

Analyzing Task Activated BOLD fMRI Signal Voxel Area and Intensity Measurements with Bootstrap Power Analysis

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Purpose: To determine how many subjects are required to detect subtle changes in functional magnetic resonance imaging (fMRI) blood oxygen level dependent (BOLD) signal characteristics in response to stepwise changes in frequency of a sensory stimulus.

Introduction: Two metrics of the BOLD signal: activated voxel area and activated voxel intensity were measured and assessed for statistical power using bootstrap power analysis in 64 individual rat subjects. An animal model was used to provide controlled background conditions for this study. The animal was maintained under a constant level of sedation, paralyzed, and placed on a respirator to limit motion artifacts. Needle electrodes were placed between the web-spaces of the subject rat's forepaw and were stimulated with DC square wave pulses with a fixed amplitude, duration, and frequency. Stepwise increases in frequency from 3, 5, 7, to 10 Hz were used and have been previously demonstrated to give stepwise increases in local field potentials using electrophysiology. The forepaw stimulation method has a long history in BOLD fMRI (1) and is currently used to test neurovascular coupling under different experimental conditions, with applications in the pharmaceutical industry (2). Higher spatial resolution is also an advantage of an animal model and is a result of using a high-field small-animal scanner. This study utilized voxel dimensions of 0.12 * 0.12 * 1 mm and a Bruker 9.4T small-animal scanner. It has been previously demonstrated that the area of voxel activation can be directly correlated to the performance of a task, such as the speed of finger-tapping in a human subject (3). This has also been demonstrated for the BOLD signal intensity in the activated voxels (3). In this study, these two metrics of BOLD signal strength were measured under controlled conditions in a rat model.

Methods: Sixty-four Sprague-Dawley rats were used in this study. Rats were sedated with a constant infusion of medetomidine anesthesia (0.1 mg/kg/hr) and pancuronium bromide (2 mg/kg/hr) and placed on an MRI-compatible ventilator. Experiments were conducted with a Bruker AVANCE 9.4T small-animal scanner. A standard gradient-echo imaging sequence was used for BOLD fMRI contrast. Scan parameters were: TE=18.76 ms, TR=2 sec, 110 images, 10 slices, 128 * 128 matrix, FOV=3.5 cm, and 1 mm slice thickness. A Grass stimulator (Model S88) with a constant current unit was used to electrically stimulate the forepaw at 2 mA amplitude, 3 ms duration, and either 3, 5, 7, or 10 Hz frequency. The forepaw was stimulated with a 40 sec OFF period followed by three periods of 20 sec ON/40 sec OFF. Activated voxels were determined with an F-test with the block design as the regressor. A p-value of 0.005 was used.

Bootstrap power analysis was used to determine statistical power for detecting differences between frequency values. The algorithm for the bootstrap statistical power analysis was as follows:

- Given original sample data, $\mathbf{X} = (\mathbf{x}_1, \dots, \mathbf{x}_N)^T$, where N = original sample size, and $\mathbf{x}_n = (m_{n1}, \dots, m_{nM})$ is the vector of M measurements for the n^{th} subject.
- Set sample size S . Initialize: power(S) = 0.0.
- For bootstrap iteration b , select S integers, i_1, \dots, i_S , at random (with replacement) from $\{1, \dots, N\}$.
- Extract the bootstrap sample $\mathbf{X}^{*b} = (\mathbf{x}_{i1}, \dots, \mathbf{x}_{iS})^T$. Note that for each subject in the bootstrap sample, the vector of measurements is preserved.
- Calculate the sample statistic using the bootstrap sample \mathbf{X}^{*b} . For example, to compare measurement parameter j with measurement parameter k , extract the corresponding values from the bootstrap data: $\mathbf{u}^{*b} = (m_{i1,j} \dots m_{iS,j})^T$ and $\mathbf{v}^{*b} = (m_{i1,k} \dots m_{iS,k})^T$. Then, calculate t^{*b} = paired t-test comparison of \mathbf{u}^{*b} and \mathbf{v}^{*b} .
- Perform hypothesis test using t-statistic: if $t^{*b} > t(1-\alpha, S-1)$, then $H = 1$; else, $H = 0$.
- Accumulate statistical power estimate: power(S) = power(S) + H / N_{Boot} .
- Repeat steps 3-7 for N_{Boot} bootstrap iterations.
- Go to step 2 for new sample size S .

Results: Figs. 1 and 2 are plots of statistical power (y-axis) vs. sample size (x-axis). Fig. 1 is the graph for area of activation (voxel count [VC]), and Fig. 2 is the plot for intensity of activation (area-under-the-curve [AUC]). Each line corresponds to a statistical hypothesis test, such as 3 Hz < 10 Hz (red line).

Conclusion: The BOLD activation area VC parameter (Fig. 1) has a higher statistical power than the BOLD intensity AUC parameter for all hypotheses tested. This demonstrates a fundamental limitation of the BOLD intensity measurement for detecting differences in underlying neuronal activity. The range of the BOLD intensity signal change is on the order of 1–3% in rats and may not be large enough to detect subtle differences. The S1FL region has a much larger voxel area (around 500 voxels) and has a much larger range to work with. This study demonstrates that using a larger sample size is preferable to past studies that have typically used sample sizes in the 5–10 rat range.

References: 1.) Hyder, F. JC BFM. 14, 649-55. 1994 2.) Van der Linden, A. NMR in BioMed. 20, 522-45. 2007. 3.) Rao S. JCBFM. 16, 1250-54. 1996.

Fig. 1: Statistical power for area of activation (VC).

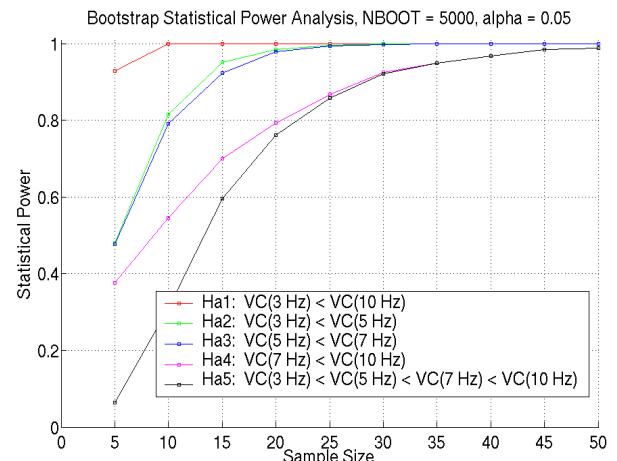


Fig. 2: Statistical power for intensity of activation (AUC).

