Neurovascular Uncoupling in Functional MRI

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Definition of Terms

Terms referring to cerebrovascular autoregulation are often used interchangeably and have been assigned different meanings according to different users and groups. Although we are not claiming to be the final authority on this issue, we would like to establish the following definitions to inform the reader and minimize uncertainty.

Cerebrovascular autoregulation refers to the mechanism that maintains constant blood flow in the brain under varying day-to-day physiological conditions, e.g., changes in blood pressure and carbon dioxide (CO_2). It is achieved through the control of resistance in precapillary blood vessels (either by relaxation or contraction of smooth muscle). It is believed that this mechanism also accounts for flow augmentation during neuronal activity [1, 2]. Cerebrovascular reserve is the remaining capacity to augment blood flow by decreasing vascular resistance (vasodilatation). Cerebrovascular reactivity (CVR) can be used as an indicator of how much cerebrovascular reserve is left in a given vascular bed. CVR is defined as the percent change in cerebral blood flow/percent change in flow stimulus. For blood oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI), CVR is the percentage change in BOLD signal per mm Hg change in end-tidal PCO_2 ($P_{ET}CO_2$). This we term BOLD-CVR. With severe chronic vascular disease (e.g., vascular occlusion or high-grade stenosis), this reserve capacity can reach its limit. The vascular bed downstream of the affected vessel is maximally dilated in order to maintain sufficient blood flow to the brain tissue at baseline. Here the autoregulatory mechanism is still intact (vasodilatation occurred) but is operating at its maximum endpoint. The reserve capacity for additional augmentation of blood flow is, therefore, exhausted.

Arterial "steal" physiology refers to a brain region where blood flow paradoxically drops when a vasodilatory stimulus is applied. Two conditions must be met for this to happen. The first is that cerebrovascular reserve must be exhausted. The second is that sufficient reserve capacity exists in surrounding tissue so flow resistance can drop in response to the vasoactive stimulus.

Introduction

Twenty percent of the baseline cardiac output is directed toward the brain, which only accounts for 2% of the body weight, underscoring the high metabolic requirements of neurons and glia. In addition, a considerable increase in cerebral blood flow (CBF) occurs during neuronal activation [3]. This high demand for blood flow is associated with a flow control pathway that is not fully understood but appears to act through the same final common effector as the cerebrovascular autoregulatory mechanism. This effector is arterial vascular resistance mediated by smooth muscle tone of the precapillary sphincter in arteries and arterioles [1, 2]. The manner in which active neurons signal for augmentation of blood flow and the reason that such a considerable flow increase is needed are not completely understood and continue to be actively investigated.

If we can assume that the final common pathway for blood flow modulation occurs through vascular resistance and arterial smooth muscle tone, then clinically relevant issues arise in patients with chronic cerebrovascular disease, i.e., vascular stenosis or occlusion.

First, functional imaging of neuronal networks using techniques that measure blood flow augmentation during activation of neuronal networks may be compromised, leading to false-negative results. The second issue, and one that

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is just beginning to emerge as a potentially new disease entity, relates to chronic exposure of neuronal networks to the impending adverse effects of vascular beds that have already responded to proximal vascular stenosis with maximal smooth muscle relaxation, i.e., vascular beds that are already operating at the extreme of the autoregulatory reserve capacity. In effect, these vascular beds are unable to respond to a neuronal signal for the augmentation of blood flow. This chapter will therefore address how the state of the flow control mechanism can be investigated using imaging, how functional imaging of neuronal activation may be compromised and will open the investigation of the adverse effects of chronically compromised blood flow control on the health of regional neuronal networks.

Control of Cerebral Blood Flow

Modulation of vascular resistance is the mechanism for controlling blood flow at the precapillary level. CBF is modulated via control of the luminal diameter of the supplying arteries and arterioles. Smooth muscle tone in these vessels directly affects blood vessel diameter and, therefore, vascular resistance. Also, vascular resistance can be affected by capillary bed outflow resistance. Therefore, resistance in sinovenous outflow pathways can also have an impact on capillary blood flow, but the discussion of venous outflow disorders is beyond the scope of this work. Modulation of arterial vascular resistance is the underlying mechanism responsible for the brain's ability to control blood flow and has been termed cerebrovascular autoregulation. This mechanism is responsive to many different physiological stimuli. The first is a pressure-responsive mechanism that maintains constant blood flow in the microcirculation through a wide range of perfusion pressures [4]. It is a smooth muscle reflex mechanism where an increase in pressure produces a rapid reflex increase in smooth muscle tone, increasing vascular resistance and vice versa. The second is a response to vasoactive metabolic molecules such as CO_2, O_2, potassium, calcium, serotonin, and endothelin [5]. The third is a vasoactive response to local neuronal activity, termed the neurovascular unit [6, 7]. As indicated previously, the final common response pathway to these stimuli is thought to be smooth muscle tone in the arterial system, including the precapillary arterioles, where the precapillary sphincter is thought to reside [1, 2]. The sphincter represents a "valve" at the interface between the arterioles and capillary bed.

The cerebrovascular autoregulation maintains metabolic homeostasis by ensuring adequate blood flow and thus constant delivery of oxygen and glucose to the brain. The mechanism also serves to remove metabolic "waste" products, under varying physiological conditions and states of neuronal activity. The coupling between neuronal activation and blood flow was first described by Roy and Sherrington [8].

Neurovascular Coupling and Functional Magnetic Resonance Imaging

Following the increased neuronal activity in the brain, the local cerebral blood flow increases much more than the cerebral metabolic rate of oxygen ($CMRO_2$), resulting in a physiological decrease in the oxygen extraction fraction (OEF) [8–10]. The increase in the amount of oxygen consumed is only about one-third of the amount delivered [11]. This effect has been termed "neurovascular uncoupling" [10]. The increase in the concentration of oxyhemoglobin and the decrease in deoxyhemoglobin appearing in draining venules underlies the basic mechanism of BOLD-fMRI for distinguishing active from stable neuronal networks.

The first application of fMRI with BOLD acquisitions was performed in an animal model by Ogawa et al. in 1990 [12], followed by Kwong et al. in humans in 1992 [13]. Their work reported that changes in the activity of the brain affected the local MR signal and provided an intrinsic mechanism for detecting brain activation. The change in signal occurs because of changes in local magnetic field strength induced by the paramagnetic effects of deoxyhemoglobin. Applying this effect using BOLD-fMRI has revolutionized the detection and analysis of neuronal networks. Clinical applications are now being used routinely for preoperative assessment of eloquent network components in relation to resectable brain lesions.

However, the underlying assumption upon which these clinical techniques are based is that the cerebrovascular autoregulatory mechanism is intact. The remainder of this discussion will focus on the effect on brain mapping and the consequences on the health and integrity of the brain itself when this condition is not met.

Assessing the Cerebrovascular Autoregulatory Reserve by Performing Cerebrovascular Reactivity Measurements

Cerebrovascular autoregulatory compensation fails when the smooth muscle in the precapillary sphincter cannot either further relax or constrict in response to a vasoactive stimulus. The ability to interrogate the existing "setpoint" of smooth muscle tone would be very useful in determining how much of an additional response is present within the vascular system. This "reactivity" assessment can be performed by determining how much of an increase or decrease in blood flow occurs in response to a given vasoactive stimulus. This is termed cerebrovascular reactivity (CVR) and is defined as

the percent change in cerebral blood flow/percent change in flow stimulus. There are numerous imaging methodologies available for making this measurement, including ultrasound, MRI, computed tomography (CT), single-photon emission CT (SPECT), and positron emission tomography (PET) using different stimuli and different imaging contrast agents. Since it is beyond the scope of this work to fully elaborate on each of these imaging modalities, we will focus on the quantitative BOLD-CVR method that we have pioneered in association with precise and independent control of end-tidal CO_2 and O_2 ($PETCO_2$ and $PETO_2$) [14]. This technique enables a Model-based Prospective End-tidal Targeting (MPET) technique [15] that allows precise iso-oxic pseudo-square wave changes in $PETCO_2$ (RespirAct, Thornhill Research Inc., Toronto, Canada) while acquiring BOLD-fMR imaging sequences. Maintaining oxygen at a normal level decreases the T1-inflow effects that might alter the BOLD signal during the acquisition [16]. The near-square wave changes in $PETCO_2$ result in a robust response of the brain vasculature that can easily be detected in the BOLD signal and can be mapped spatially (Fig. 23.1a) [17, 18]. CVR is defined as a percent change in BOLD signal/mm Hg change in $PETCO_2$. The relationship of CVR as a measure of cerebrovascular reserve capacity against changes in cerebral blood flow has been validated using arterial spin labeling (ASL) MRI [19] and gold standard Diamox-challenged $^{15}O(H_2O)$-PET [20].

Exhausted Cerebrovascular Reserve Associated with Steal Physiology

In general, vascular diseases impair the ability of the feeding vasculature to deliver adequate flow to the microcirculation. Cerebrovascular autoregulation can compensate for supply deficits through vasodilatation, decreasing the vascular resistance. However, in the case of severe chronic cerebrovascular disease, arterial smooth muscle is maximally relaxed in order to maintain sufficient blood flow at baseline. With maximal smooth muscle relaxation of the precapillary sphincter, the reserve capacity has reached its limit, the vascular resistance is at a minimum, and further flow augmentation is not possible. However, normal surrounding vascular beds are still able to lower vascular resistance. The overall effect is a diversion of blood toward the lower resistance vascular bed. Under these conditions, a flow stimulus such as

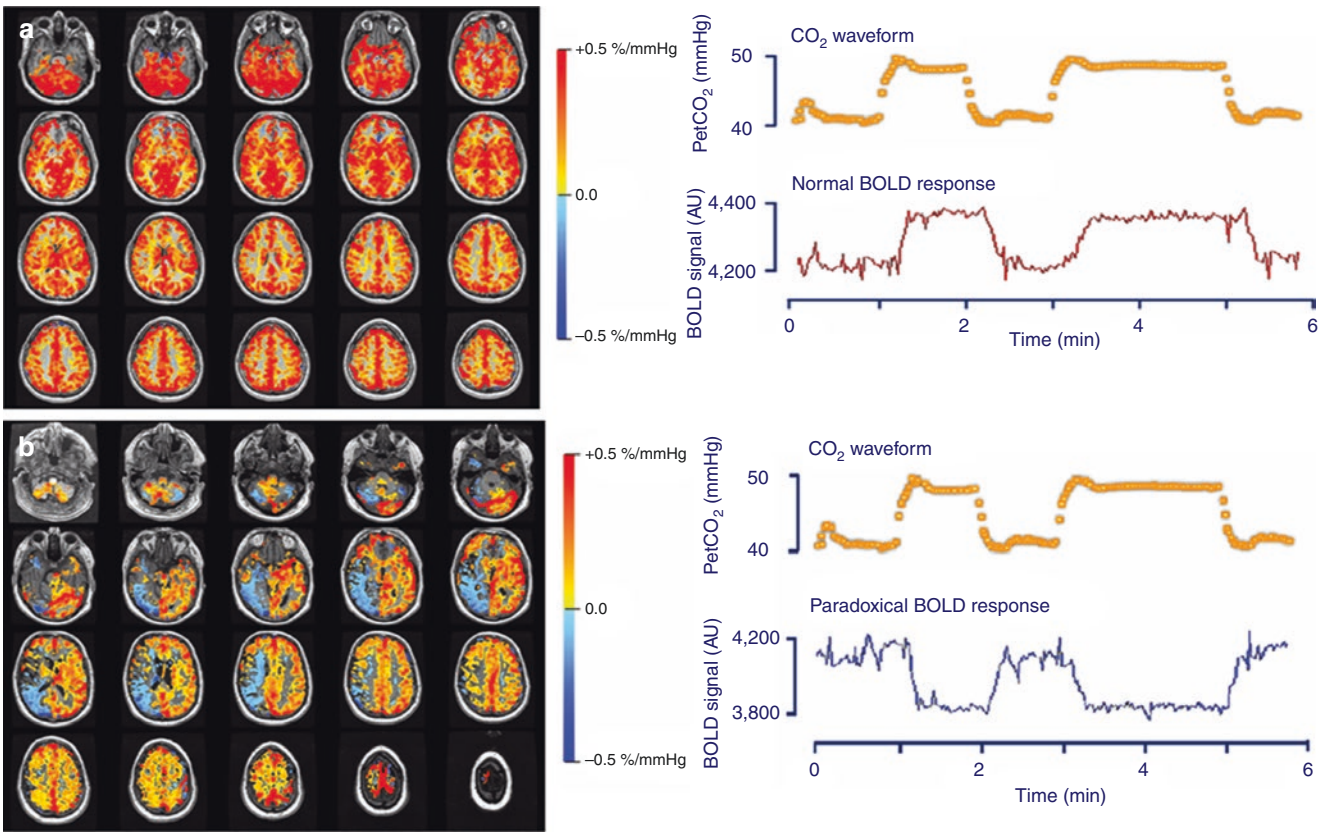

Fig. 23.1 Spatial CVR maps acquired with BOLD-MRI and precise control of $PETCO_2$. Near square wave changes in end-tidal CO_2 ($PETCO_2$) induce robust increases in the raw BOLD signal (arbitrary units), enabling fMRI-type signal analysis. (**a**) shows a normal increase in BOLD signal during a hypercarbic stimulus, resulting in a spatial CVR map showing normal reactivity. Note the diminished response in the white matter compared to the gray matter. This is a normal finding [18]. (**b**) is an example of a paradoxical decrease in BOLD signal during hypercarbia, demonstrating an area with exhausted autoregulatory reserve on the spatial CVR map (*blue area*) disease

Table 23.1 Summary of key BOLD-MRI CVR research demonstrating exhausted cerebrovascular reserve associated with steal physiology and its impact on normal appearing brain tissue on conventional MR imaging

Authors	Subjects	Findings
Mandell et al. [18]	28 young healthy subjects (age range 22–42)	Young healthy subjects exhibit steal physiology in the deep white matter
Mandell et al. [19]	38 patients with severe cerebrovascular steno-occlusive disease	Brain areas exhibiting steal physiology demonstrate a decrease in CBF
Fierstra et al. [21]	17 patients with severe unilateral cerebrovascular steno-occlusive disease	Patients exhibiting unilateral steal physiology with normal appearing brain tissue on conventional MRI, demonstrate an 8% thinner cerebral cortex as compared to the contralateral, unaffected hemisphere
Conklin et al. [22]	22 Moyamoya patients with unilateral steal physiology, 12 age-matched healthy controls	Normal appearing white matter exhibiting steal physiology is spatially correlated with elevated ADC in patients with Moyamoya disease
Fierstra et al. [23]	29 patients with severe cerebrovascular steno-occlusive disease and preoperative steal physiology	Successful regional revascularization and reversal of steal physiology is followed by restoration of cortical thickness
Conklin et al. [24]	42 patients with carotid occlusive disease and impaired BOLD-CVR, 12 age-matched healthy controls	Normal appearing white matter exhibiting impaired BOLD-CVR is spatially correlated with elevated ADC in patients with carotid occlusive disease
Sebök et al. [25]	25 patients with severe symptomatic cerebrovascular steno-occlusive disease	Presence of crossed cerebellar diaschisis is associated with severely impaired supratentorial BOLD-CVR and worse clinical outcome
Van Niftrik et al. [26]	28 patients with severe symptomatic cerebrovascular steno-occlusive disease, 15 age-matched healthy controls	Presence of ipsilateral diaschisis is associated with thalamic impaired BOLD-CVR, thalamic atrophy, and worse clinical outcome

CBF cerebral blood flow, *ADC* apparent diffusion coefficient, *MRI* magnetic resonance imaging, *BOLD* blood oxygen level-dependent, *CVR* cerebrovascular reactivity

carbon dioxide will increase flow to the normal territory and decrease flow to the territory with exhausted autoregulatory reserve ("steal physiology").

Using the term *impaired* autoregulation to describe this process may be erroneous since the autoregulatory mechanism itself is not defective. The cerebrovascular reserve, however, has reached its limit, and therefore, the autoregulatory mechanism can no longer drop the vascular resistance when further flow augmentation is needed. This process may be more appropriately named "exhaustion of cerebrovascular reserve."

With BOLD-MRI assessment of CVR, brain areas with an exhausted cerebrovascular reserve can be mapped (Fig. 23.1b, Table 23.1) [18, 19, 21–26]. These areas show a paradoxical response in BOLD signal during hypercarbia and a decrease in CBF [19].

The Consequences of Exhausted Cerebrovascular Reserve Associated with Steal Physiology on Neuronal Network Mapping Using Task-Based BOLD MRI and BOLD-CVR

Functional MRI depends on an adequate response of the cerebrovascular autoregulatory mechanism to augment blood flow when a vasodilatory stimulus is applied. The increase in blood flow results in a washout of deoxyhemoglobin that can be detected in the BOLD signal. In chronic cerebrovascular disease, with progressive stenosis, cerebrovascular reserve gets progressively smaller resulting in a parallel decrease in BOLD signal, eventually leading to a paradoxical (negative) BOLD signal when the autoregulatory reserve is exhausted (Fig. 23.1b) [27]. Under these conditions, augmenting flow under any stimulus including neuronal activation is theoretically not possible. If there is no awareness of this flow-limiting condition, the analysis of fMRI data can be erroneous. Analysis of the BOLD signal response to neuronal activation eventually requires the application of a threshold to distinguish active neuronal network components from inactive tissue. If the threshold is decreased, more activation is observed. In fact, thresholds can be lowered enough to show virtually any anatomical site as a component of the network map (Fig. 23.2) [28]. This bias can lead to the inclusion of a false-positive activation in the fMRI map [29]. In addition, false-negative errors may also occur, leading to the erroneous conclusion of adaptive plasticity as an explanation for the pattern of neuronal activation. The case summarized in Figs. 23.3 and 23.4 highlight the importance of these issues. It is also important to recognize that other disorders can have a secondary effect on brain blood flow, which can impair the flow response to neuronal activation. For example, brain tumors or arteriovenous malformations (AVMs), either by virtue of local mass effect or from arterial-venous shunting,

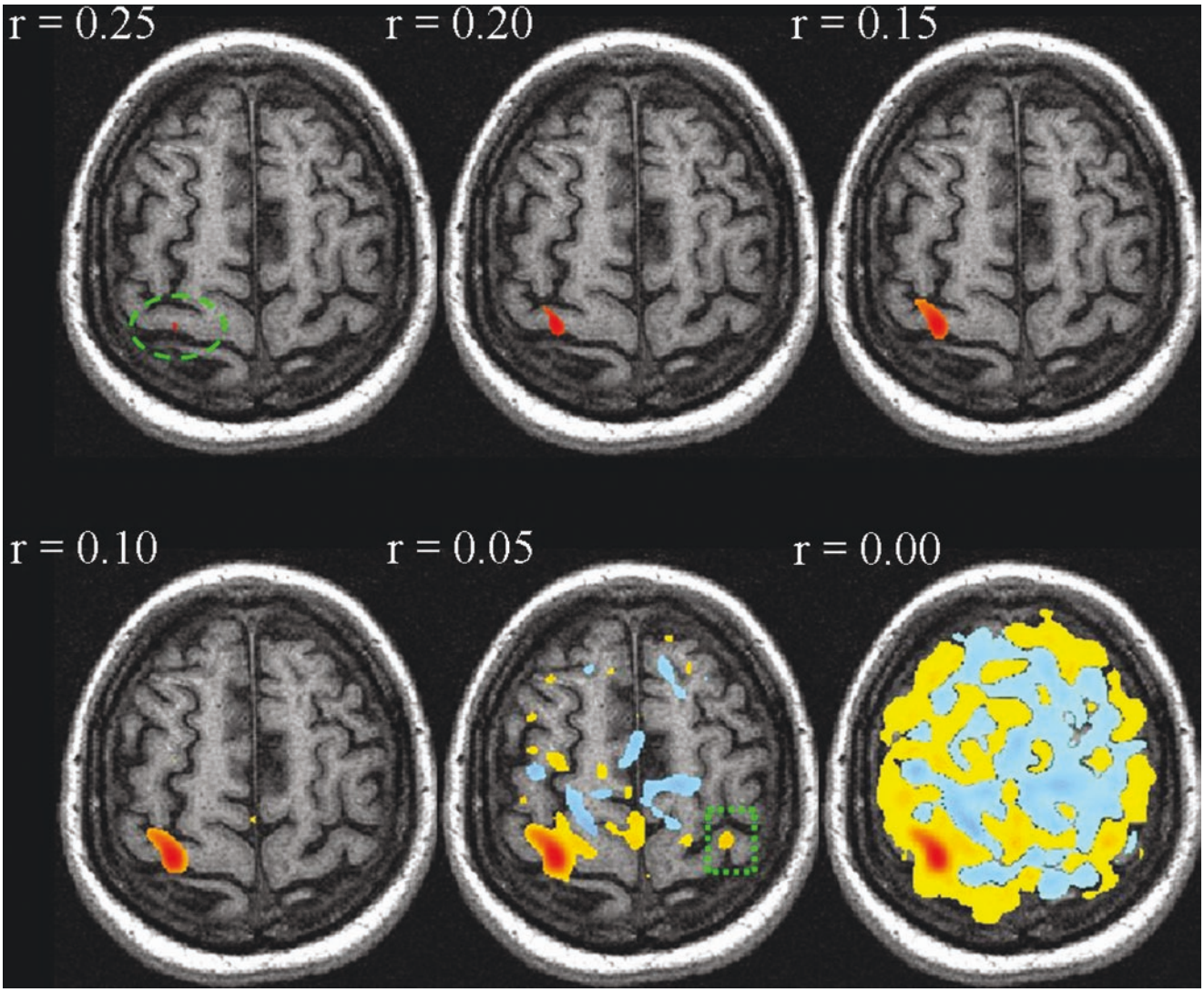

Fig. 23.2 Influence of thresholding on the fMRI map of a fingertapping task. fMRI maps were generated following the acquisition of a left-hand finger tapping fMRI paradigm. The upper left image shows voxels with the highest *r*-correlation (*green dashed circle*) during the task. This was obtained by increasing the threshold until only one final group of voxels remained. Not surprisingly, these voxels were in the expected location of the hand homunculus in the primary motor cortex controlling left-hand function. Lowering the activation threshold reveals greater spatial activity, eventually leading to visible activity in the left primary motor cortex (*green dashed square*). It is common to see activation in both motor cortices during unilateral hand tasks [28]. Lowering the threshold even further to zero reveals "activation" (or "deactivation" *in blue*) of the whole brain. Care must be taken when interpreting patterns of functional networks since the number and extent of constituents are threshold-dependent

can alter CVR and local flow dynamics. False-negative activation of eloquent tissue in the vicinity of such a lesion can occur, potentially increasing the risk of an adverse surgical outcome. The solution is to map CVR using BOLD-fMRI either with precision control of CO_2 or using a breath-hold to elevate CO_2 (Fig. 23.5). The BOLD-CVR map can then be compared to the fMRI map for confirmation that blood flow increases are possible in the area of interest distal to a stenosis, in the vicinity of a tumor, or near an AVM, thus validating the fMRI response. The breath-hold CVR method can be performed using the same BOLD sequence as the fMRI acquisition and analyzed using the same software [30]. As in fMRI, the "task" consists of a 25-s breath-hold each minute for 4–5 min. Although not quantitative, the method is robust enough to determine whether steal physiology is present (Fig. 23.5).

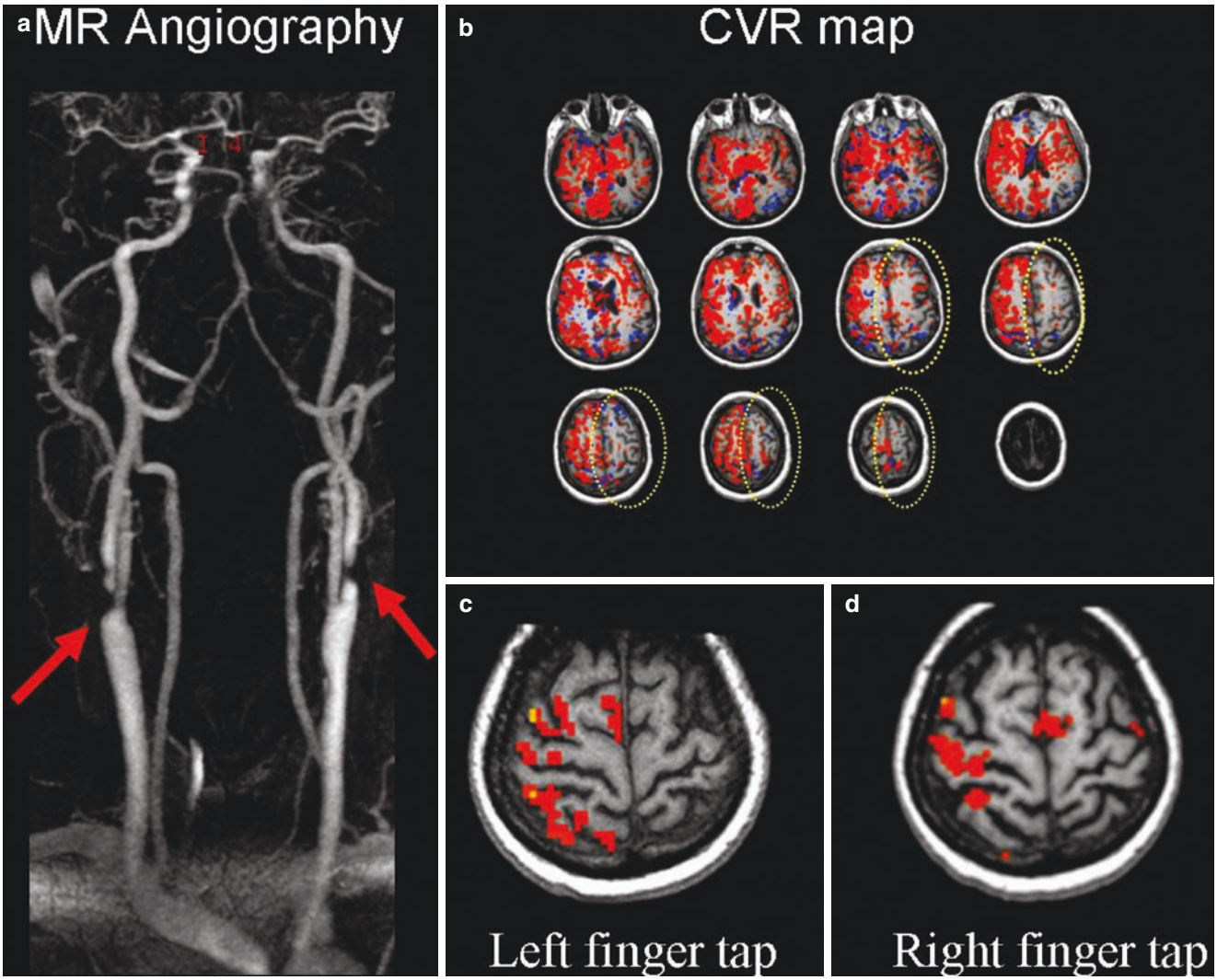

Fig. 23.3 Plasticity vs. absence of neurovascular response? A 70-year-old man with shaking hand syndrome. His right hand became uncontrollable during use such that the latter part of his signature became progressively illegible. (**a**) shows bilateral high-grade stenosis (>90%) of the internal carotid arteries (*red arrows*). (**b**) Interestingly, despite similar stenoses, autoregulatory reserve on the BOLD-CVR map was exhausted only on the left side (*yellow dashed circles*). (**c**) fMRI map shows the expected right motor cortex activation during left finger tapping. (**d**) A right finger tapping paradigm showed no activation in the left hemisphere. However, there was considerable activation in the ipsilateral hemisphere. This was initially felt to be the result of a shift in control of the right hand to the right hemisphere until the BOLD-CVR map revealed an absence of the neurovascular response. The fMRI map was therefore deemed unreliable in this case. Interestingly, validation of the neurovascular response has not been performed in most fMRI research studies of patients with ischemic stroke, who by definition would have a high probability of neurovascular uncoupling

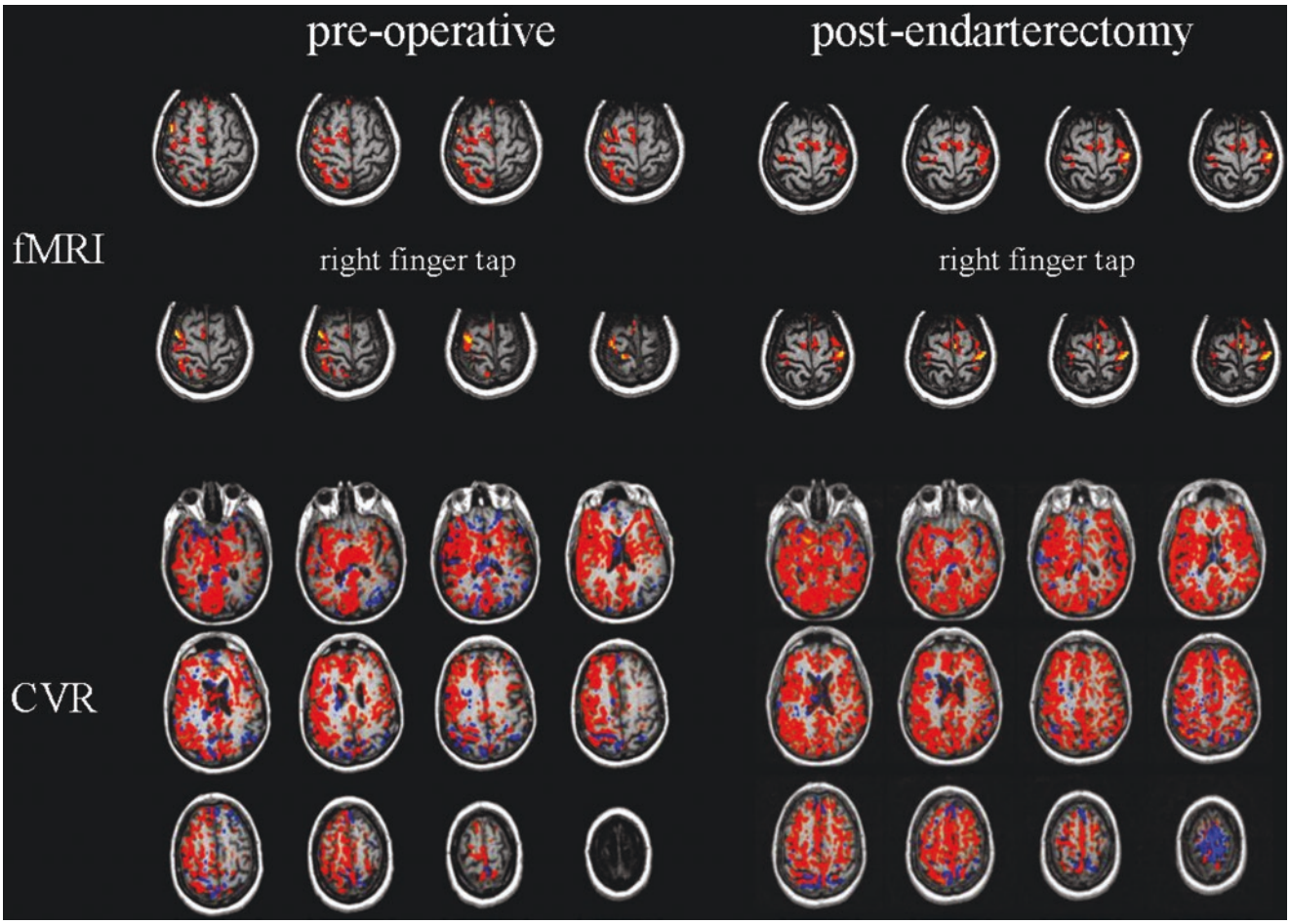

Fig. 23.4 Motor cortex activation before and after revascularization. These are pre-and post-endarterectomy fMRI and BOLD-CVR maps of the same patient in Fig. 23.3. Postoperatively, the neurovascular coupling has been restored to the left hemisphere, and control of the right upper extremity has "shifted" back to the left hemisphere according to the fMRI map. Shifting of motor control, as seen on the fMRI maps, is more likely the result of reestablished neurovascular coupling rather than plastic changes in the brain

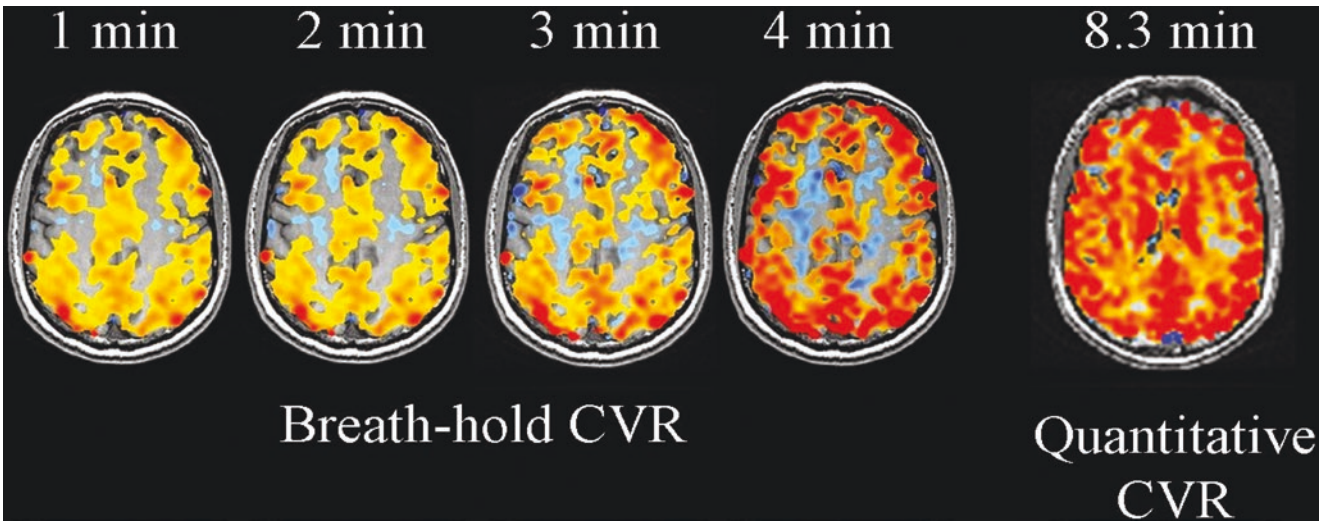

Fig. 23.5 Efficacy of breath-hold BOLD-CVR for establishing the presence of normal neurovascular coupling. Hypercarbia is inducible during breath-holding and can be used to generate non-quantitative maps of CVR. These maps are sufficient to establish the presence of positive versus absent versus paradoxical reactivity. Twenty-five-second breath-holds per minute for 4 min can yield high-quality CVR maps similar to that obtained using precision control of end-tidal CO_2. Since the end-tidal values of CO_2 are not available during breath-hold (unless arterial blood gases are monitored continuously), the breath-hold CVR maps are not quantitative

Distinguishing Hemodynamics from Embolic Neurological Events

Ischemia can be the result of embolic occlusion of arteries distal to an embolic source such as a clot within the heart or an atherosclerotic plaque in the cervical carotid artery. The ability to distinguish between these possibilities is important since treatment will vary accordingly. For example, medical management is usually indicated in symptomatic patients with carotid plaques associated with low-grade stenoses. High-grade stenoses in excess of 90% can produce symptoms by embolic, hemodynamic, or combined mechanisms. If there is a hemodynamic component with steal physiology, there is a higher risk of disabling ischemic stroke than if the condition is purely embolic [31]. The only effective treatment for steal physiology is revascularization. BOLD-CVR is clearly capable of identifying the presence of steal physiology, although the application of this technique in patients is not generally practiced, primarily because of the overall low incidence of steal physiology in patients with cerebrovascular diseases and because of technical challenges in implementing CVR analysis.

The Long-Term Consequences of Chronic Steal Physiology on the Brain: "The Neurovascular Uncoupling Syndrome"

The brain areas demonstrating exhausted cerebrovascular reserve with steal physiology are at high risk for developing a future acute ischemic event [32–34]. However, steal physiology can occur episodically and can exist over a long period of time without ictal signs of ischemia but may still affect the integrity of both gray and white matter.

The pathological effects of acute ischemia are well characterized—acute severe reduction of blood flow in the core of an infarct results in complete loss of neurons. Surrounding the infarct core is the penumbra suffering from reduced blood flow, where viable neurons are at risk of death if blood flow is not restored in a timely fashion. However, selective neuronal necrosis has been observed despite timely restoration of blood flow in brain regions thought to represent tissue with reversible injury [35].

Less well understood is the chronic brain exposure to episodes of sublethal hypoperfusion. This question of whether chronic episodic ischemia can produce pathological effects short of frank infarction in humans has been a longstanding question and difficult to document. We have addressed this question by studying patients who have a chronic steno-occlusive disease with unilateral exhausted cerebrovascular reserve associated with steal physiology. Patients showing normal cortex without evidence of visible ischemic injury on conventional MRI were investigated. The thickness of the cortex in the region of steal physiology was compared with the cortical thickness in the normal hemisphere and was found to be 8% thinner [21]. Although the reasons for this reduction in thickness have not been verified with histology, the following are possible explanations. Hypoperfusion might lead to selective loss of neurons or a decrease in cerebral blood volume (CBV). It is, however, more likely that CBV would be normal or even increased since maximal vasodilatation is present. Furthermore, decreased CBV is thought to occur only in the setting of stage III ischemia [36, 37], which is seen in the core of an acute infarct. Another explanation is the loss of neuroglial complexity with loss of volume in the neuropil. Chronic exposure of neurons to flow insufficiency during activation may result in a loss of synaptic density and decreased dendritic arborization. Under these conditions, neurons divert metabolic resources toward survival over function [38, 39]. Another possible mechanism is that these episodes of hypoperfusion during activation may cause inhibition of protein synthesis resulting in delayed neuronal death [40].

White matter is not immune to these effects, although the mechanism may be different. Conklin et al. [22, 24] performed apparent diffusion coefficient (ADC) measurements in the white matter of subjects with unilateral steal physiology and cortical thinning but without structural abnormalities on conventional imaging. ADC values in the steal hemisphere were significantly elevated compared to the normal hemisphere suggesting the presence of chronic injury. It remains to be determined if the findings represent degeneration secondary to injury of neuronal cell bodies on the side of the thinner cortex or due to the direct effects of steal physiology and episodic ischemia on the axons themselves.

The vascular deficit may also have a direct effect on glial cells. Astrocytes play a supporting role in the neurovascular unit [41]. When the autoregulatory reserve is exhausted, astrocyte metabolism may be impaired increasing the vulnerability of the neurons to injury. Inversely, or more likely in tandem, is the potential loss of these supporting cells due to pruning of neuronal complexity. Metabolic stress on oligodendrocytes resulting in "decay" of myelin may be an alternative explanation for elevated white matter water diffusion.

Follow-up work by our group has been performed employing cortical thickness measurements in patients previously identified with cortical thinning who underwent successful surgical revascularization and normalization of CVR [23]. Thirty of 30 hemispheres showed increased cortical thickness indicating that revascularization can reverse cortical thinning. This observation would favor a reversible cause of neuroglial injury as selective neuronal necrosis would not be expected to recover. Perhaps restoration of flow augmen-

tation following revascularization restored metabolic balance and reversed degeneration in the neural networks and supporting cells.

Overall, the underlying pathophysiology is complex and not well understood. Nevertheless, these studies demonstrate the first indication that areas with steal physiology show structural changes in brain tissue. Neurons in the affected brain regions operate in an environment where inadequate blood flow is present during activation leading to diminished delivery of nutrients and diminished removal of waste products. We now believe that this condition should be referred to as true neurovascular uncoupling since the normal increase in blood flow during neuronal activation is no longer occurring. If cortical thinning and increased white matter diffusion correlate with deterioration in neurocognitive and functional performance measures specific to the affected vascular territory, it would be appropriate to consider defining the disorder as "neurovascular uncoupling syndrome."

Conclusion

The considerable increase in cerebral blood flow that occurs during increases in neuronal activity can be mapped using fMRI. Pulse sequences sensitive to blood flow, such as arterial spin labeling or sequences sensitive to magnetic field inhomogeneities (produced by deoxyhemoglobin) such as long echo time gradient echoes (BOLD imaging) can be used to create functional maps of neuronal activity. With these maps, the ability to show the relationship between resectable brain lesions and eloquent cortex has become the standard of practice for presurgical planning. Interpretation of the fMRI maps must consider the integrity of neurovascular coupling. If there is doubt, an assessment of BOLD-CVR can be performed either quantitatively using tight control of CO_2 or with a breath-hold CVR analysis. This can also be performed in the research setting to validate fMRI studies in subjects with vascular diseases who, for example, may be undergoing plasticity analysis following acute ischemic stroke.

Another important potential clinical application of BOLD-CVR is in distinguishing embolic from hemodynamic ischemic events, especially for the identification and referral of patients with steal physiology for revascularization either via endarterectomy, angioplasty with stenting, or even extracranial-intracranial (EC-IC) bypass in the case of the occluded carotid or middle cerebral artery (MCA).

In the future, detection and treatment of steal physiology in patients who do not have discrete ischemic events but have evidence of cortical thinning and increased white matter water diffusion ("neurovascular uncoupling syndrome") may be important in order to prevent accelerated neurological deterioration within the affected vascular territory via elective revascularization.

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