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Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging

(cerebral blood flow/blood oxygenation/visual cortex/positron emission tomography/magnetic susceptibility)

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ABSTRACT **We report that visual stimulation produces an easily detectable (5–20%) transient increase in the intensity of water proton magnetic resonance signals in human primary visual cortex in gradient echo images at 4-T magnetic-field strength. The observed changes predominantly occur in areas containing gray matter and can be used to produce high-spatial-resolution functional brain maps in humans. Reducing the image-acquisition echo time from 40 msec to 8 msec reduces the amplitude of the fractional signal change, suggesting that it is produced by a change in apparent transverse relaxation time T_2^*. The amplitude, sign, and echo-time dependence of these intrinsic signal changes are consistent with the idea that neural activation increases regional cerebral blood flow and concomitantly increases venous-blood oxygenation.**

Magnetic-resonance imaging (MRI) of rodent brains at high (7-T) magnetic-field strength shows proton signal-intensity alterations related to blood oxygenation in regions close to local blood vessels (1–3). We have termed this phenomenon blood oxygenation-level-dependent (BOLD) contrast and have demonstrated that the underlying mechanism is a magnetic-susceptibility variation caused by deoxyhemoglobin, an endogenous paramagnetic contrast agent. It was further demonstrated that this magnetic-susceptibility effect could be used to measure *in vivo* changes in hemodynamics. For example, pharmacologically induced changes in cerebral blood flow and oxygen utilization produce measurable changes in BOLD contrast in the rat cerebral cortex. Similar results have recently been demonstrated in cat brain (4).

There is increased evidence that a local elevation in human-brain venous-blood oxygenation accompanies an increase in neuronal activity (5–8). For example, positron emission tomography imaging experiments demonstrate stimulation-produced increases in regional cerebral blood flow without significantly changing local oxygen use, thus predicting an elevation in venous-blood oxygenation (6, 7). This result suggested that BOLD contrast imaging could be used to map human mental operations. To examine whether detectable intrinsic magnetic-susceptibility changes are produced in the human brain in response to neuronal activation, we studied the effect of visual stimulation on gradient echo images of human visual cortex acquired at high-magnetic-field strength. In general, high-field strength increases the magnitude of susceptibility contrast effects, accentuating BOLD contrast.

MATERIALS AND METHODS

MRI experiments were done with a 4-T whole-body imaging system with actively shielded gradient coils [Sisco (Sunnyvale, CA)/Siemens (Erlangen, F.R.G.)]. Approval for these human experiments was obtained from the institutional review board of the University of Minnesota Medical School. Radiofrequency power deposition was kept two orders of magnitude below Food and Drug Administration specific-absorption rate guidelines. A snugly fitted head holder with a curved-surface radiofrequency coil (14 cm in diameter) was used to limit motion artifacts. High-resolution longitudinal relaxation time T_1-weighted images were obtained by using a fast imaging steady-state precession (FISP) (9)-based fast-gradient-recalled echo sequence [echo time (TE) = 8 ms; repetition time (TR) = 13 ms; 0.5-cm slice width] with 256-phase-encoding steps segmented in four blocks of 64 interleaved steps. An adiabatic inversion pulse followed by an inversion recovery time of 1.2 s was used to generate T_1-weighted precontrast, which, at 4 T, enhances the white-matter signal (10, 11). For the visual-stimulation experiments, consecutive gradient echo images were obtained from the average of two scans by using a FISP pulse sequence (TE = 40 ms; TR = 45 ms; 64-phase-encoding steps; 128 complex readout points; time interval between scans = 2 s; 1-cm slice thickness), producing an effective image-repetition rate of ≈10 s. The images were zero-filled to 256 × 256 before Fourier transformation. The plots of signal-intensity change versus image number were digitally filtered (gaussian filter: 2-point width). Images in the figures were segmented from full images and displayed using IMAGE 1.37 software from the National Institutes of Health.

Experiments were done on six normal human volunteers. The occipital pole of the head of each subject was fitted in the head holder with a curved-surface radiofrequency coil, so as to increase the signal-to-noise ratio from the area encompassing primary visual cortex. Binocular visual stimulation was provided by light-tight goggles containing light-emitting diode (LED) arrays (model S10VS goggles; Grass). In some experiments, binocular hemifield visual stimulation was made. In this case, subjects were kept in the dark and, during the visual-stimulation period, were instructed to fixate on a small green LED located directly ahead at a distance of ≈15 cm, the longest direct distance possible within the magnet bore. Hemifield peripheral stimulation was then provided by an alternating 5-cm square red/green checkerboard LED display (model S10VS, box display; Grass) at the same distance but centered either 8 cm to the left side or 8 cm to the right side of the fixation point. The box was moved from one hemifield position to the other between image sequences but during the same imaging session. For all experiments, heart rate and arterial blood oxygenation were monitored throughout an imaging session by using a Nonin fiber-optic oximeter.

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Abbreviations: BOLD, blood oxygenation-level dependent; MRI, magnetic resonance imaging; LED, light-emitting diode; TE, echo time; TR, repetition time; FISP, fast-imaging steady-state precession.

RESULTS

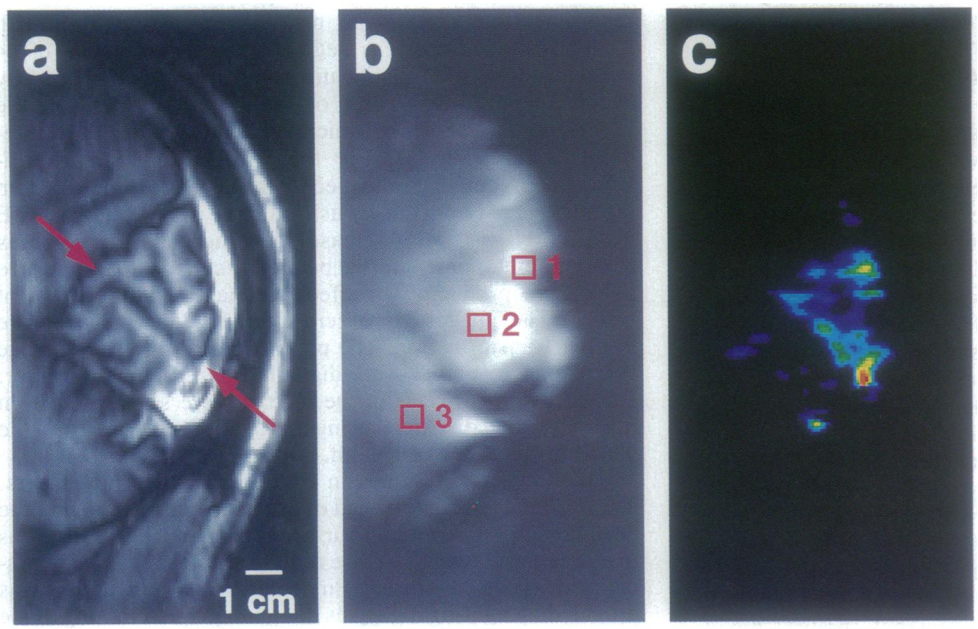
Our basic experimental finding is that visual stimulation transiently increases the magnitude of the water proton signal in the primary visual cortex. This result is illustrated in Fig. 1 for an experiment that used a sagittal plane that included the calcarine fissure, the anatomical location of human primary visual cortex, and in Fig. 2, where the image plane was positioned at an oblique angle parallel to the bank of this fissure.

Our procedure was to first make high-contrast T_1-weighted sagittal images (0.5-cm slice width) of the occipital lobes, in which the signal from white matter was enhanced, to locate the calcarine fissure. A continuous time series of gradient echo images [FISP pulse sequences (9); TE = 40 ms] containing periods of visual stimulation was then either taken in this sagittal plane (Fig. 1) or in an oblique plane (Fig. 2) along the calcarine fissure. The series contained 85 images acquired at a rate of one image every 10 s. The first 20 images were acquired without visual stimulation and represented the control condition. Then binocular patterned-flash visual stimulation (10 Hz) was provided first during the 100-s period between images 20–30 and for a second 150-s time period between images 50–65.

The signal intensity in several regions of interest outlined by boxes in Fig. 1*a* (sagittal image) and Fig. 2*a* (oblique image) were calculated for each gradient echo image in the sequence. The time course of the signal intensity for each box region is shown in Fig. 1*d* (sagittal image) and Fig. 2*d* (oblique image). At some, but not all, box locations, an increase is observed for each of the two stimulation periods that occurred during the image sequence acquisition. The signal change follows the time course of stimulation: an increase commences with onset of visual stimulation, and a decrease commences with offset of stimulation. The return to baseline level after stimulation occurred within 10–20 s.

When the sum of eight images acquired during a visual-stimulation period are subtracted from the sum of eight images acquired during a period without stimulation, a localized change in signal intensity is seen in the region corresponding to human visual cortex. This localized change is displayed as a pseudocolor map in Fig. 1*c* (sagittal image) and Fig. 2*c* (oblique image). Comparing these maps with the corresponding T_1-weighted images (Figs. 1*a* and 2*a*) demonstrates that large changes were observed in the gray-matter areas located in proximity to the dark regions in the T_1-weighted images.

A stimulus-produced localized increase in signal intensity was observed within the known anatomical location of the human primary visual cortex in all patterned binocular photic stimulation experiments (six subjects; 48 visual-stimulation periods; 12 sagittal, 36 oblique). The largest fractional



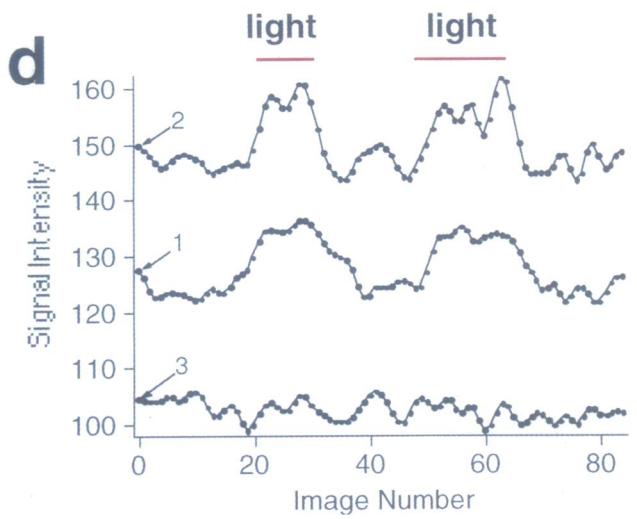


FIG. 1. Intrinsic signal changes in sagittal-brain images produced by photic stimulation. (*a*) Sagittal-slice image of the occipital pole taken with an inversion recovery pulse sequence. The oblique line is oriented along the bank of the calcarine fissure. (*b*) Gradient echo image (FISP sequence; TE = 40 ms) at the same anatomical location. (*c*) Pseudocolor map of the difference in signal intensity between the average of eight images acquired during photic stimulation and eight images taken in the dark. (*d*) Time course of signal-intensity changes (in arbitrary units) for regions indicated by the three boxes outlined in *b*.

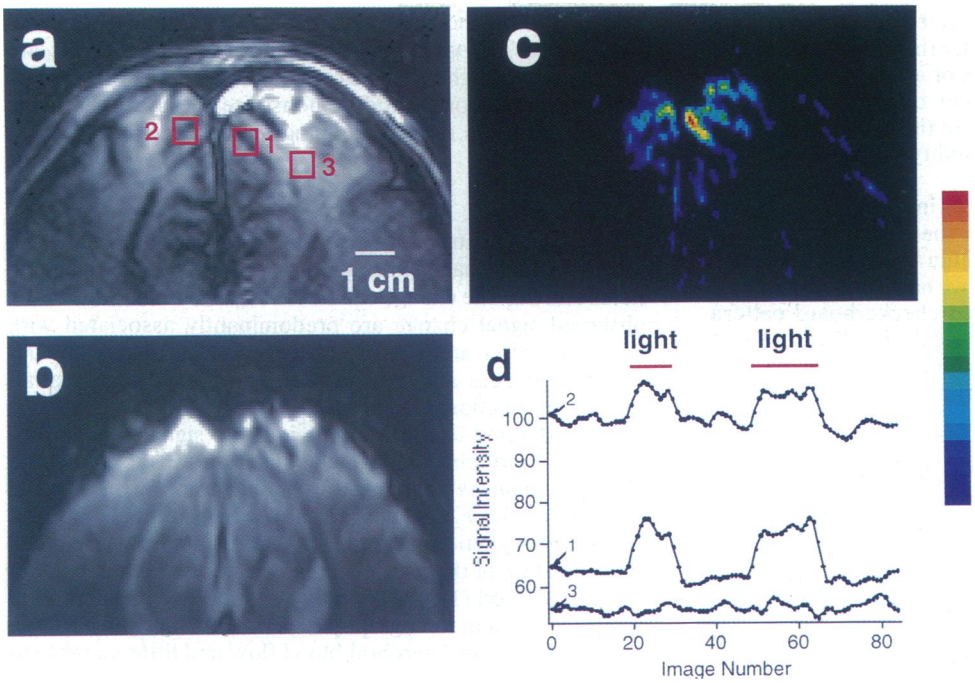


FIG. 2. Intrinsic signal changes produced by photic stimulation in oblique brain images along the calcarine fissure. (*a*) T_1-weighted image of the brain taken with the slice axis oriented parallel to the calcarine fissure. The occipital pole is at the top of the image. (*b*) Gradient echo image (FISP sequence; TE = 40 ms) at the same anatomical location. (*c*) Pseudocolor map of the difference in signal intensity produced by photic stimulation. (*d*) Time course of changes in signal intensity for regions indicated by the three boxes outlined in *a*.

changes in signal intensity in a given image sequence ranged between 5% and 20% (mean 8.2%; SD = 3.3%). Although global changes in signal intensity can be observed when heart rate changes (data not shown), in all experiments reported here, heart rates did not change during or after visual stimulation. The signal intensity during the period without visual stimulation fluctuated with a SD of 2% and contains contributions from both instrumentation noise and physiology-related changes in signal intensity. The individual contributions from these two sources were not quantitatively determined in these experiments.

Were the observed changes in signal intensity produced by a change in T_2^* (or T_2) due to a magnetic-susceptibility variation accompanying an alteration in blood oxygenation (1), then reducing the echo time used in the imaging-pulse sequence should reduce the fractional signal-intensity change. We examined this in two experiments. After a reduction in TE from 40 ms to 8 ms, with all other acquisition parameters held constant, the overall signal intensity was higher, but the fractional change in signal intensity produced by visual stimulation was reduced >3-fold; this difference is illustrated in Fig. 3. At short TE, the stimulation-induced signal-intensity changes were not easily detectable in the presence of a background-signal fluctuation of ≈2%. This result indicates that the signal change seen upon stimulation at 40-ms echo time is not strongly related to a change in T_1 or a change in the steady-state $z-$ magnetization—for example, that produced by an increased flow of blood water molecules into the observing slice (a "T_1^*" effect, see ref. 12). Were T_1- or T_1^*-related phenomena responsible for the stimulation-induced signal change, the fractional change of the signal is expected to be TE independent, contrary to our measurements.

Changes in signal intensity caused by T_2^* effects in gradient echo images are TE-dependent, consistent with the TE dependence of our observed signal change. Whether sensory stimulation produces changes in T_2 observable in spin-echo images requires further study. If similar changes are observed in spin-echo experiments, this would suggest that dynamic averaging of the field variation around venous blood vessels by water diffusion at a given echo time is appreciable. If similar changes are not seen, the field variation extends far beyond the water-diffusion distance. Which effects are important will depend on the size of blood vessels in human brain responsible for the BOLD image signal in a particular imaging condition (field strength, echo time, and spatial resolution) (13).

Dependence of image-signal intensity on venous-blood oxygenation measured in rodent brains at 7 T (S.O. and T. M. Lee, unpublished work) can be used to roughly interpret the size of signal changes seen in our experiments. Such an analysis suggests that, at 4 T, a 4% change in image signal intensity would be produced by a 50% increase of regional cerebral blood flow. The changes we observed in the present study were much larger. This result may indicate that regional-cerebral-blood-flow increases in the gray matter may be significantly higher than the value of 30–75% determined by a positron-emission tomography study under a similar stimulus paradigm (7). Positron-emission tomography functional activation studies have been reconstructed to an average resolution of between 0.5 and 2 cm. Such a resolution necessarily includes contributions from gray and white matter. One consequence of this resolution may be to diminish the intensity of the gray-matter signal. It is interesting to note that a stimulus-produced increase in blood volume with no change in blood oxygenation enhances the susceptibility-

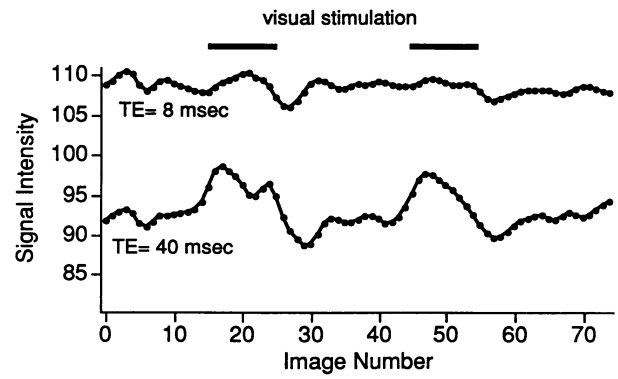


FIG. 3. Reducing TE reduces amplitude of the visual stimulation-induced intrinsic signal change. The time course of intrinsic signal changes observed at a fixed caudal position in primary visual cortex are shown for TE = 40 ms and TE = 8 ms. Other experimental conditions were as in Fig. 2, except that patterned-flash visual stimulation was provided between images 15–25 and 35–55.

difference effect and would be expected to produce a decrease in the water proton signal under the conditions used in these experiments. Our observation of an increase in signal intensity indicates that venous-blood oxygenation has increased to such an extent that, despite the probable increase in blood volume, the overall susceptibility-difference effect is greatly reduced.

The good spatial resolution observed in the functional brain maps in Figs. 1*c* and 2*c* suggested the feasibility of using intrinsic signal changes to map within an individual brain area. To demonstrate this capability we had subjects fixate on an LED while a reversing red/green checkerboard pattern was present in either the left or the right visual field. Fig. 4 shows that this visual stimulus produced a lateralized activation in more rostral areas of primary visual cortex. A high-resolution T_1-weighted image taken along an oblique slice parallel to the subject's calcarine fissure is shown in Fig. 4 *Upper Left*, where the left- and right-hand sides of the subject's brain are indicated. In the image, three regions of interest are outlined with boxes. One position is located in the caudal region, near the occipital pole. This region of primary visual cortex is known to respond to visual input from the macular portion of the retina (14). The other two boxes are located more rostral, in areas known to respond to visual stimulation in left and right perimacular and peripheral visual space (14). The time course of signal intensity at these three regions of interest are shown both for left-field stimulation (L traces) and right-field stimulation (R traces). The box corresponding to the macular region of the retina shows an increased intensity for both L and R stimuli, as expected, because the subject fixated on an LED for both L and R stimulus paradigms. In contrast, the more rostrally positioned box in the left occipital lobe only shows a signal increase for right-visual-field stimulation, whereas a similarly located box in the right occipital lobe only shows a signal increase for left-visual-field stimulation. These results are consistent with the well-known hemifield lateralization of primary visual cortex and demonstrate the use of intrinsic signal changes in refined mapping of brain regions.

DISCUSSION

We have demonstrated that sensory stimulation produces an intrinsic signal change in gradient-echo MRI at high-magnetic fields and that the change can be followed in time. Sites of the observed signal change are predominantly associated with the gray-matter areas easily observed in corresponding T_1-weighted images and can be used to produce high-spatial-resolution functional brain maps.

The reduction of the stimulus-induced signal change produced by shortening the image-acquisition TE shows that the observed changes are caused by a change in T_2^* (or T_2). We suggest that the T_2^* changes are caused by a stimulus-induced change in magnetic susceptibility that results from a reduced concentration of the paramagnetic species deoxyhemoglobin in venous blood (1–3). This interpretation is consistent with positron emission tomography experiments that show a large increase in regional cerebral blood flow and little increase in oxygen utilization (6, 7), thus predicting a localized increase in venous-blood oxygenation.

Our human imaging experiments were motivated by a study of BOLD contrast in rodent brains. BOLD contrast was first observed in high-field (7-T) gradient echo images of rodent brains (1, 15) as dark lines surrounding highly deoxygenated venous blood vessels. *In vitro* blood phantom experiments and image simulation (2) have demonstrated that BOLD contrast in short echo times is primarily a T_2^* effect due

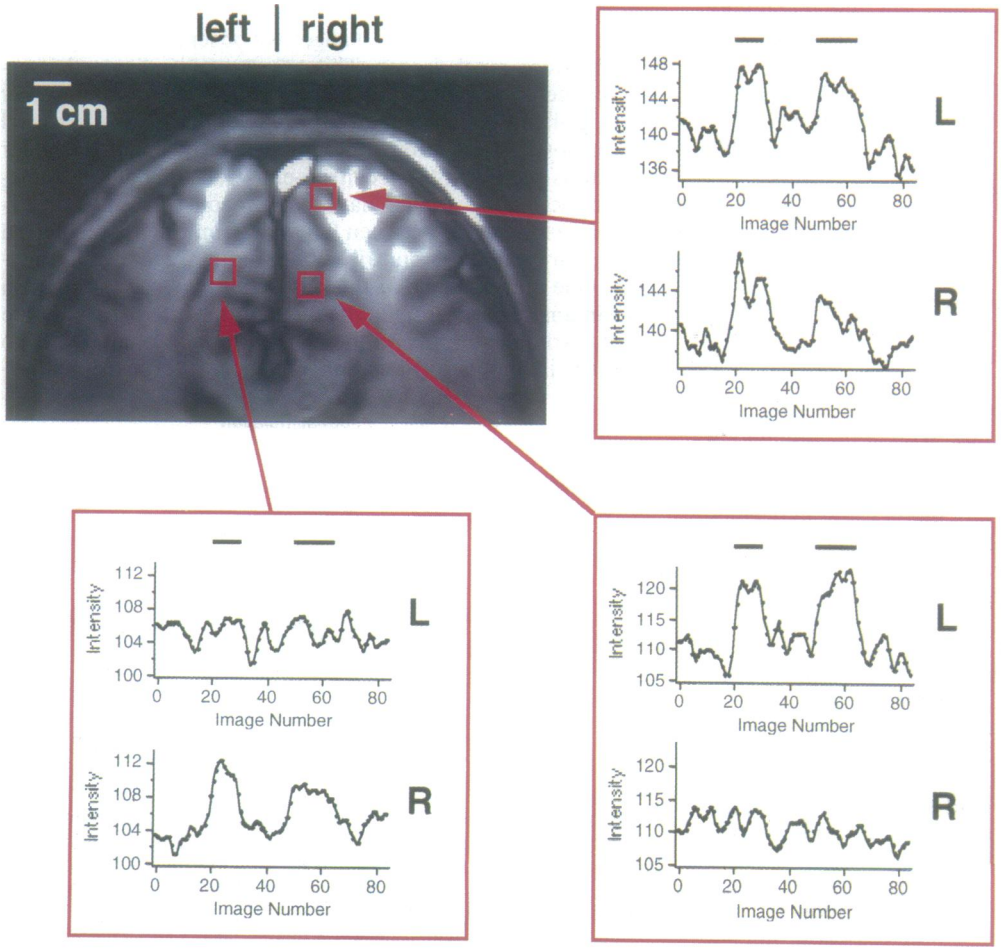


FIG. 4. Lateralized signal-intensity changes produced by right-field or left-field photic stimulation. (*Upper Left*) T_1-weighted image of the brain taken with the image slice plane oriented parallel to the calcarine fissure, as in Fig. 2*a*. (*Upper Right* and *Lower*) Time courses of signal-intensity changes for regions indicated by the three boxes in *Upper Left*. For each box, the signal-intensity change produced by left (L) and right (R) visual fields are shown. The upper box is located near the area of visual cortex corresponding to the macular region of the retina and responds to both L and R stimulation paradigms (*Upper Right*). The more rostrally located boxes show only a signal change when visual stimulation occurs in the contralateral visual hemifield (*Lower*).

to a magnetic-susceptibility variation caused by deoxyhemoglobin, an endogenous paramagnetic contrast agent.

It was previously shown by Thulborn *et al.* (16) that the T_2 relaxation of blood water depends on the degree of oxygenation of the blood, and the magnetic-susceptibility effect induced by erythrocytes containing deoxyhemoglobin was responsible for the T_2 rate change. The consequence for MRI of these T_2 characteristics of blood water has been reviewed by Brooks and Di Chiro (17). Compared to these T_2 effects on blood water, BOLD contrast in gradient echo images has an important additional feature. Part of the contribution to BOLD contrast comes from tissue water around the blood vessel and less from blood water itself. This situation is because the field distortion that produces the image change extends to the area around the blood vessel at distances twice or more the radius of the vessel. Therefore, there is an amplification in terms of the number of water molecules contributing to the image contrast. Blood water in minor vessels is very difficult to image in brain tissue because of the small fractional blood volume and the limited image resolution.

That BOLD contrast could be used to measure *in vivo* changes in hemodynamics was demonstrated in rat-brain imaging experiments (3), where pharmacologically induced changes in cerebral blood flow and oxygen utilization produced measurable changes in BOLD contrast in the cerebral cortex. Turner *et al.* (4) recently showed that transient anoxic conditions produced a large temporary decrease in intrinsic image signals at 2-T field, using echo-planner imaging technique. A quantitative analysis of BOLD image signal changes has recently been made, including those observed under conditions where venous blood vessels are not well resolved, a condition appropriate for human-brain experiments (S.O., T. M. Lee, and B. Barerre; unpublished work). The measurements we report here of changes in human visual cortex signal intensity produced by visual stimulation are, in general, consistent with the predictions made in this earlier work on BOLD contrast.

The method we demonstrated here is totally noninvasive and based on physiology-dependent intrinsic signal changes to provide well-resolved functional brain maps. It is a practical improvement over dynamic susceptibility-contrast imaging of neurally induced changes in cerebral blood volume using echo-planar techniques together with bolus injections of exogenous contrast agents (18). Although the latter imaging method clearly demonstrated the promise of MRI methods in functional mapping, the use of exogenous contrast agents limits its practical utility because only a limited number of scans can be done on an individual. Because our method uses intrinsic signals, repetitive measurements can be taken on a single subject. It is increasingly evident that the mapping of human mental operations may require many scans on a single individual because of an intra-subject variability in location of discrete brain areas that cannot be compensated for with a standardized coordinate system. Another advantage of the intrinsic signal-change method is that temporal information about the onset and offset of the change in hemodynamics is obtained. Dynamic susceptibility-contrast imaging cannot provide this temporal information.

In some of our experiments, the increased signal intensity produced by visual stimulation was accompanied by an undershoot in the signal intensity in the recovery period immediately after stimulus termination. For example, this undershoot is prominent in the TE = 40-ms signal-intensity time course shown in Fig. 3. We do not understand the origin of this effect, but a similar phenomenon has been reported in oxygen-electrode measurements of tissue oxygen level in human visual cortex (5).

The MRI functional mapping method described is based on intrinsic signal changes that rise and decay on the seconds time scale. In the present study, we used a FISP image-acquisition pulse sequence. The sequence can be run with a shielded gradient coil system without particularly strong gradient strength to acquire images, but the single-scan imaging time was dictated essentially by TE and the number of steps required for the image resolution. Echo-planar imaging methods (19) could provide a much shorter imaging time for a single scan. For T_2^*-dependent imaging, however, there is a limit in the length of the echo train, especially in high-magnetic field, which, in turn, limits the image resolution. Although further technical development may be required, it should be possible to follow spatial changes in blood oxygenation that may occur on the sub-second time scale, although this measurement will necessarily require some sacrifice of spatial resolution and signal-to-noise ratio.

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