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SPECIAL ISSUE TITLE: AGING AND CEREBROVASCULAR HEALTH: STRUCTURAL, FUNCTIONAL, COGNITIVE, AND METHODOLOGICAL IMPLICATIONS

Age-related changes in cerebrovascular health and their effects on neural function and cognition: A comprehensive review

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Abstract

The process of aging includes changes in cellular biology that affect local interactions between cells and their environments and eventually propagate to systemic levels. In the brain, where neurons critically depend on an efficient and dynamic supply of oxygen and glucose, age-related changes in the complex interaction between the brain parenchyma and the cerebrovasculature have effects on health and functioning that negatively impact cognition and play a role in pathology. Thus, cerebrovascular health is considered one of the main mechanisms by which a healthy lifestyle, such as habitual cardiorespiratory exercise and a healthful diet, could lead to improved cognitive outcomes with aging. This review aims at detailing how the physiology of the cerebral vascular system changes with age and how these changes lead to differential trajectories of cognitive maintenance or decline. This provides a framework for generating specific mechanistic hypotheses about the efficacy of proposed interventions and lifestyle covariates that contribute to enhanced cognitive well-being. Finally, we discuss the methodological implications of age-related changes in the cerebral vasculature for human cognitive neuroscience research and propose directions for future experiments aimed at investigating age-related changes in the relationship between physiology and cognitive mechanisms.

KEYWORDS

aging, cerebrovascular health, cerebrovascular reactivity, cognitive aging, dementia, neurovascular coupling

1 | INTRODUCTION

A healthy vascular system is a crucial component by which a healthy lifestyle leads to improved cognitive outcomes in aging. A substantial body of evidence documents the existence of associations between measures of vascular functioning and cognition. Within this literature, an intuitive narrative is typically provided, stating that the brain relies on adequate blood flow for proper functioning, and thus a healthy cerebrovasculature is important for cognition because it is responsible for that blood flow.

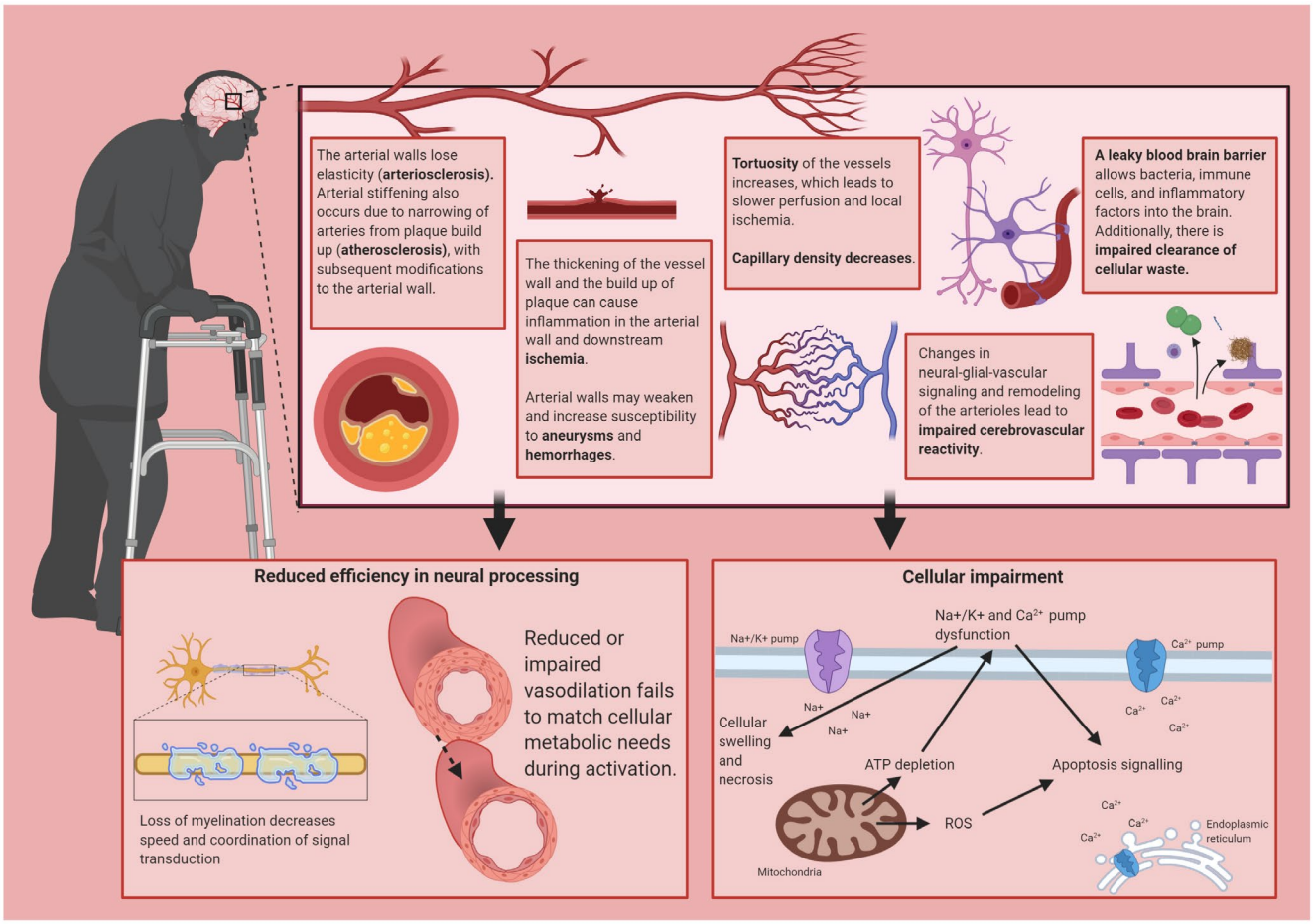

FIGURE 1 Cerebrovascular damage progresses from loss of elasticity in the larger arteries to distal downstream damage to the microvasculature. Impaired cerebrovascular function leads to reduced efficiency in neural processing through damaged myelination and impaired neurovascular coupling mechanisms. Eventually, cerebrovascular dysfunction leads to ischemia, causing cellular impairment or cell death. Together, these effects manifest as reductions in cognitive function

In this review, we attempt to move beyond this intuitive argument and discuss how the physiology of the cerebrovasculature changes with age and how these changes lead to differences in cognitive outcomes. Importantly, despite many overlapping mechanisms, distinct changes to vascular health follow diverging trajectories over the life span and respond differently to interventions. By discussing specific physiological mechanisms, we aim to provide a framework for generating hypotheses about the efficacy of proposed factors that contribute to enhanced well-being in aging. Furthermore, we highlight how age-related changes in physiology may affect common measurements of neural function, and particularly those that depend on vascular correlates of neural function for inferences regarding changes in brain function across the life span.

2 | HOW DOES THE CEREBROVASCULATURE AFFECT NEURAL FUNCTION?

Before discussing age-related changes to the cerebrovasculature, it is important to understand how physiological factors may influence cognition (Figure 1). Ideally, research could inform interventions on vascular physiology that would maximize the potential benefits for cognition. Importantly, optimal interventions may differ between different ages and starting health status. For example, in healthy young participants, an intervention may prioritize the prevention of future cell death, whereas in older, unhealthy adults, an intervention may prioritize increased brain plasticity. We begin our discussion by identifying the mechanisms by which vascular dysfunction leads to impaired cognition, which can be viewed as the end targets for cerebrovascular interventions.

2.1 | Impaired vasculature leads to cellular dysfunction

The main mechanism by which vascular impairments lead to cellular damage, and eventually cellular death, is through ischemia, a condition in which restricted blood flow limits oxygen delivery to tissue. However, different brain regions vary in their vulnerability to ischemia.

Impaired vasculature may also lead to exposure to inflammatory factors or toxicity, as well as disordered signaling at the neurovascular unit, a functional complex of neurons, cellular, and extracellular components that mediate local interactions with vasculature, all of which can impair cellular function. In addition to these factors, aging also results in cellular dysfunction through non-vascular mechanisms, which may exacerbate and interact with the damage caused by vascular dysfunction.

2.1.1 | Exhausted ATP in ischemia leads to cellular dysfunction and cell death

The human brain is particularly susceptible to ischemia-induced damage. First, when cells die in the adult brain, they are rarely replaced (Kumar et al., 2019), with long-lasting effects that accumulate over time. Second, ischemia wreaks havoc on the brain due to unique metabolic factors. The cellular components of the neurovascular unit dominate brain metabolic function. This unit operates within a narrow metabolic window, in that it has a relatively high metabolic demand but low metabolic reserve. High metabolic demands are needed mainly to operate energy-guzzling ion-pumps required for high-frequency firing rates and neural communication. At the same time, brain cells store much less glycogen than those in other bodily organs (Duran & Guinovart, 2015). Thus, with disruption of a continuous supply of oxygen and glucose, there is rapid exhaustion of the available adenosine triphosphate (ATP) in the cells (Fricker et al., 2018), leading to cellular dysfunction.

Extreme ischemia in the brain can elicit local spurts of depolarization and hyperpolarization that can propagate to neighboring regions in a wave-like manner called "spreading depolarization" or "spreading depression," exacerbating perturbations to homeostasis over progressively larger areas (Cozzolino et al., 2018; Xing et al., 2012). When there is a shortage of ATP, energy-intensive ion pumps are unable to maintain the polarization of neurons necessary for homeostasis (Hayashi & Abe, 2004; Xing et al., 2012). The resulting depolarization leads to the release of neurotransmitters (especially glutamate) and inhibits reuptake (Xing et al., 2012). Glutamate binds to membrane receptors that promote an influx of calcium, sodium, and water into the cell (Xing et al., 2012). Calcium has a wide range of signaling effects (Brini et al., 2014). Under normal circumstances, calcium is involved in synaptic signaling and neurotransmission, but excess calcium initiates apoptotic mechanisms and causes damage within the internal cellular environment (Brini et al., 2014; Fricker et al., 2018; Lipton, 1999; Xing et al., 2012). Calcium dysfunction is often implicated in cellular damage and death following ischemia (Fricker et al., 2018). However, neuronal cell death can also occur via different ischemia-mediated signaling cascades (see Fricker et al., 2018, for an excellent review on the mechanisms of neuronal cell death and ischemia). In addition, reperfusion of tissue often induces a surge in the generation of reactive oxygen species (ROS), which promotes the neutrophil activity that can further exacerbate injury (Kalogeris et al., 2012).

Most of these mechanisms are studied in events of profound acute ischemia, such as stroke or transient ischemic attacks (TIAs). However, many of these mechanisms may have different effects in chronic or subacute low levels of ischemia (Fricker et al., 2018). In fact, paradoxically, some of these mechanisms seem to be designed to prevent cell death in the long term (Fricker et al., 2018; Hwang et al., 2017). That said, metabolic instability between neurons and the astrocytes that mediate neural-vascular communication leads to chronic low-level hypoxia or brief acute hypoxic events. Such events are hypothesized to lead to an increased probability (or frequency) of cellular damage and dysfunction even in the absence of a full-fledged stroke (Li et al., 2019; Peers et al., 2007; Peers et al., 2009).

2.1.2 | Ischemic susceptibility

The whole brain is prone to ischemic damage but some regions are more prone than others. Among these are the so-called "watershed"[1] or border-zone areas—a term used to indicate regions wherein blood supply is more labile owing to their location along distal ends of non-anastomosing major arterial systems (Figure 2) (Momjian-Mayor & Baron, 2005). Watershed regions are classically described in two distinct categories: (a) cortical areas between the major arterial territories (the anterior [ACA], middle [MCA], and posterior cerebral arteries [PCA]) or (b) internally, in the periventricular white matter between the deep and superficial parts of the MCA or between the superficial parts of the MCA and ACA; Mangla et al., 2011; Momjian-Mayor & Baron, 2005). The vulnerability of these areas is thought to be related to ischemia due to episodes of low perfusion pressure, caused by accumulating damage to the upstream arteries (Torvik, 1984). Substantial individual variability exists in the territorial distribution of major arteries, leading to comparable variability in watershed areas (van der Zwan & Hillen, 1991).

In addition to the watershed phenomenon, several other characteristics make certain areas more susceptible to

[1]The term "watershed" comes originally from a German analogy of an irrigation system. "Die letzten wiesen" ("the last field") was translated to "watershed," with the disadvantage of incorrectly implying a description of drainage rather than perfusion (Bladin et al., 1993).

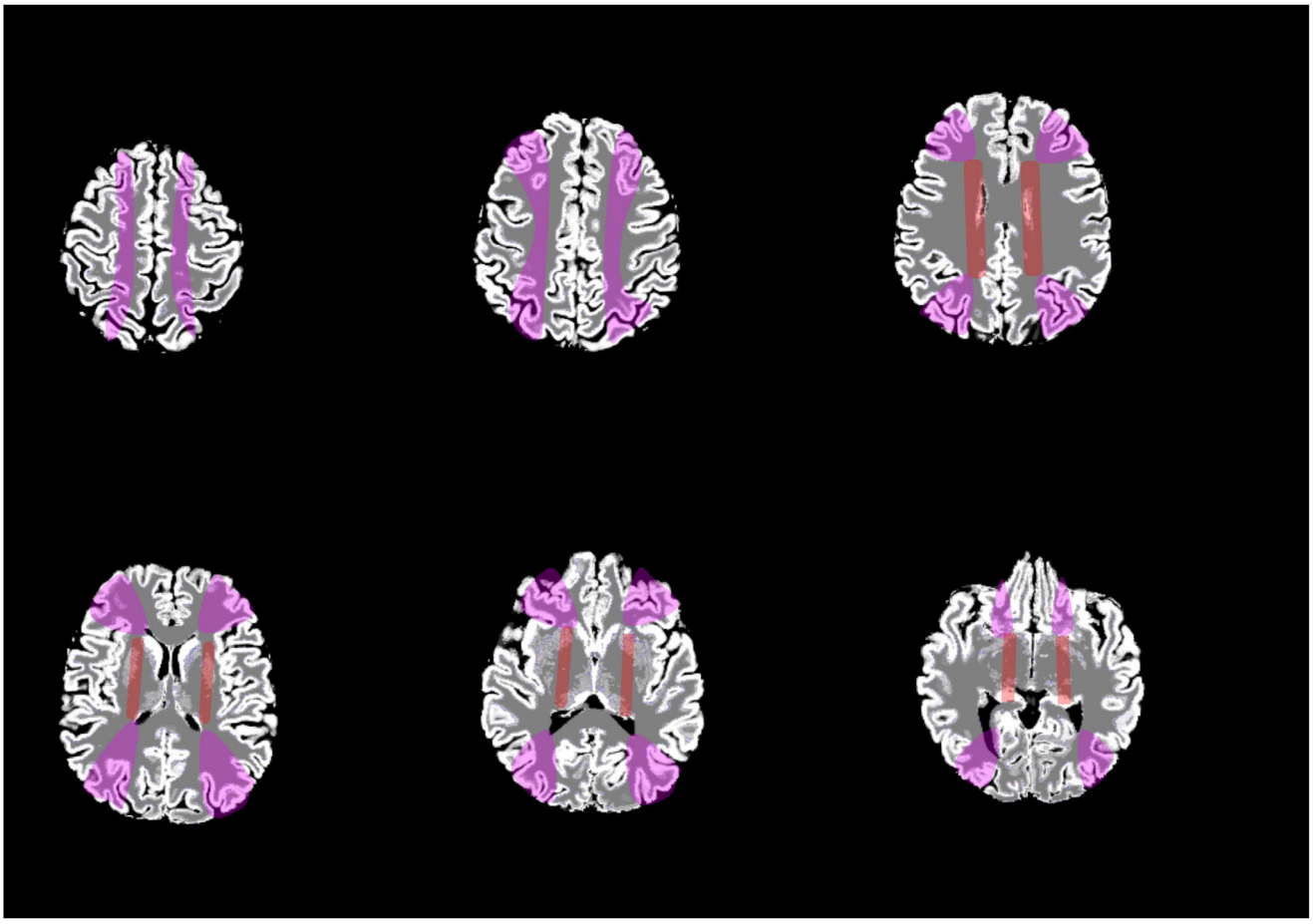

FIGURE 2 Watershed regions in the brain exist in areas between the ends of major feeding arterial systems. Classically, these regions are described in two categories. Regions on the cortex between the major arterial systems feeding the cortex (purple), or internal regions in the periventricular white matter (red) between the superficial and deep branches of the middle cerebral artery or the middle cerebral and anterior cerebral arteries. The cortical watershed regions (purple) usually encompass a thin fronto-parasagittal wedge from the anterior horn of the lateral ventricle to the frontal cortex, a parieto-temporo-occipital wedge from the occipital horn of the lateral ventricle to the parieto-occipital cortex, or a strip on the superior cortex. The internal watershed areas are usually found in white matter, corona radiata, or the centrum semiovale

vascular damage than others. For example, susceptibility varies depending on (a) proximity to the root of feeding arteries; (b) intrinsic differences in tissue characteristics, with white matter being more vulnerable to ischemia than gray matter, and oligodendroglial injury preceding neuronal injury (Pantoni et al., 1996); and (c) location in the caudal-to-rostral axis. That is, there is a broad caudal-to-rostral (inferior-to-superior in humans) increase in susceptibility to neuronal injury during ischemia (Brisson et al., 2013; Centonze et al., 2001; Wytrzes et al., 1989; Young, 2009). This gradient has been elaborated within the gray matter, with neurons in the neocortex, hippocampus, striatum, and thalamus more vulnerable than neurons in the hypothalamus, cerebellum, or brainstem (Brisson et al., 2013). Even within the rostral portion, there is heterogeneity, with CA1 in the hippocampus, caudate, putamen, insula, precentral gyrus, inferior frontal gyrus, and middle frontal gyrus appearing to be the most susceptible (Payabvash et al., 2011). There is also striking regional variation, with distinct boundaries, in anoxic depolarization and its spreading depression in hypoxia (Brisson et al., 2013, 2014; Spong et al., 2016).

The mechanisms that determine these regional differences in ischemic susceptibility are not yet well understood. However, in CA1 one mechanism underlying vulnerability to ischemia has been established. CA1 cells have remarkable Ca^{2+} mobilization potential, which increases calpain activation in response to ischemia and thus increases calpain-mediated lysosomal rupture (Liang et al., 2016). Finally, it is worth noting that regional differences in metabolic demand are sometimes presented as an explanatory factor for ischemic susceptibility (Luigetti et al., 2012; Payabvash et al., 2011). This explanation, however, does not satisfactorily account for the specific regional differences within rostral brain regions because the regions with the highest resting metabolic rates (Horwitz et al., 1984) do not overlap with those displaying the highest vulnerability.

Critical future work will need to explore the replicability and exact mechanisms behind specific differences in ischemic vulnerability.

2.1.3 | Exposure to inflammatory or toxic factors

Inflammation or damage to the vasculature can expose brain parenchyma to molecules that have signaling (or other) effects that impair cellular function. Sustained inflammation contributes to the pathology of many nervous system diseases, including those common in aging (Calcia et al., 2016; Freeman & Ting, 2016; Iadecola & Anrather, 2011; Martini & Willison, 2016; McGeer & McGeer, 2013; Najjar et al., 2013; Ransohoff, 2016; Skaper et al., 2018). Inflammatory mechanisms are extremely important for protecting against microbes (Klein et al., 2017). However, chronic or disproportionate inflammatory responses cause collateral damage to otherwise healthy tissue, such as through the production of ROS (Rock & Kono, 2008).

Microglia have a principal role in the propagation and consequences of inflammatory signaling in the brain. These cells are classified as pro-inflammatory ("M1 microglia") or neuroprotective ("M2 microglia") (Tang & Le, 2016). Chronic systemic inflammation can lead to non-resolving neuroinflammation, with activated microglia releasing inflammatory cytokines, mediating synaptic loss, and phagocytic cells (Hong et al., 2016; Skaper et al., 2018). Mast brain cells amplify neuroinflammation through chemical interactions with activated glia (Skaper et al., 2018).

Damage to the blood–brain barrier (BBB), a term used to describe properties of the cerebrovasculature that allow for tight regulation of molecule transport in and out of the brain, introduces even more damaging inflammatory cells and toxins that are normally excluded from the neuronal environment. These circulating immune cells infiltrate the brain parenchyma and produce additional ROS and inflammatory cytokines (Wang et al., 2007), which may create a vicious cycle of BBB lesions creating inflammation, which in turn create further damage to the BBB. An associated cause of damage to the parenchyma resulting from impaired cerebral vasculature can come from the increased presence of toxins, either through their reduced clearance or by allowing toxic agents to enter the brain through a weakened BBB (Zhao et al., 2015). Although research on age-related BBB dysfunction is usually focused on the increased exposure of the brain parenchyma to inflammation and toxicity, it is also likely that BBB dysfunction would increase exposure to pathogens, since microbial invasion of the central nervous system (CNS) typically involves some induction of BBB dysfunction (Kim, 2008; Shoemark & Allen, 2015). Even in the absence of full CNS infections, increased microbial load would also increase inflammatory collateral damage as immune cells fight the infection. It should be noted that chronic hypertension, because of associated vasoconstriction, may also lead to impaired blood flow in some watershed areas, which may in turn create local inflammation, endothelial lesions, and damage to the BBB, triggering the vicious circle described above (Jennings et al., 2021).

2.1.4 | Disordered signaling at the neurovascular unit

Ischemic and inflammatory processes can disrupt the neurovascular unit responsible for the homeostatic signaling mechanisms promoting normal brain function. Disordered signaling between endothelial cells, support glia, and neurons leads to impaired neuronal function, even in the absence of explicit exposure to inflammatory factors or external toxins (Guo & Lo, 2009). Astrocytes play a central role in the homeostasis of glutamate concentrations (Guo & Lo, 2009). The dysfunction of this homeostatic mechanism is hypothesized to contribute to augmented excitotoxicity, which plays a role in both vascular and non-vascular pathologies (Guo & Lo, 2009).

2.2 | Impaired vasculature leads to reduced efficiency in neural processing

Beyond direct neuronal damage caused by failing vascular mechanisms, there are also impairments to neural processing driven by dysfunction of mechanisms that support the coordination of neurons at the circuit-level. These vascular impairments can be broadly categorized as reductions in (a) the finely controlled cerebrovascular reactivity that supports the dynamic metabolic needs of brain parenchyma, resulting in loss of neural efficiency; and (b) the insulating effects of myelin, which support fast and well-timed axonal signal transduction (saltatory conduction).

2.2.1 | Impaired cerebrovascular reactivity

During neural activity, local vasodilation ensures that an increase in the flow of oxygenated blood sufficiently meets the metabolic demands of local tissue in a dynamic process known as functional hyperemia (Chen et al., 2014; Nippert et al., 2018). This neurovascular coupling, resulting in rapid increases in ATP synthesis, is thought to be necessary for efficient neural processing (Abdelkarim et al., 2019). The mechanisms controlling the vasomotility at the core

of the vascular response are complex and multi-faceted, and the role of changes in cerebrovascular reactivity in cognitive aging is a subject of intense study and debate, in part due to the profound implications for the interpretation of human neuroimaging in aging research (Abdelkarim et al., 2019). Mounting evidence points to a role for reduced cerebrovascular reactivity in age-related cognitive decline (Abdelkarim et al., 2019; Fabiani, Gordon, et al., 2014; Hutchison et al., 2013; Tarantini et al., 2015; Tarantini, Yabluchanksiy, et al., 2017; Toth et al., 2017; Yabluchanskiy et al., 2021).

How could age-related reductions in cerebrovascular reactivity disrupt cognition in aging? Reduced neural efficiency results from disruption of the ratio of perfusion change that accompanies changes in neural metabolism (Abdelkarim et al., 2019). This ratio is known to be maintained at ~2:1 in the young healthy system. Age-related disruption of this ratio would result in a lack of blood-derived resources (such as oxygen, lactate, and glucose) that could cause bottlenecks in ATP synthesis and impair the finely tuned timing of signaling in neuronal circuits. There is evidence of such disrupted neurovascular coupling in both normal and pathologically aging humans (Hutchison, Lu, et al., 2013; Toth et al., 2017) as well as experimental evidence of impaired cognition in animals after inhibiting neurovascular coupling (Tarantini et al., 2015; Tarantini, Yabluchanksiy, et al., 2017).

2.2.2 | Impaired myelination

Oligodendrocytes play a critical role in signal transduction through their role in axon myelination. The myelin sheath, formed by oligodendrocytes, acts as an important electric insulator. Oligodendrocytes also form functional connections between glial cells and neuronal axons, wherein oligodendrocytes support the function and integrity of the axons by active glucose transport processes (Lee et al., 2012; Saab et al., 2013; Simons & Nave, 2016).

Oligodendrocytes are susceptible to ischemia, and resulting damage may lead to denuded axonal regions with slower conduction velocity (Pantoni et al., 1996). Note that the loss of the myelin sheath (and, therefore, of saltatory conduction) may also result in increased metabolic demands due to an increase in the axonal area. An increase in the movement of ions, and therefore additional activation of the ATP-dependent ion pumps, would be required for maintaining local ionic homeostasis. For this reason, demyelination is more likely to occur in watershed regions of the white matter. In addition, vascular damage may directly lead to oxidative damage and a microenvironment that causes gliosis and prevents the integration of oligodendrocyte progenitor cells (Kohama et al., 2012). These factors may suggest that white matter lesions in watershed areas could represent early indicators of vascular-related brain damage.

In humans, diffusion tensor imaging (DTI) is used to noninvasively study the white matter microstructure by assessing measures of diffusion anisotropy (Pierpaoli & Basser, 1996). Using DTI, age-related degradation in white matter integrity regionally influences neural activity, as measured with fMRI (Bennett & Rypma, 2013), and cognitive performance (Conley et al., 2020; Jolly et al., 2017; Tan et al., 2019). Evidence is accumulating regarding the role of myelination in learning-related plasticity to support the precise timing needed for signal integration and oscillatory coupling (Fields, 2015). Overall reduced conduction velocities may globally impair speed of processing. This line of research also implies that new learning and the precise timing of established circuits would be impaired by focal myelin damage. Age-related degradation in anterior white matter is associated with decreased processing speed and poorer working memory (Gratton et al., 2009). Age-related degradation in the central white matter is associated with poorer episodic memory (Walker et al., 2017). Finally, age-related degradation in the posterior white matter is associated with poorer inhibition and greater task switching costs (Kennedy & Raz, 2009a). Some evidence for causality has been found, with preceding changes in fractional anisotropy in certain white matter tracts, predicting subsequent changes in processing speed 2 years later (Oschwald et al., 2019). Vascular risk factors are known to modify the age differences in white matter integrity and their effects on cognition (Jacobs et al., 2011; Kennedy & Raz, 2009b). Thus, it is likely that at least some of the age-related degeneration in myelination is driven by changes to vascular health (Tan et al., 2019).

3 | HOW DOES THE CEREBROVASCULATURE CHANGE WITH AGE?

In the previous section, we discussed mechanisms by which impaired vascular health leads to impaired neural function and cognitive performance in aging. The vascular system changes greatly over the life span. Here, we survey major categories of age-related changes to the cerebrovasculature, and review the mechanisms leading to those changes and how they propagate to the impairments in cellular health and signaling discussed in the previous section.

3.1 | Arterial inflammation

Arterial inflammation is intimately related to the onset and progression of arterial stiffening and is involved in all of the

vascular changes discussed in this review (Jain et al., 2014; Mozos et al., 2017). The mechanisms involved in vascular inflammation are complex, multi-faceted, and often lead to "vicious cycles" wherein the result of inflammatory processes leads to more inflammation (Dai et al., 2012; de Almeida et al., 2020; Jain et al., 2014; Mills & Bhatt, 2004; Mozos et al., 2017; Raz & Daugherty, 2018).

Inflammation encompasses many signaling cascades at the immune system's disposal to respond to injury or infection. These signals can result in altered cellular behavior, which are useful or harmful depending on the size of the reaction and the circumstances leading to the inflammation. Chronic, low-grade inflammation has been increasingly implicated in contributing to a number of diseases (Minihane et al., 2015). Typically, in discussions of age-related decline in vascular health, there are two major manifestations of inflammatory contributions: Plaque formation (atherosclerosis) and other contributions grouped under the umbrella of oxidative stress.

Atherosclerosis is now considered to be a specific chronic inflammatory disease (Cecelja & Chowienczyk, 2012; Libby, 2012; Libby et al., 2002; Mills & Bhatt, 2004; Mozos et al., 2017). Atherosclerosis begins in adolescence as fatty streaks of cholesterol begin to deposit in the walls of the large arteries (McGill et al., 2000). Inflammatory cells accumulate in early plaque formation (Libby, 2012; Mozos et al., 2017). Monocytes mature into macrophages within the plaque and form foam cells as they take up lipoproteins in the plaque (Libby, 2012; Mozos et al., 2017). Eventually these macrophages die and form a necrotic core in the plaque. Pro-inflammatory signaling additionally contributes to fibrosis, smooth muscle cell proliferation, and additional inflammation at the site of the plaque (Libby, 2012; Mozos et al., 2017).

There is also an intimate connection between inflammation and oxidative stress, thought to be the root cause of biological aging (Chelombitko, 2018; Ferrucci & Fabbri, 2018). The oxidative stress hypothesis of aging is that ROS are produced as a by-product of aerobic metabolism, that, over time, inflicts mounting oxidative damage to a variety of macromolecules and lead to over-oxidation of redox-sensitive protein thiols, dramatically impairing redox-regulated signaling (Harman, 1956; Sohal & Orr, 2012). Raz and Daugherty (2018) introduced a model that applies these ideas specifically to the brain and reviews the tools available to study oxidative stress in the human brain non-invasively. ROS are now known to act as signaling molecules and participate in the initiation, progression, and resolution of inflammation (Chelombitko, 2018). At the same time, many inflammatory responses trigger the proliferation of more ROS (Chelombitko, 2018). Thus, the ROS overproduction that accumulates in aging may promote age-related inflammation underlying a wide range of degenerative processes.

3.2 | Arterial stiffening

One of the earliest measurable changes in vascular function, after arterial inflammation, is arterial stiffening, or arteriosclerosis (see Figure 1). In the elderly, arterial stiffness is associated with cognitive decline and age-related pathology including Alzheimer's Disease and other dementias (Hanon et al., 2005). In addition, it is related to cerebral small vessel disease (CSVD) and related infarctions in the brain including white matter hyperintensities, lacunar infarcts, cerebral microbleeds, and volumetric decline (Henskens et al., 2008; Singer et al., 2014). This relationship to CSVD, usually through models of increasing pulse pressure (the difference between systolic and diastolic blood pressure and velocity), is thought to be the primary mechanism by which gradual arterial stiffening throughout the life span manifests as damage and disease later in life (Tarumi et al., 2014; Tarumi & Zhang, 2018). Arterial stiffening appears to precede many negative changes to the rest of the cerebrovasculature, brain health, and cognition. Since it is measurable by non-invasive methods, it is a prime candidate to target for prevention and/or early interventions.

Elastic fibers, collagen, and smooth muscle cells support the arterial wall (Wagenseil & Mecham, 2012). The elastic components of the arterial wall deteriorate over the life span, due to a number of mechanisms that are pervasive in aging. Arterial stiffness appears to follow an exponential trajectory, with the rate increasing with age (AlGhatrif et al., 2013). Starting around age 30, carotid artery distensibility and compliance begin to decrease (Reneman et al., 1986). In adults, once damaged, elastic fibers are generally not replaced (Wagenseil & Mecham, 2012). Instead, collagen, rather than elastin, is produced, which increases stiffness (Todorovich-Hunter et al., 1988; Wolinsky, 1970). In addition, throughout the life span, elastic layers can calcify (Dao et al., 2005), and elastic fibers may also form protein–protein crosslinks (Dao et al., 2005; Konova et al., 2004; Wagenseil & Mecham, 2012).

A common additional contributor to arteriosclerosis in aging is atherosclerosis, where plaques develop in the walls of arteries and cause their lumen to narrow (Falk, 2006; Kattoor et al., 2017; Libby, 2012; Ross, 1995). Atherosclerosis is dangerous because rupturing plaques can cause clotting or embolisms. In addition, atherosclerotic plaques weaken the vascular wall, which can lead to aneurysms. The onset of atherosclerosis appears as reversible fatty streaks in the arterial walls as early as adolescence (Kunz, 2000; Stary et al., 1994). However, the degree to which early stages of atherosclerosis contribute to the arterial stiffening is still a matter of debate (Cecelja & Chowienczyk, 2012; Farrar et al., 1991).

Arteries remodel to withstand repetitive hemodynamic stresses to the arterial wall (Lasheras, 2006). This remodeling is responsible for some of the stiffening. In some cases, this

process fails, and the arterial wall weakens and distends forming an aneurysm. The most serious potential consequence of a cerebral aneurysm is that it may rupture and cause a hemorrhagic stroke. Aneurysms may also interact with arterial flow in complex ways and affect flow pulsatility, which has downstream consequences on microvasculature (Hussein et al., 2018). In the brain, this process most commonly occurs in the intracranial arteries surrounding the Circle of Willis (Lasheras, 2006). Cerebral aneurysms are relatively rare (about 0.4%–3.7%), and usually do not occur until middle-age or later (Keedy, 2006; Weir, 2002). Most cerebral aneurysms are asymptomatic (Keedy, 2006). Symptomatic cerebral aneurysms are known to leak blood and contribute to ischemic cerebrovascular disease (Wagner & Stenger, 2005), but the degree to which smaller, unruptured cerebral aneurysms lead to sub-clinical impairments that could contribute to normal age-related cognitive impairment remains unclear.

Cerebral blood flow (CBF) pulsatility has been directly correlated to carotid pulse pressure, and predictive of white matter hyperintensities (Tarumi et al., 2014). Increases in central pulse pressure following arterial stiffening are transmitted into the brain via higher flow and lower resistance vascular beds (Mitchell, 2008; Mitchell et al., 2011; Tarumi et al., 2014; Webb et al., 2012). Although there is evidence for functional dampening of pulsatility through the structure of the carotid arteries (Schubert et al., 2011), microvasculature must also remodel with ramifications to downstream function and reactivity (Mitchell et al., 2005). Cerebral arterial pulsatility appears to increase according to an exponential function (Tarumi & Zhang, 2018).

A large component of pulsatility of pulse pressure waveforms is the arterial wave reflection returning primarily from bifurcations in peripheral vessels (van de Vosse & Stergiopulos, 2011; Westerhof et al., 1972). It has been hypothesized that pulsatility in CBF is primarily from wave reflections from peripheral vascular beds with high resistance, rather than the vascular bed of the brain itself (O'Rourke & Safar, 2005; Tarumi et al., 2014). In aging, the reflected wave becomes larger in amplitude and arrives earlier, leading to a pronounced systolic peak in the pulse wave, increase in systolic pressure, and increased pulse pressure (van de Vosse & Stergiopulos, 2011). Interestingly, there appears to be a relationship between the reflected wave component of the pulse pressure wave and an individual's height, where smaller heights predict earlier returns of the reflected wave (London et al., 1995), which may augment central pressure and contribute to sex differences in CBF, pressure, and pulsatility (Tarumi et al., 2014).

Until recently, most of the methods used to assess arterial stiffness in humans focused on measurements taken from areas outside of the brain or using transcranial Doppler ultrasound to make a single measurement of cerebral arterial stiffness from the middle cerebral artery. These measurements would then be correlated to brain health and cognition. These types of measurements have been reviewed extensively elsewhere (Badji, Sabra, et al., 2019; Laurent et al., 2006; Townsend et al., 2015).

The gray matter of the thalamus, as well as the white matter of the corpus callosum, internal capsule, corona radiata, and the superior longitudinal fasciculus appear to be particularly vulnerable to arterial stiffening (Badji, Sabra, et al., 2019; Pauline et al., 2016; Tarumi et al., 2015). Using DTI and magnetization transfer imaging together, it is possible to separate axonal integrity from myelination (Badji, Noriega de la Colina, et al., 2019). Interestingly, arterial stiffness seems to be associated with axon degeneration as opposed to demyelination (Badji, Noriega de la Colina, et al., 2019). Both arterial stiffening and the subsequent brain damage have been related to cognitive abilities, including speed-of-processing, executive skills, memory, verbal learning, and visuo-spatial function (Badji, Sabra, et al., 2019).

More recently methods have been introduced, using diffusive optical tomography to measure the amplitude, timing, and shape parameters of the pulse wave (pulse-DOT; Fabiani, Low, et al., 2014; Tan et al., 2017) and MRI (Furby et al., 2019; Warnert et al., 2016; Yan et al., 2016), that allow researchers to non-invasively measure arterial stiffness in the brain of healthy, normally aging humans. These methods increase the precision with which the effects of cerebral arterial stiffness on brain health and cognition can be assessed, allowing for the examination of regional variability in vascular health (Figure 3).

Tan and colleagues (2019) found that optical measures of cerebral arterial stiffness predicted white matter signal abnormalities and cognitive performance in a sample of normal aging adults. Furthermore, they observed regional specificity in these effects. Specifically, the arterial territory perfused by the middle cerebral artery showed the largest correlation between stiffness measures and white matter abnormalities. Chiarelli, Fletcher and colleagues (2017) found an association between individual differences in regional cortical volumes and local optical measures of cerebral arterial stiffness. Such observations of regional specificity highlight one of the major advantages of measuring arterial stiffness directly from the cerebral arteries rather than from the periphery. Other studies, using the same techniques, have demonstrated local specificity for predicting cognitive performance. In the article that introduced this technique, Fabiani, Low, et al. (2014) found evidence for a double dissociation wherein measures of arterial compliance in the left middle cerebral artery territory (supplying Broca's area) were related to performance on a verbal fluency task but not on a working memory task. Conversely, arterial compliance in the precentral arteries (supplying bilateral dorsolateral prefrontal cortices) was related to performance on the working memory task, but

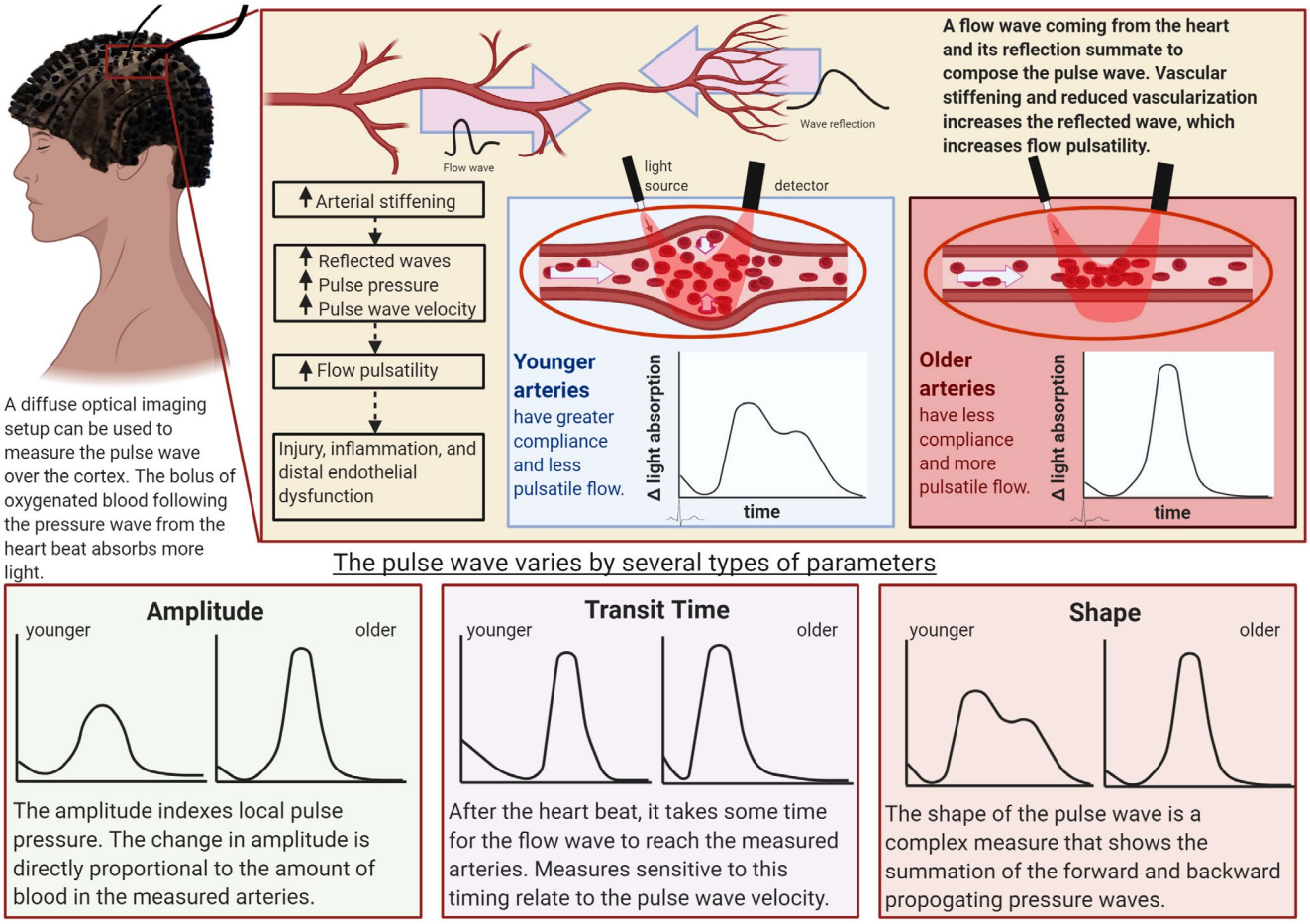

FIGURE 3 Arterial stiffness can be measured using diffuse optical tomography, which is sensitive to different properties of the pulse flow wave propagating through local arteries (pulse-DOT). These properties include amplitude of the flow wave, reflecting local pulse pressure, transit time, reflecting upstream arterial compliance, and shape, which is a complex combination of both downstream and upstream vascular properties and reflects flow pulsatility. These properties change with age and correlate to other measures of brain health and cognition

not on the verbal fluency task. In a separate study, Tan et al. (2017) showed a regional effect in which performance on a working memory task was related to arterial compliance localized to the frontoparietal cortex, but not with the global measures of compliance. At present, optical imaging techniques are more mature in their ability to investigate these local differences than the emerging work in MRI, but the MRI work is evolving quickly (Furby et al., 2019; Warnert et al., 2016; Yan et al., 2016).

Although the mechanisms that cause arterial stiffening begin early in life, there is growing evidence to support the possibility of prevention and even its reversibility. In terms of lifestyle, increased aerobic exercise, caloric restriction, dietary content, and weight loss are known to attenuate, and sometimes reverse, the progression of arterial stiffening (Dai et al., 2012; Oh, 2018). Ongoing work to develop pharmaceutical interventions specifically targets repairing damage (e.g., through elastin synthesis / breaking collagen cross-links) or preventing the signaling cascades involved in the causes of subsequent arterial stiffening (e.g., arterial wall inflammation) or the arterial stiffening itself (Dai et al., 2012; Najjar et al., 2005).

3.3 | Decreased cerebrovascular reactivity

Vascular reactivity refers to the ability of a blood vessel to dynamically dilate or constrict after exposure to some stimulus. In the brain, cerebrovascular reactivity (CVR) is critically important in maintaining cerebral autoregulation, the phenomenon of stable CBF over a large range of arterial pressures (Armstead, 2016). CVR underlies neurovascular coupling (the dynamic control of local blood flow in response to increased metabolic needs due to neural activity; Filosa, 2010; Hosford & Gourine, 2019; Iadecola, 2017).

Vascular regulation is mainly controlled by the dilation and constriction of the vascular smooth muscle surrounding arteries and arterioles, and possibly by actin-containing pericytes surrounding the capillaries, although there is an ongoing debate regarding the classification of these actin-containing

cells near arteriole-capillary borders (Fernández-Klett et al., 2010; Hall et al., 2014; Hill et al., 2015; Kornfield & Newman, 2014; Peppiatt et al., 2006; Vates et al., 2010; Yemisci et al., 2009). This vascular regulation is critical for maintaining appropriate blood flow throughout the brain, as vessel walls relax to dilate when pressure drops and constrict when pressure increases (Cipolla, 2009; Greene & Lee, 2012). The vasomotor function of cerebral vessels can be stimulated extrinsically by hypo/hyperoxia, hypo/hypercapnia, or by introducing chemical vasodilators or vasoconstrictors (Chiarelli et al., 2007; Lu et al., 2014; Sicard & Duong, 2005). The ability to stimulate vasodilation in the cerebral vessels, particularly through the inhalation of CO_2-enriched gases, gives researchers an opportunity to harmlessly measure differences in vascular reactivity across groups, treatments, or even regions of the brain.

Interestingly, cerebral reactivity does appear to differ across the brain. Gray matter has more vascular reactivity than the white matter (Rostrup et al., 2000; van der Zande et al., 2005). Although extant research is not completely consistent, there seems to be a general pattern wherein the posterior brain (occipital, parietal, and cerebellum) has greater reactivity than more anterior regions (frontal, temporal, and insular regions; Last et al., 2007; Novak, 2012). However, Zhao et al. (2009) found that, while reactivity was lower in the MCA compared to the PCA vascular territory, the ACA territory had reactivity more similar to the PCA territory. This result suggests that differences in reactivity may depend on arterial territory distributions, or on localized regional stiffening. More research is needed to determine whether resting differences in reactivity are driven by regional tissue differences or by differences in the arterial territories. One critical outstanding question is the extent that regional differences in vascular reactivity could interact with age-related decline. For example, Catchlove, Macpherson et al. (2018) hypothesized that regions with initial lower CVR would be more affected by declines in perfusion than areas with greater initial reactivity. This is in line with current conceptions of cerebrovascular reserve, where cerebrovascular autoregulatory capacity is thought to dampen and control other age-related vascular dysfunction up to some critical point, where autoregulatory functions can no longer compensate (Davenport et al., 2012; Novak, 2012).

In addition to flow regulation, the cerebrovasculature also responds to local metabolic needs of tissue through neurovascular coupling and functional hyperemia. In functional hyperemia, blood flow is coupled to metabolism at a ratio of ~2:1 in healthy adults and supports neuronal activity and processing efficiency (Abdelkarim et al., 2019). This process is facilitated by the neurovascular unit (Iadecola, 2017). Generally, this process is maintained through changes in a group of metabolite concentrations resulting from neuronal metabolism. Increased potassium ions, ATP, and adenosine in the extracellular space all act as signaling molecules to induce vasodilation through smooth muscle relaxation (Abdelkarim et al., 2019; Girouard & Iadecola, 2006; Iadecola, 2017). Additionally, nitric oxide (NO) released from the active neurons also relaxes the vascular smooth muscle cells (Abdelkarim et al., 2019; Iadecola, 2017). In fact, blockade of neuronal NO synthase (nNOS) seems to have the greatest effect on the neurovascular response, reducing it by an average of 65% across 11 studies (Hosford & Gourine, 2019). Finally, astrocytes, which detect glutamate in the synapse, release signaling prostaglandins (prostaglandin E2) and epoxyeicosatetraenoic acids (EETs) that cause the vascular smooth muscle cells to vasodilate (Abdelkarim et al., 2019; Iadecola, 2017).

Unfortunately, these signaling pathways can become directly impaired with aging (Tarantini et al., 2017), although nutritional interventions may help prevent deficiencies (Gratton et al., 2020). Even beyond that, other age-related changes in molecular processes, often related to inflammation, can increase the presence of other vasodilators and vasoconstrictors that may impair neurovascular coupling. Normally, astrocytes maintain non-overlapping domains of interaction with the blood vessels (Abdelkarim et al., 2019; Bushong et al., 2002). This distribution is critical for the coordination of signaling on the vessel, as astrocytes propagate signals to other astrocytes through endfoot-endfoot Ca^{2+} signaling (Abdelkarim et al., 2019; Attwell et al., 2010; Cauli & Hamel, 2018; Chen et al., 2014; Tian et al., 2010). In aging, inflammation causes cell hypertrophy in the astrocytes, which disrupts this spreading Ca^{2+} signaling by impairing the hemichannel contacts between astrocytic endfeet (Abdelkarim et al., 2019; Sofroniew, 2009). In addition, inflammatory cytokines and ROS activate inducible nitric oxide synthase (iNOS), which has the effect of upregulating NO, and glial reactivity causes higher intracellular Ca^{2+} levels in astrocytes, both of which increase vasodilatory signaling (Abdelkarim et al., 2019; Jiang & Cadenas, 2014; Sofroniew, 2009). However, aging also increases the presence of potent vasoconstrictors, including thromboxane, angiotensin II, and endothelin-1 (Abdelkarim et al., 2019; Brandes et al., 2005; Jia et al., 2019; Scioli et al., 2014). Thus, how the balance of vasodilation and vasoconstriction changes with age, and the subsequent degree of neurovascular coupling dysfunction, is difficult to predict, and probably differs across the brain. The extent of regional variation in neurovascular coupling with aging is not yet known but increased inflammatory signaling might be the root cause of age-related changes in vasomotor signaling, suggesting that areas with greater inflammation would also suffer the most impairment in neurovascular coupling.

Clearly, the control of CVR is multi-faceted and complex. This complexity has made it difficult to reach a clear consensus regarding how much CVR changes with age, a topic covered

in depth by **Yabluchanskiy et al.** (**2021**). Some age-related changes induce more vasodilation, while others induce vasoconstriction, while still others disrupt signaling over space (Figure 4). These opposing forces may make it complicated to study age-related disruptions to vascular reactivity. The literature reflects this difficulty, with some articles reporting age-related decreases in hypercapnic vascular reactivity (De Vis et al., 2015; Gauthier et al., 2013; Ito et al., 2002; Kastrup et al., 1998; Lu et al., 2011; Peng et al., 2018; Reich & Rusinek, 1989; Schieve & Wilson, 1953), others reporting age-related increases (Zhu et al., 2013), and still others reporting relatively stable reactivity over the life span (Barnes et al., 2012; Carey et al., 2000; Catchlove, Parrish, et al., 2018; Coverdale et al., 2017; Galvin et al., 2010; Murrell et al., 2012; Rosengarten et al., 2003; Yam et al., 2005). Complicating matters further, some studies have reported differences between hypocapnic reactivity and hypercapnic reactivity as a function of age (Galvin et al., 2010; Murrell et al., 2012; Zhu et al., 2013). Within these studies, both decreases (Yamaguchi et al., 1979; Zhu et al., 2013) and increases (Galvin et al., 2010; Murrell et al., 2012) in hypocapnic responses have been observed.

Considering this mixed body of evidence, it is important to note that the "normal" aging population is rarely free of cardiovascular risk factors or of some degree of vascular impairment, and that cardiorespiratory health itself is largely dependent on age (Laurent, 2012; Lloyd-Jones et al., 2005). If CVR changes as a downstream consequence of other forms of vascular impairment, it would be expected that these CVR changes would vary depending on the health of the sample. Owing to the complexity of the mechanisms underlying CVR, it is possible that samples will have differently weighted impairments promoting increased vasodilation, increased vasoconstriction, or otherwise disrupted neurovascular signaling mechanisms. A study by Coverdale et al. (2017) found that while there was no difference in CVR between older and younger adults in their sample, mean arterial pressure increased more during hypercapnia for older than younger adults, suggesting that a central hemodynamic response may compensate

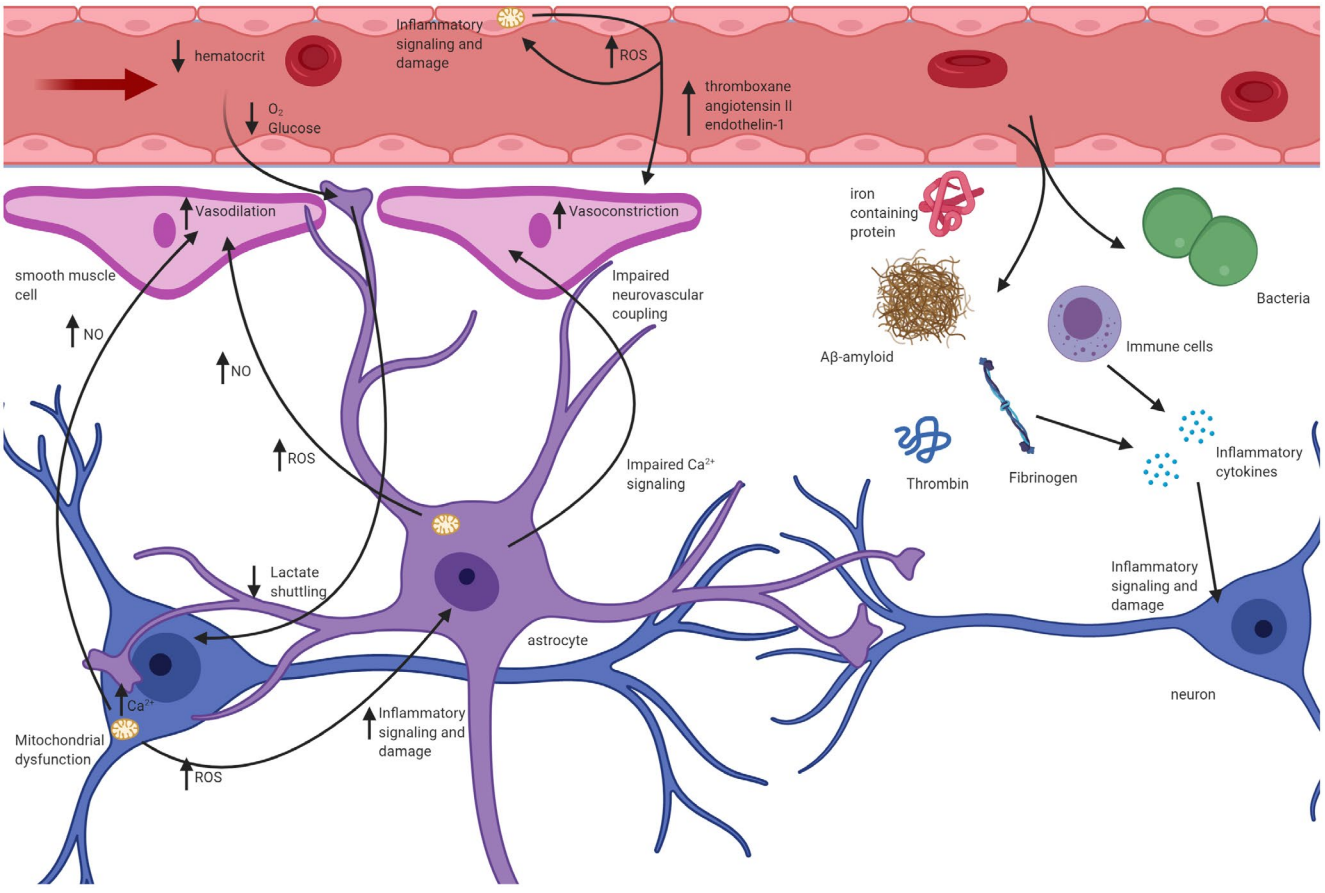

FIGURE 4 This simplified view shows how some of the signaling mechanisms involved in neurovascular coupling are disrupted in aging. Increases in NO resulting from mitochondrial dysfunction and inflammatory signaling at the neurovascular junction promote vasodilation. In contrast, inflammatory signaling in endothelial cells promote potent vasoconstriction. Overall, inflammatory signaling, from mitochondrial dysfunction or from exposure to external toxins coming through an impaired BBB, may lead to impairments in the coordinated neurovascular coupling mechanisms that dilate local vasculature in response to neural activity

for a diminished vasomotor capacity. This intriguing finding highlights that there are both local and central hemodynamic mechanisms at play in controlling CVR, which further increases the complexity of age effects. Finally, it is possible that sex-related differences play a substantial role in age-related changes in CVR. In one study a significant change was observed in women but not in men (Kastrup et al., 1998). Matteis et al. (1998) suggested that age differences in CVR in women may be explainable by pre-menopausal versus post-menopausal status. Together, these results demonstrate the care needed to investigate such a complex system.

In some cross-sectional and longitudinal studies showing differences in CVR with age, the onset of changes in CVR varied between 35 and 60 years (Peng et al., 2018; Reich & Rusinek, 1989), which roughly corresponds to the age range in which changes in pulse pressure become evident (Pinto, 2007). However, most CVR studies to date look at simple splits between younger and older groups, so future work with larger samples is needed to clarify the onset of changes. Some intriguing evidence suggests that the trajectory of age-related changes is sigmoidal, with the fastest acceleration of decline between 40 and 60 (Peng et al., 2018). This pattern would be unexpected if dysfunction of CVR is mainly rooted in inflammatory processes but would be expected if hormonal changes due to menopause are responsible for a large proportion of the age-related variance. However, the study demonstrating this sigmoidal relationship collapsed their analysis across sexes. Future research should consider the potential effect of menopause in affecting CVR as a covariate deserving of further investigation.

Failure of autoregulatory vascular mechanisms could reflect either signaling deficits or a breaching of the limits of cerebrovascular reserve. Either way, dysfunctional autoregulatory mechanisms could lead to insufficient blood flow at low perfusion pressures or damaging amounts of blood flow at high perfusion pressures, which could result in subsequent ischemia (O'Rourke & Safar, 2005). Similarly, dysfunctional neurovascular coupling could cause transient bouts of ischemia locked to neural activation, which could impair the efficiency of neural communication in the short term and cause damage to the cells in the long term (Abdelkarim et al., 2019; De Silva & Faraci, 2017; Iadecola, 2017). There is a paucity of research assessing the degree to which changes in CVR are preventable or reversible in humans. However, if age-related CVR changes are strongly determined by prior vascular dysfunction, it would be expected that CVR dysfunction would also be preventable and reversible to the same degree that arterial inflammation and stiffness are, and according to the same mechanisms. There is evidence to support this hypothesis in animals, where neurovascular uncoupling is reversible through interventions that improve endothelial health (Park et al., 2007; Toth et al., 2014).

Studies that address how age-related CVR changes correspond to cognition are still sparse. In a 4-year longitudinal study, Peng and colleagues (2018) found that longitudinal CVR changes were associated with changes in processing speed and episodic memory, but not working memory or reasoning, with the fastest declines in CVR in the temporal lobe. Similar results were published by Catchlove, Parrish, et al. (2018), finding that age-related CVR reductions were most prominent in temporal lobe, and that temporal lobe CVR correlated with memory performance and attention tasks with speed-of-processing components, independently of age, gender, and education level. These findings are supported by research in animals. In mice, age-dependent impairment of neurovascular coupling in the hippocampus correlated with reduced performance on a spatial memory task (Lourenço et al., 2018). There is also a wealth of research relating CVR impairment to age-related cerebral pathologies, including mild cognitive impairment and Alzheimer's Disease (Alwatban et al., 2019; Bär et al., 2007; Cantin et al., 2011; Chen, 2018; Glodzik et al., 2013; Gongora-Rivera et al., 2018; Heun et al., 1994; Kalaria, 2010; Kelleher & Soiza, 2013; Richiardi et al., 2015; Sánchez-Catasús et al., 2017; Silvestrini et al., 2006; Viticchi et al., 2012; Yezhuvath et al., 2012). Overall, this research suggests that age-related declines in CVR are mostly present in the temporal lobe, although future work will help to confirm and clarify the details of the effects of age on regional CVR and cognition.

3.4 | Leaky BBB

A functional BBB plays a critical role in maintaining CNS function (Erdő et al., 2017). Disruption of the BBB has a devastating impact on brain function and is associated with age-related brain pathologies including Alzheimer's Disease (Iadecola, 2013; Montagne et al., 2015; Snyder et al., 2015; Sweeney et al., 2015, 2018, 2019). The causal direction between vascular dysfunction and these diseases is a topic of ongoing research (Erdő et al., 2017). A recent theoretical model proposed a "two-hit" process, wherein cerebrovascular damage modulated by genetic, environmental, and lifestyle factors disrupt the BBB (hit 1), which directly causes neuronal injury, but can also accelerate amyloid β-peptide (Aβ) pathology (hit 2) through impaired clearance of Aβ and increased Aβ production (Cockerill et al., 2018; Sweeney et al., 2015; Zhao, Nelson, et al., 2015; Zhao, Sagare, et al., 2015). Accumulation of Aβ would then exacerbate BBB impairment through increased inflammation.

Permeability of the BBB increases with age (Farrall & Wardlaw, 2009). Since the BBB is a functional term that encompasses endothelial cells, astrocytes, microglia, pericytes, and neurons, as well as tight junctions and structural attributes of the capillaries, there is a vast literature on age-related BBB

dysfunction that spans all of these functional components (Erdő et al., 2017; Mooradian, 1988; Popescu et al., 2009; Profaci et al., 2020; Zhao, Nelson, et al., 2015). Here, we focus on age-related decline in the ability of the BBB to prevent neurotoxic and inflammatory proteins from entering the brain and to efficiently remove neurotoxic metabolic waste products.

BBB breakdown leads to accumulation of toxins that damage neurons either directly or indirectly. Hemoglobin and free iron cause the production of ROS and oxidant stress to neurons (Bell et al., 2010; Zhao, Nelson, et al., 2015). Blood-derived proteins such as fibrinogen, thrombin, and plasminogen degrade the neuronal extracellular matrix and increase ROS and inflammation (Bell et al., 2010; Halliday et al., 2016; Hultman et al., 2013; Zhao, Nelson, et al., 2015; Zipser et al., 2007; Ryu & McLarnon, 2009). Albumin, another blood-derived protein, causes vasogenic edema (Blennow et al., 1990; Montagne et al., 2015; Sweeney et al., 2015; Zhao et al., 2009). Finally, the loss of immune privilege can result in the entry of autoantibodies and immune cells that damage neurons (Erickson & Banks, 2019; Hammer et al., 2014; Sweeney et al., 2015; Zhao, Nelson, et al., 2015).

In humans, the degree of accumulated toxicity in normal aging in the absence of pathology and its impact on normal age-related cognitive decline is still unknown. Interestingly, BBB disruption does not always lead to brain damage, suggesting that BBB function and its relation to neuronal damage may depend on its etiology (Erickson & Banks, 2019). For instance, some therapeutic strategies depend on transient disruptions of the BBB, which are well tolerated (Doolittle et al., 2014; Lipsman et al., 2018). Future research will need to elucidate the circumstances in which BBB disruption is tolerated or detrimental.

In animal models, the extent of BBB damage appears to be lessened or preventable through exercise (Małkiewicz et al., 2019; Souza et al., 2017). Furthermore, exercise ameliorates damage from BBB disruption after hypoperfusion (Lee et al., 2017). A high-fat diet also seems to increase BBB permeability in mice, particularly in models of induced insulin resistance (de Aquino et al., 2018; Salameh et al., 2019; Yamamoto et al., 2019). Thus, there is a strong prediction that exercise and diet could modulate BBB permeability in humans, although research is currently lacking. According to the two-hit model of BBB dysfunction, BBB permeability is probably modifiable at the level of the first "hit" through modulation of initial upstream vascular damage and inflammation. After the second "hit," with the introduction of pathological processes, a vicious cycle may be initiated whereby dysfunction causes more dysfunction, which may be more difficult to reverse.

Recently, Senatorov et al. (2019) investigated a mechanism of BBB impairment on cognition in normal aging in both mice and humans. In this landmark study, they found evidence of BBB dysfunction beginning in middle-age in mice, which they replicated with dynamic contrast-enhanced imaging in humans, showing a linear increase in BBB permeability after age 40. This article highlights potentially early changes in BBB function with age, even in the absence of disease. The most widely used method to measure BBB permeability is dynamic contrast-enhanced MRI (Tofts & Kermode, 1991). This method is effective at quantifying major disruptions of the BBB because it is sensitive to the permeability of the very large molecules used as contrast agents, such as gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) (Barbier et al., 2002; Starr et al., 2009; van de Haar et al., 2016). However, minor disruptions due to aging and indicative of the early stages of pathology are more difficult to measure. In addition, the injection of a potentially toxic tracer, whose risk increases in cases of BBB dysfunction, is not an ideal tool (Kanda et al., 2016; Olchowy et al., 2017). The recent development of non-contrast MRI techniques to measure BBB permeability will contribute to the growing research on BBB dysfunction in humans in the future (Evans et al., 2020; Lin et al., 2018; Shao et al., 2019).

3.5 | Loss of microvasculature

Aging is related to rarefaction of the microvasculature, although there is variability across brain areas, microvasculature components, and in findings across studies. The most substantial loss of microvasculature appears to occur in cortical arterioles (Sonntag et al., 1997, 2007). In contrast, the density of arterioles extending from the pia to the white matter remain similar across age (Knox & Oliveira, 1980), and arteriole density in some areas, such as the subiculum of the hippocampus, has even been shown to increase with age (Bell & Ball, 1981). There also appears to be some age-related change in the capillary density in the cortex and hippocampus, but this evidence is more equivocal (Brown & Thore, 2011; Riddle et al., 2003; Sonntag et al., 2007). When observed, declines in capillary density are lower, 10%–30%, compared to those in cortical arterioles (~40%) (Sonntag et al., 2007). Capillary density also does not seem to decline linearly with age. Some studies suggest that capillary density actually increases during middle-age, but declines in late senescence (Hunziker et al., 1979; Sonntag et al., 2007; Wilkinson et al., 1981). The mechanism underlying this trajectory might be related to vascular responses to hypoxia. Under normal circumstances, vascular density increases during periods of hypoxia or inflammation (Boero et al., 1999; Pober & Sessa, 2015). This responsiveness to hypoxia seems to decline with age (Chavez & LaManna, 2003; Rivard et al., 1999). Thus, if brain hypoxic episodes increase due to other vascular dysfunctions related to aging, the body may

respond by increasing microvascular density until the ability to compensate effectively is impaired. Studies of these processes have not separately investigated declines in arteriole and capillary density, and future work will need to investigate the reason for the differences between these microvascular components.

Intuitively, in a well-functioning vascular tree, capillary density should not change, since it represents the distances between cells and the point of oxygen and nutrient exchange. Decreasing density would increase this distance, impairing tissue function. This reasoning is less clear when it comes to arterioles. Rarefaction of arterioles on the cortical surface could reflect vascular dysfunction, leading to hypoperfusion and ultimately neuronal damage. However, it is also possible that this is an active mechanism used to efficiently control blood flow and blood supply. A reduction in brain metabolism could precede arteriole rarefaction.

Currently, there is evidence that supports both hypotheses, which are not mutually exclusive. Research in microvascular plasticity has revealed that the microvasculature does indeed adapt to the metabolic needs of tissue, both increasing and decreasing in response to metabolic need (Argandoña & Lafuente, 1996, 2000; Black et al., 1987; Sirevaag et al., 1988; Sonntag et al., 2007). It should be noted that experiments on the effects of reduced metabolism have shown decreases in *capillary* density, which would not be predicted by the "intuitive" view discussed above. This suggests that microvasculature at all levels may respond to neuronal activity. The extent of microvascular plasticity to learning is reduced in age (Black et al., 1989). Despite these age-related reductions, the causal direction of the relationship between neural metabolic needs and microvasculature plasticity is still unclear. Decreases in neuronal plasticity would predict decreases in microvascular plasticity, and insufficient vascular plasticity would predict insufficient resources to generate and maintain new synapses and other neuronal growth. Therefore, the direction of causality is plausible in either direction (Sonntag et al., 2007). It is possible that declining metabolic needs reflective of neuronal senescence could drive the observed microvascular loss.

There is evidence to suggest that age-related decreases in circulating hormones affect the density of surface arterioles (Norling et al., 2020; Sonntag et al., 1997). Particularly, circulating plasma insulin-like growth factor 1 (IGF-1) correlates strongly with arteriole density (Norling et al., 2020; Sonntag et al., 1997). Injections of growth hormone in old animals increase IGF-1 and cortical arteriole density (Sonntag et al., 2000). Similarly, fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) are known to influence angiogenesis and microvascular plasticity (Kräling & Bischoff, 1998; Moens et al., 2014; Rosenstein et al., 1998) and be involved in exercise-induced angiogenesis (Ding, Li, Zhou, et al., 2006; Gao et al., 2014; Tang et al., 2010; Voss et al., 2013). However, it remains unclear whether these factors mediate age-related vascular changes. After injury, however, VEGF-enhanced angiogenesis results in increased BBB leakage. Thus, it is not clear whether these factors are solely beneficial to the microvasculature (Argaw et al., 2009, 2012; Nag, 2002; Zhang et al., 2000; Zhang & Chopp, 2002).

Evidence of age-related CBF changes, partially regulated by the density of cerebral arterioles and capillaries, faces similar problems of interpretation. For instance, CBF also decreases with age in regionally distinct ways (Aanerud et al., 2012; Ainslie et al., 2008; Lu et al., 2011; Martin et al., 1991; Stoquart-ElSankari et al., 2007; Zimmerman et al., 2014). Like arteriole rarefaction, CBF begins to decline in middle age (Lu et al., 2011; Schultz et al., 1999). Like CVR, CBF is also tightly coupled to cellular metabolism (Kuschinsky, 1990). In fact, this coupling is so strong that imaging researchers continue to debate the extent that age-related decreases in CBF reflect more than just decreases in the partial gray matter volume within the voxels they quantify (Chen et al., 2011; Meltzer et al., 2000). Therefore, future research is needed to determine the direction of causality between CBF decline and metabolic decline in aging.

CBF does increase after aerobic exercise interventions (Chapman et al., 2013; Espeland et al., 2018; Kleinloog et al., 2019). In fact, Zimmerman et al. (2014) found that the decline in cardiorespiratory fitness, strongly dependent on physical activity level, mediated the effect of aging on CBF, suggesting that age-related decreases in perfusion are related to decreases in fitness and are substantially offset by exercise.

Aerobic exercise is known to increase circulating growth factors including VEGF, brain-derived neurotrophic factor (BDNF), and IGF-1 (Bowie et al., 2021). Thus, it seems possible that exercise effects on CBF are mediated by the effect of these increased circulating growth factors on arteriole or capillary density. CBF can be increased through exercise intervention (**Stillman et al., 2021**), and greater cardiorespiratory fitness predicts increased volume in certain brain regions, which has been hypothesized to be partially due to angiogenesis (Fletcher et al., 2016). There is some existing evidence in animals that exercise increases capillary density within regions of the brain related to motor functions (Black et al., 1990; Ding et al., 2004; Ding, Li, Yao, et al., 2006; Isaacs et al., 1992; Kleim et al., 2002; Rhyu et al., 2010; Swain et al., 2003) and the hippocampus (Borght et al., 2009; Kerr et al., 2010). However, evidence from in vivo two-photon imaging in the motor cortex of young-adult mice failed to find any changes in vascular structure after a period of long-term exercise (Cudmore et al., 2017). Interestingly, in a study by Rhyu et al. (2010), no change in vascular density as a result of exercise was observed in middle-aged monkeys, but an effect was observed in older monkeys, suggesting that exercise-related increases in vascular density might depend on some prior age-related decline. Because the areas

examined in many of these studies were restricted and the findings not always replicable, it is still unclear what the full extent of angiogenesis is in response to exercise and under what circumstances it occurs. Specifically, it remains unclear whether exercise-induced angiogenesis is a reflection of increased metabolic activity in the brain during exercise, or instead, an effect of increases in circulating growth factors and hormones produced elsewhere in the body (e.g., muscles) (Delezie & Handschin, 2018; Gardner et al., 2020). The fact that most studies specifically examine angiogenesis in motor areas makes interpretation particularly difficult, since these areas are the locations where exercise would be expected to primarily increase neuronal metabolic activity and plasticity.

Given this evidence, it seems likely that some microvascular loss and CBF decline is related to declining metabolism, and some is related solely to the impairment of mechanisms that promote angiogenesis. Future research with longitudinal designs will be needed to clarify whether loss of cerebral microvasculature precedes neural damage, and whether this microvascular rarefaction directly contributes to age-related cognitive decline.

3.6 | Changes in microvascular morphology

Coincident with general age-related reduction in microvascular density, the morphology of small vessels also changes. These changes include increased small vessel tortuosity[2] and thickening of the veins and venules (Fang, 1976). These phenomena may also exert deleterious effects on brain parenchyma.

Arterioles that supply the deep white matter begin to become more tortuous at around age 50 (Akima et al., 1986; Brown & Thore, 2011; Hassler, 1967; Thore et al., 2007). Tortuosity increases the amount of blood pressure needed to maintain sufficient flow in the vessels (Moody et al., 1991). Because of the watershed principle considered earlier, it is likely that tortuosity increases the vulnerability of specific areas, such as portions of the white matter, which may be particularly vulnerable to low blood flow. Indeed, increased tortuosity may be involved in leukoaraiosis (i.e., white matter abnormalities characterized by localized loss of myelin), which is thought to reflect ischemic hypoxia in the white matter (Brown & Thore, 2011; Marek et al., 2018; Thore et al., 2007).

A related cerebral vascular pathology is periventricular venous collagenosis. In this condition, vein and venule wall thickness increases, narrowing the lumen, and restricting flow (Brown & Thore, 2011). Some degree of venous thickening in periventricular white matter occurs in normal aging (Moody et al., 1995). In some cases, excessive collagen deposition causes more severe thickening, that exacerbates leukoaraiosis (Brown & Thore, 2011). This more severe venous collagenosis is relatively common, appearing in over half of autopsied patients over age 60 who did not die from degenerative brain diseases, although the sample included cardiovascular-disease patients, which might inflate the frequency of occurrence (Moody et al., 1995). Within the patients who had periventricular venous pathology, over 75% also had advanced leukoaraiosis, suggesting a strong association (Moody et al., 1995).

In samples of living older adults, it is most common to assess microvascular pathology by measuring white matter hyperintensities (WMHs) with T2-weighted MRI (Prins & Scheltens, 2015). However, this measurement may not be sensitive to differences at the microvascular level. Periventricular WMHs may follow different patterns than other subcortical WMHs. In living older persons, large ranges (~25%–95%) in the prevalence of WMHs have been observed, suggesting that differences in sample characteristics and measurement methods play a large role (Breteler et al., 1994; Habes et al., 2016; Leeuw et al., 2001; Longstreth et al., 1996; Prins & Scheltens, 2015; Söderlund et al., 2003; Zhuang et al., 2018).

In leukoaraiosis lesions, there is preferential loss of oligodendrocytes and increased apoptosis within the lesion (Brown et al., 2000, 2002a). The loss of these cells may reduce structural support for arterioles, increasing their propensity to twist into tortuous configurations (Brown et al., 2002b). White matter lesions are associated with impaired cognitive function and age-related neurodegenerative diseases. Declining cognitive ability in areas of processing speed, executive function, and memory are all related to white matter lesion load (Debette & Markus, 2010; Prins et al., 2005; Prins & Scheltens, 2015; Vermeer et al., 2003). In addition, white matter lesions also are involved in the etiology and pathogenesis of age-related dementias, including Alzheimer's disease (Brickman et al., 2015; Debette & Markus, 2010; Kalaria & Ihara, 2013; Prins & Scheltens, 2015; Sudre et al., 2017; Wardlaw et al., 2015).

Like other age-related changes corresponding to microvascular damage discussed above, controlling arterial stiffness and inflammation can help to prevent the appearance and progression of WMHs (Prins & Scheltens, 2015).

[2]The phenomenon of increased small vessel tortuosity can potentially lead to confusion in the language between interacting methodologies for assessing cerebrovascular health. Particularly, methods that focus on measuring blood flow in only the arterial compartment will typically refer to arterial transit time as the time that blood takes to move from one point in the arterial tree to another point in a large or small artery. This process is very fast (a few hundred milliseconds or less) and may become faster in aging as the flow velocity increases due to arterial stiffening (Fabiani, Low, et al., 2014). However, methods that focus on tissue perfusion as their measurement of blood flow are designed to be sensitive to blood movement through the arterioles and capillaries. This process is much slower (on the order of 1–2s) and typically becomes slower in aging because of decreased velocities through the microvasculature (W. Dai et al., 2017).

Hypertension and high diastolic blood pressure have been identified as risk factors predicting the presence of WMHs and their progression (Goldstein et al., 2005; Gottesman et al., 2010). Additionally, optical measures of arterial compliance have shown a strong relationship between arterial stiffness and white matter lesions (Tan et al., 2019). There is some evidence that treating hypertension is effective in controlling WMHs' appearance and progression (Verhaaren et al., 2013), whereas the evidence is mixed regarding the effect of physical activity (Burzynska et al., 2014; Carmelli et al., 1999; Fleischman et al., 2015; Gow et al., 2012; Ho et al., 2011; Podewils et al., 2007; Rosano et al., 2010; Rovio et al., 2010; Sen et al., 2012; Torres et al., 2015; Tseng et al., 2013; Venkatraman et al., 2020; Willey et al., 2011). Thus, it is still unclear whether exercise interventions are likely to prevent and/or slow the progression of WMHs and under what circumstances exercise may be effective. These microvascular morphological changes and related white matter lesions are usually considered to be non-reversible and progressive, although there is some evidence that, under certain circumstances, white matter lesions may be at least partially reversible (Yamada et al., 2010). Until more supports for reversibility emerges, interventions should be primarily focused on prevention and slowing.

3.7 | Interactions with other factors

The changes specific to the cerebrovasculature outlined in this review occur in the larger context of other age-related physiological changes in the body, which together interact to influence brain and cognitive health. Most of these peripheral physiological changes interact in negative ways, either by exacerbating changes in the cerebrovasculature or by increasing the likelihood of hypoperfusion.

One of the most important exacerbating factors is the presence of hypertension, a condition that exists in the majority of individuals over age 60 (Fryar et al., 2017). In this special issue, **Jennings et al.** (**2021**) present an extensive discussion of the interaction between hypertension and alterations to the cerebrovasculature. There is evidence that arterial stiffening precedes hypertension (Dernellis & Panaretou, 2005; Kaess et al., 2012; Liao et al., 1999; Najjar et al., 2008; Oh, 2018; Oh et al., 2017; Weisbrod et al., 2013). The presence of hypertension, once established, predicts decreases in cerebral microvascular density and increases in microvascular tortuosity, leading to distal hypoperfusion despite the higher pressure in the arteries (Brown & Thore, 2011; Han, 2012). In addition, hypertension may exacerbate arterial stiffening and lead to increased pulsatility, which may directly damage endothelial cells downstream and contribute to increasing leakiness in the BBB (de Montgolfier et al., 2019; Mitchell, 2014).

In addition to the direct effects of arteriosclerosis on hypertension, there are many associated factors that contribute to the onset of hypertension. Interacting systemic effects include sympathetic nervous system activation and increased levels of the circulating vasoconstrictor angiotensin, which are compounded by obesity, psychological stress, and existing vascular damage (Haspula & Clark, 2018; Villapol & Saavedra, 2015). The relationship between the aging brain and sympathetic/parasympathetic tone is further elaborated in this issue by **Thayer et al.** (**2021**). Because of its strong connection to arterial stiffness and cerebral vascular disease, it is difficult to separate hypertension effects from the effects of other vascular impairments. Hypertension has been linked to declining brain health, including decreased gray matter volume, decreased cortical thickness, decreased fractional anisotropy, and increased white matter lesions (Gonzalez et al., 2015; Jennings & Zanstra, 2009; Sabisz et al., 2019). It has also been linked to declining cognition across a number of domains, including memory, executive function, and processing speed (Iadecola et al., 2016). Ongoing research is working to resolve the ways in which hypertension exacerbates or causes other forms of vascular damage, and how it leads to cognitive decline.

Diagnosing hypertension can be difficult, since systemic blood pressure is continuously distributed in the population, and diagnostic criteria have changed over time (Brown & Haydock, 2000). Whereas systolic blood pressure tends to increase throughout the life span, changes in diastolic pressure are more variable. On average, diastolic pressure increases up to the 50s before gradually decreasing (Pinto, 2007). Pulse pressure is thought to reflect pulsatility and represent a greater cardiovascular risk factor than mean pressure (Blacher et al., 2000).

Another major interacting factor is decreased estrogen and other ovarian hormones in women after menopause. Estrogens are neuroprotective, and their loss during aging is associated with increased neuroinflammation, mitochondrial dysfunction, and cognitive impairment (Gurvich et al., 2018; Zárate et al., 2017). Age-related loss of ovarian hormones at the time of menopause has been hypothesized to partially explain increased female susceptibility to Alzheimer's Disease (Li & Singh, 2014). Declining sex hormone levels in women, and their protective actions on the cerebral vasculature (Zárate et al., 2017) and promotion of angiogenic activity (Yu et al., 2017), may represent the loss of a previously protective mechanism that interacts with other cerebrovascular risk factors.

There is evidence to suggest that the increased risk for developing late Alzheimer's Disease associated with the ε4 allele of the apolipoprotein E gene (APOE4) is due to the role of this gene in the development of atherosclerosis within the cerebrovasculature (Tai et al., 2016). Thus, atherosclerosis may occur through both direct and indirect signaling and interactions with other risk factors covered in this review (Sudre et al., 2017; Tai et al., 2016).

A number of other age-related physiological changes in the periphery may have a direct impact on the amount of oxygen transported to the brain. Muscles that support breathing become weakened and modifications to the pulmonary air sacs may reduce air exchange (Lee et al., 2016). Death of natural pacemaker cells in the sinoatrial node of the heart can result in slower heart rate (Steenman & Lande, 2017). In addition, the heart wall may thicken and reduce the amount of blood held in the chamber (Steenman & Lande, 2017). Blood volume itself may decrease, and new red blood cells may be produced at a slower rate (Price, 2008). All of these changes can reduce oxygen and nutrients flowing to the brain, contributing to reduced cognitive function. The brain has many adaptive compensatory mechanisms in place to control oxygen supply, but as cerebrovascular health is taxed, other physiological changes may contribute to exceeding the cerebrovascular reserve, resulting in hypoperfusion.

Finally, the recent global spread of the SARS-CoV-2 virus has led to questions about potential long-term health consequences to cerebrovascular health in infected individuals. Early on in the pandemic, it was observed that older adults with cerebrovascular diseases or vascular risk factors were at the highest risk of infection with the poorest prognosis for outcomes (Fan et al., 2020). Although still speculative, there are fears that persistent neuroinflammatory effects from SARS-CoV-2 infection may trigger the onset or exacerbate the progression of psychiatric and neurodegenerative diseases in the long term and may represent a significant interacting risk factor in the future of cerebrovascular aging (Iadecola et al., 2020; Serrano-Castro et al., 2020).

4 | SYNTHESIS: TRAJECTORIES OF CEREBROVASCULAR IMPAIRMENT

Age-related changes to the cerebrovascular system cause a loss of vascular function, which propagates to neuronal health and manifests as cognitive decline. However, the mechanisms leading to vascular-system changes are heterogeneous, and vary in their preventability, reversibility, and time course. Understanding this heterogeneity is critical for targeting specific aspects of cerebrovascular health and appropriately treat different types and levels of dysfunction. We have discussed these points in the previous subsections, which are summarized in Table 1.

The onset of cerebrovascular dysfunction depends on a cascade of events and alterations. For example, in hypertension, arterial stiffening seems to occur first. Arterial stiffening, however, seems to depend on arterial inflammation, so it would be expected that preventive anti-inflammatory interventions would reduce arterial stiffening and thus hypertension. Somewhat surprisingly, many classes of medications for hypertension work well at reducing blood pressure, but do not treat the factors that caused the hypertension to appear in the first place. Strikingly, there is little evidence that hypertension treatment improves cognitive performance (Iadecola et al., 2016; **Jennings et al., 2021**). A major theme of this review is that many types of age-related cerebrovascular dysfunction begin early in life, and are therefore partially preventable or even reversible with appropriate lifestyle adjustments to diet/fasting and exercise (see **Aghjayan et al., 2021**; Stillman et al., 2021, in this issue; Dong et al., 2020).

We have reviewed evidence for a general pattern of age-related cerebrovascular decline beginning with vascular inflammation, which precedes or co-occurs with declines in arterial elasticity. As arterial elasticity decreases, pulsatility increases, which leads to a variety of interacting types of downstream damage to the cerebrovasculature, including BBB impairment, impaired CVR, and hypoperfusion through changes to microvascular density and morphology. This damage at the microvascular level then impairs the function of the brain parenchyma, which manifests behaviorally as cognitive decline and is likely a causative factor in age-related brain pathology.

The trajectory of cerebrovascular pathology depends on the mathematical function that the causative mechanism

TABLE 1 A summary of age-related cerebrovascular decline

	Onset	Preventability	Reversibility	Time course
Arterial inflammation	~20	Partial	Yes	~Likely exponential
Arterial stiffening	~30	Partial	Yes, up to critical zone	~Likely exponential
Arterial weakening	~40	Partial	No	Not strongly related to age (in cerebral arteries)
Decreased vascular reactivity	~35–60	Likely	Likely	Possibly sigmoidal
Leaky blood–brain barrier	~40	Partial	Likely	Context dependent
Loss of microvasculature	~50	Likely	Likely	Microvascular density increases before decreasing to floor
Tortuosity of small vessels	~50	Unknown	Unknown	Unknown

follows. At a simplified level, a distinguishing separation may be identified between processes that have positive feedback loops causing more dysfunction, and processes that do not. When a "vicious-cycle" arises, where a mechanism of dysfunction causes even more dysfunction, the resulting pathology often follows an exponential trajectory, whereas when a positive feedback loop does not exist, the process is expected to be more linear. In reality, the body has many homeostatic mechanisms in place, which serve to blunt runaway damage from a positive feedback loop of dysfunction. In addition, multiple aspects of the system interact with each other, and so their dysfunction is not cleanly separable. Even so, this view may offer a simplified framework for making predictions, while more complex and accurate biophysical models are developed.

Through this lens, it is apparent that many types of cerebrovascular damage are expected to follow vicious-cycle patterns. At the cellular level, mitochondrial dysfunction, and the production of increased ROS, is an example of a vicious cycle that causes widespread dysfunction throughout the body and is thought to be one of the factors primarily responsible for the aging process (Kriete et al., 2010; Sohal & Orr, 2012). The damage from this vicious cycle impairs signaling and causes damage at a cellular level, which directly contributes to even greater mitochondrial dysfunction. Similarly, arterial stiffening can cause higher pulse pressure, which further exacerbates stiffening. The downstream damage to the microvasculature caused by increased pulsatility may also follow a vicious cycle pattern. Damage to the BBB would be expected to let in inflammatory factors that further contribute to damage. The potential for these positive-feedback cycles highlight the importance of early intervention and predict that cerebrovascular dysfunction would grow slowly at first but accelerate rapidly toward the end of the life span. Although there may be many interacting systems that contribute to eventual cognitive decline, this pattern may lead to the nonlinear longitudinal declines in cognitive ability observed across many cognitive domains, with the most rapid acceleration of decline at the oldest ages (Schaie et al., 2004).

On a more positive note, there is ample evidence that most of these types of damage are somewhat preventable, or even reversible, and that their progression can be slowed. This fact highlights the resilience of the body and implies the presence of biological mechanisms that can be exploited to ameliorate cerebrovascular decline. This fact also makes the cerebrovascular system a particularly appealing therapeutic target. If we intervene before too much neural damage has accumulated, it may be possible to diminish the impact of vicious cycle mechanisms by simply removing environmental factors that exacerbate damage, giving the body's natural healing mechanisms an edge to stave off accumulating damage, or by adding environmental factors that are known to improve vascular outcomes. In addition, the fact that behavioral interventions can have such an impact on cerebrovascular health presents opportunities for pharmaceutical interventions. As the mechanistic details behind how behavioral interventions lead to improved outcomes are fully elucidated, those same mechanisms can be targeted through pharmaceuticals. Recent promising pre-clinical studies have targeted age-related vascular dysfunction through strategies of supplementing IGF-1 (Quipildor et al., 2019), reducing mitochondrial oxidative stress (Csiszar et al., 2019), or boosting the activity of sirtuins (signaling proteins involved in regulating metabolism) (Tarantini et al., 2019).

Although this review does not focus on the structural, functional, and cognitive age-related changes that have been highlighted by their own vast literatures, it is important to examine the temporal relationship of how impaired cerebral vascular health might interact with these other age-related brain changes and cognition. Kong et al. (2019) have advanced a hierarchical model to link these factors. This model suggests that at least some of the variance accounting for age-related changes in cognitive performance follows a cascade that begins with vascular impairments that lead to structural changes detectable with MRI. Structural changes lead to alteration in functional network dynamics that finally predict altered cognition (Figure 5). Although the correlational structure between measures in that study was consistent with such a framework, future longitudinal work should confirm or revise it. An important question for future directions in early diagnosis and intervention is whether large-scale anatomical changes, such as the visible white matter abnormalities and cortical atrophy measures reported in this article, are necessarily evident before changes in brain functional dynamics are visible.

5 | METHODOLOGICAL CONSIDERATIONS IN NEUROCOGNITIVE AGING RESEARCH

Many of the age-related physiological changes discussed in this review affect the interpretation of measures from many of the commonly used tools in psychophysiological and cognitive neuroscientific research. This is because many tools measure different parts of the neurovascular coupling response that is often used to infer neural activity (Figure 6).

5.1 | Measuring age-related metabolic changes

The cerebral metabolic rate of oxygen ($CMRO_2$), measuring how much oxygen is consumed by the brain during metabolism, is often considered a summary index of brain

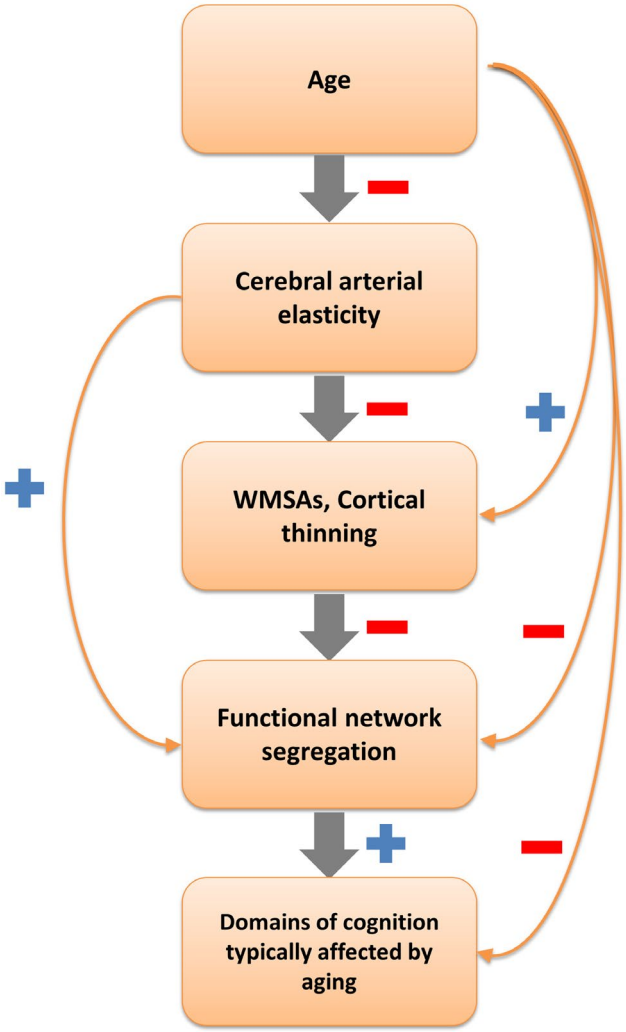

FIGURE 5 A framework for viewing the effects of cerebrovascular impairment on cognition as a hierarchical cascade of effects. Gray arrows represent the hypothesized cascade. Orange arrows represent pairwise relationships between the levels. The signs next to the arrows represent the direction of the pairwise relationships. WMSAs, white matter signal abnormalities. From Kong et al. (2020), reprinted with permission

metabolic activity. However, an interesting discrepancy exists regarding age-related changes in $CMRO_2$ depending on whether it is measured using MRI (see Rodgers et al., 2016 for a review of these methods) or positron emission tomography (PET). Studies using MRI-based methods have reported variable effects of age on resting $CMRO_2$, including increases (Lu et al., 2011; Peng et al., 2014), decreases (De Vis et al., 2015), or no change (Catchlove, Macpherson, et al., 2018). However, PET-based studies have mostly shown decreases in $CMRO_2$ (as well as in glucose uptake) with aging (Aanerud et al., 2012; Eustache et al., 1995; Goyal et al., 2017; Ibaraki et al., 2010; Kuhl et al., 1982; Yamaguchi et al., 1986), although some studies found no age differences (Aanerud et al., 2017; Pantano et al., 1984).

These disparities across methods also extend to task-evoked changes in metabolism, with the blood-oxygen-level-dependent (BOLD) MRI signal showing increases with age in task-evoked activity, particularly in prefrontal and parietal regions involved in executive functions (Cabeza et al., 2004; Cappell et al., 2010; Daselaar et al., 2003; Hutchison et al., 2013; Park et al., 2003) and reductions in more posterior visual processing regions (Davis et al., 2008). Findings like these have been interpreted as functional compensation, especially because task-evoked activity in sensory areas often decreases with age, which is often interpreted as an impairment in sensory processing (Cabeza et al., 2018; Park & Reuter-Lorenz, 2009; Schneider-Garces et al., 2010). Due to the lower temporal resolution, age-related changes in task-related metabolic changes are less well-studied using PET. However, in one study of dynamic changes assessing glucose metabolic rate using PET, researchers found smaller task-based metabolic increases as a function of age in medial frontal and cingulate areas during a verbal memory task (Hazlett et al., 2010).

One possibility for this discrepancy is rooted in intrinsic limitations to the techniques that will push correlations with age in opposing directions. In PET, images are often lower resolution, which may increase the relative contribution of the CSF partial volume fraction in a cortical voxel due to brain atrophy with aging (Peng et al., 2014). Thus, it is possible that cortical $CMRO_2$ decreases, not because of real metabolic change in the existing tissue, but rather because there is less metabolically active tissue being measured. This potential effect of atrophy would explain why, in PET, decreases in $CMRO_2$ are prominent in association areas, where age-related atrophy is most evident, and unobserved in primary motor and sensory areas, where tissue volume is usually relatively spared across the life span (Aanerud et al., 2012; Fjell et al., 2009; Kennedy & Raz, 2015; Raz et al., 2005).

MRI methods also face limitations that may bias measurement. These limitations have to do with the somewhat less direct measurements of $CMRO_2$, which depend on measurements of blood flow. These blood flow measurements do not automatically take into account individual differences in hematocrit, which may differ by sex (Grau et al., 2018), change with age (Aanerud et al., 2012; Mahlknecht & Kaiser, 2010), and have a high correlation with CBF (Xu et al., 2018). They are also affected by scanning parameters, such as the choice of location that determines the flow measurement (Liu et al., 2013; Peng et al., 2014). If the capacity to carry oxygen decreases with age and is not properly accounted for, it may be wrongly concluded that increases in blood flow correspond to greater increases in oxygen. This troubling possibility highlights the importance of building a better understanding of how properties and limitations of specific brain measurement techniques and samples affect results and

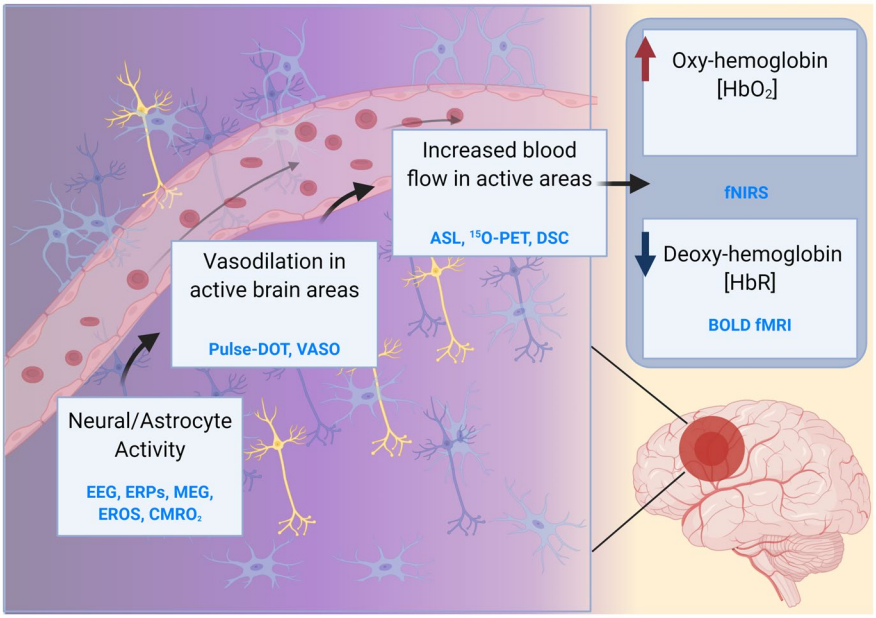

FIGURE 6 Commonly used methods in cognitive neuroscience and psychophysiological research primarily measure different components of neurovascular coupling. In neurovascular coupling, cellular metabolism at the neurovascular unit signals local vasodilation. This increases blood flow to active areas, which interacts with metabolism to alter the nearby blood oxygenation. ASL, arterial spin labeling; BOLD fMRI, blood-oxygen-level-dependent functional magnetic resonance imaging; $CMRO_2$, cerebral metabolic rate of oxygen; DSC, dynamic susceptibility contrast perfusion imaging; EEG, electroencephalogram; ERPs, event-related potentials; EROS, event-related optical signal; fNIRS, functional near-infrared spectroscopy; MEG, magnetoencephalography; ^{15}O-PET, oxygen-15 positron emission tomography; Pulse-DOT, brain arterial pulse wave measured with diffuse optical tomography; VASO, vascular-space-occupancy magnetic resonance imaging

emphasizes the importance of multi-modal techniques and accruing complementary data across multiple modalities and experimental paradigms.

Another intriguing possibility is that declines in glucose and oxygen consumption are not perfectly coupled, and that the extent of their coupling varies by age. Recent evidence that glucose consumption (CMRGlc) declines more with age than oxygen consumption (Goyal et al., 2017; Kuhl et al., 1982) supports this hypothesis. This finding has been interpreted as a reduction in glucose use that is not metabolized by oxidative phosphorylation, reasoning that a 1:6 relationship between glucose and oxygen is used to supply oxidative phosphorylation, and the whole quantity of $CMRO_2$ is used for this purpose (Goyal et al., 2017). Excess glucose is hypothesized to be associated with intermediary metabolism used for biosynthesis and neuroprotection through the pentose phosphate pathway, relevant especially to synaptic plasticity (Goyal et al., 2017). However, it is also possible to interpret the metabolic change, at least in part, as an excess of oxygen that is not efficiently used for oxidative phosphorylation. It is known that mitochondria use more oxygen than is required for oxidative phosphorylation, resulting in a "proton leak" estimated to be ~20% (Engl & Attwell, 2015; Rolfe & Brown, 1997). Mitochondrial efficiency in oxidative metabolism also decreases with age (Gómez & Hagen, 2012). Therefore, it seems plausible that the greater reduction in CMRGlc compared to $CMRO_2$ also represents some decrease in oxygen used for oxidative phosphorylation, which may contribute to increase ROS. The possibility of uncoupling between glucose and oxygen metabolism, mediated by either inefficient oxygen use or declining glucose metabolic processes, suggests that, at the very least, $CMRO_2$ results should be interpreted cautiously as a proxy for neural metabolism. Confusing interpretation even further, cerebral declines in metabolism differ by sex (Goyal et al., 2019), with females having less metabolic decline compared to men of the same age. Future research, possibly using PET/MRI simultaneous imaging, is needed to resolve these discrepancies and better understand how metabolic processes change in aging.

5.2 | Considerations for BOLD imaging

Declines in neurovascular coupling mechanisms alone, independent from changes in metabolism, predict changes in BOLD signal with age (Fabiani, Gordon, et al., 2014). This result blurs the interpretation of age-related BOLD signal changes, a measurement often used experimentally to theorize about the mechanisms of age-related cognitive change. The varying vascular phenomena that may specifically contribute to BOLD signal changes are explicated in detail by **Yabluchanskiy et al. (2021)**

Some changes in BOLD response that contribute to a decreased signal in older adults have been known for some time and are extensively discussed in the literature, including changes in signal timing (Zhao et al., 1998) and increased voxel-wise noise (D'Esposito et al., 1999). More recently, researchers have become more concerned about changes in both neurovascular coupling and in neurovascular energetics, both discussed earlier in this review, and how they may confound interpretations of the BOLD signal in aging (Abdelkarim et al., 2019; **Zhao et al., 2021;** West et al., 2019; Wright & Wise, 2018). If there are age-related differences in neurovascular coupling or neurovascular energetics, then a difference in BOLD signal between older and younger participants could be produced independently of a difference in neural activation (Figure 7; conceptually adapted from Wright & Wise, 2018). However, clarifying the details of how age-related changes in neurovascular coupling and metabolism interact is important for interpreting results of functional imaging studies in age-related samples that depend on the BOLD signal, and may have non-intuitive consequences. This is because the BOLD signal comes about through complex, interacting physiological mechanisms, which predicts, on the one hand, that greater oxidative metabolism during neural activity would reduce the oxygenation of the blood and reduce the BOLD signal but, on the other hand, that the typical functional hyperemia accompanying oxidative metabolism will overcompensate for that decreased oxygenation in the blood, and end up leading to greater oxygenation overall.

To give some illustrative examples, if CVR was completely impaired, but oxidative metabolism remained constant, there is an expectation of a *negative* BOLD signal in response to activation, as local deoxy-hemoglobin levels increased. If oxidative metabolism increased, but the amount of vasodilation from neurovascular coupling remained constant, the BOLD signal would decrease. If oxidative metabolism decreased, but the amount of vasodilation from neurovascular coupling remained constant, the BOLD signal would increase. These examples are meant to illustrate that a deeper understanding of both neurovascular energetics and neurovascular coupling is critical for the interpretation of BOLD experiments in the cognitive neuroscience of aging. In addition, evidence suggests that even under normal, healthy conditions, neurovascular coupling is not a linear function, with reduced increases in the hemodynamic response at higher levels of neuronal activity (Fabiani, Gordon, et al., 2014).

Similar reasoning has led Abdelkarim et al. (2019) to propose that age-related decreases in the BOLD signal in some paradigms could reflect increased metabolic activity unmatched by CBF due to impaired neurovascular coupling, in contrast to an interpretation of decreased metabolic activity. This is particularly relevant to explaining a consistent discrepancy in functional aging studies, where

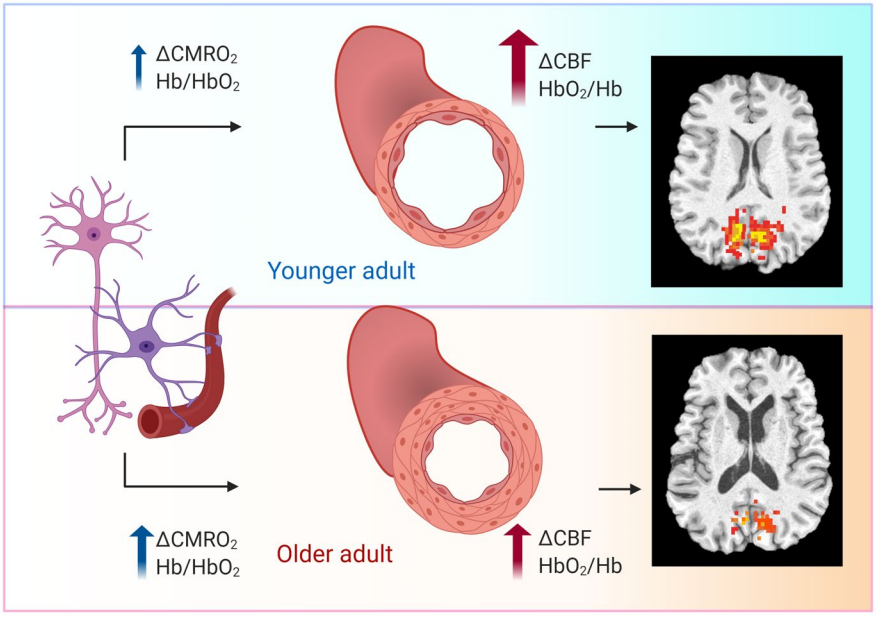

FIGURE 7 Changes in both neurovascular energetics and neurovascular coupling could mediate differences in the BOLD signal in aging. In younger adults, neural activity leads to an increase in oxygen extraction, which increases the ratio of deoxy/oxy-hemoglobin. However, this change is offset by a much larger increase in CBF from local vasodilation. Overall, there is a robust BOLD signal coupled to the neural activity. In older adults, both neurovascular energetics and neurovascular coupling mechanisms may change. In this example, the same task-related neural activity may lead to greater oxygen usage in older adults, due to lower metabolic efficiency. The increase in deoxy-hemoglobin in older adults compared to younger adults may lower the BOLD signal. In addition, impaired neurovascular coupling may reduce vasodilation, leading to smaller decreases in the ratio of deoxy/oxy-hemoglobin. Together, these lead to a reduced signal-to-noise in the BOLD signal of older adults

older adults have *greater* activation than younger adults at low task demands, but younger adults have greater activation than older adults at high task demands (Abdelkarim et al., 2019; Schneider-Garces et al., 2010). An interpretation of age-related changes in terms of increased metabolic demands for similarly difficult tasks, representing reduced efficiency, may offer a complementary view to one based on an account of limited "neural resources" at the core of the compensatory scaffolding models of cognitive aging (Cappell et al., 2010; Reuter-Lorenz & Park, 2014; Schneider-Garces et al., 2010).

In addition to these neurovascular physiological contributions to differences in the BOLD response, there may also be differences in low-frequency oscillations in BOLD signal that are less well studied. Bright and colleagues (2020) recently showed that vascular physiology may be organized in networks that mirror known neuronal networks. It remains unclear whether these vascular networks change with age, and how they relate to age-related changes in neural networks or whether they present a possible artifact when analyzing changes in functional network dynamics in aging.

Future work should strive to incorporate new methods or multiple modalities that can help to resolve changes in flow, blood volume, $CMRO_2$, and oxygenated/deoxygenated hemoglobin. Non-BOLD fMRI, such as vascular space occupancy (VASO) in particular may be even more important for studying cognitive aging in the burgeoning research area of depth-dependent laminar-fMRI, since vascular physiology can differ across depths (Goense et al., 2012; Huber et al., 2019), and layer-dependent functional signals may be easier to resolve using methods sensitive to blood volume rather than oxygenation (Huber et al., 2018, 2019, 2020).

5.3 | Considerations in interpreting perfusion

In general, researchers must be careful not to overinterpret perfusion as a proxy for metabolism and vascular function. For example, we may be tempted to explain a region's vulnerability to vascular damage by pointing out a region's higher metabolic demand, using perfusion rate as a proxy for metabolic activity to support the argument. However, in different circumstances, we may want to explain a region's vulnerability to vascular damage because of its already poor vascular health, such as its low vascularization or capillary pressure. Here, we may be tempted to use the same measure of perfusion rate as a proxy for vascular health. In the first example, higher perfusion rates predict vulnerability, while in the second example, lower values predict vulnerability. We should always keep in mind that perfusion measures inherently reflect both metabolic and vascular information and be very careful of their interpretation.

6 | CONCLUSIONS

In this review, we have shown that some aspects of age-related changes in cerebrovascular health are well characterized, while others are still poorly understood. Future research should pay special attention to cerebrovascular health factors that are hypothesized to *directly* contribute to cognitive impairment, but whose mechanisms are not fully known or accepted. How CVR changes with age, and the mechanisms behind those changes, present a good example of this type of research. The literature up to this point has not reached a consensus, with studies pointing to unreliable age-related effects that sometimes go in opposite directions. At the same time, CVR is hypothesized to directly affect the efficiency and speed of cognitive operations. Intriguingly, Peng et al. (2018) showed a function of age-related decline in CVR that accelerated most in middle-age rather than old age, presenting a strong case for the possible importance of early intervention.

Another direction of future research should elucidate the impact of minor ischemia, and its potential relationship to chronic inflammation, on downstream damage. Most studies on the mechanisms responsible for cellular damage and impairment after ischemia come from studies where large ischemic insults are experimentally induced. A critical missing link in the literature is to formally connect these same mechanisms to the long term, chronic low-level ischemia or periodic, acute bouts of short-lived ischemia that likely occur in normal aging, and their respective effects on cognition.

There is still room for major innovation in both therapeutic and basic research determining how normal age-related declines in vascular functioning can manifest as disease, and how interventions targeting vascular health can ameliorate both normal age-related cognitive decline and prevent or treat age-related neurodegenerative disease. Whether vascular dysfunction is the cause or consequence of many neurodegenerative diseases is still unknown, and very likely, vascular dysfunction and other pathogenic processes interact in complex ways that differ across diseases. Exciting innovations in non-invasive methods should help promote this work and lead to advancements in therapeutic strategies. For example, there is mounting evidence of BBB dysfunction in a number of neurodegenerative diseases as well as evidence that BBB impairment can be treated in rodents (Senatorov et al., 2019). However, there is currently no direct evidence for reversing BBB damage through an intervention in humans. New methods may allow the investigation of this research question in the near future.

Finally, a major implication of the research presented here, which has shown that cerebrovascular damage accumulates across the life span and eventually leads to neural impairment, is that using cognitive performance as a primary outcome measure may track levels of impairment that occur too late to be clinically useful. For optimal outcome,

the various vicious cycles involved in cerebrovascular aging should be interrupted when the damage is still very subtle. Truly, the research covered in this review shows that there is evidence for improvements in cognition based on interventions targeting vascular health, even at older ages, when vascular damage has likely already translated to some level of neural damage. However, given that there is a strong connection between cerebrovascular health and cognitive impairment and that cerebrovascular health may begin to decline well before significant changes in cognitive impairment are observed, a therapeutic strategy focusing strongly on prevention is well justified. To that end, cerebrovascular health measures should be considered as alternative or complementary primary outcome measures to cognitive performance, even though, in the end, it is cognitive ability that we want to preserve.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Ben Zimmerman: Conceptualization; Visualization; Writing-original draft; Writing-review & editing. **Bart Rypma:** Conceptualization; Funding acquisition; Writing-review & editing. **Gabriele Gratton:** Conceptualization; Funding acquisition; Writing-review & editing. **Monica Fabiani:** Conceptualization; Funding acquisition; Writing-review & editing.

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