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NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 31 (2006) 66 – 75

Blood volume and hemoglobin oxygenation response following electrical stimulation of human cortex

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Received 14 June 2005; revised 23 September 2005; accepted 18 November 2005
Available online 15 February 2006

Our understanding of perfusion-based human brain mapping techniques relies on a detailed knowledge of the relationship between neuronal activity and cerebrovascular hemodynamics. We performed optical imaging of intrinsic signals at wavelengths sensitive to total hemoglobin (Hbt; which correlate with cerebral blood volume (CBV)) and deoxygenated hemoglobin (Hbr) directly in humans during neurosurgical operations and investigated the optical signals associated with bipolar cortical stimulation at a range of amplitudes. Cortical stimulation elicited a rapid focal increase in Hbr (initial dip) in all subjects. An equally rapid increase in Hbt (<200 ms), with a slightly higher signal-to-noise ratio, was also highly localized for <2 s in spite of the non-columnar nature of the stimulus, after which the signal spread to adjacent gyri. A later decrease in Hbr (>3 s), which is relevant to the blood oxygen level dependent (BOLD) signal, was poorly localized. Increasing the stimulus amplitude elicited a linear increase in the area of the optical signal for Hbt and the initial dip but not the late decrease in Hbr, and a nonlinear increase in optical signal amplitude with a plateau effect for initial dip, Hbt and late decrease in Hbr.

Introduction

The field of human brain mapping has undergone a revolution in the past 10 years as a result of technical advances in high-resolution perfusion/oxygenation-based techniques such as fMRI and optical recording of intrinsic signals (ORIS). Both techniques are based on the work of Roy and Sherrington (1890) who observed a coupling between electrical activity and cerebral blood flow (CBF) in the microcirculation (Roy and Sherrington, 1890). More recently, Fox and Raichle (1986) demonstrated that increases in CBF, which occur 1–2 s after the neurons become active, are far greater than increases in metabolic demand ($CMRO_2$) (Fox and Raichle, 1986; Fox et al., 1988). This mismatch leads to an increase in oxygenated hemoglobin (HbO_2), which causes a relative decrease in the concentration of Hbr and is the basis of the BOLD signal seen with fMRI (Ogawa et al., 1990). It is still controversial whether the increase in $CMRO_2$ causes a transient focal increase in deoxygenated hemoglobin (Hbr) in the first few hundred milliseconds after the neurons become active (Devor et al., 2003; Forsting et al., 1993; Frostig et al., 1990; Nemoto et al., 1999; Sheth et al., 2003; Malonek and Grinvald, 1996; Ernst and Henning, 1994; Mayhew et al., 1999; Vanzetta and Grinvald, 1999; Menon et al., 1995;Hu et al., 1997; Kim et al., 2000; Lindauer et al., 2001; Logothetis et al., 1999; Frannson et al., 1998; Mandeville et al., 1999; Silva et al., 2000). Critics contend that this "initial dip" is an epiphenomenon of the experimental method, based on species, level of anesthesia, data analysis method or merely secondary to changes in blood volume (Buxton, 2001; Buxton et al., 1998; Lindauer et al., 2001).

The putative existence of this early increase in Hbr is of critical importance. As a mapping signal, the early $CMRO_2$-related increase in Hbr may have a more precise spatial correlation with the population of active neurons than the later CBF-related decrease in Hbr that forms the basis of the BOLD mapping signal. One hypothesis for the inconsistent presence of the initial dip is based on a theoretical tissue oxygen buffer (Buxton et al., 1998). In this model, activation of a small population of neurons may not sufficiently increase $CMRO_2$ to affect an increase in Hbr, whereas higher levels of activation will overcome the buffer. In support of this theory, Suh et al. (2005) recently demonstrated a large increase in Hbr following epileptiform events, in which enormous populations of neurons are simultaneously active.

Another potential mapping signal arises from very early activity-related increases in cerebral blood volume (CBV), which were initially thought to be less localizing than the initial dip (Frostig et al., 1990; Malonek and Grinvald, 1996). Recent animal data, however, have shown that increases in CBV may be highly localized within the first 2 s after the electrophysiological event, potentially offering a better signal-to-noise ratio than the initial dip

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Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2005.11.030

(Sheth et al., 2003; Erinjeri and Woolsey, 2002; Hess et al., 2000; Nemoto et al., 2004; Sheth et al., 2004). Although as a mapping signal, its utility may depend on the columnar distribution of microvascular modules (Sheth et al., 2004; Vanzetta et al., 2004; Woolsey et al., 1996).

Our understanding of the spatiotemporal dynamics of perfusion and oxygenation associated with neuronal activity arises mainly from animal experiments on normal sensory processing of columnar activity. Whether these data apply to the human brain and to non-columnar activity is unclear since techniques with sufficient resolution to address these questions, such as ORIS or oxygen-sensitive electrodes, are invasive and difficult to perform on the human brain for both technical and ethical reasons.

The recent implementation of ORIS in the neurosurgical operating room for human brain mapping has generated a great deal of excitement since it potentially has the highest combined spatial and temporal resolution of any human imaging technique (Cannestra et al., 2001; Cannestra et al., 1998; Haglund et al., 1992; Pouratian et al., 2003; Sato et al., 2002a; Shoham and Grinvald, 2001; Haglund and Hochman, 2004). At isosbestic wavelengths of hemoglobin where HbO_2 and Hbr reflect light equally (525, 545, 570.5 and 583 nm) (Sheth et al., 2003), ORIS measures total hemoglobin (Hbt), which is directly proportional to CBV and CBF assuming that the concentration of red blood cells remains constant (Nemoto et al., 2004; Mayhew et al., 2000). At higher wavelengths (600–650 nm), the majority of the signal arises from the oxygenation state of hemoglobin since Hbr absorbs light with three times the absorption coefficient of HbO_2 (Malonek and Grinvald, 1996; Sato et al., 2002b) Hence, a decrease in light reflection indicates an increase in Hbr. With multiwavelength imaging and a modified Beer–Lambert law calculation, it is possible to directly calculate Hbr, HbO_2 and Hbt.

Several groups have reported intraoperative single wavelength imaging of intrinsic signals, ranging from 605 to 695 nm, in response to sensory and epileptiform events, with little investigation into the spatial specificity of the various components of the intrinsic signal (Cannestra et al., 1998; Haglund and Hochman, 2004; Haglund et al., 1992; Pouratian et al., 2003; Sato et al., 2002a; Shoham and Grinvald, 2001). Optical responses have generally been monophasic with little evidence or mention of an initial dip. We used the opportunity provided by patients with epilepsy who are undergoing a craniotomy for implantation of subdural electrodes to investigate the spatiotemporal dynamics of perfusion and oxygenation associated with the activation of graded populations of neurons using multiwavelength ORIS. We chose to activate the cortex with bipolar cortical stimulation since this form of direct cortical stimulation produces highly localized current flow in a non-columnar distribution, exciting nearly 90% of adjacent cells with rapid spatial fall-off, and the number of responding cells varies directly with the amplitude of stimulation, with a plateau effect (Butovas and Schwarz, 2003; Nathan et al., 1993).

Methods

Subjects

Eight patients undergoing craniotomy for resection of medically intractable epilepsy gave consent for the imaging procedure described below, which was approved by the Institutional Review Board at Weill Cornell Medical Center. Most patients had undergone a prior craniotomy for implantation of electrodes to record interictal and ictal electrographic data and for stimulation mapping of motor, sensory, and language cortex. Hence, prior to ORIS, the location of the seizure focus as well as surrounding functional cortex was known. ORIS was performed during a second operation when electrodes were removed from the brain, just prior to resective surgery. ORIS was performed under general anesthesia consisting of isoflurane (<0.2%) and remyfentanyl (1 μg/kg/h). All other anesthetic agents were discontinued 20 min prior to the start of the experiment.

Electrical stimulation and recording

Two 4-contact strip electrodes (interelectrode distance—1 cm; Ad-Tech, Madison, WI) were placed on surface of the brain adjacent to one another (Fig. 1B). The two distal contacts of one strip were used for electrical stimulation, while the two distal contacts of the second strip were used to record surface potentials from an adjacent gyrus (Fig. 1B). The use of two separate strips allowed for maximal flexibility in choosing the site of stimulation and recording. Stimulation was performed on the crest of a gyrus, either within the epileptic focus (4 subjects) or in an adjacent brain (4 subjects) in either the parietal or frontal lobe, at least 1 cm from the Sylvian fissure or other large superficial veins. The epileptic focus was defined as areas of ictal onset or interictal spiking during chronic recordings from the surface of the brain with implanted electrodes. Stimulation outside of this area was considered "adjacent" brain.

Bipolar stimulation was delivered either from an Ojemann Stimulator (Integra Neurosciences) or an S-12 stimulator (Grass-Telefactor), triggered by the ORIS computer. Biphasic trains of 1 ms pulses were delivered at 60 Hz for 2 or 3 s at amplitudes of 1 to 4 mA. The amplitude and stimulation lengths were similar to parameters used during electrical stimulation mapping of the human brain for neurosurgical procedures (Ojemann, 1991). Parameters remained constant within a given experiment.

Electrocorticography data were amplified (Grass 1P511) and digitized at 2000 Hz (CED Power 1401, Cambridge, UK) and recorded onto a PC using Spike 2 (Cambridge Electronic Design, Cambridge, UK). Online examination was performed to ensure the absence of afterdischarges and spreading depression for each trial (Fig. 1D). Recordings looked similar for all non-rejected stimulation trials, and therefore other examples are not shown. The EKG was taken directly from the anesthesia machine and digitized onto a PC and recorded with an oscilloscope (BK Precision, 2120B) and window discriminator (FHC) to trigger the ORIS acquisition computer.

Optical imaging

A sterile glass footplate (4 × 4 cm) was placed on the surface of the brain over the electrodes for stabilization and to dampen the movement artifacts caused by heartbeat and respiration. A custom-made camera holder with gross and fine $x-y-z$ manipulators was used to suspend the camera over the surface of the brain (Imager 3001D—analog camera, Optical Imaging Inc., Germantown, NY) (Fig. 1A). A single 35 mm lens was used for image acquisition since a back-to-back lens system did not provide an adequate field of view (Schwartz et al., 2004; Ratzlaff and Grinvald, 1991). We performed 3 × 3