Complexity in the spatiotemporal hemodynamic response to sensory stimulation in the un-anesthetized rat

C. J. Martin[1], J. Berwick[2], Y. Zheng[2], and J. Mayhew[2]
[1]Radiation Oncology and Biology, University of Oxford, Oxford, Oxfordshire, United Kingdom, [2]University of Sheffield

Introduction: Blood oxygen level dependent (BOLD) signals are used in functional magnetic resonance imaging (fMRI) to localize and quantify task-dependent changes in brain activity. As the BOLD signal is an indirect marker of neural activity, characterization of both the spatial and temporal hemodynamic response functions (changes in cerebral blood flow, volume and oxygen consumption) are critical for the accurate interpretation of functional imaging data. Our goal in this study was to use optical imaging spectroscopy (OIS) in a previously developed un-anesthetized rat model to extend current understanding of the spatiotemporal hemodynamic changes that underlie both positive and negative BOLD signals. OIS measures changes in the spectrum of remitted light from brain tissue which can be compared to known absorption spectra in order to calculate changes in hemoglobin concentration and oxygenation.

Methods: Under surgical anesthesia the skull was exposed and a section overlying somatosensory cortex was thinned to translucency. An imaging chamber was then placed over the thinned region of skull and secured with skull screws and dental cement. To deliver electrical stimulation to the awake animals, Teflon coated tungsten microwires were chronically implanted into the contralateral whisker pad and fed subcutaneously to a connector adjacent to the imaging chamber. The animals were treated with an analgesic and left to recover for 3-5 days. For each imaging experiment, trained animals were placed into a harness and to reduce head movements, a pneumatically operated clamp secured the implanted imaging chamber and therefore the head. A medical endoscope was used to provide both illumination of the cortex and transmission of the remitted images to a digital camera. Stimulation consisted of a 16-second, 5Hz pulse train (0.4mA) with an individual pulse width of 0.3ms. The spectral analysis of remitted images produced 2-D maps, over time, of changes in oxyhemoglobin (HbO_2), deoxyhemoglobin (Hbr) and total hemoglobin (HbT) concentration (A).

Results and Conclusions: The main finding of this study was that monotonic stimulation of the contralateral whisker pad in awake rats led to a complex spatiotemporal hemodynamic response in somatosensory cortex that included both positive responses (A & B) and negative surrounding hemodynamic changes (A & C). The magnitude and spatial extent of these response features changed throughout the stimulation period and some regions of cortex were characterized by 'biphasic' hemodynamic changes, where initial increases in blood oxygenation and volume (total hemoglobin concentration) at stimulation onset were succeeded by below baseline decreases in blood oxygenation and volume as stimulation continued. The present data reveal a number of features in the hemodynamic responses to sensory stimulation of un-anesthetized rats that are not present in comparable studies in anesthetized animals. These findings extend those of previous studies conducted in anesthetized animals and may have important implications for our understanding of the hemodynamic changes that underlie both positive and negative BOLD fMRI signals. The results also suggest that anesthesia may have a significant impact on the spatiotemporal hemodynamic response function and further research is required to determine the significance of this for the applicability of findings from studies in anesthetized animals to neuroimaging studies in awake humans and animals.