Functional Mapping of the Human Visual Cortex at 4 and 1.5 Tesla Using Deoxygenation Contrast EPI

R. Turner, P. Jezzard, H. Wen, K. K. Kwong, D. Le Bihan, T. Zeffiro, R. S. Balaban

The effects of photic stimulation on the visual cortex of human brain were studied by means of gradient-echo echo-planar imaging (EPI). Whole-body 4 and 1.5 T MRI systems, equipped with a small *z* axis head gradient coil, were used. Variations of image intensity of up to 28% at 4 T, and up to 7% at 1.5 T, were observed in primary visual cortex, corresponding to an increase of blood oxygenation in regions of increased neural activity. The larger effects at 4 T are due to the increased importance of the susceptibility difference between deoxygenated and oxygenated blood at high fields.

INTRODUCTION

Gradient-echo imaging, using a relatively long echo time, has been shown by several authors (1–3) to show clearly the effects of changes in blood oxygenation. Deoxygenated blood, which is more paramagnetic than oxygenated blood (4), acts as an endogenous contrast agent. The experimental evidence is consistent with the hypothesis that the change in relaxation rate is linearly proportional to the change in total deoxyhemoglobin content with each voxel (in voxels not containing large vessels). Thus, an increase of signal implies a decrease of deoxyhemoglobin within the voxel.

Kwong et al. (5) have used this phenomenon to study changes in human visual cortex produced by photic stimulation. Volunteers were subjected to intermittent periods of stimulation by binocular goggles containing flashing light-emitting diodes, while a series of gradient-echo echo-planar imaging (EPI) images was collected at 2- to 3-s intervals. Regions of interest on the banks of the calcarine fissure were found to display rises in intensity well correlated with the periods of stimulation, with a risetime of several seconds for each period. Ogawa et al. (6) have obtained consistent results working at a static field of 4 T, using the FISP sequence.

These results, indicating a rise in blood oxygenation during neural activity, are consistent with the findings of Cooper et al. (7) using recordings of polarographic oxygen with gold electrodes applied to the cortex of human subjects, and with the PET findings of Fox and Raichle (8), showing a much greater fractional change in cerebral blood flow than in oxygen utilization during somatosensory stimulation. Similar results were reported in cat brain during electrical stimulation by Lübbers and Leniger-Follert (9).

Given that for higher magnetic fields the effect of susceptibility variations is heightened, it was of interest to determine whether large changes due to photic stimulation would be observable using our 4 T whole-body MR system. To make a fair comparison, EPI experiments at 4 and 1.5 T were conducted on the same volunteer, selecting as far as possible the same slice through the occipital cortex. We present comparative results at 1.5 T using an echo-planar sequence previously described (10).

THEORY

The most comprehensive theoretical investigation of the effects on MRI signal of an intravascular paramagnetic agent is that of Fisel et al. (11). They used a numerical simulation to assess the decrease in signal caused by the phase incoherence created when nuclear spins move in the locally inhomogeneous magnetic fields associated with the blood vessels. The vessels were approximated as arrays of spheres or cylinders, and the attenuation produced in both spin-echo and gradient-echo images was assessed. This attenuation was expressed in the form of the change ΔR_2 in relaxation rate which would be observed if the vessels were filled with a substance whose magnetization differs by an amount M from their surrounding tissue. If the substance is more paramagnetic than tissue, with a susceptibility difference from surrounding tissue of $\Delta\chi$, then

$$M = \Delta x B_o$$

If the Einstein diffusion length $\sqrt{2D \cdot TE}$ (where D is the diffusion coefficient of water) is somewhat larger than the typical vessel size, as for capillaries and smaller venules in brain tissue, a quadratic dependence of $\Delta R_2{}^*$ on M is expected, for spherical magnetized regions. This is predicted both for gradient echo and spin-echo images, with echo times of 40 ms or greater. In this regime the major variation of the field which the spins experience arises from their diffusive motion past the less diamagnetic vessels. The refocusing pulse in the spin-echo sequence is unable to compensate for this effect. For the cylindrical model the exponent is reduced to 1.6. Thus for a constant echo time the change in relaxation rate for a given change in blood susceptibility should vary as a power of the static field B_0 in the range 1.6 to 2.0.

Several authors (4, 12, 13) have shown that fully deoxygenated red cells have a susceptibility 0.2 ppm greater than fully oxygenated blood. In experiments at 2 T with cats undergoing anoxia (3), a change from 100% arterial hemoglobin oxygen saturation to 40% saturation was

MRM 29:277–279 (1993)

From the Laboratory of Cardiac Energetics, NHLBI, National Institutes of Health, Bethesda, Maryland (R.T., P.J., H.W., R.S.B.); NMR Center, Massachusetts General Hospital, Boston, Massachusetts (K.K.K.); Department of Diagnostic Radiology, Clinical Center, NIH, Bethesda, Maryland (D.L.B.); and Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, Maryland (T.Z.).

Address correspondence to: Dr. Robert Turner, Building 10, Room B1D161, Laboratory of Cardiac Energetics, NHLBI, National Institutes of Health, Bethesda, MD 20892.

Received June 9, 1992; revised October 21, 1992; accepted November 16, 1992.

0740-3194/93 $3.00

found to produce a 15% decrease in image intensity in brain grey matter, for an echo time of 40 ms. Results at 1.5 T (5) using photic stimulation with human volunteers showed a 1–3% increase in signal intensity in the visual cortex during stimulation. Since this implies a corresponding decrease in ΔR_2^*, this is consistent with an increase in blood oxygenation, as discussed above.

Thus, experiments at 4 T using photic stimulation should give an increase of relative signal during stimulation by a factor of up to $(4.0/1.5)^2 = 7.1$, for fixed echo time.

METHOD

Four volunteers (ages between 24 and 46) were studied in a 4.0 T whole body imaging system fitted with shielded transverse gradient coils, and a small (27 cm in diameter) z-gradient coil (14) which gave sufficiently large gradients and fast enough rise times to allow EPI. To avoid RF coupling problems, and not for signal-to-noise ratio (SNR) reasons, a surface coil was used for RF transmission and reception, at 170.74 MHz.

A GE Omega console was used to obtain EPI images which were sufficiently free from artifact that significant anatomical detail could be observed. Some geometrical distortion is inevitable at tissue-bone-air interfaces, especially around the petrous bone and the nasal sinuses. The excellent magnet shim allows satisfactory 128 × 128 gradient-echo EPI images to be obtained with a 20-cm field of view (FOV). However, it was found to be more convenient for this study to use 64 × 64 images, which had an echo time of 25 ms, FOV 160 mm, slice thickness 5 to 10 mm, and total acquisition time 41 ms. Longer echo times gave images of poor quality, as was expected given the large frequency differences caused by spatial susceptibility variations at this field.

Sagittal and coronal slices, with 5-mm slice thickness, were selected intersecting the calcarine fissure and other portions of the primary visual cortex. Coronal slices with 6-mm slice thickness, for comparison with 1.5 T results, were also obtained at various positions through the occipital lobes of the brain. The repeat time was 3 s. Acquisition can be performed in a multislice mode, with up to 16 slices in a *TR* period of 3 s, but this was not done due to limited data postprocessing capabilities.

Photic stimulation was provided by light-proof binocular goggles fitted with light-emitting diodes which could be caused to flash at varying rates (Model S10VS, Grass Instruments), in this case 16 Hz (known to produce significant stimulation (5)). After the subject had rested in darkness for several minutes, 64 images were obtained during each experimental run. The stimulus was initially off for 30 s (10 images), and was then alternately switched on and off for 10 images at a time, the final four images being obtained with the stimulus off. The images were reconstructed without use of a phase-correction algorithm, and transferred to a workstation for analysis. Difference images were calculated, in which the mean of images 4 through 10 was subtracted from subsequent images, to provide improved visualization of contrast changes. The first few images were excluded from this calculation because they showed marked effects of progressive magnetic saturation, since brain tissue T_1 is on the order of several seconds at 4 T.

For comparison, similar experiments were conducted with six volunteers using a GE 1.5 T Signa scanner, fitted with the same head gradient coil, but using a standard 3- or 5-inch Signa RF surface coil. Special GE software (10) was used to obtain 64 × 64 pixel matrix gradient echo EPI images, each image taking 36 ms to obtain, with an echo time of 40 ms. A single reference scan served to perform a software phase correction for each of 64 subsequent imaging scans. Coronal or sagittal slices through the occipital lobe were obtained. The stimulus conditions were as described above. Image FOV was 16 cm, with a 6-mm slice thickness.

RESULTS

For the 4 T images and the Signa 1.5 T images (Figs. 1 and 2) the difference images showed highly localized changes of intensity during stimulation. The position of these regions corresponded closely to the calcarine fissure and other regions of primary visual cortex. The SNR at both fields was typically 100 or greater in the most posterior parts of the brain. SNR optimization at 4 T is continuing. Since T_1 increases and T_2^* decreases with static field a

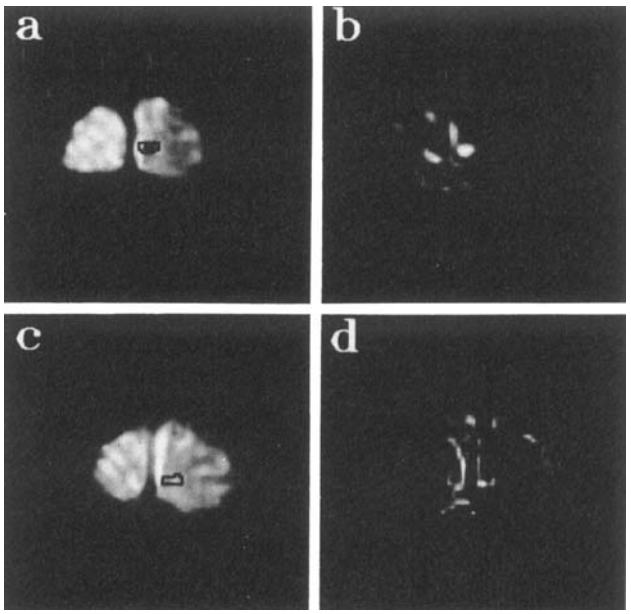

FIG. 1. Coronal EPI images at 4 and 1.5 T of the occipital lobes of the brain of a volunteer, showing activated cortical regions. Images, obtained using surface coils, had 64 × 64 pixel matrix, 10-mm slice thickness, 16 cm FOV, and were interpolated for display to 128 × 128 pixel matrix. Care was taken to select the same slice at each field. Differences in field homogeneity account for most of the visible differences in the images at the two fields. (a) Source image at 4 T, *TE* 25 ms, acquisition time 41 ms. A region of interest in the calcarine fissure is outlined. (b) Difference image at 4 T, obtained by subtracting the brain resting state image from the image after 25 s of photic stimulation. (c) Source image at 1.5 T, *TE* 40 ms, acquisition time 36 ms. A region of interest in the calcarine fissure is outlined. (d) Difference image at 1.5 T, obtained as in (b).

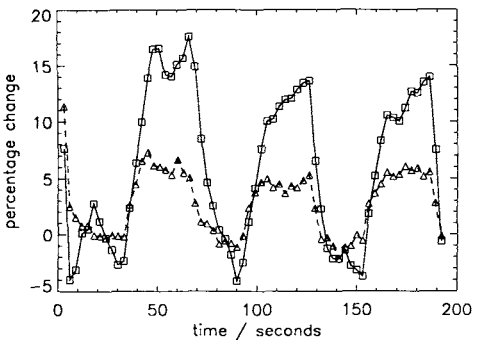

FIG. 2. Plot of fractional change in 4 T (squares) and 1.5 T (triangles) EPI image intensity versus time in the eight-voxel regions of interest in the visual cortex shown in Fig. 1, for a volunteer experiencing alternate 30-s periods of rest and photic stimulation. Details of acquisition for the 4 and 1.5 T data are described in the caption for Fig. 1.

direct comparison of SNR is not appropriate with the sequence parameters chosen.

In the image data acquired at 4 T a variation of typically 15% (mean 15.1%, SD 6.0%, $n = 20$) of image intensity in the active regions was observed, though changes of up to 28% could be seen in small regions of interest in some subjects. Here n refers to the number of studies, not the number of subjects. At 1.5 T a smaller difference in image intensity was seen, of 3–7% (mean 4.7%, SD 2.0%, $n = 15$), which was easily masked by the misregistration effects of slight movements of the volunteer. Such motions can produce spurious changes of 15% or more in difference images.

At both fields, consistent with the observations of Kwong et al. (5), and Ogawa et al. (6), an increase of signal was noted during stimulation, with a rise time of 4 to 10 s, which appeared to be volunteer-dependent. This increase is interpreted as arising from an increase in blood flow sufficient to dilute the deoxyhemoglobin in the blood to a level below that of the resting state. During the second and third periods of darkness, the signal from the visual cortex generally dropped below its resting value, suggesting continued oxygen uptake following return of blood flow to normal. No changes in signal could be seen from tissue clearly outside the visual cortex, for instance in the observable part of the cerebellum.

The change of signal intensity was compared for a single volunteer, examined using the same photic stimulus, in a coronal slice of the same thickness and approximately the same position through the visual cortex. Figure 2 shows the change in image intensity with time, as a percentage of baseline, during three photic stimulation episodes at both fields studied. For a region of interest in the position of the calcarine fissure giving a large change in signal with photic stimulation, at 4 T the peak-to-peak signal change was 20 ± 3%, and at 1.5 T it was 6 ± 0.5%. This corresponds to an increase by a factor of 5 ± 1 in change of relaxation rate, given the longer echo time used at 1.5 T. The overall regions of increased intensity with stimulation in the two studies correspond well, showing that the less intense activated regions increase proportionately with the most intense, at both fields studied. A quantitative comparison is hard to make globally, because it would require precise image registration across studies.

DISCUSSION

At 4 T the contrast changes with activation are more easily observable than those seen by Kwong et al. (5) at 1.5 T. The evidence from comparative studies with a single volunteer suggests that the dependence of the deoxygenation contrast on static field is greater than linear, the exponent being in the range 1.5 to 1.8. While further experimental work is needed, it appears that our theoretical understanding of the field dependence of the effect is incomplete.

The magnitude of the changes at 4 T, coupled with the intrinsic signal-to-noise gain achievable at this field, implies that functional brain mapping by MRI will benefit considerably by the use of high magnetic fields. Details of the time dependence of vascular changes with activation and brain response to more subtle stimuli will be open to study. The increased SNR at 4 T will enable whole-head multislice examinations with good time resolution, so that experiments to observe temporal and spatial patterns of change in brain activity accompanying sequential processing are now conceivable.

ACKNOWLEDGMENT

The authors thank Fred Heineman, Bruce Rosen, and Tim Pons for useful discussions and encouragement, and the NIH *in Vivo* NMR Research Center for use of its excellent facilities.

REFERENCES

1. S. Ogawa, T-M. Lee, A.S. Nayak, P. Glynn, *Magn. Reson. Med.* **14,** 68 (1990).
2. S. Ogawa, and T-M. Lee, *Magn. Reson. Med.* **16,** 9 (1990).
3. R. Turner, D. Le Bihan, C. T. W. Moonen, D. Despres, J. Frank, *Magn. Reson. Med.* **22,** 159 (1991).
4. K. R. Thulborn, J. C. Waterton, P. M. Matthews, G. K. Radda, *Biochim. Biophys. Acta.* **714,** 265 (1982).
5. K. K. Kwong, et al., *Proc. Natl. Acad. Sci. USA* **89,** 5675 (1992).
6. S. Ogawa, et al., *Proc. Natl. Acad. Sci. USA* **89,** 5951 (1992).
7. R. Cooper, D. Papakostopoulos, H. J. Crow. Rapid changes of cortical oxygen associated with motor and cognitive function in man, *in* Blood Flow and Metabolism in the Brain (M. Harper, et al., Eds.). Churchill Livingstone, Aviemore, Scotland (1975).
8. P. T. Fox, M. E. Raichle, *Proc. Natl. Acad. Sci. USA* **83,** 1140 (1986).
9. D. W. Lübbers, E. Leniger-Follert, *Ciba Found. Symp.* **56,** 21 (1978).
10. R. Turner, et al., *Radiology* **177,** 407 (1990).
11. C. R. Fisel et al., *Magn. Reson. Med.* **17,** 336 (1991).
12. R. A. Brooks, G. Di Chiro, *Med. Phys.* **14,** 903 (1987).
13. R. M. Weisskoff, S. Kiihne, *Magn. Reson. Med.* **24,** 375 (1992).
14. R. Turner, D. Le Bihan, A. S. Chesnick, *Magn. Reson. Med.* **19,** 247 (1991).