NeuroImage 49 (2010) 457–466

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

BOLD fMRI using a modified HASTE sequence

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ARTICLE INFO

Article history:
Received 13 April 2009
Revised 16 July 2009
Accepted 17 July 2009
Available online 28 July 2009

Keywords:
BOLD
Functional MRI
Turbo spin echo
GRAPPA
Neuronal localization

ABSTRACT

For more than a decade, turbo spin echo (TSE) pulse sequences have been suggested as an alternative to echo planar imaging (EPI) sequences for fMRI studies. Recent development in parallel imaging has renewed the interest in developing more robust TSE sequences for fMRI. In this study, a modified half Fourier acquisition single-shot TSE (mHASTE) sequence has been developed with a three-fold GRAPPA to improve temporal resolution as well as a preparation time to enhance BOLD sensitivity. Using a classical flashing checkerboard block design, the BOLD signal characteristics of this novel method have been systematically analyzed as a function of several sequence parameters and compared to those of gradient-echo and spin-echo EPI sequences. Experimental studies on visual cortex of five volunteers have provided evidence suggesting that mHASTE can be more sensitive to extra-vascular BOLD effects around microvascular networks, which leads to more accurate function localization. The studies also show that the activation cluster size in mHASTE increases with the refocusing RF flip angle and TE while decreasing with the echo number (n_{center}) used to sample the *k*-space center. Compared to spin-echo EPI, mHASTE incurs an ~50% reduction in activation cluster size and an ~20% decrease in BOLD contrast. However a higher signal-to-noise ratio and a spatially more uniform temporal stability have been observed in mHASTE as compared to the EPI sequences when the scan times are held constant. With further refinement and optimization, mHASTE can become a viable alternative for fMRI in situations where the conventional EPI sequences are limited or prohibitive.

Introduction

Since the introduction of blood oxygen level dependent (BOLD) contrast in early 1990's (Kwong et al., 1992; Ogawa and Lee, 1990; Ogawa et al., 1993), functional MRI (fMRI) based on BOLD (Kwong et al., 1992; Ogawa et al., 1992) has been widely used in research and clinical applications. BOLD contrast relies on regional magnetic susceptibility changes resulting from variations in deoxyhemoglobin concentration related to brain activities. Such changes occur in both brain parenchyma (e.g., the gray matter) and blood, making fMRI signals sensitive to not only neuronal activation but also to hemodynamic modulations (e.g., blood flow) (Ogawa and Lee, 1990; Ogawa et al., 1993).

Gradient-echo echo planar imaging (GE-EPI) is the most commonly used technique for BOLD fMRI due to its high data acquisition efficiency, high sensitivity to T_2* effects, and low specific absorption rate (SAR) at high magnetic fields (e.g., ≥3 T). However, as GE-EPI signal is also sensitive to T_2* changes in and around draining veins (Boxerman et al., 1995; Duyn et al., 1994; Kim et al., 1994; Lai et al., 1993; Lee et al., 1995; Menon, 2002; Segebarth et al., 1994; Ugurbil et al., 2000), a mismatch between the observed BOLD signals and the actual neuronal activities can occur, which compromises function localization. To address this problem, EPI based on spin echoes (SE) featuring a mixture of T_2 and T_2* contrast has been employed by a number of groups (Bandettini et al., 1994; Jones et al., 1998; Lowe et al., 2000; Norris et al., 2002; Oja et al., 1999; Parkes et al., 2005; Thulborn et al., 1997; van Zijl et al., 1998). The benefits of SE-EPI in function localization can be further enhanced at high fields (e.g., ≥3 T) where extra-vascular (EV) BOLD effects (mainly through diffusion-facilitated dynamic averaging) become more dominant (Duong et al., 2002; Ugurbil et al., 2003; Yacoub et al., 2003, 2005; Zhao et al., 2004). With a refocusing pulse, SE-EPI refocuses the intravascular (IV) static dephasing effects (especially those in large veins), leading to BOLD signals weighted more towards the microvasculature networks which correlate more closely with neuronal activities. Although the overall BOLD contrast is reduced in SE-EPI, the functional specificity can be greatly improved. Additionally, the dephasing effects caused by both

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doi:10.1016/j.neuroimage.2009.07.044

main magnetic field inhomogeneities and magnetic susceptibility variations are also reduced, alleviating problems with signal voids and image distortions commonly seen in GE-EPI.

The benefits of SE-EPI can in principle be further enhanced by employing multiple RF refocusing pulses. For more than a decade, several groups have devoted considerable efforts to developing and demonstrating turbo spin echo (TSE) methods for fMRI. Constable et al. (1994) and Gao et al. (1995) both showed that fully sampled multi-shot TSE was capable of performing BOLD fMRI with high in-plane resolution at 1.5 T or 1.9 T. By introducing an extra time interval to incorporate T_2* weighting into the TSE signal, BOLD signal detection with U-FLARE (i.e., a single-shot TSE sequence) has been demonstrated (Niendorf, 1999; Norris et al., 1993) and analyzed in a recent paper (Norris, 2007). With a bolus injection, Koshimoto et al. showed that half Fourier acquisition single-shot TSE (HASTE) may even outperform gradient-echo methods in absolute quantifications of capillary blood volume and flow (Koshimoto et al., 1999). Recently, HASTE was combined with SENSE (Pruessmann et al., 1999) to obtain temporal resolution and BOLD sensitivity very close to those of SE-EPI (Poser and Norris, 2007a, b).

These promising results of TSE-based fMRI methods have motivated us to further develop a TSE method to take advantage of the specificity in functional localization with improved BOLD sensitivity while maintaining an adequate temporal resolution by using an optimized parallel imaging technique. To optimize the sensitivity to BOLD contrast, the signal characteristics of TSE as a function of a number of important acquisition parameters must be fully understood. Therefore, the purpose of this study is two-fold. First, we will develop a single-shot TSE sequence in conjunction with GRAPPA (Griswold et al., 2002) in order to achieve a temporal resolution comparable to EPI sequences for BOLD fMRI. Second, we will systematically analyze the signal characteristics of the new sequence, and compare the performance of this sequence with SE- and GE-EPI under identical conditions.

Methods

Pulse sequences

A single-shot TSE sequence was developed and implemented to achieve high data acquisition speed while maintaining an acceptable SAR level. The sequence, which will be referred to as modified HASTE (mHASTE), was based on a commercial HASTE sequence (Siemens Medical Solutions, Erlangen, Germany). As shown in Fig. 1, a major feature of mHASTE was the inclusion of a preparation time (T_p) between the excitation RF pulse and the echo train in order to accentuate the EV dynamic averaging effects (Poser and Norris, 2007a). T_p can be set to any value longer than one echo spacing (ESP). In this study, we used an upper limit of 80 ms for T_p because of the following considerations. Firstly, it typically required 8 slices to cover the visual cortex of the subjects. With a TR of 2000 ms, the total sequence length was 250 ms accordingly. This imposed an upper limit of ~80 ms for T_p. Secondly, a T_p of 80 ms corresponded to a TE of ~112 ms (see the next paragraph on the relationship between T_p and TE), which was sufficiently long for studying T2/T2* contrast in BOLD. In the sequence, the first echo was refocused at T_p by a 2.56 ms three-lobe SINC pulse (i.e., θ_1), whose flip angle was fixed at 180° to maximize the transverse magnetization. All subsequent refocusing pulses (i.e., θ_2) were 2 ms single-lobe SINC pulses producing an echo train for phase encoding. The θ_2 pulses had the same flip angle between 90° and 180°, except for the flip angle of the first pulse which was set to $90° + \theta_2/2$ for signal intensity and stability considerations (Hennig and Scheffler, 2000). For simplicity, this first pulse in the echo train is also referred to as θ_2 throughout this paper.

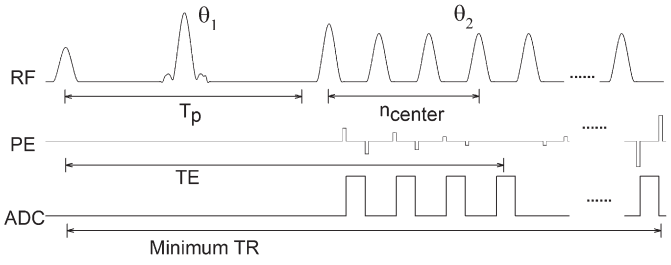

Fig. 1. A pulse sequence diagram of mHASTE. T_p is inserted between the excitation pulse and the echo train to enhance BOLD contrast, and can be set between 6.5 and 80 ms. θ_1 is held at 180°, while θ_2 (i.e. all pulses in the echo train) can vary from 90° to 180° (note that the first pulse of the echo train is actually set to $90° + \theta_2/2$). n_{center} is the number of θ_2 pulses before the *k*-space center line acquisition, and TE is determined by $T_p + ESP \times n_{center}$, where ESP is the echo spacing. The crusher gradients straddling θ_1 on all three axes are not shown for simplicity. These crushers are designed with a gradient area of 55 mT . ms/m. The sequence is used with GRAPPA (acceleration factor = 3), resulting in an echo train length of only 12–18.

GRAPPA (Griswold et al., 2002) was used with three-fold acceleration and separately collected reference scans, reducing the echo train length (ETL) to as few as 12 to 18 for an image with a 64×64 matrix size. We employed a *k*-space sampling scheme that was identical to that of a conventional HASTE sequence, starting on the partially acquired side and going towards the other end monotonically. The TE of the mHASTE sequence was defined as the interval between the excitation and the acquisition of *k*-space center line, and determined by T_p and the echo number of the *k*-space center line acquisition (i.e., n_{center} in Fig. 1): $TE = T_p + ESP \times n_{center}$. The echo spacing was fixed at 6.5 ms with a bandwidth of 320 Hz/pixel throughout this study. Different values of θ_2, TE and n_{center} were experimented to study their influence on BOLD signal characteristics, as detailed in the following sections.

For comparison, both fully sampled GE- and SE-EPI data were also acquired with scanning parameters chosen closely to those used in mHASTE, except for a smaller excitation flip angle (i.e. 70°; the Ernst angle) in GE-EPI, and different TEs (30 ms in GE-EPI and 80 ms in SE-EPI). The bandwidth for both EPI sequences was 2442 Hz/pixel. For all three sequences, the images acquired during the first two TRs were discarded as dummy scans in order to achieve equilibrium. Performing dummy scans was particularly important for mHASTE, as unstable magnetization was observed to result in large signal variations in images acquired during the first two TRs.

Subjects and stimulus

A total of 5 healthy volunteers (two males and three females; 24–28 years old; mean age = 25.6 years) with written consent participated in this study under a protocol approved by the Institutional Review Board. All subjects had normal or corrected-to-normal vision. Four of the subjects participated in more than one experiments described below. During scanning, the subject's head was fixed in the coil with soft padding to minimize motion. Visual stimuli used in fMRI consisted of three blocks of 20 s/20 s rest/active flickering black and white checkerboard. Each session lasted 140 s (ended with an extra 20 s rest). The total scan time varied with different experimental designs, but all within 50 min.

Data acquisition and analysis

All experimental studies were conducted on a Siemens Trio TIM 3 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) with a commercial 12-channel phased-array head coil. The key scanning parameters for all sequences that were held constant throughout this study were: FOV = 220×220 mm^2, voxel size = $3.4 \times 3.4 \times 5$ mm^3, slice thickness/gap = 5/2.5 mm, TR = 2 s. Eight transverse slices containing the calcarine fissure were selected. These slices were sufficient to cover the whole visual cortex in all subjects in the study.