The Relationship Between Cognition and Cerebrovascular Reactivity: Implications for Task-Based fMRI

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Elucidating the brain regions and networks associated with cognitive processes has been the mainstay of task-based fMRI, under the assumption that BOLD signals are uncompromised by vascular function. This is despite the plethora of research highlighting BOLD modulations due to vascular changes induced by disease, drugs, and aging. On the other hand, BOLD fMRI-based assessment of cerebrovascular reactivity (CVR) is often used as an indicator of the brain's vascular health and has been shown to be strongly associated with cognitive function. This review paper considers the relationship between BOLD-based assessments of CVR, cognition and task-based fMRI. How the BOLD response reflects both CVR and neural activity, and how findings of altered CVR in disease and in normal physiology are associated with cognition and BOLD signal changes are discussed. These are pertinent considerations for fMRI applications aiming to understand the biological basis of cognition. Therefore, a discussion of how the acquisition of BOLD-based CVR can enhance our ability to map human brain function, with limitations and potential future directions, is presented.

Keywords: functional magnetic resonance imaging, cerebrovascular reactivity, cognition, aging, caffeine, multiple sclerois, Moyamoya, small vessel disease

INTRODUCTION

Cerebrovascular reactivity (CVR) reflects the ability of the cerebral blood vessels to respond to a vasoactive stimulus and is primarily sensitive to arterial compliance [1, 2]. Blood oxygenation level-dependent (BOLD) functional MRI is an effective technique for measuring CVR. The BOLD signal originates from changes in the local concentration of deoxyhemoglobin (dHb), which primarily occurs in the post-arteriolar component of the cerebral vasculature. The change in the local concentration of dHb is predominantly driven by increases in cerebral blood flow (CBF), which reduces venous dHb via a dilution effect and thus increases the BOLD signal [3, 4]. In conventional task-based or resting-state BOLD fMRI, increases in the cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood volume (CBV) associated with increased neuronal activity both act to increase dHb and hence attenuate the CBF dominated BOLD signal increase. With a direct vasodilator stimulus used for CVR mapping, such as carbon dioxide (CO_2), $CMRO_2$ changes are assumed to be negligible and a robust positive BOLD signal is measurable that primarily reflects

the increase in CBF [5, 6]. CVR can also be measured using other MRI techniques including those sensitized exclusively to CBF (e.g., arterial spin labeling), macrovascular blood flow (e.g., phase contrast flow imaging), or CBV [1, 7–9]. In addition, there are non-MRI techniques available for measuring CVR, such as transcranial doppler, which measures blood flow velocity within the middle cerebral artery [10], and [15O] positron emission tomography [11, 12]. Yet BOLD fMRI is the more broadly used modality for CVR mapping in clinical and research settings owing to its sensitivity to vascular properties, combined with its safety, availability, higher spatial resolution, and reproducibility [13]. The sensitivity and spatial resolution of BOLD fMRI also explain its popularity as a cognitive neuroscience tool for mapping neural activity. Neural activity increases oxygen metabolism; however, BOLD signal increases occur in the context of increased CMRO$_2$ due to coupled, but proportionally larger, CBF increases [14–16].

While CVR primarily assesses vascular compliance, it is also evident that CVR is linked to cognitive functioning. Much of this evidence has emerged from research investigating pathological conditions such as vascular disease and dementia, where both regulation of cerebral vasculature and cognitive function are affected [17–19]. There are differences in the underlying mechanisms leading to the resultant hyperemia in CVR and task-based BOLD activation, however both rely on vessel contraction and dilation. Furthermore, the BOLD response to hypercapnia has shown to account for a large amount of the task-induced BOLD variability [20]. Therefore, the aim of this paper is to review the link between CVR and cognitive processes, and to highlight the importance of acquiring CVR data to accompany task-based fMRI data when investigating the biological underpinnings of cognition.

The first two sections of this review outline how CVR and neural activity are mapped using BOLD fMRI. Initially, an overview of how changes in arterial CO$_2$ are coupled to modulations in CBF are presented. The following section is focussed on task-based fMRI and discusses the mechanisms underpinning neurovascular coupling. Both of these sections emphasize recent findings. In sections Neurological Conditions and Normal Physiology, focus is shifted to example situations where both CVR and cognitive functioning are altered in the study population. We demonstrate that modulations to task-based BOLD activation are also often found in such cases, and provide the motives for collection of CVR data to aid the interpretation of fMRI activation maps. Neurological diseases hallmarked by vascular and microstructural variations are discussed in detail. However, vascular and cognitive alterations are also observed in normal physiology, such with caffeine consumption and aging, and this is discussed in section Normal Physiology. Finally, it has become increasingly clear that the integration of multiple imaging modalities improves our ability to map the human brain. Techniques for correcting BOLD-based assessments of brain activity using CVR (i.e., hypercapnic normalization) and the advantages and pitfalls of this analytical approach, are discussed in section Integration of BOLD-Based Assessments of CVR and Neural Activity: Hypercapnic Normalization.

CVR AND BOLD SIGNAL

Cerebral blood flow (CBF) is normally controlled by regulatory mechanisms including cerebral autoregulation, the partial pressure of arterial blood gases, and neurovascular coupling (NVC) [21]. NVC is discussed in detail in section Neural Activity and BOLD Signal. Cerebral autoregulation keeps blood flow consistent with changing cerebral pressure. The Hagen-Poiseuille equation describes the changes in cerebrovascular resistance as:

$$F = \frac{\pi P r^4}{8 \eta l}$$

Where blood flow (F) is proportional to cerebral pressure (P) and vessel radius (r) and inversely proportional to fluid viscosity (η) and vessel length (l). The purpose of cerebral autoregulation is to ensure continued blood supply to the brain across broad variations in blood pressure, which is achieved by manipulating vascular resistance. Changes in cerebrovascular resistance are also observed with changes in partial pressure of arterial CO$_2$ (PaCO$_2$) [22]. The relationship between PaCO$_2$ and CBF is sigmoidal; when PaCO$_2$ is between ∼20 and 60 mm Hg, there is an increase in CBF of ∼3–4% for every 1 mm Hg increase in PaCO$_2$. The CBF response is diminished above this PaCO$_2$ range [21, 23, 24]. The increased CBF in response to PaCO$_2$ decreases the concentration of dHb via dilution and robustly increases the BOLD signal, allowing for significant signal detection; there is a relatively large BOLD signal difference (∼1–2%) between isocapnic and hypercapnic states, when a moderate level of hypercapnia is induced (∼5–8 mm Hg above baseline levels).

There are numerous mechanisms leading to vasodilation. Increased CO$_2$ results in increased carbonic acid in the blood, that leads to hyperpolarization of the smooth muscle cells and vasodilation [2]. CO$_2$ in the blood lowers the pH and changes the muscle tonus of the vessel wall [25]. An increase in CBF is observed following this reduction in pH, which functions to washout the excess CO$_2$ and regulate pH levels. The increased CO$_2$ in the cerebral spinal fluid (CSF) from hypercapnia is known to result in vascular relaxation [26]. Central chemoreceptors located in regions throughout the brainstem, cerebellum, and hypothalamus, which are sensitive to CSF pH, modulate respiratory rate to regulate CO$_2$ levels [27]. Indeed, increasing the fraction of inspired CO$_2$ stimulates the breathing rate to increase, in order to achieve CO$_2$ elimination [28].

End-tidal partial pressure of CO$_2$ (P$_{ET}$CO$_2$) is a close proxy measure of PaCO$_2$ and is therefore used in CVR studies. The total volume of exhaled air is comprised of CO$_2$ within the alveoli and the physiological dead space. Physiological dead space is inhaled air that does not participate in gas exchange and includes non-perfused air within the alveolar and anatomical dead space. Anatomical dead space is the air within the nose, trachea and bronchi that make up the conducting airways. The function of the conducting airways is to channel inhaled air to the respiratory zone where gas exchange occurs; that is, the alveolar surface [29, 30]. In healthy adults, the alveoli dead space is negligible and anatomical dead space comprises all of the non-perfused air. However, excessive air within the alveoli that is not perfused

increases the alveoli component of dead space [30]. This excess air within the alveoli typically indicates less efficient CO_2 removal and is associated with pulmonary diseases. It will result in a slightly lower ($\sim \leq 5$ mm Hg) $P_{ET}CO_2$ relative to $PaCO_2$ [31], however, this does not preclude $P_{ET}CO_2$ from being a robust indicator of $PaCO_2$, and is used in the determination of CVR, calculated as $\Delta\%BOLD/\Delta P_{ET}CO_2$ (mm Hg) [2].

Elevated $PaCO_2$ results in a robust vasodilatory response and CBF increase, and therefore, experimental manipulations that increase $P_{ET}CO_2$ are used to measure CVR. Breath-holding is one such approach that is low-cost and low-risk. A benefit to the breath-hold approach is that it is more accessible than gas inhalation because it requires less equipment. The monitoring of $P_{ET}CO_2$ is highly desirable however, because of variability in the participant breath-hold performance that can be accounted for if measured $P_{ET}CO_2$ is included as a statistical regressor in CVR quantification [32]. Comparisons of breath-hold paradigms to CO_2 inhalation methods have shown consistent CVR results [33, 34], supporting this method as a reliable technique for calculating CVR. Inhaling gas mixtures containing increased concentrations of CO_2 is controllable and more precise than breath holding, and therefore a desirable approach to increasing $PaCO_2$. This is achieved using MRI-compatible breathing circuits that allow for the administration of gas mixtures and the precise recording of $P_{ET}CO_2$ [35]. There are different types of breathing circuits available; further information on these can be found in references [2] and [36].

NEURAL ACTIVITY AND BOLD SIGNAL

Task-based BOLD fMRI reflects neural activity indirectly through NVC [15, 37–40]. NVC is the tightly linked relationship between regional neural activity and changes in blood flow [39]. It is independent of perfusion pressure, and results from the close communications between neurons, glia, and arterioles. The functional hyperemia coupled to neural activity changes ensures that activated neural cells have a constant supply of oxygen and glucose [41]. Arteries commence dilation within hundreds of milliseconds of neuronal activity, and return to baseline within seconds of stimulus termination [14]. The venous side is slower to dilate, taking tens of seconds, and appears to have smaller blood volume changes than the arterial side [42]. There has been a recent wealth of research focussed on describing the roles of specific cell types and their signaling resulting in arteriole dilation [43]. For instance, there is strong evidence for the role of glutamatergic cells in signaling the commencement of arterial dilation. Blood flow increases in conjunction with excitatory pyramidal cell activity have been demonstrated in rodent models [44, 45]. CBF, and to a lesser extent CBV, have been shown to correlate with post-synaptic local field potentials but presynaptic activity does not appear to trigger hemodynamic changes [46]. Astrocytes are important in maintaining basal blood flow [47] and have been implicated in NVC due to their close proximity to both the microvasculature and neurons [48], but how they contribute to NVC remains the topic of debate [47, 49]. An intriguing hypothesis is that endothelial cells in blood vessels can directly detect changes in neural activity, and therefore may be more involved in NVC than previously thought [50–52].

Neural functioning requires a balance of excitation and inhibition, hence recent work has also focused on understanding how inhibitory neurons generate vascular changes. There is evidence from electrophysiology studies demonstrating that gamma power local field potentials, driven by γ-aminobutyric acid (GABA) interneurons, are correlated with hemodynamic changes [53]. GABAergic interneurons are diverse in morphology and physiology, with subtypes characterized by their gene expression and cell innervation [54]. They play an essential role in cortical function by inhibiting excitatory or inhibitory post-synaptic neurons, and while connections remain mostly focal, some GABAergic interneurons extend to the vasculature [55].

Significant progress has been made in understanding the unique role of GABAergic cells in NVC using optogenetic stimulation [56, 57]. Selective photo-stimulation of inhibitory cells can be achieved using a mouse model expressing channelrhodopsin-2 (ChR2) in GABAergic neurons. ChR2 is a light-sensitive cation channel that can induce neuronal depolarization [58]. A study by Vazquez et al. [59] used a ChR2 mouse model and targeted photo-stimulation to selectively activate GABAergic interneurons. Blood flow, volume, and oxygenation increases were observed following photo-stimulation of GABAergic interneurons. Stimulation of certain GABAergic neurons has also resulted in decreases in blood volume in adjacent cortical tissue [60]. This decrease in blood volume is consistent with suggestions that negative BOLD fMRI may reflect neural inhibition [61–63]. Indeed, there is increasing evidence supporting the role of inhibitory neurons in driving NVC and shaping the BOLD response [64]. Some of the work investigating the negative BOLD response is discussed in greater detail the next section.

Hemodynamic Responses to Neural Activity and CO_2

The traditional positive BOLD response (PBR) to neural activation is modeled in task-based fMRI using a hemodynamic response function (HRF). The HRF in its canonical form is typically described using the sum of two gamma functions. In gray matter, the time-to-peak is ~ 6 s from the onset of neural activity, however significant spatial heterogeneity in the shape and timing parameters of HRF has been observed in healthy brains [65, 66] and in different clinical populations [67, 68]. Characterizing temporal HRF parameters may reveal important physiological information not evident from the amplitude of the response alone, which is the main parameter of interest when calculating fMRI activation maps [68, 69]. HRF parameters such as time-to-peak and full-width at half-maximum are influenced by blood flow and NVC, may be important for probing information regarding neuronal duration [70].

Focus has also been placed on understanding negative BOLD responses (NBRs) in task-based fMRI. These responses are identified as stimulus-induced decreases in BOLD signal intensity relative to baseline, or inverted PBRs. Different

hypotheses have been suggested to explain the underlying mechanisms of the NBR. One such suggestion is centered on it having purely vascular origins, emerged from research indicating that negative BOLD changes may result from a redistribution (steal) of CBF to adjacent, active cortical regions [71, 72]. Other research has provided conflicting evidence; for instance, NBRs have been identified in brain regions distant from simultaneously occurring PBRs, with these NBR regions having distinct arterial territories [61, 73]. Decreases in neuronal activity accompanying NBRs have suggested a neural origin, with much of the literature supporting this [62, 63, 74–77]. Influential findings from Shmuel et al. [63] demonstrated significant correlations between NBRs and decreases in local field potentials and multiunit activity, measured directly from the primary visual cortex of monkeys. This has been verified in human work using combined electroencephalography (EEG) fMRI, where negative CBF and BOLD changes in NBR regions demonstrate concomitant EEG changes [75, 78]. Although there has been progress made in the attempt to understand the response properties of the NBR [78, 79], further work elucidating how and when NBRs occur and the associated biophysical changes is essential for the accurate interpretation of this signal.

Analyses of BOLD responses to vasoactive stimuli have shown that temporal parameters may reflect important aspects of vascular function in CVR. Typically, CVR mapping considers only the amplitude of the BOLD response to the vasoactive stimulus; however, accounting for temporal variations across the brain may improve CVR estimation accuracy. Identifying temporal variation may also provide novel physiological information. For instance, a slower response may reflect slower vessel dilation due to vascular pathology. The speed of the BOLD response to changes in $P_{ET}CO_2$ has shown to reflect pathophysiology in patients with steno-occlusive disease [80]. Slower BOLD responses to CO_2 have also been demonstrated in patients with mild cognitive impairment and Alzheimer's Disease (AD) [17]. Analytic approaches to account for temporal delays have been put forth [81–83] and shown to improve CVR mapping in patients with blood flow abnormalities [84].

NEUROLOGICAL CONDITIONS

Abnormal NVC, or even complete uncoupling, can occur when the cascade of events from neuronal activity to functional hyperemia is disrupted. This is known to occur in clinical conditions such as in brain tumors and cerebrovascular disease, and CVR mapping may be effective in improving task-based fMRI interpretation in these instances [85]. The utility of CVR may extend beyond mapping vascular changes to also inform our understanding of cognition. In this section, this argument is made by placing focus on example neurological conditions where CVR, cognitive and task-based fMRI alterations occur. The first two diseases discussed, cerebral small vessel disease and Moyamoya Disease, are characterized by vascular abnormalities. Such vascular-driven diseases are obvious candidates to benefit from CVR mapping. However, the utility of CVR may extend beyond diseases with vascular etiologies, to those that

are microstructurally-driven. Therefore, Multiple Sclerosis is discussed in section Multiple Sclerosis.

Cerebral Small Vessel Disease

Cerebral small vessel disease (SVD) refers to a collection of abnormalities affecting the small blood vessels, including the capillaries, arterioles and venules, in the gray and white matter [86]. SVD is strongly associated with advanced age, and has been recognized as a common cause of stroke [87, 88] and dementia [89]. Indeed, SVD is tightly interwoven with AD. Due to the contribution of SVD to AD pathogenesis, the distinction between the two is increasingly blurred [90]. Imaging features of SVD are heterogenous and can present as white matter hyperintensities (WMH), lacunar infarcts, microbleeds, perivascular spaces, and atrophy [88, 91]. SVD types can demonstrate regional preference, for instance, cerebral amyloid angiopathy (CAA) pathology disproportionately affects the occipital cortex. CAA is characterized by the accumulation of amyloid-β predominantly in the arterial walls of the leptomeningeal space and cerebral cortex [92, 93]. SVD types can also be distinguished based on etiology, with sporadic appearances being distinct from those with known genetic etiologies, such as Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL).

Endothelial dysfunction has been suggested as contributing to the pathogenesis of SVD, resulting in stiff vessels with low reactivity [94, 95]. Concordant results have been reported in studies implementing CO_2 challenges to measure CVR in SVD patients. Lower gray matter CVR has been demonstrated in SVD patients [96], and in patients with AD and mild cognitive impairment [97], compared to healthy controls. CVR reductions may show spatial heterogeneity, with AD patients showing reduced anterior (prefrontal, insular, anterior cingulate) CVR [98]. This study also found that the brain regions with reduced CVR did not overlap with regions showing reduced baseline CBF in AD patients, owing to vasoreactivity being sensitive to different pathology than CBF. Lower CVR in both gray and white matter in SVD is positively associated with WMH volume [99], and increases in WMH over time in patients with CADASIL [100]. A systematic literature review was performed by Blair et al. [95], who suggested that the relationship between CVR and WMH is unclear due to inconsistent findings [95]. The authors of this review further suggest that differences in imaging protocols might contribute to these inconsistencies. Another limitation is the lack of research incorporating temporal information into CVR analyses, which has shown to improve CVR estimation and provide important physiological information in patients with SVD [101]. Furthermore, more longitudinal research is warranted, as regions with reduced CVR have shown to precede the appearance of WMH [102].

Cognitive impairment is a common occurrence in patients with SVD. The severity and type of cognitive impairment is highly variable across patients, which may reflect the differences in pathology load and location [103–106]. Cognitive domains frequently impaired in SVD include processing speed and executive function [107], however patients tend to show impaired cognitive abilities across a broad range of domains [108]. This

is demonstrated by **Table 1**, which highlights the range of cognitive impairment observed in SVD. This table summarizes findings from example research studies implementing behavioral assessments to test different cognitive domains in these patients. The studies reported in **Table 1** were found using a PubMed search, and search terms included medical subject headings (MeSH) "cerebral small vessel disease," and each of the assessable cognitive domains [115]. The searched domains were "perception," "motor skills," "attention," "memory," "executive functioning," "processing speed," "language," and "verbal skills." When selecting articles for **Table 1**, preference was given to recently published literature with an age and gender-matched control group.

Investigating potential imaging markers of SVD, including its pathogenesis and ongoing physiological changes, is an essential research endeavor [18]. Task-based BOLD fMRI changes in SVD have shown to reflect CVR and cognitive findings, and may potentially provide imaging markers of disease processes. Sensory tasks targeting activity in the visual and motor cortices report reduced BOLD signal amplitude in the visual cortex in patients with CAA [116]. Analysis of the temporal characteristics of these BOLD signal reveals wider and delayed responses in CAA patients compared to aged-matched healthy controls [68]. Longitudinal research has shown that BOLD responses in the occipital cortex of CAA patients decrease over time [117]. These BOLD signal changes may be specific to CAA due to pathology largely affecting the occipital cortex; no such BOLD activation reductions to visual and motor tasks were observed in CADASIL patients [118]. SVD patients have also demonstrated alterations in BOLD activation to cognitive fMRI tasks. Reductions in BOLD signal amplitudes and spatial extent of activation to an attention task have been reported in patients with SVD [119]. This is supported by resting-state fMRI showing reduced frontoparietal connectivity in these patients [120]. Disease processes disrupting neural networks may cause changes in neural activity, reflected by the cognitive and BOLD data. However, vascular abnormalities, as reflected by CVR findings, will also affect task-based BOLD signal in these patients and present a challenge when interpreting BOLD activation maps. When implementing fMRI to investigate SVD imaging markers, CVR may be an important addition to the imaging protocol by providing insight into vascular changes and guide interpretation of fMRI activation.

Moyamoya Disease

Moyamoya disease (MMD) is an idiopathic vasculopathy, characterized by reduced regional cerebral perfusion due to arterial occlusion or stenosis. From the branches of these narrowed arteries, collateral vascular networks form which radiologically appear as a "puff of smoke" (which gave the Japanese name *Moyamoya*) [121]. Patients with MMD often present with headaches, transient ischemic attacks, and intracranial hemorrhage. Intervention typically involves revascularization surgery. This improves cerebral perfusion to the cerebral vascular territories afflicted, and has shown to have good outcome regarding mortality and quality of life [122].

Comparisons of BOLD CVR to gold-standard CBF mapping using [^{15}O] positron emission tomography [11] and angiography

[123] show promising results for CVR in patients with MMD. These findings demonstrate the utility of CVR for assessing which brain regions are afflicted by changes in cerebral perfusion in MMD, and for tracking post-intervention reorganization. Vascular steal is commonly observed in CVR maps in patients with MMD. This phenomenon is observed as negative CVR within brain regions affected by arterial narrowing when a vasoactive stimulus such as CO_2 is applied [124]. Negative CVR can be observed in an example patient in **Figure 1A** below. NBRs in the context of CVR are attributed to the permanently vasodilated state of the affected vessels, which is necessary to ensure sufficient perfusion in the resting baseline state. When $PaCO_2$ increases, these vessels cannot decrease vascular resistance any further to meet this change in demand. Therefore, blood flow is diverted from these regions to brain regions with intact vasodilatory response [126]. Vascular steal in MMD has been associated with increased risk of stroke [127, 128], cortical thinning [129], and increased diffusion in white matter [130]. However, pre-operative appearance of negative CVR has been associated with improved surgical outcome [131]. Negative CVR has shown to resolve following revascularization surgery, representing normalized cerebral perfusion [126, 132].

Cognitive deficits have been described as a common symptom in patients with MMD, with ~30% of patients demonstrating cognitive impairment [133]. Cognitive studies in pre-surgical MMD are summarized in **Table 2**, where the same search strategy outlined for SVD and **Table 1** in section Cerebral Small Vessel Disease above was applied. Cognitive impairment in patients with MMD may be attributed to hypoperfusion [138], as chronic ischemia may cause reduced axon density [139] and decrease cognitive network communication efficiency. While task-based fMRI can be used to clarify neural networks associated with certain cognitive tasks, regional ischemia and perfusion alterations in MMD complicate the ability to identify neural activity through a BOLD response. Mazerolle et al. [140] showed this in pre-operative MMD patients when visual-motor tasks were performed. When patients performed a simultaneous visual-motor task, BOLD activation in the motor cortex of the afflicted hemisphere was not detectable, although prominent activation of the visual cortex was observed. However, when the motor task was performed in isolation (i.e., without concurrent visual stimulation), robust BOLD activation was detected in the afflicted hemisphere. Therefore, the activation of the visual cortex, which had intact CVR, resulted in vascular steal from the MMD-afflicted motor cortex with impaired reactivity. **Figures 1B,C** highlights altered task-based fMRI activation maps during a concurrent visual-motor task. These results support the necessity of CVR when fMRI is performed in patients with MMD.

Multiple Sclerosis

Multiple sclerosis (MS) affects the central nervous system and is characterized by focal regions of demyelination, gliosis, and axonal degeneration. The majority of patients demonstrate a relapsing-remitting (RRMS) form at onset, hallmarked by discrete episodes of neurological impairment followed by periods of remission [141]. Gradual neurodegeneration leads to secondary progressive MS (SPMS), where remission periods

TABLE 1 | Summary of research studies highlighting the cognitive domains impaired in cerebral small vessel disease.

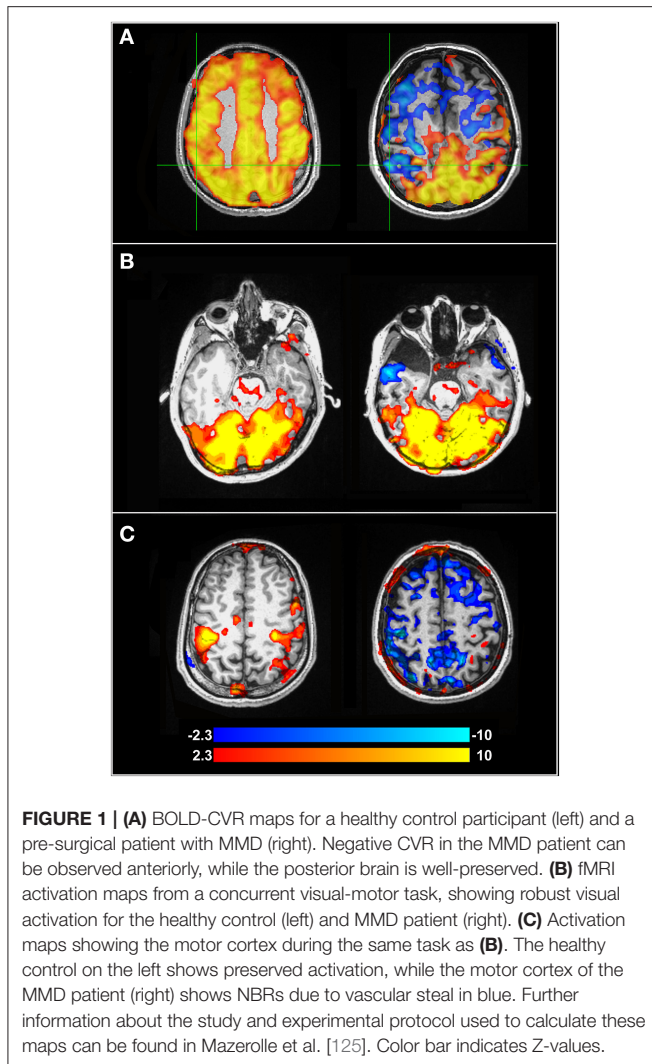| References	Study population(s)	N (N Female)	Mean age	Cognitive domain(s) assessed	Tests administered	Main findings
Dey et al. [109]	SVD	23 (12F)	71 ± 5.5	Attention, Executive functioning	Neuropsychology test battery	Groups differed in subjective SC ($P = 0.008$), but not neuropsychological tests.
	Healthy older adults (HOA)	23 (14F)	69.3 ± 4.6	Subjective cognitive complaints (SC)	Cognitive Failures Questionnaire; Dysexecutive Questionnaire	
Su et al. [110]	SVD	68 (27F)	66.2 ± 8.1	Motor skills	Lower and upper extremities- behavioral tests	SVD performed worse than HOA on lower extremities tests ($P < 0.01$).
	HOA	702 (474F)	56.3 ± 9.0			
Metoki et al. [111]	SVD	106 (36F)	69.5 ± 9.6	General cognitive impairment	Mini-Mental State Examination (MMSE)	SVD group had significantly lower MMSE scores ($P < 0.001$).
	HOA	35 (13F)	69.6 ± 9.3	Working memory (WM)	Digit Span Test of WMS-III[†]	SVD group had significantly lower WM scores ($P < 0.001$).
				Long-term memory (LTM)	Immediate and delayed recall subtests of WMS-III[†]	SVD group had significantly lower LTM scores ($P < 0.001$).
Cao et al. [112]	SVD with vascular mild cognitive impairment (VaMCI)	32 (9F)	67.5 ± 9.6	All cognitive domains	Neuropsychology test battery	VaMCI performed worse than NCI on all domains ($P < 0.01$) except language.
	SVD with no cognitive impairment (NCI)	23 (6F)	67.4 ± 8.5			
Lawrence et al. [113]	SVD (over 3 years)	98 (33F)	69 ± 9.9	All cognitive domains	Neuropsychology test battery	Executive functioning was the only cognitive domain to significantly decline over 3 years.
Herbert et al. [114]	SVD	45 (20F)	69.7 ± 8.2	Verbal fluency (phonemic and semantic)	COWAT[‡]; Animals and Tools Tests	SVD group performed worse on both verbal fluency tests compared to HOA ($P < 0.001$).
	Alzheimer's Disease (AD)	24 (12F)	74.5 ± 6.5	Memory, Executive functioning, Processing speed	The Brief Memory and Executive Test	AD group performed worse on semantic verbal fluency test compared to HOA ($P < 0.001$).
	HOA	80 (45F)	68.1 ± 7.9	General cognitive impairment	Mini-Mental State Examination (MMSE)	

[†]Wechsler Memory Scale-Third Edition.
[‡]controlled oral word association test.

subside and continuous progression of the disease occurs. A minority of patients (< 10%) have primary progressive MS (PPMS) where the progressive form is evident from onset [142]. MRI indications of MS include multiple lesions dispersed through the white matter, in particular lesions adjacent to the ventricles and cerebral cortex, as assessed with T_2-weighted sequences. Lesions may also demonstrate gadolinium enhancement as evidenced on post-contrast T_1-weighted images, indicating acute localized breakdown of the blood brain barrier [143]. Even normal-appearing white matter (NAWM) on MRI may be affected by mild inflammation and gliosis in MS, despite these regions largely retaining myelin [144, 145]. While the pathogenesis of MS remains to be fully elucidated, the most widely accepted proposition is that it is an autoimmune disease, with inflammation and neurodegeneration playing a critical role in lesion development and disease progression [146].

Vascular dysfunction has been reported in patients with MS [147]. Studies evaluating CBF have shown hypoperfusion in MS patients relative to healthy controls [148], including regions with NAWM [149]. However, the literature on CVR

in MS has provided conflicting results. Findings of decreased CVR in MS patients compared to controls using transcranial Doppler ultrasonography (TCD) [150] has been supported by reported global decreases in gray matter CVR using CBF-sensitized arterial spin labeling (ASL) [151]. However, other studies also using TCD and ASL report no CVR differences between MS patients and controls [152, 153], leading to an inconclusive picture regarding CVR impairment in MS. However, variations in disease severity and cognitive impairment amongst MS patients might underlie these conflicting CVR results. One study reported no significant differences in CVR between MS patients and healthy control groups, but when looking within the patient group only, CVR was significantly reduced in those with cognitive impairment compared to those with intact cognition [154]. Studies pooling subjects in terms of disease course (e.g., RRMS and SPMS) and cognitive impairment may be a contributing factor to the inconsistent CVR findings.

Cognitive decline in MS can be found across all stages of disease progression. As demonstrated by **Table 3** (which followed the search criteria outlined in section Cerebral Small

FIGURE 1 | (A) BOLD-CVR maps for a healthy control participant (left) and a pre-surgical patient with MMD (right). Negative CVR in the MMD patient can be observed anteriorly, while the posterior brain is well-preserved. **(B)** fMRI activation maps from a concurrent visual-motor task, showing robust visual activation for the healthy control (left) and MMD patient (right). **(C)** Activation maps showing the motor cortex during the same task as **(B)**. The healthy control on the left shows preserved activation, while the motor cortex of the MMD patient (right) shows NBRs due to vascular steal in blue. Further information about the study and experimental protocol used to calculate these maps can be found in Mazerolle et al. [125]. Color bar indicates Z-values.

Vessel Disease), MS patients have demonstrated impairment across a broad range of cognitive domains. Cognitive decline is not ubiquitous; approximately half of all patients with MS do not exhibit any impairment in cognition [163]. However, the presence of cognitive decline in MS has been associated with reduced BOLD activation during cognitive tasks. Patients with poorer cognitive performance have shown decreased extent of BOLD activation to memory and attention tasks [164, 165]. MS patients with intact task performance have shown additional regions of brain activation compared to healthy controls [166–168]. This association between cognitive performance and BOLD activation in MS has been explained as functional reorganization. In a study comparing MS progression sub-types, Loitfelder et al. showed that the extent of BOLD activation to a processing speed task increased from patients with clinically isolated syndrome, to RRMS, and was most extensive in patients with SPMS [169]. It was reasoned that this was evidence for neuroplasticity changes to increasing tissue damage; more neural networks were required to compensate for those that were damaged by lesions and atrophy. As neural networks become increasingly

damaged, communication between network nodes is less efficient. However, communication affecting neuronal activity is not the only breakdown, as the cells governing neurovascular coupling are also damaged. Damage to the neurovascular unit results in insufficient communication between neurons and the vasculature, and unmet nutrient and oxygen requirements [147]. Reduced BOLD response magnitude to cognitive tasks in MS patients may reflect decreased neural activity and/or disrupted NVC, but disentangling these requires more information, such as CVR mapping.

NORMAL PHYSIOLOGY

Caffeine

Caffeine is a commonly used ergogenic aid due to it being a psychostimulant of the central nervous system. The most prominent mechanism of action is as an adenosine receptor A_1 and A_{2A} antagonist. By blocking the action of inhibitory neurotransmitter adenosine on these receptors, caffeine produces a stimulation effect through disinhibition [170]. It has been long known that adenosine is a regulator of cerebral vasodilation [171]. As an antagonist, caffeine causes a vasoconstrictive effect and reduces CBF [172, 173]. Most studies investigating the neurovascular effects of caffeine consumption administer a dose of 200 mg, which decreases baseline CBF by 30–35% and increases oxygen extraction fraction (OEF) by 15–27% [174–177]. This inverse relationship between CBF and OEF is intuitive, as a reduction in flow would require an increase in OEF to maintain oxygen metabolism rates. But does baseline $CMRO_2$ change after caffeine consumption? The literature is inconsistent. For instance, baseline $CMRO_2$ has been reported as unchanged [177], increased [178] and decreased [176] following caffeine consumption.

The effects of caffeine on CVR appears somewhat more consistent. When characterizing the influence of caffeine on CVR in the motor and visual cortices, one study showed that caffeine increased BOLD-CVR in these regions while having no effect on CBF-CVR [179]. Similarly, Merola et al. [176] reported an increase in BOLD-CVR across the gray matter after caffeine, relative to caffeine-free baseline. Some example CVR maps from individuals who participated in caffeine and caffeine-free placebo conditions are shown in **Figure 2**. This figure highlights some increased CVR with caffeine, although inter-subject variability is also evident. One interpretation that has been previously linked to increased task-induced BOLD signal changes following caffeine is that a decreased CBF baseline may result in a larger relative BOLD amplitude change [181]. However, further work found that caffeine-induced reductions in resting CBF were not a strong predictor of stimulus-induced BOLD activation [182]. Further research investigating how caffeine influences CVR, and whether this in dependent on factors such as baseline physiology, is therefore warranted.

The cognitive effects of caffeine are well-known and appreciated by frequent consumers. The ingestion of up to 300 mg has shown to enhance alertness, attention, and reaction time performance [183, 184]. How caffeine affects task-induced BOLD signals appears to be dependent on the specific task

TABLE 2 | Summary of research studies highlighting the cognitive domains impaired in Moyamoya disease.

References	Study population(s)	N (N Female)	Mean age	Cognitive domain(s) assessed	Tests administered	Main findings
He et al. [134]	MMD with infarction	19 (9F)	41.9 ± 11.7	All cognitive domains	Neuropsychology test battery	MMD with infarction performed worse than MMD asymptomatic on tests of complex arithmetic ($P = 0.03$) and short-term memory ($P = 0.01$). Both MMD groups performed worse than HC on tests of intelligence, spatial imagination, working memory and computational ability ($P < 0.02$).
	MMD asymptomatic	21 (7F)	39.4 ± 10.2			
	Healthy controls (HC)	20 (8F)	42.61 ± 3.9			
Shi et al. [135]	MDD	49 (25F)	38.5 ± 9	Intelligence	Wechsler adult intelligence test	MMD performed worse that HC on intelligence ($P = 0.002$).
	HC	23 (14F)	37.6 ± 9.1	Prospective memory (PM)	Cambridge prospective memory test	MMD performed worse that HC on PM ($P < 0.0005$).
				Immediate memory; Retrospective memory (RM); Verbal fluency (VF); Visual breadth	Repeatable battery for the assessment of the neuropsychological status test	MMD performed worse that HC on tests of VF and RM ($P < 0.006$).
				Executive functioning	Stroop test; Trail making test; Wisconsin card sorting test; Continuous performance test	MMD performed worse that HC on tests of executive functioning ($P < 0.003$).
				Attention	Posner attention test	MMD performed worse that HC on attention ($P < 0.0005$).
Miyoshi et al. [136]	MMD (over 2 years)	70 (57F)	43 ± 8	Intelligence	Wechsler adult intelligence scale- revised	Unchanged cognitive scores over 2 years.
				Memory	Wechsler memory scale	
				Visuospatial abilities	Rey-osterreith complex figure test	
Fang et al. [137]	MMD	49 (25F)	27.9 ± 14.1	Executive functioning	Stroop; Hayling Sentence Completion Test (HSCT); Verbal Fluency (VF); N-Back; Sustained Attention to Response Task (SART)	MMD groups scored worse than HC on VF, HSCT and SART ($P < 0.001$).
	HC	47 (25F)	27.1 ± 14.7	Subjective feelings about executive functioning	Dysexecutive Questionnaire	There was no difference between MDD and HC groups on the Dysexecutive Questionnaire.

performed. There is some evidence showing no change to passive visual stimulation-induced BOLD activation following caffeine consumption, despite significantly fewer activated CBF voxels acquired simultaneously [185]. In a different study [186] where a visuo-motor task that required continual alertness to visual cues was implemented, significant BOLD increases with caffeine ingestion were found. These increases corresponded to regions that have been implicated in attention networks, including the basal ganglia, thalamus, putamen and insula. This finding is consistent with other work showing that caffeine increases BOLD activation during a working memory task [187]. This discrepant effect of caffeine on BOLD activation to low-level sensory tasks vs. high-level cognitive tasks was investigated in a single study [188]. This work showed that caffeine reduced BOLD activation in the visual and motor regions to sensory tasks, and consistent with the prior findings outlined above, increased activation in the superior frontal gyrus, paracingulate cortex, and

frontal pole to an attention task. An important feature of these research findings is that BOLD modulations to cognitive tasks induced by caffeine may not be replicated in populations with cognitive decline. For instance, a longitudinal study evaluating the effects of caffeine in older adults [189] reported that those who exhibited cognitive decline across time were less sensitive to caffeine-induced BOLD modulations than those showing cognitive stability.

The research discussed here highlights that caffeine modulates both vascular and neural activity, and underscores how the BOLD signal is a complex interplay between these components. As such, task-induced BOLD signal changes following caffeine consumption are highly dependent on the neural networks engaged by the task, and the level of alertness it requires. BOLD-CVR appears to increase following caffeine ingestion; this suggests that changes in task-induced BOLD activation with caffeine may be partly explained by vascular contributions.

**TABLE 3 |** Summary of research studies highlighting the cognitive domains impaired in multiple sclerosis.

References	Study population(s)	N (N Female)	Mean age	Cognitive domain(s) assessed	Tests administered	Main findings
Goitia et al. [155]	RRMS	36 (30F)	39.2 ± 10.2	Fluid intelligence (FI)	Matrix reasoning subtest of wechsler adult intelligence scale-III	RRMS patients showed impaired scores on FI compared to HC ($P < 0.001$).
	HC	42 (29F)	37.1 ± 10.7	Executive functioning (EF)	Wisconsin cart sorting test; Verbal fluency; Trail making test B	RRMS patients showed impaired scores on all tests of EF compared to HC ($P < 0.05$).
				Multitasking	Hotel task	There was no difference between groups on hotel task.
				Social cognition (SC)	Faux pas	RRMS patients showed impaired scores on SC compared to HC ($P < 0.001$).
Pitteri et al. [156]	RRMS	51 (38F)	36.7 ± 9.1	Information processing speed under low, medium, and high visual-attentional load	Videogame with manipulated visual-attention load	RRMS patients were slower under low and medium load ($P < 0.01$) and less accurate under high load ($P < 0.001$) than HC.
	HC	20 (7F)	34.2 ± 12.3			
Carotenuto et al. [157]	MS (RRMS, SPMS)	55 (32F)	45.9 ± 14.3	Olfactory function	The University of Pennsylvania Smell Identification Test (UPSIT-40)	MS patients showed lower olfactory function than HC ($P = 0.02$).
	HC	20 (10F)	40.1 ± 13			
Kouvatsou et al. [158]	MS (RRMS, SPMS)	38 (23F)	36.9 ± 9.6	Working memory: Phonological loop (PL)	Digit recall; Word recall; Non-word recall	MS group scored worse than HC on all measures of PL ($P < 0.0005$).
	HC	27 (24F)	33 ± 7.3	Working memory: Visuospatial sketchpad (VS)	Block recall; Mazes task; Visual patterns test	MS group scored worse than HC on Block and Mazes Recall ($P < 0.0005$).
				Working memory: Central executive (CE)	Backward digit recall; Backward block recall; Listening recall	MS group scored worse than HC on all measures of CE ($P < 0.0005$).
				Working memory: Episodic buffer	California verbal learning test (Greek adapted version); Logical Memory I- immediate story recall	MS group scored worse than HC on Immediate story recall ($P < 0.0005$).
Aladro et al. [159]	RRMS	88 (58F)	41.6 ± 8	Episodic memory (EM)	Logical memory I and II, and Family pictures I and II of the WMS-III[†]	MS group scored worse on all EM tests than HC ($P < 0.003$).
	HC	40 (24F)	41.6 ± 8.4			
Migliore et al. [160]	RRMS (no cognitive impairment)	24 (13F)	42.3 ± 9.4	Processing speed, Executive functioning	Task-Switching paradigm	RRMS patients showed worse performance than HC on task-switching ($P < 0.05$).
	HC	25 (13F)	42.8 ± 10.2			
Planche et al. [161]	Late-RRMS (LRRMS, disease duration > 10 years)	41 (34F)	51.3 ± 10	All cognitive domains	Neuropsychology test battery	Information processing speed was the most frequently impaired domain across all groups.
	SPMS	37 (28F)	50.2 ± 9.7			SPMS more frequently affected than LRRMS in all domains except language ($P < 0.01$).
	PPMS	23 (14F)	52 ± 8.4			More SPMS than PPMS patients impaired at visuospatial construction ($P < 0.05$).
Roth et al. [162]	RRMS	20 (17F)	43.5 ± 8.9	Attention	Attention Network Test (ANT)	ANT accuracy was lower for SPMS than HC ($P = 0.006$).
	SPMS	20 (16F)	50.7 ± 6.2	Information processing speed	Simple Reaction Time (SRT); Choice Reaction Time (CRT) Tasks	Patients (both groups) had longer reaction times than HC on SRT and CRT ($P < 0.001$).
	HC	40 (31F)	46.2 ± 8.7			

[†]wechsler memory scale- third edition.

Further work exploring the link between caffeine-induced changes to CVR and task-based BOLD activation maps is required.

Aging

Healthy aging of the brain includes structural and vascular changes [190]. Evidence for structural changes in healthy older
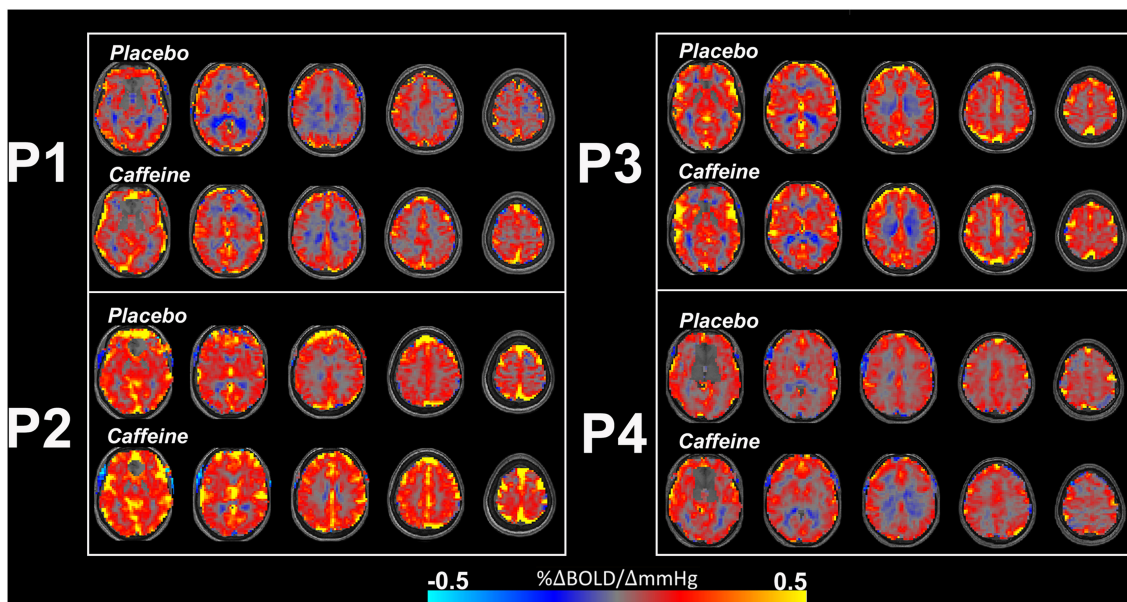
FIGURE 2 | Example BOLD-CVR maps from 4 participants (P1, P2, P3, and P4) who ingested placebo (upper rows) and caffeine (lower rows) pills across two separate scan sessions, 48 h apart. The caffeine condition shows some increased CVR, such as in P1, although there is individual variation and increased CVR is not immediately apparent in every individual. Negative CVR is also evident (in cool colors) in regions close proximity to the ventricles. CVR maps are overlaid on participant's own T_1-weighted structural image. Further information about the experimental protocol used to obtain these maps can be found in Specht et al. [180]. Color bar indicates CVR (%ΔBOLD/ΔmmHg).

adults includes cortical thinning, with frontal regions appearing to show accelerated rates of thinning with increasing age relative to temporal and occipital regions [191, 192]. Vascular alterations include changes in cerebral microvascular organization and capillary function [193] and indicate a functional decline of the neurovascular unit with age [194, 195]. These alterations at the microvascular level may lead to the changes observed at the macrovascular level. Macrovascular aging is characterized by increased arterial stiffness, corresponding to increased pulse pressure and impaired vascular endothelium function [196], and increased prevalence of hypertension [197]. MRI demonstrates CBF decreases with age [190, 198]. CVR is a useful method for tracking age-related changes to vascular health. Most studies utilizing CVR to investigate aging have focused on age-related diseases; however, important research findings have elucidated CVR changes with disease-free aging to understand how the healthy brain progresses throughout the adult lifespan. In this section, it will be argued that obtaining complementary physiological information such as CVR should be considered a priority for all fMRI investigations in aging populations, especially when comparing to younger adults.

CVR decreases in gray matter have been consistently reported with healthy aging [198–200]. CVR changes with age have also shown spatial heterogeneity. In cross-sectional studies, decreases in CVR within frontal [201] and temporal lobes [202] with increasing age have been reported. To assess CVR changes over time, a longitudinal study by Peng et al. [203] characterized changes over 4 years in participants aged 20–88 years. It was

reported that CVR decreased linearly with increasing age across the whole brain, but the temporal lobes showed the fastest rate of decline. The occipital lobes were the most resistant to age-related decline in CVR. However, inter-subject variation was evident in this longitudinal study. Lifestyle factors are likely contributors to variation in CVR. Indeed, exercise and fitness level is positively associated with CVR in healthy older adults [204]. CVR can also reflect cognitive changes with aging. Catchlove et al. [202] showed that CVR in the temporal lobes was associated with memory and attention performance in older adults. Further investigations of healthy brain aging and CVR are required. In particular, it would be important to investigate how the temporal characteristics of the CVR response relate to cognitive changes with aging.

Task-based fMRI studies have shown BOLD activation decreases with increasing age during tasks of visual attention [205, 206], working memory [207, 208] and memory encoding [209, 210], as would be expected if such cognitive functioning decreases with age. However, neural activity-mediated BOLD changes with age also show significant heterogeneity. One meta-analysis reported decreased prefrontal cortex activation in older adults during working memory tasks, while other task-engaged regions including the cingulate and parietal cortex remained unaffected throughout adulthood [207]. Other studies reveal conflicting findings by showing increased frontal lobe activation in older adults compared to younger cohorts during working memory tasks [211–213]. These inconsistent findings reflect increased variability in fMRI activation patterns in the older groups.

Two example patterns of age-related changes to BOLD activation that have been reported in the literature are hemispheric asymmetry reduction, and posterior-to-anterior shift. The first describes a shift in BOLD activation to cognitive tasks from unilateral to bilateral with increasing age [214–216]. That is, older adults more often recruit both cerebral hemispheres for tasks that show unilateral engagement in younger adults. The recruitment of both hemispheres in older adults has been associated with better task performance, and has been suggested to be a compensatory mechanism [217]. The second pattern, the posterior-to-anterior shift, describes findings of decreased activation in the occipital and temporal regions, and increase frontal activation during a variety of cognitive tasks, and this is also hypothesized to reflect compensatory mechanisms [218]. As outlined above, CVR also decreases with age, thus complicating the interpretation of task-based BOLD activation shifts. This is illustrated in **Figure 3**. Gauthier et al. exemplified these interpretation challenges by demonstrating that groups of older and younger adults showed similar BOLD activations to the Stroop task (i.e., executive functioning), however, CVR was reduced in the older group [219]. This demonstrates that BOLD activations to cognitive tasks cannot be directly compared between groups of different ages, as underling metabolic activity cannot be inferred from BOLD activation maps alone. Similar BOLD activation profiles between the older and younger adults in the context of reduced CVR means that metabolic activity was likely different between the groups [220]. Overall, the complex neurobiological and heterogenous changes that occur with age are reflected in the highly variable and inconsistent task-based BOLD findings in the literature.

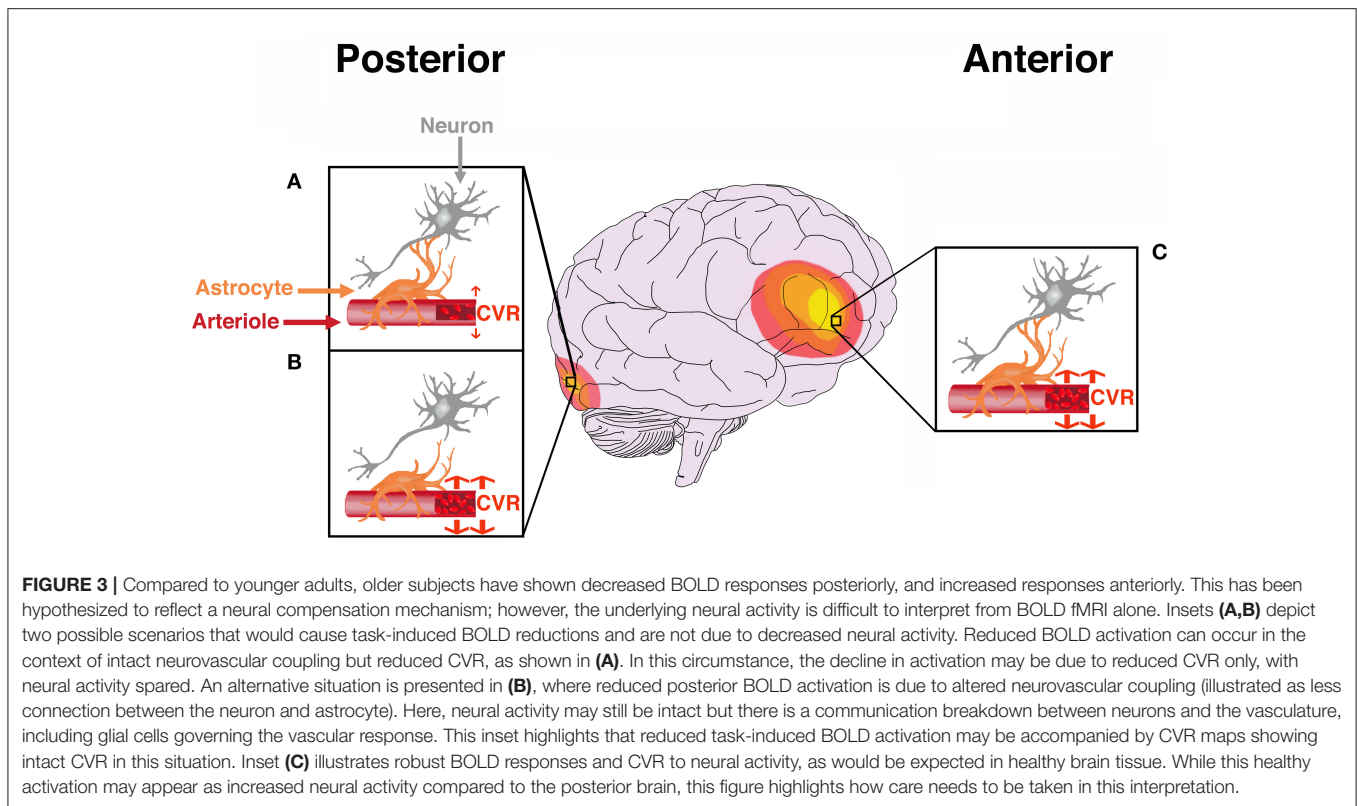# INTEGRATION OF BOLD-BASED ASSESSMENTS OF CVR AND NEURAL ACTIVITY: HYPERCAPNIC NORMALIZATION

This review paper has emphasized that adding CVR to task-based fMRI protocols may improve interpretation of BOLD activation maps. One analytical approach that integrates CVR is using it to correct activation maps through hypercapnic normalization. This was initially suggested by Bandettini and Wong [221] as a way to minimize signal contributions from large blood vessels. The premise of this work was that BOLD signal magnitude is highly weighted by baseline cerebral blood volume (CBV). They noted that a very large BOLD signal change of 15% would be observed in a voxel with 20% CBV, compared to a moderate 2.5% signal change in a voxel with 5% CBV, assuming all other parameters are identical. Removing this activation bias from voxels with higher CBV might be achieved using hypercapnia-induced BOLD signal changes. The authors suggested that hypercapnia induces consistent venous oxygenation changes across the brain, and any spatial variation in BOLD intensity would presumably be due to resting CBV and vessel size. The division of activation-induced signal change by hypercapnia BOLD signal change would return a normalized task-induced activation map void of influences from large vessels. This was investigated using a hypercapnia stimulus

where subjects inhaled a 5% CO_2 gas mixture, and performed a motor task. The peak activation observed in the motor task prior to normalization was in the sagittal sinus; after normalization the peak signal shifted to the brain parenchyma and therefore improved spatial specificity toward neuronal function.

This work was followed up by Cohen et al. [222] who investigated the effects of magnetic field strength on hypercapnic normalization. Similar to Bandettini and Wong [221], a motor task and 5% CO_2 hypercapnia stimulation was implemented. At a magnetic field strength of 4 T, the findings were consistent with Bandettini and Wong [221], where voxels containing large vessels were highly activated by the motor task but showed low normalized BOLD signal. Furthermore, these voxels were located in regions distant to the site of neural activity. At 7 T, the effect of hypercapnic normalization was less apparent due to the expected increased sensitivity to smaller blood vessels at this higher field strength. Research studies following Cohen et al. [222] capitalized on hypercapnic normalization to improve signal specificity. The breath-hold hypercapnia approach for increasing CBF was implemented to normalize BOLD-activation to a motor task [223] and a working memory task [224]. These studies found that hypercapnic normalization reduced the influence of vascular variability between subjects. A study by Handwerker et al. [20] implemented hypercapnic normalization to reduce vascular variability in task-induced BOLD signal in order to improve group comparisons between older and younger adults. Normalization removed age-related differences in some of the regions of interest, in particular those in frontal brain regions. A strong linear relationship between task-induced and hypercapnia BOLD signal was found and the authors suggested that hypercapnia response variability accounts for a large amount of the BOLD signal variability observed during the task. However, inter-subject variation increased in the older group after hypercapnic normalization, in contrast to the findings of Thomason et al. [224] and Biswal et al. [223].

These conflicting findings were examined in detail by Liau et al. [225]. To address inter-subject variability, their study investigated different approaches to hypercapnic normalization. The first method utilized a voxel-wise approach where the task-induced BOLD response for each voxel is divided by the hypercapnic BOLD response from the corresponding voxel. The second method was also a division tactic but used each subject's averaged hypercapnia BOLD responses within ROIs, rather than a voxel-wise implementation. The selection of ROIs was based on voxels demonstrating significant task and hypercapnic BOLD activation. A third method shifted from the division tactic and modeled hypercapnic BOLD responses as covariates. The covariate-normalized approach fit the task-induced BOLD response amplitudes to linear regression models where the hypercapnic BOLD responses were regressors. The amplitudes of the task-induced signals were then normalized by the slope of the regression lines. The authors found that the covariate-normalized approach demonstrated reduced inter-subject variability compared to the division methods.

The inclusion of CVR information into task-based fMRI has shown to improve comparisons between older and younger adults in a memory encoding task [226]. This study showed

FIGURE 3 | Compared to younger adults, older subjects have shown decreased BOLD responses posteriorly, and increased responses anteriorly. This has been hypothesized to reflect a neural compensation mechanism; however, the underlying neural activity is difficult to interpret from BOLD fMRI alone. Insets **(A,B)** depict two possible scenarios that would cause task-induced BOLD reductions and are not due to decreased neural activity. Reduced BOLD activation can occur in the context of intact neurovascular coupling but reduced CVR, as shown in **(A)**. In this circumstance, the decline in activation may be due to reduced CVR only, with neural activity spared. An alternative situation is presented in **(B)**, where reduced posterior BOLD activation is due to altered neurovascular coupling (illustrated as less connection between the neuron and astrocyte). Here, neural activity may still be intact but there is a communication breakdown between neurons and the vasculature, including glial cells governing the vascular response. This inset highlights that reduced task-induced BOLD activation may be accompanied by CVR maps showing intact CVR in this situation. Inset **(C)** illustrates robust BOLD responses and CVR to neural activity, as would be expected in healthy brain tissue. While this healthy activation may appear as increased neural activity compared to the posterior brain, this figure highlights how care needs to be taken in this interpretation.

that the two age groups had more comparable activation maps after hypercapnic normalization. Similar findings were reported in a study comparing adults with different fitness levels [227]. These comparisons would have been otherwise confounded by vascular changes without the information given by CVR. Overall, hypercapnic normalization has strong potential for addressing intrinsic limitations of BOLD fMRI.

CONCLUSION

Few studies exist that use CVR to inform interpretation of task-based BOLD activation. However, it is becoming increasingly clear that changes in CVR, cognition, and task-induced BOLD activation are highly interrelated. This is evident in patients with neurological conditions, both vascular and microstructurally-driven; and in normal physiology following caffeine consumption, and in healthy brain aging. These are just a few examples discussed here and not a comprehensive list. Correction procedures such as hypercapnic normalization can

be performed to correct task-based BOLD activation by CVR, although further research into this and other image integration approaches is warranted.

AUTHOR CONTRIBUTIONS

RW and GP conceived the idea and wrote the manuscript, and completed **Figures 2**, **3** with MM. MM and EM shaped and edited the manuscript. EM analyzed the data from and completed **Figure 1**. All authors contributed to the article and approved the submitted version.

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