BIASLESS: Detecting Brain Activation in fMRI Data Without Prior Knowledge of Mental Event Timing

David N. Levin and Stephen J. Uftring
Department of Radiology, University of Chicago, Chicago, IL 60637

Introduction: Activation is often identified in fMRI data by assuming that the temporal waveform of an activated voxel resembles a certain reference waveform (1). The latter is usually taken to be the convolution of an impulse function (the putative hemodynamic response) with a "timing" function that represents the hypothesized temporal sequence of mental events. For example, the timing function may be taken to be a series of step functions or spikes, representing mental events occurring in "block" or "single trial" protocols, respectively. Clearly, these methods may fail to detect activation at unanticipated times. Furthermore, these techniques may fail if the actual hemodynamic response function differs from the assumed one and/or if the linearity (convolution) assumption is violated (2).

This paper describes how to analyze fMRI data without making any of these assumptions. Instead, our analysis is based on the following simple premise: the time course of signal in activated voxels will not vary significantly when a given task protocol is repeated by the same individual or when the same task protocol is performed by different individuals. We refer to the new method as BIASLESS because it attempts to achieve Biasless Identification of Activated Sites by Linear Evaluation of Signal Similarity. The technique is illustrated by using it to detect brain activation during hand sensorimotor tasks in both block and single trial protocols.

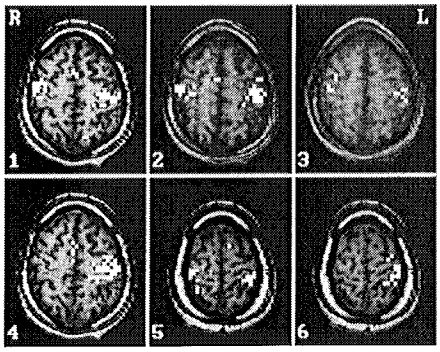
Methods: In the "block" protocol experiment, each of three normal right-handed subjects (two males, one female) underwent two consecutive fMRI scans (T2* echo planar axial images) while performing a hand-clenching task. Scans were performed on a 1.5 T Signa (GE) scanner (TR/TE 5000/60, 20 slices with 7 mm slice thickness and 1 mm inter-slice spacing, 240 mm FOV, 64 x 64 matrix). During each scan the subject was asked to quickly clench and unclench one (or both) hands in synchrony with visual cues that were flashed on a screen every second (the words "right" or "left" or "right and left"). Each 6-minute scan was divided into 12 blocks of 30 s duration (4 "right", 2 "left", 2 "right and left", 4 rest), which were in the same intermixed sequence for all scans. The 72 volumes of image data from each scan were registered (3), transformed into a Talairach coordinate system, resampled on a 4 x 4 x 4 mm grid, and linearly "detrended" on a voxel-by-voxel basis. We computed the correlation coefficient (*cc*) between time series at identical Talairach coordinates for each pair of scans (same subject or different subjects). According to the BIASLESS criterion, activated voxels were required to exceed a *cc* threshold and be part of a cluster of 5 or more contiguous voxels. For comparison, each data set was also used to identify clusters of voxels that contained signals significantly correlated with a block-like reference waveform describing the periods of right hand motion (with or without left hand motion).

The two male subjects also underwent two consecutive fMRI scans with the above scan parameters while performing hand clenching according to a "single trial" protocol. Specifically, they performed a single act of clenching/unclenching (right or left hand) whenever they saw the appropriate word ("right" or "left") flashed on the screen. During each 6-minute scan, they were given 24 such cues (12 "right", 12 "left") in the same randomized sequence. The above-described BIASLESS method was applied to each pair of scans (same subject or different subjects) to identify activated voxels: i.e., voxels at identical locations that contained correlated signals and met a cluster criterion. Each activation map in this report was superposed on the average anatomical image of the subjects whose fMRI signals contributed to that map.

Results: Figure 1 is the BIASLESS activation map of voxels in which correlated signals ($cc > 0.6$) were generated by the two block protocols performed by subject 1. Figure 2 is the BIASLESS activation map of voxels that were correlated ($cc > 0.4$) during the block protocols performed by subjects 1 and 2. Figure 3 is the BIASLESS activation map showing voxels in which there was correlation ($cc > 0.25$) between *all pairs* of signals generated by the three subjects who performed the block protocol. *All three of these maps demonstrate activation of the bilateral hand sensorimotor areas, despite the fact that they were created without any prior knowledge of the nature or timing of metal events.* Figure 4 is an activation map of voxels in subject 1 that contained signals correlated ($cc > 0.5$) with the block reference waveform describing right hand movement. This commonly used method reveals the activation of the left sensorimotor cortex, but it fails to detect the activation of the right sensorimotor cortex because of the "biased" nature of the reference waveform.

Figure 5 is the activation map generated by applying the BIASLESS method ($cc > 0.45$) to the two single trial protocols performed by subject 1. *Notice that activation was detected in bilateral sensorimotor cortices without the use of prior knowledge of the timing or nature of mental events.* Figure 6 shows voxels in subject 1 that contained signals correlated ($cc > 0.4$) with a block reference waveform describing instances of right hand movement during the single trial protocol. Although the activation of the left sensorimotor cortex is seen, this method fails to reveal the activation in the opposite hemisphere because the reference waveform was designed to detect mental events coincident with right hand motion.

Conclusions: Unlike several commonly-used techniques for analyzing fMRI data, the BIASLESS method can detect brain activation without making detailed prospective assumptions about the timing of mental events. Furthermore, BIASLESS is not dependent on specific assumptions about the shape or linearity of the BOLD response to stimuli, as long as that response is reproducible between scans. This suggests that the BIASLESS approach could be used to "screen" fMRI data in order to detect tissue that is activated and has unanticipated time courses. Then, the temporal waveform at activated sites can be examined retrospectively in order to understand the nature of that activity.



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