Linear dependence of neuronal oscillations on hypercapnia level: implications for CO_2 calibrated fMRI

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Target audience: Researchers with an interest in fMRI calibrated BOLD or the cerebral physiological effects of CO_2.

Purpose: Hypercapnia is used widely in fMRI as a vasodilatory stimulus. However, the assumption is generally made that hypercapnia does not affect underlying neuronal activity and metabolism. Studies of the effect of hypercapnia on cerebral metabolic rate of oxygen metabolism ($CMRO_2$) have yielded conflicting results[1-4], albeit tending towards a small decrease with hypercapnia. More direct measurements of the underlying neuronal activity during hypercapnia have been made recently using electroencephalography (EEG)[2] and magnetoencephalography (MEG)[5]. These studies show broadband desynchronisation (decrease in oscillatory amplitude) during hypercapnia. Sensory, neurochemical, or other biophysical mechanisms have been suggested, however the exact origin of the desynchronisation is unclear. Here we implement a graded hypercapnic challenge, including milder levels of hypercapnia below the sensory threshold. We aim to probe the relationship between neuronal oscillations and hypercapnia to assess the suitability of hypercapnia for calibrated BOLD fMRI[6].

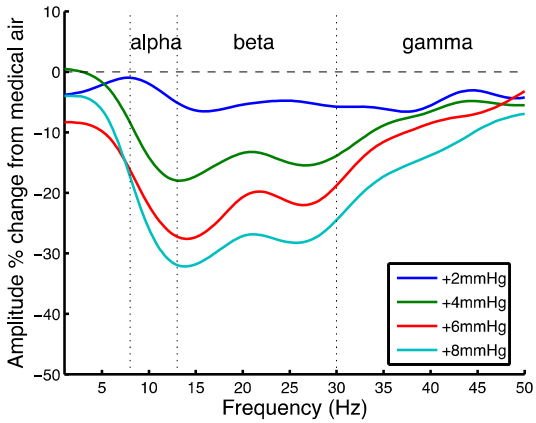

Fig1: Amplitude % change spectrum of each hypercapnia level, relative to medical air.

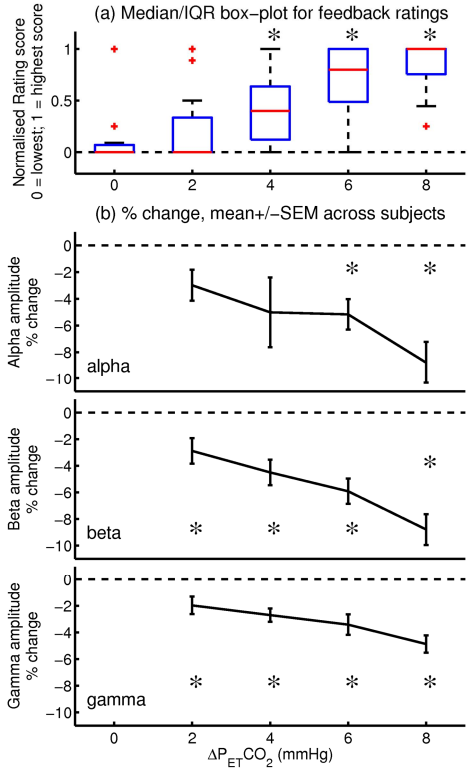

Fig2: (a) Normalised ratings scores (b) % change from medical air periods at each frequency band.
**denotes significant change from medical air (P<0.05 Bonferroni corrected)*

Methods: MEG recordings (CTF 275-channel radial gradiometer, 600 Hz sampling) were made in ten healthy subjects (30±4yr; 3F/7M). Flow rates of two inspired gases (medical air and 5% CO_2 balanced with air) were adjusted manually to reach end-tidal PCO_2 ($P_{ET}CO_2$) targets. The 40 minute experiment consisted of 5 minutes of medical air (normocapnia), followed by 5-minutes of hypercapnia, repeated across 4 different levels of hypercapnia. $\Delta P_{ET}CO_2$ levels (relative to normocapnia) of +2, +4, +6 & +8 mmHg were presented in a pseudo-randomised order. Subjects rated their level of breathlessness using a visual feedback task, presented for 10s every 100s throughout the experiment. The MEG dataset was split into 2s epochs and noisy epochs (muscle artefacts, noise spikes) discarded. The 20s during and following each rating task were also discarded. For MEG analysis the SAM beamformer estimated source space activity which was then band-pass filtered and the Hilbert amplitude envelope calculated for each frequency band at 1s temporal resolution.

Results: Amplitude spectra for each condition are plotted in *Fig1*, showing broadband desynchronisation during hypercapnia, with similar spatial distributions to Hall et al.[5] occurring at +8mmHg (not shown). *Fig2* plots feedback scores and average %change in alpha (8-13Hz), beta (13-30Hz) and low gamma (30-50Hz) band amplitudes, showing approximately linear relationships with $\Delta P_{ET}CO_2$. Although there is a significant ($P=7\times10^{-4}$) correlation between rating scores and beta band decrease across all levels, the beta band decrease was still present in the +2mmHg condition (P = 0.01), where only 3 (of 10) subjects had elevated ratings above medical air periods.

Discussion: The effect of hypercapnia on neuronal oscillations is graded, and not a simple switch at a certain level. Our data suggests that hypercapnia induced neuronal desynchronisation remains below the sensory threshold, suggesting that the breathless sensation is not the dominant contributor. Whilst not a direct correlate of metabolic demand, the apparent linear relationship observed here could be used to infer a linear dependence of $CMRO_2$ with $\Delta P_{ET}CO_2$[5]. Therefore, the violation of the isometabolic assumption in hypercapnia calibrated BOLD[6] could be corrected for by using two or more levels of hypercapnia to regress out the linear metabolic dependence on hypercapnia.

Conclusion: We rule out a sensory mechanism for the hypercapnia neuronal desynchronisation, whilst the linear relationship observed suggests a method for overcoming metabolic changes during hypercapnia in calibrated fMRI.

References: [1]Chen and Pike, JCBFM 2010, 30:1094; [2]Xu *et al.* JCBFM 2011, 31:58; [3]Jain *et al.* JCBFM 2011, 31:1504; [4]Murphy *et al.* Proc. ISMRM 2013, 21:3343; [5]Hall et al. NeuroImage 2011, 58:1034; [6]Davis *et al.* PNAS 1998, 95:1834.

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