



Published in final edited form as:

Psychophysiology. 2021 July ; 58(7): e13718. doi:10.1111/psyp.13718.

Age-related alterations in the cerebrovasculature affect neurovascular coupling and BOLD fMRI responses: Insights from animal models of aging

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Abstract

The present and future research efforts in cognitive neuroscience and psychophysiology rely on the measurement, understanding, and interpretation of blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to effectively investigate brain function. Aging and age-associated pathophysiological processes change the structural and functional integrity of the cerebrovasculature which can significantly alter how the BOLD signal is recorded and interpreted. In order to gain an improved understanding of the benefits, drawbacks, and methodological implications for BOLD fMRI in the context of cognitive neuroscience, it is crucial to understand

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

the cellular and molecular mechanism of age-related vascular pathologies. This review discusses the multifaceted effects of aging and the contributions of age-related pathologies on structural and functional integrity of the cerebral microcirculation as they have been investigated in animal models of aging, including age-related alterations in neurovascular coupling responses, cellular and molecular mechanisms involved in microvascular damage, vascular rarefaction, blood–brain barrier disruption, senescence, humoral deficiencies as they relate to, and potentially introduce confounding factors in the interpretation of BOLD fMRI.

Keywords

aging; microcirculation; neurovascular coupling; senescence

1 | INTRODUCTION

Basic neuroscience research has established that the brain undergoes extensive changes with advancing age (Wright & Wise, 2018). Basic cognitive aging research has established that psychological function (e.g., episodic and working memory, reasoning, planning, and problem solving) also undergoes extensive age-related changes. The notion that relationships may be found between changes in the aging brain and changes in cognitive performance has led to a generation of research in humans aimed at exploring age-related changes in brain–behavior relationships (see Abdelkarim et al., 2019). Neuroimaging modalities, most prominently functional magnetic resonance imaging (fMRI), have been utilized extensively in this enterprise. fMRI measures blood-oxygen-level-dependent (BOLD) signal that arises from a complex interplay of neural, glial, and vascular elements (Figure 1).

Thus, most “neurocognitive aging” studies using fMRI have focused on age-group differences in BOLD signal amplitude. Broadly speaking, this literature has not produced a consistent picture of relationships between age differences in performance and BOLD signal. We argue that reliance on preclinical studies that permit direct measurement of the physiologic components (i.e., vascular, glial, and neural) that together give rise to the BOLD signal can help resolve this confusion and shed light on which of the components in this neural-vascular complex are most closely associated with the pervasive performance changes that characterize the adult aging process.

2 | CELLULAR MECHANISMS UNDERLYING BOLD

A common misconception is that BOLD directly measures brain regional oxygen consumption, and therefore, neuronal activity. However, this is largely not the case as stimulus-evoked BOLD signals generally represent a decrease in deoxyhemoglobin concentration, and thus, reflect regional increases in blood oxygenation. Early observations from Roy and Sherrington (Roy & Sherrington, 1890) first characterized the intimate relationship between brain function and cerebral blood flow (CBF). They observed task-evoked cerebral vasodilation and attributed it to the increased demand for oxygen and nutrients in response to increased neuronal activity, leading them and other researchers to build on the hypothesis that CBF changes reflect a tight coupling between cellular energy requirements and vascular delivery of glucose and oxygen. Several scientists working in

the field of vascular neuroscience have built on these findings to make significant advances in understanding how the underlying vascular, vascular-associated glia, and parenchymal cells contribute to stimulation-evoked hyperemic responses (Attwell et al., 2010), also named neurovascular coupling (NVC). The intuitive idea that changes in CBF are directly controlled by metabolic activity has been revisited over the past decade. A range of cellular mechanisms have been implicated in contributing to NVC responses (Hillman, 2014). In particular, astrocytes (Metea & Newman, 2006; Petzold & Murthy, 2011; Stobart et al., 2013; Takano et al., 2006; Wells et al., 2015), pericytes (Peppiatt et al., 2006), interneurons (Cauli et al., 2004), smooth muscle cells, and endothelial cells (Chen et al., 2014), have been proposed to play a role in the local control of blood through a feedforward mechanism involving neuronal signaling and neurotransmitters (Attwell & Iadecola, 2002; Lauritzen, 2005; Takano et al., 2006). Excellent reviews² (Hillman, 2014; Tarantini et al., 2017) explore in detail current understanding of the molecular dynamics of neurovascular coupling responses, how they change in aging, and feature schematic illustrations to exemplify candidate mechanisms. Recent evidence supports the idea that astrocytes play an important role in linking neurotransmitter activity to vascular responses, and astrocyte-evoked BOLD signal may associate with oxygen consumption without modulation of neuronal activity (Pellerin & Magistretti, 2004; Takata et al., 2018). In this view, neurovascular coupling responses underlying generation of the BOLD signal would be evoked through activated glial mechanisms modulated by neuronal signaling, rather than by mechanisms that sense energy consumption. However, due to difficulties in reconciling astrocytic distribution, their connectivity, and intracellular Ca^{2+} transient timings with the spatiotemporal properties of neurovascular coupling, some studies (Chen et al., 2011; McCaslin et al., 2011; Nizar et al., 2013) have challenged the involvement of astrocytes, while others suggest that neurovascular coupling might be mediated by diffusion of products of neuronal activity without the involvement of glial cells. As there is no single mechanism that has been irrefutably demonstrated, the controversy regarding which mechanism, or combination of mechanisms, is responsible for the generation of the BOLD response is open for investigation. Another often-overlooked source of signaling molecules mediating neurovascular coupling is the vasculature itself. Previous work has identified endothelial hyperpolarization as a rapid mechanism by which neurovascular coupling responses may quickly propagate (Bagher & Segal, 2011; Figueroa & Duling, 2009) through gap-junctions within the endothelium itself with little attenuation (Wofle et al., 2011). An additional endothelial-mediated mechanism involves the slow propagation of endothelial Ca^{2+} waves (Tallini et al., 2007) that elicit smooth muscle cell relaxation via release of endothelial-derived NO and prostanoids such as prostacyclin (de Wit & Griffith, 2010). In part, the BOLD signal detected by fMRI reflects hemodynamic changes within the brain, which in turn are driven by metabolic alterations and neuronal activity (Keilholz et al., 2017). However, the link between BOLD changes and neuronal activity is indirect, and may be influenced by several nonneuronal processes as well, which include motion and physiological cycles, differences in the physiological baseline which contribute to intra- and intersubject variabilities, and the use of anesthesia alters neural activity, vascular tone, and NVC (Keilholz et al., 2017). Despite the lack of a unified theory, the predominant view is that some combination of the mechanisms listed above must work together to generate the blood flow response and the BOLD signal (Attwell et al., 2010).

3 | AGE-RELATED IMPAIRMENT OF NEUROVASCULAR COUPLING RESPONSES

The quickly growing field of geroscience has posed itself as an interdisciplinary approach that combines preclinical animals studies and clinical knowledge (Csipo et al., 2019) to understand the relationship between the biology of aging and the pathophysiology of chronic age-related diseases. A range of recent studies both in elderly patients and rodent models shows that aging significantly impairs neurovascular coupling responses (Balbi et al., 2015; D'Esposito et al., 2003; Fabiani et al., 2014; Park et al., 2007; Schroeter et al., 2007; Sorond et al., 2013; Tarantini et al., 2016; Tarantini, Valcarcel-Ares, et al., 2018, 2019; Tarantini et al., 2019; Tong et al., 2012; Zaletel et al., 2005). In aging, changes in the cerebrovascular ultrastructure caused by arteriosclerotic processes, increases in vascular oxidative stress (Logan et al., 2019; Tarantini, Valcarcel-Ares, et al., 2018, 2019; Tarantini et al., 2019), progressively dysfunctional cellular components of the neurovascular unit, and the age-related decline of important humoral vasoprotective factors (IGF-1) (Toth et al., 2015), all are believed to be important contributors to the impairment of neurovascular coupling responses and cognition. Notably, age-related changes in resting-state CBF have been identified in humans (Bertsch et al., 2009; Restom et al., 2007; Zhang et al., 2017). In studies using arterial spin labeling (ASL) perfusion MRI, that were persistent despite efforts to correct for age-related morphological changes (Chen et al., 2011). Measurement of CBF is integral to the measured BOLD signal as studies have suggested an inverse relationship between resting CBF and BOLD fMRI signal (Zebrowitz et al., 2016). The age-related changes in resting CBF have been tentatively attributed to alterations of end-tidal pCO₂ (De Vis et al., 2015). In murine models, resting CBF does not appear to change as a function of age (Tarantini et al., 2019) while evidence from isolated rodent cerebral arteries suggest that aging is associated with a decrease in baseline CBF (Faraci & Heistad, 1998). Collectively, age-related changes in BOLD signal have been shown to decrease significantly when lower baseline CBF is accounted for, reinforcing the view that observed age-related BOLD fMRI differences must account for a substantial vascular contribution (Zebrowitz et al., 2016). Although the exact mechanisms of neurovascular coupling are not completely understood, the extant evidence suggests that aging of the cerebrovascular system and age-related cerebrovascular pathologies can influence the BOLD signal independently of neural activity and must be accounted for with appropriate study design, correct analysis, and interpretation of BOLD fMRI data when comparing age groups.

3.1 | Phenotypic alterations of the vascular structure in aging

With age, the structural integrity of the cerebrovasculature is altered (Farkas et al., 2000; Li et al., 2018), thus, compromising cerebral circulation and leading to potential functional consequences such as increased risk for neurodegeneration and declining cognitive function. Among the age-related phenotypic changes observed in the cerebrovasculature are increased thickness of capillary basement membrane (Alba et al., 2004), age-related rarefaction (Tarantini et al., 2016; Tarantini et al., 2016; Tucek et al., 2014) in animal models, and decreased cerebral capillary density in aged humans (Brown et al., 2007; Meier-Ruge et al., 1980; Riddle et al., 2003). Vascular rarefaction is of particular interest in the context of BOLD fMRI signal interpretation, as variations in the pulse sequences and magnetic field

intensity can bias the BOLD signal to larger vessel sizes (Mueller-Bierl et al., 2007). Arterial stiffness, a feature often present in the larger vasculature of aged individuals (O'Rourke & Hashimoto, 2007) may also be present in the smaller cerebral arterioles and be implicated in experimentally observed CBF pulsatility increases (Springo et al., 2015) despite the overall baseline CBF decreases (Tarumi et al., 2014). These structural alterations may impact vascular elasticity and perfusion capacity possibly influencing CBF and functional changes during stimulus-evoked functional hyperemia which in turn could impact BOLD fMRI signal magnitude and timing (Brown et al., 2003). Additionally, recent evidence has shown that the interaction between increased adiposity and aging can be detrimental for neurovascular function, cerebrovascular integrity, and cognitive function. In their study, Csiszar et al (Tucsek et al., 2014) found that aging exacerbates the obesity-induced decline in microvascular density both in the hippocampus and in the cortex of mice fed a high-fat diet. The extent of hippocampal microvascular rarefaction and the extent of impairment of hippocampal-dependent cognitive function positively correlated, thus, indicating that obesity must be considered as a variable when analyzing BOLD signal in aged individuals.

3.2 | Oxidative stress, microvascular inflammation, and endothelial dysfunction in aging

Chronic, low-grade inflammation has been identified as a hallmark of aging (Cervellati et al., 2018; Royce et al., 2019), the term “Inflammaging” (Franceschi et al., 2000; Franceschi & Campisi, 2014; Wilhelm et al., 2017) has been used to emphasize this close association between aging and the accompanying age-related low-grade sterile inflammatory processes taking place. Growing evidence suggests that the combination of aging and inflammation accelerates the development of vascular and microvascular pathophysiological processes due to the increased generation of reactive oxygen species (ROS) through increased NAD(P)H oxidase activity (Adler et al., 2003; Donato et al., 2007; Jacobson et al., 2007; van der Loo et al., 2000), and through inefficient mitochondrial oxidative phosphorylation (Balaban et al., 2005; Lesnefsky & Hoppel, 2006; Sure et al., 2018) promoting endothelial dysfunction (Donato et al., 2007). Heightened inflammatory status also associates with microvascular dysfunction in the eye (Lipecz et al., 2019). Direct evidence from animal models of aging has suggested that oxidative stress and endothelial dysfunction are critical players in the etiology of age-related cerebrovascular impairment (Fulop et al., 2018) and neurovascular uncoupling (Costea et al., 2019; Park et al., 2007; Tarantini et al., 2016; Toth et al., 2014). In endothelial cells mitochondria and NADPH oxidases are major sources for ROS production (Carvalho & Moreira, 2018; Tarantini, Valcarcel-Ares, et al., 2018, 2019). Endothelium-derived nitric oxide (NO) is a potent vasodilatory gasotransmitter and its production and bioavailability has been found to be an important contributor to NVC responses (Toth et al., 2015). In aging, highly reactive excess superoxide ($O_2^{\cdot-}$) molecules sequester free NO to form peroxynitrate ($ONOO^-$) thus decreasing bioavailability of endothelium-derived NO, impairing the dilatory capability of the cerebrovasculature (Csiszar et al., 2002; Park et al., 2007; Tarantini et al., 2016; Tarantini et al., 2017; Tarantini et al., 2018). In support of the role of endothelial dysfunction in impaired NVC responses, experimental evidence suggests that treatments that restore endothelial function (Tarantini et al., 2018; Tarantini et al., 2019), improve NO bioavailability (Wiedenhoeft et al., 2019), inhibit NADPH oxidases (Park et al., 2007), or reduce cerebrovascular oxidative stress (Kiss et al., 2019; Tarantini et al., 2019; Toth et al., 2014) can improve NVC responses

in aged animals. Recent experimental studies in mouse models of aging have shown that old mice overexpressing human catalase in the mitochondria (MCAT) also benefit from attenuated age-related oxidative stress, improved microvascular endothelial function and preserved NVC responses (Csiszar et al., 2019). It should be noted that in addition to chronological aging, accelerated cerebrovascular aging associated with pathological conditions (e.g., obesity (Csipo et al., 2018), hypertension (Girouard & Iadecola, 2006; Iadecola & Gottesman, 2019)) also impair endothelial function and neurovascular coupling responses and thereby likely modulate the BOLD signal.

3.3 | Age-related loss of vasodilatory capacity

In addition to impaired response to dilatory stimuli, the intrinsic ability of cerebral vessels to dilate was found to be impaired in aged rodents (Tamaki et al., 1995) and in older humans (Csipo et al., 2019; Fluck et al., 2014) potentially as a consequence of age-related vascular stiffening. Inhalation of higher concentration of CO₂ (hypercapnia) has been used to study vascular reactivity in rodent models (Balbi et al., 2015) as well as humans (Fluck et al., 2014; Riecker et al., 2003). Despite the intrinsic limitations of studies involving hypercapnia such as the rate of metabolism and respiratory function as confounding variables, the observed evidence suggests that aged vessels exhibit a lower degree of cerebrovascular reactivity, leading to impaired stimulus-evoked vasodilation. Interestingly, evidence from arteries isolated in aged rodents also show aged vessels display a reduced response to endothelium-dependent vasodilators (Mayhan et al., 1990). Age-related impairment of vascular reactivity may result in decreased BOLD fMRI signal measurements and an overall misrepresentation of stimulus-evoked neural responses in aged individuals compared to younger groups.

3.4 | Role of astrocytes and aging

Astrocytes are among the most prevalent glial cells in the brain and their ideal positioning at the interface between neurons and microvessels allows for their fine end-feet processes to intimately contact and facilitate communication between neuronal synapses and the cerebral microvasculature (Mishra, 2017). Mounting evidence over the past 15 years has revealed that astrocytes play a crucial role in the mediation of NVC responses (Filosa et al., 2016) by releasing vasodilator metabolites of arachidonic acid and ATP. In recent basic research studies, many astrocyte-derived vasoactive signals have been identified and their role on vessel relaxation or contraction has been confirmed (Filosa et al., 2016). Numerous studies conducted in rodent brain slices and in experimental animals have provided evidence in support of astrocytic participation in the regulation of cerebrovascular tone (Attwell et al., 2010; Carmignoto & Gomez-Gonzalo, 2010; Gordon et al., 2007; Iadecola & Nedergaard, 2007) and in modulation of NVC responses in animal models in vivo (Hosford & Gourine, 2019; Tarantini et al., 2015; Xu et al., 2008).

During the stimulus-evoked increase in neuronal activity, many proposed pathways are activated to produce NVC responses, and some evidence has also considered the more direct forms of signaling from activated neurons to vessels (Cauli & Hamel, 2010). A majority of studies performed primarily in brain slices suggest that astrocytes first respond to elevations in extracellular glutamate as the main signal activating neurovascular responses (Fergus

& Lee, 1997; Zonta et al., 2003). Mechanistically, the presence of glutamate stimulates a group 1 metabotropic glutamate receptor (mGluR)-dependent elevation of astrocytic intracellular Ca^{2+} via IP_3 signaling resulting in a arteriolar vasodilatory response (Zonta et al., 2003). The increase in end-feet Ca^{2+} activates calcium sensitive phospholipase A2 which releases arachidonic acid, which is promptly converted by cyclooxygenases into prostaglandins such as PGE2 or PGI2, and by epoxygenases to epoxyeicosatrienoic acids (EETs; Figure 1). Prostaglandins and EETs bind to EP receptors, activate TRPV4 (Nilius et al., 2003) and large conductance BKCa channels. In vivo animal studies and brain slice work support this view by showing that astrocytic Ca^{2+} transients result in release of arachidonic acid metabolites (Carmignoto & Gomez-Gonzalo, 2010; Koehler et al., 2009; Takano et al., 2006). Interestingly, in specific experimental settings, arachidonic acid metabolites have been shown to elicit vaso-constriction instead of vasodilation (Dabertrand et al., 2013), notably under pathological conditions arachidonic acid can be metabolized into 20-hydroxyeicosatetraenoic acid (20-HETE), a vasoactive constrictor molecule (Toth et al., 2013). This evidence suggests that age-related pathologies such as hypertension must be accounted for in the analysis of BOLD fMRI signals as astrocytic contribution to neurovascular hyperemic responses might become impaired.

Because the manner in which aging affects astrocytes is not completely understood, many studies are interrogating the multifaceted consequences of astrocytic aging, including alterations in Ca^{2+} wave patterns (Mathiesen et al., 2013) and age-related changes in arachidonic acid metabolite production and release (Keleshian et al., 2013). Recent evidence from rodent studies suggests that, in addition to the newly discovered astrocyte heterogeneity, some astrocytic populations may switch to a “reactive” phenotype during aging (Clarke et al., 2018), resulting in the development of astrogliosis (Rodriguez-Arellano et al., 2016), a pro-inflammatory state characterized by complement activation (Boisvert et al., 2018), synapse elimination, and neuroinflammation. Since astrocyte reactivity and dysfunction are newly discovered key features of age-related pathologies (Matias et al., 2019), a better understanding of age-related changes on astrocytic phenotypes hold the promise of ameliorating potential confounding factors in the interpretation of BOLD fMRI signal in aging populations.

3.5 | Neurovascular energetics in aging

Evidence from several laboratories indicate that the age-dependent neurovascular uncoupling, or impairment of NVC response magnitude, could be exacerbated by age-related alterations in the cerebral metabolic rate of oxygen (CMRO_2) (Lourenco et al., 2018; Peng et al., 2014; Schwarzbauer & Heinke, 1999) or impaired cellular energetics in the neurovascular unit (Tarantini, Valcarcel-Ares, et al., 2018, 2019; Tarantini et al., 2019). The moment-to-moment equilibrium between local O_2 supply and consumption after neuronal activation follows a biphasic nature, with an immediate initial increase in regional O_2 consumption followed by a positive component follows as the supply overcomes the demand with increased CBF (Thompson et al., 2003). Experiments performed on Wistar rats have shown that aging has no effect on the initial rise of tissue oxygen demand, but older rats showed a significantly higher tissue oxygen supply during the hyperemic response despite an impaired CBF response. These results suggest the presence of an age-related

decrease in regional CMRO₂ (Lourenco et al., 2018). Other studies have shown both basal and maximal O₂ consumption-rate decrease in aged mouse brain slices (Dias et al., 2016) and an age-related reduction in oxidative phosphorylation in F344 rats (Lam et al., 2009), suggesting a critical role for cellular bioenergetics in preserving healthy NVC responses. In vivo murine studies have shown that even short-term treatments aimed at improving cellular energetics are successful in restoring NVC responses (Tarantini, Valcarcel-Ares, et al., 2018, 2019; Tarantini et al., 2019). However, in the context of age-related changes that may affect BOLD fMRI signal interpretation, the relationship between neurovascular uncoupling and CMRO₂ may have the strongest confounding effect. The higher O₂ demand with diminished supply observed in rodent studies (Lourenco et al., 2018) would result in increased venous deoxy-hemoglobin concentrations (Hutchison et al., 2013; Lu et al., 2011), partially explaining how age-related changes in CMRO₂ and CBF would affect the BOLD fMRI response signal.

Another fundamental feature contributing to vascular aging is mitochondrial dysfunction (Chistiakov et al., 2012; Chistiakov et al., 2014; Sobenin et al., 2013; Ungvari et al., 2007, 2008). Age-dependent impairment in mitochondrial function is associated with decline in mitochondrial oxidative phosphorylation, state 3 respiration, and diminished activity of complexes I and IV in the electron transport chain, resulting in increased electron leakage, diminished ATP yield, and generation of mitochondrial ROS (Dai et al., 2012). Recent evidence in animal models demonstrated that ATP and its metabolites (ADP and adenosine) are also important gliotransmitters released by astrocytes upon neuronal stimulation (Heinrich et al., 2012; Toth et al., 2015). In rodents, astrocyte-derived ATP was found to contribute to stimulus-evoked cerebrovascular dilation by increasing NO production (Toth et al., 2015). In humans, ATP synthesis capability has been found to decrease 8% every decade of life (Short et al., 2005) as most cell types experience altered cellular energy homeostasis. Still, little is known about the relationship of aging on purinergic signaling and its contribution to vasomotor responses, thus, introducing confounding factors affecting the interpretation of BOLD fMRI signals.

3.6 | Senescence

Cellular senescence is a state in which cells no longer go through the stages of the normal cell cycle and do not divide to create new cells. Despite its name, cellular senescence occurs throughout life, and serves to maintain healthy tissue by preventing proliferation of potentially tumorous cells. Under normal, healthy conditions, senescent cells signal for their own removal from tissue. In aging, however, this does not always occur, and senescent cells accumulate in tissue and assume a specific phenotype known as the senescence-associated secretory phenotype (SASP). Cells expressing SASP can secrete inflammatory substances that might harm nearby tissue, and their accumulation has been associated with age-related disease (Campisi et al., 2011; van Deursen, 2014; Ovadya & Krizhanovsky, 2014). The available evidence indicate that endothelial senescence associates with a substantial increase in the release and/or production of pro-inflammatory chemokines and cytokines that exacerbate the heightened inflammatory status of the aged vasculature (Morgan et al., 2013; Ungvari et al., 2019). Also senescent endothelial cells contribute to endothelial dysfunction in aging and worsen the pathophysiological conditions associated

with accelerated vascular aging (Brandes et al., 2005; Herrera et al., 2010; Kida & Goligorsky, 2016; Pantsulaia et al., 2016) which may in turn affect negatively neurovascular coupling responses and affect BOLD signal. Due to the crucial importance of astrocytes in mediation of neurovascular coupling, evidence in favor of the importance of astrocyte senescence in the impairment of neurovascular coupling has been growing in recent years (Cohen & Torres, 2019; Csipo et al., 2020; Lye et al., 2019). Senescent astrocytes demonstrate increased levels of intermediate glial fibrillary acidic proteins and vimentin filaments, increased expression of pro-inflammatory cytokines (including interleukin-6 (Bhat et al., 2012)) and increased accumulation of proteotoxic aggregates which are thought to play a role in age-related neuroinflammation and neuronal degeneration (Salminen et al., 2011). Importantly, anticancer treatments, including irradiation (Yabluchanskiy et al., 2020) and chemotherapy (Carlson et al., 2018) can cause neurovascular senescence, which associate with significant impairment of neurovascular coupling responses.

3.7 | Age-related IGF-1 deficiency

Changes in the systemic milieu in aging is associated with complex changes in the circulating levels of vasoprotective endocrine factors (Kiss et al., 2020; Schafer & LeBrasseur, 2019; Ungvari et al., 2018, 2020; Zhang et al., 2019). Decrease in circulating insulin-like growth factor 1 (IGF-1) as a consequence of aging has recently been shown to exert detrimental effects on various aspects of endothelium-dependent vasodilation (Toth et al., 2015) and contribute to microvascular rarefaction (Norling et al., 2019; Sonntag et al., 1997; Tarantini et al., 2016; Tarantini et al., 2016). Extensive early research has determined that the reduction in IGF-1 is an important component of the age-related decline in cognitive function in multiple species including humans (Frater et al., 2018; Norling et al., 2020; Sonntag et al., 2013). Additionally, genetic IGF-1 deficiency was shown to impair vascular function (Bailey-Downs et al., 2012; Bailey-Downs et al., 2012; Csiszar et al., 2008; Fulop et al., 2018; Tarantini et al., 2016; Tarantini et al., 2016; Tarantini et al., 2016; Tarantini et al., 2017; Toth et al., 2014), including neurovascular coupling responses in rodent models (Toth et al., 2015). A recent study suggested that systemic circulating IGF-1 protects against features of cognitive and sensorimotor decline with aging in male mice (Farias Quipildor et al., 2019). Given the close relationship between age-related circulating IGF-1 deficiency and endothelial health and neurovascular coupling responses, it is plausible that IGF-1 levels may play an important role in the modulation of the BOLD signal.

3.8 | Age-related pathologies

Lipopolysaccharide (LPS)-induced encephalopathy induces neuroinflammation. Long-term neuroinflammation is associated with aging and subsequent cognitive impairment (CI). A recent study used parametric MRI approaches to assess cerebrovascular, blood–brain-barrier (BBB), metabolic and free radical level changes associated with LPS-augmented neuroinflammation, and found that LPS-exposed rat brains had decreased relative cerebral blood flow (rCBF), increased BBB disruption, decreased N-acetyl aspartate (NAA; a neuronal marker), and increased levels of free radicals detected in vivo, compared to saline-treated controls (Figure 2) (Towner et al., 2018), (Towner et al., 2019). These findings imply that increased neuroinflammation results in cerebrovascular, neuronal metabolic and

free radical changes, which are similar to the mechanistic alterations underlying age-related BOLD fMRI change.

3.9 | Aging and exercise

Emerging research demonstrates that exercise is associated with improving several cognitive outcomes (Loprinzi et al., 2018). For example, recent evidence has suggested that physical exercise in aging can play a role in improving neurogenesis, gliogenesis, angiogenesis, cerebral circulation, and growth factor production, as well as parahippocampal function (Loprinzi, 2019a) and modulating episodic memory function (Loprinzi, 2019b). These novel findings imply that increased physical activity in aging may promote beneficial microvascular effects that would contribute to a more effective and responsive cerebral circulation to neuronal activity, potentially affecting that relationship between cerebral perfusion and cognitive load. Therefore, exercise may be considered a contributing confounding variable in the interpretation of BOLD fMRI signals in elderly individuals.

4 | FUNCTIONAL NEAR-INFRARED SPECTROSCOPY IN AGING AND AGE-RELATED DISEASES

Since the original studies in cognitive neuroscience to understand the physiochemical states of brain tissues (Logothetis, 2008), BOLD fMRI has gained currency in neuroimaging and clinical applications (Bauer et al., 2014; Lang et al., 2014). However, the use of BOLD fMRI to date remains somewhat limited mainly due to increasing interest in examining brain activity during exercise, or in populations that are not typical or suitable for the fMRI imaging including infants, those with abnormal aging, or those with limited functional capabilities. The use of BOLD fMRI for research purposes is also limited to large academic centers that are equipped with the expensive technology but compete with the use of the fMRI for clinical purposes. In aging neuroimaging research, fMRI allowed to identify age-related change in hemodynamic pattern in the brain regions responsible for age-related decline in executive function (Wilckens et al., 2017). Physiological modulation of these brain regions demonstrated a less specific cerebral activation and recruitment of additional brain regions in older adults when compared to young controls (DiGirolamo et al., 2001; Milham et al., 2002). However, the cost and ecological burden associated with use of fMRI modalities in aging research have prevented large-scale studies on age-related diseases and development of prospective medical interventions. Therefore, the necessity of new alternative tools with complementary strengths where fMRI is limited led to development of functional near-infrared spectroscopy (fNIRS).

The fNIRS technology originated from Jobsis work (Jobsis, 1977). This work provided the first evidence that near-infrared light can be transmitted through biological tissues. A number of in vivo and human studies allowed for development of the first, although limited, commercially available fNIRS instruments in 1989 (Scarapicchia et al., 2017). Further advancement in fNIRS technology and data analysis allowed for broader application and use in the laboratory and clinic (Huppert et al., 2009; Lagerwaard et al., 2020; Lv et al., 2009). Modern fNIRS tools allow non-invasive and nonionizing methods for measuring functional integrity and hemodynamic brain activity that is spectroscopically extracted from

measured concentrations of oxygenated, deoxygenated and total hemoglobin within the brain tissues and, since the original implementation, fNIRS has proven to be a useful tool to study normal and altered brain functions (Yucel et al., 2017). Recent studies that utilized fNIRS to investigate age-related changes in the brain have also used same paradigms applied in fMRI research. In the field of psychophysiology, and in other disciplines, it remains as a topic of intense debate whether the hemodynamic responses measured by fNIRS or fMRI can be correlated to neuronal responses and/or cognitive load. A study from Fabiani et al. have discovered the presence of a proportional relationship between neuronal and hemodynamic responses using a combined approach (Fabiani et al., 2014). In this work, young and older individuals were found to exhibit a quadratic relationship between neuronal and hemodynamic effects, with reduced increases of the hemodynamic response at high levels of neuronal activity. Although the relationship between neuronal and vascular measures of brain function departs substantially from linearity between younger and older adults, these findings highlighted that the neurovascular coupling becomes impaired in older adults, meanwhile the neuronal response remains unchanged. These clinical findings further substantiate basic science evidence that aging and other age-related changes (i.e., obesity, lack of exercise, etc.) impair cerebrovascular integrity and its function potentially introducing confounding variables when interpreting vascular outcomes (with fNIRS or fMRI) in elderly patients. Earlier studies compared fNIRS-related brain activation in the prefrontal cortex of healthy young and older adults and provided consistent evidence of the signal observed within the regions responsible for cognitive tasks implemented when compared to BOLD fMRI signal (Habeck, 2010; Vasta et al., 2017; Vermeij et al., 2012, 2014, 2017). In these studies, the authors reported a consistent overactivation of the prefrontal cortex during a relatively low cognitive load in older adults, suggesting a compensatory mechanism. When comparing concentrations of oxygenated hemoglobin in older adults without mild cognitive impairment and in those with nonamnestic and amnestic mild cognitive impairment, Yoon et al. found a progressive decrease in the mean accumulated oxygenated hemoglobin values from normal aging to amnestic cognitive impairment (Yoon et al., 2019). When using fNIRS approach in older adults with mild cognitive impairment and mild Alzheimer's disease, researchers found a general decline in functional connectivity from normal aging to Alzheimer's disease with more profound laterality in older adults with Alzheimer's disease during a verbal fluency task (Tang & Chan, 2018). Another study has also reported abnormal patterns of hemodynamic response across groups of normal aging, mild cognitive impairment, and moderate/severe Alzheimer's disease in older adults. In this study, the authors demonstrated greater and steeper reductions in oxygenated hemoglobin concentrations as disease severity developed from mild cognitive impairment to Alzheimer's disease (Li et al., 2018).

Additionally, stimulus intensity and cognitive load have been shown to affect younger and older adults differently. In a human study, participants viewed a single fixation cross at the center of a radial yellow and blue checkerboard flickering at three frequencies (2, 4, and 8 Hz) during the stimulation blocks. Younger participants' neurovascular response increased as the task became more intense, similar findings were obtained in a study comparing younger and older adults using fNIRS during 1-back and 2-back testing (Figure 3).

The fNIRS methodology was further applied in age-related pathologies such as hypertension. In the study by Bu et al., the authors report altered neurovascular coupling measured as a significant decrease in wavelet phase coherence and effective connectivity during resting and standing period in subjects >60 years of age with systolic and diastolic blood pressure over 150 and 90, respectively (Bu et al., 2018). Authors also reported a strong correlation between continuous fNIRS findings and the Montreal Cognitive Assessment cognitive scores in the group of hypertensive older adults, indicating strong contribution of hypertension to cognitive decline in aging. Functional NIRS has also been studied in age-related pathologies such as cancer to measure changes in brain hemodynamics after chemotherapy.

The use of fNIRS technology has also been proposed for longitudinal assessment and monitoring of the cancer treatment related cognitive impairment (Jean-Pierre, 2014). Recent data show that cancer patients after the chemotherapy presented with unbalanced increases in activation in prefrontal cortex regions during cognitive stimulation (Jean-Pierre et al., 2015). These findings were comparable to other that reported similar results in human subjects with cognitive decline. Finally, fNIRS was found useful as a monitoring, therapeutic, and research tool in stroke patients (Yang et al., 2019). The fNIRS has been extensively used for poststroke upper and lower limb function recovery, balance control, and motor learning. In these studies, functional improvements after stroke were associated with improved activation in prefrontal and sensorimotor cortex brain regions (Hara et al., 2013; Hatakenaka et al., 2012; Kato et al., 2002; Mihara et al., 2012; Miyai et al., 2002, 2003; Rea et al., 2014; Takeda et al., 2007). Spontaneous activity in prefrontal cortex oxygenation was also found to be altered in older adults and in patients with cerebral infarction (Li et al., 2010). Several other studies have investigated the dual-task interference between cognitive and physical performance in poststroke subjects. Authors reported that prefrontal cortex activation might prioritize physical demands in poststroke subjects (Mori et al., 2018), unlike in healthy elderly (Holtzer et al., 2016).

Current limitations for fNIRS use are mainly due to technological constraints. Changes in hemoglobin concentrations evoked by neuronal activity can be masked by body physiology related to cardiac cycle, breathing, or blood pressure fluctuations (Csipo et al., 2019). Current approaches to eliminate this interference, that originates from scalp, skull, and brain itself, include frequency-based algorithms and recently emerging time-domain NIRS approach that enables “null-distance” depth resolution (Pifferi et al., 2016). Further, current use of fNIRS technology will significantly benefit from a routine implementation of the diffuse correlation spectroscopy, a technique that is sensitive to red blood cells motion and that may provide a complementary index of blood flow within the measured brain areas (Durduran & Yodh, 2014; Sutin et al., 2016). Additionally, since evidence gathered by analysis of BOLD fMRI may be expensive and studies may often be underpowered as a consequence of high-equipment costs, alternative approaches such as fNIRS are emerging to investigate neurovascular coupling in aged individuals (Csipo et al., 2019). While limited by its inferior spatial resolution and penetration depth, fNIRS has a much higher temporal resolution than fMRI, allowing for measurements of rapid concentration changes in both oxygenated and deoxygenated hemoglobin. Assessment of neurovascular coupling responses by functional near-infrared spectroscopy in humans provides an affordable method to assess

hemoglobin concentration changes in cortical brain areas which provides consistent results when compared with fMRI.

5 | PERSPECTIVES

The basic science studies reviewed here demonstrate how much has been learned in the past decade about the effects of aging on vascular and neurovascular function. The interaction between the age-associated vascular changes and neuronal signals can affect the interpretation and conclusions that can be drawn from BOLD signal analysis. Thus, it is now more evident that BOLD fMRI studies which involve aging as a biological variable must deliver alternative strategies to account for the compromised vascular and neurovascular health in older individuals, as measured differences in BOLD signal may not be attributable only to neural activity. More recent studies seeking to understand the effect of aging on brain function have developed and validated several techniques that aim to separate vascular and neuronal signals when performing BOLD fMRI scans. However, more research is needed to develop and facilitate the adoption of such approaches as a common analysis tool. Further preclinical fMRI studies investigating cerebrovascular outcomes (such as NVC, rarefaction, and BBB permeability) on aged rodents will be of critical importance as the challenges to resolve the components underlying the BOLD signal to better understand the effects of aging on the brain cerebrovasculature remain unanswered.

ACKNOWLEDGMENT

This work was supported by grants from the American Heart Association (ST), the Oklahoma Center for the Advancement of Science and Technology (to AC, ZU), the Presbyterian Health Foundation (to ZU), the NIA-supported Geroscience Training Program in Oklahoma (T32AG052363), and the Cellular and Molecular GeroScience CoBRE (1P20GM125528).

Funding information

National Institute on Aging, Grant/Award Number: 1P20GM125528 and T32AG052363; American Heart Association; Oklahoma Center for the Advancement of Science and Technology; Presbyterian Health Foundation; Geroscience Training Program in Oklahoma, Grant/Award Number: T32AG052363; Cellular and Molecular GeroScience CoBRE, Grant/Award Number: 1P20GM125528

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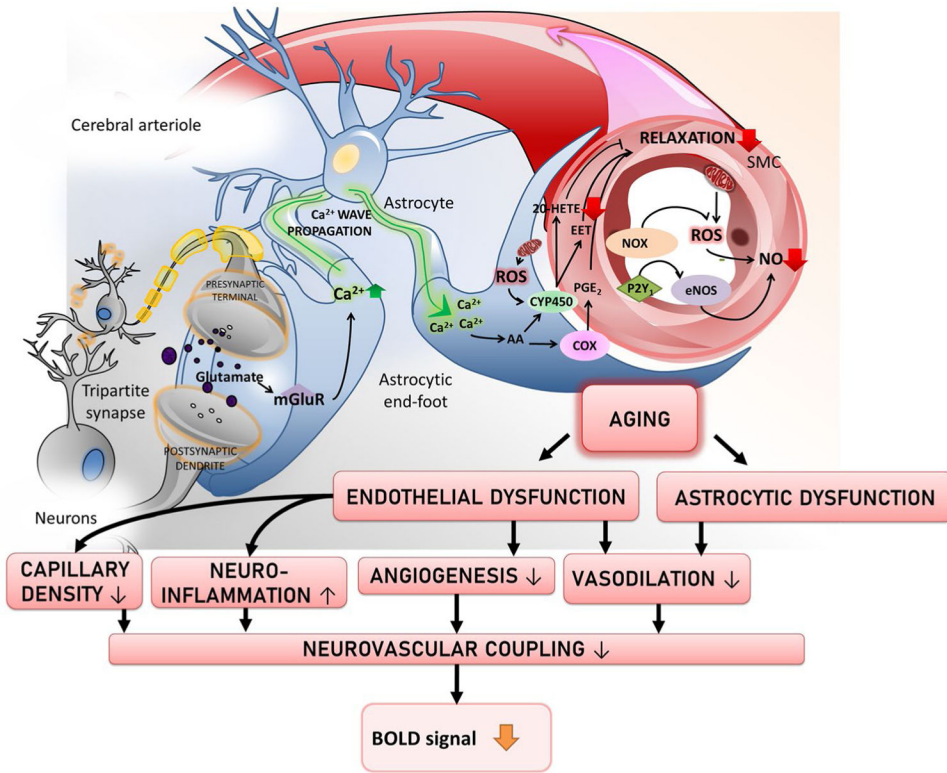
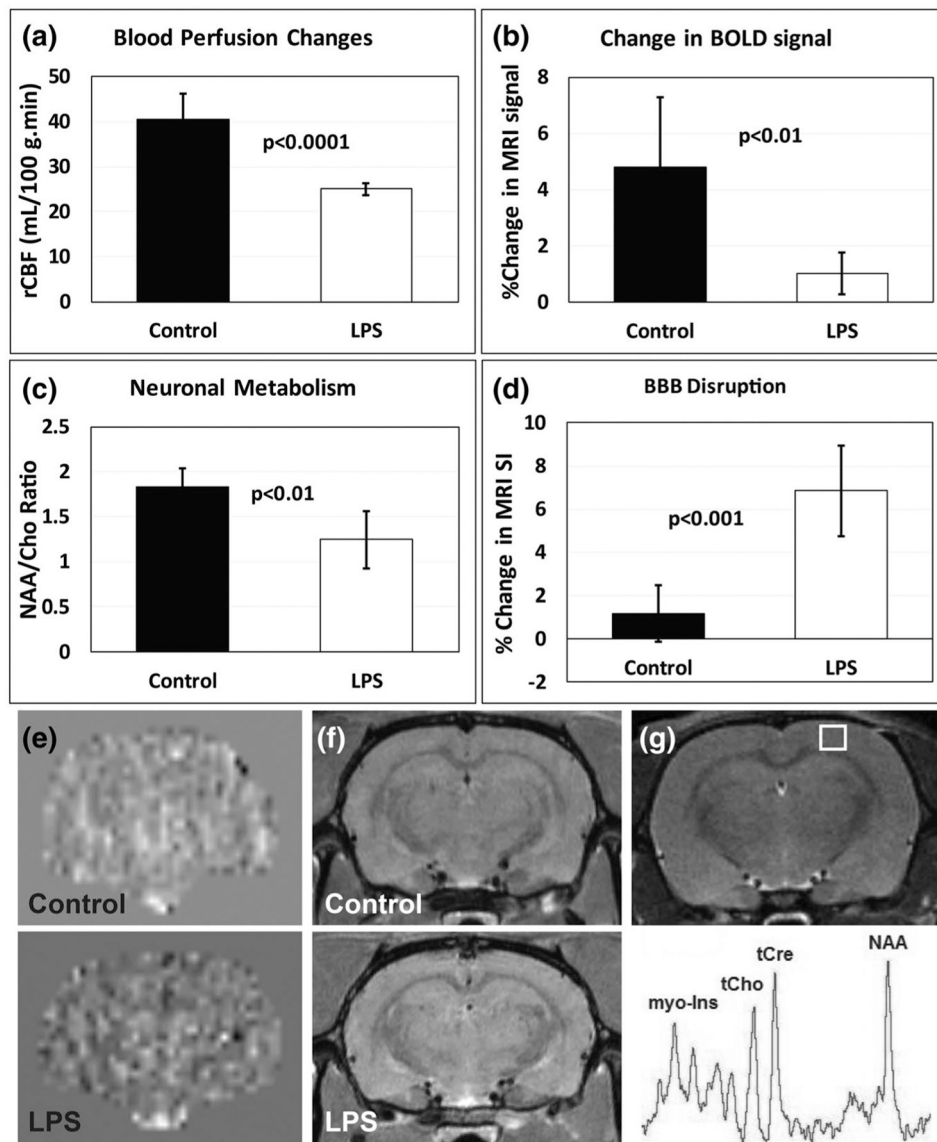


FIGURE 1. Schematic illustration of how aging and age-related vascular changes affect the neurovascular coupling processes that contribute the BOLD response

**FIGURE 2.**

LPS-induced neuroinflammation-associated cerebrovascular and neuronal changes in rat cerebral cortex. (a) Relative cerebral blood flow (rCBV) significantly decreases with LPS-induced neuroinflammation ($p < .0001$), compared to saline controls ($n = 6/\text{group}$). (b) Blood-oxygen level-dependent (BOLD) contrast in functional MR images (fMRI) from LPS-exposed rat brains are significantly less than controls ($p < .01$) ($n = 6/\text{group}$). (c) The neuronal metabolite N-acetyl aspartate (NAA) is significantly decreased in LPS-exposed rat cortex ($p < .01$) ($n = 6/\text{group}$). (d) Blood–brain barrier (BBB) disruption is significantly increased in LPS-exposed rat cerebral cortex compared to controls ($p < .001$) ($n = 6/\text{group}$). Measured as a percent change in MRI signal intensity obtained post-Gd-DTPA MRI contrast enhancement. (e) Representative rCBF maps obtained from control or LPS-exposed rat brains. (f) Representative contrast-enhanced (CE) MR images post-Gd-DTPA in control or LPS-exposed rat brains. (g) Representative MR image depicting the cortical region for

obtaining a MR spectrum. Metabolites: myo-inositol (myo-Ins); total choline (tCho); total creatine (tCr); and N-acetyl aspartate (NAA). All data were obtained 6 weeks post-LPS or saline treatments. Data modified from references (Towner et al., 2018) and (Towner et al., 2019). BOLD fMRI data are unpublished

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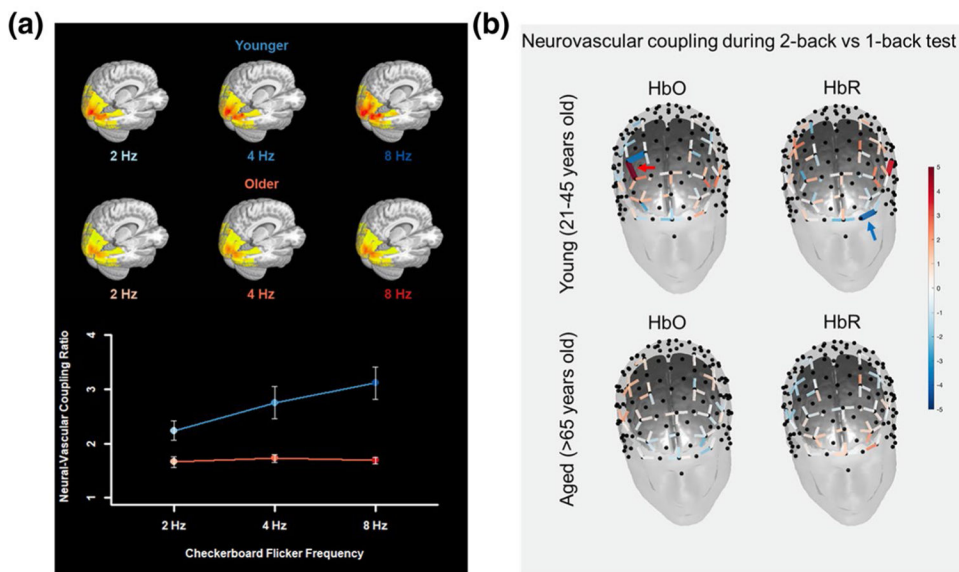


FIGURE 3.

Aging is associated with impaired neurovascular coupling responses during increasing cognitive load. (a) Neural-vascular coupling ratio (ratio of fractional CBF signal change to fractional CMRO₂ signal change) in response to visual checkerboard stimulation using MRI. The coupling ratio was greater in younger than older adults across frequencies and increased with increasing frequency in younger adults but older adults. The neural-vascular coupling ratio was calculated from the reciprocal of parameter weights from a 2 (Age-Group) × 3 (Flicker-Frequency) mixed-effects linear model predicting CMRO₂, with CBF as a covariate. The coupling ratio was greater in younger adults than older adults. There were significant main effects of both Age-Group in NVC ratio, $t(47) = 4.027$ ($p = 2.044 \times 10^{-4}$), (linear) main effect of Flicker-Frequency condition in NVC ratio, $t(94) = 4.615$ ($p = 3.056 \times 10^{-5}$). The ratio increased with increasing frequency more for younger adults than older adults. The Age-Group × Flicker-Frequency interaction effect was significant, $F(2, 94) = 9.473$ ($p = 1.879 \times 10^{-4}$). (b) fNIRS assessment of neurovascular coupling responses during 1- and 2-back cognitive task in four healthy young (21–45 years of age) and four healthy aged individuals (>65 years of age). Analysis was performed using a pipeline based on General Linear Model (GLM) approach created using the Brain AnalyzIR toolbox. For this comparison, we evaluated neurovascular coupling responses between a more challenging 2-back task and less challenging 1-back task using the contrast [2-back–1-back]. Solid lines represent statistically significant change ($q < 0.05$, corrected p value) in hemodynamic response between more challenging cognitive task versus less challenging task. We observed an increase in neurovascular coupling responses in young individuals during a more challenging cognitive task, evidenced by a statistically significant increase in the oxy-hemoglobin (HbO) in dorsolateral prefrontal cortex (red arrow) and a statistically significant decrease in the deoxy-hemoglobin (HbR) in left lateral frontopolar cortex (blue arrow). No statistically significant difference in neurovascular coupling responses during increasing cognitive load was observed in older adults. These data suggest an impaired neurovascular coupling response in aged individuals