
Preface to the Series

Under the guidance of its founders Alan Boulton and Glen Baker, the Neuromethods series by Humana Press has been very successful since the first volume appeared in 1985. In about 17 years, 37 volumes have been published. In 2006, Springer Science+Business Media made a renewed commitment to this series. The new program will focus on methods that are either unique to the nervous system and excitable cells or which need special consideration to be applied to the neurosciences. The program will strike a balance between recent and exciting developments like those concerning new animal models of disease, imaging, in vivo methods, and more established techniques. These include immunocytochemistry and electrophysiological technologies. New trainees in neurosciences still need a sound footing in these older methods in order to apply a critical approach to their results. The careful application of methods is probably the most important step in the process of scientific inquiry. In the past, new methodologies led the way in developing new disciplines in the biological and medical sciences. For example, Physiology emerged out of Anatomy in the nineteenth century by harnessing new methods based on the newly discovered phenomenon of electricity. Nowadays, the relationships between disciplines and methods are more complex. Methods are now widely shared between disciplines and research areas. New developments in electronic publishing also make it possible for scientists to download chapters or protocols selectively within a very short time of encountering them. This new approach has been taken into account in the design of individual volumes and chapters in this series.

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Preface

The link between cerebrovascular autoregulation and brain function, also known as “functional hyperemia,” is a phenomenon with a long tradition in neuroscientific laboratory investigation. The earliest hypothesis, from the late 1770s, was called the Monro-Kelly doctrine in which CBF was thought to be constant under both physiological and pathological conditions. The later work of Roy and Sherrington in the 1890s proposed that ‘*its vascular supply can be varied locally in correspondence with local variations of functional activity*’, now named neurovascular coupling. In 1945, Kety and Schmidt first described a method of quantifying CBF in humans and brought brain blood flow research into a new exciting era. Through the middle to late twentieth century, advances in functional imaging techniques including fMRI, PET, and SPECT have improved our understanding of the relationship between brain activity and brain energy supply in awake humans. Neurovascular and neurometabolic coupling are critical to supplying the energy demands of brain tissue during both normal physiological function and pathological conditions. Nevertheless, most leaps in our understanding of neurovascular coupling have come from the laboratory, where high spatial and temporal resolution can be recorded using techniques that would be considered too invasive to use in humans. This book will bring the reader up-to-date with the current state-of-the-art techniques in measuring blood flow in the brain in the ongoing investigation of neurovascular coupling.

Each chapter in this book describes a different technique, or combination of techniques, applied to a specific species in either a healthy or an abnormal brain. It is important that most of these techniques can be applied to a variety of species to measure different aspects of neurovascular coupling in both normal and pathological brain states. Hence, the examples provided represent the interest of the specific laboratory reporting on the technique but not the sole application of this technique. This book thus provides a framework from which a multitude of additional experiments could be performed as these techniques are applied to a variety of other species and other regions of the cortex or pathological conditions. What is apparent from an overview of these chapters is the increasing importance and power of optical techniques in neurovascular coupling research. Likewise, the noninvasive nature of optical techniques render them useful in the neurosurgical operating room for use in humans, another common theme among these chapters. Likewise, in almost every chapter, multiple techniques are combined in order to measure signals from multiple sources, not just hemodynamic but also neuronal, metabolic, or glial. The combination of multiple techniques allows investigators to render conclusions on the coupling dynamics between these various sources of the signals.

In the opening chapter, Kennerley, Boorman, Harris, and Berwick use simultaneous fMRI and intrinsic optical spectroscopy to measure hemoglobin-based signals in an anesthetized rodent during whisker stimulation. While IOS provides high resolution 2-dimensional hemodynamic data, fMRI provides broader spatial sampling of the blood oxygen level dependent (BOLD) signal from the whole brain. By combining the two techniques, the sources of the BOLD signals are examined in more detail. In the next chapter, Radhakrishnan, Franceschini, and Srinivasan then use optical coherence tomography

(OCT) to measure neuronal and hemodynamic activity in rat somatosensory cortex in multiple cortical layers correlated with electrical recordings. OCT examines cortical hemodynamic activity in a laminar fashion providing layer-specific information at depths not available to IOS by using higher wavelengths with greater penetration depths. Continuing the exploration of neurovascular coupling mechanisms during normal somatosensory stimulation, Winn and Ko examine the role of adenosine and other neuropharmacological interventions in the regulation of cerebral blood flow during sciatic nerve stimulation. In order to obtain higher resolution and eliminate the influence of anesthesia, which has been shown to temper hemodynamic reactivity, Shih, Drew, and Kleinfeld use *in vivo* two-photon laser scanning microscopy in the awake mouse to measure RBC velocity and lumen diameter of small vessels using injection of fluorescent-conjugated dextrans during spontaneous activity and in response to somatosensory stimulation.

In the second section of the book, authors employ additional techniques to examine neurovascular coupling in the visual system. In this section, a particular emphasis on techniques for sampling deep brain structures is provided. Bélanger, Souza, Pouliot, Casanova, and Lesage measure neurovascular coupling in deep brain structures using confocal fiber-optic endomicroscopy to measure both calcium dye fluctuations in neurons and hemodynamic activity in the superior colliculus of the anesthetized rat. Likewise, Li and Freeman use the APOX, a deep probe sensor to simultaneously measure tissue oxygenation and neuronal activity in the central visual pathway of anesthetized cats. They find increased spatial localization of oxygen-based measurements of the initial dip compared with CBF or CBV. Vanzetta, Deneux, and Grinvald use widefield CCD- and CMOS-based imaging of intrinsic absorption of light to measure the RBC velocity in the cortex in the awake macaque and the anesthetized rodent to measure normal visual responses and spreading depression. This group also explores the utility of this technique in cat retina. Finally, Sato and Tanifuji use intrinsic optical signals to measure deoxyhemoglobin in the higher visual cortex of monkeys and correlate their findings with electrical recordings.

In the next section of the book, the investigators use several different techniques to examine neurovascular coupling during epilepsy. First, Xu, Paisansathan, and Pelligrino demonstrate the critical role of glia in vasodilation in anesthetized rats using video microscopy following both sciatic nerve stimulation and epileptic events. Zhao, Ma, Harris, and Schwartz show that IOS can be coupled with flavoprotein autofluorescence to measure oxygen metabolism along with hemoglobin signals during epileptic events in anesthetized rat. Then Kim, Hyder, and Blumenfeld use fMRI and LFP measurements to examine the etiology of the negative BOLD signal and its relationship to neuronal activity in anesthetized rodent models of epilepsy. In their data, it is clear that neurovascular uncoupling may be specific to pathological brain states. Ma, Zhao, Harris, and Schwartz use simultaneous IOS and either voltage sensitive dye or wide-field calcium imaging to examine neurovascular coupling in epileptic events in the anesthetized rat cortex. Again, uncoupling in pathological states is demonstrated. Finally, Jiang employs photoacoustic tomography to explore hemodynamic events associated with rodent seizures through an intact skull. The value of this technique, which will be further explored in later chapters, is the ability to measure hemodynamics through an intact skull, which provides translational techniques for noninvasive measurements in humans for clinical diagnostic purposes.

In the final section of the book, the investigators introduce a variety of additional neurovascular measurements which are used to examine cerebrovascular disease states such as ischemia, hemorrhage, and spreading depression. Piilgaard and Lauritzen correlate measurements of tissue oxygenation measured with polarographic electrodes, cerebral

blood flow with laser Doppler flowmetry, and local field potential during spreading depression in anesthetized rats. Kazmi, Richards, and Dunn use laser speckle contrast and multi-exposure speckle imaging of cerebral blood flow during strokes in animal models and show the adaptability of the technique for use in humans during neurosurgical procedures. Finally, Ugliaro, Pfeil Barbour, and others describe the use of diffuse optical tomography, which is based on near-infrared spectroscopy, to measure hemoglobin-based signals during ischemia and subarachnoid hemorrhage transcranially in Bonnet Macaque.

This book provides an overview of a variety of techniques currently available to examine neurovascular coupling in both health and disease. It is impossible to cover all modern neurovascular methods in one single volume. We hope that this book can serve as the handbook for researchers to study neurovascular coupling in normal and pathological brain states. Understanding normal neurovascular coupling during sensory, visual, and ultimately higher order functions such as language and memory will be critical in the development of novel brain mapping techniques that can be employed in humans. However, the propagation of these techniques to diagnose disease will require a complete understanding of how neurovascular coupling mechanisms break down in disease states to permit accurate interpretation of vascular signals as a surrogate for neuronal activity. We hope that readers will enjoy this book and will help in further developing new methods for the next edition.

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