Application of IR thermometry to understanding brain function

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ABSTRACT

Gliomas are a deadly class of brain tumor for which surgery is currently standard treatment. However, important functional areas must be avoided during tumor removal. Currently intraoperative stimulation-based mapping addresses this, however it has low spatial resolution (~ 1cm) and requires many stimulations. We explore an alternate approach to functional mapping via infrared thermography. Activated brain tissue recruits additional blood supply (neurovascular coupling), which raises local temperature. Intraoperative thermal imaging (ITI) can map several areas simultaneously with relatively high resolution (~0.1 mm). We present our experiences using ITI on two glioma patients, and compare our findings to the stimulation-based gold standard. Initial data suggests good correspondence between these methods, and opens possibilities for a complementary approach. Ultimately, the goal of ITI is to improve patient outcomes by precisely defining the extent of surgical resection and prevent postoperative neurologic deficits.

Keywords: Infrared, Thermal Imaging, Brain, Glioma, Medical Imaging, Surgical Planning

INTRODUCTION

Precise localization of functional brain areas is required to avoid neurological damage from brain tumor surgery.[1] These regions, termed "eloquent areas" are invaded by glioma-type brain tumors in a majority of cases.[2] Over time there have been many attempts to map brain function using invasive and non-invasive methods. These methods break down into three groups: 1) pre-surgical imaging that helps determine potential success and risks of surgery; 2) intraoperative methods for online mapping during surgery; 3) extra-operative methods which surgically implant grids of electrodes to monitor brain signals for several days afterwards.[3] The latter is typically done in epilepsy or seizure cases. Each approach contains specific goals, assumptions, and risks.

Pre-surgical mapping methods tend to be non-invasive (beyond mild radiation exposure) and directly or indirectly measure neuronal activity. The primary methods used clinically for measuring pre-surgical activity include electroencephalography (EEG), Positron Emission Tomography (PET), and functional Magnetic Resonance Imaging (fMRI). Each method has advantages and disadvantages for use in pre-surgical mapping.

EEG uses electrodes placed on the scalp to provide a measure of the aggregate electrical activity within a sensitive volume under the electrode. The result is a time series of electrical activity which can be used for seizure identification. With proper experimental design, presentation and analysis, it is possible to collect an event-related potential (microvolts), which is a time locked average across numerous trials of the same task to generate an electrical response. These changes can be mapped to the surface of the brain. The advantage of EEG is the high temporal resolution, the low cost, and easy setup and execution. The disadvantages are the low spatial resolution, sensitivity to motion and impedance, low signal amplitude, presence of other electrophysiologic signals, and limitation that neuronal activity can cancel out due to the convolutions of the brain surface. Nevertheless, EEG is widely used in the diagnosis of epilepsy and is very common in psychology labs around the world.

Imaging methods such Positron Emission Tomography (PET) and functional MRI (fMRI) have been developed and applied to mapping brain function in normal subjects and neurosurgery candidates. PET imaging uses a radioactive positron emitter attached to a key molecule that will then bind to a receptor to mark a physiologic event. The most used radioligand is FluoroDeoxyGlucose (FDG). The radioactive form of fluorine is attached to a glucose molecule. This in turn is injected into the bloodstream and is taken up by cells as a result of energy expenditure. The FDG signal detected is a marker of metabolism and can easily label hypermetabolic tissues such as brain tumors. When a subject/patient is asked to perform a task during the presence of FDG, it can measure the metabolism related to that particular function. An alternative way to measure this activation induced metabolism is to use a radiolabeled version of water. The advantage is

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that specific radiolabeled ligands can directly measure the physiologic process of interest. The half-life of "hot" water is very short requiring it to be generated on site in a cyclotron which is very expensive. While PET directly measures physiologic signals, the exams are slow, have poor resolution, expose the patient to radiation, and are expensive.

Functional MRI was developed in the early 1990's and has been the tool of choice for investigating brain function. This method exploits differences in the magnetic properties of deoxyhemoglobin and oxyhemoglobin. The signal contrast has been dubbed Blood Oxygenation Level Dependent (BOLD) signal.[4] It is possible to detect brain activation due to neurovascular coupling –a large blood flow increase in response to local neural activation. When a particular region of the brain is involved in a task, there is local metabolism from the neuronal firing. In response to this, the local vasculature is dilated and there is a sizable increase in blood flow that follows roughly in 2 seconds and peaks about 6 seconds from the start of the activity. This hemodynamic response is slow compared to the electrical propagation that occurs. Nevertheless, with knowledge of the delay and shape of this blood flow response, it is possible to generate activation maps. Furthermore, with the proper timing of the stimuli it is possible to measure millisecond differences using this sluggish response.[5] Functional MRI has become the primary method of mapping brain function.

The goal of pre-surgical mapping is to identify the lesion, its proximity to eloquent function, and the brain network involved in that function.[6] This provides critical information to the surgeon and patient to make the best possible decision of how to treat the lesion and how to navigate during surgery. If the decision is to go to the operating room, it is important to co-register the presurgical findings with the patient's anatomy in the operating room using a neuronavigation system. There are technical issues with this such as methods, accuracy, positioning of the patient, and blocking the real-time tracking. However, the biggest issue is the shift in the brain once the skull has been opened and the dura cut. This relieves the pressure in the skull causing the brain to shift from the pre-surgical position. It is possible to utilize intra-operative imaging (CT or MRI) but this is slow and cumbersome. Often the surgeon must cognitively transform the pre-surgical data to the current position of the brain.

Intraoperative imaging methods can be roughly divided into those which identify tumor tissue or those which map patient-specific functional regions.[7,8] Direct electrical stimulation (DES) during awake craniotomy is currently the gold-standard for intraoperative mapping, and uses pulses of electrical current to stimulate candidate functional zones.[9-11] Patients are tested with DES while awake, and participate in tasks related to the mapped areas. For example, a patient may attempt to name objects during stimulation, and interruption of the action suggests the stimulated region is responsible for object naming.[12] Similar approaches are utilized for testing nuances of motor and language function. Stimulation may also be used to elicit motor or sensory function, which analogously implicates the stimulated region. Creating a patient-specific functional map during the operation is essential to account for individual anatomical variance. Moreover, tumor invasion to functional areas has been known to modify the cortical distribution of neural functions.[13-16] This is particularly important in brain tumor surgery, where the function areas of most interest are those adjacent to the tumor itself. Lastly, by performing intraoperative mapping, the results are coregistered with the surgical field by default. Preoperative mapping (TMS, fMRI, MET, DTI) need intraoperative confirmation to account for brain shift - nonlinear distortions in neuroanatomy that occur due to CSF leakage, gravity, and medication.[17-21]

While DES is the current gold standard for functional mapping, there remain significant weaknesses. (1) DES has low spatial resolution (~1 cm),[22] and therefore cannot precisely identify boundaries of eloquent regions. (2) DES may cause seizures.[23, 24] (3) DES causes non-physiologic alteration of networks, and is thus liable to produce false-negatives (e.g. supplementary motor cortex).[3] (4) DES suffers from low mapping efficiency, as only one area of cortex can be sampled at a time. (5) DES generates a path of current under the stimulation probe that does not discriminate which tissue type it affects. Thus, both gray matter and white matter can be stimulated. This may result in false long-distance connections due to the underlying white matter activation.[25] These weaknesses are further exacerbated in expansive tumor resections, which require longer stimulation protocols and high precision. A safe, efficient, and high precision intraoperative imaging technique could extend survival time while preserving function. Considering this need, numerous other imaging modalities have been explored.

Intraoperative MRI has been used to compensate for anatomical changes after brain shift, with dual goals of tumor identification and aiding interpretation of preoperative imaging in the context of the surgical site. It has shown arguably most success when used in conjunction with other intraoperative imaging techniques. However, this method has a costly setup, is not widely available, has not shown clinical benefit in some studies, and lengthens operation times.

Intraoperative ultrasound, like intraoperative MRI, can image anatomy after brain shift without exposing the patient to radiation. Ultrasound is low-cost, widely available, and can use Doppler imaging to measure blood flow.[26,27] However, it tends to underestimate the extent of the tumor (as compared to MRI), image quality suffers with deeper lesions, and the cost-effectiveness has not been proven. Moreover, the quality of ultrasound images is notoriously operator-dependent. Neurosurgeons do not typically receive training in ultrasound guidance, and there is a learning curve for adoption of this technology.

Fluorescence-guided surgery uses tumor-specific dyes to guide the surgical resection. Currently, 5-aminolevulinic acid (5-ALA) and fluorescein are most widely used markers, and both carry high sensitivity and specificity for tumor tissue (about 80% each). With fluorescent contrast, surgeons can achieve larger extents of resection, particularly in malignant tumor cases.[28] Fluorescence-guided surgery has demonstrated synergistic benefit with intraoperative MRI. While extent of resection is a primary indicator of survival for glioma cases, increasing extent of resection by fluorescent-guided surgery does not reliably increase survival time.[26] This technique only informs the neurosurgeon about the extent of the lesion and not about the underlying function of the surrounding brain tissue. Lastly, anaphylaxis is a dangerous potential complication of 5-ALA use.

With awake craniotomies and DES becoming the gold-standard approach to handling gliomas, simply identifying the tumor extent is no longer sufficient for intraoperative imaging. Patient-specific functional maps must be created to avoid postoperative neurologic deficits. This inherently limits the long-term utility of intraoperative MRI, ultrasound, and fluorescence-guided surgery alone. Intraoperative electrocorticography (ECoG) uses a grid of electrodes to measure high frequency electrical fluctuations (gamma band, ~20-80Hz). Done in conjunction with a task, ECoG can map several cortical areas in parallel, and has good correspondence with DES.[29] However, ECoG suffers from low spatial resolution (5-10 mm), on par with DES. Functional ultrasound creates high spatiotemporal resolution images of local hemodynamics (which are coupled with neural activity), however images are 2D within the cortex so whole-craniotomy mapping is unfeasible.[30,31] If eloquent areas are to be mapped precisely, a new general approach is desired. Optical technologies typically benefit from high spatial resolution, are noncontact/noninvasive, and do not produce side effects of seizures or anaphylaxis. Therefore, optically-based functional imaging for use in brain tumor surgery is an active area of research.

Dynamic intrinsic optical imaging (DIOSI) examines cortical function by measuring small changes in tissue reflectance within two narrow frequency bands. By comparing the reflectance for each wavelength as a function of time, low-frequency oscillations (0.02 – 0.1 Hz) due to local hemodynamic changes can be observed.[32] When an area of cortex is functionally activated, neurovascular coupling causes an increase in local perfusion. This mechanism is already used in BOLD fMRI to perform functional imaging. Using granger causality, the correspondence of DIOSI with ECoG was found to be 83%. However, acquisition times for this method are typically long (minutes), which hinders its overall clinical utility. Also, intrinsic optical imaging is known to suffer from cardiopulmonary artifacts and significant noise from ambient conditions.[33]

Similarly, Laser Speckle Imaging (LSI) has been used to examine microvasculature blood flow during awake craniotomy. Functional mapping can then be performed, relying on the same neurovascular coupling mechanism described above.[34] Capillary blood flow significantly increases in the hand motor areas during a contralateral hand clench task. Laser Doppler Imaging has also been attempted, as a means of intraoperatively measuring cortical blood velocity.[35] However, most cortical changes in flow from neural activation are due to vasodilation, which increases flow while keeping velocity nearly constant.[30] Despite interesting preliminary results, work on either of these modalities has been limited.

METHOD

Infrared thermography infers the temperature of objects by capturing the spectral distribution of their emitted blackbody radiation. Functional mapping through intraoperative thermal imaging (ITI) during awake craniotomy has been performed successfully in humans.[36] The increase in local perfusion via neurovascular coupling also increases the temperature of activated areas. This method benefits from a temperature gradient between the warm brain and the cold operating room, whereby perfusion generates a thermal contrast. As an added benefit, ITI can identify tumors and their margins, as tumor-induced angiogenesis increases local tissue perfusion.[31,37] In the operating room, contact with cold air

causes cooling of the cortical surface, but this effect is diminished in areas of higher perfusion so tumors may appear warmer. However, high grade tumors have substantial central necrosis and edema, which can create a cooler region within the warm region of high perfusion.[38,39] Recognizing and quantifying this pattern may help grade tumors before they are resected, which is not currently possible. While ITI for tumor identification has seen experimentation with promising results, more data is needed before it can be applied clinically for this purpose.[39-41] However as a functional imaging method, ITI addresses major shortcomings of DES and of other mapping methods:

(1) Spatial resolution is much higher in ITI (~100 μm) compared to DES (~1 cm).
(2) ITI is noncontact and noninvasive, avoiding adverse events (seizures, anaphylaxis) and maintaining the sterile field.
(3) Mapping with ITI moves beyond the knockout paradigm of DES, measuring a more physiologic network activation.
(4) ITI captures the entire craniotomy at once, mapping all exposed regions of a trial simultaneously. DES can only map one area per trial at one time, suffering from low mapping efficiency. This allows ITI to perform trial averaging to improve the functional map.
(5) ITI uniquely captures both anatomy (visible spectrum) and physiology (IR spectrum) in the same image, allowing for side-by-side comparison. Not only is this joint approach simpler, but it also critically bypasses image coregistration error.
(6) ITI is relatively simple to use and is low-cost, so advancements in this technology can permeate to level of community hospitals and impact patients beyond only academic centers. The system that would be required for ITI is limited to the device, a laptop, stimulation delivery via sound or video, and behavioral monitoring devices like a microphone and movement sensor. This can easily be packaged in a way that would be deployable in most surgical suites.
(7) ITI is captured at video frame rates and higher (>30 fps). This affords a high temporal signal that can be exploited to understand the network structure of complex tasks such as language. We are just at the verge of being able to exploit these signals to determine causal relationships, improve the statistical processing by utilizing the temporal information, and determine critical hubs of function that should be avoided during surgery.
(8) ITI is based on temperature which is something that people understand and can grasp. Surgeons and patients can embrace the concepts of how it works and how it will help with the procedure.

One potential weakness of thermal imaging is that it can only capture the surface temperature. Depth of penetration is limited to microns, and brain tumors or eloquent regions may lie deeper than that. However it must be observed that temperature on the brain surface is related to the temperature of underlying brain tissue. Heat from a warm body may diffuse to induce a warmer surface, which can then be measured with today's sensitive IR camera systems. The majority of structures of interest are deeper than several microns, yet ITI has been successfully applied. Depth of penetration is not significant limitation in practice. Furthermore, as the operation takes place, it is possible to map inside the resection cavity to sample the deeper tissue.

Here we present our experiences with intraoperative thermal imaging in two patients. Both are glioma patients who underwent awake craniotomy at Northwestern. Patients undergo a sedation-awake-sedation technique for neuroanesthesia. In the initial sedation phase, remifentanil (0.1μg/kg/min) is titrated for a respiratory rate of 8-12/min and supplemented with propofol (10-25 μg/kg/min). Selective scalp blocks are then performed using a mixture of tetracaine (1%) and lidocaine (1%) with epinephrine (1:200,000). Six scalp nerve blocks are performed on each side for supratrochlear, supraorbital, zygomatico-temporal, auriculotemporal, lesser occipital, and greater occipital coverage. A ring block is performed along the incision line within the scalp level (0.5-1% lidocaine with epinephrine 1:200,000). Following local anesthetic administration, the patient's head is secured using a standard 3-point Mayfield head-holder. Following craniotomy, all intravenous sedation is held and the dura is opened. At this point, the patient is awake and able to see, hear and speak. Direct electrical stimulation (DES) cortical mapping is performed upon exposure of the cortical surface using an Ojemann cortical bipolar stimulator with 5mm spacing (60 Hz, biphasic, 1 ms pulse duration, 2-3 sec stimulation duration). Stimulation occurs in 1cm increments throughout the exposed cortex. Mapping is started at 1mA and steadily increased to 8mA or until positive motor (overt contraction) or language (speech arrest during counting and/or naming error during Boston naming task) sites are identified in at least 2 out of 3 trials. Once this threshold is found, the remainder of the mapping session is conducted at that same current amplitude. Positive stimulation sites are

marked with a paper label while negative sites remain unmarked. In addition, positive sites are localized and stored within the neuronavigation system, from which three-dimensional coordinates of each positive site can be reconstructed for subsequent analyses and comparisons. Finally, high resolution digital images of the exposed cortex and DES-based map are obtained for coregistration with the infrared camera field.

RESULTS

Thermal images were subsequently captured on a FLIR T450sc infrared camera (resolution 320 x 240, thermal sensitivity < 30 mK). The camera was mounted on a tripod adjacent to the patient, and adjusted to maximize the area of the craniotomy within the camera's field of view. Care was taken to ensure that no peripheral heat sources were reflected into the field of view of the camera. Recording continued throughout an interval of no activity to establish a baseline signature. This was followed by several intervals of tasks. While the image in Figure 1 is static, pulsation of the brain is clearly visible in the operating room. The brain is a non-rigid organ, and is constantly moves due to respiratory (~0.2 Hz) and cardiac cycles (~1 Hz). Motion introduces unwanted fluctuations into the thermal signal, with variable amplitude across space. This artifact must be corrected in real-time for the data to be surgically useful. Currently, the only real-time approach for correcting brain motion in thermal images uses a pixel-wise low-pass filter (0.1 Hz cutoff frequency), at the cost of temporal information.[42] It is possible to exploit the high temporal and spatial resolution of ITI to identify the cardiac and respiratory signals in the small pial arterioles (see figure 2). One can then retrospectively synchronize the thermal data by referencing these signals. For example, one could utilize data collected at the peak of the cardiac pulsations to remove this motion effect. This can be done with the respiration signal that is embedded as well.

Figure 1. Intraoperative thermal image. The warm craniotomy site can easily be distinguished from the rest of the surgical field. During surgery, the brain surface falls below core body temperature because of exposure to the cold operating room environment. Arteries supply the brain surface with blood, which creates thermal contrast in the areas of perfusion. Large vessels run in the sulci, which allow differentiation between gyri.

In order to utilize the temporal signal from ITI, the trials need to be synchronized with the stimulation presentation and recording of the behavioral response. Armed with this information it is possible to trial average and investigate causal relationships. The synchronization is typically accomplished by having a single computer control all the devices and record the signals to a master file. This is true of any functional mapping study be it ITI, EEG or fMRI.

In this proof of concept study we did not have a time lock between the stimulation and recording of the ITI data. The goal was to develop a working protocol and measure the thermal changes related to simple motor tasks to give an understanding of the problem. Figure 3 describes an experiment conducted in one patient with a large hypercellular frontal lobe lesion. Once DES had been performed (positive sites represented by pieces of paper), ITI was conducted with a

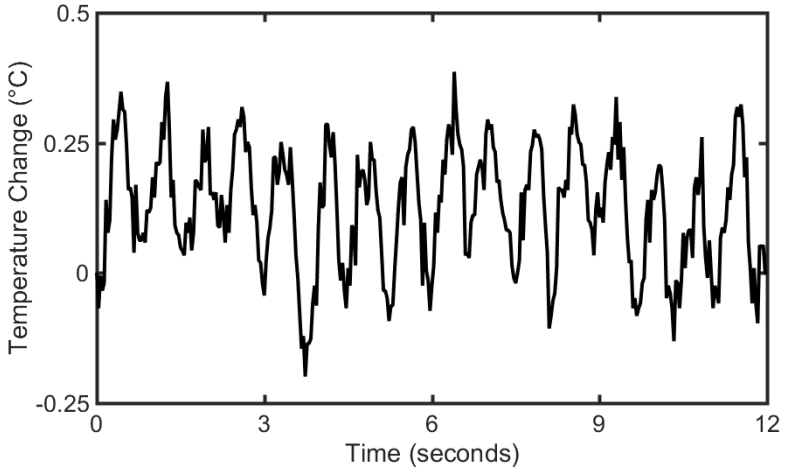
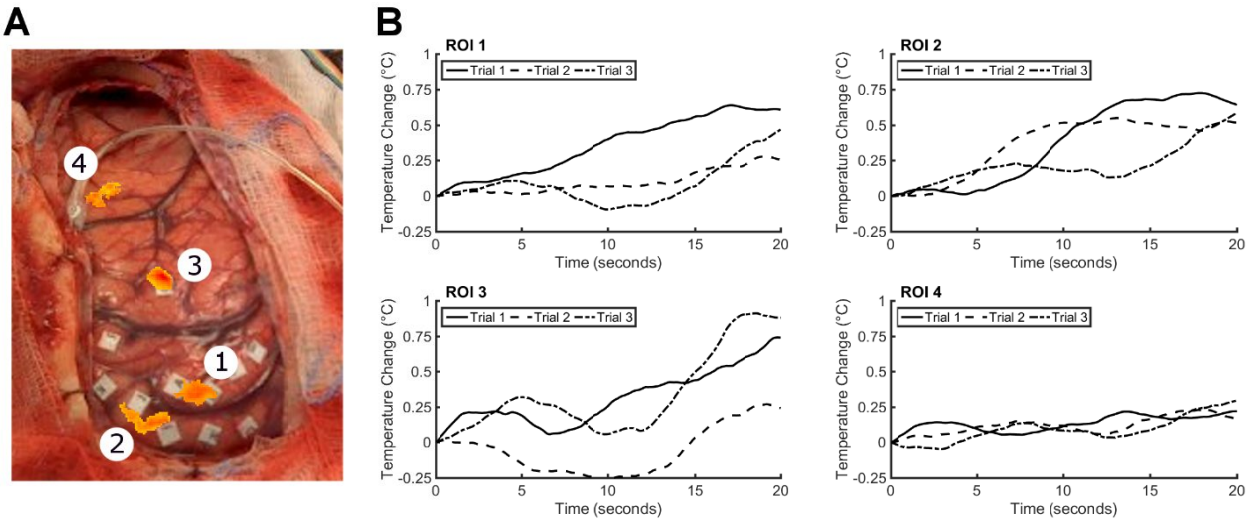


Figure 2. Physiologic thermal fluctuations, captured from a small pial arteriole without task activation. Both cardiac (1Hz) and respiratory (0.2 Hz) fluctuations can be seen. The significance of the high frequency thermal fluctuations is currently unclear.

simple fist clenching task. A baseline period was monitored and then the patient performed a single fist clench that was held for several seconds and was repeated 3 times. The colored activation regions 1-3 on figure 3A demonstrate regions that expressed temperature increases in all three of the fist clenching tasks. Region 1 represents the motor cortex, region 2 is the sensory cortex and region 3 is just anterior to motor. Region 4 represents a negative control area that experienced elevated temperature during the baseline task. While limiting testing was done in this study, it demonstrates the localized function that is comparable to DES and obtain in a very short time without any risk to the patient. In figure 3B, it is possible to see the variability in the subject's response due to performance. One of the nice features of ITI is that the entire field of view is monitored and the data can be averaged over trials. In DES, if the neurosurgeon stimulates during a



trial when the subject doesn't perform the task well, it might be misinterpreted as a positive site.

Figure 3. Example thermal fluctuations for regions of interest. Areas 1-3 demonstrated temperature elevation during task trials. Area 4 is a negative control region identified from baseline activation. Strong increases in temperature are seen across trials, within 15 seconds of stimulus onset. In figure 3A, the orientation of the patient is such that the top of the image is anterior (towards the nose) and the right side of the image is superior (top of the head). The lesion is the roughly between regions of interest 3 and 4. The pieces of paper are regions where DES had a positive response during the testing of motor or language function. The time courses in B demonstrate the temporal changes in temperature as well as the variability of the response from the patient due to performance.

It is possible to create thermal maps from different tasks performed in this patient (Figure 4). The thermal maps are cropped to the craniotomy to help orient the results. Each map was formed by representing the change in temperature signal relative to baseline prior to the behavioral task. In a baseline map (figure 4B), the subject was instructed to hold still and do nothing. In figure 4C, the subject was instructed to clench their right hand which activates the left motor and sensory cortices (red regions). In figure 4D, the patient is instructed to clench their non-affected hand (left) as a higher-level control task. In this case, there is very little thermal change as expected. Using several different tasks and control tasks provides confidence to the neurosurgeon that the highlighted regions are in fact involved in the hand clenching process.

DISCUSSION

While intraoperative thermal imaging is not new, its potential for brain mapping of eloquent regions has remained unexplored. With demand for efficient functional localization increasing, ITI is well-poised to fill in this gap. Thermal signatures of brain activity are robust, and the ability to map several areas simultaneously will increase efficiency. The nature and pattern of thermal activation, as a hemodynamic effect, can be easily understood and related back to BOLD fMRI. Temperature is familiar variable in the clinical setting, and we hope this will increase adoption of this method. Our preliminary results show good correspondence with DES, the gold standard, and moving forward we will more precisely characterize the relationship between these two methods.

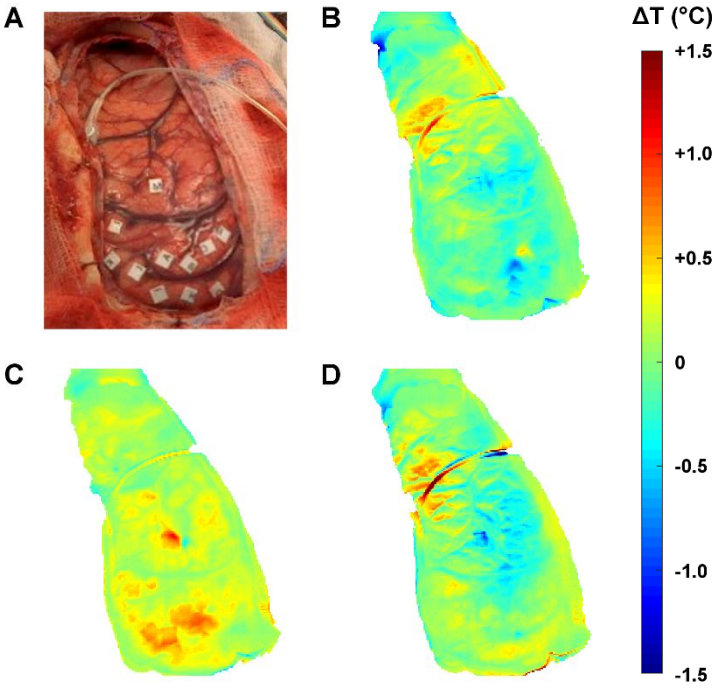


Figure 4. Thermal imaging distinguishes functional brain regions in a motor mapping task. (A) Visual-spectrum image of left frontal craniotomy. Direct electrical stimulation confirmed hand motor (black circle) and hand sensory (white circle) sites. (B-D) Activation heatmaps for baseline (B), right hand clench (C), left hand clench (D) conditions. Changes in temperature are calculated using a 5-second moving average to filter respiratory and cardiac artifact. Correspondence between color and temperature change is shown by the colorbar to the right. Heatmaps are masked to include only the craniotomy window.

To maximize clinical utility, the ITI method presented will be integrated into a system that monitors cortical temperature and behavioral stimuli, responses, simultaneously. Additionally, physiological signals such as heart rate, respiration, end tidal CO2 and O2 are understood to affect cerebral blood flow. These parameters are already monitored during surgery, and a parallel feed to our system can be established. To better understand the interaction of these signals with temperature, we will utilize a breath hold or delivery of CO2 gas to globally increase cerebral blood flow. This approach has been used successfully in fMRI to demonstrate which regions can generate an activation induced blood flow change (intact neurovascular coupling). Understanding the maximum physiologic thermal fluctuations possible on the brain surface are critical to interpreting ITI results.

With the spectacular developments being made in the field of optics and photonics, there are numerous new possibilities that will facilitate intraoperative mapping. One that is perhaps most promising is wideband (white light or IR) measures which can provide a voxel by voxel spectrum of the underlying tissue. Tumors may be functionally characterized by angiogenesis and heightened metabolic activity. We are hopeful that wideband spectroscopy will efficiently capture the chemical make-up of tissue, and by scanning across space a parallel map of metabolism may be established in time that is clinically feasible.

By combining this with thermal and functional imaging, tumor characterization can be approached from multiple angles. We would like to move beyond simply localizing the extent of the lesion, but be able to predict pathological grade without the need for a physical sample. The tumor grade is an important clinical variable, which currently has limited characterization prior to surgery. A multimodal approach would open new possibilities for surgical planning, estimating lesion severity before resection has begun.

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