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NEUROVASCULAR SATURATION THRESHOLDS UNDER HIGH INTENSITY AUDITORY STIMULATION DURING WAKE

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Abstract—Coupling between neural activity and hemodynamic responses is important in understanding brain function, interpreting brain-imaging signals, and assessing pathological conditions. Tissue state is a major factor in neurovascular coupling and may alter the relationship between neural and hemodynamic activity. However, most neurovascular-coupling studies are performed under anesthetized or sedated states which may have severe consequences on coupling mechanisms. Our previous studies showed that following prolonged periods of sleep deprivation, evoked hemodynamic responses were muted despite consistent electrical responses, suggesting that sustained neural activity may decrease vascular compliance and limit blood perfusion. To investigate potential perfusion limitations during natural waking conditions, we simultaneously measured evoked response potentials (ERPs) and evoked hemodynamic responses using optical-imaging techniques to increase intensity auditory stimulation. The relationship between evoked hemodynamic responses and integrated ERPs followed a sigmoid relationship where the hemodynamic response approached saturation at lower stimulus intensities than the ERP. If limits in blood perfusion are caused by stretching of the vessel wall, then these results suggest there may be decreased vascular compliance due to sustained neural activity during wake, which could limit vascular responsiveness and local blood perfusion. Conditions that stress cerebral vasculature, such as sleep deprivation and some pathologies (e.g., epilepsy), may further decrease vascular compliance, limit metabolic delivery, and cause tissue trauma. While ERPs and evoked hemodynamic responses provide an indication of the correlated neural activity and metabolic demand, the relationship between these two responses is complex and the different measurement techniques are not directly correlated. Future studies are required to verify these findings and further explore neurovascular coupling during wake by assessing local field potentials, vascular expansion, hemodynamic response localization.

Key words: ERP, neurovascular coupling, NIRS.

INTRODUCTION

Neural activation increases regional blood flow and volume to deliver metabolites and remove waste products from activated tissue (Sokoloff, 1981; Attwell and Laughlin, 2001). The coupling between neural activity and blood supply is important for understanding brain function and physiological control. Additionally, brain imaging technologies, such as diffuse optical imaging, functional magnetic resonance imaging (fMRI), and positron emission tomography (PET), rely on metabolic measurements as indicators of neural activity. These measured signals are consequences of the coupling between neural activation and hemodynamic responses. However, neurovascular coupling can be influenced by a number of factors such as stimulus parameters (Blood et al., 1995; Nemoto et al., 2004), oxygen supply (Sicard and Duong, 2005), and vascular responsiveness (Piilgaard and Lauritzen, 2009), each of which is influenced by behavioral state. In order to properly interpret hemodynamic measurements evoked by neural activation, a better understanding of neurovascular coupling is required, especially under waking conditions.

Neural activation increases synaptic activity in the surrounding tissue region, which releases glutamate and triggers astrocytic activation. Neurons and astrocytes respond by releasing vasoactive agents that trigger blood vessel dilation, increasing regional blood flow (Iadecola and Nedergaard, 2007; Jakovcevic and Harder, 2007). While both neurons and astrocytes participate in the hemodynamic response, we measured electrical signals from neural activation. Following neural activation, initial increases in hemodynamic activity are localized to cortical column regions and later response components spread across the tissue (Malonek and Grinvald, 1996; Woolsey et al., 1996; Sheth et al., 2004a). Initial studies of neurovascular coupling showed a greater increase in oxygen supply than consumption following neural activity, describing the phenomenon as ''watering the entire garden for the sake of one thirsty flower'' (Malonek and Grinvald, 1996) implying that much more blood is delivered than is required. However, these studies were performed under

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Abbreviations: CBF, cerebral blood flow; ECG, electrocardiography; ERPs, evoked response potentials; HbT, total hemoglobin; LEDs, light-emitting diodes; HbO2, oxyhemoglogin; Hb, deoxyhemoglobin; EEG, electroencephalography; CBV, cerebal blood flow; fMRI, functional magnetic resonance imaging; PET, positron emission tomography.

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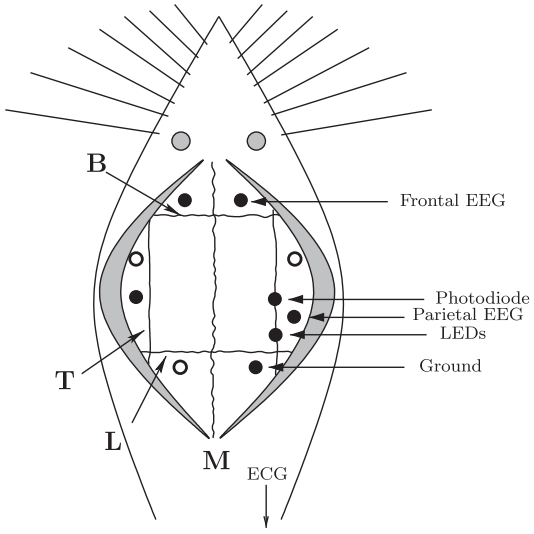

Fig. 1. Rats were implanted with two light-emitting diodes (LEDs, 660 and 880 nm) placed over the right parietal lobe and a photodiode placed 3-cm rostral to the LEDs. Bregma (B), lambda (L), the midline (M), and the temporal ridge (T) were used for positioning reference. Blunted stainless steel screw electrodes were placed in the frontal and parietal lobes (closed circles), measuring potential differences from the ground electrode placed in the occipital lobe. Additional screws were placed in the skull to support the implant (open circles). An electrocardiography (ECG) wire was placed next to the thoracic cavity. This figure was modified from Schei et al. (2009).

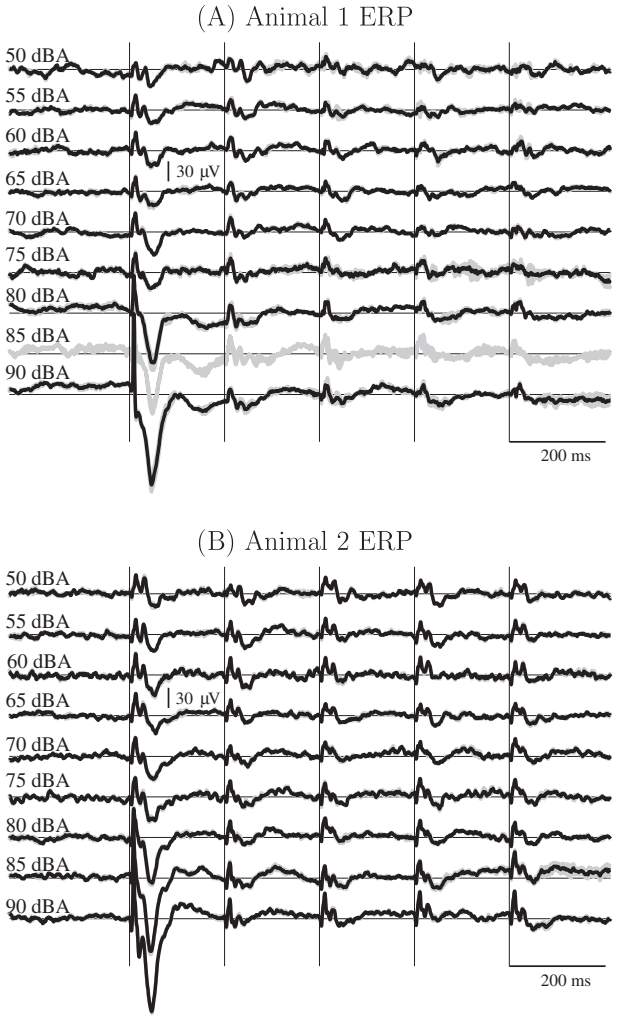

Fig. 2. Average (black traces) and standard error (gray traces)-evoked response potentials (ERPs) to different intensity stimuli illustrate typical recordings from two different animals. The vertical lines represent the train of five-speaker clicks (5 Hz, 8–22 s ISI). The largest responses followed the first-speaker click and habituation effects muted the subsequent responses to the following four-speaker clicks. For increasing stimulus intensity, we observe increased ERP amplitudes following the first click.

anesthesia, a state in which basal neural activity and metabolic demand are relatively low compared to wake, and is therefore likely to influence the neurovascular response. When compared to the anesthetized state, increased basal neural activity during waking results in increased metabolite demand which causes vascular stretching to supply that demand, thereby limiting subsequent perfusion increases during evoked activity (Schei et al., 2009).

In order to investigate the relationship between neural activity and hemodynamic responses, graded increases in stimulation are needed. Previous studies using varying stimulation frequency have shown linear coupling between neural activity and cerebral blood flow (CBF) (Gerrits et al., 1998; Ngai et al., 1999; Matsuura and Kanno, 2001; Martindale et al., 2003; Ureshi et al., 2004) and cerebral blood volume (CBV) (Martindale et al., 2003; Sheth et al., 2003) in rodents. Other studies varying stimulation intensity have shown nonlinear coupling between evoked field potentials and CBF (Nielsen and Lauritzen, 2001; Jones et al., 2004; Hewson-Stoate et al., 2005; Ureshi et al., 2005) and hemoglobin oxygenation (Devor et al., 2003; Sheth et al., 2004b). To explore the potential for saturation of blood perfusion during wake, we measured evoked responses from the auditory cortex in rats to different stimulation intensities. This paradigm alleviates potential habituation effects that appear with high-frequency stimulation.

Tissue state has profound effects on vascular compliance resulting in state-dependent-evoked responses and neurovascular coupling (Jones et al., 2008; Schei et al., 2009). Previous studies under sleep deprivation conditions have suggested that there may be limits to evoked vascular responses when the tissue has experienced prolonged periods of wake (Schei and Rector, 2011). While many studies have investigated neurovascular coupling under a variety of anesthetics, few have studied these responses during natural waking activity. Therefore, the evaluation of neurovascular coupling under different tissue states is of critical importance in order to better understand brain function, thereby better interpreting brain imaging signals and evaluating pathological conditions. We investigated the relationship between evoked neural and hemodynamic responses in awake animals to assess potential limitations in vascular responsiveness following high-intensity stimulation. We chronically implanted animals with electrodes and optodes to simultaneously measure evoked response potentials (ERPs) and regional changes in hemoglobin oxygenation from the auditory