Characterization of the proton-density change contribution to spin-echo fMRI data: The SEEP contrast mechanism

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Introduction

The SEEP contrast mechanism was first described in the spinal cord where it produces larger signal changes than in the brain and so is more easily detected.[1,2] The proposed mechanism is increased production of extracellular fluid at sites of increased perfusion pressure, and/or swelling of astrocytes as they take up glutamate from the extracellular space. Detailed studies of the signal intensity changes in the spinal cord as a function of echo time demonstrated both the BOLD effect and a non-linear relationship with signal intensity changes of 3.3% at an echo time of 11 msec. From this data a two-component model was developed which described a BOLD component and a proton-density change in a separate water component. The latter was determined to have a T_2 of 71 ± 21 msec, and to undergo a proton-density change of 5.6% upon neuronal activation. Studies carried out in the brain with proton-density weighted spin-echo fMRI demonstrated areas of activity immediately adjacent to areas of BOLD activity with very little overlap. Signal intensity changes were measured to be 1.9% ± 0.3% at 3 T [3], 1.9% ± 0.2% at 1.5 T [4], and 2.1% ± 0.2% at 0.2 T [5], under similar acquisition conditions. Studies carried out in the brain with a high statistical threshold $p < 10^{-4}$ have also demonstrated the SEEP hemodynamic response function.[4] Other groups have also demonstrated the proton-density change component in fMRI of the brain[6,7] and spinal cord[8].

Other groups have proposed that these observations may instead reflect blood volume changes, or may be artefacts arising from insufficiently stringent statistical thresholds being used for analysis, or that the proton-density change simply does not occur. The present study was designed to investigate these possibilities by 1) characterizing the transverse relaxation properties of the apparent proton-density change water component, and 2) by obtaining inversion-recovery (IR) prepared data to null the signal arising from blood.

Methods

In order to characterize the relaxation properties of the water component in which the apparent proton-density change occurs, multi-echo spin-echo image data were acquired in a functional imaging time series. Image data were obtained with a matrix size of 128 x 128, FOV = 20 cm, 3 mm thick slices with 3 mm gaps, 8 slices, TR = 1100 msec and 4 echoes separated by 12 msec or 27 msec in separate acquisitions. Data sets were acquired alternately with the two echo spacings to describe the fMRI time course. Two data sets with each echo spacing were acquired with the subject at rest, again with the subject performing a two-hand finger touching task, and then again with the subject relaxed. Data were analyzed after applying rigid-body registration, by computing the correlation with a box-car paradigm with data acquired at each of the 8 echo times. Absolute signal intensity differences were determined between rest periods and task periods at each echo time.

Separate studies were carried out with inversion-recovery single-shot fast spin-echo imaging with an inversion time (TI) of 832 msec to null signal from blood ($T_1 \approx 1200$ msec at 1.5 T) [9,10,11]. The image voxel size was identical to that in the preceding studies and TE = 32 msec. Image data were acquired every 11 sec to describe a time course with the volume imaged 10 times per condition with 2 task conditions interleaved with 3 rest conditions. Data were analyzed following rigid body registration using a general linear model.

Results and Discussion

Absolute signal intensity changes between rest and stimulation demonstrated a consistent mono-exponentially decaying function of TE corresponding to a proton density (p.d.) change of 6.2% ± 0.1% and a T_2 of 89 ± 11 msec with an echo spacing of 12 msec, and a p.d. change of 5.9% ± 0.1% and a T_2 of 93 ± 6 msec with an echo spacing of 27 msec. The natural logarithm of all data points fit a linear function of TE with $R^2 = 0.992$ characterized by a T_2 of 89 ± 3 msec. In comparison, data obtained previously in the spinal cord demonstrated a proton-density change of 5.6% in a water component with a T_2 of 71 ± 21 msec[1]. The possibility of contributions from motion were investigated by carrying out the analysis without registration, and with image shifts required for registration applied in the opposite direction to that used for registration. Mis-registration or no registration created roughly equal signal intensity offsets at all echo times, making the signal differences a non-exponentially decaying function of TE. It is therefore concluded that the signal intensity changes observed are not due to motion.

Data obtained with IR-prepared single-shot fast spin-echo consistently demonstrated activity in the appropriate motor areas with signal intensity changes of 4.9% ± 0.9%. With an inversion time of 832 msec the signal from blood is nulled, and that from gray matter is reduced to 20% of its non-IR-prepared value. The observed signal intensity changes therefore cannot arise from blood, unless the blood moves into the slice between the inversion-pulse and the imaging sequence. However, if in-flowing blood is the source of the observed signal changes then the fractional signal changes would be amplified by a factor of 5 by the effect of the inversion pulse on the background intensity. The signal intensity changes observed are consistent with previous studies, and so do not demonstrate any contribution from blood in the slice, or in-flowing blood.

Conclusions

The data obtained demonstrates that there is a proton-density change component in spin-echo fMRI data that does not arise from the blood and is therefore extravascular in origin. The observed proton-density change of approximately 6.0% occurs in a water component with a T_2 of 89 msec, consistent with that of gray matter.[12]. The data obtained provides strong support for the proposed theory of the SEEP contrast mechanism.

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