

Neurovascular Coupling in Health and Disease: Revisiting the Hemodynamic Response Function

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Symposium

Conventional functional MRI analyses implicitly assume that the hemodynamic response function (HRF) has the same shape and latency across individuals. However, it is known that the HRF can vary across healthy individuals, brain regions within an individual, and physiologic states. Much of that variance can be usefully ignored in the course of answering many questions; however, this symposium highlights four distinct areas of active research where variance in the HRF really matters. Presentations cover a variety of methodological approaches (fMRI, fNIRS, EEG, electrophysiology, and diffuse correlation spectroscopy) across human and animal models. The proposed symposium is a clear example of using state-of-the-art tools from cognitive neuroscience to elucidate the basic biology of neurologic diseases. Better techniques for dealing with variability in neurovascular coupling is central to ensuring that observed findings are genuinely reflective of underlying biological mechanisms. This symposium will help neuroimaging researchers understand why the HRF may vary, how to best measure this variability, what implications this variability has for analyses, which methods are most robust to this variability, and what this variability can tell us about different brain states.

Objective

1. Be able to list brain states or diseases that lead to variability in the hemodynamic response function.
2. Become familiar with neuroimaging approaches to measuring variability in the hemodynamic response function.
3. Learn about cutting-edge methods for analyzing functional MRI data that take into account variability in the hemodynamic response function.

Target Audience

The target audience includes neuroimaging researchers who rely on the hemodynamic response function in their analytic pipeline regardless of the brain states or diseases they study.

Presentations

Neurovascular Coupling in Cerebrovascular Disease and Dementia

Dysregulation and structural alterations of the brain vasculature is an early event in Alzheimer's disease (AD) otherwise characterized by a neurodegenerative process, an amyloid- β (Ab) pathology, neurofibrillary tangles and increased neuroinflammation. Using a transgenic mouse model of a cerebrovascular pathology reminiscent of that seen in AD brains, except for the Ab deposits, we measured chronically (up to 9 months of age) hemodynamic and neuronal activity changes in the neurovascular coupling (NVC) response to whisker stimulation, together with cognitive performance in spatial and executive memory tests. Whisker-evoked NVC responses deteriorated over time as the cerebrovascular pathology progressed. The reductions were strictly attributed to hemodynamic impairments without any alterations in stimulus-evoked increases in neuronal activity (local field potentials, LFPs). No memory deficits were seen at any age indicating preserved cognitive function. These observations indicated that NVC reliably captured disease progression, and that it reflected the failure of the vascular compartment to increase blood flow in response to enhanced neural activity. They suggest that impaired NVC responses do not necessarily reflect altered neuronal function, raising caution in the interpretation of clinical brain imaging data in patients with a cerebrovascular pathology. In order to further assess the impact of progressive alterations in brain vessels on imaging data, resting state connectivity maps measured by changes in blood oxygenation levels using optical imaging of intrinsic signals in either awake or anesthetised mice are currently being quantified in transgenic mouse models of AD and cerebrovascular pathology.

Presenter

Edith Hamel, PhD FRSC, McGill University Montreal, Quebec
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Abnormal Hemodynamic Responses as a Window into the Mechanisms of Stroke Recovery

Previous functional MRI studies in stroke patients have found a delay in the time to peak (TTP) hemodynamic response function (HRF) in the affected hemisphere. The TTP measures how much time it takes for an increase in cerebral blood flow, secondary to elevated neural activity, to reach the venous system and, therefore, depends on both the neural and vascular response to a stimulus. The goals of our study were to determine what underlying factors contribute to the delayed TTP in stroke patients, understand how those delays influence conventional fMRI analyses, and develop fMRI methodologies that are robust to those delays. We studied the HRF in stroke patients with visual field cuts using a full-field visual stimulus and a bilateral motor task. We observed a delay in the stimulus-evoked TTP and a pronounced initial dip that was specific to perilesional tissue in early visual cortex at one week and one month post-stroke. The presence of the initial dip suggests that the origin of the delayed TTP in stroke patients is a sluggish vascular response, not a slow neural response, since the initial dip occurs when the activity-dependent decrease in local blood oxygen levels have not yet been compensated for by increased cerebral

blood flow. Simulations of BOLD data with varying HRF parameters led to systematically erroneous results and type 2 errors when a canonical HRF was employed in the analysis. Randomizing the stimuli and using voxel-specific custom HRFs ameliorated those issues and allowed us to study post-stroke neuroplasticity in voxels that had not shown significant activity when the analysis employed a canonical HRF. Possible underlying mediators of a delayed vascular response in stroke patients require further study and may include impaired cerebral autoregulation, circuitous collaterals, and stenotic vessels.

Presenter

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Neuro-Vascular Coupling and Changes in Cerebral Hemodynamics as a Function of Intracranial Pressure

The healthy brain can regulate blood flow despite changes in cerebral perfusion pressure (CPP), which is the pressure difference between mean arterial pressure and intracranial pressure (ICP). Blood flow regulation is impaired in many diseases, including traumatic brain injury, hydrocephalus, sepsis, and stroke. Treatment based on optimizing blood flow regulation have shown promise for neurological outcome in patients. However, the relationship between blood flow regulation and neurovascular coupling is not understood. We have established an animal model, which allows for evaluation of neurovascular coupling as a function of CPP by actively manipulating ICP. We have measured neuronal activity with electroencephalography (EEG) during elevated ICP, therefore changes in CPP, and hemodynamic changes with near-infrared spectroscopy (NIRS). Blood flow regulation was measured in terms of Lassen's autoregulation curve using diffuse correlation spectroscopy (DCS). At each level of CPP, changes in neurovascular coupling were evaluated in terms of changes in the hemodynamic response function (HRF). The shape of the HRF was found to be dependent on autoregulation intactness, linking neurovascular coupling to blood flow regulation. This talk will summarize the optical imaging setup, experimental procedures, and data analysis. Implications for clinical translation will be discussed.

Presenter

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Assessing Various Hemodynamic Responses in Hypercapnia Using Functional MRI

Elevated carbon dioxide (CO₂) in breathing air is widely used as a vasoactive stimulus to assess the cerebral vascular response to hypercapnia (i.e., "stress test" for the brain), which has been proven to be a useful imaging technique for many brain diseases. Blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) is commonly used to study these cerebrovascular responses. Two key limitations in obtaining accurate CVRs are the difficulties in assessing 1) the exact arrival time of arterial CO₂ at each voxel, as the CO₂ travels with the blood in the brain; 2) the exact regional hemodynamic responses. In this study, we developed a novel analytical method to accurately calculate the arrival time of elevated CO₂ at each voxel. In addition, various hemodynamic response functions were derived to quantitatively describe the temporal brain reactions to a CO₂ stimulus. In summary, we demonstrated that our approach greatly improves the traditional method by allowing us to spatial-

specifically map 1) the blood arrival time, 2) the hemodynamic response, and 3) the CVR during CO₂ challenge accurately.

Presenter

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