BRAIN RESEARCH 1317 (2010) 116–123

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BRAIN RESEARCH

Research Report

Comprehensive correlation between neuronal activity and spin-echo blood oxygenation level-dependent signals in the rat somatosensory cortex evoked by short electrical stimulations at various frequencies and currents

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ARTICLE INFO

Article history:
Accepted 29 December 2009
Available online 6 January 2010

Keywords:
BOLD
fMRI
Forepaw
Neurovascular coupling
SEP

ABSTRACT

It is essential to elucidate the relationship between blood oxygenation level-dependent (BOLD) signals and neuronal activity for the interpretation of the functional magnetic resonance imaging (fMRI) signals; this relationship has been quantitatively investigated by animal studies measuring evoked potentials as indices of neuronal activity. Although most human fMRI studies employ the event-related task design, in which the stimulus duration is short, few studies have investigated the relationship between BOLD signals and evoked potentials at short stimulus durations. The present study investigated this relationship in the somatosensory cortex of anesthetized rats by using electrical forepaw stimulation at a short duration of 4 s and comprehensively analyzed it at different frequencies (1–10 Hz) and currents (0.5–2.0 mA). Somatosensory evoked potential (SEP) responses were measured at the scalp using silver ball electrodes. The sum of the peak-to-peak amplitude (ΣSEP) and average SEP (avg. SEP) responses were calculated. BOLD signals were obtained using a spin-echo echo-planar imaging sequence at 7 T. The relationship between the avg. SEP and BOLD signals varied with frequency, whereas that between ΣSEP and BOLD signals showed a significant correlation at varying frequencies and currents. In particular, the relationship between ΣSEP and ΣBOLD, which is the sum of the BOLD signals obtained at each time point reflecting the area under the BOLD response curves, mostly converged, irrespective of the frequency. Our results suggest that ΣBOLD obtained using a spin-echo sequence reflects the neural activity as quantified by ΣSEP, which was determined at different frequencies and currents.

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Abbreviations: BOLD, blood oxygenation level-dependent; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen consumption; EPI, echo planar imagining; TE, echo time; fMRI, functional magnetic resonance imaging; LDF, laser Doppler flowmetry; SEP, somatosensory evoked potential; T_2, transverse relaxation time

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doi:10.1016/j.brainres.2009.12.084

1. Introduction

Functional magnetic resonance imaging (fMRI) based on blood oxygenation level-dependent (BOLD) effect has been widely used in neuroscience and psychology to study brain function. fMRI reflects cerebral hemodynamic changes, and its signals have been interpreted by assuming a neuronal hemodynamic response (Friston et al., 1995) based on the 19th century hypothesis of Roy and Sherrington (1890) that neuronal activity induces an increase in the regional cerebral blood flow (CBF). Thus, fMRI is an indirect method for assessing neuronal activity. Therefore, it is essential to elucidate the relationship between BOLD signals and neuronal activity for interpreting the fMRI signals; this relationship has been investigated mainly by animal studies measuring evoked potentials as indices of the neuronal activity in the somatosensory cortex (Brinker et al., 1999; Van Camp et al., 2006; Goloshevsky et al., 2007; Huttunen et al., 2008; Sanganahalli et al., 2009). Although most of the human fMRI studies employ the event-related task design that has a short stimulus duration, animal studies generally investigate the relationship between BOLD signals and evoked potentials with a stimulus duration of several tens of seconds (Brinker et al., 1999; Van Camp et al., 2006; Goloshevsky et al., 2007; Huttunen et al., 2008; Sanganahalli et al., 2009). Unlike BOLD studies, numerous optical studies performed using laser Doppler flowmetry (LDF) (Ngai et al., 1999; Matsuura and Kanno, 2001; Ureshi et al., 2004, 2005) and optical imaging (Devor et al., 2003; Martindale et al., 2003; Sheth et al., 2003, 2004; Jones et al., 2004; Hewson-Stoate et al., 2005; Martin et al., 2006) have investigated the hemodynamic responses such as CBF and deoxygenated hemoglobin changes to neuronal activity in the rat cortex with a short stimulus duration (2–5 s) (Matsuura and Kanno, 2001; Martindale et al., 2003; Sheth et al., 2003, 2004; Jones et al., 2004; Ureshi et al., 2004, 2005; Hewson-Stoate et al., 2005; Martin et al., 2006). Thus, an animal fMRI study with short stimulus duration is expected to bridge the results of the optical studies using short stimulus durations and those of the BOLD studies using long stimulus durations.

Furthermore, most of the optical studies performed using electrical stimulation varied either in frequency (Ngai et al., 1999; Matsuura and Kanno, 2001; Martindale et al., 2003; Sheth et al., 2003; Ureshi et al., 2004), or current (Jones et al., 2004, Ureshi et al., 2005), or both (Sheth et al., 2004; Hewson-Stoate et al., 2005). Animal fMRI studies on somatosensory activation investigated the relationship between BOLD signals and neuronal activities by changing the stimulus frequency while maintaining a fixed current strength (Brinker et al., 1999; Van Camp et al., 2006; Goloshevsky et al., 2007; Huttunen et al., 2008; Sanganahalli et al., 2009), and few fMRI studies have comprehensively investigated this relationship at different stimulus frequencies and currents.

Thus, the present study aimed to investigate the relationship between BOLD signals and neuronal activities in the somatosensory cortex of anesthetized rats for forepaw electrical stimulation at a short duration of 4 s by changing both frequencies (1–10 Hz) and currents (0.5–2.0 mA). BOLD signals with a spin-echo echo planar imagining (EPI) sequence at 7 T and scalp-based somatosensory evoked potentials (SEP) were obtained from individual rats.

2. Results

The BOLD activity during the electrical stimulation of the forepaw was observed in the somatosensory cortex contralateral to the forepaw stimulation. The mean time course of changes in BOLD signals from the 5 most activated pixels in the somatosensory cortex is shown in Fig. 1A. The BOLD signal intensity increased approximately 1.0 s after the onset of stimulation and continued to increase even after the offset of stimulation. Higher stimulation currents were associated with long-lasting post-offset changes in the BOLD signals. Neither an initial dip nor a post undershoot was observed for any stimulation frequencies or currents. Fig. 1B shows how the BOLD signals varied with changes in stimulation frequencies and currents. BOLD signal values (avg. BOLD and ΣBOLD) increased monotonically with an increase in the stimulation current for any stimulation frequency; this increase was significant (Friedman's test $\chi^2>8.22$, $df=2$, $p<0.05$). The peak of the avg. BOLD was observed at either 3 Hz (Wilcoxon's test $Z>2.07$, $p<0.05$ for 1 and 10 Hz) or 5 Hz (Wilcoxon $Z>2.19$, $p<0.05$ for 1 and 10 Hz) for both stimulation currents of 1.0 and 2.0 mA, although there was no significant difference between the stimulus frequencies of 3 and 5 Hz ($p>0.3$). On the other hand, the peaks of ΣBOLD appeared at 3 Hz for 1.0 mA (Wilcoxon $Z=2.67$, $p<0.01$ for 1, 5, and 10 Hz) and 2.0 mA (Wilcoxon $Z=2.67$, $p<0.01$ for 1 and 10 Hz and Wilcoxon $Z=1.84$, $p<0.07$ for 5 Hz) (Fig. 1B). Although not statistically significant (Friedman's test $\chi^2<7.13$, $df=3$, $p>0.05$), BOLD signals associated with 0.5-mA stimulation also appeared to peak at 3 Hz.

SEP amplitude during the stimulation of the forepaw is shown in Fig. 2. For a stimulation frequency of 1 Hz, the SEP amplitude remained constant throughout the 4-s stimulation period (Fig. 2A). For 3 Hz, there was a gradual decline in the amplitude from the initial SEP, and for both 5 and 10 Hz, there was almost an immediate inhibition reaching a steady-state level (Fig. 2A). For higher stimulus frequencies, the SEP amplitudes showed an oscillating pattern attributed to inhibitory mechanisms that have been observed by other researchers (Matsuura and Kanno, 2001; Herman et al., 2009). The avg. SEP and ΣSEP values with changes in stimulation frequencies and currents are shown in Fig. 2B. Both avg. SEP and ΣSEP increased significantly with an increase in the stimulation current strength for any stimulation frequency (Friedman's test $\chi^2>14.22$, $df=2$, $p<0.01$). However, the frequency dependence differed greatly. The avg. SEP values decreased with an increase in the stimulation frequency for all stimulus currents: adjacent values along stimulus frequency differed significantly (Friedman's test $\chi^2=27$, $df=3$, $p<0.01$) (Fig. 2B). On the other hand, the ΣSEP values significantly peaked at 3 Hz for 1.0 and 2.0 mA (Wilcoxon $Z>2.54$, $p<0.05$) (Fig. 2B). This frequency dependence of ΣSEP is in agreement with the results for the BOLD signals (Fig. 1B).

Fig. 3 shows the relationship between the BOLD signals and SEP amplitudes for different stimulus frequencies and currents. Although there was a linear correlation between avg. SEP and the BOLD signals for each stimulation frequency (Figs. 3A and B), the slopes differed. On the other hand, the slopes for ΣSEP and a BOLD signal at each stimulus frequency tended to converge (Figs. 3C and D). Furthermore,