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White Matter Microstructure in Brain Aging: Human and Animal Models

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Up to half of all cases of Alzheimer disease are attributable to modifiable risk factors including subclinical cardiovascular disease (CVD).¹ Additionally, subclinical CVD risk factors like hypertension and diabetes can negatively impact risk for and development of depression in older adults.^{2,3} When considered in the context of significant declines in CVD and stroke mortality in the United States⁴ (particularly in individuals 65–74 years of age),⁵ it appears older adults with CVD and associated risk factors are living longer but they are not living well. For example, ~50% of adults age 65 years and older who are diagnosed with hypertension are living with uncontrolled high blood pressure.⁶ This figure does not include individuals in the pre-diagnostic states of disease (e.g., pre-hypertension). Thus, well over half of the U.S. population is at risk for increased cerebral white matter damage leading to cognitive decline, dementia, and/or depression.⁷ Reducing the prevalence of subclinical CVD risk factors by even 10% would reduce dementia cases attributable to these factors by 150,000 in the United States and 720,000 worldwide,¹ saving \$6.8 billion in annual health care and long-term care services in the United States alone.⁸ Additionally, given recent estimates that 3.4%, or approximately 2.6 million adults, 50 years and older have vascular depression in the United States alone,⁹ determining targets for risk modification in vascular brain aging and treatment response in individuals already diagnosed is a critical priority in aging.

The past 10 to 15 years have seen an exponential increase in investigations of white matter alterations associated with subclinical CVD risk factors as they impact normal and pathological aging. Initial studies showed the mere presence of white matter damage lowered the threshold for dementia in older adults;¹⁰ furthermore, subclinical CVD risk and associated white matter damage appeared to result in a unique depressive–dysexecutive profile in some older adults with depression.² Around this same time, magnetic resonance imaging (MRI)–based neuropathology studies in older adults revealed that confluent white matter damage usually represented cerebral small vessel disease.¹¹ These findings led to the introduction of new nomenclature, including “vascular depression,”^{2,3} and for increased calls in the literature to advance our understanding of “vascular risk-factor-related cerebral small vessel disease.”^{12,13}

Much of this work has taken advantage of advanced MRI techniques and relied less on the microstructural studies of vascular brain aging afforded by animal model work in this area, particularly as it relates to aging and depression. Additionally, most human studies of subclinical CVD risk and brain aging to date have focused on overt white matter damage as seen on T2FLAIR MRI and/or specific metrics of white matter integrity gleaned from

diffusion tensor imaging (DTI). Although these studies have outlined a substantial amount of the gross neuropathology and associated white matter circuitry involved in vascular brain aging, little is known about the pathological underpinnings of this white matter damage—that is, the underlying white matter microstructure driving alterations in affected individuals. This lack of consensus makes targeted treatment development and implementation difficult.

It was because of these difficulties in developing interventions that target microstructural aspects of white matter damage that the contributors to this themed issue of *The American Journal of Geriatric Psychiatry* (AJGP) came together for a panel presentation on “Alternative Techniques for Quantifying White Matter in Aging and Late-life Depression” at the 12th annual meeting of the International College of Geriatric Psychoneuropharmacology.¹⁴ This initial meeting led to the current series of manuscripts on “New Findings and Novel Techniques: Uncovering the Microstructural Abnormalities of White Matter Damage Associated with Late-life Depression and Dementia” in this issue of AJGP.

This series of papers explores methods to probe white matter microstructural damage and present results related to brain structure and function across human and animal models of vascular brain aging. Dr. Olusola Ajilore compares novel metrics for network efficiency gleaned from graph theory–based network analysis techniques.¹⁵ This work demonstrates the utility of these techniques as it relates to cognitive profiles of aging and depression in one of the most widely implemented neuroimaging techniques in the field (i.e., DTI). Next, I present the results of a recent review of the technical development and application of novel neuroimaging procedures that target specific aspects of white matter microstructure in vivo conducted in conjunction with my Vascular Integrity to Advance Longevity (VITAL) Laboratory.¹⁶ This review highlights advances in available neuroimaging techniques, including a multi-component relaxometry technique termed mcDESPOT¹⁷ (or multicomponent driven equilibrium single pulse observation of T1 and T2) to probe for at-risk brain tissue that precedes lesion appearance. Furthermore, we highlight the development of techniques to measure axonal integrity that represent future directions for MR research. When taken together, these innovative and sensitive neuroimaging techniques have the potential to identify underlying white matter microstructural alterations that occur before overt white matter damage occurs, providing possible biomarkers of “at-risk” tissue that could be useful in intervention studies of risk modification and treatment response.

In order to understand where the next microstructural targets may be, Dr. Ahmad Khundakar highlights current work using animal models of vascular brain aging.¹⁸ Dr. Khundakar reviews the state of cellular morphometry in animal models of late-life depression using the latest in postmortem neuro-pathological techniques. His work provides further insights into white and gray matter damage associated with cardiovascular pathology in the aging brain. Finally, in order to place all of this work within the larger context of vascular brain aging, Dr. John T. O’Brien discusses all the presented methods, both in vivo and postmortem.¹⁹ He reminds us that, in conjunction with accumulating evidence from large-scale longitudinal studies of brain aging and sub-clinical vascular risk—by definition studies that relied on the best available MRI techniques of their day—the field of vascular brain aging continues to provide some of the strongest evidence of “The Clinical Significance of White Matter Changes.” It is only through the continued development in image acquisition and analysis, the cross-fertilization of ideas between animal models of aging and human studies and direct comparisons across antemortem and postmortem levels of analysis, particularly longitudinal analyses, that we will continue in our progress toward long-term risk reduction and improved treatment response in vascular brain aging.

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