Original Research

Dynamic MR Imaging of Human Brain Oxygenation during Rest and Photic Stimulation[1]

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Dynamic FLASH (fast low-angle shot) magnetic resonance (MR) imaging was used to monitor changes in brain oxygenation in the human visual cortex during photic stimulation. The approach exploits the sensitivity of the gradient-echo signal to susceptibility changes induced by varying concentrations of paramagnetic deoxyhemoglobin in the cerebral blood pool. After the onset of binocular photic stimulation (10 Hz, red light, checkerboard), there was a distinct increase in the MR signal in the calcarine cortex within 6–9 seconds, indicating a decrease in the total deoxyhemoglobin concentration. After the stimulation was switched off, the MR signal returned to a basal value within a similar period of time. Assuming enhanced blood flow and only a minor increase in oxygen consumption (production of deoxyhemoglobin) during physiologic activation, the results reflect an enhanced supply of diamagnetic oxyhemoglobin and an increase in the partial oxygen pressure in the capillary and venous blood pools. In addition, a decrease in the basal MR signal in the calcarine cortex was observed during the first 60–90 seconds of persistent activation, which may be understood as an autoregulatory adaptation to increased overall brain activity associated with information processing due to continuous perception of visual stimuli.

Index terms: Blood, MR, 10.1214 • Blood, flow dynamics • Brain, function, 10.1214 • Brain, MR, 10.1214 • Rapid imaging

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Abbreviations: FLASH = fast low-angle shot, PET = positron emission tomography, RF = radio frequency, ROI = region of interest.

THE AVAILABILITY OF OXYGEN is fundamental to brain energy metabolism. The control of its supply through blood flow and its metabolic utilization have been shown to be coupled with brain function (1). Regional cerebral blood flow, oxygen extraction fractions, and glucose consumption rates have been measured with different modalities, such as xenon indicator techniques (2), transcranial Doppler ultrasonography (3), and positron emission tomography (PET) with radioactive tracers (4). Dynamic magnetic resonance (MR) imaging (5) in conjunction with a bolus application of an exogenous contrast agent (6,7) has provided access to determination of regional cerebral blood volume (8,9) and has recently been extended to reinvestigation of the increase in cerebral blood volume during photic stimulation (10).

The MR imaging method is based on the sensitivity of a gradient-echo sequence such as FLASH (fast low-angle shot) or echo-planar imaging to signal dephasing in local magnetic field gradients. The signal intensity is determined by the net molecular magnetic moment of the chosen contrast agent and may be enhanced by the use of long echo times, large voxel sizes, and high magnetic field strengths. Transient changes in tissue susceptibility after administration of a bolus of a paramagnetic contrast agent may then be monitored by continuous sequential imaging with a time resolution of a few seconds or less.

In the present study, the concept of transient susceptibility contrast was used to determine regional changes in brain oxygenation in the visual cortex of healthy human subjects during rest and photic stimulation. In this method, signal intensity is due to differences in the magnetic susceptibility of blood induced by the presence of paramagnetic deoxyhemoglobin in red cells (11,12). Thus, high-spin deoxyhemoglobin acts as an effective endogenous contrast agent, as opposed to low-spin diamagnetic oxyhemoglobin. Changes in the concentration of deoxyhemoglobin are tightly linked to oxygen saturation and may be directly and noninvasively followed with fast gradient-echo MR imaging. Respective contrasts were found in 7–8.4-T MR imaging studies of rat brain (13,14) and

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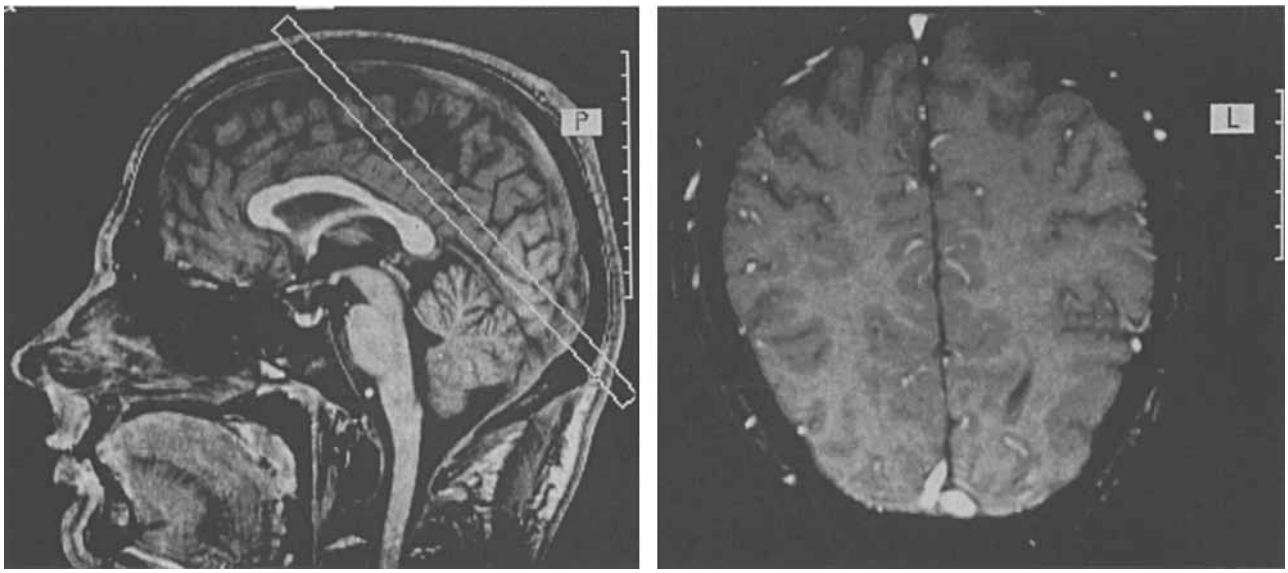


a. b.

Figure 1. Anatomic definition of the brain section used for functional imaging of the calcarine cortex. **(a)** Sagittal image from a three-dimensional data set (radio-frequency [RF]–spoiled FLASH sequence, 20° flip angle, TR msec/TE msec = 15/6, 32 × 256 × 256 matrix, 4-mm partition thickness, 2-minute acquisition time) depicting the position, orientation, thickness, and field of view of the section selected for functional imaging. **(b)** Corresponding oblique single-section MR image (RF-spoiled FLASH sequence, 70° flip angle, 100/6, 256 × 256 matrix, 4-mm section thickness, 26-second acquisition time) depicts gray matter, white matter, cerebrospinal fluid, and blood vessels.

in 2.0-T echo-planar imaging studies of anoxia in cat brain (15).

• MATERIALS AND METHODS

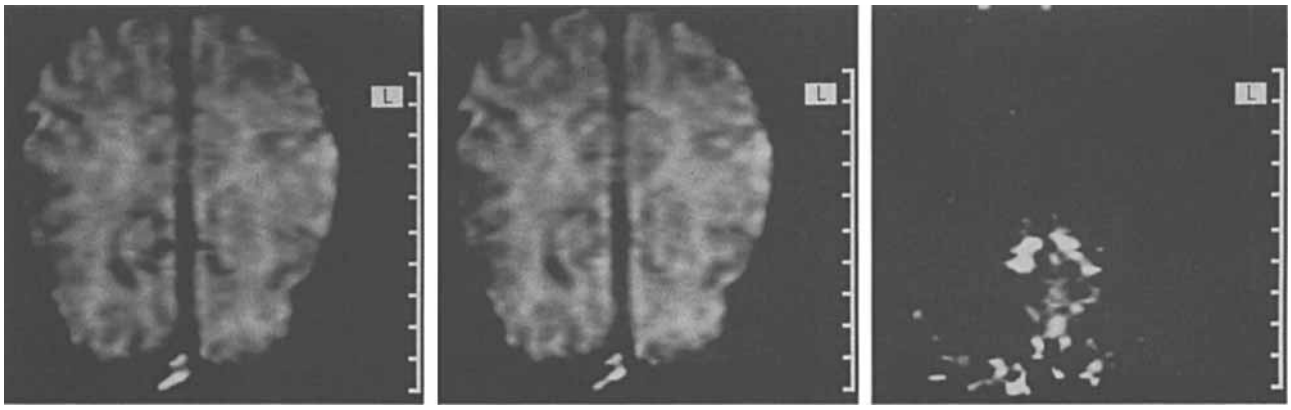
All studies were performed at a magnetic field strength of 2.0 T with a Magnetom imager (Siemens, Erlangen, Germany) and the standard circularly polarized head coil (Siemens). For functional investigations of the visual cortex, an oblique image orientation was defined in sagittal three-dimensional FLASH MR imaging, as shown in Figure 1a. An assessment of gray matter, white matter, cerebrospinal fluid, and blood vessels in the selected section was obtained by means of single-section FLASH MR imaging, as shown in Figure 1b. Dynamic changes in the concentration of deoxyhemoglobin were monitored with a series of susceptibility-sensitized FLASH MR images (RF spoiled, 40° flip angle, 46.874/38), with a time resolution of 3 seconds and a spatial resolution of 1.5 × 3.0 × 8.0 mm, or 36 μL (64 × 128 matrix, 200-mm field of view, 8-mm section thickness). Additional experiments were performed with an even faster FLASH sequence (RF spoiled, 20° flip angle, 23.437/14), yielding a time resolution of 1.5 seconds. Typically, 64 sequential images were acquired in investigational periods of 1.6 and 3.2 minutes, respectively.

Binocular photic stimulation was accomplished with pulses of red light (10-Hz frequency) transmitted into the magnet via glass fiber optics, as used for metabolic studies with localized proton MR spectroscopy, in which there was a 50% decrease in cerebral glucose but no consistent increase in lactate with photic stimulation (16). The latter finding contradicts work by others (17) and needs further study. The arrangement comprised a matrix of 5 × 4-point sources (15 × 15-mm checkerboard) for each eye of the subjects (50-mm distance, 18° view angle). The protocols of activation were as indicated in the figures (see below). A total of 10 examinations were performed in six healthy adults (24–29 years old; mean, 27.5 years). The volunteers wore earplugs and were advised to keep their eyes closed during dark phases. Written informed consent was obtained from all subjects prior to the investigation.

• RESULTS

Figure 2 shows changes in brain oxygenation in a healthy volunteer during resting conditions in the dark (Fig 2a) and physiologic activation by photic stimulation (Fig 2b). Each image represents the average of four consecutive acquisitions. In Figure 2b most areas of the calcarine cortex are brighter because of a reduction in the mean deoxyhemoglobin concentration. Reversed effects were observed when the stimulation was switched off. Figure 2c shows the difference image of Figures 2b and 2a. It may be regarded as a functional oxygenation map, with intensities that are directly proportional to the net decrease of deoxyhemoglobin. The map suggests a remarkable increase in oxygen saturation confined to the visual cortex. Although it displays some internal heterogeneity, there is no activation in other areas of the brain.

Figures 3 and 4 summarize ROI evaluations of signal intensity changes observed in two subjects for different stimuli (Fig 3a–3c) and within different parts of the calcarine cortex (Fig 4), respectively. The results are compared with data obtained from a control region in frontal paramedian gray matter (Fig 4d). The



a. b. c.

Figure 2. Functional imaging of regional changes in brain oxygenation during photic stimulation. **(a)** Average of four consecutive susceptibility-sensitized MR images in the dark phase (RF-spoiled FLASH sequence, 46.874/38, 40° flip angle, 64 × 128 matrix, 200-mm field of view, 8-mm section thickness, −40° transverse to coronal angulation, 3-second acquisition time for each image). **(b)** Average of four consecutive images obtained during binocular photic stimulation (10 Hz, red light, 5 × 4-point sources) immediately after the acquisitions shown in **a.** **(c)** Difference image **(b − a)** indicates a net increase in oxygenation in the visual cortex.

stimulation protocols comprised different durations of activation periods and recovery phases in the dark state. They were all measured during the same examination, with intermediate resting periods in the dark of at least 10 minutes. In Figure 3, the selected ROI covered the entire visual cortex of both hemispheres, excluding potential contributions from the sagittal sinus. The spatial heterogeneity indicated in Figure 2c was further investigated by comparing ROI data from the anterior (Fig 4a), posterior (Fig 4b), left (Fig 4c), and right (Fig 4d) regions of the visual cortex. Although the same activation pattern was accurately reflected in all regions, there were differences in the amplitudes of the signal enhancement.

• DISCUSSION

Variations in gradient-echo MR imaging signal intensities during different states of brain activity are directly related to fluctuations in the concentration of paramagnetic deoxyhemoglobin in the cerebral blood pool. Dynamic MR imaging of transient changes, therefore, allows a rapid and noninvasive assessment of *relative* changes in regional brain oxygenation. In the present study, the finding of an overall reduction in the deoxyhemoglobin level with photic stimulation is believed to originate mainly in the venous rather than the arterial part of the blood pool, since the oxygen saturation in the arterial blood remains more or less constant (≈95%). It may be understood as the net result of a substantially increased supply of oxygen stemming from enhanced blood flow in the posterior cerebral artery (3), outweighing the increase in deoxyhemoglobin due to enhanced cerebral blood volume and elevated oxygen consumption (4).

The data presented in Figures 3 and 4 reveal a number of additional findings. After the onset of photic stimulation the MR signal increased in the visual cortex but not in other parts of the brain. The signal increase was 5% in three of six subjects and 3%, 2%, and 1.5% in the other three subjects, respectively. However, repeat measurements indicated predominance of intraindividual rather than interindividual physiologic variations. For example, the volunteer with a 2% signal increase had a 4% increase with the same protocol in a second study. Therefore, more careful control of the subjects with respect to their systemic condition (eg, monitoring of blood pressure) may become important for studies of brain activation.

In all subjects, the maximum signal intensity occurred within a period of 6–9 seconds (two to three images), with no signal change during the first 3 seconds of stimulation. These findings were confirmed by series of 1.5-second images (see below). The effect was fully reversible, yielding a similar temporal characteristic for return to the dark state. This lag time, or "hysteresis," in brain oxygenation may be attributed to the limiting speed at which blood flow can be effectively enhanced or reduced in brain parenchyma, in agreement with Doppler studies reporting a latency of about 5 seconds (3).

A careful examination of the time course of the MR signal revealed a decrease in the baseline intensity in the visual cortex during the first 60–90 seconds of the various stimulation protocols that was not seen in control regions. This decrease, by about 2%–3%, is of almost the same magnitude (but of opposite sign) as the rapid response to stimulation. The corresponding deoxygenation may be understood as an autoregulatory adaptation by the metabolism to the increased energy demand of enhanced overall "background" activity, which has no direct link to an acute stimulus but is related to the information processing associated with the continuous perception of visual stimuli. For this process, the increased production of deoxyhemoglobin is not counterbalanced by a corresponding change in blood flow and oxygen delivery. Interestingly, the increased oxygenation level that can be reached through stimulation after a lower-level steady-state equilibrium has been established is close to the original oxygenation level in the resting dark

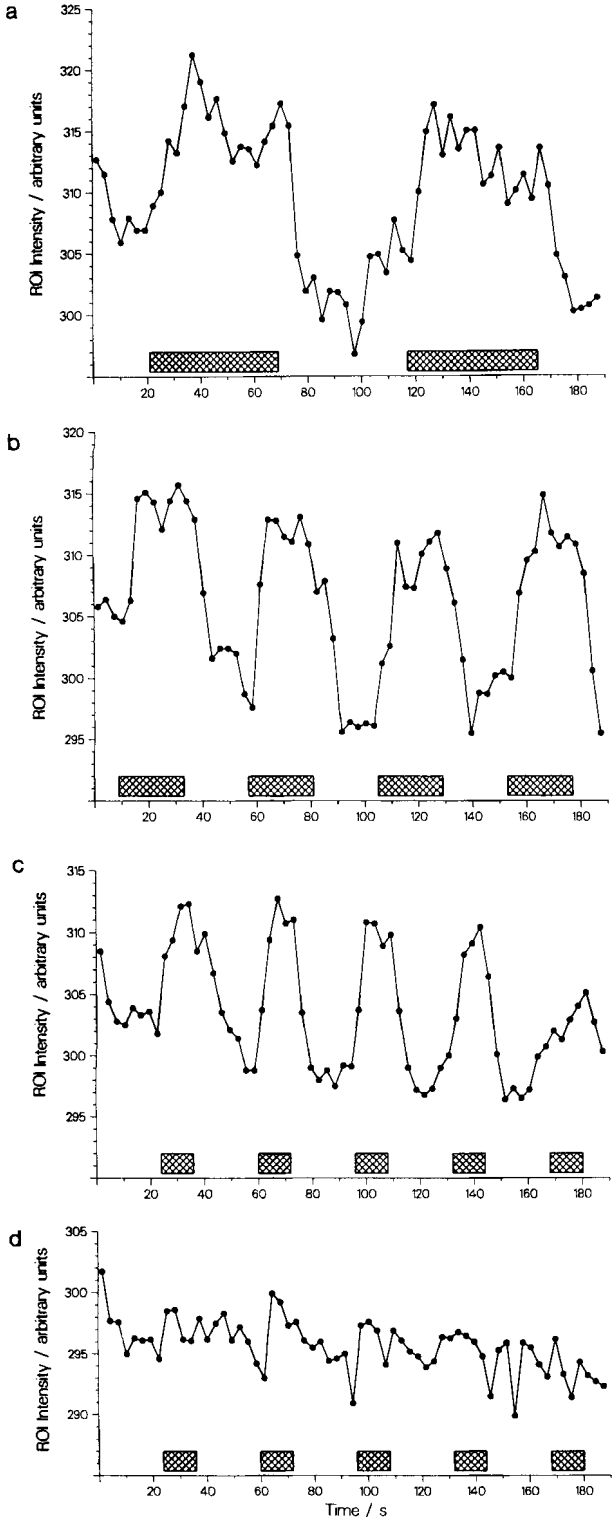


Figure 3. Time course of brain oxygen saturation in the visual cortex for different protocols of photic stimulation. The data represent region-of-interest (ROI) intensities in a 31-mm-diameter sphere centered on the visual cortex. The cross-hatched bars indicate periods of photic stimulation: (*a*) 48-second stimulation, 48-second darkness; (*b*) 24-second stimulation, 24-second darkness; (*c*) 12-second stimulation, 24-second darkness; (*d*) same protocol as in *c* but from a control region in frontal midline gray matter.

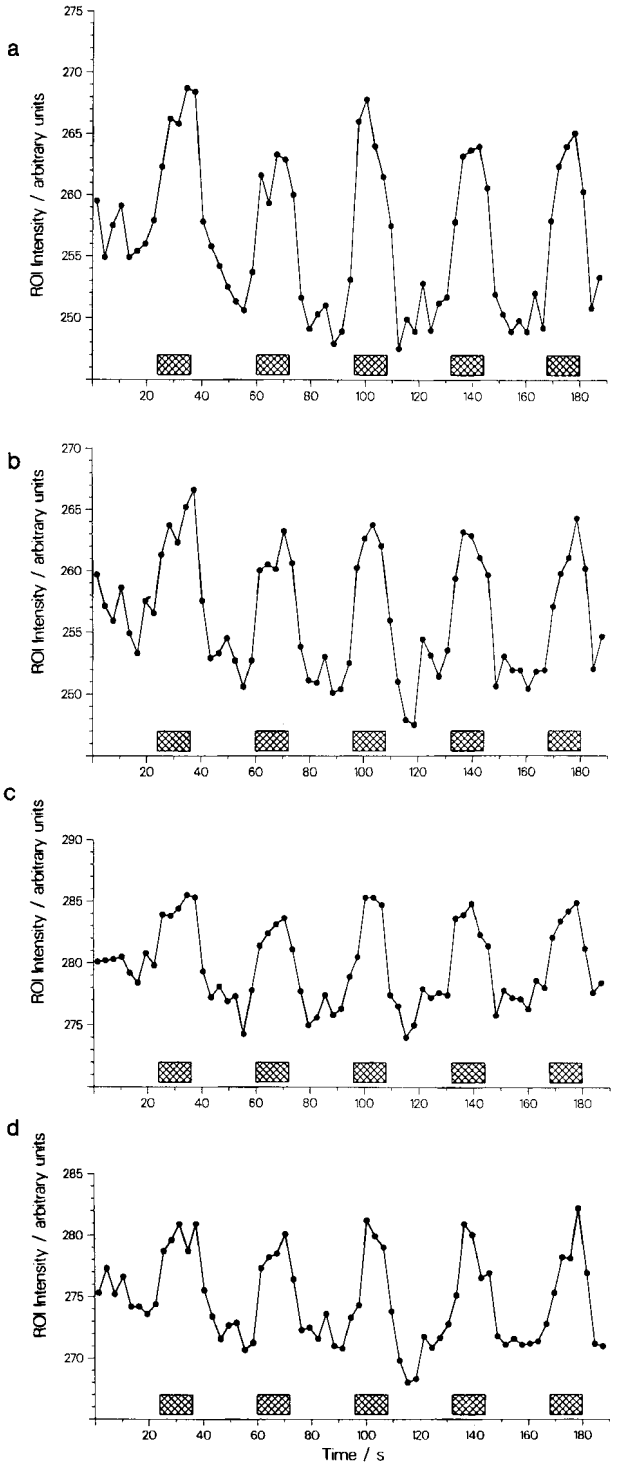


Figure 4. Time course of brain oxygen saturation in different areas of the visual cortex during photic stimulation (12-second periods of stimulation [cross-hatched bars], 24-second periods of darkness): (*a*) anterior midline region of the visual cortex (horizontal box, 28 × 12 mm), (*b*) posterior midline region (centric sphere, 19-mm diameter), (*c*) left posterior region without contributions from the longitudinal fissure (vertical box, 9 × 19 mm), (*d*) corresponding right posterior region (vertical box, 9 × 19 mm).

state. In retrospect, this finding explains why earlier static investigations in either the dark state or during persistent stimulation did not result in substantial intensity differences.

Doppler and PET studies have shown that stimuli of different complexity cause differences in flow velocity and regional patterns of brain activity, respectively. With the setup in the present study (10-Hz binocular checkerboard), there was no spatial variability in the qualitative response to stimulation. All parts of the visual cortex exhibited a synchronous change in oxygen saturation. Differences in magnitude, such as a 6% signal increase in the anterior area (Fig 4a) versus a 3.5% increase in the posterior regions of the right and left hemisphere (Fig 4c, 4d), probably reflect differences in tissue vascularization modulating quantitative changes in cerebral blood volume.

Similar results were obtained for both the rapid response to stimulation (oxygenation) and the slow approach to a new equilibrium (deoxygenation) when the period of stimulation was prolonged (144 seconds) or the recovery phase in the dark state was shortened (12 seconds). The latter experiments were performed with a time resolution of 1.5 seconds. Although the resulting signal increase during stimulation was reduced from 5% to about 2.5% at the shorter echo time, the simultaneous improvement in the signal-to-noise ratio still allowed an unambiguous assessment of relative changes in the deoxyhemoglobin concentration. For example, the shape of the response curve for the protocol used in Figure 3b (24-second stimulation, 24-second dark recovery) could be perfectly reproduced with the higher time resolution. However, if a 12-second stimulation was followed by a dark phase of only 12 seconds, the trapezoidal response curve assumed a triangular shape. This phenomenon obviously reflects mutual overlap of the aforementioned 6–9-second lag times in brain oxygenation.

It is worth noting that the present observations provide a serious complication for exogenous contrast agent–enhanced MR imaging measurements of cerebral blood volume during physiologic activation (10). While the inflow of paramagnetic gadopentetate dimeglumine *decreases* the MR signal, the simultaneous reduction of paramagnetic deoxyhemoglobin on stimulation *increases* the MR signal. The overlap of the two effects cannot be resolved in a single experiment. Pertinent MR imaging studies are therefore expected to underestimate the increase in cerebral blood volume under activated conditions.

In conclusion, the present work demonstrates the feasibility of a rapid and noninvasive assessment of relative changes in regional brain oxygenation with a conventional fast MR imaging sequence. It shows transient states of hyperoxemia in the visual cortex during photic stimulation and slow deoxygenation, probably due to associated neural (and glial) activity. The ease and simplicity of the MR imaging approach, its general availability, and its combination with anatomic and metabolic insights are expected to substantially broaden future studies of physiologic activation related to cognitive and mental processes in the functioning human brain. Widespread applications to studies of pathologic states in brain disease are foreseeable. ●

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• ADDENDUM

Recently, related work on human brain oxygenation has been published or brought to our attention from other laboratories. It has been reported that a signal increase occurs in 1.5-T echo-planar images of the motor cortex during task activation (18), in the visual cortex during photic stimulation (19), and in 4.0-T gradient-echo images during photic stimulation (20).

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