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Effects of astrocytic dynamics on spatiotemporal hemodynamics: Modeling and enhanced data analysis

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ABSTRACT

The effects of astrocytic dynamics on the blood oxygen-level dependent (BOLD) response are modeled. The dynamics are represented via an astrocytic response function that approximates the effects of astrocytic activity, including delay between neural activity and hemodynamic response. The astrocytic response function is incorporated into a spatiotemporal hemodynamic model to predict the BOLD response measured using functional magnetic resonance imaging (fMRI). Adding astrocytic dynamics is shown to significantly improve the ability of the model to robustly reproduce the spatiotemporal properties of the experimental data such as characteristic frequency and time-to-peak. Moreover, the results are consistent across different astrocytic response functions, thus a simple impulsive form suffices to model the effective time delay of astrocytic responses. Finally, the results yield improved estimates of previously reported hemodynamic parameters, such as natural frequency and decay rate of the flow signal, which are consistent with experimentally verified physiological limits. The techniques developed in this study will contribute to improved analysis of BOLD-fMRI data.

1. Introduction

When neurons in a specific region of the brain are active, local cerebral blood flow (CBF) increases in the associated vasculature. This response, termed functional hyperemia (Roy and Sherrington, 1890), can be detected with functional magnetic resonance imaging (fMRI) based on the blood oxygen level-dependent (BOLD) signal (Buxton, 2009). From its inception by Ogawa et al. (1990), studies using BOLD-fMRI to understand human neurophysiology have multiplied at an increasingly rapid rate [see for example the review article by Bandettini (2012)]. These studies have given insights into the following: resting state of human brain (Biswal et al., 1995), regional brain activation in response to cognitive or sensorimotor tasks (Friston, 2009), and functional connectivity networks of brain areas (Fox and Raichle, 2007; Seeley et al., 2009; Buckner et al., 2013), among other applications. The recognition of BOLD-fMRI's significance in basic and clinical neuroscience entails a fundamental understanding of its driving mechanisms together with details of its spatiotemporal properties.

A number of models have been formulated, which quantitatively address the temporal (Buxton et al., 1998, 2004; Friston et al., 2000; Robinson et al., 2006) and spatiotemporal (Drysdale et al., 2010; Aquino et al., 2012, 2014a) dynamics that underlie the BOLD signal. They have been successful in predicting hemodynamic response functions (HRFs) that express the BOLD response to an impulsive localized stimulus. The HRF can be convolved with an arbitrary stimulus function to obtain the BOLD response to that specific stimulus. The formulated HRFs successfully predict many aspects of the hemodynamic response observed in fMRI experiments, including signal amplitude (Buxton et al., 1998; Friston et al., 2000) and the presence of hemodynamic waves (Aquino et al., 2012). Despite their success in predicting the main features of the BOLD signal, existing hemodynamic models do not yet incorporate the precise mechanisms of neurovascular coupling (NVC)–the intercellular communication from neurons to microvessels via astrocytes that mediates functional hyperemia (Harder et al., 1998; Koehler et al., 2006). Inclusion of the effects of NVC is fundamental for understanding neurophysiology and interpreting fMRI data in both the healthy and diseased brains, with evidence of connections between impaired NVC and neurodegeneration (Girouard and Iadecola, 2006; Hamilton et al., 2010), for example.

Astrocytes typically have star-shaped morphologies with small cell bodies and radial branched processes (Oberheim et al., 2009). In the human cortex, protoplasmic astrocytes have a cell body approximately

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10 μm in diameter and an overall diameter of about 150 μm. They are anatomically situated between neurons and arterioles, serving as intermediary cells in neurovascular communication (Filosa and Blanco, 2007; Filosa et al., 2016; Nuriya and Hirase, 2016). Their processes have been estimated to contact tens of thousands of synapses per cell, while their end-feet extend to nearby capillaries and arterioles (Haydon and Carmignoto, 2006). Their important role in NVC was proved by Metea and Newman (2006), who showed that dilation of blood vessels is blocked when neuron-to-astrocyte signaling is interrupted. This is in agreement with other experiments that revealed how CBF is regulated by astrocytes (Paulson and Newman, 1987; Harder et al., 1998; Koehler et al., 2006; Lind et al., 2013; Masamoto et al., 2015). Moreover, separate compartmental modeling of astrocytic dynamics has showed that activity of astrocytes can account for the timing of empirically observed cerebral blood volume (CBV) and deoxyhemoglobin (dHb) changes in vascular components following neural stimulation (Bennett et al., 2008a, 2008b).

Astrocytes do not exhibit excitable behavior similar to those of neurons or muscular fibers. When stimulated, they do not generate membrane electrical changes, but instead show oscillations in cytosolic calcium levels as a response. This is why several studies have proposed the hypothesis that astrocytes facilitate NVC via a calcium signaling pathway. This pathway demonstrates that neurotransmitters released from synapses of neurons trigger intracellular Ca^{2+} elevations. The Ca^{2+} elevations result in the release of vasoactive agents to nearby microvessels, thereby leading to vasodilations and/or vasoconstrictions (Bennett et al., 2008a; Anderson and Nedergaard, 2003). Other studies, instead, have proposed that astrocytes facilitate NVC via a potassium ion signaling. Paulson and Newman (1987) hypothesized that astrocytes redistribute neuronal activity-induced extracellular K^+ elevations to the vasculature via their end-feet, termed as "K^+ siphoning". On the other hand, Filosa et al. (2006) and Longden and Nelson (2015) have proposed that astrocytes' intracellular Ca^{2+} elevations can lead to efflux of K^+ from their end-feet that hyperpolarizes smooth muscle cells and dilate arterioles.

Regardless of the specific pathway, the internal signaling system of astrocytes and the transport of molecules/ions from astrocytes to blood vessels together contribute to a finite temporal delay in the CBF response. Indeed, recent work by Masamoto et al. (2015) using optogenetic manipulation found that the temporal delay of the onset of the increase of CBF after astrocytic activation is approximately 0.7 ± 0.7 s. This accounts for part of the delay in the increase of BOLD signal after stimulus onset in fMRI experiments (DeYoe et al., 1994; Buckner et al., 1996).

Here, we incorporate astrocytic dynamics into a recent spatiotemporal hemodynamic model of BOLD (Drysdale et al., 2010; Aquino et al., 2012, 2014a) to better predict the spatiotemporal properties of the BOLD response to a stimulus. The dynamics are represented via an astrocytic response function that approximates the function of astrocytes in mediating the effects of neural activity on vasodilation.

The technical note is organized as follows: In Section 2, we describe potential signaling pathways between neurons, astrocytes, and arterioles to clarify the role of astrocytes in NVC. We then summarize a physiologically based spatiotemporal hemodynamic model (Drysdale et al., 2010; Aquino et al., 2012, 2014a) and modify it to introduce the effects of astrocytic dynamics on the BOLD signal. We also include a description of fMRI data acquired from a study of evoked responses in the visual cortex (Aquino et al., 2012) and use the data to test the accuracy of our modified hemodynamic model. In Section 3, we discuss the results of fitting the modified model to experimental data and verify their robustness. We also show how prior estimates of physiological hemodynamic parameters (Friston et al., 2000) are refined as a result of including astrocytic dynamics. Finally, in Section 4, we summarize our results and highlight the implications of our study.

2. Theory and methods

The main focus of this technical note is to understand the effects of astrocytes on the dynamics of the BOLD signal and resulting estimates of physiological parameters. In this section, we provide an overview of the physiological role of astrocytes in NVC. We outline the key equations of a hemodynamic model derived from properties of cortical tissue (Drysdale et al., 2010; Aquino et al., 2012, 2014a) and show how astrocytic effects can be included in the model. We then compare the prediction of the resulting model with fMRI data from a visual experiment of Aquino et al. (2012).

2.1. Overview of NVC involving astrocytes

NVC is a critical intermediate step in linking neural activity to the corresponding vascular response. Experiments have shown that astrocytes play a crucial role in NVC by receiving neuronal signals and relaying them to arterioles; however, the specifics remain to be a contentious topic. Several studies hypothesized that astrocytes facilitate NVC via a calcium signaling pathway (Zonta et al., 2003; Metea and Newman, 2006; Haydon and Carmignoto, 2006; Lind et al., 2013; Filosa et al., 2016). This potential signaling pathway is simplified in Fig. 1.

Figure 1 shows that in the presence of neural activity, neurotransmitters, such as glutamate (Glu) from neuron-neuron synapses and Gamma-aminobutyric acid (GABA) from neuron-astrocyte synapses, bind to metabotropic receptors (mGluR for Glu and $GABA_B$ for GABA) of surrounding astrocytes. Activations of these receptors have been shown to evoke an increase in intracellular calcium concentration of astrocytes found in brain slices (Dani et al., 1992), in situ (Porter and McCarthy, 1996), and in vivo (Wang et al., 2006; Lind et al., 2013; Otsu et al., 2015). If the receptors are highly activated, Ca^{2+} waves propagate from the astrocytes' cell bodies toward their end-feet resulting in a flow of vasoactive agents, such as nitric oxide (NO), arachidonic acid (AA), and epoxyeicosatrienoic acid (EET), to nearby arterioles (Koehler et al., 2006; Filosa et al., 2016). The build-up of vasoactive agents hyperpolarizes smooth muscles of the arterioles, which leads to vascular dilation (Zonta et al., 2003; Anderson and Nedergaard, 2003; Haydon and Carmignoto, 2006; Metea and Newman, 2006) and an increase in CBF.

Other studies hypothesized that astrocytes instead facilitate NVC via a potassium signaling pathway (Paulson and Newman, 1987; Filosa et al., 2006; Longden and Nelson, 2015; Longden et al., 2016; Nuriya

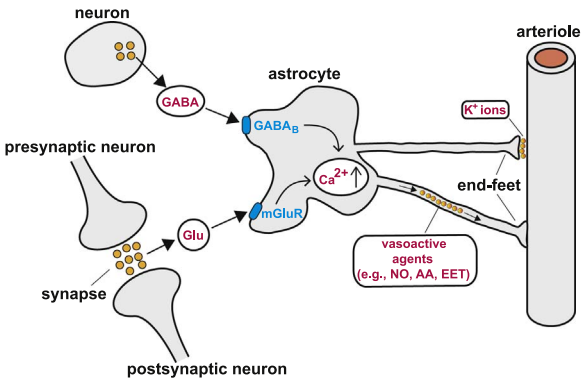

Fig. 1. Schematic diagram of a microdomain showing potential signaling pathways from neurons to astrocytes and arterioles. Neurotransmitters, such as Glu from neuron-neuron and GABA from neuron-astrocyte synapses, act on metabotropic receptors of nearby astrocytes. Activation of the receptors triggers an increase in intracellular calcium concentration of astrocytes. This calcium elevation can possibly lead to the following phenomena: (i) flow of vasoactive agents (e.g., NO, AA, EET) toward the end-feet that can directly influence arterioles and induce vasodilation or (ii) activate BK-type K^+ channels in the end-feet, causing efflux of K^+ ions that induce vasodilation. For both cases, vasodilation results in increases of CBF that are ultimately reflected in the BOLD signal.

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