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REVIEW

Neurovascular unit dysregulation, white matter disease, and executive dysfunction: the shared triad of vascular cognitive impairment and Alzheimer disease

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Abstract Executive dysfunction is the most important predictor for loss of independence in dementia. As executive function involves the coordination of distributed cerebral functions, executive function requires healthy white matter. However, white matter is highly vulnerable to cerebrovascular insults, with executive dysfunction being a core feature of vascular cognitive impairment (VCI). At the same time, cerebrovascular pathology, white matter disease, and executive dysfunction are all increasingly recognized as features of Alzheimer disease (AD). Recent studies have characterized the crucial role of glial cells in the pathological changes observed in both VCI and AD. In comorbid VCI and AD, the glial cells of the neurovascular unit (NVU) emerge as important therapeutic targets for the preservation of white matter integrity and executive function. Our synthesis from current research identifies dysregulation of the NVU, white matter disease, and executive dysfunction as a fundamental triad that is common to both VCI and AD. Further study of this triad will be critical for advancing the prevention and management of dementia.

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Introduction

White matter is well recognized to be particularly vulnerable to cerebrovascular injury (Black et al. 2009; Iadecola 2013). Accordingly, white matter pathology is commonly seen in vascular cognitive impairment (VCI) (Kalaria 2016), most often presenting with cognitive slowing and executive dysfunction (Filley 2005, 2016). This vulnerability has been attributed, in part, to the nature of cerebral vascular anatomy (Markus et al. 2000; Mandell et al. 2008; Iadecola et al. 2009; Wang et al. 2016; Lin et al. 2017). However, the active and contributing role of glial cells in white matter vascular injury has been demonstrated by the inhibition and modulation of these cells in recent experimental models (Lee et al. 2013; Hou et al. 2015; Liu et al. 2015; Qin et al. 2017; Miyanohara et al. 2018; Manso et al. 2018; Fowler et al. 2018). As the effector cells of CNS homeostasis, glial cells present crucial targets for therapeutic intervention and neuroprotection (Di Benedetto and Rupprecht 2013; Prokop et al. 2013; Ahmed et al. 2017). This pertains to VCI as well as Alzheimer disease (AD), as the role of both cerebrovascular and executive dysfunction is now increasingly appreciated as common factors of AD (Korczyn 2002; Girouard and Iadecola 2005; Kirova et al. 2015; Cloutier et al. 2015; Kalaria 2016; Guarino et al. 2019). Finally, investigation of the

neurovascular unit (NVU) in neurodegenerative disease has identified an important intersection between cerebrovascular and glial pathology (Zlokovic 2011). In the context of the most prevalent forms of dementia, AD and VCI, emerging discoveries of the pathological and functional correlates of white matter disease are discussed in this review.

White matter pathology and cognitive function

The neurological sciences have historically favored the study of gray matter, even though white matter occupies 40–50% of the adult human brain (Filley 2005). Although Jean-Martin Charcot described the white matter lesions observed in multiple sclerosis and amyotrophic lateral sclerosis in the nineteenth century (Kumar et al. 2011), it would not be until 1965 that the notion of *cerebral disconnection* as a broad white matter-centric mechanism for cognitive impairment would be introduced by Norman Geschwind (Filley 2005). Following advances in neuroimaging, the term *white matter dementia* was introduced as a theoretical syndrome in 1988 to expand the neuroanatomical scope of dementia research (Filley 2016). Despite the central role of white matter pathology in VCI (Black et al. 2009; Iadecola 2013), gray matter continues to be the research focus of cognitive function and dysfunction. However, diffusion-weighted magnetic resonance imaging (DW-MRI) has recently led to great advances in characterizing microstructural disruptions of white matter, shedding light on the functional correlates of white matter pathology. Concurrently, studies have begun to identify the active role of glial cell dysfunction in neurodegenerative disease involving white matter (Kaminsky et al. 2016; Jäkel and Dimou 2017). The striking abundance of white matter in the frontal lobes, the seat of integration and coordination, underscores the importance of white matter for higher-level domains of cognition requiring distributed processing, including executive function (Filley 2005). The preservation of white matter integrity, and executive function in turn, is crucial to the preservation of functional independence (Razani et al. 2007; Johnson et al. 2007; Mlinac and Feng 2016). Therefore, the development of clinical or radiological means to evaluate white matter integrity and characterizing its pathological correlates will be central to identifying new therapeutic targets for managing and preventing dementia.

Assessment of white matter integrity

White matter degeneration can present in the form of volume loss, measured with neuroimaging as gross atrophy on postmortem studies. More subtle forms of white matter degeneration include microstructural changes that alter molecular diffusion characteristics as measured by DW-MRI, including an early form of this technique, diffusion tensor imaging (DTI) (Jones et al. 2013). DTI relies on the differential displacements of water molecules, driven by differences in tissue ultrastructure (Soares et al. 2013). One of the most common metrics used in DTI is fractional anisotropy (FA), which quantifies the average restriction of water molecule movement within a voxel. FA measures range from 0 to 1, with low values seen in the CSF-filled ventricles where water diffusion is unrestricted in all three dimensions, and high values in myelinated white matter tracts such as the corpus callosum, where water movement is greatly restricted to move primarily along the direction of the axons (Salat et al. 2005; Soares et al. 2013).

In normal aging (Gunning-Dixon and Raz 2000; Van Petten et al. 2004; Hedden and Gabrieli 2004; Head et al. 2004; Grieve et al. 2007; Madden et al. 2009; Sasson et al. 2013; Fjell et al. 2016; Rabin et al. 2018) and in many different neurodegenerative conditions (Bozzali et al. 2001; Smith et al. 2011; Metzler-Baddeley et al. 2014; Lin et al. 2014; Cesar et al. 2015; Alves et al. 2016; Atkinson-Clement et al. 2017), loss of FA in white matter has been correlated with cognitive impairments, most often with processing speed and executive function. A loss of FA in white matter tissue, where FA is expected to be high, indicates ultrastructural changes that are presumed to be predominantly the result of demyelination or alterations in myelin (Salat et al. 2005; Jung et al. 2010; Soares et al. 2013). However, FA also reflects axonal caliber, injury, and density, as well as uniformity of fiber direction and gliosis. Research continues to characterize the specific histopathological correlates of DTI metrics, including FA, and how these radiological–histopathological correlates change in different disease contexts (Salat et al. 2005; Wei et al. 2015; Leemans et al. 2019). Despite this, and with some controversy (Jones et al. 2013), DTI measures such as FA are widely inferred as a measure of white matter integrity. The limitations of this interpretation are well detailed by Jones et al. (2013), but the appeal to using DTI measurements to infer functionally deleterious changes is

supported by findings of cognitive correlates (Salat et al. 2010). While abnormal white matter diffusion parameters may be biologically and clinically relevant correlates, researchers should maintain caution in interpreting the specific physiological basis of these findings.

The clinical utility of measuring ultrastructural white matter changes is further demonstrated by the potentially diagnostic and prognostic value of leukoaraiosis. Also known as white matter hyperintensities, leukoaraiosis is the radiological phenomenon of diffuse signal changes in cerebral white matter, appearing relatively hypodense on CT or hyperintense on T2 MRI (Clarke et al. 2000; Pettersen et al. 2008; Kalaria et al. 2012; Cai et al. 2015; Brickman et al. 2015; Lee et al. 2016). Leukoaraiotic white matter has increased diffusivity, as measured by DW-MRI (O'Sullivan et al. 2004; Altamura et al. 2016), and leukoaraiosis is an important risk factor for stroke, dementia, and death (Debette and Markus 2010; Brickman et al. 2012; Brickman 2013). The term leukoaraiosis, derived from the Greek leuko (white) and araiosis (rarefaction), was coined intentionally so as not to assume any particular disease etiology (Hachinski et al. 1987); similarly, white matter hyperintensities are strictly a radiological description that does not imply etiology. Still to this day, the exact processes that causes leukoaraiosis have not been determined. Vascular pathology is commonly proposed as the underlying mechanism of leukoaraiosis (Black et al. 2009; Wardlaw et al. 2015; Shi and Wardlaw 2016; Ter Telgte et al. 2018), although dysregulation of glial cells, blood–brain barrier (BBB) integrity, and inflammatory processes have also been implicated (Raz et al. 2012; Huang et al. 2018; Chen et al. 2018).

White matter vascular pathology

White matter is particularly sensitive to vascular disruption (Black et al. 2009; Iadecola 2013). In a study of healthy subjects, when mild hypercapnia was induced to produce systemic vasodilation, a significant steal phenomenon was observed that resulted in reduced blood flow to white matter (Mandell et al. 2008). The very regions that had reduced blood flow matched the common neuroanatomical locations of leukoaraiosis, namely periventricular white matter (Mandell et al. 2008; Black et al. 2009). This was also supported by a previous study of subjects with leukoaraiosis that had normal blood flow to gray matter but reduced white matter blood flow (Markus et al. 2000). Reduced blood flow indicates a poorer cerebrovascular reserve in white matter, and the white matter regions that are relatively more prone to leukoaraiotic changes indeed fall within the "watershed" regions in between the major arterial zones of the brain (Markus et al. 2000; Mandell et al. 2008; Iadecola et al. 2009; Wang et al. 2016; Lin et al. 2017). Moreover, white matter has been shown to be highly vulnerable to ischemic injury, with increased susceptibility seen with age (Wang et al. 2016). The greater white matter vulnerability to ischemia is attributed to a relative paucity of collateral blood flow in deep white matter (Iadecola et al. 2009). The high sensitivity of oligodendrocyte precursor cells to both ischemia-induced oxidative stress (Wang et al. 2016) and fibrinogen extravasated across a disrupted BBB (Petersen et al. 2017, 2018) further impair remyelination after vascular injury.

Hypertension, a highly prevalent vascular condition, also correlates with disruptions of white matter structure (Skoog 1998; Li et al. 2016) and is a key risk factor for leukoaraiosis (Raz et al. 2003; van Dijk et al. 2004). At the same time, the presence of leukoaraiosis is more common in subjects with orthostatic hypotension (Oh et al. 2014) and increased pulse pressure (Kim et al. 2011a; Wang et al. 2015). Cerebral small vessel disease (SVD) is an umbrella term for pathologies of perforating cerebral arterioles, capillaries, and venules (Shi and Wardlaw 2016) and is associated with systemic vascular risk factors such as hypertension, atherosclerosis, diabetes mellitus, and atrial fibrillation (van Norden et al. 2011). Cerebral SVD also often manifests as leukoaraiosis (Black et al. 2009; Wardlaw et al. 2015; Shi and Wardlaw 2016; Ter Telgte et al. 2018), and thus, white matter is generally thought to be susceptible to common systemic cardiovascular conditions. A lot of histopathological heterogeneity has been observed in leukoaraiosis, so that in general, any vascular conditions that cause cerebral hypoperfusion, BBB disruption, chronic ischemia, microinfarcts, venous collagenosis, vessel tortuosity, or vessel wall thickening is also thought to cause leukoaraiosis (Gouw et al. 2011; Lin et al. 2017; Ter Telgte et al. 2018). Cerebrovascular disease, the underlying neuropathology of VCI, is very heterogeneous, and multiple types of cerebrovascular lesions can be observed in a single brain. Universally accepted neuropathological criteria for VCI do not exist (Korczyn et al. 2012; Sachdev et al. 2014), and the correlations between the breadth of cerebrovascular disease and its range of clinical manifestation are an area of

ongoing research (Kalaria et al. 2004; Jellinger 2013; Kalaria 2016). However, it is informative to classify cerebrovascular disease according to major etiological categories (Jellinger 2013; Smith 2017):

- *Large vessel disease or atherosclerosis*: proliferation of the intima (atheroma) in medium and large arteries, with accumulation of cholesterol and leukocytes that can lead to plaque formation and calcification. Plaques can rupture, causing local thrombosis and a single large brain infarct, or plaques can produce emboli and multiple infarcts.
- *Small vessel disease*: reduced compliance in arterioles and capillaries due to arteriosclerosis, lipohyalinosis, arteriolosclerosis, and amyloid angiopathy, resulting in lacunar infarcts, even smaller microinfarcts, small hemorrhages, and extravasations of blood known as microbleeds.
- *Cardiac*: cardioembolic injury, commonly attributed to atrial fibrillation, as well as any condition that impairs cerebral perfusion such as cardiomyopathy, cardiogenic shock.
- *Other systemic disease*: sickle cell disease, autoimmune conditions such as vasculitis, and noncardiogenic causes of circulatory shock.

Cerebrovascular lesions can be further categorized according to distribution: focal, multifocal, or diffuse. Focal lesions can be attributed to any of the etiologies described above, but focal lesions that result in VCI are usually the result of an infarct in functionally critical regions. Focal lesions affecting the mesial temporal lobe, anterior cingulate cortex, caudate, thalamus, angular gyrus of the dominant hemisphere, and key white matter areas can result in strategic infarct dementia (Korczyn et al. 2012). Multifocal lesions of large vessel etiology can result in multiple infarct dementia (Korczyn et al. 2012). Multifocal or diffuse lesions of small vessel etiology are particularly heterogeneous and are seen in VCI attributed to multiple lacunar infarcts, Binswanger disease, hypertensive angiopathy, and cerebral amyloid angiopathy (Korczyn et al. 2012; Rosenberg 2018). In two hereditary cerebrovascular conditions that can result in VCI, dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Jellinger 2013) and Moya Moya disease (Yamashita et al. 1983), both small and large vessel disease are seen in a multifocal/diffuse distribution.

The categories of cerebrovascular pathologies outlined here are far from exhaustive but do capture some of the breadth of factors involved. Further considerations related to neuropathological staging include lesion severity and location(s). Sampling strategies and the detection of white matter lesions, including noninfarct lesions such as demyelination, vacuolation, and diffuse gliosis, are also in ongoing development and will likely play an important role in correlating cerebrovascular disease and VCI (Kalaria et al. 2004; Jellinger 2013; Kalaria 2016). This will also contribute to developing a better understanding of the relationship between white matter vascular pathology and leukoaraiosis.

White matter vascular insufficiency and gliosis

In addition to the large variety of vascular abnormalities observed in leukoaraiotic white matter, many active and dystrophic glial cells are also observed. This includes dysfunctional oligodendrocytes, clasmatodendritic astrocytes (abnormal astrocytes with swollen soma and short blunt processes), and activated microglia (Gouw et al. 2011; Joutel and Chabriat 2017; Hase et al. 2018; Fillingham et al. 2019). As glial cells actively maintain white matter integrity and homeostasis, they present important targets for therapeutic intervention (Di Benedetto and Rupprecht 2013; Prokop et al. 2013; Ahmed et al. 2017). Astrocytes interact with microglia in inflammatory conditions and are an important factor in both white matter maintenance and inflammation (Harry and Kraft 2008; Matute and Ransom 2012; Lundgaard et al. 2014; Heppner et al. 2015; Kaminsky et al. 2016). However, neuroinflammation in neurodegenerative diseases is thought to be driven primarily by microglia, which are involved in both cytokine secretion and phagocytosis (Di Benedetto and Rupprecht 2013; Jäkel and Dimou 2017; Ahmed et al. 2017). Indeed, preclinical studies have shown that the inhibition of white matter microglia protected white matter integrity and cognitive function after cerebral hypoperfusion by induced bilateral carotid artery stenosis (see Table 1). Cognitive and white matter protection has also been demonstrated by shifting microglia activation to favor M2 polarization, the anti-inflammatory microglia phenotype (see Table 1). On the contrary, mice subject to chronic cerebral hypoperfusion with knockout of CD73,

Table 1 Inhibition and modulation of microglia protects white matter integrity and cognitive function in rodent models of cerebral hypoperfusion

Treatment	Study	Proposed primary mechanism	Outcomes
Cardiotonic pill*	Lee et al. (2013)	Inhibition of microglial activation	Attenuated loss of white matter MBP Attenuated ERK and p38MAPK expression Attenuated inflammatory cytokines expression
Dimethyl fumarate	Fowler et al. (2018)	Modulation of microglia and macrophage	Attenuated white matter microglial/macrophage density Attenuated MIP-1α expression Rescued peak latency of evoked compound action potentials
Fingolimod	Qin et al. (2017)	Shifting microglia toward M2 polarization via STAT3 signaling	Attenuated white matter microglial activation and inflammatory cytokine expression Attenuated demyelination and disorganization of Ranvier nodes Promoted oligodendrocytogenesis Rescued working memory
Minocycline	Manso et al. (2018)	Inhibition of microglial proliferation	Reduced white matter microglial density and microglial proliferation Rescued peak latency of evoked compound action potentials
Minocycline	Miyanohara et al. (2018)	Inhibition of microglia and macrophage	Reduced white matter microglial density Rescued exploratory behavior
Knockout/knockdown	Study	Proposed primary mechanism	Outcomes
CX3CR1/ Fractalkine-Receptor siRNA KD	Liu et al. (2015)	Inhibition of CX3CL1/CXCR1 neuron–microglia signaling cascade	Attenuated p38MAPK and PKC expression Attenuated inflammatory cytokine expression Reduced white matter lesion scores Rescued water maze escape latency
TRPM2 KO	Miyanohara et al. (2018)	Inhibition of TRPM-mediated activation of microglia	Attenuated loss of myelin and oligodendrocytes Attenuated increase of microglial density Attenuated increase of inflammatory cytokines Rescued exploratory and alternation behavior

MBP = myelin basic protein; *ERK* = extracellular signal-regulated kinases; *p38MAPKs* = p38 mitogen-activated protein kinase; *MIP-1α* = macrophage inflammatory protein 1α; *PKC* = protein kinase C

*Herbal medicine composed of *Salvia miltiorrhiza*, *Panax notoginseng*, and *Dryobalanops aromatica* Gaertner

which promotes M2 polarization (Xu et al. 2018), had increased levels of white matter reactive astrocytes, activated microglia, and proinflammatory cytokines, resulting in poorer white matter lesion scores and impaired working memory (Hou et al. 2015). In stroke-prone renovascular hypertensive rats, astrocyte and microglia proliferation was reduced by an agonist of the peroxisome proliferator-activated receptor-γ agonist, pioglitazone; this reduced white matter lesion scores, Morris water maze impairment, aberrant arteriolar remodeling, and chronic white matter expression of proinflammatory cytokines (Lan et al. 2015). Thus, microglia play a central role in the vulnerability of white matter to vascular insufficiency.

Despite the importance of both microglia and astrocytes in maintaining white matter in neurodegenerative disease and in health, there is a relative paucity of literature on how dysregulation of these white matter glial cells affects executive function. In two rodent studies, white matter microglial activation was associated with executive dysfunction (Kim et al. 2016; Arinrad et al. 2017), and two recent postmortem studies of dementia pugilistica and alcohol-related neuropathology also demonstrated an association between executive dysfunction with white matter astrocytosis (Kim et al. 2011b; De La Monte and Kril 2014). The prevalence and burden of diseases that can induce dysregulation of white matter microglia and astrocytes, and consequentially, impair white matter integrity and executive function, warrants more research.

White matter pathology and executive dysfunction

Concurrent with a growing interest in the role of glial cells in cerebrovascular insufficiency-induced white matter pathology, the specific cognitive manifestations of white matter disease have also been a focus of recent studies. Disruption of projection fibers is well appreciated as a cause for sensorimotor deficits. However, cognitive deficits can arise from the disruption of association fibers, which are crucial for facilitating the distributed processing needed for executive function. Executive function refers to a group of interdependent cognitive functions that enable planning, mental manipulation, and control over goal-directed behavior. The core subdomains of executive function are inhibitory control, working memory, and cognitive flexibility (Diamond 2013), which all rely on information processing in the prefrontal cortex (PFC) and its extensive connections with other cortical and subcortical brain regions. Although specific locations of leukoaraiosis do associate with impairments of specific subdomains (Smith et al. 2011), leukoaraiosis in any region is also correlated with hypometabolism in the PFC and global impairments of executive function (Tullberg et al. 2004; Madden et al. 2009; Smith et al. 2011). The substantial convergence of fiber pathways that connect the PFC may explain how pathology in even a small focal white matter lesion could affect metabolism in the entire frontal cortex and cause broad impairments of executive function (Filley 2005).

Of all cognitive domains, executive function is often the most sensitive to both environmental and physiological stressors (Diamond 2013). Accordingly, executive function declines in late adulthood (Diamond 2013; Harada et al. 2013), which has been linked to disruptions of white matter integrity (Gunning-Dixon and Raz 2000; Van Petten et al. 2004; Hedden and Gabrieli 2004; Head et al. 2004; Grieve et al. 2007; Madden et al. 2009; Sasson et al. 2013; Rabin et al. 2018). Even in normal aging, white matter volume shows a greater decline than gray matter volume (Guttmann et al. 1998; Salat et al. 2005). For patients diagnosed with dementia or at risk of dementia, one of the most difficult challenges is the loss of functional independence, and the cognitive domain that best predicts current and future functional independence is executive function (Razani et al. 2007; Johnson et al. 2007; Mlinac and Feng 2016). This emphasizes the importance of supporting general white matter health for maintaining functional independence. The three core subdomains of executive function will be reviewed herein.

Inhibitory control

Inhibitory control of attention, thought, behavior, and emotions constitutes one of the core subdomains of executive function (Diamond 2013). Inhibitory control of attention can occur involuntarily, as with the filtering of stimuli at the level of perception such as background noise at a cocktail party. Inhibitory control of attention can also occur voluntarily, as when effort is made to ignore stimuli that distract from goal-directed behavior (Diamond 2013). The inhibition of both mental representations and behavior can be best appreciated in conditions where such inhibition is impaired; intrusive memories and thoughts are a core component of post-traumatic stress disorder (Levy and Anderson 2008; Falconer et al. 2008), substance addiction (Baler and Volkow 2006), and the obsessive component of obsessive-compulsive disorder (Penadés et al. 2007), while impairments of behavioral inhibition are also seen in substance addiction (Baler and Volkow 2006) and the compulsions seen in obsessive-compulsive disorder (Penadés et al. 2007). Lastly, inhibitory control of emotions is regularly required in social interaction and maintaining motivation while delaying gratification through arduous tasks, such as writing a dissertation (Diamond 2013).

The PFC is responsible for regulating and inhibitory control over attention, thought, behavior, and emotions. The inferior frontal gyrus in the ventrolateral PFC (VLPFC) plays an important role in inhibition via direct connections to other cerebral cortices, basal ganglia, the subthalamic nucleus, and cerebellar cortices (Chambers et al. 2009; Arnsten and Rubia 2012). In particular, the right VLPFC has been associated with behavioral inhibition, whereas the bilateral actions of the VLPFC contribute more to inhibition of attention and thoughts (Garavan et al. 1999; Chambers et al. 2009; Arnsten and Rubia 2012). Inhibition of emotions appears to rely more on the bilateral activation of the ventromedial PFC (VMPFC), which has extensive connections with the amygdala, hypothalamus, nucleus accumbens, and brainstem nuclei (Chambers et al. 2009; Arnsten and Rubia 2012). Both the VMPFC and VLPFC are considered to initiate top-down control of inhibition but other structures downstream are also crucial to inhibitory control, namely the basal ganglia and supplementary

motor areas (Chambers et al. 2009). While focal lesions in any of these structures may cause specific impairments of inhibition, white matter lesions in any of the circuits that connect these structures will also impair inhibitory control (Arnsten and Rubia 2012).

Working memory

Another core domain of executive function is working memory, defined as the function of holding and manipulating information that is not perceptually present (mental representations) (Diamond 2013). Working memory is often further distinguished by verbal and nonverbal (visual–spatial) content and is utilized in all instances of mental math, mental reorganization or revision of information, and relating different pieces of information such as verbal translation; working memory is essential for reasoning. Working memory may often be miscategorized as a type of short-term memory rather than a subdomain of executive function, but working memory is more closely linked to executive function in terms of neuroanatomy, childhood development, and function (Diamond 2013).

There is considerable controversy over whether working memory is a dissociable cognitive domain. Of course, working memory and short-term memory are highly inter-related. This is demonstrated by short-term memory tasks that require a longer (suprathreshold) number of information items, wherein working memory is automatically engaged to organize the information. The key distinction between working memory and short-term memory is that the former involves manipulations of information in addition to the mental holding of that information. Holding information activates the VLPFC during tasks that require either working memory or short-term memory, while working memory-dependent tasks involving the manipulation of information are also associated with activation of the dorsolateral PFC (DLPFC) (Diamond 2013). Similarly, working memory and inhibitory control are often functionally interdependent and show high neural co-activation (Diamond 2013). Working memory directs inhibitory control, while inhibitory control regulates the information that can occupy working memory. This has led many to view inhibitory control as derivative; like a spotlight, the function of working memory to enhance specific goals or thoughts may inherently repress unwanted goals or thoughts, that is, inhibitory control. Others still maintain that working memory and inhibitory control are dissociable domains, and that mental suppression requires more than just a relative lack of mental enhancement. While this debate continues (Diamond 2013), most will agree that all subdomains of executive function are highly interdependent.

Cognitive flexibility

Cognitive flexibility, often referred to as behavioral flexibility in the context of animal studies, builds on both inhibitory control and working memory. Cognitive flexibility describes the ability to change perspectives or goals, which involves the inhibition of current thoughts or goal-directed behaviors and the engagement of new ones (Diamond 2013). Representative tasks that require cognitive flexibility include design fluency, verbal fluency, and category fluency, wherein a subject is asked to, respectively, think of different uses of a table, different words that begin with a certain letter, or alternate sequentially between letters and numbers (Diamond 2013). Accordingly, cognitive flexibility is considered to be crucial for creativity. Lesions of the dorsomedial PFC (DMPFC) produce the most consistent impairments of different types of fluency (Robinson et al. 2012; Chapados and Petrides 2013).

Another common task that requires cognitive flexibility is task switching. A relatively simple form of task switching is known as reversal, such as when a rewarding option is changed from a left switch to a right switch. Lesions of the orbitofrontal cortex (OFC), located between the VMPFC and VLPFC (Carlén 2017), result in reversal impairments (Dalley et al. 2004; Bizon et al. 2012). A more complex form of task switching is known as set shifting, which requires a subject to redirect their attention between different sets of cues; this is exemplified by the Wisconsin Card Sorting Task, wherein subjects need to shift between sorting rules that depend on shape, color, or number (Robinson et al. 1980). In contrast to reversal, set shifting is impaired by lesions of the DLPFC (Dalley et al. 2004; Bizon et al. 2012).

Both reversal and set-shifting tests have also been adapted for rodent studies, wherein maze-based or operant-based challenges require rodents to reverse behavior or shift behavior according to attentional sets (Bizon et al. 2012). Although the functional divisions of the PFC do not arrange in the same neuroanatomical topography in rodents, reversal and set-shifting impairments are similarly doubly dissociated in rats (Floresco et al. 2009). Additional pathways between the PFC,

thalamus, and striatum that also contribute to set-shifting behavior are also conserved across species (Floresco et al. 2009), further supporting the interpretation that behavioral flexibility in rats is still very informative for the study of cognitive flexibility in humans (Bizon et al. 2012; Carlén 2017).

Alzheimer disease

The high co-occurrence of cerebrovascular disease and AD (Toledo et al. 2013; Arvanitakis et al. 2016; Smith 2017) has prompted research on whether the two diseases may have synergistic neuropathological and cognitive effects (Iadecola 2004; Zlokovic 2005, 2011; Kisler et al. 2017; Sweeney et al. 2019). The Nun Study found that AD pathology was far more likely to correlate with dementia if cortical infarcts or lacunar strokes were also present (Snowdon et al. 1997). This finding has been replicated, with a recent meta-analysis of 2856 cases from 10 studies finding that compared to patients with post-mortem evidence of AD, patients with both AD neuropathology and cerebrovascular disease were three times more likely to have had clinical dementia (Azarpazhooh et al. 2018). In a large postmortem study from the National Alzheimer's Coordinating Centre, 80% of patients diagnosed with AD were also found to have cerebrovascular pathology, significantly greater than the 67% of subjects that had cerebrovascular pathology but no cognitive impairment (Toledo et al. 2013). Furthermore, a recent large cross-sectional study with participants of the Religious Orders Study and the Rush Memory and Aging Project found the odds of a clinical diagnosis of AD to be increased in participants that had cerebral atherosclerosis or cerebral arteriosclerosis, confirmed postmortem (Arvanitakis et al. 2016). Thus, the prevention and treatment of cerebrovascular disease is likely to play an important role in reducing the burden of AD dementia in addition to VCI (Hachinski and Sposato 2013; Pase et al. 2017; Azarpazhooh et al. 2018).

Role of glia in Alzheimer disease

Both neuritic plaques and neurofibrillary tangles (NFT) are associated with astrocytosis and microgliosis (Serrano-Pozo et al. 2011b). Whereas the cerebral burden of amyloid β peptide (Aβ) plateaus early after symptom onset (Serrano-Pozo et al. 2011b; Jack et al. 2013), astrocytosis and microgliosis continue to increase linearly as the disease progresses (Serrano-Pozo et al. 2011b). Moreover, astrocytosis and microgliosis are correlated with NFT burden and loss of cortical thickness (Serrano-Pozo et al. 2011b), raising the question of whether these glial responses are merely reacting to the AD pathology or playing a central role in the disease mechanism (Heppner et al. 2015). As glial cells are fundamental to the maintenance of CNS homeostasis, including inflammatory processes, glial cells present a favorable therapeutic target for modifying the course of AD (Di Benedetto and Rupprecht 2013; Prokop et al. 2013; Ahmed et al. 2017).

Neuroinflammation in AD is thought be driven primarily by microglia, the brain's resident myeloid cells, which are involved in both cytokine secretion and phagocytosis (Prokop et al. 2013; Heppner et al. 2015). This is distinct from the conditions that are traditionally defined as neuroinflammatory diseases, namely multiple sclerosis and the different forms of encephalitis, which are driven by peripheral leukocytes that migrate into the CNS from systemic circulation (Heppner et al. 2015). The adaptive immune response, mediated primarily by T and B lymphocytes, has not been implicated in AD neuroinflammation, so the mechanisms seen in most autoimmune conditions are unlikely to be observed in AD. Furthermore, astrocytes are also directly involved with AD neuroinflammation (Von Bernhardi and Eugenín 2004; Heppner et al. 2015). Unlike in multiple sclerosis, traumatic injury, or ischemic stroke, astrocytes in AD do not typically form glial scars even though they upregulate the expression of glial fibrillary acidic protein (Heppner et al. 2015). Instead, reactive astrocytes appear to modulate microglial function and play an important role in Aβ degradation (Von Bernhardi and Eugenín 2004; Pascual et al. 2012; Heppner et al. 2015). This is further complicated by the observation of senescent or dystrophic microglia and astrocytes associated with prolonged exposures of high Aβ concentrations, which may indicate a crucial decompensation in the course of AD (Thal 2012; Streit et al. 2014; Heppner et al. 2015). It remains to be determined which specific processes in AD neuroinflammation are protective and which are detrimental (Prokop et al. 2013; Heppner et al. 2015).

Both preclinical and clinical studies suggest a critical role of glial-mediated inflammation in AD. Cognitive and neuropathological profiles of transgenic mouse models of AD have been improved by a breadth of molecules with anti-inflammatory properties:

rapamycin, minocycline, pioglitazone, thalidomide, etanercept, and celastrol, all of which modulate tumor necrosis factor-α (TNF-α) signaling and the activation of proinflammatory microglia and astrocytes (Corbett et al. 2015; Calsolaro and Edison 2016; Decourt et al. 2016). TNF-α is a proinflammatory cytokine that plays a pivotal role in inflammation throughout the body, and its expression is increased by both neurons and glial cells during both acute and chronic brain injury (Decourt et al. 2016). Aβ activates several TNF-α-dependent pathways, including cyclooxygenase (COX)-mediated inflammatory processes (Medeiros et al. 2010). Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce these inflammatory processes by inhibiting COX in neurons, microglia, and astrocytes (Krause and Müller 2010; Zhang et al. 2018), and NSAIDs may also offer neuroprotection by COX-independent pathways such as the direct promotion of nonamyloidogenic processing of amyloid precursor protein (Kukar and Golde 2008; Zhang et al. 2018; Sanz-Blasco et al. 2018). Cohort studies have shown promise in reducing the risk of AD, with the most recent meta-analysis of 236,000 participants from 16 cohort studies citing a 19% relative risk reduction of AD diagnosis (Zhang et al. 2018). This supports the potential of anti-inflammatory drugs as a disease-modifying therapy, but the optimal NSAID type and dose and the duration and timing of treatment have yet to be identified. Skepticism over this direction of research is raised by several studies that showed an increased incidence of AD among NSAID cohorts (Zhang et al. 2018). The only randomized-controlled trial of NSAID intervention did find reduced AD incidence if treatment was initiated in asymptomatic individuals, but increased incidence if treatment was initiated in patients with cognitive impairment or dementia (Breitner et al. 2011), suggesting that the timing of NSAID intervention with regard to disease stage is a crucial factor. This consideration is likely to extend to other anti-inflammatory drug trials, such as the anti-TNF-α biologic, etanercept, which showed favorable but nonsignificant trends in phase-II trial of patients with mild to moderate AD (Butchart et al. 2015).

In AD, glial cell density increases throughout gray matter tissue, but also in white matter (Andrade-Moraes et al. 2013). Oligodendrocytes provide important tropic supports to neurons, but Aβ is toxic to oligodendrocytes in vitro (Roth et al. 2005; Sachdev et al. 2013). Histological changes of white matter are commonly observed in AD; while oligodendrocyte density is decreased, postmortem evaluation has found astrocyte and microglia numbers to be increased in the white matter of patients with AD dementia (Tomimoto et al. 1996; Sjöbeck and Englund 2003). Positron emission tomography studies have also identified increased white matter inflammation in AD patients (Raj et al. 2017; Jeong et al. 2017).

White matter changes in Alzheimer disease

Much of AD continues to be defined by pathological changes in gray matter, but white matter degeneration is also observed in AD, both on imaging and in histological samples (Bronge et al. 2002; Zhang et al. 2007; Agosta et al. 2011; Migliaccio et al. 2012; Lin et al. 2014). In AD, white matter degeneration can range from demyelination to gross atrophy (Agosta et al. 2011; Maier-Hein et al. 2015; Lee et al. 2016). The specific patterns of white matter atrophy may also be crucial to differentiating potentially distinct forms of AD (Migliaccio et al. 2012). Whereas late onset AD more typically featured white matter atrophy in the medial temporal regions, early onset AD features greater cingulate atrophy (Migliaccio et al. 2012). Atypical variants of AD include the logopenic variant of primary progressive aphasia (lv-PPA), which features more left parietal white matter atrophy, and posterior cortical atrophy (PCA), which features more occipital white matter atrophy. Compared to late onset AD, more white matter atrophy in the lateral temporal cortex, parietal cortex, cingulum, and corpus callosum were observed in early onset AD, lv-PPA, and PCA (Migliaccio et al. 2012). Thus, specific patterns of white matter atrophy may aid in characterizing specific forms of AD.

This has prompted the possibility that white matter disease may be a core feature of AD (Sachdev et al. 2013). Whether white matter atrophy is due to local degenerative changes or secondary to remote neuronal injury, i.e., due to Wallerian or anterograde, degeneration has not been determined (Agosta et al. 2011). Currently, there is more evidence in favor of white matter atrophy as a secondary process, as gray matter and white matter volume loss are usually correlated (Agosta et al. 2011). However, primary local damage and retrograde damage in the context of AD cannot be ruled out (Agosta et al. 2011). Oligodendrocytes may be sensitive to the increased concentrations of Aβ seen in the brains of patients with AD, and loss of oligodendrocytes due to increased concentrations of Aβ could contribute to white matter demyelination and consequent degeneration

(Roth et al. 2005; Sachdev et al. 2013). Moreover, the specific patterns of diffusion tensor changes seen in AD are not suggestive of Wallerian degeneration (Pierpaoli et al. 2001; Song et al. 2002; Agosta et al. 2011). While gray matter and white matter volume loss may be correlated in AD, white matter damage seen in MCI showed no relationship with gray matter atrophy (Agosta et al. 2011; Maier-Hein et al. 2015). This suggests that especially in the early stages of disease, white matter may undergo atrophy due to local injury and retrograde degeneration as well as secondary degeneration due to gray matter injury and anterograde degeneration (Agosta et al. 2011). The growing evidence of glial dysregulation as a common feature of AD also suggests potential inflammatory mechanisms by which white matter could be damaged directly (Goldberg and Ransom 2003; Sachdev et al. 2013; Raj et al. 2017), independent of gray matter senile plaques and NFT (Serrano-Pozo et al. 2011a).

Any observed primary local damage could also be attributed to vascular injury, as white matter is particularly sensitive to vascular disruption (Mandell et al. 2008; Wang et al. 2016; Li et al. 2016) and cerebrovascular disease is highly comorbid with AD (Toledo et al. 2013; Smith 2017). However, there is a considerable overlap in the findings that are conventionally attributed to purely AD and purely vascular neuropathologies (Groves et al. 2000; de la Torre 2004; Girouard and Iadecola 2005; Kalaria and Ballard 2006; Rodrigue 2013), with many proposing that vascular disruption may be central to AD as well (Moody et al. 1997; de la Torre 2002, 2004; Kalaria et al. 2012; Cai et al. 2015; Brickman et al. 2015). The intersection of AD and VCI may be most apparent in leukoaraiosis (Clarke et al. 2000; Pettersen et al. 2008; Kalaria et al. 2012; Cai et al. 2015; Brickman et al. 2015; Lee et al. 2016). Leukoaraiosis is associated with disruptions of white matter integrity (O'Sullivan et al. 2004; Altamura et al. 2016) and vascular pathology (Pantoni and Garcia 1997; Wardlaw et al. 2003; Basile et al. 2006; Mandell et al. 2008; Conklin et al. 2014; Bernbaum et al. 2015; Shi and Wardlaw 2016; Huang et al. 2018), but leukoaraiosis is also an important risk factor for AD (O'Sullivan et al. 2004; Brickman 2013; Altamura et al. 2016) and leukoaraiosis volume has also been correlated directly with the severity of cognitive and functional impairment in AD (Ble et al. 2006; Stout et al. 1996; Diaz et al. 1991). Recently, CSF concentrations of Aβ were found to correlate with leukoaraiosis volume (Van Westen et al. 2016; Pietroboni et al. 2018). In the Dominantly Inherited Alzheimer Network (DIAN) study, which follows a cohort of carriers of genetic mutations known to cause early onset AD (PSEN1/2, APP), leukoaraiosis volume began to increase significantly 6 years prior to estimated symptom onset (Lee et al. 2016). Specifically in the parietal and occipital lobe, leukoaraiosis was significantly increased as early as 22 years prior to estimated symptom onset. This offers strong support for leukoaraiosis as a core feature of AD and a potential biomarker (Lee et al. 2016). However, the pathological basis of leukoaraiosis has yet to be identified. While many studies suggest a vascular etiology for leukoaraiosis (Wardlaw et al. 2015), dysregulation of astrocytes in the BBB (Huang et al. 2018) and genetic variation related to inflammation have also been implicated (Raz et al. 2012). Though dysregulation of astrocytes and aberrant inflammation can certainly be initiated by vascular pathology, AD-related proteinopathies may also drive the dysregulation of glial cells and neuroinflammation, as discussed above. While leukoaraiosis may already be an informative predictor for dementia, further research is needed to characterize the etiology of leukoaraiosis in the context of AD.

The neurovascular hypothesis of Alzheimer disease

In recognition of the high comorbidity between AD and VCI, the *neurovascular hypothesis of AD* proposes that the interaction of amyloid pathology and cerebrovascular disease is a core mechanism that leads to neuronal injury and cognitive impairment (Zlokovic 2005). The neurovascular hypothesis directs focus to the NVU, which is composed of neurons, astrocytes, endothelial cells, myocytes, pericytes, crucial extracellular components, and resident immune cells (Muoio et al. 2014). A crucial component of the NVU is the BBB, which segregates the interstitial microenvironment of the CNS and regulates the clearance of neurotoxic molecules such as Aβ. The NVU also regulates the coupling of blood flow and local metabolic demands, known as hyperemia or neurovascular coupling (Girouard and Iadecola 2005; Tarantini et al. 2017). Thus, the NVU is crucial to protecting the brain from both AD pathology and cerebrovascular disease. At the same time, the NVU can be directly disrupted by both of these diseases as well as systemic vascular conditions (Iadecola 2004; Girouard and Iadecola 2005; Zlokovic 2011; Deane et al. 2012; Halliday et al. 2016; Zenaro et al. 2017). Experimental studies have generated evidence in

support of the neurovascular hypothesis, identifying potential therapeutic targets that may prevent important neurodegenerative disease mechanisms (Iadecola 2004; Girouard and Iadecola 2005; Zlokovic 2011; Deane et al. 2012; Carnevale et al. 2012; Williams et al. 2012; Jin et al. 2015; Halliday et al. 2016; Zenaro et al. 2017).

The NVU and blood–brain barrier

Autoregulation of large vessels maintains near-constant blood flow to a large vascular territory, accomplished by intravascular regulation of the luminal diameter to compensate for fluctuations in systemic blood pressure. In contrast, coupling occurs at the microscopic level of the vascular bed, accomplished through a complex coordination between NVU cells responding to fluctuations in the metabolic demands of the local parenchyma (Muoio et al. 2014). Myocytes are the smooth muscle cells that make autoregulation of arteries and arterioles possible, and myocytes communicate with downstream pericytes via gap junctions (Borysova et al. 2013). Pericytes are also contractile cells that regulate blood flow at the level of capillary beds and individual capillaries, and pericytes have been found to communicate with both endothelial cells and astrocytes (Muoio et al. 2014). Astrocytes are considered to be the key detector of abluminal metabolic demands, receiving glutamatergic signals from neurons and interneurons (Muoio et al. 2014). To relay these signals and affect local blood flow, astrocyte endfeet release vasoactive substances such as eicosanoids which directly stimulate or inhibit the contraction of pericytes (MacVicar and Newman 2015). Additionally, astrocyte endfeet release potassium ions into blood vessels and onto myocytes, inducing vasodilation (MacVicar and Newman 2015). Endothelial cells also modulate vascular tone and relay signals of vascular tone to astrocytes (Muoio et al. 2014). Importantly, cells of the NVU are mutually dependent on crucial extracellular trophic factors during both development, maintenance, and ultrastructural remodeling (Muoio et al. 2014). The NVU directs the formation, maintenance, and remodeling of the BBB, which regulates the passive and active diffusion of molecules and ions both into and out of the brain parenchyma. The physical barrier of the BBB is formed in part by the complex basement membrane that is maintained by both endothelial cells and astrocytes (Zenaro et al. 2017). More recently, the primary inflammatory cells of the brain, microglia, have also been found to respond to ischemia and contribute to BBB and vascular remodeling by cytokine signaling. Dysregulation of any of the NVU cells or microglia can contribute to a dysfunctional BBB.

NVU dysfunction

The NVU maintains neurovascular coupling and the microenvironment of the CNS, promoting healthy CNS function. However, vascular conditions can lead to dysregulation of the NVU, disrupting CNS homeostasis. Hypertension, ischemic stroke, and covert or "silent" brain infarcts (SBI) are among the most prevalent vascular etiologies that can cause NVU dysfunction. The NVU is essentially the site at which small vessel disease occurs; arteriolosclerosis, lipohyalinosis, microbleeds, and microhemorrhages indicate profound disruption of the NVU (Rosenberg 2017). Due to the diffuse nature of small vessel disease, NVU dysregulation is likely to exist well beyond the immediate temporal or anatomical proximity of detectable cerebrovascular lesions, such as SBI. Impaired coupling results in oligemia, hypoxia, and mitochondrial-mediated oxidative stress (Zlokovic 2011), with further injury propagated by dysregulated inflammation (Barakat and Redzic 2016; Zenaro et al. 2017; Thurgur and Pinteaux 2018). Meanwhile, a "leaky" BBB can result in extravasation of circulating molecules and proteins that have toxic and proinflammatory effects in the brain (Zlokovic 2011; Rosenberg 2017). BBB dysfunction has even been shown to be an independent biomarker of cognitive dysfunction (Nation et al. 2019). Interestingly, peripheral sources of circulating Aβ can enter the CNS, induce Aβ-related pathology, and disrupt neuronal function (Zlokovic 2011; Deane et al. 2012; Bu et al. 2018); this can be prevented by molecular interventions that target specific molecules in the NVU (Deane et al. 2012). Thus, NVU dysfunction can exacerbate or result in AD pathology. In turn, abluminal pathology such as AD can also propagate dysregulation of the NVU and BBB, creating a self-propagating pathological cycle.

Hypertension and the NVU

Hypertension is a highly prevalent condition, affecting 31.1% of the global adult population, of which fewer than a third achieve blood pressure control (Mills et al. 2016). Hypertension is also recognized as a leading vascular risk factor for stroke and dementia (Tzourio

2007; Kennelly et al. 2009), including AD (Oveisgharan and Hachinski 2010; Iadecola 2014; Livingston et al. 2017). Experimental animal models of comorbid hypertension have been shown to exacerbate AD-related pathology (Díaz-Ruiz et al. 2009; Gentile et al. 2009; Carnevale et al. 2012, 2016; Csiszar et al. 2013; Cifuentes et al. 2015). However, while the connection between hypertension and cerebrovascular disease is well established (Tzourio 2007; Kennelly et al. 2009), it remains inconclusive whether antihypertensive therapy reduces AD incidence (Lithell et al. 2004; Peters et al. 2008; McGuinness et al. 2009; Perrotta et al. 2016). The recent SPRINT-MIND study demonstrated a reduced incidence of cognitive impairment in subjects with intensive blood pressure control (Williamson et al. 2019), supporting the role of blood pressure management in cognitive protection. In addition to dysregulating cerebrovascular autoregulation, hypertension can also disrupt neurovascular coupling (Girouard and Iadecola 2005). This was observed in an experimental hypertensive rodent model that had an attenuated blood low response to whisker stimulation (Kazama et al. 2003), which was further exacerbated by neocortical application of Aβ or by transgenic expression of pathogenic amyloid precursor protein (Faraco et al. 2016a). Similarly, in a clinical cohort study using positron emission tomography, hypertensive subjects demonstrated a reduced hemodynamic change during a memory task (Jennings et al. 2005). Moreover, hypertension has been shown to cause BBB leakiness and the proinflammatory activation of microglia and astrocytes (Setiadi et al. 2018). Perivascular macrophages, resident immune cells that are distinct from microglia, have also been found in mice to release reactive oxygen species in response to hypertension, resulting in neurovascular and cognitive dysfunction (Faraco et al. 2016b). These are some of the mechanisms by which hypertension can disrupt the NVU and CNS function, even in the absence of detectable cerebrovascular disease (Girouard and Iadecola 2005).

Ischemic stroke, silent brain infarcts, and the NVU

The lifetime risk of ischemic stroke in the Framingham study was found to be 18% for women and 15% for men at 55 years of age (Seshadri et al. 2006). Disturbingly, SBI are also found in 10–20% of the general elderly population, increasing with age and hypertension (Vermeer et al. 2007; Fanning et al. 2014) to as high as 62% in select elderly populations with other significant morbidity (Nakagawa et al. 2000). SBI most often affect the subcortical white matter, basal ganglia, thalamus, and the infratentorial region (Vilar-Bergua et al. 2016). While the chronic impact of SBI on proximal intact NVUs is difficult to investigate, it is likely to demonstrate similar processes seen in ischemic strokes and small vessel disease. Following ischemic stroke, autoregulation and coupling are impaired even in brain regions that appear uninjured (Girouard and Iadecola 2005). Similarly, in a transient middle cerebral artery occlusion model, BBB disruption can be observed 30 days after injury, even in the contralateral hemisphere (Garbuzova-Davis et al. 2014). When striatal lacunar infarcts were modeled in a transgenic mouse model of AD, increased APP, tau, and inflammatory microglia were observed in the cortex and hippocampus (Whitehead et al. 2010). In this same study, anti-inflammatory treatment reduced the area and density of amyloid precursor protein near the injury site. Thus, inflammation may play an important role in propagating AD-related pathology following NVU injury by ischemic stroke and SBI.

Abluminal injury: Alzheimer disease pathology and the NVU

Aβ is generally cleared from the brain by enzymatic degradation or by active clearance across the BBB, mediated by the low-density lipoprotein receptor-related protein (LRP) pathway. Endothelial cell LRP1 binds and initiates clearance of abluminal unbound Aβ as well as ApoE-bound Aβ; interestingly, ApoE ε4 inhibits this active transport of Aβ out of the brain (Zlokovic 2011). By impairing the clearance of Aβ, reduced expression of LRP1 in blood vessels has been associated with AD in both preclinical and clinical studies (Zlokovic 2011). However, Aβ can impair its own clearance by oxidizing LRP1, which was observed in the hippocampal tissue of AD patients (Owen et al. 2010). As Aβ is toxic to virtually all cell types in the NVU, increased concentrations of Aβ, as seen in AD, can directly disrupt the NVU (Veszelka et al. 2013; Erickson and Banks 2013). Additionally, dysregulated inflammation induced by AD pathology can further disrupt the NVU, while failure of perivascular macrophages to clear Aβ can contribute to its accumulation in the brain (Hawkes et al. 2009; Erickson and Banks 2013; Faraco et al. 2016b). Thus, the disruption of the

NVU may be either a cause of AD, a consequence of AD, or both. In any case, there is a strong indication that the NVU has a central role in neurodegenerative disease.

White matter pathology and the neurovascular hypothesis

The neurovascular hypothesis offers a potential understanding of AD that is non-neuron-centric (Zlokovic 2005), as it draws attention to the important role of non-neuronal cells in the NVU. Similarly, the often-overlooked factor of white matter disease may also play an important role in the neurovascular hypothesis; disruption of NVUs in periventricular white matter, which is particularly vulnerable to cerebrovascular pathology (Markus et al. 2000; Raz et al. 2003; Vicario et al. 2005; Mandell et al. 2008; Black et al. 2009; Wang et al. 2016; Li et al. 2016), may contribute to the accumulation of cerebral Aβ and, in turn, AD. Both in pre-clinical and clinical studies, AD pathology is associated with impaired coupling (Tarantini et al. 2017; Kisler et al. 2017). Dramatic pericyte loss is observed in the white matter of patients that had AD, which is also accompanied with demyelination (Montagne et al. 2018). This was further investigated in transgenic mice lacking cerebral pericytes, which developed white matter dysfunction, white matter atrophy, hippocampal and cortical atrophy, and cognitive impairments (Montagne et al. 2018). Furthermore, a transgenic mouse model of AD treated with simvastatin, a cholesterol-lowering drug, showed improved coupling and cognition (Tong et al. 2012).

The role of proinflammatory astrocytes and microglia in NVU injury, white matter integrity, and cognitive impairment is also strongly supported; recent experimental animal studies showed that targeted modulation of astrocyte- and microglia-mediated inflammation protected white matter ultrastructure, white matter function, and cognition following chronic hypertension (Lan et al. 2015) and hypoperfusion bilateral common carotid artery stenosis (Table 1). In elderly individuals with hypertension and/or diabetes mellitus type 2, neurovascular coupling was measured by changes in blood flow velocity in the middle cerebral artery during a series of cognitive evaluations. More responsive coupling was correlated with better scores on cognitive flexibility tasks and higher white matter FA, an indicator of white matter integrity (Sorond et al. 2013). In the same study, consumption of cocoa flavanol for 30 days improved coupling and behavioral flexibility scores, which was attributed to the beneficial effects of cocoa flavanols on systemic and cerebral vascular function (Sorond et al. 2013). Altogether, these studies strongly indicate that white matter inflammation and cerebrovascular disease play an important role in the pathogenesis of executive dysfunction and AD.

Conclusion

Although the NVU, white matter disease, and executive dysfunction have been relatively understudied in dementia, advances in cognitive testing and imaging technology have provided recent leaps in characterizing this triad, refining what may have been previously referred to as white matter dementia. The disease processes of the aging cerebral vasculature and brain parenchyma are synergistic at the NVU. In particular, NVU dysfunction is likely to underlie the vulnerability of white matter to cerebrovascular injury and, in turn, executive dysfunction. Thus, NVU dysfunction may be the fundamental disease process that accounts for the frequent comorbidity of VCI and AD. This is supported by studies of neurodegenerative pathology, the epidemiology of mixed dementia, and the neurovascular hypothesis of AD. This also highlights the manifold importance of characterizing NVU dysfunction and identifying associated therapeutic targets. Fortunately, the cells that form the NVU are relatively biologically accessible and are actively involved in maintaining brain homeostasis, further supporting the therapeutic potential of intervention at the NVU. Targeting the glial cells of the NVU promises to preserve white matter integrity and executive function, which are now clinically quantifiable and, above all, important for preserving the quality of life in older age and for patients diagnosed with dementia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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