**Neurovascular Coupling Relationship between Spontaneous EEG and CBF Responses Is Sensitive to Anesthesia Depth**

X. Liu1,2, X-H. Zhu1, Y. Zhang1, and W. Chen1,2

1CMRR, radiology, University of Minnesota, Minneapolis, MN, United States, 2Biomedical Engineering, University of Minnesota, Minneapolis, MN, United States

**Introduction** It has been demonstrated in our previous study [1] that spontaneous cerebral blood flow (CBF) and electroencephalography (EEG) simultaneously recorded from rat primary somatosensory cortex are tightly coupled under burst-suppression anesthesia induced by isoflurane. On the other hand, other studies [2-3] have reported that the rat brain can exhibit distinct hemodynamic responses to external stimulation under different anesthesia levels, which may indicate a significant effect of anesthesia depth on neurovascular coupling relationship. One relevant and interesting question is whether the neurovascular coupling between spontaneous CBF and EEG in a resting brain also is sensitive to anesthesia depth. To answer this question, we analyzed the hemodynamic response function (HRF) linking spontaneous CBF and EEG signals measured under two isoflurane anesthesia conditions (1.8% vs. 2.0%). The results indicate that a small isoflurane dose change (0.2%) has a substantial effect on HRF.

**Methods** Four Sprague-Dawley rats were first anesthetized with ~2% isoflurane (ISO 2.0). Two EEG electrodes (GRASS TELEFACTOR, RI) were inserted through two small holes on the skull into the bilateral S1FL regions (primary somatosensory cortex, forelimb region) of rats, with a ground electrode in their nose. Two Laser Doppler Flowmetry (LDF) probes (Oxford Optronix, UK) were placed just under the EEG electrodes through the same holes. The EEG signals were sampled at 1 kHz and then band-pass filtered (0.5-30 Hz), while the CBF signals were sampled at 10 Hz. The simultaneous CBF/EEG recordings were performed when the rats were in uniform darkness (regarded as the resting state) and when all monitored physiological parameters became stable [1]. The data acquisition was repeated when the concentration of isoflurane was reduced to ~1.8% (ISO 1.8).

The continuously recorded CBF/EEG signals were first cut into 300-second segments. For each segment, a HRF, which was modeled as a gamma probability density function (PDF) with two floating parameters, was convoluted with the amplitude of EEG (extracted by Hilbert transform); and the result was then fitted to the simultaneously-recorded CBF signals to determine the parameters and thus estimated (best-fitted) HRF for this segment. The amplitude of HRFs under ISO 2.0 condition was adjusted according to the ratio of fitting slope under these two conditions, with those under ISO 1.8 condition unchanged. In addition to the above “deconvolution” analysis, correlation coefficients between the EEG amplitude and CBF were also calculated for different temporal lags to give a correlation function for each segment.

**Results** Figure 1 illustrates how the estimated HRFs can describe the neurovascular coupling between the spontaneous CBF and EEG signal changes using two segment data measured under ISO 1.8 and ISO 2.0 conditions from a representative rat. The spontaneous EEG amplitude was convoluted with the estimated HRF, and the result was then compared with the simultaneously-recorded CBF (left panel in Fig. 1). To make the comparison clearer, the low-pass filtered (< 1 Hz) CBF time courses were thickened, darkened, and overlapped on original ones. The resemblance between the convolutions and the measured CBF indicates that the deconvolution was successful for both conditions. Interestingly, the estimated HRFs from these two segments exhibit quite different characteristics (right panel in Fig. 1): the HRF for the ISO 2.0 segment was characterized with a longer latency-to-peak and a wider dispersion. A summary from all rats (Fig. 2A) suggests a generic phenomenon showing a consistent HRF change between the two anesthesia conditions with a small 0.2% difference of isoflurane dose. Such a change of neurovascular coupling can also be viewed from a different perspective based on the comparison of correlation functions between the spontaneous EEG (amplitude) and CBF (Fig. 2B), showing the similar change under two anesthesia conditions as observed in Fig. 2A.

**Discussion** In this study, we found that the hemodynamic response function, which quantifies the neurovascular coupling between spontaneous hemodynamic and neuronal activity changes, becomes more dispersive with delayed latency-to-peak when anesthesia deepens slightly. This trend is consistent with the previous studies focusing on the comparison of stimulus-evoked responses, instead of spontaneous activity, between awake and anesthetized rats [2] or between lightly (1.1% isoflurane) and deeply (2.1% isoflurane) anesthetized rats [3]. In contrast, we observed a significant, reliable HRF change even within a very narrower range of anesthesia depth (0.2% isoflurane difference). This finding suggests that neurovascular coupling is sensitive to anesthesia dose, and its dependence on anesthesia depth could have impact on quantification of neurovascular relationship for understanding the resting brain connectivity and stimulus-evoked BOLD responses in the anesthetized brains.

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**References**