Focused high frequency repetitive transcranial magnetic stimulation for localisation of the unexposed primary motor cortex during brain tumour surgery

V Rohde, L Mayfrank, M Weinzierl, T Krings, J M Gilsbach

J Neurol Neurosurg Psychiatry 2003;74:1283–1287

Objective: To investigate if intraoperative focused high frequency repetitive transcranial magnetic stimulation (rTMS) can localise the primary motor cortex without exposure of the cortical surface.

Methods: A high frequency train (357 Hz) of four suprathreshold magnetic stimuli was delivered transcranially to the region of the rolandic area during brain tumour operations in 12 patients. To induce a focal magnetoelectric field, the flat figure of eight coil (outer diameter of each loop 7 cm) was used. Motor evoked potentials (MEP) were recorded in eight muscles of the upper and lower contralateral extremities. The first stimulation site was 2.5 cm behind the bregma, the second site 2 cm, and the third site 4 cm dorsal to the first stimulation site. If no MEP were obtainable, stimulation was repeated in anteroposterior direction at more laterally located sites. Using neuronavigation, each stimulation site was correlated with the underlying cortical anatomy.

Results: Stimulation was performed at a total of 42 sites (in two patients, maximum stimulation at the three initial sites failed to evoke a motor response). In four patients, MEP were obtained only from one stimulation site. This site exactly overlayed the primary motor cortex. In eight patients, MEP could be elicited from more than one stimulation site. In seven of the eight patients, the site from which MEP with peak amplitudes were elicited, corresponded to the primary motor cortex. In total, the primary motor cortex was correctly identified on the basis of electrophysiological findings in 11 of 12 patients (92%). In two patients, only the more lateral stimulation sites permitted MEP recording.

Conclusion: Intraoperative focused rTMS is highly sensitive for localisation of the primary motor cortex. Focused rTMS as a localising instrument alleviates the need of motor cortex exposure and, thereby, can contribute to minimise the surgical approach to brain tumours in the rolandic area.
The intraoperative motor threshold of each stimulation site (6.5 cm behind bregma) dorsal to the first stimulation site, was defined by stepwise increase of the stimulator output (10% steps, starting with 60% of the maximum stimulator output(2.5 T)) before the investigation. According to the literature the motor threshold is lowest and the MEP amplitudes are highest if stimulation directly overlies the primary motor cortex.11 12 Thus, the authors hypothesised that the site with the lowest motor threshold and/or the site that allows to obtain MEP of peak amplitudes localises the primary motor cortex. Accordingly, the lowest stimulation intensity, which allowed to elicit a motor response from at least one stimulation site, was applied during the motor cortex localisation procedure. In our patients, this stimulation intensity ranged between 70% and 90% of the maximum stimulator output. If no MEP were obtainable at the three medial sites despite maximum stimulation intensity, stimulation was repeated in anteroposterior direction again more laterally (3 cm to 5 cm from the midline). At each site, the train of four stimuli was repeated at least once. As the authors in this feasibility study aimed to merely localise the precentral gyrus, no attempts were made to identify different cortical representation of the upper and lower limb muscles. Thus, the stimulation coil was exclusively moved in anteroposterior direction and not mediolaterally along the motor strip. During the whole investigation, the orientation of the coil (tangential to skull, the handle pointing strictly dorsally) was kept unchanged. The figure of eight coil, which induces a highly focal electrical field at the junction of the two loops, was used for motor cortex activation. The outer diameter of each loop of the figure of eight coil was 7 cm.

Subdermal concentric needle electrodes were used for recording MEP. The active electrode was placed over the muscle belly, referenced to an electrode placed over the muscle tendon. The ground electrode was placed on the leg, proximal to the knee.13 14 As tumours could dislocate the cortical representation of upper and lower limb muscles in both anteroposterior and mediolateral direction, the authors believed that the muscles that will be activated by focused magnetic stimulation at the selected sites are not exactly predictable. In addition, stimulation at bordering sites where overlapping muscle representations occur, might elicit responses by several muscles.15 In consequence, the authors used recording electrodes in the contralateral abductor pollicis brevis, forearm flexor, biceps brachii, triceps brachii, anterior tibial, abductor hallucis, adductor longus, and quadriceps femoris muscles. The signal was amplified 2000 to 5000 times. The low cut off and high cut off filters were set at 30 Hz and 3000 Hz. About 20 minutes were required for cortical stimulation and MEP recording. Each scalp stimulation site was matched with the underlying cortical anatomy using frameless stereotaxy.

### Frameless stereotaxy

Frameless stereotaxy was performed with the EasyGuide Neurosystem (Philips Medical Systems, Best, Netherlands), which consists of a mobile workstation, an optical localising system with two infrared sensitive cameras positioned on a single camera stand and pointers with infrared light emitting diodes. External fiducials were placed on the patient's scalp and T1 weighted magnetic resonance (MR) imaging was performed. The data were transferred to the workstation to reconstruct an individual 3-D model of the patient's head and brain. The coordinates of the reconstructed 3-D model were correlated with the head position by touching the fiducials on the patient's skin with the pointer, which links the tip of the pointer with its representation on the screen. The system inaccuracy was tolerated if the root mean square error (RMSE), which compares the relation of the fiducial position on the MR images with the registered fiducials on the patient's head, was below 3.5 mm. The skin position of the junction region of the figure of eight coil was related to the underlying gyral anatomy by stepwise virtual elongation of the pointer from the scalp to the cortical surface. As identification of the cortical anatomy on MR images was crucial for verification of the electrophysiological testing in this preliminary study, patients with grossly distorted anatomy, which made anatomical identification of sensorimotor cortex impossible, were excluded.

### RESULTS

Stimulation was performed at a total of 42 sites (in two patients, maximum stimulation at the three initial sites failed to evoke a motor response). In all 12 patients, MEP contralateral to the stimulation and tumour site could be obtained by rTMS from at least one muscle, but the number of

---

<table>
<thead>
<tr>
<th>N</th>
<th>Age (y)/sex</th>
<th>Tumour</th>
<th>Location</th>
<th>1: 2.5 cm behind bregma (SMA)</th>
<th>2: 2 cm behind stimulation site 1 (precentral gyrus)</th>
<th>3: 4 cm behind stimulation site 1 (postcentral gyrus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59/M</td>
<td>meningioma</td>
<td>frontal</td>
<td>0.39 mV</td>
<td>0.38 mV</td>
<td>0.07 mV</td>
</tr>
<tr>
<td>2</td>
<td>54/M</td>
<td>glioma</td>
<td>parietal</td>
<td>0.20 mV</td>
<td>0.50 mV</td>
<td>0.44 mV</td>
</tr>
<tr>
<td>3</td>
<td>64/M</td>
<td>glioma</td>
<td>frontal</td>
<td>0.28 mV</td>
<td>3.89 mV</td>
<td>0.30 mV</td>
</tr>
<tr>
<td>4</td>
<td>26/M</td>
<td>glioma</td>
<td>frontal</td>
<td>0.03 mV</td>
<td>0.20 mV</td>
<td>0.07 mV</td>
</tr>
<tr>
<td>5</td>
<td>75/F</td>
<td>metastasis</td>
<td>parietal</td>
<td>0.43 mV</td>
<td>1.14 mV</td>
<td>0.56 mV</td>
</tr>
<tr>
<td>6</td>
<td>77/M</td>
<td>meningioma</td>
<td>parietal</td>
<td>no CMAP</td>
<td>6.12 mV</td>
<td>5.45 mV</td>
</tr>
<tr>
<td>7</td>
<td>49/F</td>
<td>meningioma</td>
<td>parietal</td>
<td>no CMAP</td>
<td>3.33 mV</td>
<td>no CMAP</td>
</tr>
<tr>
<td>8</td>
<td>39/F</td>
<td>glioma</td>
<td>frontal</td>
<td>0.01 mV</td>
<td>5.27 mV</td>
<td>no CMAP</td>
</tr>
<tr>
<td>9</td>
<td>52/F</td>
<td>meningioma</td>
<td>frontal</td>
<td>minimal signal</td>
<td>0.17 mV</td>
<td>no CMAP</td>
</tr>
<tr>
<td>10</td>
<td>32/M</td>
<td>glioma</td>
<td>frontal</td>
<td>no CMAP</td>
<td>minimal signal</td>
<td>no CMAP</td>
</tr>
<tr>
<td>11</td>
<td>39/F</td>
<td>glioma</td>
<td>frontal</td>
<td>no CMAP</td>
<td>0.9 mV</td>
<td>no CMAP</td>
</tr>
<tr>
<td>12</td>
<td>61/M</td>
<td>glioma</td>
<td>frontal</td>
<td>no CMAP</td>
<td>0.05 mV</td>
<td>no CMAP</td>
</tr>
</tbody>
</table>
stimulation sites, which allowed to evoke MEP, varied. In 4 of 12 patients, reproducible MEP could be elicited only from the stimulation site, which was 4.5 cm behind the bregma (fig 1). Virtual elongation of the pointer of the frameless stereotactic device indicated that this scalp stimulation site exactly overlaid the praecentral gyrus. In three patients, reproducible electromyographic responses could be obtained from two stimulation sites. As shown by neuronavigation, MEP with the maximal amplitude could be obtained from the stimulation site 4.5 cm behind bregma, which corresponded to the praecentral gyrus. In two patients, MEP with lower amplitudes could be elicited from the first stimulation site (2.5 cm behind bregma), which overlaid the supplementary motor area. In one patient, MEP with lower amplitudes were obtained following stimulation 6.5 cm behind bregma. This site corresponded to the postcentral gyrus. In the remaining five patients, MEP could be recorded from three stimulation sites. In four of the five patients, MEP with the highest amplitude could be obtained from stimulation site 2 (4.5 cm behind bregma), which corresponded to the praecentral gyrus. In one patient, MEP with the highest amplitude were elicited after stimulation 2.5 cm behind bregma. Neuronavigation showed that this stimulation site overlaid the supplementary motor area. In summary, either the stimulation site from which the peak amplitude could be obtained or the only site, which allowed to elicit evoked potentials, indicated the praecentral gyrus correctly in 11 of 12 patients (92%) (table 1).

DISCUSSION
It was not before the development of the figure of eight coil, which induces a more focal electrical field at the junction of the loops than the standard flat circular coil, that somatotopic mapping of the praecentral gyrus without opening of the skull in awake patients possible. The correlation of focused TMS with MR imaging, functional MR imaging, and direct electrical motor cortex stimulation showed, that focused TMS reliably permits the detection of the motor cortex gyral sites of distinct muscles of the arm and leg. The stimulation site that allows to elicit muscle action potentials with peak amplitudes indicates the representation of the tested muscle in the primary motor cortex with an inaccuracy of only 0.5 cm. The threshold for a muscle response is lowest if the stimulation site directly overlies the cortical representation.

MEP after TMS are largely suppressed by most anaesthetics, which might explain that the technique of TMS seldomly has been transferred into the operation theatre for assessment of the motor system. Recent experiments have demonstrated that MEP recording is always realisable in anaesthesied humans if not a single, but a high frequency train of four transcranially applied magnetic stimuli is delivered.

The reliable identification of the primary motor cortex before and during surgery is of paramount interest for the neurosurgeon. High quality MR images, functional MR
imaging, positron emission tomography, magnetoencephalography, and dipole source analysis of somatosensory evoked potentials have been used for preoperative motor cortex identification. Our research group successfully used single-focused magnetic cortical stimulation for motor cortex localisation in awake patients with brain tumours before surgery. However, independent of the mode of functional data collection, neuronavigation is always required for the transfer of the preoperatively collected information into the operative field. Drainage of cerebrospinal fluid and tumour debulking inevitably result in a certain shifting of the brain. In consequence, neuronavigation, which has to rely only on preoperatively obtained data, becomes an increasingly inaccurate tool during surgery. Thus, the surgeon could rely on the neuronavigationally transferred functional data only at the very beginning of the operation. For updating the preoperative image information, electrophysiological tests have been applied. Direct cortical electric stimulation and MEP recording as well as median nerve stimulation and localising the area of phase reversal of somatosensory evoked potentials allows to identify the precentral gyrus and the central sulcus reliably during surgery. As the stimulation respectively the recording electrode has to be placed onto the cortex, exposure of the motor strip in vicinity to the tumour is mandatory. Thus, skull and dural openings larger than for mere tumour removal are required for intraoperative motor cortex identification. This counteracts the ongoing efforts to minimise the surgical approaches.

On the search for an intraoperative brain shift independent localising tool, which supports the concept of minimal surgical invasiveness, the authors brought together their experiences with focused TMS in awake patients and rTMS in anaesthetised humans. The authors show in this pilot study, that focused rTMS is able to determine the localisation of the primary motor cortex intraoperatively with high accuracy and sensitivity. In contrast with electrical stimulation of the cortex and somatosensory evoked potentials phase reversal, exposure of the motor cortex is not required. In analogy to mapping studies in awake humans, stimulation of the primary motor cortex is predominantly indicated by MEP of peak amplitude. It is in accordance with the electrophysiological literature, that MEP of lower amplitude sometimes could be obtained after stimulation of the supplementary motor area and the postcentral gyrus.

CONCLUSION
Focused rTMS can localise the primary motor cortex during brain tumour surgery with high accuracy and sensitivity. In contrast with the most commonly used localising techniques, direct electrical cortical stimulation and somatosensory evoked potentials phase reversal, exposure of the brain surface at risk is not required, which supports the concept of minimised invasiveness of the surgical intervention. Preoperative repetitive or single TMS for motor cortex identification could be useful for rapid intraoperative definition of the optimal initial stimulation site before substantial tumour removal and cerebrospinal fluid drainage. However, preoperative TMS could not be a substitute for intraoperative TMS as brain shift results in a progressive incongruence of the findings. With refinements of the bulky coil design provided, focused rTMS can become a useful localising tool for patients, in whom minimalised access to the lesion is planned or in whom excessive shifting of the brain dislocates the motor cortex beneath the opening of the dura and the skull.

ACKNOWLEDGEMENT
We thank Ferhan Ustener for assistance during the intraoperative electrophysiological testing. The work was presented in parts at the 50th annual meeting of The German Society of Neurological Surgeons, Munich, June 1999.

Authors’ affiliations
V Rohde, L Mayfrank, M Weinzierl, J M Gilbsch, Department of Neurosurgery, Aachen University, Germany
T Krings, Department of Neuroradiology, Aachen University

Funding: the work was supported by grants of the Stiftung Tumorforschung Kap-Hals given to the first author.

Competing interests: none declared.

REFERENCES
Focused high frequency repetitive transcranial magnetic stimulation for localisation of the unexposed primary motor cortex during brain tumour surgery

V Rohde, L Mayfrank, M Weinzierl, T Krings and J M Gilsbach

*J Neurol Neurosurg Psychiatry* 2003 74: 1283-1287
doi: 10.1136/jnnp.74.9.1283

Updated information and services can be found at:
[http://jnnp.bmj.com/content/74/9/1283](http://jnnp.bmj.com/content/74/9/1283)

These include:

**References**

This article cites 27 articles, 4 of which you can access for free at:
[http://jnnp.bmj.com/content/74/9/1283#BIBL](http://jnnp.bmj.com/content/74/9/1283#BIBL)

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections

- CNS cancer (184)
- Neurooncology (237)
- Surgical oncology (144)

**Notes**

To request permissions go to:
[http://group.bmj.com/group/rights-licensing/permissions](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to:
[http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to:
[http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)