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Signal contributions to heavily diffusion-weighted functional magnetic resonance imaging investigated with multi-SE-EPI acquisitions

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ABSTRACT

Diffusion-weighted (DW) functional magnetic resonance imaging (fMRI) signal changes have been noted as a promising marker of neural activity. Although there is no agreement on the signal origin, the blood oxygen level dependent (BOLD) effect has figured as one of the most likely sources. In order to investigate possible BOLD and non-BOLD contributions to the signal, DW fMRI was performed on normal volunteers using a sequence with two echo-planar acquisitions after pulsed-gradient spin-echo. Along with the changes to the signal amplitude ($\Delta S/S$) measured at both echo-times, this sequence allowed changes to the transverse relaxation rate (ΔR_2) to be estimated for multiple b-values during hypercapnia (HC) and visual stimulation (VS). $\Delta S/S$ and ΔR_2 observed during HC were relatively insensitive to increasing b-value. On the other hand, $\Delta S/S$ demonstrated a clear dependence on b-value at both echo-times for VS. In addition, ΔR_2 during the latter half of VS was significantly more negative at $b = 1400$ s/mm^2 than for the time-courses at lower b-value, but ΔR_2 during the post-stimulus undershoot was independent of b-value. The results have been discussed in terms of two models: the standard intravascular-extravascular model for fMRI and a three-compartment model (one intra- and two extravascular compartments). Within these interpretations the results suggest that the majority of the response is linked to changes in transverse relaxation, but possible contributions from other sources may not be ruled out.

Introduction

MRI with blood oxygen level dependent (BOLD) contrast has been widely used as a functional imaging tool, and it is now one of the most important methods in the neuroscience field (Ogawa et al., 1992, 1993). The BOLD signal reflects deoxyhaemoglobin concentration changes in the bloodstream in response to changes to the cerebral metabolic rate of oxygen (CMRO2), cerebral blood flow and cerebral blood volume (CBV). Therefore, BOLD reveals changes in neural activity only indirectly (Buxton, 2012; Obata et al., 2004). For this reason many researchers have attempted to develop diffusion-weighted functional MRI (DW fMRI) methods that provide more direct information about neural activation (Aso et al., 2009; Darquie et al., 2001; Harshbarger and Song, 2004; Jin and Kim, 2008; Jin et al., 2006; Kershaw et al., 2009; Kohno et al., 2009; Le Bihan et al., 2006; Miller et al., 2007; Yacoub et al., 2008). An example of this is the two-phase functional diffusion model that Le Bihan et al. introduced as a means to interpret heavily DW fMRI (Le Bihan et al., 2006). Within this model, tissue water molecules are said to undergo slow exchange between a slow-diffusion phase (SDP) and a fast-diffusion phase (FDP), and the fMRI signal change is understood as an expansion (contraction) of the SDP (FDP) during the application of a stimulus. Hence, it was hypothesised that measuring changes to the SDP expansion coefficient might provide an MRI-based method for directly observing cell swelling during neuronal activity. If that hypothesis holds true, DW-fMRI would become a functional imaging method with the potential to directly detect neural activity.

Motivated by this possibility, Miller et al. (2007) performed a DW-fMRI study using a protocol similar to that of Le Bihan et al. They observed similar signal changes not only during visual stimulation (VS), but also under hypercapnia (HC), which suggests that the DW-fMRI signal changes are largely due to the haemodynamic response

Abbreviations: BOLD, blood oxygen level dependent; CBV, cerebral blood volume; CMRO2, cerebral metabolic rate of oxygen; CSF, cerebrospinal fluid; DW, diffusion-weighted; EPI, echo planar imaging; EV, extravascular; FDP, fast-diffusion phase; FIV, fast intravascular phase; fMRI, functional magnetic resonance imaging; HC, hypercapnia; IV, intravascular; MPG, motion-probing gradient; PGSE, pulsed-gradient spin echo; PSCR, positive stimulus-correlated response; PSU, post-stimulus undershoot; SDP, slow-diffusion phase; VS, visual stimulation.

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rather than neuronal cell-swelling. On the other hand, other groups have found the response to hypercapnia at high b-value to be significantly smaller than that during visual stimulation (Kuroiwa et al., 2008; Urayama et al., 2008). Overall, no conclusive agreement on the origin of the DW-fMRI signal has been arrived at, but the BOLD effect has figured as one of the most prominent suggested sources (Rudrapatna et al., 2012).

As originally proposed, the BOLD signal model for fMRI consists of intravascular (IV) and extravascular (EV) contributions so that the fractional signal change $\Delta S/S = (\Delta S_i + \Delta S_e)/S$ (Buxton et al., 1998). The EV BOLD model predicts that ΔS_e increases with TE, so it is often convenient to characterise the EV contribution as a change in the transverse relaxation rate of a single-exponential decay $S_e = S_{0e} \exp(-TE\, R_{2e})$. However, to also account for a possible non-BOLD contribution ($\Delta S_{0e}/S_{0e}$), the change can be written as $\Delta S_e \approx [\Delta S_{0e}/S_{0e} - TE\, \Delta R_{2e}]\, S_{0e} \exp(-TE\, R_{2e})$. The IV contribution ΔS_i is thought to be substantially attenuated for $b > 200$ s/mm^2 (Le Bihan et al., 1988), so that in the limit of large b it is expected that $\Delta S/S \approx \Delta S_e/S_e = \Delta S_{0e}/S_{0e} - TE\, \Delta R_{2e}$. Note that if ΔS_{0e} is zero then the total signal change is due to ΔR_{2e} alone. Now, if the IV–EV model is an adequate description for DW-fMRI, a measurement of $-\Delta R_2$, which represents minus the change to the overall apparent transverse relaxation rate R_2, should approach $-\Delta R_{2e}$ and have a time-course with shape similar to that of $\Delta S/S$ at high b-value. It follows that simultaneous measurements of $\Delta S/S$ and $-\Delta R_2$ may provide useful information to investigate the contribution of BOLD and other effects to DW-fMRI signal changes.

In this work, a second 180-degree RF pulse was added to a standard pulsed-gradient SE (PGSE) echo-planar imaging (EPI) sequence so that the transverse magnetisation refocuses again at TE2 (Fig. 1). Along with the usual b-value dependent changes to the signal amplitude obtained from DW-fMRI experiments, the EPI acquisitions at TE1 and TE2 allowed the transverse relaxation rate ($R_2 = 1/T_2$) at different diffusion weightings to be estimated during the performance of a task. Experiments were performed for both hypercapnia and visual stimulus tasks.

Materials and methods

This study was approved by the Institutional Ethics Committee of the National Institute of Radiological Sciences, Chiba, Japan and signed informed consent was obtained from each participant.

Data acquisition

DW fMRI experiments during HC and VS were conducted on a whole-body 3 T MRI system (Signa HDx, GE Healthcare, Milwaukee, WI, USA). Acquisitions were performed using a multiple SE EPI sequence with PGSE diffusion-weighting (Fig. 1). The diffusion-weighting gradients were placed on either side of the first refocusing RF-pulse and directed along the readout axis. The repetition time (TR) was 2000 ms for the VS, and 1000 ms for the HC experiments. The following imaging parameters were common to both the VS and HC experiments: TE1 = 71.3 ms, TE2 = 129.2 ms, 64 × 64 matrix, 3.75 × 3.75 × 5 mm^3 pixel size, and 4 slices. The amplitude of the pulsed gradient was altered while the timing was fixed to obtain b-values of 1, 200 or 1400 s/mm^2. Pairs of b-values were selected (either b = 1400 and 1, or 1400 and 200 s/mm^2), and the higher and lower diffusion weightings were alternated every TR to minimize the effects of motion. Since the highest b-value images have lower SNR, a b-value of 1400 s/mm^2 was included in both pairs of diffusion weightings to increase the number of data points. The order of the b-value pairs was alternated to avoid possible systematic bias.

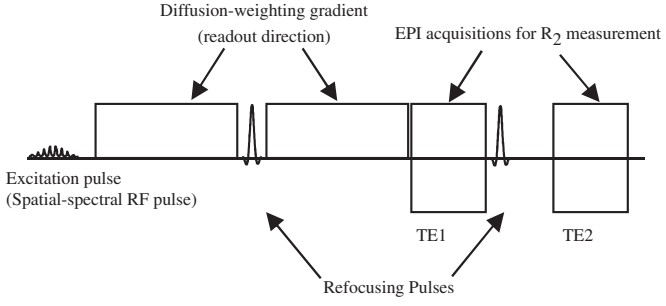

Fig. 1. Pulsed-gradient spin-echo (PGSE) with double EPI acquisition. After standard PGSE diffusion-weighting, MR signals at two echo-times (TE1 = 71.3 ms and TE2 = 129.2 ms) were obtained so as to estimate R_2 at each b-value.

Hypercapnia

Eight healthy volunteers participated in the HC experiments. To induce temporary hypercapnia, 5% CO_2 gas (together with 21% O_2 and 74% N_2) was administered for 60 s followed by 120 s of normal air with end-tidal CO_2 monitored. The paradigm consisted of 2 cycles of 60 s administration and 120 s rest repeated once for each b-value pair on each volunteer. Imaging slices were set to cover the same parts of the visual cortex as for the VS experiments.

Visual stimulation

Twelve healthy volunteers participated in the VS experiments. Visual stimulation was provided by a black-and-white checkerboard alternating at 8 Hz. A small horizontal arrow was placed in the center of the checkerboard, and it randomly changed direction from right to left or from left to right during activation. To avoid sleepiness and monitor vigilance, the subjects had to push a mouse button if the arrow changed direction. Prior to the DW fMRI experiments, a T_2*-BOLD fMRI experiment with slices covering the whole brain was performed to search for the most activated slice in the visual cortex. The VS protocol for this preliminary experiment was 3 cycles of 30 s activation and 30 s rest. The four slices used for DW fMRI were selected from a functional map created by the Brain Wave software (GE Healthcare). After slice selection, DW fMRI during VS was performed with a stimulation paradigm of 4 cycles of 40 s activation and 80 s rest. The paradigm was repeated twice for each b-value pair on each volunteer.

Data processing

After smoothing all images (3 × 3 spatial + 7-point (HC) or 3-point (VS) temporal box filters) and averaging over all stimulus cycles, activated pixels in the first-echo (TE1) image sets were identified for both HC and VS with a pixel-by-pixel *t*-test analysis between stimulation and baseline time points. The intervals for the HC data set were 15 time points during CO_2 administration (31–60 s after onset) and 16 points (149–180 s after onset) to define the baseline. The intervals selected for the *t*-test applied to the VS data set were 5 central time points during VS (16–34 s after stimulus onset) and 9 points (88–120 s after onset) to define the baseline. All voxels in the b = 200 and 1400 s/mm^2 data sets with t-value of more than 4 at TE1 ($p < 10^{-4}$, uncorrected for multiple comparisons) were defined as activated, and the same voxels were used to perform the analysis of all b-value and TE data from a particular subject. The regions of interest (ROIs) were manually selected from the whole cortex (except the frontal cortex) for HC and from the activated pixels in the visual cortex for VS. The frontal cortex was ignored for HC because of the susceptibility artefact in the vicinity of the frontal sinus. The DW fMRI time-series were averaged over the ROI selected for each subject before the fractional signal change was calculated. Note that the two repetitions of the acquisition paradigm performed for the VS experiments were analysed separately and the resultant time-series were averaged. The time-series were then averaged over all subjects for both the first and second echoes.