Thalamic stimulation and functional magnetic resonance imaging: localization of cortical and subcortical activation with implanted electrodes

Technical note

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The utility of functional magnetic resonance (fMR) imaging in patients with implanted thalamic electrodes has not yet been determined. The aim of this study was to establish the safety of performing fMR imaging in patients with thalamic deep brain stimulators and to determine the value of fMR imaging in detecting cortical and subcortical activity during stimulation.

Functional MR imaging was performed in three patients suffering from chronic pain and two patients with essential tremor. Two of the three patients with pain had undergone electrode implantation in the thalamic sensory ventralis caudalis (Vc) nucleus and the other had undergone electrode implantation in both the Vc and the periventricular gray (PVG) matter. Patients with tremor underwent electrode implantation in the ventralis intermedius (Vim) nucleus. Functional MR imaging was performed during stimulation by using a pulse generator connected to a transcutaneous extension lead. Clinically, Vc stimulation evoked paresthesias in the contralateral body, PVG stimulation evoked a sensation of diffuse internal body warmth, and Vim stimulation caused tremor arrest.

Functional images were acquired using a 1.5-tesla MR imaging system. The Vc stimulation at intensities provoking paresthesias resulted in activation of the primary somatosensory cortex (SI). Stimulation at subthreshold intensities failed to activate the SI. Additional stimulation-coupled activation was observed in the thalamus, the secondary somatosensory cortex (SII), and the insula. In contrast, stimulation of the PVG electrode did not evoke paresthesias or activate the SI, but resulted in medial thalamic and cingulate cortex activation. Stimulation in the Vim resulted in thalamic, basal ganglia, and SI activation.

An evaluation of the safety of the procedure indicated that significant current could be induced within the electrode if a faulty connecting cable (defective insulation) came in contact with the patient. Simple precautions, such as inspection of wires for fraying and prevention of their contact with the patient, enabled the procedure to be conducted safely. Clinical safety was further corroborated by performing 86 MR studies in patients in whom electrodes had been implanted with no adverse clinical effects.

This is the first report of the use of fMR imaging during stimulation with implanted thalamic electrodes. The authors’ findings demonstrate that fMR imaging can safely detect the activation of cortical and subcortical neuronal pathways during stimulation and that stimulation does not interfere with imaging. This approach offers great potential for understanding the mechanisms of action of deep brain stimulation and those underlying pain and tremor generation.

Key Words: chronic pain • deep brain stimulation • functional magnetic resonance imaging • periventricular gray matter • somatosensory cortex • thalamus

In the past several years, numerous studies have demonstrated the utility of functional magnetic resonance (fMR) imaging for human brain mapping both in normal and pathological conditions. At the same time, there has been a resurgence of interest in the use of chronic thalamic or deep brain stimulation (DBS) for treating medically refractory movement disorders and chronic pain. The dramatic results achieved with DBS have provided great promise for expanding the clinical scope of this technique. These advances, however, have not been paralleled by progress in understanding the mechanisms of action of DBS. It is unclear whether DBS causes a blockade or activation of neuronal pathways, or a combination thereof, to achieve its effects.

Functional imaging is ideally suited to DBS because of its consistent and controllable stimulation of the brain,
yielding reproducible clinical effects. Recently, there have been reports of positron-emission tomography (PET) studies made during DBS in patients with Parkinson’s disease and chronic pain. However, PET scanning has limitations such as the need for group data averaging, low spatial/temporal resolution, and the requirement for injection of radioactive tracers. Functional MR imaging is advantageous because it is noninvasive, has superior spatial/temporal resolution, can provide functional mapping information in individual patients, and is widely available.

There have been no previous reports of fMR imaging studies in patients with implanted thalamic electrodes. An important issue has been the safety of performing MR imaging in patients with implanted electrodes, because there is a potential for radiofrequency (RF) and gradient magnetic fields to induce currents in, and cause heating of, the implanted electrode.

In this study, our objectives were to determine the safety and efficacy of using fMR imaging during DBS and to discover whether fMR imaging could detect the activation of cortical and subcortical pathways that underlie the clinical response to DBS.

Description of Technique

Safety Evaluation

Potential electrical hazards may be encountered when performing MR imaging in a patient with implanted electrodes, which can arise from the electromotive force (EMF) induced by RF and gradient pulses. In considering a “worst-case scenario” in an fMR imaging session, the EMF can be induced in the loop composed of patient, implanted electrode, connecting wires, and external cable linked to a pulse generator. A potentially hazardous situation arises if the patient becomes the only significant resistance in this loop. This occurs if the external cable becomes frayed and provides a very good electrical contact with the patient. In this theoretical maximum-risk scheme, a voltage drop with a magnitude equal to the induced EMF would appear across the patient, causing an electrical current with potential heating of tissue adjacent to the electrode.

To assess the magnitude of this maximum theoretical hazard, induced measurements of EMF were made. For this purpose, a planar loop consisting of 1.6-mm-diameter copper wire was shaped to conform to the largest possible area in the bore of the MR imaging system. The peak-to-peak voltage (Vp–p) of the EMF induced in this loop was measured by using an oscilloscope connected to the wire loop via a 50-Ω coaxial cable and an impedance-matched 10-dB attenuator. Measurements were made for spin-echo, gradient-echo, and spiral-pulse sequences on a 1.5-tesla MR magnet. The loop was placed in both the horizontal and transverse planes to assess the contributions from RF and gradient pulses, respectively.

The power dissipated in the tissues adjacent to the electrode was computed as EMF²/R, where R is the calculated resistance of the brain tissue surrounding a cylindrical electrode 10.5 mm long and 1.3 mm in diameter (assuming a conductivity of 0.1 siemens). The specific absorption rate in watts per kilogram around the electrode was computed as conductivity times EMF² divided by density (1000 kg/m³) and by radial distance. The adiabatic temperature rate of change was computed as specific absorption rate divided by the heat capacity of the tissue (4200 J per degree Celsius).

Patient Population

Three patients with refractory chronic pain and two patients with essential tremor were studied. Two of the patients with chronic pain had traumatic spinal cord injuries with ensuing intractable, disabling neuropathic pain described as constant, steady, and burning. These patients had undergone electrode implantation into the thalamic sensory ventralis caudalis (Vc) nucleus. The third patient had sustained a surgical iatrogenic injury to the trigeminal nerve and, subsequently, developed incapacitating neuropathic pain characterized by steady burning and an evoked component of touch and cold allodynia. This patient underwent implantation of electrodes into the Vc and peri-ventricular gray (PVG) matter.

Stereotactic Electrode Implantation

The patients underwent stereotactic implantation of quadripolar DBS electrodes (model 3287; Medtronic, Minneapolis, MN) guided by single-cell microelectrode recording and stimulation. This procedure has been described in detail previously. The microelectrode recording and stimulation allow for the optimum placement of the electrode in the Vc nucleus at a location where stimulation results in contralateral paresthesias in the patient’s area of pain. Placement of the PVG electrode is based on physiological localization and anatomical targeting (typically 5 mm anterior to and at the level of the posterior commissure and 2 to 3 mm lateral to the wall of the third ventricle). Microstimulation in this area can result in a diffuse sensation of warmth or a generalized feeling of well being. Similarly, microelectrode recording and stimulation were used to determine the optimum target in the ventralis intermedius (Vim) nucleus for implantation of the electrodes.

All implanted electrodes were tunneled beneath the galea and connected to an extension lead that exited the scalp to allow for transcutaneous testing during the test trial period. To avoid a large magnetic susceptibility artifact from the excess wiring and connectors in the subgaleal space, wires were placed as far anteriorly as possible so that the areas of interest were not obscured on the MR images.

Test Trial

Subsequent to the initial implantation, the patients underwent a test trial period of 5 to 7 days. During this time, stimulation was achieved by connecting the transcutaneous extension leads to a standard pulse generator device (model 3628 screenr; Medtronic). Bipolar stimulation was performed using the pole combinations evoking contralateral paresthesias in the patient’s area of pain (Vc stimulation: 2–4 V, 50–85 Hz, and 100–200 μsec pulse width), vagus, generalized sensation of warmth (PVG stimulation: 2 V, 25–50 Hz, 75–100-μsec pulse width), and tremor arrest (Vim stimulation, 2–4 V, 150 Hz, 60-μsec pulse width). The fMR imaging studies were per-
formed during the test trial period. After the test trial, patients with significant pain relief (>50% pain reduction) or tremor abolition underwent a procedure in which a permanent implantable pulse generator (IPG) device (Itrel II; Medtronic) or an RF-coupled device (Xtrel; Medtronic) was placed internally.

Experimental Design

Preparation and Positioning of Patients. All patients gave informed consent to the procedure. The patients clearly understood the experimental design and were free to withdraw at any time from the study. Before entering the imaging room, test stimuli were delivered to verify the effect of the previously determined settings. The patients were then placed supine on the MR imaging table. Immobilization was achieved by supporting the patient's head with a custom-designed deflatable bag containing small plastic spheres. Evacuation of air from this device securely and comfortably immobilized the patient's head.

A second trial of stimulation was performed to verify the exact threshold of stimulation-induced paresthesias. There were no differences in thresholds when the patient was outside or inside the magnet. Patients were instructed to relax, keep their eyes closed, and not to speak or move throughout the procedure. A member of the experimental team was present next to the imaging table at all times during the procedure.

Imaging Sequence. Imaging was performed using a 1.5-tesla MR imaging system (GE Signa Echospeed; General Electric Medical Systems, Milwaukee, WI). After a sagittal localizer image had been obtained, high-resolution T1-weighted gradient-echo images were obtained to provide anatomical information on which data from the functional images were superimposed. Images were acquired in the axial plane encompassing the thalamus to the vertex and in the coronal plane from the anterior portion of the lateral ventricle to the somatosensory cortex. Functional data were obtained using a spiral acquisition through k space in 11 contiguous slices that were 7 mm thick. Other sequence parameters included an 880-msec repetition time, a 40-msec echo time, a 69° flip angle, and 80 msec per spiral, with four spiral acquisitions. The field of view was 30 cm. All 11 slices were repeatedly imaged every 3.52 seconds with an inplane resolution of 2.4 mm.

Task Design. One cycle consisted of 30 seconds of stimulation and 30 seconds of rest. Each experiment consisted of eight cycles. Within each period of stimulation, an up-and-down ramp of pulse generator voltage was accomplished within 2 to 3 seconds. The thalamic electrodes were activated using the transcutaneous lead connected to the pulse generator. The pulse generator was kept outside the imaging room, test stimuli were delivered to verify the effect of the previously determined settings. The patients were instructed to relax, keep their eyes closed, and not to speak or move throughout the procedure. A member of the experimental team was present next to the imaging table at all times during the procedure.

Statistical Analysis. Images were corrected for motion by using automated image registration.18,32,33 Images were analyzed using “Stimulate” software (Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, MN). An analysis of task-related activation was performed by calculating, on a pixel-by-pixel basis, the coefficient of correlation (r value) between the time series data and a square reference waveform corresponding to the task sequence. Pixels with r values greater than 0.25 were color coded and overlaid on the high-resolution anatomical images. Pixels overlying vessels were not considered.

Each cluster of task-related significant pixels was designated as a region of interest (ROI). Evaluation of each ROI was accomplished by observing the detailed relationship between the signal intensity changes and the alternating time course of the stimulation cycle. Functional MR imaging data affected by patient motion can falsely indicate areas of brain activation despite relatively stringent correlation thresholds, even though their time-course signals are not truly correlated with the stimulus cycle. This arises from the nonrandom nature of the motion-induced signal changes, which violates the assumptions underlying the use of a simple correlation test. Therefore, all ROIs were subjected to a more stringent criterion such that only time courses exhibiting a “saw-tooth” pattern were accepted. Specifically, the mean signal of each stimulus “on” condition was required to be higher than the adjacent “off” conditions during each of the eight activation cycles. If this criterion was not satisfied, the data were excluded. This is a rather stringent condition, but it does significantly reduce the number of false-positive activations arising from patient motion.

Results

Thalamic Sensory Nucleus Stimulation

At paresthesia-evoking intensities, Vc stimulation resulted in activation of primary somatosensory cortex (SI) in all three patients with pain. In most cases, areas of cortical activation corresponded to the body parts in which the paresthesias were experienced. These activations were consistent with the classic somatotopic (homuncular) organization of body parts in two of the three patients. Figure 1 demonstrates a robust activation in the SI with stimulation of the right-sided Vc electrode (3 V, 100 Hz, 200-μsec pulse width), resulting in paresthesias involving the left upper extremity, trunk, and proximal lower extremity. An ROI analysis (Fig. 2) of the pixels denoted by the green box in Fig. 1 reveals the exact nature of the signal correlation with respect to the stimulus cycle. This saw-tooth pattern was required of all ROIs in this study.

Figure 3A demonstrates characteristic activation of the SI in another patient experiencing paresthesias predominantly in her lower extremity and mildly in her upper extremity (3.2 V, 75 Hz, 150-μsec pulse width). The area of activation (arrow in Fig. 3A) is consistent with the somatotopy based on the classically described homuncular organization of the lower extremity. When stimulation intensity was decreased to a subthreshold level (no paresthesias at 2.5 V), there was no activation of the SI (Fig. 3B), even at less stringent r-value thresholds.

In addition to activation of the SI, we observed stimulation-related activation of other parts of the somatosensory perception pathways including the thalamus, secondary somatosensory cortex (SII), and insula.
Periventricular Gray Matter Stimulation

In contrast to Vc, PVG matter stimulation did not activate the SI, but did activate the cingulate cortex (Fig. 4). This was consistent with the clinical response, because PVG stimulation evoked a generalized, diffuse, warm sensation, but no paresthesias. Additionally, stimulation of the PVG electrode resulted in a relatively diffuse activation of the medial wall of the third ventricle in proximity to the electrode poles (Fig. 5).

Ventralis Intermedius Stimulation

Stimulation of the Vim electrode resulted in activation of the thalamus and basal ganglia. As with PVG, thalamic activation was observed in close proximity to the electrode (Fig. 6). In addition, activation of the SI was also observed in both patients.

Safety of fMR Imaging and Implanted Electrodes

The greatest risk to the patient undergoing fMR imaging with an implanted electrode occurs when the patient becomes part of a current loop that also consists of the electrode and the connecting wires (connecting the DBS electrode to the pulse generator). This particular situation can only occur if the insulation of the connecting wire is frayed and is in good contact with the patient’s body.

It is known that EMFs are induced in wire loops placed in the changing magnetic fields produced in an MR imaging system (either caused by RF or applied magnetic field gradients). Also EMFs increase with the cross-sectional area of the wire loop. For this purpose we chose to measure the induced EMF within a wire loop that was the maximum size that could fit into the bore of the MR imaging system. This was performed to determine the worst possible scenario.

The oscilloscope measurements of EMFs induced in the largest possible wire loop filling the magnet bore demonstrated gradient-induced EMFs of up to 12 Vp-p, and RF EMFs of up to 7.5 Vp-p. The maximum power dissipated as a result of the gradient-induced EMF of 12 Vp-p (estimated tissue resistance 850 Ω) is 14 mW. Neglecting heat dissipation such as that via blood flow, the estimated peak rate of temperature rise at the electrode surface is 1°C/minute. Therefore, in the worst case scenario, in which the patient becomes part of a large electrical loop from contact with a connecting wire with insufficient insulation, some heating of brain tissue could occur.

In a practical clinical setting, over the past 2 years, we have performed 86 MR imaging studies in patients with implanted thalamic and subthalamic electrodes. This study included 78 patients who underwent anatomical MR imaging and eight patients who underwent fMR imaging studies. None of these patients reported any discomfort or adverse effects while undergoing the studies. Although all eight patients undergoing fMR imaging had transcutaneous wires, the 78 patients who underwent anatomical MR imaging had DBS units attached to either transcutaneous wires or implanted IPG units. The IPG devices either turned off or, less commonly, turned on during the study. There were no adverse effects of MR imaging on the functioning of the stimulators or the IPG units; the stimulation parameters and the clinical response did not change after imaging.

Discussion

During the past several years, fMR imaging has become one of the most widely used tools for studying the functional neuroanatomy of the brain. At the same time, there
has been a resurgence in the use of DBS for refractory movement and pain disorders. Despite these strides, a better understanding of the mechanisms of action of DBS is still lacking.

We believe that fMR imaging is an ideal tool to use to increase our understanding of the mechanisms of action of DBS. Deep brain stimulation results in a direct and controlled brain stimulation coupled with a consistent and clearly defined clinical response. These features used in conjunction with fMR imaging provide a unique opportunity for studying the circuitry and mechanisms underlying tremor and pain.

Our primary objective was to determine the feasibility of performing fMR imaging during stimulation. This combined approach has not previously been reported, primarily because of the safety concerns of placing patients...
with implanted thalamic electrodes in the MR scanner. Several recent reports have provided additional safety information. Dormont, et al.,15 did not observe any adverse effects in five patients who underwent anatomical MR imaging with implanted thalamic electrodes. Similarly, Brooks and associates6 reported no negative findings in patients with depth electrodes who underwent MR imaging. Zhang and colleagues34 found no significant heating (using measurements and calculation of the worst-case scenario) in patients with bilateral intracranial depth electrodes undergoing MR imaging. Chou, et al.,7 used fiberoptic sensors to measure temperature changes in a phantom model of spinal stimulators. Their findings demonstrated a maximum temperature rise of 2°C during a 26-minute imaging session.

Our clinical observations are in agreement with these previous studies. There were no adverse clinical effects noted in any of our 86 patients with implanted electrodes. Functional MR imaging studies can be performed safely, provided that the patient does not become part of a large closed loop involving a frayed connecting wire. There is no additional risk due to the actual presence of wires in the bore of the magnet because the cabling contains paired electrode wires so that a loop in the cable does not constitute a loop in the electrical circuit that would be capable of picking up magnetic field–induced EMFs. Therefore, the only risk of tissue heating caused by the wires themselves arises from the possibility that the electrical component of the RF field induces an EMF in the wires; however, this has been shown to produce a negligible temperature increase.24 We have estimated that a frayed connecting wire in direct contact with the patient could result in a temperature rise of 0.1°C/minute (neglecting heat dissipation caused by blood flow). Simple safety precautions, however, such as inspection of the cable for fraying or shredding of the insulation and preventing its direct contact with the patient, will alleviate any potential safety concerns. An additional safety measure involves the connecting wire’s position; it should exit the bore of the magnet opposite the patient’s head and body. Overall, anatomical and functional imaging of patients with implanted thalamic electrodes in a clinical 1.5-tesla MR system is safe.

Currently, fMR imaging can only be performed in patients with DBS electrodes connected to transcutaneous testing wires. In patients in whom IPG units are already implanted, the MR imaging can turn these units off or, less commonly, on. Thus, performing fMR imaging in a patient with an implanted IPG unit is not a feasible option. In patients with IPG units who undergo anatomical MR imaging, it is recommended that the units be turned off and set at 0-V intensity prior to entering the MR imaging room. It must be emphasized that additional safety studies are required in patients with RF-coupled receivers. At this time, we do not recommend performing fMR imaging in patients with these RF receivers.

Patients with chronic pain who have implanted Vc electrodes can be an ideal study group for assessing the efficacy and sensitivity of fMR imaging. Stimulation of these
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electrodes evokes reproducible paresthesias in the contralateral body. In every patient, fMR imaging demonstrated activation of the SI with stimulation of the Vc electrode. In cases in which subthreshold stimulation of the Vc electrode was used, no SI activation was seen. Similarly, PVG stimulation did not activate the SI, but activated the cingulate cortex. In addition to the SI, activation of the other components of the somatosensory perception pathway, such as the thalamus, SII, and insula, were observed with Vc stimulation. The robust pattern of cingulate cortex activation with PVG stimulation is intriguing because of the proposed role of the cingulate on the emotional/affective component of pain perception. In this context, it is also interesting to note that recent fMR imaging studies conducted by Davis and coworkers9,10,13,14 have also demonstrated activation of the SI, SII, insula, and cingulate cortex with noxious and nonnoxious stimuli. Thus, the observed pattern of fMR imaging–detected cortical and subcortical activation with DBS correlates with our understanding of the known neuroanatomical and physiological pathways and is further confirmed by the observed clinical response. Additionally, the stimulation procedure does not appear to interfere with the imaging.

In this study, we also observed occasional inconsistencies between the location of the reported paresthesias and the fMR imaging–detected cortical activation in relation to expected classic homuncular somatotopy. This disparity between functional imaging somatotopy and the classic homunculus also has been reported recently16 and warrants further investigation.

The corresponding DBS-coupled activation of the thalamus and SI is intriguing because the prevailing theories on the mechanisms of DBS action implicate a “depolarizing blockade” concept of neuronal inhibition. This phenomenon may be related to the frequency of stimulation because we typically use lower frequencies in patients with chronic pain (< 85 Hz) than in those with tremor (> 120 Hz). However, our observed differential activation of the lateral thalamus, with high-frequency stimulation of the Vim electrode (Fig. 6), and activation of the medial thalamus, with low-frequency stimulation of the PVG electrode (Fig. 5), provide additional support to a more complex mechanism of action of DBS, rather than a simplified concept of depolarizing blockade. It should also be recognized that the observed activations near an electrode may be a reflection of a localized nonphysiological increase in blood flow from direct stimulation rather than an activation of neuronal pathways. Further studies using this combined approach will provide a better understanding of the mechanisms of action of DBS.

In this study, we have only reported a few specific activations detected by fMR imaging. A more comprehensive analysis of activation of various structures and correlation with the clinical response in more patients with refractory pain and tremor is currently in progress. Furthermore an analysis of regions of deactivation or inhibition should not be overlooked. Indeed, our preliminary findings in patients with Vim electrodes for refractory essential tremor demonstrate inhibition of the contralateral cerebellum (data not shown), an observation that has also been shown by previous PET studies.12,25

In evaluating the ROI signal-intensity measurements, we also observed a higher percentage of signal-intensity increases with stimulation than we typically see in conventional fMR imaging studies. Typical task-related average signal increases are on the order of 1 to 2%. However, we observed higher changes, up to 8%, with stimulators. This disparity may be attributable to the direct and, possibly, more powerful activation of neuronal pathways via these electrodes located close to thalamic neurons. Conventional fMR paradigms may measure a weaker activation of the pathways. The signal changes observed in fMR imaging arise from alterations in blood oxygenation because the local vasculature responds to increased demand from adjacent neurons. Several groups have extensively modeled this mechanism. Although the total blood volume fraction of approximately 4% places some upper limits on the maximum attainable signal increase, these models typically predict a signal that increases as a result of a blood flow increase toward an asymptote of approximately 8%.5 Additional studies regarding the level of signal change with DBS stimulation are warranted.

As this combined approach of fMR imaging and DBS improves our understanding of the neuronal pathways and their aberrations in pain and movement disorders, the potential clinical applications and delineation of prognostic variables become more pertinent. For example, not all patients who experience paresthesias in their area of pain obtain clinical pain relief with Vc stimulation. One can speculate that those patients who do respond may have preferential activation of areas that are not activated in patients who do not respond. The utility of fMR imaging in this context can be invaluable.

In summary, this novel combined approach is safe and is able to localize various cortical and subcortical structures and pathways. As the clinical application of DBS expands, this approach can provide a potentially powerful tool for conducting additional studies that will further our understanding of the basic mechanisms of DBS action and the pathophysiological mechanisms of pain and tremor.

References


cingulate cortex during painful, thermal, and motor tasks in individual subjects. Neuroimage 7:5426, 1998 (Abstract)

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