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Evidence that cerebral blood volume can provide brain activation maps with better spatial resolution than deoxygenated hemoglobin

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With the aim of evaluating the relative performance of hemodynamic contrasts for mapping brain activity, the spatio-temporal response of oxy-, deoxy-, and total-hemoglobin concentrations were imaged with diffuse optical tomography during electrical stimulation of the rat somatosensory cortex. For both 6-s and 30-s stimulus durations, total hemoglobin images provided smaller activation areas than oxy- or deoxy-hemoglobin images. In addition, analysis of regions of interest near the sagittal sinus vein show significantly greater contrast in both oxy- and deoxy-relative to total hemoglobin, suggesting that oximetric contrasts have larger draining vein contributions compared to total hemoglobin contrasts under the given stimulus conditions. These results indicate that total hemoglobin and cerebral blood volume may have advantages as hemodynamic mapping contrasts, particularly for large amplitude, longer duration stimulus paradigms.

Keywords: Hemodynamic contrasts; Hemoglobin; Diffuse optical tomography; Diffuse optical imaging; Near-infrared spectroscopy; Deoxy-hemoglobin; Total hemoglobin

Introduction

The blood oxygenation level dependent (BOLD) signal common to functional Magnetic Resonance Imaging (fMRI) is predominately due to the paramagnetic properties of deoxy-hemoglobin ([HbR]). With high arterial saturation (~99%), appreciable concentrations of [HbR] are generally only present in capillary and venous vessels. One potential problem when mapping neural activity with [HbR] is that significant modulations in [HbR] can occur in larger veins distal and distant to the area of neuronal activation (Frahm et al., 1994). In an effort to over come this problem, MRI methods, such as flow crushing gradients, have been developed to quench the BOLD image contrast in large veins and provide improved mapping of brain activity (Boxerman et al., 1995). Recent studies using fMRI method alternatives to the BOLD signal indicate that both flow sensitive contrasts (Duong et al., 2002; Kim and Ugurbil, 2003; Lee et al., 2002; Silva et al., 1999) and CBV contrasts (Gautama et al., 2003; Leite et al., 2002; Mandeville et al., 2001; Vanduffel et al., 2001) can provide advantages over the BOLD signal including better contrast to noise ratio, smaller activation areas, and reduced draining vein effect. In this contribution, we use Diffuse Optical Tomography (DOT) to examine the spatio–temporal evolution of [HbR], oxy-hemoglobin ([HbO]), and total hemoglobin ([HbT]) contrasts in response to electrical stimulation of rat forepaw with the aim of determining the relative imaging performance of each contrast.

Results of previous invasive reflectance optical intrinsic signal (OIS) imaging studies suggest a complex dependence of the hemodynamic activation area upon the specifics of the stimulus type. OIS imaging has proven to be an extremely useful technique for imaging brain function, with the advantage of being able to spatially resolve superficial arteries, capillaries, and veins (Grinvald et al., 1986). Early work by Frostig et al. suggested that reflectance OIS measurements at oxygenation sensitive wavelengths (λ = 600–630 nm) are better localized (smaller activation areas) than reflectance images at a total hemoglobin sensitive wavelength (λ = 570 nm) during visual stimulus in cats (Frostig et al., 1990). Recent work imaging single whisker stimuli in mice also found smaller activation areas for a deoxy sensitive wavelength (λ = 610 nm) relative to activation maps at a total hemoglobin wavelength (λ = 540 nm) (Erinjeri and Woolsey, 2002). On the other hand, Sheth et al. found that the magnitude of CBV related optical measures (λ = 570 nm) exhibits a stronger correlation with the magnitude of evoked field potential (Sheth et al., 2003) than oximetric (λ = 610 nm) contrasts, and that both CBV and early time oximetric contrasts were capable of columnar localization in the rat somatosensory cortex (Sheth et al., 2004a). However, OIS results need to be interpreted with caution since they are strongly weighted towards superficial vasculature response. In addition, recent methodological advances, that use more rigorous tissue optic models including a full spectral decomposition with

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appropriate wavelength dependent pathlengths (Devor et al., 2003; Dunn et al., 2003; Kohl et al., 1998; Mayhew et al., 1999; Sheth et al., 2004a), have not yet been used to assess spatial extent. Thus, invasive reflectance OIS characterization of activation areas remains an active area of research.

Non-invasive diffuse optical imaging (DOI) methods, that utilize near infrared spectroscopy have also been used to map both deoxy- and oxy-hemoglobin (Boas et al., 2002; Villringer and Chance, 1997; Yodh and Boas, 2003). As yet, methods equivalent to flow crushing gradients have not been developed for DOI, suggesting that functional imaging of [HbR] with DOI will be adversely affected by contrast in large vessels. However, as with OIS, other DOI hemodynamic contrasts are available. DOI can image both hemoglobin types, and reinterpretation of the two types provides a cerebral blood volume (CBV) measure through the total hemoglobin concentration ([HbT]), and a measure of hemoglobin oxygen saturation (StO_2). DOI methods, including the point measure technique commonly known as Near Infrared Spectroscopy (NIRS), have been used to non-invasively monitor human brain activity during a variety of functional activities, including motor (Franceschini et al., 2003; Obrig et al., 1996; Toronov et al., 2000), visual (Heekeren et al., 1997; Meek et al., 1998; Takahashi et al., 2000), auditory (Chen et al., 2002; Sakatani et al., 1999; Zaramella et al., 2001), and cognitive tasks (Chance et al., 1993; Fallgatter and Strik, 1998; Tsujimoto et al., 2004). In contrast to PET and MRI, DOI does not use a rigid fixed scanner but instead employs a wearable imaging cap. A DOI cap is optimally suited for brain imaging in several novel situations not amenable to scanner geometries, including pediatrics (Chen et al., 2002; Hebden, 2003; Hintz et al., 1999; Kusaka et al., 2001b, 2004; Meek et al., 1998; Sakatani et al., 1999; Taga et al., 2003), and tasks in adults such as studies of gait (Miyai et al., 2001, 2003; Saitou et al., 2000), sleep (Kusaka et al., 2001b; McGown et al., 2003; Spielman et al., 2000), and longitudinal bedside imaging (Hintz et al., 1999; Keller et al., 2000; Kusaka et al., 2001a; Sokol et al., 2000). Typically, DOI methods use a grid of interlaced source and detectors and utilize only nearest neighbor measurements. A more robust tomographic form of imaging, diffuse optical tomography (DOT), employs source-detector pairs with overlapping measurement volumes, such that each detector receives light from multiple distinguishable sources, and data inversion procedures that provide self-consistent solutions among the multiple measurement pairs (Boas et al., 2002; Oleary et al., 1995; Yodh and Boas, 2003). We recently demonstrated that tomographic approaches incorporating both nearest and second nearest neighbor measurements provide significantly improved images compared to the more common interpolation between nearest neighbor only measurements (Boas et al., 2004). In small animal models, where imaging performance is significantly enhanced, volumetric diffuse optical tomography has been used recently to map cerebral hemodynamics during motor function (Culver et al., 2003c; Siegel et al., 2003; Yu et al., 2003), focal ischemia (Bluestone et al., 2004b; Culver et al., 2003b), and global hypoxia and hypercapnia (Bluestone et al., 2004a; Culver et al., 2002).

While insight into the hemodynamic response as measured by DOT can be gained from fMRI and OIS, the point spread functions, depth sensitivities, and vascular compartments weightings to the measured signals, vary significantly between the different brain mapping methods. In addition, DOT of brain activity is relatively new compared to invasive optical imaging and fMRI. The goal of this study was to compare the spatial extents of functional activation maps generated from [HbO], [HbR], and [HbT] contrasts using diffuse optical tomography. To facilitate a comparison with fMRI, we followed the animal preparation and stimulus protocol in a set of previously published fMRI studies in which CBV and BOLD contrasts were used to map the evoked response to stimulation of the rat somatosensory cortex (Mandeville et al., 1998, 1999a, 2001).

Materials and methods

Animal preparations

Adult male Sprague–Dawley rats (300–325 g) were anesthetized (Isoflurane 1–1.5%, N_2O 70%, O_2 30%) and catheters were placed into a femoral artery to monitor the arterial blood pressure and into a femoral vein for drug delivery. The body temperature was maintained at 36.7 ± 0.5°C. The animals were tracheotomized, mechanically ventilated, and fixed on a stereotactic frame. The pressure cycled ventilator was adjusted as needed to maintain a nominal end-tidal CO_2 of 38 ± 5 Torr. After surgery, isoflurane was discontinued, and anesthesia was maintained with a 50 mg/kg intravenous bolus of α-chloralose, followed by continuous intravenous infusion of 30–45 mg/kg/h, adjusted to stabilized MAP at 100 ± 10 mm Hg.

Functional activation paradigm

Twenty-seven gauge hypodermic needles cleaned of silicone solvent were attached in pairs across both the right and left forepaws. Stimulation involved 200 μs constant current pulses at 3 Hz repetition, with amplitude 1 or 2 mA. Two pulse trains were used; (a) 6 s stimulation followed by 54 s rest, and (b) 30 s stimulation followed by 90 s rest. Between 8 and 32 blocks were acquired with either the right or the left forepaw individually stimulated.

Diffuse optical tomography instrumentation

These studies employed a frequency-encoded continuous wave imaging system with 9 dual wavelength sources (laser diodes, 9 at 690 nm and 9 at 830 nm) and 16 avalanche photodiode (APD) detectors. The source lasers are square-wave modulated, each at a separate frequency spanning 4–8 kHz, with 200 Hz spacing. Outputs of the 16 APD modules were AC-coupled, amplified and digitally sampled at 16 bits at a rate of 40 ksps. The system provides the following performance: detection sensitivity with a noise equivalent power, $\mathrm{NEP} = 0.04\mathrm{pW}/\sqrt{\mathrm{Hz}}$ fixed gain dynamic range (linear to 1%) >60 dB, and inter source-detector-pair channel cross-talk <−60 dB. The optode array covered a flat region of the rat head extending 7.5 mm either side of midline, and from 4 mm anterior to 11 mm posterior of bregma. Both the sources and the detectors were coupled through 200 μm fibers to a 25 mm × 25 mm rubber pad (see Fig. 1). The rubber pad was flexible and allowed to conform to the slightly curved geometry of the rat head. The light from each source was detected by all 16 detectors, for a total of 144 source-detector pairs, at both the 690 nm and 830 nm wavelengths. Coupling of the fibers to the tissue was established by monitoring the light levels for each source and detector.