Experimentation with a Transcranial Magnetic Stimulation System for Functional Brain Mapping

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Abstract

We describe functional brain mapping experiments using a transcranial magnetic stimulation (TMS) device. This device, when placed on a subject's scalp, stimulates the underlying neurons by generating focused magnetic field pulses. A brain mapping is then generated by measuring responses of different motor and sensory functions to this stimulation. The key process in generating this mapping is the association of the 3D positions and orientations of the TMS probe on the scalp to a 3D brain reconstruction such as is feasible with a magnetic resonance image (MRI). We have developed a system which not only generates functional brain maps using such a device, but also provides real-time feedback to guide the technician in placing the probe at appropriate points on the head for achieving the desired map resolution. Functional areas we have mapped are the motor and visual cortex. Validation experiments to date have consisted of repeatability and symmetry tests for mapping the same subjects several times. Applications of the technique include neuranatomy research, surgical planning and guidance, treatment and disease monitoring, and therapeutic procedures.

Technical Topics: Rigid image registration; Real-time instrument tracking

Medical Topics: Neurosurgery; Functional brain mapping

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Summary Page

1. **What is the original contribution of this work?**

   We develop and test a new application—non-invasive brain mapping. In doing so we integrate 3D surface registration and tracking techniques for not only generating the brain maps, but also for interactively guiding the technician in acquiring the data for the maps.

2. **Why should this contribution be considered important?**

   By mapping different regions of the brain and testing our approach we are validating new functional mapping techniques which may have wide applicability in both clinical and neuro-anatomy research fields. Our brain mapping application also explores an integrated solution for registration and tracking, two problems which are often present in medical applications.

3. **What is the most closely related work by others and how does this work differ?**

   Similar registration techniques have been proposed by Szeliski and Lavallee, Feldmar, Jiang, and Pelizzari. This work differs in some of the details of the registration method, but the primary novelty of the paper is in the application—brain mapping.

4. **How can other researchers make use of the results of this work?**

   While some medical applications of 3D registration and tracking have already been explored, many more are on the horizon. The experience gained by our study of integrated solutions to registration and tracking problems and of the brain mapping application may support others as they explore related domains.

5. **If this work extends or relates closely to some other previously published work, state precisely how it differs from that work.**

   Initial results were reported in the 1996 IEEE Workshop on Mathematical Methods in Biomedical Image Analysis. In this paper we report results of mapping new regions of the brain, the visual cortex, and results on validation testing.

6. **Categories which characterize the work:**

   An integrated system which is clinically tested on at least one case.

1 Motivation

Functional brain mapping, consisting of the association of motor, sensory, and perception functions with different regions of the brain, is currently an active research area with a wide range of potential applications. Sample applications include (1) neuroanatomy research into the structure and functioning of components of the brain, (2) study of neurological disease origination, progression and diagnosis, (3) surgical planning and guidance of biopsy and resection procedures, (4) treatment monitoring, and (5) neurological therapeutic procedures. Current techniques for functional brain mapping utilize 3D medical scanners to image the brain while the subject undergoes an activity aimed at activating the functional area of interest. Scanners currently used for this purpose are single photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI). The ability of these scanners to capture brain activity results from their sensitivity to such factors as metabolism rate and blood oxygenation. The benefit of such scanners is their ability to quickly capture 3D snapshots of the complete brain activity. They are limited, though, by their high cost and passive control of functional activation.

A promising approach to avoiding these limitations is the use of a transcranial magnetic stimulation device (Cadwell Laboratories Inc., Washington USA and Magstim Company Ltd, England) for actively stimulating different parts of the brain. Such devices consist of a circular or figure-8 shaped coil, termed the TMS probe, which can deliver single magnetic field pulse stimuli or pulse trains. One of our sample coils is shown in Figure 1. There is no direct electrical contact with the subject—the device works by inducing small electrical currents (estimated at $< 50mA$) in tissue using brief magnetic pulses that are focused in front of the coil. The magnetic field generated by the coil passes through the scalp and skull without attenuation, but causes excitation of cortical neurons. We have explored stimulation of both the motor cortex and visual cortex. Excitations in the motor cortex result in measured peripheral responses of the affected muscles. Excitations of the visual cortex briefly inhibit interpretation of the affected visual field. The peak magnetic fields are similar to those used with MRI scanners, except that magnetic stimulator pulses are very short ($< 1msec$). Resulting energy dissipation in tissue is minimal ($< 0.25mJ$). The advantages of such a device are:

- Low cost and ease of use—the device is highly portable with few constraints on applicability.
- Active functional activation—rather than trying to spot brain activity when the subject performs different actions, the TMS attempts to directly stimulate certain brain regions and monitor resulting impact. By using latency measures to track response times, most voluntary responses are eliminated. In principle, this leads to functional mapping that is highly localized both spatially within the brain and temporally for ease of acquisition.

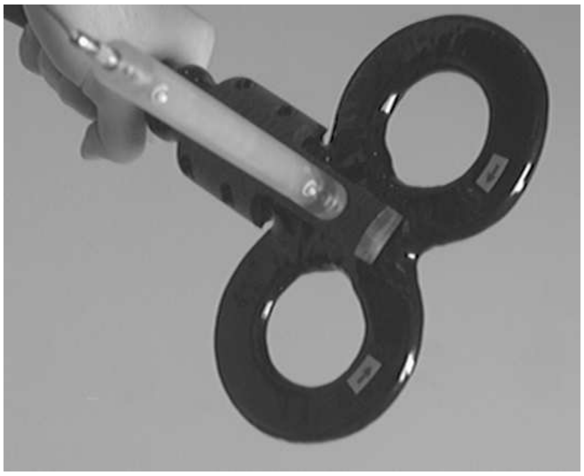

Figure 1: Stimulation coil used for TMS mapping. Note the rod mounted orthogonal to the plane of the coil–two LEDs are fixed on the rod for tracking the position and orientation of the coil.

While research is on-going on the biological implications of such a device, the physics of the generated magnetic field, and the development of psychophysical experiments which gauge brain function, we are exploring the technical problems of converting the TMS data, locations of TMS probe stimulations, and associated muscular/sensory responses to a 3D functional brain map. The heart of our problem is:

1. Register the subject's MRI scan, the subject position during transcranial magnetic stimulation, and the TMS probe positions/orientations to the same coordinate frame. For maximum accuracy we would like to avoid a fiducial based system.
2. Track the subject's head motion in order to maintain the registration. Head clamps are to be avoided both for the subject's comfort and to allow free access to the whole head region.
3. Combine the TMS probe positions and orientations, TMS responses, subject-to-MRI transform, and head motion to generate a functional brain mapping on any 3D surface rendered from the MRI scan. Real-time visualization of the current probe pose in the MRI coordinate frame along with an encoding of previously probed locations is to be used to guide the acquisition of subsequent stimulation points. Such guidance avoids redundant probings, reduces acquisition time, and supports accurate delineation of "hot spot" boundaries.

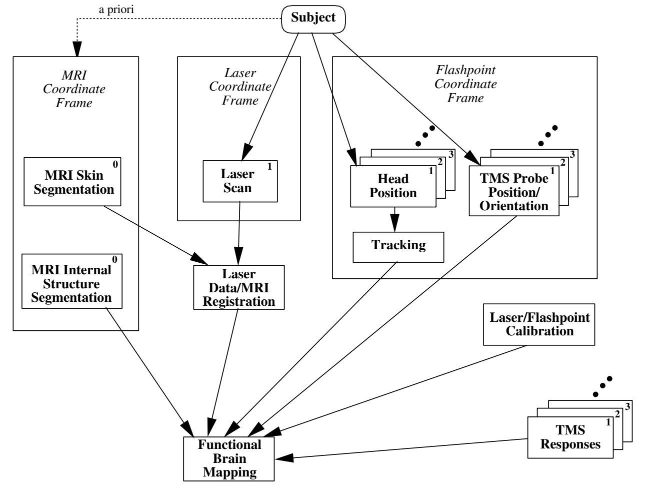

Figure 2: Architecture of functional brain mapping system.

In [4] we reported preliminary results of applying a TMS system to mapping the motor cortex. We have since extended the capabilities of the system to simplify the mapping process by providing real-time status feedback, thus allowing us to map a larger number of subjects. We have also extended the application to include the visual cortex and have begun validatation experiments for evaluating the mapping performance on the motor cortex. We first give a brief description of our TMS registration/tracking system in Section 2, followed by sample results from the application of our system to mapping the motor and visual cortex in Section 3. Validation test results are described in Section 4.

2 Functional Mapping System

The system we have developed to generate the TMS brain maps is shown in Figure 2. We work with three different coordinate systems:

MRI: The MRI data is captured in the scanner coordinate frame. The data itself is segmented into skin surface for registration and internal structures for brain mapping visualization, all within this coordinate frame.

Laser: The laser scanner provides 3D data of the subject's scalp surface as positioned for transcranial magnetic stimulation. We use a laser striping triangulation system consisting of a laser unit (laser source and cylindrical lens mounted on a stepper motor) and a camera. Here the coordinate frame of the acquired points is centered at a fixed point within the working volume of the laser system.

Flashpoint: This is a 3D tracking system (IGT Inc., Colorado, USA) consisting of 3 linear cameras which localize flashing IR LEDs. The system can track a number of LEDs simultaneously. We mount two LEDs on the TMS coil (specifying its 3D position and orientation, with twist the only degree of freedom not measured) and tape five LEDs on the subject's scalp for tracking head motion. Redundant LEDs are used for tracking head position in case motion is great enough to block up to two of the LEDs. The position and orientation information returned by the system are represented in a coordinate frame centered at a fixed point within the working volume of the Flashpoint cameras.

The goal of the system is to integrate all of these coordinate systems into a single reference frame. That is, we need to relate sampled TMS probe points to the corresponding points in the MRI scan, which we do by using the laser coordinate system as an intermediary. The laser scanner (laser and its associated camera) and Flashpoint system (three linear cameras) are mounted on the same bar which is attached to a movable arm for ease of placement. Since we fixate the laser and Flashpoint systems relative to each other, we perform an off-line calibration to obtain the Flashpoint-to-laser transform. This transform is then constant for all subsequent TMS data collections. The transform from laser data to MRI coordinates, though, must be computed for each TMS data collection since it depends on the subject's pose during the mapping session.

2.1 Mapping Procedure

A sample data collection procedure, from the perspective of the subject, is:

1. Acquire an MR image of the subject prior to the TMS session. Segment the scan, using automated techniques by [11, 16] and semi-automated techniques at Brigham & Women's Hospital, into desired anatomical structures, such as skin, cortical surface, white matter, etc.
2. Set up TMS data collection:
   - For motor cortex mapping, place muscle activity sensors on muscles of interest. Muscle activation with latencies of about 15 to $30msec$ indicate successful stimulation.
   - For visual cortex mapping, place subject in front of a computer screen which will flash sequences of letters that the subject will attempt to read. False readings indicate successful visual activity suppression.
3. Place Flashpoint LEDs on rigid points of the subject's scalp. Currently these are loose LEDs taped to the skin such that they will not interfere with the TMS probing, while spaced widely apart on the head. For visual cortex mapping we place the LEDs on a tight-fitting swim cap so that they are visible during stimulation on the back of the head.

Figure 3: Subject set up for TMS stimulation. LEDs taped to face are used for tracking head motion.

4. Laser scan the subject—the laser plane is swept across the subject's head collecting 3D positional data of visible skin surfaces. At the same time the positions of the five LEDs taped to the subject's head are acquired by the Flashpoint system.

5. Collect TMS data—the TMS probe is placed at various points on the subject's scalp. At each point, the TMS generates a brief magnetic pulse and the responses from the muscle sensors or subject's view of the computer screen are recorded. The position and orientation of the TMS probe are recorded by the Flashpoint system at the same time. 3D renderings of the subject's MRI skin superimposed with TMS points are generated during the data collection to chart progress and guide continued stimulations.

An example of a subject outfitted with the LEDs for tracking and placement of the TMS for stimulation is shown in Figure 3.

2.2 Laser Data / MRI Registration

The key to achieving high accuracy in this application is the registration of the MRI data with the actual subject. We accomplish this task by aligning skin surface from the MRI data to skin surface from the subject acquired with a laser scanner. Accuracy requirements are relatively high as many of the active brain centers being studied are on the order of a few mm^3 in volume. Thus the overall accuracy, including any tracking errors, should be within about $1-2mm$, which is generally not much larger than the voxel resolution of the MRI scan.

The basis of the registration algorithm we use has been previously described in [3, 4, 6, 7, 8]. The first step is an initial alignment for which we use a coarse manual positioning of the laser data relative to the MRI data. We then refine the alignment of the two data sets by minimizing an evaluation function that measures the amount of mismatch between the two data sets. In particular, we sum, for all transformed laser points, a term that is a sum of the distances from the transformed laser point to all nearby MRI points, where the distance is weighted by a Gaussian distribution. If vector ℓ_i is a laser point, vector m_j is an MRI point, and $\mathcal{T}$ is a coordinate frame transformation for which we are solving, then the evaluation function for a particular transformation is

$$E_1(\mathcal{T}) = -\sum_i \sum_j e^{-\frac{|\mathcal{T}\ell_i - m_j|^2}{2\sigma^2}}.$$

Because of its formulation, the objective function is quite smooth, and thus facilitates "pulling in" solutions from moderately removed locations in transformation space. By starting with large σ we achieve a large region of convergence and by gradually decreasing the value of σ we lock in on the well-localized minimum. In order to minimize this evaluation function we use the Davidon-Fletcher-Powell (DFP) quasi-Newton method [13].

As a final step we use a rectified least squares distance measure to ensure we've reached an optimal solution and to derive an easily interpreted error measure. We again use DFP to minimize the evaluation function:

$$E_2(\mathcal{T}) = \left[\frac{1}{n} \sum_i \min \left[d_{\max}^2, \min_j |\mathcal{T}\ell_i - m_j|^2 \right] \right]^{\frac{1}{2}}$$

where $d_{\max}$ is a preset maximum distance used to limit the impact of outliers. This second objective function is more accurate locally, since it is composed of saturated quadratic forms. We apply several random perturbations to solutions obtained with this function to search for possibly better solutions nearby.

We combine the registration and tracking data to obtain the functional brain mapping using these transforms:

- $\mathbf{F_L}$ — transformation from Flashpoint coordinates to laser coordinates; calibrated a priori.
- $\mathbf{L_M}$ — transformation from laser coordinates (head at time 1) to MRI coordinates; computed from the dynamic registration procedure.
- $\mathbf{H_r^t}$ — transformation of head from time t to reference position at time 1.

We have also collected the following TMS data:

- C_p^t, C_o^t — position and orientation of TMS coil at time t, $t \in [1, T]$, in Flashpoint coordinates.

- For motor cortex mapping we receive r_j^t, the measured first response of muscle j to stimulation t and d_j^t the latency from stimulation to the response.
- For visual cortex suppression we record the letters the subject saw flashing on the computer screen. The set of letters are separated into left and right fields of view for separating the processing of the two sides by brain.

In order to compute the brain mapping we need to map the TMS responses to the brain surface using the measured coil positions/orientations and associated transformations. To perform this mapping, for each stimulation t, we process those MRI surface points, $S[i]$, that are sufficiently close to $\mathbf{L_M F_L H_r^t} C_p^t$ to have been possibly stimulated by the pulse. For each $S[i]$ we compute the distance, $d^t[i]$, to the line defined by the point $\mathbf{L_M F_L H_r^t} C_p^t$ and the orientation $\mathbf{L_M F_L H_r^t} C_o^t$. For motor cortex mapping we are currently using a Gaussian weighting function proportional to that distance to "spread" the response r_j^t to the points $S[i]$. The purpose of this (simple) weighting function is to interpolate across the stimulations to obtain a smooth and visible map. If we let $map_j^t[i]$ represent the mapping of response j to stimulation t on the selected surface, then $map_j^t[i] = G(d^t[i], \sigma) r_j^t$, with G being the Gaussian weighting function. We then let $map_j[i]$, the composite mapping from all stimulations, be the maximum $map_j^t[i]$ over all t, which are then normalized over i.

For visual cortex mapping we treat the responses as binary and thus directly map the points that caused positive suppression in the left and/or right fields of view to the MRI surface points, $S[i]$.

3 Mapping Results

We have performed the TMS brain mapping on ten subjects thus far, two of whom were neurosurgery patients. Figures 4 and 5 show two methods for visualizing the motor strip mapping for one of the subjects. Figure 4 displays the minimum latency response (above threshold) for all the muscles evaluated. Figure 5 displays the response strength for one muscle.

Figure 6 shows the visual cortex mapping for another subject. We see that the visual suppression effects are well localized.

4 Validation Testing

Although our functional mappings were positively reviewed by radiology and neurology specialists, it is difficult to validate the results as we have no functional map ground truth for the tested subjects. We are thus pursuing three avenues for validating our results:

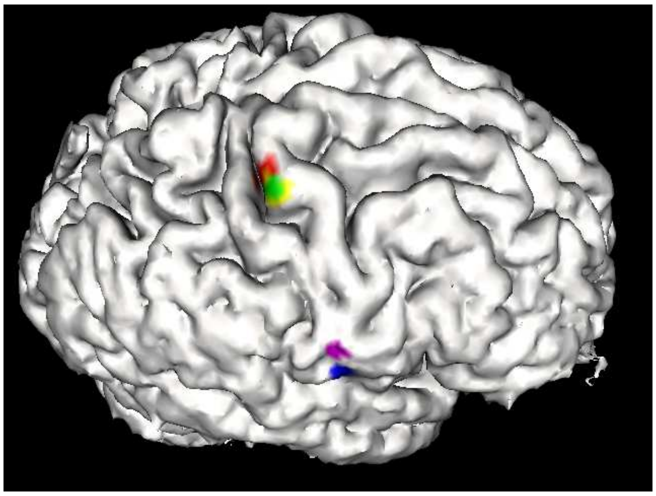

Figure 4: Motor cortex mapping showing minimum latency response for the following muscles: index finger (red), forearm (yellow), biceps (green), left jaw (blue), and right jaw (purple).

Map repeatability: At a minimum we would like to duplicate functional mapping results on the same subject at different time points. Such results are not definitive indicators of mapping accuracy, but do gauge the reliability of our registration and tracking techniques in the context of functional mapping. We have run such repeatability trials on two subjects in which we mapped the same side of the motor cortex at two different time points. Figure 7 shows the biceps muscle maps generated for one of the subjects at two time points. Initial measurements on distances between minimum latency stimulations of the same muscle resulted in repeatability errors of about $1cm$ or less. We are pursuing more accurate methods of evaluating repeatability such as weighting multiple small latency stimulations by their response amplitudes and using the same stimulation grid pattern which is saved for each subject with his MRI scan.

Map symmetry: In addition to repeatability we can also perform symmetry tests in which we compare motor cortex maps generated on the two sides of the brain. Quantitative evaluation of such results is difficult to achieve, but qualitatively we expect the two sides of the motor cortex to be symmetric. We have initiated such symmetry trials and are exploring result analysis techniques, such as evaluating whether the motor cortex lies on corresponding gyri.

Surgical validation An exact validation can be obtained in the operating room in the case of craniotomy surgeries. Surgeons currently use electrical stimulators to directly stimulate the brain surface when they are operating near the motor or sensory cortex. By tracking the position of such stimulators relative to an MR

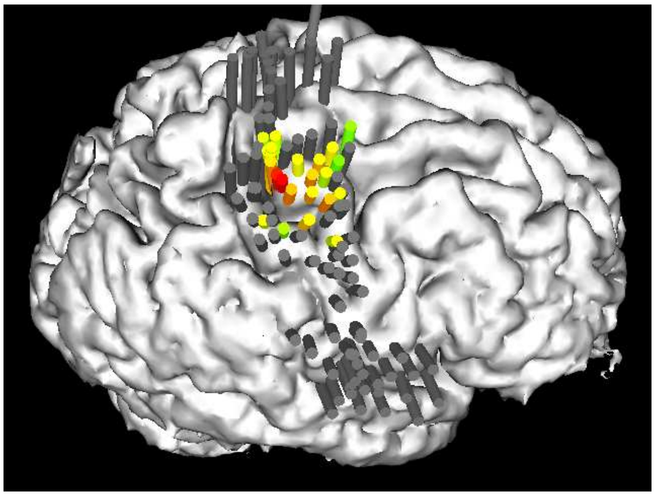

Figure 5: Oriented stimulation probes color-coded by response of index finger muscle. Response strength varies from none (black) to small (green) to stronger (yellow) to strongest (red).

scan on which we have overlaid the functional mapping we can verify the maps. Such tracking in the operating room can be performed using [8]. We have not yet had the opportunity to perform such quantitative validation, but in the neurosurgery case which we had mapped, the surgeon qualitatively validated our results as accurate.

5 Related Work

Several other groups have reported registration methods similar to ours, but for different applications. Pelizzari et al [12] have developed a method that matches retrospective data sets, (MRI, CT, PET), to one another. This work also uses a least squares minimization of distances between data sets, although with a different distance function and with more operator guidance required. One goal of their work was to register MRI/CT data with PET data to obtain functional mappings. Lavallee and Szeliski [15] also perform a least-squares minimization of a distance function to match data sets. Here, the distance is weighted by an estimate of the inverse variance of the measurement noise, and the Levenberg-Marquardt method is used to find the minimum. Once an initial solution is found, points with large errors are removed and the minimization is repeated to refine the pose. They also applied their registration approach to multi-modality registration, in part to obtain functional maps. Other related registration techniques include [2, 5, 10, 14, 17].

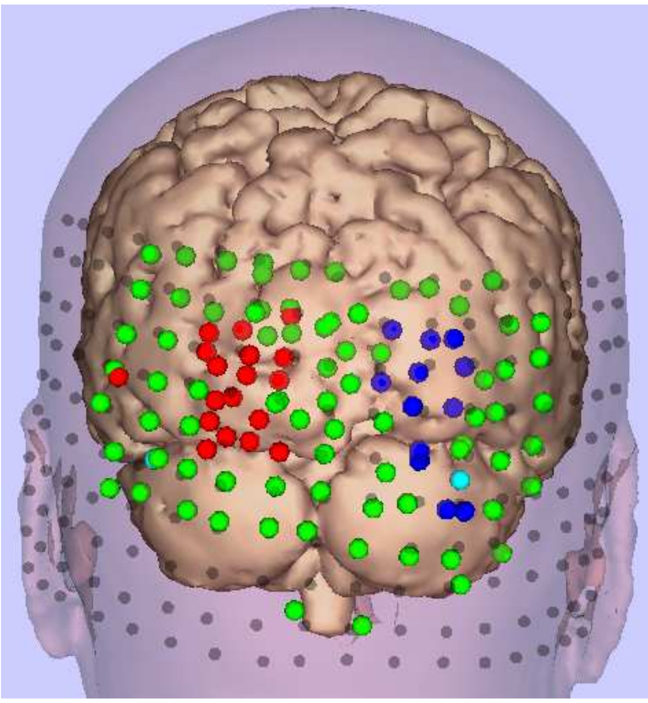

Figure 6: Visual cortex mapping showing stimulation points color-coded by visual suppression response. Suppressed right visual field is shown in red; suppressed left visual field is shown in blue; suppression of the center of the field is shown in cyan; no suppression is shown in green. The small black spheres are a virtual grid drawn on the model to aid in uniform mapping.

6 Summary

We have reported on an initial system combining 3D registration and 3D tracking techniques to generate functional brain maps from transcranial magnetic stimulation responses. Promising results have been obtained for mapping the motor cortex and visual cortex. Initial validation testing has shown reliable registration and tracking performance. Further testing is ongoing.

Such a functional mapping system has applications in:

- Surgical planning—identification of proximity of tumors to vital functional brain regions.
- Surgical guidance—tracking surgical activity relative to vital functional brain regions.
- Neuroscience research—building functional anatomical atlases and correlating functional maps with disease processes.
- Diagnosis—evaluating damage to functional activity of the brain.
- Therapy—using TMS as a therapeutic tool [1] in treating such conditions as depression and akinesa.

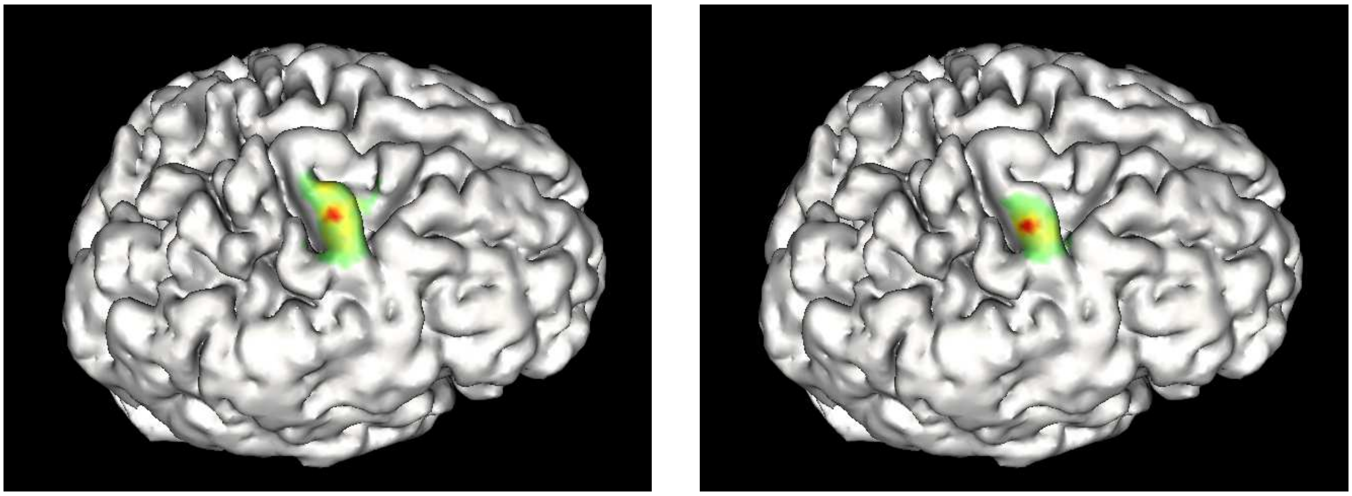

Figure 7: Comparison of the motor cortex mapping of the same subject at two time points. Amplitude maps are shown for the biceps muscle. Response strength varies from small (green) to large (red).

7 Acknowledgments

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