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Isoflurane anesthesia effect in functional imaging studies

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In our recent studies on isoflurane-anesthetized cats (Zhao et al., 2007), we reported that post-stimulus BOLD undershoot signals induced by visual stimulation were observed both within the parenchyma and at the pial surface, but that the parenchymal signals were localized to the middle of the visual cortex, improving the spatial specificity as compared to positive gradient-echo BOLD signals. Since post-stimulus BOLD undershoots have also been observed in humans, improved spatial localization within the cortex is likely to be achieved in high-resolution human fMRI studies if signals from the inner cortex and the cortical surface can be clearly differentiated. To support this argument in the context of awake humans *vs*. our anesthetized animal model, we cited a paper by Martin et al. which reported awake *vs*. urethane-anesthetized rat studies (Martin et al., 2006). Our initial interpretation of their paper was that the detailed dynamic properties were different between awake and urethane-anesthetized animals, but that the 'general' pattern of responses was similar, based on gamma-variate fittings (see Fig. 6 in (Martin et al., 2006). However, the choice of anesthetic agents in Martin's (Martin et al., 2006) and our studies (Zhao et al., 2007) is different (urethane *vs*. isoflurane). Therefore, the reference to Martin's work comparing awake and urethane-anesthetized rats was not complete, and it was probably not even appropriate because their findings might be urethane-specific. In this letter we discuss isoflurane-specific findings which are much more relevant to our argument for the similarity between awake *vs*. anesthetized hemodynamic response patterns.

Previous functional studies comparing awake *vs*. isoflurane-anesthetized responses have been performed with visual stimulation in both monkeys (Shtoyerman et al., 2000) and cats (Fukuda et al., 2005). Even though the magnitude of responses in both monkeys and cats is reduced with isoflurane, the general response shape of the deoxyhemoglobin (dHb)-weighted optical imaging signal time courses is similar. Note that the change in dHb-weighted optical imaging signals ($\Delta R/R$) is thought to be analogous to the BOLD response. In the primary visual cortex of monkeys (Shtoyerman et al., 2000), 605-nm wavelength dHb-weighted signal responses to 3-s stimulation were obtained for awake and for 1% isoflurane-anesthetized conditions; times to early negative peak (2-3 s after the onset of stimulation) and later positive peak (5-7 s) were consistent (see Fig. 4 as well as Fig. 10B). Similar responses were also detected from the cat visual cortex for awake and 0.5-1.0% isoflurane-anesthetized conditions (Fukuda et al., 2005). Dr. Fukuda - currently at the University of Pittsburgh - supplied original 620-nm wavelength dHb-weighted data used in their paper (Fukuda et al., 2005), which were reprocessed to show averaged time courses of optical responses to 2-s stimulation in visual area 18 (five cats; error bars = 1 SD). Time courses from both awake (filled square) and anesthetized cats (open circles) display biphasic behavior, with an initial decrease and later increase in reflected light intensity (i.e., an initial increase and later decrease in dHb content). The times to the early dip (2-3 s after the onset of stimulation), and the later positive peak (5-6

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s) were consistent for awake and anesthetized conditions. Further studies are needed which compare dHb time courses in awake and isoflurane-anesthetized animals for different stimulus types and durations in order to determine whether our isoflurane-anesthetized animal studies (Masamoto et al., 2007;Zhao et al., 2007) are directly applicable to awake conditions.

Overall, evoked hemodynamic response patterns in isoflurane-anesthetized animals are similar to those in awake animals, albeit with reduced magnitude (Shtoyerman et al., 2000;Fukuda et al., 2005). Thus, our original argument for similar dHb response patterns between awake and isoflurane-anesthetized cats appears to be valid. Since different anesthetics influence neurovascular coupling differently, we completely agree with Martin's point that caution is required when extrapolating the findings from anesthetized animal studies to human fMRI.

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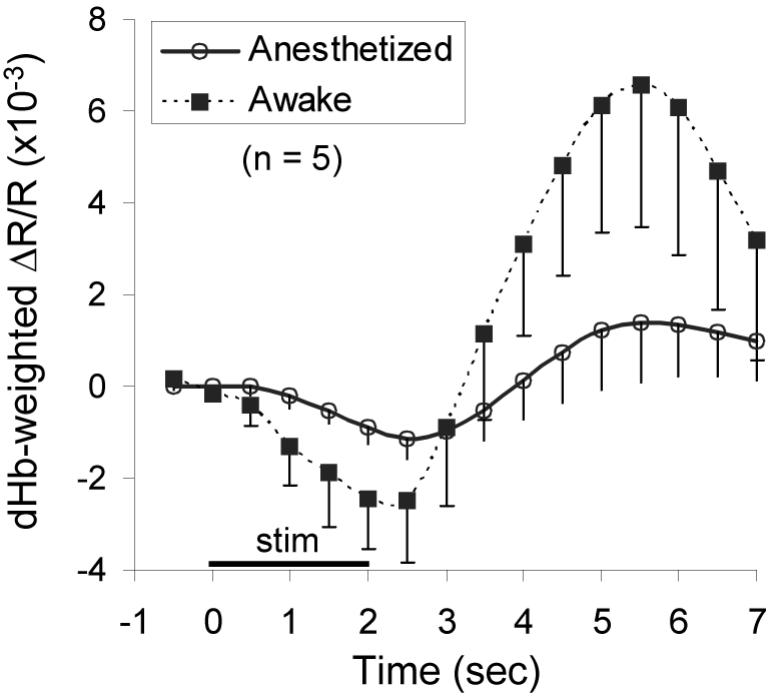

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