

Influence of Sevoflurane on Regional CBF and Functional Connectivity and Implications Related to Brain/Behavior during General Anesthesia

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Introduction The effects of sevoflurane on regional cerebral blood flow (rCBF) are observed across the brain cortices but are highly region-specific, with increases in rCBF limited primarily to subcortical structures and the insula and decreases observed primarily in neocortical regions [1]. The functional connectivity within sub-neural networks appears to be much less affected by sevoflurane [2]. With the assumption that both the resting state rCBF and functional connectivity are associated with the same underlying neuronal processes, we wanted to test whether or not a decrease in CBF during anesthesia would lead to a decrease in functional connectivity, and increased CBF lead to increases in connectivity. Discrepancies between the changes in rCBF and connectivity caused by sevoflurane might suggest the differences in the neuronal processes with which they are associated. In this study, we used regions where rCBF was significantly altered by sevoflurane as seeds to define functional sub-networks, and assessed changes in functional connectivity associated with changes in rCBF. Implications of the results are discussed.

Materials and Methods BOLD and PASL imaging was performed on a 3 T Siemens (Erlangen, Germany) Trio MR system with a CP head coil. Images for the resting state were acquired with BOLD and PASL MRI in N=14 healthy human subjects during the anesthesia-free/awake condition and 0.5 MAC sevoflurane anesthesia. PASL data covered 10 AC-PC aligned axial slices with slice thickness=6mm, gap=3mm, FOV=256mm, matrix size=64×64, TR=3s, TE=21ms, TI=1.4s, flip angle=90°. BOLD volumes were collected using a single-shot gradient EPI sequence: 33 interleaved slices with a thickness of 4mm, no gap, FOV=256mm, matrix size=64×64, TR=2s, TE=31ms, flip angle=90°. For each condition, awake or anesthesia, 2 PASL runs of 170 volumes and 3 BOLD runs of 210 volumes were carried out. Regional CBF was estimated from the PASL acquisitions [3] for each condition and compared between conditions to identify cortical regions where sevoflurane led to significant changes in rCBF. Group analyses were performed in the MNI reference space using a non-linear registration ([www.biomedcentral.com](http://www.biomedcentral.com/info/publishing_adv.asp)) (Fig. 1). Seed regions were first identified in the reference space and transformed to the individual subject space for connectivity analysis. For each BOLD run, data were temporally and spatially realigned and corrected to remove slice mean and drift after the first 10 volumes were discarded. Signal at each voxel was low-pass filtered at a cut-off frequency of 0.08 Hz with a 4th degree elliptical filter and the 6 estimated motion parameters were regressed from the data [4], as were the mean signals of white matter and CSF. Cardiac and respiratory signal were continuously recorded during the study and used to remove the physiological noise [5]. Connectivity maps were computed using primary visual (left BA17, where rCBF was significantly suppressed by sevoflurane) and left insula (where rCBF was significantly increased) cortex as the seed regions. Seed-to-whole brain connectivity was computed in single-subject space and then transformed into the reference space using a non-linear registration.

Results and Discussion Connectivity maps to the insula seed region revealed significant connections with the ACC, SII and the middle frontal gyrus bilaterally (Fig. 2), resembling the spatial pattern of rCBF increased by sevoflurane (Fig. 1). The anesthesia effect on connectivity was minimal - with only bilateral SII and the left middle frontal gyrus reduced, while connectivity with the ACC and the left putamen were increased. Seeding in BA 17 revealed significant connections only within the visual cortex (Fig. 3). Higher order visual areas in the cuneus (BA 19) and the lingual gyrus showed stronger connectivity under anesthesia than in the awake condition. No region showed decreased functional connectivity under anesthesia when using the visual cortex as the seed. In contrast to the resting state CBF, which is significantly altered by sevoflurane in a regionally-specific manner, the BOLD functional connectivity is preserved under sevoflurane anesthesia, consistent with previous results showing that functional connectivity remained essentially unchanged even under deep anesthesia in monkeys [6]. However, the observation in this study is inconsistent with those reported in another human study by Peltier et al [7], where the functional connectivity (calculated using unilateral motor areas as seeds) was significantly suppressed by sevoflurane. The results in our study suggest (1) the resting state CBF and functional connectivity are not directly linked - the resting state rCBF reflects the total resting state neuronal activity and the observed changes in rCBF are likely associated more with local processes such as local potential maintenance, neuronal spiking, neuroreceptor release etc., while the BOLD functional connectivity mainly reflects only long distance communication between cortical regions; (2) an anesthetic agent could change the nature of this long distance cross talk, e.g., change the rate and the amplitude of the synchronized neuronal burst [8], but amplitude changes do not affect functional connectivity as long as sufficient SNR is present; and (3) the regional neural activity is mainly responsible for the brain's responses to external stimulation while long-distance communication is related to the brain's house keeping; hence the term intrinsic connectivity that is often used to describe these correlations.

Conclusion This work examined the relationship between local changes in rCBF and BOLD based functional connectivity in the awake and anesthesia state in humans. Regional CBF was significantly altered by sevoflurane across the brain while the network properties as measured using BOLD functional connectivity remained largely undisturbed. These discrepancies in the responses between rCBF and functional connectivity suggest that they are not associated with the same functional components of the underlying neuronal processes in general.

References [1] Qiu et al 2008, HBM 29:1390-9; [2] Martuzzi et al 2010, NeuroImage 49:823-34; [3] Detre et al 1992, MRM 23(1):37-45; [4] Laufs et al 2007, Brain 130:e75; [5] Glover et al 2000, MRM 44:162-7; [6] Vincent et al 2007, Nature 447:83-6; [7] Peltier et al 2004, NeuroReport 16(3):285-8; [8] Erchova et al 2002, European J NeuroSci 15(4):744-52.

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