Modeling the hemodynamic response in stimulus-evoked mouse fMRI

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Purpose: Advancements in temporal and spatial resolution of fMRI have enabled new applications such as the translation to mice and an increased focus on fast and small signal changes. Yet, the standard analysis tools may not be appropriate for these conditions as the intrinsic assumptions of linearity relating stimulus and hemodynamic response and the use fixed shapes of the hemodynamic response function (HRF) may not be valid. In particular for stimulus induced BOLD fMRI in mice, region-specific signal shapes, unavoidable interactions with the anesthetics as well as contributions from peripheral confounds, have to be considered in the statistical analyses. Here we show for an electrical stimulation paradigm in mice that the sensitivity and specificity of the BOLD fMRI signal can be noticeably improved by employing appropriate experimental designs and analysis approaches.

Methods: Mice (n=5-6 per group) were anesthetized with medetomidine (0.2mg/kg/h i.v.), intubated, paralyzed and mechanically ventilated. BOLD responses were elicited by electrical hindpaw stimulation (0.5ms pulses of 1mA). Two stimulus designs were used: A block design (4 repetitions with 20s on, 120s off period) and an event-related (ER) design (single pulses with 20-30s interstimulus inverval). The fMRI measurements were conducted on a 9.4T MR system (Bruker) with a cryogenic phased-array receive coil and a linearly polarized volume transmit coil. A GE-EPI sequence was used with TE/TR=10ms/1s, FOV=23.7x14mm^2, acquiring 12 interleaved coronal slices per second with 0.26x0.23x0.5mm voxel size. All analysis steps were performed in AFNI (afni.nimh.nih.gov/afni). The MR data were coregistered to a template and corrected for slice timing, motion and slow signal drifts. The ER data was fitted voxel-wise by three methods: General linear models using 1) a basis set of cubic splines (CS) spaced 2s apart (7 parameters), 2) SPM basis functions (a gamma variate and its temporal and dispersion derivative, 3 parameters) as well as nonlinear regression by modeling the HRF with four half-cosines (4cos) representing initial dip, rise to peak, drop to post-stimulus undershoot and return to baseline (7 parameters). Statistical maps (F-tests over all parameters, FDR P<0.01) and traces of anatomically defined ROIs are shown in Fig. 1. The same analyses were done for the block design data, replacing the cubic spline method with a fixed-shape HRF obtained from the S1 ROIs of the ER experiments (1 parameter), shown in Fig. 2. Goodness of fit was estimated by calculating reduced χ^2 values.

Results: The ER design produced more specific responses compared to the block design indicated by the reduced BOLD signal in the control ROI located in the visual cortex. Both designs showed bilateral activation although with a significantly stronger amplitude on the contralateral side. For the ER design, statistical maps of all methods showed similar patterns. The CS model had a tendency for over-fitting as seen in the widespread activation maps and the low χ^2_r value in the control region. The SPM model produced a relatively poor fit in the ER design and untypical signal shapes consisting of multiple peaks in the noisier block design. The fixed HRF model performed poorly outside the S1 region. The 4cos model performed reasonably well for both ER and block design shown by the absence of extreme χ^2_r values while providing a simple analytic curve. In the control region all methods had a tendency to fit the relatively strong noise.

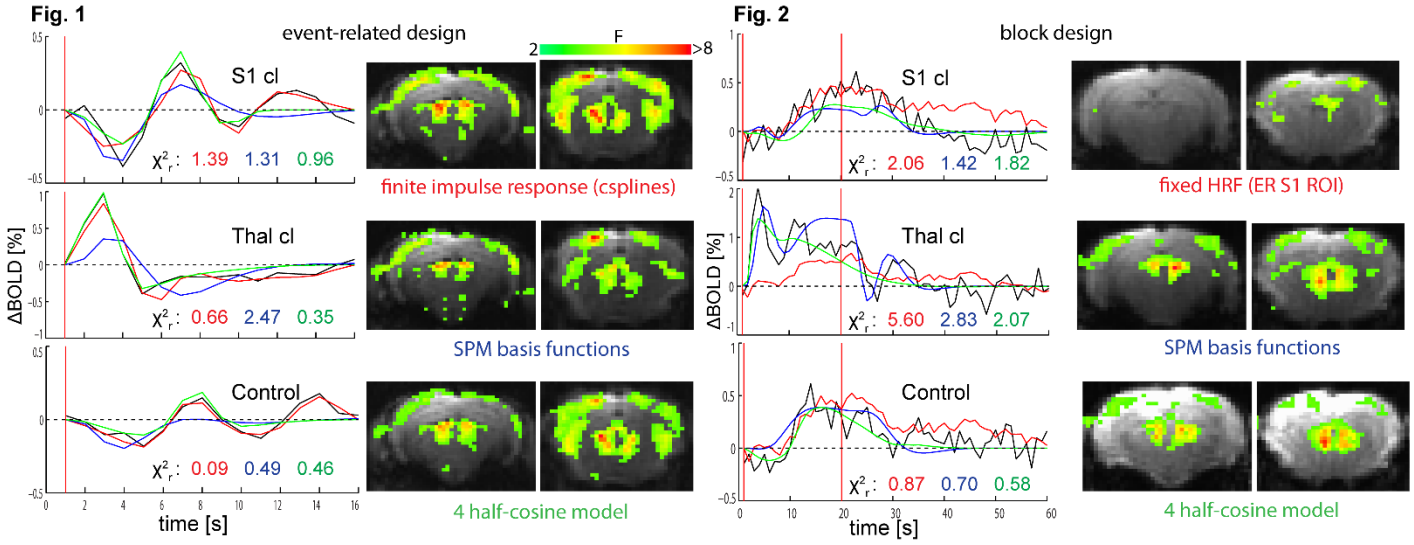

Fig. 1: Left: Average BOLD signal traces (black) in different ROIs to single stimulus pulses (red vertical line) and model fits using cubic splines (red), SPM basis functions (blue) and 4 half-cosines (green). Right: Statistical parametric maps (FDR P<0.01) for the three models, showing a posterior and anterior coronal slice.
Fig. 2: Left: Average BOLD signal traces (black) in different ROIs to 20s stimulus blocks (between red vertical lines) and model fits using the S1 HRF obtain from Fig.1 (red), SPM basis functions (blue) and 4 half-cosines (green). Right: Statistical parametric maps (FDR P<0.01) for the three models, showing a posterior and anterior coronal slice (left side = contralateral to stimulus).

Conclusions: Mouse fMRI is a powerful tool that allows new insights into the mechanisms of neurovascular coupling or provide relevant information on disease mechanisms. Yet, our initial studies revealed that stimulus evoked BOLD responses contain significant non-specific contributions arising from systemic hemodynamic changes and that the HRF varies significantly across brain regions[2]. The pronounced BOLD signal transients in mice require robust analysis approaches and experimental designs that minimize variability of the responses. Further studies using conditions with different HRF responses, e.g. be using different anesthetics such as isoflurane, propofol and urethane, as well as computer simulations are warranted to optimize the fMRI analysis procure.

References: 1) Schroeter A, Schlegel F, Seuwen A, Grandjean J, Rudin M. (2013) Effect of four commonly used anesthetics on stimulation-induced and resting state fMRI signal in mice. Proc. Intl. Soc. Mag. Reson. Med. 21 p.2300. 2) Schroeter A, Schlegel F, Seuwen A, Grandjean J, Rudin M. (2014) Specificity of stimulus-evoked fMRI responses in the mouse: The influence of systemic physiological changes associated with innocuous stimulation under four different anesthetics (under review)