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Separating slow BOLD from non-BOLD baseline drifts using multi-echo fMRI

Jennifer W. Evans [a,*], Prantik Kundu [a], Silvina G. Horovitz [b], Peter A. Bandettini [a]

[a] Section on Functional Imaging Methods, LBC, NIMH, NIH, Bethesda, MD, USA
[b] Human Motor Control Section, MNB, NINDS, NIH, Bethesda, MD, USA

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ABSTRACT

The functional magnetic resonance (fMRI) baseline is known to drift over the course of an experiment and is often attributed to hardware instability. These ultraslow fMRI fluctuations are inseparable from blood oxygenation level dependent (BOLD) changes in standard single echo fMRI and they are therefore typically removed before further analysis in both resting-state and task paradigms. However, some part of these fluctuations may be of neuronal origin, as neural activity can indeed fluctuate at the scale of several minutes or even longer, such as after the administration of drugs or during the ultradian rhythms. Here, we show that it is possible to separate the slow BOLD and non-BOLD drifts automatically using multi-echo fMRI and multi-echo independent components analysis (ME-ICA) denoising by demonstrating the detection of a visual signal evoked from a flickering checkerboard with slowly changing contrast.

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Introduction

The functional magnetic resonance imaging (fMRI) baseline is known to drift over the course of an experiment (Aguirre et al., 1997; Zarahn et al., 1997). These drifts are nonlinear, vary by voxel, and are difficult to distinguish from slow changes in brain response to pharmaceutical drugs (Wise et al., 2004) or spontaneous fluctuations in the resting state (Biswal et al., 1995). They are attributed to scanner instability (Smith et al., 1999), pooling of blood in veins (Lee et al., 1995), subject motion and incomplete motion correction (Bandettini et al., 1993), and brain physiology changes (Yan et al., 2009). In standard single echo blood oxygen level dependent (BOLD) fMRI, the non-BOLD drifts are inseparable from the data making the detection of slow BOLD related change difficult. We show that it is possible to do this with multi-echo (ME) fMRI.

Common approaches to remove drift in preprocessing of single echo fMRI data have involved using linear, low-order polynomial or spline models (Bandettini et al., 1993; Liu et al., 2001; Kay et al., 2008), high pass filtering (Lund et al., 2006), or ICA component removal (Thomas et al., 2002). Improper modeling and removal of drifts affects the sensitivity of the statistical results (Lowe and Russell, 1999) and also limits the task or frequencies which can be measured in these experiments. For task paradigms the strategy has been to use box-car and repetitive event designs using frequencies that exceed scanner drift frequencies (Birn et al., 2002). For resting state scans, the data are typically band-pass filtered to remove frequencies that are deemed unlikely to be functionally relevant (Cordes et al., 2001). However, these approaches do not work in the case of an experiment that has only one transition (e.g. bolus injection of a drug) or very slow changes (sleep, circadian rhythms, transcranial magnetic stimulation (TMS)). In these cases it is particularly important to properly model the baseline changes in order to accurately measure the desired BOLD responses, which is complicated by long run lengths and potentially coupled subject motion.

There are several dual-echo techniques that have been proposed that attempt to capture baseline drift in a very short echo acquired in the space before the standard echo (Talagala et al., 1999; Bright and Murphy, 2013; Ing and Schwarzbauer, 2012). However, there will always be some BOLD weighting in the measured short echo time series due to the long acquisition window required to obtain the images, which increases the effective echo time (TE). Speck and Hennig (1998) used an eight echo acquisition to simultaneously map both T_2^* and spin density or inflow effects over a few slices in the brain. The ability to calculate both of these parameters at every time point comes at the cost of reduced brain coverage and increased repetition time due to the large number of echoes required to obtain good simultaneous parameter estimates. This makes the method difficult to extend to cognitive studies, which typically require whole brain coverage. An alternate MRI functional imaging technique that intrinsically measures a quantitative baseline is arterial spin labeling (ASL) (Aguirre and Detre, 2012). ASL time series do not exhibit signal drifts owing to the subtraction of the control and tag images to generate flow images. Wang et al. (2003) demonstrated the benefits of using ASL for long task block lengths and runs separated in time by over 2 min in length. Notably, the BOLD data in this study was high-pass filtered and inherently limited their ability to detect the longer block tasks. However, the reduced coverage, slower measurement times, and lower signal-to-noise ratio

* Corresponding author at: 10 Center Dr., Bldg. 10, Rm 1D73, Bethesda, MD 20892, USA.
E-mail address: jennifer.evans@nih.gov (J.W. Evans).

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(SNR) of ASL, as compared to BOLD fMRI, remain problematic for applications to many studies (Wang et al., 2011). Furthermore, the insensitivity of ASL to slow motion and drifts is at the expense of enhanced motion sensitivity to short-term motion on the time scale of the TR arising from the pairwise image subtractions.

Improvements in imaging acquisition have made it possible to trade high resolution single echo images for coarser resolution at multiple echo times per repetition with minimal sacrifice in repetition time (TR) and spatial coverage for fMRI (TEs: 14,30, 46 ms, 2 s TR, 28 slices with cubic resolution of 3.5 mm, for example). Multi-echo acquisition enables the measurement of TE-dependence of the signal (Peltier and Noll, 2002) but is still more frequently used in quantitative $T2^*$ measurements than in fMRI (Gowland and Bowtell, 2007). In the context of fMRI, the acquired echoes are typically combined to improve the overall image SNR and recover signal dropout (Posse et al., 1999; Poser et al., 2006). The recently developed multi-echo independent components analysis (ME-ICA) denoising method (Kundu et al., 2013) uses TE-dependence throughout the analysis pipeline to separate the data into primarily BOLD and non-BOLD subspaces in an automatic, data driven way that is based on the principles of BOLD contrast. ME-ICA differs from other automated ICA component selection methods in that no restrictions are placed on the time–frequency or anatomical localization characteristics of the components in the selection process. Therefore, it has the potential to separate artifactual, hardware-related drifts, which would fall into the non-BOLD subspace, from hemodynamic signal changes that are likely of neuronal relevance. Importantly, this enables study of low-frequency BOLD components that would ordinarily be discarded in the band-pass filtering step that is conventionally applied during preprocessing.

In this study, we use a visual task with slowly changing contrast over 5 min as an example of a slow BOLD change and we compare conventional preprocessing to ME-ICA denoising. As well, we investigate the temporal, amplitude properties of the time series and the sensitivity of the methods in differentiating two slow slope changes. We demonstrate the ability to separate the sigmoid task response from baseline drifts using ME-ICA denoising in a case where the task is undetectable in conventionally preprocessed data.

Methods

Subjects

Fifteen healthy volunteers (aged 21–39, 8 males) participated in this study. Informed consent was obtained for each subject in accordance with the Combined Neuroscience Institutional Review Board of the National Institutes of Health. Subjects were instructed to remain awake, lie still and fixate on the cross in the center of the screen during all visual tasks. The entire experiment had a duration of an hour and a half of imaging, which consisted of one anatomical and seven functional scans.

MR Image acquisition

Scanning was performed on a 3T Skyra (Siemens GmBH, Germany) using a 32 channel head coil. A whole brain 3D T1 MPRAGE anatomical scan was performed with a cubic resolution of 1 mm (TR: 2.5 s, TI: 1.1 s, TE: 5.4 ms, flip angle: 7°), matrix 256 × 256 × 256, field-of-view 25.6 cm, 6 min, followed by a 10 minute resting state scan and 7.5 minute multi-echo EPI fMRI visual tasks with scan parameters of TE: 13, 30, 43 ms, TR: 2 s, at a cubic resolution of 3.5 mm with GRAPPA acceleration factor 2 over 28 slices covering the whole brain (flip angle 90°, matrix 64 × 64, field-of-view 22.4 cm, interleaved slice acquisition). Four dummy scans preceded each run to ensure steady-state equilibration for the saved data. Respiratory and cardiac traces were recorded using respiratory bellows and pulse oximeter with AcqKnowledge software (BIOPAC Systems Inc., Goleta, CA).

Visual contrast tasks

The visual stimuli consisted of a full visual field checkerboard reversing from black to white at a rate of 7.5 Hz. The timing and amplitude of the stimuli are illustrated in Fig. 1 and consist of a) a contrast localization run with 15 s blocks of one of four different contrast levels: 2.5%, 5%, 20%, and 100%, alternating with a fixation cross (0% contrast), there are a total of 16 contrast blocks or four repetitions of each contrast b) a long block of 80 s at 20% contrast followed by 80 s of fixation (0% contrast) c) a long block of 80 s at 5% contrast followed by 80 s of fixation d) a shorter block of 60 s at 20% contrast followed by 100 s of fixation e) a sigmoid ramp (at slope of −1/40) from 20% to 0% contrast over the course of 2 min and f) a sigmoid ramp (at a slope of −1/60) from 16% to 0% contrast transition over the course of 5 min. Instructions to fixate on the cross in the middle of the checkerboard were reiterated between scans to ensure the subject remained awake and on task for the duration of the experiment. The flanking pairs of 15 s blocks at 80% in each task served as an embedded vigilance check for task compliance and are not explicitly considered further.

Preprocessing

Processing of the fMRI data was performed using AFNI (Cox, 1996), compile date: 17 Dec, 2013. Each echo was pre-processed separately as described below prior to ME-ICA denoising.

Single echo

The anatomical image was first skull-stripped and then warped to Talairach coordinates (auto_tlrc, TT_N27 template). The anatomical image was then registered to the first frame of the middle echo (30 ms) data and 12 parameter affine coregistration was computed using the local Pearson correlation (LPC) cost function (Saad et al., 2009) with the gray matter segment of the EPI base image (3dSeg) as the LPC weight mask. Motion correction (3dvolreg) for all echoes was performed using the first frame of the middle echo as reference. The estimated six-parameter rigid body motion parameters were combined with the anatomical–functional coregistration parameters into a single alignment matrix. The images from each TE were slice-time corrected (3dTshift) and subsequently simultaneously motion corrected and spatially aligned (3dvolreg) using the combined alignment matrix.

Optimal echo combination

The optimal echo time for imaging the BOLD effect is where TE equals T_2^*, however, T_2^* varies across the brain and as such, single echo images are not optimally sensitive to this variation. The acquisition of multiple echoes enables the calculation of an "optimal" T_2^* weighted average of echoes that recovers signal in drop-out areas and improves contrast-to-noise (CNR) ratio throughout the brain (Posse et al., 1999; Poser et al., 2006). The optimal echo combination (OC) as found in Poser et al. (2006) used here is described below.

The signal at an echo, n, varies as a function of the initial signal intensity S_o and transverse susceptibility $T_2^* = 1 / R_2^*$ and is given by the mono-exponential decay:

$$S = S_o \cdot e^{-TE_n/T_2^*} \tag{1}$$

which can be linearized to simplify estimation of T_2^* and S_o as the slope and intercept of a line by least squares fitting:

$$ln(S) = ln(S_o) - TE_n \cdot R_2^* \tag{2a}$$

$$T_2^* = -\frac{TE_n}{ln(S/S_o)} \tag{2b}$$