Optical measurement of hemodynamic changes in the contralateral motor cortex induced by transcranial magnetic stimulation

Ilkka Nissilä[1], Kalle Kotilahti[1], Soile Komssi[4,5], Seppo Kähkönen[2,3], Tommi Noponen[1], Risto J Ilmoniemi[2] and Toivo Katila[1,2]

[1] Laboratory of Biomedical Engineering, Helsinki University of Technology, P.O. Box 2200, FIN-02015 HUT, Finland
[2] BioMag Laboratory, Engineering Centre, Helsinki University Central Hospital, Finland
[3] Cognitive Brain Research Unit, University of Helsinki
[4] Department of Physical Sciences, University of Helsinki
[5] Department of Radiology, Helsinki University Central Hospital
[1,2,3,5] Helsinki Brain Research Center, Helsinki, Finland

Abstract

Transcranial magnetic stimulation was used to activate the left motor cortex of four volunteers. The consequent hemodynamic changes in the right motor cortex were measured with optical imaging. Different stimulus intensities were applied, and a sham measurement was made in which the coil was tilted 90 degrees from its tangential orientation, so that it the induced electric field is not sufficient to activate the cortex. The TMS-evoked changes were compared with an ipsilateral finger tapping task. The primary somatosensory cortex (S1) was localised based on the N20m response evoked by median nerve stimulation. It was found that magnetic stimulation induces a decrease in the 830 nm signal in the contralateral motor cortex. For one subject, the optical data was coregistered with anatomical MRI, and the optical activation was found strongest in the hand area of the motor cortex.

1 Introduction

1.1 Connectivity studies using TMS and a neuroimaging method

Transcranial magnetic stimulation (TMS) can be used to activate areas of the cortex non-invasively. The subsequent activity can be imaged directly using EEG. [1] While scalp-recorded EEG provides an excellent temporal resolution, the spatial resolution is not very good. In addition to the direct neuronal response, changes in the blood flow and oxygen consumption are coupled to neuronal activity. PET [2], fMRI [3] and NIRS [4] can be used to study the hemodynamic response. Optical imaging has the advantage that the magnetic field does not affect the optical measurement directly. On the other hand, the measurement is technically challenging due to the additional motion artefacts that may occur due to the presence of the stimulation coil. Previously, it was shown with single-channel NIRS that hemodynamic changes take place directly under the stimulation coil, although the measurement was not performed simultaneously with the magnetic stimulation. [4] The goal of this study was to show that optical imaging can be used to study the hemodynamic changes in secondary activation areas, especially the contralateral motor cortex.

2 Materials and methods

2.1 Subjects

Four subjects were studied, all were healthy and right handed. The mean age was 25 years. One of the subjects was female and three were male.

2.2 Technical details of optical imaging

2.2.1 Instrumentation

A frequency-domain optical imaging system with five time-multiplexed source fibers and four detectors was used. [5] The light source was a laser diode with an optical wavelength of 830 nm, which is sensitive to changes in the concentration of oxyhemoglobin. The signals from the four detectors were measured in parallel. The optical fibers and fiber bundles were made of non-metallic materials.

The holder for the optical fibers was made of a thermoplastic material. It was bent to match the shape

of the subject's head and fastened to the head with Velcro straps. In order to provide a more rigid fit to the subject's head, the hair was wet before the optical measurements. To reduce the attenuation due to hair, compressed air was used to move the hair away before each optode was connected to the skin.

2.2.2 Imaging sequence

The magnetic stimulation was active for 30 s at a time; 15 pulses were delivered at 2-s inter-stimulus intervals. This was followed by a rest period of 30 s. The measurement consisted of ten complete 1-min epochs, with an extra rest period at the beginning of measurement. Optical imaging was active throughout the measurement, except for a 5-s transition time between the stimulation and rest periods.

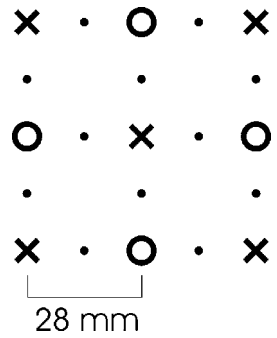

Fig. 1 Layout of the optical fibers. X = source, O = detector fiber, dot = center of sensitivity

The optodes were placed in a 3x3 grid (see **Fig 1**). The separation between the optical fibers was approximately 28 mm. Only the source/detector pairs with this distance were used to form the image, as the sensitivity to cortical tissue and the signal-to-noise ratio are then adequate.

2.2.3 Data analysis

The activation maps were based on the AC amplitude of the detected signal. A drift removal algorithm was applied to reduce the effect of slow changes in the contact between the optodes and tissue. A third-order polynomial was fit to the rest data for each source-detector pair, and subtracted from the data. [6]

The data used in the images was calculated by taking the mean of the amplitude values for each condition and source-detector pair, and dividing the difference between the means by the total mean;

$$map(i) = \frac{mean(active(i)) - mean(rest(i))}{mean(rest(i))}.$$

In order to evaluate the statistical significance of the change, Student's T-test was used. While the T-test assumes that the residual noise is white, which is not true for optical measurements due to the contact problem, the test result does give insight into the data. Also, maps based on the correlation between the measured signal and the stimulation state were calculated.

The source for the signal change was taken to reside in cortical tissue in the center between the source and detector positions. Since the image data was acquired from 12 locations, the in-between values of the maps were calculated using a cubic interpolation algorithm. Positive changes were designated with warm colours, and negative changes with cold colours. An increase in oxyhemoglobin causes a decrease in the amplitude, and thus shows up as negative values in the activation maps.

2.2 Magnetic stimulation

A commercial magnetic stimulator (Magstim Ltd.) was used to deliver the current pulses to a figure-of-eight coil. A laptop was used to trigger both the magnetic stimulator and the PC which collected the optical data. The stimulation was targeted to the area of the left primary motor cortex controlling the muscles for the right thumb. To localise the motor area and to estimate the motor threshold (MT), the EMG signal from the muscles of the right thumb was monitored, while a series of test pulses were delivered. After finding the optimal coil position for activating the abductor pollicis brevis, the threshold intensity was determined.

During the experiment, the subject sat in a chair, and the subject's neck was supported with a vacuum pillow. The coil was connected to the backrest of the chair using a mechanical arm. The optical fiber holder was cut so that it touched neither the chair nor the stimulation coil during the experiment.

A sham measurement was made for two subjects, in which the figure-of-eight coil was positioned in a rectangular angle to the surface of the head, so that it caused an auditory and a touch response, but did not activate cortical neurons directly.

2.3 MEG

The right somatosensory cortex was localised using median nerve stimulation and MEG. 100 stimuli were given to the subject at 5-s intervals. The responses on the right hemisphere were considered, and a dipole was fit to the peaks at times 20 ms and 35 ms after the onset of the stimulus.

3 Results

Representative difference images (see 2.2.3) of two subjects are given for both the contralateral TMS and ipsilateral finger tapping task. The images represent the 56 mm x 56 mm area where the optical fibers were located on the right hemisphere. **Fig 2** is a semitransparent 3D visualisation of the anatomical MR image for subject 2, including markers for the positions of the optical fibers. (See **Fig 5** for the corresponding optical image.)

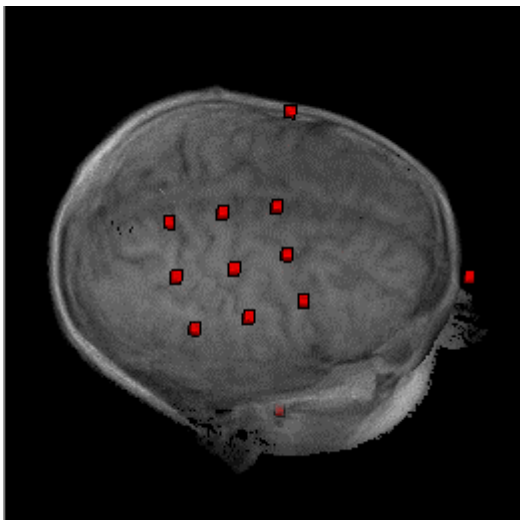

Fig. 2 MRI of subject 2, with markers for the positions of the optical fibers in the TMS measurement.

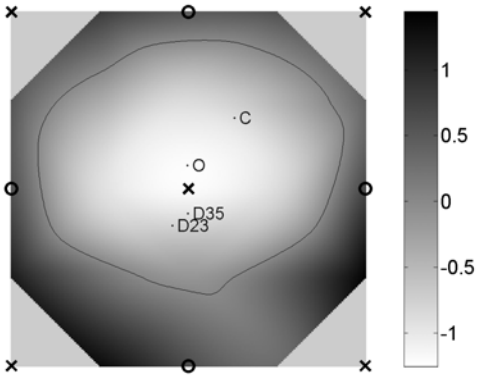

Fig. 3 Subject 1, TMS at 110% of MT, image based on relative change in optical signal (%). O = center of optical activation, C = estimated coil position, DN = dipole fit to MEG data at N ms.

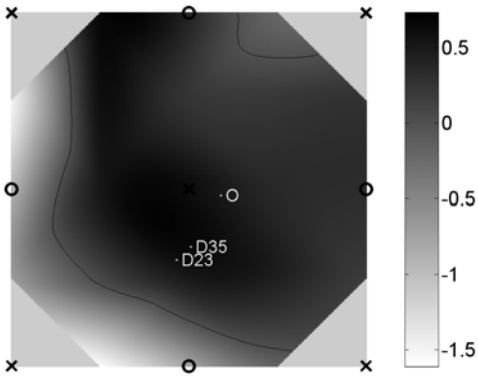

Fig. 4 Subject 1, finger tapping of the right thumb. Image based on relative change in optical signal (%). O = center of optical activation, DN = dipole fit to MEG data at N ms.

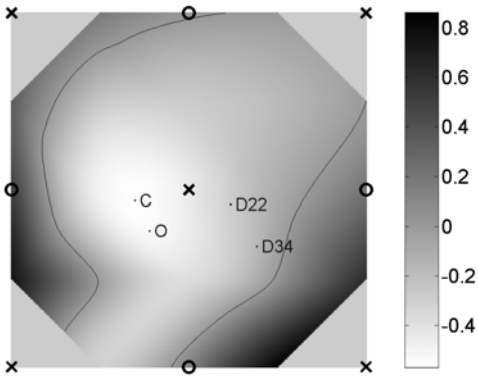

Fig. 5 Subject 2, TMS at 110% of MT. O = center of optical activation, C = estimated coil position, DN = dipole fit to MEG data at N ms.

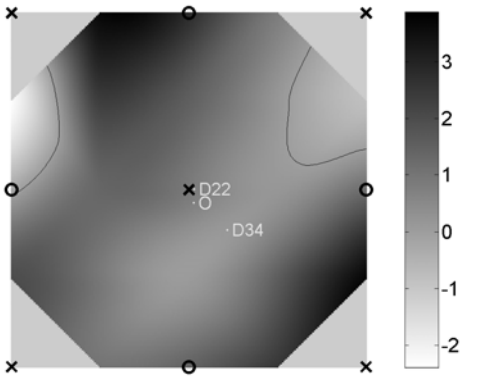

Fig. 6 Subject 2, finger tapping of the right thumb. O = center of optical activation, DN = dipole fit to MEG data at N ms.

In the optical images, negative values indicate an increase in absorption, which normally occurs due to an increase in the concentration of oxygenated blood. The thin dark line in the images separates the positive areas from the negative. In all of the TMS maps, corresponding to the strongest stimulation intensity that was used for each subject, there is a decrease in the signal. In the ipsilateral finger tapping tasks, there is an increase in the signal in the corresponding area, which can be interpreted to mean inhibition of the right motor cortex in right-hand finger tapping.

The MEG dipoles corresponding to the peaks at 20 ms and 35 ms are indicated in the images, and the position of the coil (after reversing the x coordinate) has been marked with a C. The center of the area of optical activation (in case of TMS) and inactivation (in finger tapping) was indicated by the letter O. For subject 1, the optical centre-of-gravity point closely matches the coil position and the dipoles. For subject 2, the coil and the optical centre are 1.5 cm posterior to the MEG dipoles. The mismatch is along the direction of the dipole, where the uncertainty in the dipole location is greatest.

Subj.	TMS	Finger tapping	Distance b/w optical activation and N20m
S1	-0.9%	+0.5%	8 mm
S2	-0.5%	+1.4%	13 mm
S3	-0.7%	+1.4%	9 mm
S4	-0.8%	N/A	14 mm

Table 1 A summary of the peak responses.

In **Table 1**, the peak values of the images are given for each subject in the TMS and ipsilateral finger tapping experiments. For subjects 2 and 3, we have verified using anatomical MRI that the center of the activated area in the optical measurements is on the primary motor cortex.

The sham measurement was performed for subject 4, and it resulted in a small signal increase over the entire image field, excluding the lower right corner, which had a decrease in signal. The latter is likely the result of auditory processing of the coil click. On subjects 1, 2 and 4, the stimulus intensity was varied from 90% MT to 110% MT, but the resulting images do not exhibit a clear dependency on the intensity.

It appears, on the other hand, that the response of the primary motor cortex to magnetic stimulation varies as a function of time. The first experiment for subject 1 produced a positive change in the image area, but the next two experiments, which were performed immediately after, produced a negative change in the signal over the motor cortex. In the lower right corner of the image, which is outside the primary motor cortex, the signal changes were still positive. This suggests that not all areas recover from the magnetic stimulation within the 30-s rest period. In order to understand the temporal behaviour of the TMS-evoked hemodynamic response on the motor cortex better, a study in which the stimulation and rest periods are varied, is required. The inter-stimulus interval may also affect the nature of the response.

4 Acknowledgements

The authors would like to thank Merja Hotakainen and Vadim Nikouline for their help with MEG and EMG, and Timo Mäkelä for the coregistration of the optical data with MRI. The research was supported by Tekes, TES, the Jenny and Antti Wihuri foundation and the graduate school Functional Studies in Medicine.

5 Literature

[1] Ilmoniemi, R. J.; Virtanen, J.; Ruohonen, J.; Karhu, J.; Aronen, H. J.; Näätänen, R.; Katila, T.: Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. NeuroReport 8 (16), 3537–3540 (1997).

[2] Paus, T.; Jech, R.; Thompson, C. J.; Comeau, R.; Peters, T.; Evans, A. C.: Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J. Neuroscience 17, 3178–3184 (1997).

[3] Baudewig, J.; Siebner, H. R.; Bestmann, S.; Tergau, F.; Tings, T; Paulus, W.; Frahm J.: Functional MRI of cortical activations induced by transcranial magnetic stimulation (TMS). NeuroReport 12 (16), 3543–3548 (2001).

[4] Oliviero, A.; Di Lazzaro, V.; Piazza, O.; Profice, P.; Pennisi, M. A.; Della Corte, F.; Tonali, P.: Cerebral blood flow and metabolic changes produced by repetitive magnetic brain stimulation. J. Neurol. 246 (12), 1164-1168 (1999).

[5] Nissilä, I.; Kotilahti, K.; Noponen, T.; Katila, T.: A method for the accurate measurement of phase in intensity modulated optical imaging, OSA BIOMED Topical Meeting (AIOPM) Technical Digest (2002).

[6] Sato, H.; Takeuchi, T.; Sakai K. L.: Temporal cortex activation during speech recognition: an optical topography study. Cognition 73, B55-B66 (1999).