveland Clinic Foundation. Reprinted from *To Improve Human Health: A History of the Institute of Medicine* (1998).

Figure 2. Multiple image types in an older adult without (top) and with (bottom) white matter lesions. Variation in periventricular lesion contrast is obvious across the different image modalities, and this variation may provide important quantitative information allowing the specification of lesion pathology. In order from left to right: T1, T2, FLAIR, diffusion tensor imaging (DTI) fractional anisotropy, DTI axial diffusivity, DTI radial diffusivity.