

Mapping the brain with MRI

Magnetic resonance imaging can provide maps of human mental operations with unprecedented spatial resolution.



Unraveling the mysteries of the human brain represents one of the great challenges of modern biology. Although animal experiments provide basic insights into human brain function, some human behaviors and abilities, such as language and mathematics, appear enormously developed or unique. The study of these functions requires ways of seeing the activity of the human brain during cognitive tasks. The anatomical structure of the living human brain can be visualized in great detail using magnetic resonance imaging (MRI). Now, a new variant of MRI is being used to provide functional maps of the human brain. These MRI-based maps have unprecedented spatial resolution and can be rapidly acquired, providing movies of brain activity.

The new MRI methods rely on changes in the blood supply to the brain that accompany sensory stimulation or changes in cognitive state (see [1] for review). There are three basic methods currently under development: blood oxygenation level dependent (BOLD) contrast imaging, blood perfusion imaging using exogenous vascular contrast agents and blood perfusion imaging using inversion recovery methods. They differ in their sensitivity, degree of invasiveness and toxicity, and sensitivity to movement-related and other artifacts.

The most impressive MRI-based functional brain maps have been produced with BOLD imaging. BOLD has its origin in the magnetic properties of hemoglobin. Deoxyhemoglobin — hemoglobin without a bound oxygen molecule — is paramagnetic, so that a blood vessel containing deoxyhemoglobin placed in a magnetic field alters the magnetic field in its vicinity. This effect increases with the concentration of deoxyhemoglobin, producing an appreciable local distortion of the magnetic field surrounding venous blood vessels. This distortion can affect magnetic resonance images of nearby water protons and therein lies the magic of the method: the effect on the water molecules is a form of signal amplification. A change in hemoglobin, a molecule present at less than millimolar concentrations in bulk brain tissue and difficult to monitor directly with MRI methods, can alter the signal characteristics of water molecules present at more than 100 000-fold higher concentrations and therefore easier to measure.

BOLD contrast was first observed in 1989, in gradient echo MRI of rat brains at high magnetic fields (7T) [2]. These images were produced with very high spatial resolution (100 μm), and individual venous blood vessels were observed as a radiating pattern of dark lines in the cerebral cortex. The level of BOLD contrast — the darkness of the lines — could be modulated up and down by pharmacologically-induced changes in cerebral blood

flow and oxygen utilization [3]. Physiologically-induced changes were also observed in bulk brain tissue where individual vessels were not resolved, in both rat and cat brain experiments [4].

These animal experiments suggested that BOLD contrast imaging could be used to measure cerebral blood oxygenation non-invasively in humans. This was of particular interest as several different lines of evidence suggested that the oxygenation state of venous blood could be used to map human cognitive operations. First, it is well established that changes in neural activity are accompanied by changes in energy metabolism, and that increased metabolic rate is correlated in many mammalian species, including humans, with an increase in blood flow that can be controlled locally [1]. If the increased supply of oxygen exceeds any increased metabolic demand, an increase in the concentration of oxyhemoglobin is produced in the venous blood supply. If the metabolic demand for oxygen exceeds the increased supply, a decrease in oxyhemoglobin is produced in the venous blood. Second, positron emission tomography (PET) imaging experiments demonstrated that stimulation produced increases in regional cerebral blood flow without significantly changing local oxygen use, thus predicting an increase in regional venous blood oxygenation [5,6]. Third, light-reflectance measurements, from primate cortex, showed intrinsic signal changes following sensory stimulation that had an optical wavelength-dependence consistent with changes in the oxygenation state of hemoglobin [7,8]. Finally, older direct measurements using oxygen-sensitive electrodes in the human visual cortex showed an increase in tissue oxygenation following visual stimulation [9].

The search for BOLD-based MRI intrinsic signal changes in humans was started independently by several groups in 1991, and the results of the experiments have been recently published [10–12]. All the groups report that sensory stimulation produces a signal intensity change in the corresponding primary sensory cortex. For example, subjects viewing an array of flashing lights had signal changes in the primary visual cortex (Fig. 1). Also, voluntary movements, such as repetitively touching the index finger to the thumb or moving the hand and arm in a figure of eight motion, produced large increases in signal intensity in the primary motor cortex. All published changes show increases in signal intensity that develop with a characteristic time of 5–10 seconds following the onset of stimulation and return to baseline when the stimulation stops. This corresponds to an increase in venous blood oxygenation, consistent with the PET, optical imaging and direct tissue oxygen measurements.

The in-plane spatial resolution of BOLD-based maps (a few mm in the published work) is impressive. The thickness of the two-dimensional slices used for imaging is approximately 1 cm, but could be reduced in the future if necessary. It is likely that the ultimate spatial resolution will be determined by signal-to-noise considerations in the MRI images, as optical reflection measurements in monkeys, based on changes in hemodynamics, show spatial resolution on the 100 μm scale. As anatomical MRI images of the subject's brain can be taken immediately before the images used for mapping, accurate registration of any observed changes in specific brain areas is possible. By this kind of comparison, it has already been observed that the signal changes are predominantly occurring in the grey matter areas of the brain.

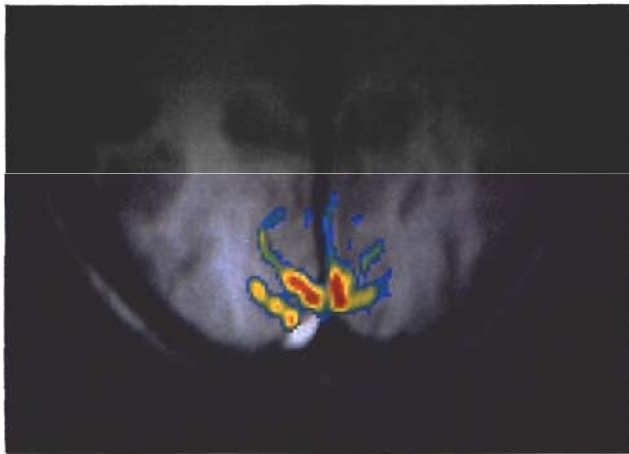


Fig. 1. MRI-based functional brain map (conditions as in [10]). An anatomical image is shown in black and white of an oblique slice through the occipital lobe of a human subject. The slice is positioned along the calcarine fissure, location of the human primary visual cortex. The superimposed coloured areas show the grey matter regions of the brain that had increased blood oxygenation during presentation of a binocular-patterned flash visual stimulus

Two recent experimental observations [10–12] are consistent with the idea that the signal intensity changes are truly BOLD based, that is produced by a change in local magnetic susceptibility produced by changes in venous oxy/deoxyhemoglobin ratios. The first is that the fractional change in signal intensity is reduced when the echo time in the MRI pulse sequence used to acquire gradient echo images is reduced [10]. The second is that the fractional change in signal intensity gets larger as the strength of the magnetic field used in the scanner increases. The first published results suggested that for binocular patterned flash stimulation at 8–10 Hz, the signal change observed in the primary visual cortex increases from 1–3% at 1.5 T magnetic field strength [11,12] to 8–20% at 4T [10]. This suggested a superlinear, possibly quadratic field-strength dependence, a result recently confirmed in experiments, reported in Berlin at the 1992 meeting of the Society for Magnetic Resonance in Medicine (SMRM), that controlled for inter-subject variability (Turner R *et al.*, NIH). Early mathematical models [13] suggested that the signal change produced by a vascular paramagnetic contrast agent, like

deoxyhemoglobin, would be linearly dependent on the magnetic field. But recent modeling efforts also discussed at the SMRM meeting have suggested that the total observed changes contain two contributions: one that is linearly dependent on the field strength and is appropriate for large blood vessels where water molecules do not diffuse very far in the field distortion during the image acquisition period, and a second contribution, quadratic in the field strength, that is appropriate for small vessels, like capillaries, where water molecules are expected to diffuse distances larger than the size of the field distortion (Menon R, Ogawa S *et al.*, University of Minnesota and Bell Laboratories).

The time courses of stimulus-induced signal changes have shown several interesting effects. The first is that following termination of the sensory stimulus, a pronounced undershoot is observed as the signal returns to baseline [10,11]. One explanation suggested for this is that the effect is caused by a difference in the recovery times of cerebral blood volume (CBV) and blood oxygenation. If blood oxygenation returned to the pre-stimulus level but the cerebral blood volume remained elevated, the BOLD effect would predict a decrease in signal intensity. A second explanation is that the cerebral blood flow (CBF) returns to pre-stimulus levels while the increased oxygen utilization is still present, so that the deoxyhemoglobin in venous blood would be transiently increased, producing a drop in signal intensity. A second feature of the dynamics at the higher signal-to-noise observed with the high magnetic field (4T), is that the signal intensity oscillates during the stimulation period. In some cases the fluctuations seem correlated in spatially separated brain areas, but their origin is still unknown. A third effect is that in some experiments, large localized decreases in signal intensity are observed. These may result from shunting away of the blood supply by areas receiving increased blood flow or, alternatively, they may represent areas with greatly increased oxygen utilization and little change in flow. Interestingly, a similar effect has been observed very recently in optical reflectance measurements from the cerebral cortex of neurosurgical patients [14].

At 1.5 T field strength, commonly used in clinical MRI systems, the signal changes observed by the BOLD contrast mechanism are only a few percent. Much larger (50–100%) changes in signal intensity can be produced by intravenous injection of an exogenous paramagnetic contrast agent. By following the time course of signal changes as a bolus of contrast agent passes through the brain, a static map of CBV or CBF can be obtained [15,16]. Perfusion-based maps of human brain function were first reported by Belliveau *et al.* [17,18]. The contrast agent they employed, Gd-DTPA, is a chelated form of a paramagnetic ion. Brain maps based upon perfusion imaging have excellent spatial resolution and can be calibrated to provide quantitative changes in CBF and CBV. In this sense, they currently represent the 'gold standard' for functional imaging. However, it is an invasive method, and toxicity problems limit the numbers of scans on a single patient. In addition, only a single map is produced by imaging during the transit of a contrast agent, and

the timecourse of the hemodynamic changes can not be measured. It is, therefore, unlikely that this method will be used extensively to answer cognitive neuroscience questions in normal subjects.

MRI has long been used for angiography in the brain and methods have been developed to measure, non-invasively, the perfusion of blood, as opposed to its state of oxygenation, in brain areas. One method, called inversion-recovery (IR), depletes the concentration of MRI-visible water protons in a brain region and measures water protons that enter the region through blood flow, providing a direct measurement of flow without the use of exogenous contrast agents. Brain maps based on the IR method have recently been demonstrated [11]. This technique also holds promise of being a quantitative measurement. One disadvantage, however, is that three-dimensional brain mapping becomes very difficult.

These new MRI methods must be compared and contrasted with existing methods in mapping human mental operations. Existing methods fall into two broad classes: direct imaging of the electrochemical activity of neurons, and indirect measurement of neural activation by imaging changes in blood supply or metabolism. The electroencephalogram (EEG) measures changes in scalp potential produced by neuronal currents within the brain. The magnetoencephalogram (MEG) measures weak magnetic fields produced by these same currents. Both methods have time resolution in the millisecond range but cannot be used directly to provide detailed maps of source location without the use of models whose validities have not yet been thoroughly demonstrated. It is likely that functional MRI imaging will be used synergistically with EEG and MEG. For example, anatomically defined areas of neural activation may be used to constrain MEG-source localization models.

Both single photon emission computerized tomography (SPECT) imaging and PET can be used to image changes in blood supply and metabolism produced by neural activation. In this sense, they measure the same changes in the brain as the new MRI techniques and are the most likely to be affected by the new technology. Most of the different forms of PET brain mapping studies have been recently reproduced, in pilot demonstrations, using BOLD contrast imaging. For example, the retinotopic organization of primary visual cortex has been demonstrated, and changes in activity due to visual mental imagery, motor imagery and language-related brain activity were all reported at the Berlin SMRM meeting. It is fairly clear that MRI already provides images with superior spatial and temporal resolution and it is likely that MRI methods will supersede PET and SPECT for functional brain mapping in humans, based on changes in blood supply. MRI offers the tremendous advantage that many repetitions of experiments can be performed on individual subjects. This is not practical with PET or SPECT due to toxicity problems.

BOLD imaging and perfusion imaging experiments are now being performed in at least a dozen MRI centers worldwide and current research is focused on several fronts. The first is aimed at producing a better biophysical

understanding of the basic observations and determining optimum image acquisition parameters for greatest signal-to-noise ratio. Extending the basic two-dimensional brain slice maps into three-dimensional maps is also being pursued. A second front is application of the methods at the present level of understanding to answer basic questions in human brain structure and function, for example mapping extrastriate areas in the normal human visual system using area-specific visual stimulation patterns. Clinical applications are also being pursued, such as mapping epileptic foci or determining the anatomical location of important language areas (such as Broca's or Wernicke's area) in patients prior to neurosurgical procedures. Mapping the brain areas involved in higher cognitive operations like visual mental imagery is also actively being pursued. It is likely that many new and interesting observations will be made, in the very near future, using the new tools of MRI-based neuroimaging.

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