Improving Sensitivity and Specificity in BOLD fMRI Using Simultaneous Multi-Slice Acquisition

Richard D. Hoge[1]; AmanPreet Badhwar[2]; Julien Doyon[2]; David Ostry[3,4]

[1] McConnell Brain Imaging Centre, Montréal Neurological Institute, Deptartment of Neurology & Neurosurgery, McGill University, Montreal, Quebec, Canada
[2] Unité de Neuroimagerie Fonctionnelle, Institut Universitaire de Gériatrie de Montréal, Université de Montréal, Montreal, Quebec, Canada
[3] Deptartment of Psychology, McGill University, Montreal, Quebec, Canada
[4] Haskins Laboratories, New Haven, CT, USA

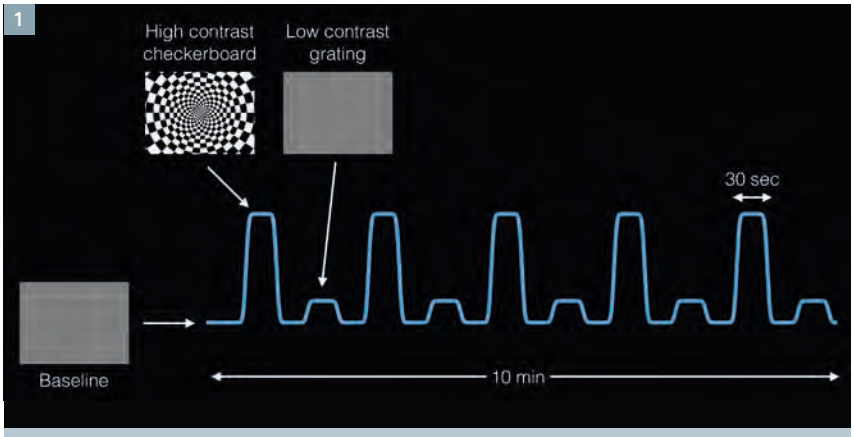
Abstract

Functional MRI techniques, which involve rapid serial imaging of the brain to detect activation-induced changes, have always placed high demands on the speed, precision, and stability of MRI systems. This is particularly true of studies requiring high spatial resolution, due to the dramatic reduction in signal amplitude with decreasing voxel volume. Recent developments in simultaneous multi-slice (SMS) encoding promise to have a major impact on functional MRI. Current trends in MRI system hardware will help maximize this impact, and expand the range of fMRI applications that are feasible in clinical practice and basic research. In this article, the authors discuss the advantages of highly accelerated fMRI and show example images from a visual activation paradigm. The future benefits of this technology include the ability to perform pre-surgical mapping with high reliability and detail, with clinically feasible exam times.

Introduction

Conventional echo-planar imaging (EPI), which has been widely adopted for functional imaging of the brain over the last decade, has typically acquired multiple 2D slices in a rapid sequence whose minimum duration is limited by the echo-time (TE) required for sensitivity to blood oxygenation, the EPI readout length, and the number of slices required. This has generally meant that, despite advances in parallel imaging that can shorten single-slice readouts, the minimum time needed to image the entire brain with typical slice thicknesses has been on the order of two seconds or more. Simultaneous multi-slice imaging removes this limitation, reducing the number of TE delays required to image the entire brain while preserving the necessary T2*-weighting.

To understand the benefits of slice-accelerated fMRI, it is helpful to recall that sensitivity in functional MRI depends ultimately on the ratio between a given functional effect size and the degree of unrelated measurement variability. This measurement variability, or noise, arises from three main sources: 1) so-called 'thermal' noise; 2) physiological fluctuations in the subject; and 3) instrumental instability. Thermal noise is physically unavoidable in electronic measurements conducted above absolute zero, but as uncorrelated Gaussian noise its impact can be systematically reduced through signal averaging or increasing the size of image voxels. Physiological fluctuations in the subject, such as cardiac or respiratory cycles, are evidently difficult to eliminate but it is possible to control for their effects through physiological noise modelling methods [1]. Instrumental instability can contribute low level signal fluctuations that, while not necessarily dominant in standard BOLD fMRI acquisitions, can limit the



1 Stimulation paradigm with high and low-intensity visual stimulation. All condition blocks were 30 seconds long, with a total run duration of ten minutes.

SNR gains achievable by managing the other noise sources. Optimizing sensitivity in fMRI generally involves identifying the dominant noise source in a particular application and reducing it until other types of noise become significant.

Acquisition speed in fMRI

In typical BOLD fMRI experiments (3 Tesla, ~3 mm resolution, 2-3 second repetition time), physiological noise is by far the dominant noise source [2]. Because of this, it has been noted that BOLD fMRI time series commonly exhibit a high degree of temporal autocorrelation [3]. This would suggest that there is little statistical power (and hence sensitivity) to be gained through increases in imaging rate, since faster sampling of an autocorrelated signal does not necessarily increase the number of independent samples. However, this reasoning applies only in the case where autocorrelated physiological noise is dominant. Indeed, the popularity of 3T fMRI at an isotropic resolution of 3 mm is likely due to the fact that further reductions in voxel size lead to a relatively precipitous drop in SNR. This drop is due to the third power loss of signal with voxel volume, which results in a shift to thermal noise as the predominant source of signal fluctuation. Conversely, increases in voxel size above 3 mm yield little improvement in signal stability, because uncontrolled physiological fluctuations are already the dominant noise source. With this in mind, it becomes apparent that acquisitions in which uncorrelated thermal noise is dominant may still stand to benefit significantly from increases in imaging rate. At 3T, this is true for situations including high spatial-resolution BOLD fMRI (e.g. ≤2 mm) and arterial spin-labeling, in which the labeling signal is generally much smaller than typical BOLD effect sizes.

Simultaneous multi-slice acquisition

While imaging rates attainable in fMRI applications have been fairly constant for many years, a recent resurgence in simultaneous multi-slice (SMS) encoding techniques has created exciting possibilities for highly accelerated functional imaging. The general concept was proposed as early as 2001 [4] but has become practical only more recently with the emergence of techniques for managing issues such as voxel tilting and aliasing [5]. SMS encoding allows substantial increases in imaging rate compared with standard sequential multi-slice methods. It is based on the parallel imaging approach [6], in which the spatial information provided by an array of localized RF coil elements is used to reduce the number of 2D Fourier samples required to generate an unaliased image. While parallel imaging has been in use for nearly a decade to reduce the time needed for standard multi-excitation images, its impact on the single-excitation readouts used for BOLD fMRI has been limited due to the need for a relatively long post-excitation echo-time (TE) in each slice, in order to achieve the T2*-weighting required for sensitivity to blood oxygenation. The advance enabled by SMS encoding has been preservation of the long TE needed for BOLD fMRI while reducing the impact of this delay on the total time needed to cover the entire brain. The result is that whole-brain acquisitions formerly requiring up to three seconds can now be performed in less than half a second. This corresponds to a factor of six or more increase in the number of images acquired per unit time, which can have a substantial impact on statistical power particularly when thermal noise is dominant. A well-known application of this has been the use of an 8x slice acceleration factor to achieve 2 mm isotropic resolution with excellent sensitivity in the Human Connectome Project (HCP) [7].

Methods

To better understand the performance gains achievable using SMS in task activation studies, the authors have performed a systematic assessment of BOLD fMRI sensitivity using a range of acceleration factors and functional effect sizes, in both thermal and physiological noise-dominated regimes. In these tests healthy human subjects underwent a visual activation study including blocks of intense visual stimulation using a high luminance-contrast radial checkerboard modulated in a temporal squarewave, as well as much weaker stimulation using low-contrast sinusoidal gratings drifting slowly across the visual field (Fig. 1). This allowed sensitivity and specificity to be assessed under conditions of both high and low-amplitude effects. The acquisitions were repeated with larger (3 mm) and smaller (2 mm) isotropic voxels sizes, to create conditions under which physiological and thermal noise are respectively dominant.

Experiments were conducted on a 3T Siemens scanner (MAGNETOM Trio, A Tim System), running software release *syngo* MR B17, and the 32-channel head coil. For comparison against accelerated acquisitions, a standard gradient-echo EPI/BOLD sequence with TR 3 s, TE 30 ms, α 90° was used as a reference. Resolutions of 3 mm isotropic and 2 mm isotropic were acquired, with respective matrix sizes of 64 x 64 and 100 x 100. The 3 mm isotropic scans had 42 slices, while the 2 mm scans had 30 slices due to the longer readout required at the higher resolution. In addition to these standard scans, both resolutions were also repeated with a slice acceleration factor of 6x using a WIP sequence[1]. The number of time points acquired over the ten minute stimulation protocol was 200 for the non-accelerated sequence, with 1,200 time points for the 6x SMS scan. The TR values for the accelerated scan was 0.5 s, and the flip angle was adjusted to the Ernst angle assuming the T1 of grey matter, corresponding to a flip angle of 45°.

[1] The product is still under development and not commercially available yet. Its future availability cannot be ensured.

All image time-series were processed using in-house software used for quantitative image analysis. Motion correction was performed, followed by spatial smoothing with 3D Gaussian kernels with FWHM values of 6 mm for the 3 mm scan and 4 mm for the 2 mm acquisition. Smoothing was performed at these widths because they were found to provide an optimal compromise between sensitivity, specificity, and spatial resolution. Following preprocessing, the time series data were fit using a General Linear Model (GLM) including separate regressors for the high and low-amplitude stimulation. T statistics were computed by dividing estimated effect sizes by the residual standard error assuming uncorrelated residuals. The resultant T values were converted to the negative logarithm of the p value, -log(p), based on the nominal degrees of freedom in the time series. Neglecting autocorrelations in the data can result in exaggerated significance levels, but the errors are modest in the standard fMRI scans, particularly for the 2 mm acquisitions. The importance of autocorrelation may be further reduced due to the attenuation of steady-state magnetization at the shorter TR values. The maps of -log(p) are referred to as significance maps in the remainder of this article.

Results

Figure 2 shows unthresholded significance maps for 3 mm scans overlaid in false color on the grayscale EPI scans for reference. Maps are shown for standard and accelerated scans, and for high and low-intensity stimulation. The color legend has been matched in all maps to allow comparison of apparent significant levels, although autocorrelated noise might artificially boost the values in the accelerated scans. Nonetheless, the region of visual activation is extremely well delineated in the accelerated scans, for both levels of stimulus intensity. Extents of activation appeared less clearly in the maps computed from non-accelerated data, although this might simply have reflected the dynamic range chosen.

Because of the potential for exaggeration of significance levels in the accelerated scans, and the clear difference in dynamic range, we also assessed activation maps with the color legends adapted to the respective maps. These alternatively displayed maps (also for 3 mm scans) are shown in Figure 3. By 'zooming' the dynamic range for the non-accelerated maps, the location and extent of active areas is indeed more apparent. However, this also amplifies the background noise (random fluctuations in the significance level following its distribution under the null hypothesis) and it can be seen that the sensitivity and spatial specificity of the accelerated maps remains superior.

Although the spatial specificity afforded by slice acceleration in the unthresholded maps shown in Figures 2 and 3 is striking, fMRI has customarily involved thresholding of activation maps after correction of significance values for the multiple comparisons inherent in image data. To assess the performance gains of SMS acquisition in this setting, the significance maps for 3 mm scans were thresholded using the false discovery rate (FDR) approach, with a threshold of 0.001. The thresholded maps are shown in Figure 4, which reveals that the non-accelerated scan failed to detect the weak activation associated with the low-contrast grating. It should be noted that relaxing the threshold sufficiently to

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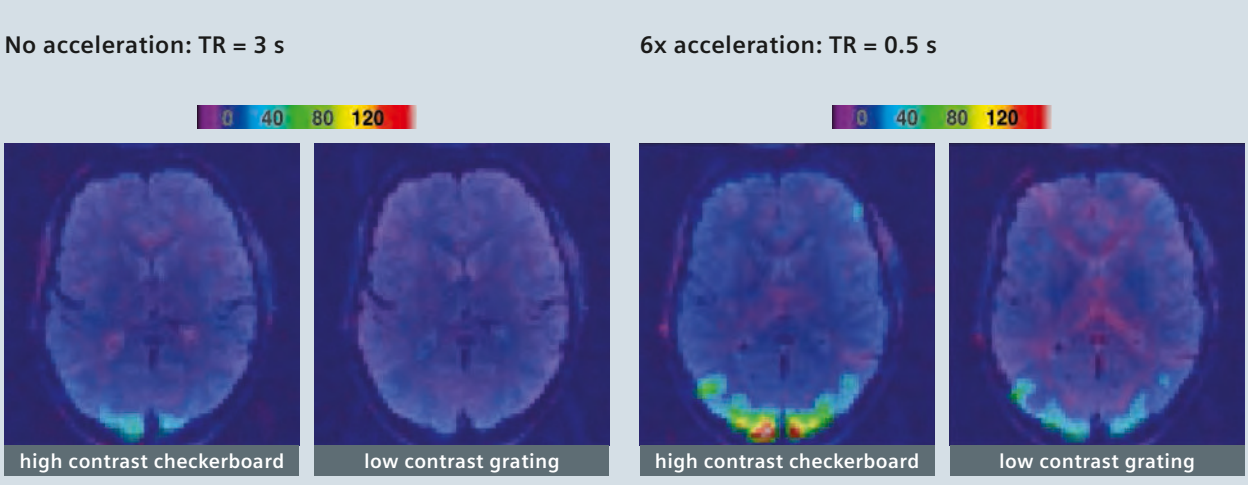

2 Significance maps for high and low-intensity stimulation, with 1x and 6x acceleration at 3 mm isotropic resolution (before smoothing). False colour significance maps are overlaid on greyscale EPI scans. Dynamic range of colour legend is equalized for both acquisitions.

reveal the patch of weak activation in the low-contrast, non-accelerated scan also resulted in the appearance of substantial swaths of non-visual artifact.

In addition to apparent improvements in the sensitivity and specificity of 3 mm scans, we also noted significant improvements in the higher resolution 2 mm scans. Figure 5 shows significance maps for the high-contrast stimulus, acquired at 2 mm resolution with and without acceleration. While the occipital visual response is readily detected in both cases, careful inspection of the maps reveals that the accelerated maps provide considerably improved delineation of cortical activation. In the maps acquired with acceleration, much of the cortical ribbon can be clearly discerned in the activation pattern, with robust specificity against background fluctuations.

Discussion and conclusions

The results shown above demonstrate that slice acceleration can substantially improve the sensitivity, specificity, and spatial detail of BOLD functional MRI. Despite concerns that gains might be limited due to autocorrelated noise, the unthresholded maps suggest that the apparent improvements reflect more than simple boosting of significance caused by inflated degrees

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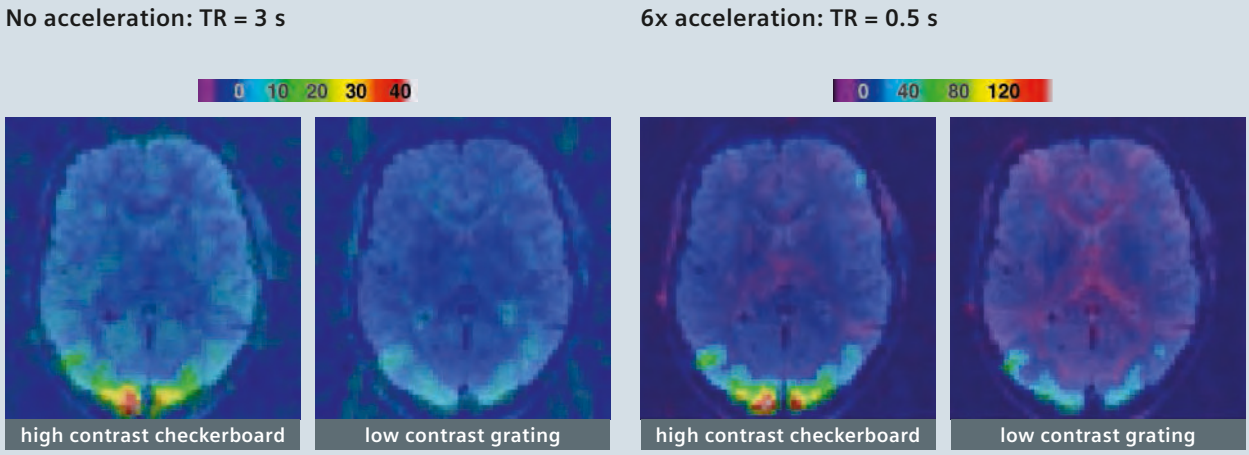

3 Significance maps for high and low-intensity stimulation from 3 mm scans, with colour legend adapted to dynamic range of respective acquisitions.

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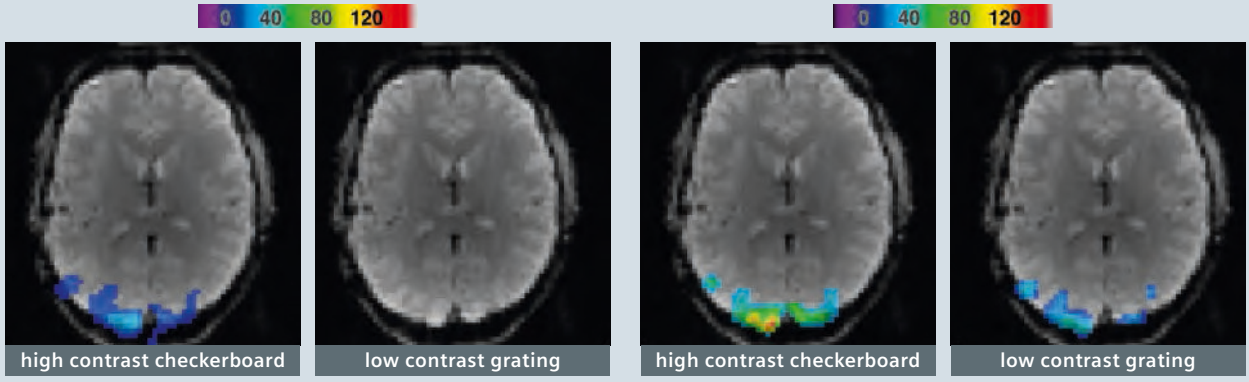

4 Significance maps for high and low-intensity stimulation during 3 mm scans, thresholded at FDR 0.001.

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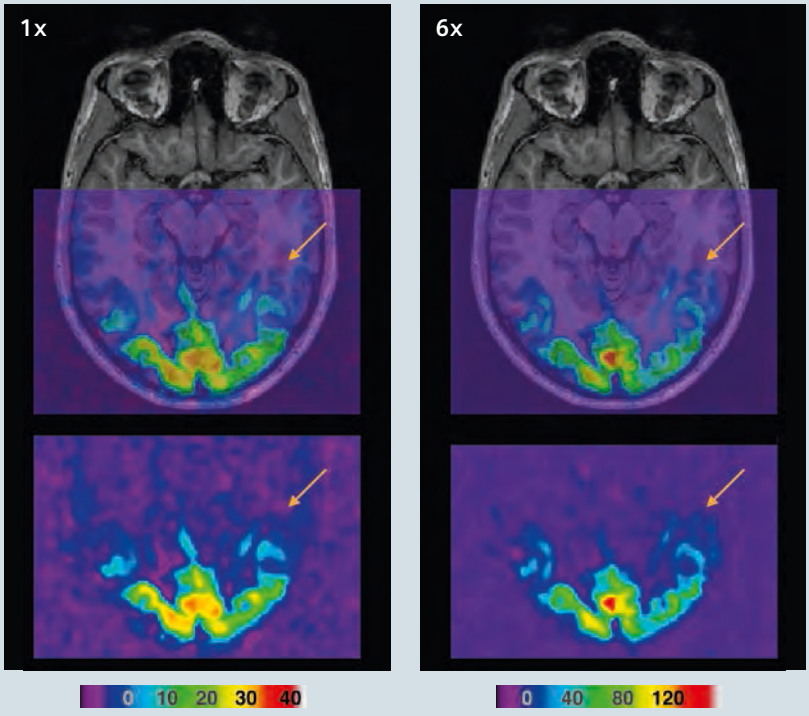

5 Significance maps high-intensity stimulation, based on 2 mm isotropic data. The orange arrows indicate a section of cortical ribbon that can be readily delineated in the 6x accelerated scan. Top row shows false color significance maps overlaid on greyscale T1-weighted scan. Bottom row shows unthresholded activation map alone.

of freedom. For clinical applications in which averaging over repeated fMRI runs is not feasible, these capabilities offer significant advantages. An obvious example is pre-surgical mapping, in which functional images of high reliability must be acquired in a relatively short time.

During the planning and optimization of protocols, considerable effort was devoted to finding suitable readout characteristics such as bandwidth, echo spacing, and matrix size. Improvements in gradient technology should increase the flexibility with which SMS techniques can be applied, while preserving and even improving image quality. A second challenge met during these experiments was related to the long reconstruction times required to generate images from the SMS raw data. Here too, improvements in scanner technology to cope with the greatly increased data throughput and complexity will play an important role.

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Contact

Richard Hoge
Room WB316
McConnell Brain Imaging Centre
Montreal Neurological Institute
3801 University Street
Montreal, Quebec H3A 2B4, Canada
Phone: +1 (514) 398-1929
Fax: +1 (514) 398-2975
rick.hoge@mcgill.ca