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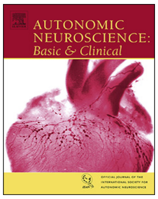

Review

How reliable is cerebral blood flow to map changes in neuronal activity?

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ABSTRACT

Neuroimaging techniques, such as functional MRI, map brain activity through hemodynamic-based signals, and are invaluable diagnostic tools in several neurological disorders such as stroke and dementia. Hemodynamic signals are normally precisely related to the underlying neuronal activity through neurovascular coupling mechanisms that ensure the supply of blood, glucose and oxygen to neurons at work. The knowledge of neurovascular coupling has greatly advanced over the last 30 years, it involves multifaceted interactions between excitatory and inhibitory neurons, astrocytes, and the microvessels. While the tight relationship between blood flow and neuronal activity forms a fundamental brain function, whether neurovascular coupling mechanisms are reliable across physiological and pathological conditions has been questioned. In this review, we interrogate the relationship between blood flow and neuronal activity during activation of different brain pathways: a sensory stimulation driven by glutamate, and stimulation of neuromodulatory pathways driven by acetylcholine or noradrenaline, and we compare the underlying neurovascular coupling mechanisms. We further question if neurovascular coupling mechanisms are affected by changing brain states, as seen in behavioral conditions of sleep, wakefulness, attention and in pathological conditions. Finally, we provide a short overview of how alterations of the brain vasculature could compromise the reliability of neurovascular coupling. Overall, while neurovascular coupling requires activation of common signalling pathways, alternate unique cascades exist depending on the activated pathways. Further studies are needed to fully elucidate the alterations in neurovascular coupling across brain states and pathological conditions.

1. Introduction

Neurons are highly demanding of energy, especially upon activation. As blood supply cannot remain constantly elevated throughout the entire brain, it is critical that a rise in cerebral blood flow (CBF) occurs in a timely and spatially restricted manner to the activated brain area to ensure adequate supply of oxygen and nutrients to the neurons at work. This tight adjustment, defined as neurovascular coupling (NVC), represents a fundamental brain function.

NVC requires complex interactions between neurons, astrocytes, and cerebral blood vessels, composed of pericytes, smooth muscle cells and endothelial cells (Girouard and Iadecola, 2006; Lecrux and Hamel, 2011). These components form the neurovascular unit (Hamel, 2006) and define a dynamic entity that governs NVC mechanisms concerned with the release of neurotransmitters, neuromodulators, and vasoactive mediators. NVC mechanisms, described as the relationship between increased neuronal activity and blood flow, have mainly been studied following an isolated sensory event (visual, somatosensory, auditory or olfactory stimulation). However, cortical neurons are under the control of subcortical modulatory pathways that drive changes in brain states, corresponding to changes in cortical activity occurring across states of sleep, wakefulness, attention, and arousal (Harris and Thiele, 2011). These inputs originate from subcortical nuclei and release specific neuromodulators, such as acetylcholine (ACh), noradrenaline (NA) or serotonin (5-HT) (Avery and Krichmar, 2017) that act through receptor-selective effects on most cells of the neurovascular unit.

Importantly, while numerous studies have investigated neuronal activity and circuits underlying sensory and neuromodulatory processing, the study of NVC mechanisms requires concomitant measurements of changes in both neuronal activity and hemodynamic signals in response to a stimulus. In this respect, pyramidal cells have been identified as “neurogenic hubs” of NVC in the somatosensory cortex (Lecrux

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Abbreviations: 5-HT, serotonin; ACh, acetylcholine; AD, Alzheimer's disease; BOLD, blood-oxygenation level dependent signal; BK, large-conductance Ca^{2+}-activated K^{+} channels; ChR2, channelrhodopsin; CBF, cerebral blood flow; EETs, epoxyeicosatrienoic acids; GABA, gamma-aminobutyric acid; Kir, inward rectifier K^{+}; MRI, channels, magnetic resonance imaging; NPY, neuropeptide Y; NVC, neurovascular coupling; NA, noradrenaline; PGE2, prostaglandin E2; SOM, somatostatin; t-PA, tissue plasminogen activator; VIP, vasoactive intestinal peptide; VGAT, vesicular GABA transporter; VCID, vascular cognitive impairment and dementia

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et al., 2011). However, GABA interneurons are particularly well positioned to orchestrate neuromodulatory signals coming from subcortical areas (Cauli et al., 2004) and sculpt cortical activity and subsequent hemodynamic responses. Deciphering the role of each cellular component of the neurovascular unit can be further achieved by measuring the hemodynamic signals upon direct activation of specific neurons, astrocytes or pericytes.

In this review, following a brief overview of the history of NVC and its general mechanisms in the cortex, we will address the following questions: (1) what happens to the tight coupling between neuronal activity and hemodynamics when different brain pathways that release distinct neurotransmitters are activated? (2) What happens to NVC when brain states are altered? And finally (3), we will address the possible consequences of disease conditions on NVC reliability.

2. A brief history of NVC in the cerebral cortex

Brain function and neuronal survival depend on a constant supply of blood from the cerebral circulation and the brain possesses several mechanisms to maintain CBF within a normal range throughout physiological states. A primary mechanism is cerebral autoregulation that keeps CBF stable across changes in mean arterial blood pressure (Strandgaard and Paulson, 1984). In addition, NVC refers to fast and localised rises in CBF in areas of increased neuronal activity evoked by a task. The underlying molecular and cellular mechanisms as well as the signalling cascades of NVC have considerably evolved in recent years, and will be presented below with key pioneer work.

In 1881, the Italian physiologist Angelo Mosso first evidenced changes in brain pulsatility (reflecting CBF) evoked by a stimulus in patients presenting skull defects (Sandrone et al., 2012). The existence of intrinsic brain mechanisms controlling this relationship was subsequently hypothesized by Roy and Sherrington in 1890, thus providing the first concept of NVC (Roy and Sherrington, 1890). Since these seminal studies at the end of the 19th century, the understanding of the relationship between CBF and neuronal activity has greatly evolved, largely due to the increased knowledge of the anatomy and function of the neurovascular unit and of concurrent advance in experimental techniques (Hyder, 2009) (Fig. 1). Hemodynamics signals can be spatially resolved across the entire brain by autoradiography using a diffusible tracer, such as ^{14}C-iodoantipyrine (Sakurada et al., 1978). In contrast, laser-Doppler flowmetry provides a high temporal resolution of the changes in velocimetry, as an index of cerebral blood flow, integrated in a volume of tissue usually approximated to 1mm^3, as captured by an optic fiber probe (Fredriksson et al., 2009) (Figs. 1, 2 and 3). More recently, brain activation has been mapped based on the changes in oxygenated and deoxygenated hemoglobin in the blood as a function of the energy demand of active neurons, referred to blood-oxygen level dependent (BOLD) fMRI (Figs. 2 and 3). Similarly, optical imaging of intrinsic signals, based on the distinct absorption spectra of oxygenated and deoxygenated hemoglobin, allows mapping of the brain surface oxygenation signals (Figs. 2 and 3). 2-Photon microscope imaging in living animals further allows visualization of brain microvessel diameter changes across cortical layers during NVC responses (Fig. 1).

The original metabolic hypothesis, viewing metabolic messengers as triggering the changes in blood supply (using oxygen consumption as an index) was initially proposed (Roland and Larsen, 1976), but the neurogenic hypothesis has subsequently emerged, stating that vasoactive mediators released by neurons drive the hemodynamic response. Accordingly, numerous vasoactive mediators of neuronal origin have been identified over the last 20 years, such as adenosine (Morii et al., 1987), nitric oxide (NO) (Dirnagl et al., 1993) and metabolites of the arachidonic acid cascade, including the cyclooxygenase-2 (COX-2) and its derivate prostaglandin E2 (PGE2) that acts on vasodilatory EP2 and EP4 receptors (Niwa et al., 2000; Lacroix et al., 2015) (Fig. 1).

Compounds associated with interneurons that exert vasoactive effects on brain microvessels include GABA (Fergus and Lee, 1997) and peptides co-expressed in GABA interneurons, such as vasoactive intestinal peptide (VIP) (Yaksh et al., 1987), somatostatin (SOM) (Long et al., 1992) and neuropeptide Y (NPY) (Tuor et al., 1990). Subsequently, single-cell stimulation of interneurons was found to translate into a vasomotor response in cortical microvessels, identifying GABA interneurons as cortical relay of NVC (Cauli et al., 2004). Further evidence of the role of GABA interneurons in cortical NVC was provided *in vivo* by pharmacology (Lecrux et al., 2011) and by specific optogenetic targeting of GABA interneurons (Anenberg et al., 2015; Uhlirova et al., 2016).

Astrocytes have emerged as key players in the communication between activated neurons and blood vessels (Zonta et al., 2003; Iadecola and Nedergaard, 2007; Koehler et al., 2009), as recently reviewed (Cauli and Hamel, 2018). Astrocyte function in NVC has been related to their ability to release vasoactive messengers, such as arachidonic acid derivatives epoxyeicosatrienoic acids (EETs) (Gebremedhin et al., 1992; Peng et al., 2002), and potassium (K$^+$) (Filosa et al., 2006) acting through multiple channels, such as large-conductance Ca^{2+}-activated K$^+$ (BK) channels on astrocytes (Girouard et al., 2010), or the inward rectifier K$^+$ (Kir) (Longden and Nelson, 2015) and TRPV4 channels on microvessels (Dunn et al., 2013). More recently, pericytes have been recognized as active participant in NVC through their capacity to modify capillary diameter (Peppiatt et al., 2006; Fernandez-Klett et al., 2010).

The dynamic of NVC signals across the vascular tree has been examined and current evidence points toward an initial hemodynamic response at the capillary level, possibly driven by pericyte dilation (Wu et al., 2006; Hall et al., 2014), and transmitted upstream to arterioles. An optimal NVC response requires an orchestrated response between

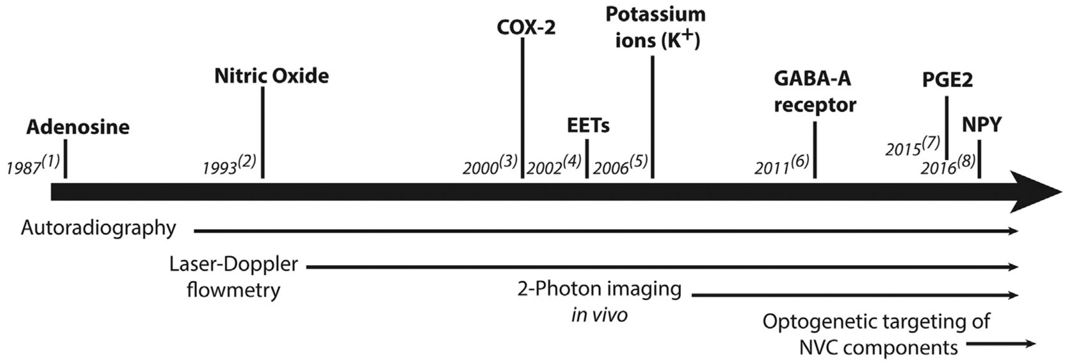

Fig. 1. Timeline of identification of some of the key mediators of the NVC responses in the cortex, and major investigation techniques. References: (1) Adenosine: Morii et al., 1987; (2) Nitric oxide (NO): Dirnagl et al., 1993; (3) COX-2: Niwa et al., 2000; (4) EETs: Peng et al., 2002; (5) K$^+$: Filosa et al., 2006; (6) GABA-A receptor: Lecrux et al., 2011; (7) PGE2: Lacroix et al., 2015; (8) NPY: Uhlirova et al., 2016.

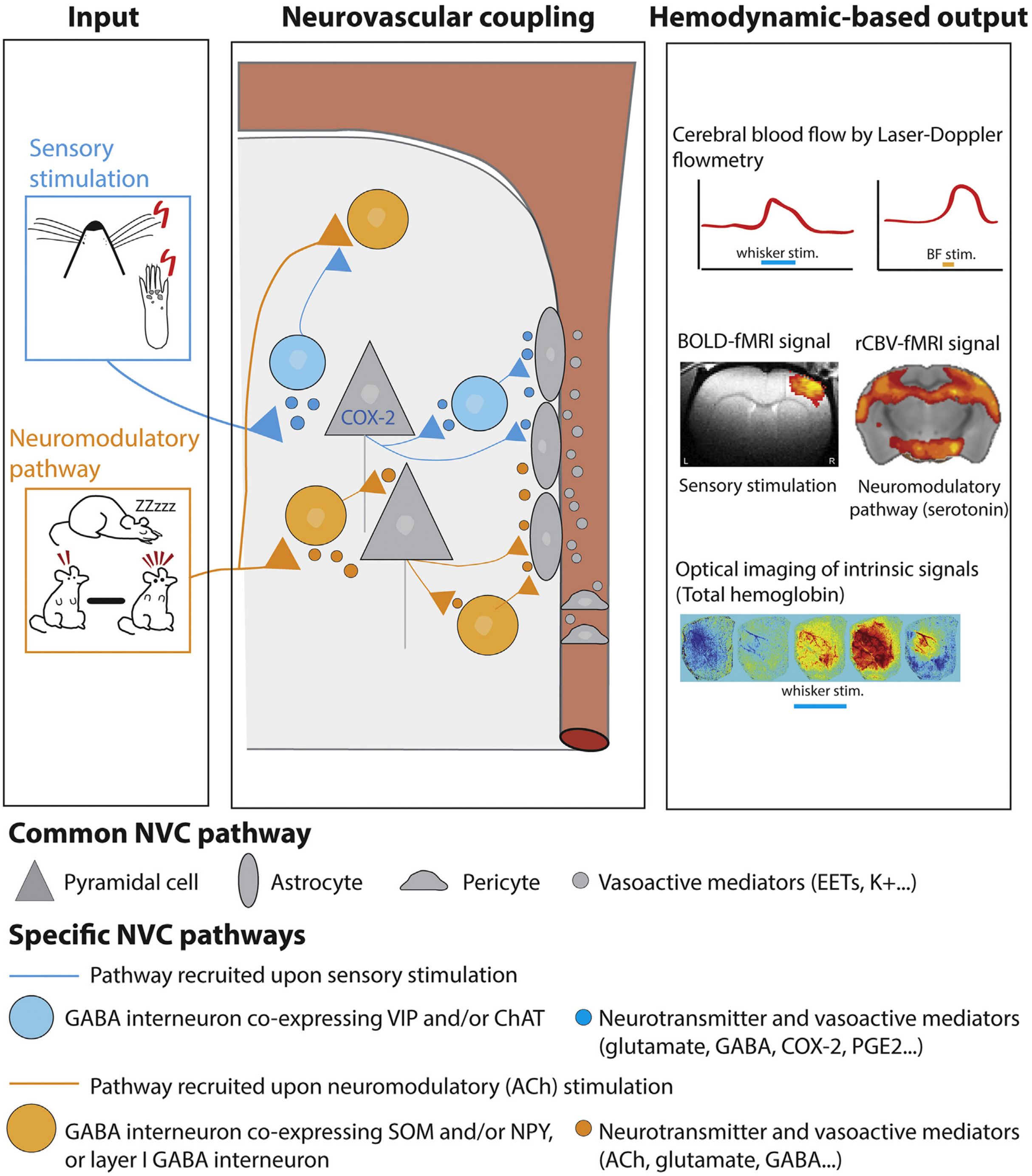

Fig. 2. The recruited neuronal network will dictate the NVC mechanisms underlying the hemodynamic-based signals in the cortex. Sensory (whisker or limb, blue pathway) or neuromodulatory (ACh, orange pathway) stimulation drives a hemodynamic response by recruiting specific network of pyramidal cells (triangle cells) and GABA interneurons (circle cells). Pyramidal cells and vasoactive mediators (small circles) released by neurons, astrocytes, pericytes or vascular cells common to both stimulation pathways are shown in grey tone. The hemodynamic-based output (right panel) can be: a blood flow response measured by laser-Doppler flowmetry, as evoked by whisker (modified from Lecrux et al. (2011) with permission) or BF ACh pathway stimulation (modified from Kocharyan et al. (2008) with permission), a change in BOLD-fMRI signals evoked by sensory stimulation (from Li et al. (2014) with permission), or chemogenetic activation of serotoninergic pathway (from Giorgi et al. (2017) with permission), or a change in optical imaging of intrinsic signals (total hemoglobin, courtesy of Dr. M. Bourourou, unpublished data) evoked by whisker stimulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

intraparenchymal and pial vessels. Indeed, in addition to upstream dilation of intraparenchymal arterioles, pial arteriolar dilation, likely triggered by astrocytic signalling at the level of the glia limitans (Xu et al., 2008) and propagated through endothelial cells (Rosenblum et al., 1990; Tian et al., 2010), also contributes to the hemodynamic response, by conveying sufficient blood to the dilated downstream vessels.

By combining hemodynamic and electrophysiological recordings, the evoked hemodynamic responses were found to correlate with changes in neuronal activity in physiological conditions (Niessing et al., 2005). Cortical neurons display different types of activity: spiking, which reflects the efferent function out of the region, and synaptic events, resulting from local processing within the neuronal network. Although still debated, current knowledge points to a stronger

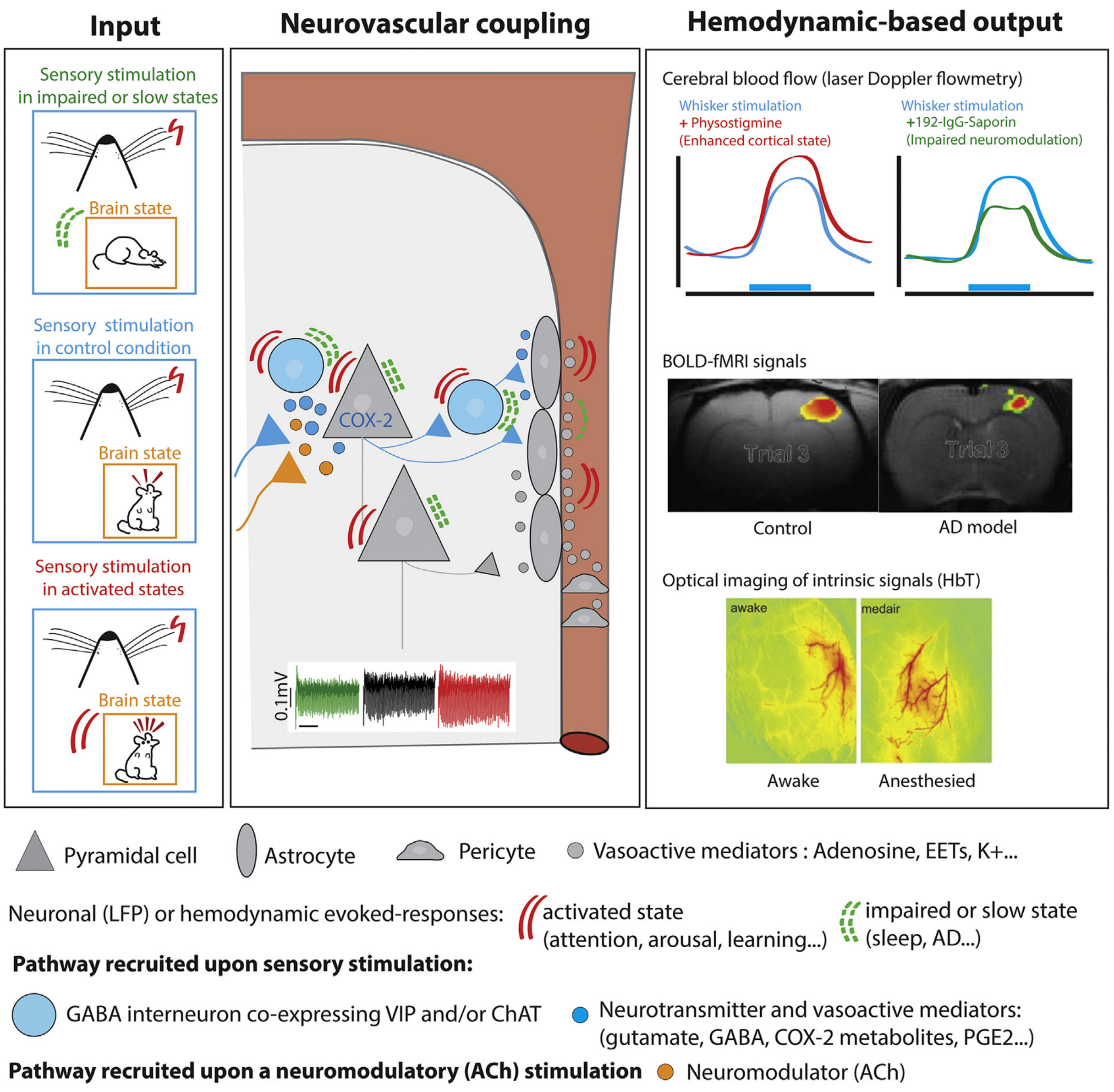

Fig. 3. NVC responses to sensory stimulation are modulated across brain states.

NVC responses driven by sensory stimulation (blue pathway) are affected by brain states, such as slow or impaired states (in green, chronically reduced cholinergic tone mimicking pathological conditions like Alzheimer's disease, AD) or active states (in red, awake states, as induced by cholinergic enhancers, in conditions of attention, arousal or learning), without altering the identity of the activated neuronal network of pyramidal cells and GABA interneurons (blue circles). As a result, ACh-mediated different cortical states, AD pathology or anesthesia can alter the neuronal responses underlying NVC (sensory-evoked local field potential, LFP, bottom of middle panel, modified from Lecrux et al. (2017) with permission) and sensory-evoked hemodynamic-based output (right panel) measured using either (top) CBF (laser Doppler flowmetry, modified from Lecrux et al. (2017) with permission), (middle) BOLD-fMRI signals (from Sanganahalli et al. (2013) with permission) or (bottom) optical imaging of intrinsic signals (total hemoglobin, from Sharp et al. (2015) with permission). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

correlation between evoked hemodynamic changes and local field potentials (LFPs), corresponding to the local processing of neuronal information (Logothetis et al., 2001; Lauritzen and Gold, 2003). Moreover, changes in hemodynamic signals correlated best with changes in neuronal activity in the higher frequency power of the LFP signal, namely the gamma band (Niessing et al., 2005; Shmuel and Leopold, 2008; Harris et al., 2014), which is described as a signature of engaged neuronal networks (Jia and Kohn, 2011). Overall, the identification of the precise neuronal correlates of hemodynamic response is complex, as it may reflect not only a single neuronal event, but rather a dynamic integration of neuronal occurrences, where oscillations in alpha, beta and gamma ranges of the LFP or multiunit activity can explain different components of the hemodynamic response, such as amplitude or timing of the signal (Murta et al., 2017). Finally, as brain oscillations are differently generated across brain regions, the correlates of the hemodynamic signals may be, at least partly, region-specific.

Overall, a task can be mapped very precisely in the brain by measuring changes in CBF. This tight relationship forms the basis of modern functional brain imaging techniques as a change in blood flow is more easily mapped than neuronal activity. These neuroimaging techniques have propelled the field of neuroscience into a new age where hemodynamic-based neuronal activity can be revealed in the whole brain, non-invasively and repeatedly.

3. Is the link between blood flow and neuronal activity dependent on the activated brain pathway?

The cortical neurovascular unit receives multiple inputs, originating from local cortical areas and from subcortical nuclei that release various neuroactive molecules. Cortical neurons can respond to glutamate, the main excitatory neurotransmitter, but also to neuromodulators such as ACh, NA, 5-HT or dopamine. Whether the initial release of a neurotransmitter or neuromodulator to alter cortical activity results in different NVC mechanisms is relatively unknown and of interest. We addressed this issue by comparing the cellular mechanisms underlying NVC responses induced by activation of a glutamatergic pathway (sensory stimulus) or a neuromodulatory pathway (subcortical cholinergic or noradrenergic pathway). As described below, both the recruited neuronal network and the vasoactive mediators released following activation of these respective pathways point to NVC mechanisms being slightly different depending on the nature of the neurotransmitter/neuromediator released in the activated cortical area (Fig. 2).

3.1. Is the blood flow response linked to the activation of a specific cellular network?

NVC is commonly studied through stimulation of a sensory pathway, where a physical stimulus is received by a sensory receptor and transduced, *via* relays in the brainstem and thalamus, to the respective area of the sensory cortex. This pathway robustly produces NVC responses in the cortex (Woolsey et al., 1996). For instance, activation of a single whisker translates into a precisely localised hemodynamic response in the corresponding barrel of the somatosensory cortex (Martindale et al., 2003). This response is mediated by the release of glutamate that locally activates pyramidal cells and GABA interneurons. At a cellular level, GABA interneurons that contain VIP and/or choline acetyltransferase (ChAT), which co-localize in a subset of interneurons are activated, whereas SOM interneurons remain largely silent (Lecrux et al., 2011). This network matches findings of optogenetic manipulations supporting a key role for VIP interneurons in selectively suppressing the activity of SOM interneurons (Lee et al., 2013; Pi et al., 2013), as seen during active whisking (Gentet et al., 2012).

In contrast to the precisely localised glutamate-mediated sensory response, stimulation of neuromodulatory systems leads to increase of blood flow across broad cortical areas. This holds true for the basal forebrain cholinergic pathway (Vaucher et al., 1995; Sato et al., 2001), the raphe nucleus serotonergic pathway (Underwood et al., 1995), the dopaminergic pathways (Choi et al., 2006) and the locus coeruleus noradrenergic pathway (Raichle et al., 1975; Toussay et al., 2013). These neuromodulatory systems innervate all cells of the neurovascular unit, namely pyramidal cells, GABA interneurons, vascular smooth muscle and endothelial cells, and perivascular astrocytes (Houser et al., 1985; Seguela et al., 1990; Vaucher and Hamel, 1995; Cohen et al., 1997; Toussay et al., 2013). Functionally, ACh released in the cortex by pharmacological manipulations or electrical stimulation of the basal forebrain recruits glutamatergic pyramidal cells and cholinoceptive GABA interneurons, primarily those that contain SOM (Kocharyan et al., 2008). In contrast, activation of the locus coeruleus-noradrenergic system recruits pyramidal cells and a broad network of cortical GABA interneurons, with no clear distinction between the different subtypes (Toussay et al., 2013). To the best of our knowledge, the precise neuronal networks and vasoactive signalling cascades recruited by other neuromodulatory systems known to drive changes in CBF, such as the serotonergic and the dopaminergic pathways, have yet to be identified.

3.2. Is the blood flow response linked to specific vasoactive mediators?

As expected, the NVC response to sensory stimulation requires activation of glutamate (NMDA, AMPA and metabotropic) (Gsell et al., 2006; Shi et al., 2008; Lecrux et al., 2011) and GABA-A receptors (Lecrux et al., 2011), in addition to the release of vasoactive mediators, including NO, K^+ and adenosine (Ko et al., 1990; Lindauer et al., 1999; Filosa et al., 2006). The full expression of the hemodynamic response further requires synthesis and release of the vasoactive arachidonic acid metabolite PGE2 (Lacroix et al., 2015) by COX-2 in pyramidal cells (Niwa et al., 2000; Lecrux et al., 2011), or EETs from cytochrome CYP450 epoxygenase in astrocytes (Liu et al., 2008; Lecrux and Hamel, 2011).

Similarly, the NVC responses to ACh and NA evoked following basal forebrain and locus coeruleus stimulation, respectively, require activation of pyramidal cells and GABA interneurons and, hence, activation of glutamate and GABA receptors (Kocharyan et al., 2008; Lecrux et al., 2012; Toussay et al., 2013), as well as the release of EETs (Lecrux et al., 2012; Toussay et al., 2013). Hence, several commonalities exist in vasoactive mediators involved in NVC responses evoked from different neuronal pathways.

However, differences in NVC signalling cascades are also apparent. For instance, the hemodynamic response to stimulation of the basal forebrain cholinergic pathway or to local ACh application does not rely on COX-2-derived vasoactive metabolites (Niwa et al., 2000; Lecrux et al., 2012). Whereas COX-2 is activated by glutamate through NMDA receptors (Pepicelli et al., 2005), it is not activated by ACh (Orman et al., 2006), suggesting that PGE2, a key vasoactive mediator in the sensory pathway, does not mediate the blood flow response to an ACh-mediated stimulus. A differential role for COX-2 metabolite is also highlighted in the NVC response to activation of the noradrenergic pathway, which was potentiated rather than reduced by COX-2 inhibition (Toussay et al., 2013). Likewise, signalling cascades in astrocytes have been shown to differ between capillaries and arterioles, suggesting the possibility of different astrocyte signalling depending on their location in the vascular tree (Mishra et al., 2016).

Overall, these studies indicate that changes in cortical blood flow are prompted by activation of specific neuronal networks and release of messengers, depending on the neuronal mediator released by the incoming afferents, which may subsequently lead to the release of distinct neuronal and astroglial vasoactive messengers on the blood vessels. This finding agrees with a model of NVC and BOLD-fMRI signals that suggests the existence of multiple neural pathways influencing the hemodynamic output (Mathias et al., 2018). Such diversity of vasoactive pathways may reflect both a highly specialized function of the brain and a protective mechanism against the failure of a specific pathway.

4. Is the link between blood flow and neuronal activity dependent on brain state?

Upon sensory stimulation, cortical activity is not only influenced by the stimulus received from the environment, but also by internal signals, in particular those corresponding to different brain states. Brain states, resulting from different levels of wakefulness, sleep, arousal or attention (Harris and Thiele, 2011), are driven by neuromodulatory systems, among which are the basal forebrain cholinergic and the locus coeruleus noradrenergic pathways (Kim et al., 2016). Given their powerful effects on cortical activity and their intimate association with all cells of the neurovascular unit, it appears essential to determine the impact of neuromodulatory systems on the NVC response to sensory stimulation.

This was addressed in our recent study (Lecrux et al., 2017) demonstrating that enhancing ACh release potentiated sensory-evoked hemodynamic and neuronal responses, evidenced by a higher power of the LFPs across cortical layers. This enhanced NVC response was attributed to increased activity within the cortical neuronal network typically recruited by a sensory stimulus, namely pyramidal cells, including those that contain COX-2, and GABA interneurons co-expressing VIP and/or ChAT, but no or virtually no cholinoceptive SOM interneurons. In contrast, an acute pharmacological increase of NA levels concurrent with sensory stimulation was found to reduce the sensory-evoked hemodynamic response in the cortex, mainly by decreasing the spread of the response (Bekar et al., 2012). This effect was reminiscent of the known ability of this pathway to shift the balance between background and stimulus-evoked signals, in particularly through inhibition of background neuronal signals (Kuo and Trussell, 2011).

Conversely, the loss of cholinergic input to the cortex by using either acute pharmacological inhibition of basal forebrain neurons (Piche et al., 2010) or chronic cholinergic denervation of the cortex (Lecrux et al., 2017), resulted in a drastic reduction (about 40%) in the hemodynamic response to sensory stimulation. Denervation did not affect the neuronal circuitry typically recruited by sensory stimulation. However, a chronic cortical cholinergic deficiency resulted in a smaller sensory map in the barrel cortex and reduced sensory-evoked neuronal responses (Lecrux et al., 2017). Noteworthy, loss of cortical cholinergic (Whitehouse et al., 1982) and noradrenergic (Heneka et al., 2006; Weinshenker, 2008) terminals is an early hallmark of Alzheimer's disease (AD). Cortical ACh denervation, usually associated with memory and cognitive deficits (Hampel et al., 2018), may be related to early altered brain states in AD, such as attentional deficit, which is the first non-memory domain affected in AD (Perry and Hodges, 1999). Further studies should investigate the precise effect of the loss of NA modulation in the impairment of the NVC responses reported in AD.

Overall, acute and chronic enhancement or impairment of brain states of attention, arousal, wakefulness, as well as alterations of the sleep/wake cycles, as mimicked by manipulations of the cholinergic and noradrenergic subcortical pathways, can modulate NVC responses to sensory stimulation (Fig. 3). The decreased NVC response to a sensory stimulus upon cholinergic denervation or NA modulation further emphasizes that cholinergic and noradrenergic tones are required for the full expression of neuronal processing and hemodynamic responses. These results suggest that an impaired sensory-evoked NVC response may reflect either a disruption of sensory pathway, an impaired neuromodulatory input, or both. Further study of the underlying mechanisms may provide useful information to interpret hemodynamic-based imaging data in pathology or in physiological conditions across varying brain states.

5. Is blood flow linked to neuronal activity in conditions of a diseased cerebrovascular unit?

Techniques such as BOLD-fMRI that rely on hemodynamic signals and NVC responses are increasingly used as a diagnostic tool in various brain diseases, and have shown alterations in AD, vascular cognitive impairment and dementia (VCID), and stroke. While the neuronal dysfunctions that occur in these pathologies can contribute to an impaired NVC, it is unclear how the concomitant alterations of the brain intraparenchymal vasculature will also affect the reliability of hemodynamic signals as markers of changes in neuronal activity, notwithstanding a possible contribution from altered pial arteriole function (Chen et al., 2014). In the following section, we will attempt to address some aspects of this question.

5.1. Neurovascular coupling alterations in AD

AD, the leading cause of dementia in late adult life, is a neurodegenerative disease typically characterized by neuronal and synaptic alterations, neurofibrillary tangles of hyperphosphorylated *tau* protein and amyloid-β (Aβ) deposits in the brain parenchyma (senile plaques) (Querfurth and LaFerla, 2010). In addition, AD is also a cerebrovascular pathology that affects each cell of the neurovascular unit (Kisler et al., 2017a). Studies have evidenced alterations in brain activation and in NVC in early-stage AD, and in cognitively intact individuals with genetic risk factors for AD (presence of one apolipoprotein ε4 (APOε4) allele) (Smith et al., 1999; Harrison et al., 2017). Alterations in fMRI signals are also seen in resting-state conditions (which measure “functional connectivity” of the brain without any stimulation or task), and specifically in the “default mode network” in AD patients (Sheline and Raichle, 2013). Structural vascular changes in AD are multifaceted and include increased capillary tortuosity, capillary rarefaction, thickened basement membrane, and degenerating capillaries (string vessels) (Love and Miners, 2016). Other alterations include vascular oxidative stress induced by Aβ species and perivascular Aβ deposits that promotes a contractile tone of the brain vasculature (Thomas et al., 1996; Park et al., 2004; Tong et al., 2005), thus reducing the dilatory capacity of the blood vessels that is essential for NVC responses. Together, these alterations contribute to the chronic cerebral hypoperfusion observed in AD that appears early in the disease process (Iturria-Medina et al., 2016). Additionally, pericytes are affected in AD (Sagare et al., 2013), possibly contributing to CBF reductions (Bell et al., 2010), neurovascular uncoupling and restricted oxygen supply to the brain (Kisler et al., 2017b).

It thus appears that alterations of the neurovascular unit, independent of those affecting neuronal function, can lead to NVC deficits. This raises caution in interpreting clinical imaging data from hemodynamic signals to make direct inference of altered neural activity in patients with cerebrovascular diseases. Indeed, the reduced perfusion signals detected in early AD by fMRI may reflect vascular dysfunction rather than altered neuronal activity.

5.2. Neurovascular coupling alterations in VCID

VCID was proposed as an umbrella term to include subjects with cognitive decline resulting from age-related cerebrovascular diseases of various origins that impair CBF. Even mild reductions in CBF have significant consequences on brain function, including cognition in the elderly (Sorond et al., 2013), as also seen in animal models of aging. Alterations of the brain vasculature in VCID consists of atherosclerosis and loss of the integrity of the vessel wall with thickened arteriolar basement membrane, increased tortuosity, and reduced number of capillaries and some become string vessels (Brown and Thore, 2011). The most common form of VCID relates to vascular damage caused by small vessel disease (SVD) that primarily affects white matter (Jellinger, 2013). Such alterations likely play an important role in functional deficits (Fields, 2010). In VCID, experimental studies have correlated NVC deficits with increased oxidative stress, which may contribute to the disease process by causing oxidative injury to vascular structures (Lourenco et al., 2017). In a transgenic mouse model of cerebrovascular disease with no neuronal or cognitive deficits that overexpresses the cytokine transforming growth factor-β1 (Wyss-Coray et al., 2000), impairments in whisker-evoked NVC responses, but not in whisker-evoked cortical glucose uptake using FDG microPET were found; indicating that the reduced NVC response resulted from dysfunctional brain vessels (Nicolakakis et al., 2011).

Together these clinical and pre-clinical findings support that a compromised brain vasculature will impact NVC responses, and that such alterations should be considered when parsing out data based on the correlation between hemodynamic response and neuronal activity in patient populations.

5.3. Neurovascular coupling alterations in stroke

Following cerebral ischemia, the dramatic reduction of blood supply leads to neuronal death in the ischemic core, while the surrounding zone - the penumbra, is a region potentially salvageable (Touzani et al., 2001). Brain imaging techniques such as fMRI-BOLD signals, based on NVC, are instrumental in assessing brain recovery following a stroke (Lake et al., 2016). The deleterious cascades in stroke share commonalities with NVC signalling, with alterations of prostaglandins, NO, calcium and K^+ pathways for instance. Accordingly, following cerebral ischemia, multiple studies have reported alterations of NVC responses to sensory stimulation or impaired cerebrovascular reactivity to hypercapnia, a response that encompasses overlapping signalling cascades, such as NO or ATP release (Kunz and Iadecola, 2009). Recently, efforts combining electrophysiological and hemodynamic measures of NVC have focused on determining the timing, extent, and nature of the impaired NVC signalling following cerebral ischemia (Sutherland et al., 2017), and by investigating long-term NVC mechanisms in the recovery phase. Weeks following a microinfarct, perilesional tissues displayed impaired hemodynamic responses but recovery of neuronal activity measured by c-Fos immunohistochemistry, pointing to neurovascular uncoupling where blood flow does not accurately match the underlying neuronal activity (Summers et al., 2017; Sutherland et al., 2017).

Functional neuroimaging, either PET or fMRI, has described altered cortical activation patterns in the acute to chronic phase following a stroke. Such reorganization could potentially translate into altered neuronal correlates of hemodynamic signals, which could have a great impact on the interpretation of neuroimaging data based on NVC. In this respect, optogenetic stimulation of layer V neurons in the motor cortex (Pendharkar et al., 2016) or thalamic neurons (Tennant et al., 2017) has been shown to promote rewiring of neuronal circuits after a stroke and improve stroke outcome. Similarly targeting specific neuronal networks and subcortical inputs involved in NVC could provide means to enhance recovery post-stroke. It is therefore essential to better understand the mechanisms underlying the perfusion signals following a stroke not only in the acute phase but also in the recovery phase where both NVC and potential compensatory mechanisms are still poorly known.

6. Concluding summary

Several recent studies point to NVC being a dynamic process, where various neuronal networks and signalling cascades of vasomediators can generate hemodynamic responses to a stimulus. The brain therefore possesses a way to specifically respond to different types of stimulation and, importantly, most likely has compensatory mechanisms against a deficiency in a given pathway.

This short review highlights the need for a precise identification of neuronal networks underlying hemodynamic signals. In particular, being able to decipher the contribution of respective excitatory and inhibitory neurons in a given hemodynamic signal would be key in assessing the integrity of the neuronal networks underlying the vascular changes, especially when referring to pathological conditions where the excitatory/inhibitory balance is compromised.

While functional brain imaging techniques easily detect task-evoked signals, signals generated at resting-state are becoming more and more popular as they overcome the limitations (constraint of task repetitions, limited activated brain area, and patient inability to perform the task) of stimulus-evoked functional studies. Yet, the cerebrovascular mechanisms underlying resting-state signals still need to be identified and better understood before drawing definite conclusions of the hemodynamic signals measured at rest. Realistically, it appears that cerebrovascular pathology may significantly affect the validity of hemodynamic signals as surrogate of neuronal activity.

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