Creation of a hemodynamic response function for BOLD fMRI in the rat brain

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Introduction: A crucial part of functional neuroimaging in the rat is the statistical analysis of the data. For BOLD fMRI the general linear model (GLM) is commonly used with the canonical basis set, where the convolution of the hemodynamic response function (HRF) with the stimulation is included as a model. The software package Statistical Parametric Mapping (SPM) [1] has implemented a canonical HRF by default, which is based on human data (human HRF). Since application of this human HRF may not be appropriate for small animal data, we have determined a generic HRF of rats, based on BOLD responses of the primary somatosensory cortex (S1).

Methods: Data were derived from experiments with SD and Fischer rats under medetomidine or isoflurane anesthesia at 9.4 T with single-shot GE-EPI (TR/TE 1000/18ms, 350x325µm² or 375x375µm², 8-14 1.2 mm thick slices) upon electrical paw, mechanical paw or optogenetic stimulation (block design). Measurements were assigned to 13 different groups according to their experimental conditions (e.g. strain, anesthesia, stimulation). A U-test determined voxelwise whether the signal during stimulation and rest period differed significantly for the S1 region on the activated side of the brain. Signal of significant voxels was summed up. The convolution of the stimulation paradigm and the canonical HRF (eq. 1) was fitted to the resulting time courses.

$$A \cdot e^{-bt} \cdot \left(\frac{b^{p_1}}{\Gamma(p_1)} \cdot t^{p_1-1} - \frac{b^{p_2}}{V \cdot \Gamma(p_2)} \cdot t^{p_2-1} \right) \qquad \text{eq.1}$$

Time courses of the normalized HRFs for the different groups were compared pairwise, using a customized functional t-test [2]. Resulting p-values were Bonferroni corrected. All HRFs were normalized and averaged across all groups that showed no differences. The canonical HRF (without amplitude *A*) was fitted to the resulting time course of the rat HRF. The resulting parameters can be implemented in SPM. To test the detection performance of the GLM, statistical analysis was performed on 20 datasets with the 1st order canonical basis set using the generic rat or, for comparison, the human HRF. Cluster sizes and t-values were compared using a U-test in SPSS.

Results: BOLD responses of 146 fMRI measurements were extracted and 71 % were fitted successfully. Due to differences between the HRFs of 1 s and 5 s stimulation duration (p=0.07), HRFs obtained from 1 s stimulation were excluded from the determination of a generic rat HRF. Averaging of the remaining HRFs delivered a generic rat HRF based on 98 BOLD measurements of 64 animals. This HRF deviated substantially from the human HRF (Fig. 1). Analysis of 20 additional datasets using the first order canonical model with the generic rat HRF instead of the human HRF revealed significantly larger BOLD clusters and t-values.

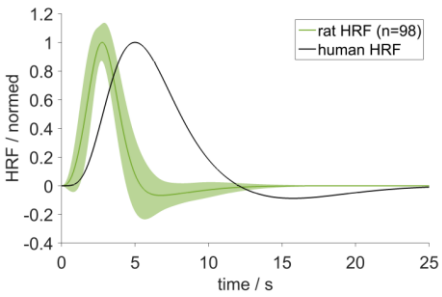

Fig. 1: The generic rat HRF (green, ± standard deviation) deviates from the human HRF (black).

Conclusion: With exception of the stimulation length, the HRF of rats is independent of the experimental conditions examined. Due to the differences between rat and human HRF, the GLM analysis of rodent data showed a significantly higher detection performance using the generic rat HRF. We therefore advise using this generic rat HRF for analysis of rat BOLD fMRI data.

References: [1] Friston, SPM12. Wellcome Trust Centre for Neuroimaging. (2017). [2] Ramsay, Functional Data Analysis with R and MATLAB. 1st ed. Springer. (2009).