

END-TIDAL CO₂ CORRECTION MODULATES THALAMIC ACTIVATION IN FMRI OF PAIN

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Thalamic activation detected in this pain FMRI study was eliminated by including values from end-tidal CO₂ monitoring in the statistical model used to create the activation maps. This modulation was seen with a concomitant 79% improvement in average model fit in the thalamus.

Background

BOLD FMRI:

- Neurons that are metabolically active during task periods extract more oxygen from blood vessels.
- Increases in blood flow overcompensate for increased oxygen extraction, causing an increase in oxyhemoglobin in the local vasculature.
- The blood oxygen-level dependent (BOLD) effect is the increase in MRI signal seen in "activated" areas of the brain with increased blood oxygenation.

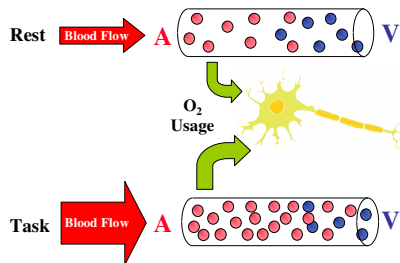


Illustration of changes in capillary blood flow and oxygenation, demonstrated to accompany neuronal activation, that cause the measurable BOLD FMRI signal change.

Previous Work:

- Data from blood oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI) of pain are particularly susceptible to physiologic noise contamination due to autonomic reactionary changes in cardiac and respiratory patterns and in cerebral blood flow (Ibinson and Small, 2004)
- End-tidal CO₂ (ETCO₂) predicts arterial CO₂, which is directly related to cerebral blood flow. End-tidal CO₂ fluctuations also correlate with significant BOLD signal changes (Wise et al., 2004).
- ETCO₂ correction can have a greater overall impact on model fit in pain studies than the combined cardiac and respiratory monitoring commonly used for fMRI physiologic noise correction (Vogt et al., 2007)
- Thalamic activation has been inconsistently reported in pain FMRI studies (Peyron et al., 2000, Apkarian et al., 2005).

References

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- Vogt et al. (2007). "Combined correction with regression for measured respiratory, cardiac, and capnometry variations in pain FMRI studies improves model fit". *Proc ISMRM* 15, 1825.
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Purpose

- These results are from a larger work studying the effects of physiologic noise correction in pain FMRI. The results presented here expand on results previously reported in the literature in three ways:
- End-tidal CO₂ as a noise regressor is unreported in the FMRI literature.
 - Physiologic noise is explored as a possible explanation for the variability in detection of thalamic activation in pain FMRI studies.
 - Model fit is examined specifically in the thalamus to determine the effect of physiologic noise correction in an area involved in pain processing.

Significance

The variable reporting of thalamic activation in FMRI of pain may be explained by cyclic variations in ETCO₂.

Methods

- Seven adult right-handed subjects (4 male) underwent whole brain FMRI scanning in this Ohio State University IRB-approved pain FMRI study.
- Imaging was performed with a General Electric Signa 1.5T scanner using a gradient echo, echo planar imaging (EPI) sequence (TE=50ms, 90° flip) in which 28 axial slices 5mm thick gave whole brain coverage, with each volume collected in TR=3s.
- Transcutaneous electric nerve stimulation (TENS), adjusted to subject rating of 5/10, was delivered to the digital nerve of the right index finger in 30s blocks, alternating OFF, then ON.
- Expired CO₂ data were recorded continuously during scanning. The end-tidal CO₂ values for each imaging volume were calculated and used as a regressor in the FMRI analysis.
- FMRI data were processed with FSL's FEAT v5.4 including correction for gross subject motion, spatial smoothing, and temporal high-pass filtering.
- Functional activation maps were calculated using general linear modeling (GLM) of the stimulus paradigm with FSL with and without the ETCO₂ data.
- Adjusted coefficient of determination (R_a²) values were calculated for each voxel time-series, as in (Razavi et al. 2003). Mean R_a² values were averaged across all voxels in a thalamus region of interest (ROI) and also across all voxels in the brain.

Results & Discussion

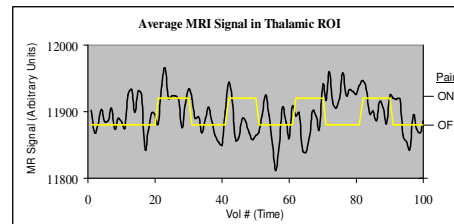
Changes in Mean R_a² Values:

- Across the whole brain – 64.88%*
- In the thalamus ROI – 79.72%*

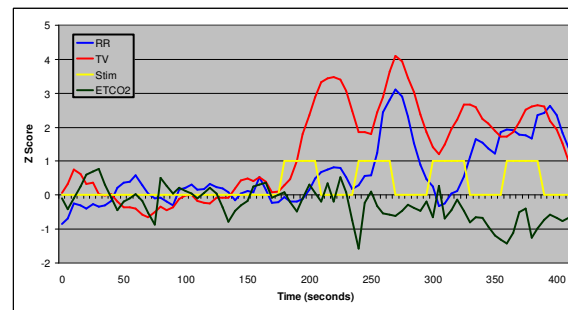
* indicates a statistically significant change in R_a² compared to no ETCO₂ correction

The adjusted coefficient of determination, R_a², is a measure of the residuals from model fitting, with the degrees of freedom adjusted for the number of parameters in the model. Thus, R_a² should only increase if the inclusion of another regressor, such as ETCO₂, explains its share of the variance in the FMRI data.

The increase seen in R_a² indicates that ETCO₂ correction improves model fit in the whole brain and, specifically, in the thalamus. This suggests that the loss of thalamic activation is the correction of a false positive activation.



Plot of average MR signal intensity (black) in the thalamus for one subject, with overlaid pain stimulus timing (yellow). The obvious disparities between the two illustrates the relatively low correlation between them. This is reflective of the low contrast to noise ratio of the FMRI signal timecourse in the thalamus. This is, in part, due to physiologic noise contamination.



Plot of respiratory and ETCO₂ changes, converted to Z-scores, relative to the baseline period, from a similar experiment (Ibinson and Small, 2004). RR = respiratory rate (blue), TV = tidal volume (red), Stim = timing of the electric nerve stimulation (yellow), and ETCO₂ (dark green). Regression analysis identified significant (p < 0.001) stimulus-induced increases in respiratory rate and tidal volume that cause significant (p < 0.001) decreases in ETCO₂ values over the course of multiple painful stimulations.

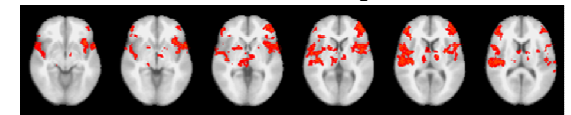
Abstract

The thalamus is a known relay center for ascending neurons in the spinothalamic tract, carrying afferent pain signals to the cerebral cortex. However, thalamic activation has been variably detected in functional imaging studies of pain (Peyron et al., 2000). Resting end-tidal CO₂ fluctuations have been shown to have an effect on the blood oxygen-level dependent FMRI signal (Wise et al., 2004). Physiologic noise correction using ETCO₂ is expected to be particularly important in pain FMRI where changes in ETCO₂ are known to occur in response to multiple painful stimulations (Ibinson and Small, 2004). In this study, ETCO₂ values recorded during pain FMRI scanning were included in the statistical model used to determine brain activation, resulting in changes in the calculated activation maps.

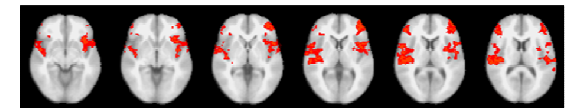
Seven right-handed subjects (4 male) participated in this 1.5T FMRI study (TR=3s, resolution=3.75mm², 28 axial 5mm slices) in which 5/10 pain was produced in four 30s epochs by electric nerve stimulation of the digital nerve of the right index finger. Expired CO₂ concentration was monitored throughout scanning and the resulting data was processed to find the end-tidal value that corresponded to each acquired brain volume. These values for each subject were used as a parameter in the general linear model for determining brain activation in FSL's FEAT v5.4. Group average activation maps were calculated with and without ETCO₂ as a model parameter, as shown in Figure 1. Statistical goodness of model fit was determined by calculating the adjusted coefficient of determination, R_a², value, for each voxel in the brain, as in (Razavi et al., 2003). Averaging over the entire brain volume, a 68% increase in R_a² was seen with the inclusion of ETCO₂ correction.

Thalamic activation detected with low resolution FMRI may be an artifact of physiologic noise and was eliminated in this 7 subject study by correcting the analysis for ETCO₂ fluctuations over the course of the experiment. The 68% improvement in overall model fit (increase in R_a²) was seen concomitant with the predominant change in the activation map being the loss of thalamic activation. These findings suggest that the change corrects a false positive activation, rather than artificially eliminating a true activation.

Activation without ETCO₂ correction



Activation with ETCO₂ correction



Activated areas in the brain, shown in red, indicate the location and extent of pain stimulus correlated BOLD signal changes. These areas are presumed to be involved in processing the pain experience. The calculated activation maps reproduced areas reported in the pain literature, including the cerebellum (not shown), insula, and somatosensory cortex. The selected slices show that thalamic activation was detected in the average maps without any correction. However, this activation is eliminated by ETCO₂ correction, demonstrating how physiologic noise can cause artifactual activations in areas with low BOLD contrast to noise ratio.

Possible Explanations for Thalamic ETCO₂ Modulation:

There are several possible explanations for the correlation between ETCO₂ and thalamic FMRI signal timecourses:

- BOLD signal changes seen in the thalamus may be due to changes in cerebral blood flow induced by vasoconstrictive changes in arterial CO₂.
- The thalamus may be involved in involuntary respiratory control. If so, it would have activity correlated to pain-induced changes in respiration and may thus show BOLD signal changes more closely temporally related to the ETCO₂ timecourse than to the stimulus paradigm.

Conclusions

- The use of end-tidal CO₂ values as a regressor in a pain FMRI experiment improves the overall fit of the statistical model used to detect "activated areas" with BOLD signal changes.
- The localized thalamic ROI improvement in R_a² seen concomitantly with the loss of thalamic activation indicates an improvement in model fit, despite the reduction in activated voxels. This suggests that ETCO₂ correction in the thalamus removed a false-positive activation, with voxel timecourses more strongly correlated to the ETCO₂ timecourse than the stimulation paradigm, the two of which are not orthogonal.
- The incongruence between calculated pain FMRI activation maps lacking thalamic activation and the known neuroanatomical synapse of ascending spinothalamic tract neurons in the thalamus is reflective of the low BOLD contrast to noise ratio and, thus, the low BOLD-FMRI sensitivity to activation in the thalamus.