Navigated transcranial magnetic stimulation for glioma removal: prognostic value in motor function recovery from postsurgical neurological deficits

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OBJECTIVE The aim of the present study was to evaluate the usefulness of navigated transcranial magnetic stimulation (nTMS) as a prognostic predictor for upper-extremity motor functional recovery from postsurgical neurological deficits.

METHODS Preoperative and postoperative nTMS studies were prospectively applied in 14 patients (mean age 39 ± 12 years) who had intraparenchymal brain neoplasms located within or adjacent to the motor eloquent area in the cerebral hemisphere. Mapping by nTMS was done 3 times, i.e., before surgery, and 1 week and 3 weeks after surgery. To assess the response induced by nTMS, motor evoked potential (nTMS-MEP) was recorded using a surface electromyography electrode attached to the abductor pollicis brevis (APB). The cortical locations that elicited the largest electromyography response by nTMS were defined as hotspots. Hotspots for APB were confirmed as positive responsive sites by direct electrical stimulation (DES) during awake craniotomy. The distances between hotspots and lesions (DHS-L) were measured. Postoperative neurological deficits were assessed by manual muscle test and dynamometer. To validate the prognostic value of nTMS in recovery from upper-extremity paresis, the following were investigated: 1) the correlation between DHS-L and the serial grip strength change, and 2) the correlation between positive nTMS-MEP at 1 week after surgery and the serial grip strength change.

RESULTS From the presurgical nTMS study, MEPs from targeted muscles were identified in 13 cases from affected hemispheres. In one case, MEP was not evoked due to a huge tumor. Among 9 cases from which intraoperative DES mapping for hand motor area was available, hotspots for APB identified by nTMS were concordant with DES-positive sites. Compared with the adjacent group (DHS-L < 10 mm, n = 6), the nonadjacent group (DHS-L ≥ 10 mm, n = 7) showed significantly better recovery of grip strength at 3 months after surgery (p < 0.01). There were correlations between DHS-L and recovery of grip strength at 1 week, 3 weeks, and 3 months after surgery (r = 0.74, 0.68, and 0.65, respectively). Postsurgical nTMS was accomplished in 13 patients. In 9 of 13 cases, nTMS-MEP from APB muscle was positive at 1 week after surgery. Excluding the case in which nTMS-MEP was negative from the presurgical nTMS study, recoveries in grip strength were compared between 2 groups, in which nTMS-MEP from APB muscle was positive at 1 week after surgery. Significant differences were observed between the 2 groups at 1 week, 3 weeks, and 3 months after surgery (p < 0.01). Positive nTMS-MEP at 1 week after surgery correlated well with the motor recovery at 1 week, 3 weeks, and 3 months after surgery (r = 0.87, 0.88, and 0.77, respectively).

CONCLUSIONS Navigated TMS is a useful tool for identifying motor eloquent areas. The results of the present study have demonstrated the predictive value of nTMS in upper-extremity motor function recovery from postsurgical neurological deficits. The longer DHS-L and positive nTMS-MEP at 1 week after surgery have prognostic values of better recovery from postsurgical neurological deficits.

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KEY WORDS awake craniotomy; transcranial magnetic stimulation; glioma; neurological deficit; rehabilitation; diagnostic technique; surgical technique

ABBREVIATIONS 5-ALA = 5-aminolevulinic acid; AH = affected hemisphere; AMT = active motor threshold; AP = anterior to posterior; APB = abductor pollicis brevis; BB = biceps brachii; DES = direct electrical stimulation; DHS-L = distance between hotspot and lesion; d-MEP = direct motor evoked potential; EMCS = epidural motor cortex stimulation; FMA = Fugl-Meyer assessment; io = intraoperative; LE = lower extremity; MMT = manual muscle testing; nTMS = navigated transcranial magnetic stimulation; OO = orbicularis oris; PA = posterior to anterior; RMT = resting motor threshold; TA = tibialis anterior; Tc-MEP = transcranial MEP; UE = upper extremity; UH = unaffected hemisphere.


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Resection of intraaxial brain tumors located within or adjacent to the motor eloquent area presents a particular challenge to neurosurgeons and patients. Although maximal resection and preservation of neurological function are key principles in surgery for brain tumors, neurosurgeons frequently encounter a dilemma between completeness of resection and conservation of motor function. In particular, when a patient is asymptomatic before surgery, postsurgical deficits become a burden to both patient and neurosurgeon. For glioblastoma multiforme, there is growing evidence that the completeness of resection has a significant impact on long-term prognosis after surgery. Also, for low-grade glioma, the extent of resection is associated with better progression-free survival and overall survival.

Contemporary technological developments have contributed to maximal resection and preservation of the eloquent area. Technological developments such as information-guided management using updated neuronavigation based on intraoperative MRI (iOMRI), neurochemical navigation with 5-aminolevulinic acid (5-ALA), serial intraoperative histopathological investigations of the resected tissue, and neurophysiological monitoring with direct electric stimulation (DES) during awake craniotomy provide good opportunities for maximal possible resection of glioma.

For conservation of neurological function, intraoperative mapping by DES remains the gold standard for detection and preservation of eloquent areas during brain surgery. In addition, preoperative mapping for the motor area using navigated transcranial magnetic stimulation (nTMS) has recently been reported as a state-of-the-art technique. Also, nTMS has been used as the presurgical mapping technique for the language eloquent area. On the other hand, individuals with brain tumors have a high incidence of neurological impairments, resulting in functional deficits for which rehabilitation services are necessary. Most commonly, immediately after the surgical removal of the brain tumor located within the primary motor area (M1) or supplementary motor area, postsurgical neurological deficits such as hemiparesis/hemiplegia may occur. Above all, supplementary motor area syndrome has been described most commonly as a result of resection of the cortex anterior to the precentral gyrus.

These postsurgical deficits can be temporary or permanent; nevertheless, there is no established measure to predict the prognosis of these neurological deficits. Therefore, prognosis is uncertain after surgery, and thus both patient and surgeon feel insecure. The objective of the present study was to evaluate the prognostic value of nTMS in recovery from postsurgical neurological deficits. To the best of our knowledge, there has been no report of a pre- and postsurgical nTMS study in which nTMS was used for its prognostic value for the recovery from postsurgical neurological deficits after glioma removal.

Methods
Study Participants
Between January 2014 and January 2015, pre- and post-surgical nTMS studies were performed in 14 consecutive patients (8 men and 6 women; mean age 39 ± 12 years) who had intraaxial brain neoplasms located within or close to the motor eloquent area. All 14 patients were right-handed. Eleven cases were newly diagnosed, and 3 cases were recurrent. Seven patients had a tumor in the right hemisphere, and 7 had a tumor in the left hemisphere. Exclusion criteria were the existence of any implanted electric device (e.g., cardiac pacemaker, cochlear implant) and intractable seizure. Patient demographic data and clinical characteristics are shown in Table 1. The ethics commission of Tokyo Women’s Medical University approved the study protocol, and each patient provided informed consent before entering the study.

Preoperative and Postoperative Evaluations
Motor function was evaluated before surgery and 1 week, 3 weeks, and 3 months after surgery by an examiner, a board-certified physiatrist. The motor function of each patient was assessed with manual muscle testing (MMT) of shoulder flexion, elbow flexion, wrist dorsiflexion, little finger abduction, and thumb abduction (where 0 indicates no movement and 5 indicates normal strength). Hand motor function was assessed with a grip strength dynamometer (T.K.K.5401, Takei Scientific Instrument Co.). As a numerical index of motor recovery of the contralesional hand, relative change of grip strength (postsurgical grip strength [kgf]/presurgical grip strength [kgf]) at 1 week, 3 weeks, and 3 months after surgery was used. In addition, to evaluate the recovery from postoperative palsy of the upper extremity (UE), the Fugl-Meyer assessment for UE (FMA-UE) was applied to an illustrative case.

Navigated TMS System
Presurgical and postsurgical motor mapping was performed with a transcranial magnetic stimulator (Rapid2, Magstim Co.) and a figure-8 coil with a diameter of 70 mm (MS20–024, Magstim Co.). A single biphasic pulse was used with a 4-second interval. A navigation system (BrainSight, Rogue Resolutions) and optical tracking system (Polaris, Northern Digital Instruments Co.) were used to depict the stimulation sites on reconstructed brain surface MRI.

Presurgical and Postsurgical Motor Mapping by nTMS
Brain mapping by nTMS was performed 3 times: before surgery, 1 week after surgery, and 3 weeks after surgery. In addition, in an illustrative case in which marked recovery from postoperative deficits was observed, follow-up nTMS was performed up to 6 weeks after surgery. A single investigator trained in the nTMS procedure performed every examination. Surface electromyography electrodes were attached to the bilateral abductor pollicis brevis (APB) muscle as a primary target muscle to detect motor evoked potential (MEP). In addition, depending on tumor location and particular clinical needs, motor eloquent areas for muscles of the contralateral limb and face, such as biceps brachii (BB), tibialis anterior (TA), and orbicularis oris (OO), were mapped preoperatively.

During the procedure, patients were seated in a reclining chair equipped with a headrest and armrest. Subjects were instructed to perform isometric contractions of the muscles being mapped.
TABLE 1. Summary of demographic data and clinical characteristics of 14 patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Tumor Location</th>
<th>Histology</th>
<th>Type of Anesthesia</th>
<th>Newly Diagnosed or Recurrence</th>
<th>Preop nTMS (sites)</th>
<th>Tumor Resection, %</th>
<th>MEP Reduction During Op</th>
<th>Intraop DES (limb)</th>
<th>nTMS 1 Wk After Op (APB)</th>
<th>MMT</th>
<th>MMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33, M</td>
<td>Rt precentral</td>
<td>AOA</td>
<td>Local (awake) + general (asleep)</td>
<td>Recurrence</td>
<td>Positive (APB)</td>
<td>95</td>
<td>Positive (hand, UE)</td>
<td>UE 80%,* LE 60%*</td>
<td>Negative</td>
<td>UE 4–5/5, LE 5/5</td>
<td>UE 4/5, LE 4–5/5</td>
</tr>
<tr>
<td>2</td>
<td>23, F</td>
<td>Lt precentral</td>
<td>OA</td>
<td>Local (awake)</td>
<td>Newly</td>
<td>Positive (APB)</td>
<td>85</td>
<td>Positive (hand, LE)</td>
<td>UE 60%, LE 60%</td>
<td>Positive</td>
<td>UE 5/5, LE 5/5</td>
<td>UE 5/5, LE 5/5</td>
</tr>
<tr>
<td>3</td>
<td>29, M</td>
<td>Lt precentral</td>
<td>AOA</td>
<td>Local (awake)</td>
<td>Recurrence</td>
<td>Positive (APB)</td>
<td>90</td>
<td>Positive (hand, UE)</td>
<td>UE 55%, LE 0%</td>
<td>Positive</td>
<td>UE 5/5, LE 5/5</td>
<td>UE 5/5, LE 5/5</td>
</tr>
<tr>
<td>4</td>
<td>39, M</td>
<td>Rt post-central</td>
<td>AO</td>
<td>Local (awake)</td>
<td>Recurrence</td>
<td>Positive (APB)</td>
<td>95</td>
<td>Positive (hand)</td>
<td>UE 0%, LE 0%</td>
<td>Negative</td>
<td>UE 5/5, LE 5/5</td>
<td>UE 5/5, LE 5/5</td>
</tr>
<tr>
<td>5</td>
<td>28, F</td>
<td>Lt precentral</td>
<td>AA</td>
<td>Local (awake)</td>
<td>Newly</td>
<td>Positive (APB)†</td>
<td>90</td>
<td>Negative</td>
<td>UE NE, LE 0%</td>
<td>Negative</td>
<td>UE 4–5/5, LE 5/5</td>
<td>UE 2–5/5, LE 5/5</td>
</tr>
<tr>
<td>6</td>
<td>65, M</td>
<td>Lt precentral</td>
<td>OA</td>
<td>Local (awake)</td>
<td>Newly</td>
<td>Negative (APB)</td>
<td>85</td>
<td>Negative</td>
<td>UE 65%, LE 10%</td>
<td>Negative</td>
<td>UE 3–4/5, LE 3–4/5</td>
<td>UE 3–4/5, LE 3–4/5</td>
</tr>
<tr>
<td>7</td>
<td>41, F</td>
<td>Rt precentral</td>
<td>OA</td>
<td>Local (awake)</td>
<td>Newly</td>
<td>Positive (APB)</td>
<td>95</td>
<td>Positive (hand, LE)</td>
<td>UE 25%, LE NE</td>
<td>NA</td>
<td>UE 5/5, LE 5/5</td>
<td>UE 4–5/5, LE 5/5</td>
</tr>
<tr>
<td>8</td>
<td>35, F</td>
<td>Lt postcentral</td>
<td>O</td>
<td>Local (awake)</td>
<td>Newly</td>
<td>Positive (APB, BB, TA)</td>
<td>95</td>
<td>Positive (hand, UE)</td>
<td>UE 0%, LE 0%</td>
<td>Positive</td>
<td>UE 5/5, LE 5/5</td>
<td>UE 5/5, LE 4–5/5</td>
</tr>
<tr>
<td>9</td>
<td>24, F</td>
<td>Rt central</td>
<td>AE</td>
<td>Local (awake)</td>
<td>Newly</td>
<td>Positive (APB, TA)</td>
<td>100</td>
<td>Positive (thumb, middle finger, UE)</td>
<td>UE 100%, LE 0%</td>
<td>Positive</td>
<td>UE 5/5, LE 5/5</td>
<td>UE 4–5/5, LE 5/5</td>
</tr>
<tr>
<td>10</td>
<td>37, F</td>
<td>Lt postcentral</td>
<td>AA</td>
<td>General (asleep)</td>
<td>Newly</td>
<td>Positive (APB, TA)</td>
<td>95</td>
<td>NA</td>
<td>UE 20%, LE 20%*</td>
<td>Positive</td>
<td>UE 5/5, LE 5/5</td>
<td>UE 5/5, LE 4–5/5</td>
</tr>
<tr>
<td>11</td>
<td>55, M</td>
<td>Rt precentral</td>
<td>GBM</td>
<td>Local (awake)</td>
<td>Newly</td>
<td>Positive (APB, OO)</td>
<td>95</td>
<td>Positive (OO)</td>
<td>UE NA, LE NA</td>
<td>Positive</td>
<td>UE 5/5, LE 5/5</td>
<td>UE 5/5, LE 5/5</td>
</tr>
<tr>
<td>12</td>
<td>45, M</td>
<td>Lt precentral</td>
<td>AA</td>
<td>Local (awake)</td>
<td>Newly</td>
<td>Positive (APB, BB, TA)</td>
<td>95</td>
<td>Positive (finger, LE)</td>
<td>UE 90%, LE NA</td>
<td>Positive</td>
<td>UE 5/5, LE 5/5</td>
<td>UE 0–4/5, LE 5/5</td>
</tr>
<tr>
<td>13</td>
<td>53, M</td>
<td>Rt precentral</td>
<td>AO</td>
<td>Local (awake)</td>
<td>Newly</td>
<td>Positive (APB, OO)</td>
<td>100</td>
<td>Positive (OO)</td>
<td>UE 0%</td>
<td>Positive</td>
<td>UE 5/5, LE 5/5</td>
<td>UE 4–5/5, LE 5/5</td>
</tr>
<tr>
<td>14</td>
<td>51, M</td>
<td>Rt precentral</td>
<td>AA</td>
<td>Local (awake)</td>
<td>Newly</td>
<td>Positive (APB)†</td>
<td>80</td>
<td>Positive (hand, thumb)</td>
<td>UE NE, LE 0%</td>
<td>Positive</td>
<td>UE 2–5/5, LE 5/5</td>
<td>UE 2–5/5, LE 5/5</td>
</tr>
</tbody>
</table>

AA = anaplastic astrocytoma; AE = anaplastic ependymoma; AO = anaplastic oligodendroglioma; AOA = anaplastic oligoastrocytoma; GBM = glioblastoma multiforme; NA = not applicable; NE = not evoked; O = oligodendroglioma; OA = oligoastrocytoma.

* Transcranial stimulation.
† Positive only under activated condition.
Any MEP amplitudes > 50 μV.51,56 If it was impossible to evoke MEPs in the resting condition, patients were instructed to abduct the thumb mildly to facilitate responses. From a previous report, it is known that the MT is lowered with active voluntary contraction compared with the resting condition. It has been reported that the MT under the activated condition (active motor threshold [AMT]) was, on average, at 82% of the RMT.42 If a positive response was not obtained with the maximum possible machine output that the patient could tolerate (i.e., 90%–100% of machine output) even under activation of the thumb muscle, the response was considered negative.

After AMT or RMT was determined, peritumoral cortical mapping was performed with 0.25-Hz stimulation of 110% RMT,51 or 100%–110% AMT. To incorporate the limits of the motor-positive responses, stimulation was performed at 30–60 sites, creating a whorl-shaped pattern. Any MEP amplitudes > 50 μV (peak to peak) were regarded as motor-positive responses and visualized in the final mapping cartography.25 The stimulus location that elicited the largest MEP was defined as a hotspot. Sites of motor-positive responses were colored by MEP amplitude, from blue (low amplitude) through yellow (medium amplitude) to red (high amplitude).

Magnetic Resonance Imaging

Using the navigation software, a brain surface image was reconstructed from a T1- or T2-weighted MR volume image. Presurgical MRI was performed no more than 3 months before surgery. For the nTMS mapping before surgery and 1 week after surgery, presurgical MRI results were used. For the nTMS mapping ≥ 3 weeks after surgery, postsurgical MRI was performed 2 weeks after surgery.

Surgical Procedures

Surgery was performed using ioMRI, according to the previously described concept of information-guided brain tumor removal, presuming maximum possible resection of the neoplasm with minimal risk of permanent postoperative neurological complications.40,41 Intraoperative MRI (Aperto, Hitachi Medical Group), updated neuronavigation, comprehensive neurophysiological monitoring, and detailed histopathological characterization of resected tissue obtained at various stages of the procedure were used routinely. In cases of high-grade gliomas, surgery was generally directed at the maximum possible removal of the contrast-enhanced area visualized on T1-weighted MRI; for low-grade gliomas, surgery was focused on maximum removal of the hyperintense area demonstrated on T2-weighted ioMRI. In cases of preoperatively presumed high-grade glioma (Cases 9 and 11), photodynamic diagnosis with 5-ALA was applied as well. In a recurrent case of malignancy (Case 4), photodynamic therapy with 5-ALA was also applied. Histopathological diagnosis of tumors was based on current WHO criteria. Two investigators, who had not performed presurgical nTMS, did the surgical planning and surgery.

Intraoperative Brain Mapping by DES

In 13 patients, tumor removal was done during awake craniotomy and was guided by DES mapping of cortical motor areas and subcortical structures. These procedures followed guidelines of the Japan Awake Surgery Conference.29 In an instance of a tumor located in the postcentral area, in which surgery was done with the patient placed prone under general anesthesia, the surgical field was centered on the medial postcentral area (Case 10). In this case, continuous MEP monitoring for UEs and lower extremities (LEs) was done, but precise motor mapping for the hand motor area using the Ojemann stimulator was not conducted during surgery.

For intraoperative brain mapping, DES was applied with repetitive square-wave biphasic current of alternating polarity (pulse width 0.5 msec, frequency 50 Hz, duration < 1 second), using a bipolar electrode probe with an interpolar distance of 5 mm and tip diameters of 1 mm. Continuous electrocorticography activity was monitored by neuromonitor (Neurofax-μ EEG-9100, Nihon Koden Co.) to detect seizures and afterdischarges. The stimulation intensity was increased steadily from 2 to 6 mA until the effect was obtained or abnormalities in electrocorticography were detected. The DES was performed using an Ojemann cortical stimulator (Integra Radionics, Inc.). The operating surgeon stimulated the nTMS hotspots, which were identified before and during the surgery. If contraction or movement of the targeted limb or muscle (e.g., hand, finger, or cheek) was observed at the nTMS hotspot, presurgical nTMS mapping results were regarded as concordant with DES.

Intraoperative MEP Monitoring

Direct MEP (d-MEP) monitoring, transcranial MEP monitoring, or both were performed during surgery.64 The strip electrode (6 serial electrodes, diameter 3 mm, distance between centers 10 mm; Unique Medical Co.) was used for the cortical stimulation in d-MEP, and coiled needle electrodes (diameter 6.5 mm, Unique Medical Co.) were used for Tc-MEP. Disposable subdural needle electrodes (NE-215B, Nihon Kohden Co.) were placed on the APB and TA muscles for measuring MEPs of UEs and LEs, respectively. Recordings of MEPs were done with a dedicated multimodal neuromonitor (Neu-
Postoperative Therapy and Rehabilitation

In cases of high-grade gliomas, adjuvant radiochemotherapy was administered as appropriate. Physical therapy, occupational therapy, and speech therapy were continued while the patient was in the hospital. All cases were regularly followed up in the outpatient clinic by 1 of 2 attending neurosurgeons.

Anatomical Analysis of nTMS Results

Using the measuring function of the TMS navigation software, the distances between the hotspots and the lesions (D_{hs-l}) were measured according to the presurgical nTMS results. The hotspot and the edge of the lesion nearest to the hotspot were plotted while referring to axial, sagittal, and coronal slices. The Euclidean distances were then calculated between these 2 plotted points. The relationship between recovery of grip strength and D_{hs-l} was analyzed.

Statistical Analysis

To evaluate interhemispheric difference and serial change of RMT, a paired t-test was applied. The correlation coefficients between presumptive prognostic predictors (e.g., D_{hs-l}, reduction of ioMEP, and nTMS-MEP at 1 week after surgery) and relative changes of grip strength were calculated. The approximation curve was depicted using the least-squares method. To compare numerical data between 2 groups, Welch's t-test was applied. To compare categorical variables, Fisher's exact test or a chi-square test was applied as appropriate. To compare numerical data among 3 groups, 1-way ANOVA was applied. Statistical significance was defined as p < 0.05.

Results

Presurgical and Postsurgical nTMS Results

Presurgical nTMS mapping was accomplished in 14 patients without any adverse events, including epilepsy or headache (Fig. 1). Prescribed antiepileptic drugs are listed in Table 2. Positive motor-response sites for contralateral APB muscle were identified in 13 patients, except for Case 6, in whom there was moderate UE paresis due to a huge brain tumor. In addition to identifying the motor area for APB muscle, motor areas for other muscles were identified (depending on clinical demand) from the tumor location. In 2 cases in which there were tumors centered on the facial motor area, peritumoral motor areas for the OO muscle were also investigated (e.g., Cases 11 and 13). In 2 cases, MEPs from the contralateral BB muscle were identified (Cases 8 and 13), and the contralateral TA muscle was identified in 4 cases (Cases 8, 9, 10, and 12). Postsurgical nTMS mapping was accomplished in 13 patients at 1 and 3 weeks after surgery. Positive nTMS-MEPs of the contralateral APB muscle were obtained in 9 of 13 patients at 1 week after surgery and in 10 of 13 patients at 3 weeks after surgery.

Presurgical and Postsurgical Physical Examination Findings

Preoperatively, 5 cases had some neurological deficits of contralateral extremities, which varied from numbness and subtle clumsiness of finger movement to moderate UE paresis. The existence of presurgical upper motor deficits was not associated with whether a patient was newly diagnosed or a recurrent case (p = 0.61, Fisher's exact test).

In all 14 patients, motor function had initially deteriorated, especially immediately after the surgery; however, most of the patients had recovered from these deficits at 3 months after surgery (Table 1). Relative changes of contralateral hand grip strength compared with presurgical grip strength were not statistically different at 1 week, 3 weeks, and 3 months after surgery, regardless of whether the case was newly diagnosed or recurrent (p = 0.57, 0.61, and 0.66, respectively; Welch's t-test).

Similarity Between Presurgical nTMS and ioDES Results

Intraoperative DES mapping for the motor area was performed in all 13 cases in which tumor removal was done during awake craniotomy. From the analysis of patients for whom both presurgical nTMS and ioDES were available (n = 13), MEP inducibility by presurgical nTMS (i.e., positive, positive only under activation, or negative) and response to ioDES (i.e., positive at cortical surface, positive only when stimulated at the cavity wall, or negative) were significantly associated (p < 0.05, chi-square test, Cramer's V = 0.68) (Table 3). In all 8 cases in which positive response from the contralateral hand was obtained by ioDES, positive responses were elicited at the presurgical nTMS hotspots for the contralateral APB muscle. In 2 cases in which the tumor was located in the lateral precentral gyrus, DES did not elicit positive responses for the contralateral hand within the operative field. Instead, DES elicited positive responses of the contralateral OO muscle at the presurgical nTMS hotspots for the OO muscle (Cases 11 and 13).
In 2 cases of anaplastic astrocytoma, in which the tumors were located near the hand knob, moderate UE paresis was observed before surgery (Cases 5 and 14). In these 2 patients, presurgical nTMS-MEPs for APB were positive only under activated conditions (i.e., MTs were exceeding-ly elevated), and coincidentally, motor responses for con-tralesional UE were not detected by ioDES on the cortical surface. In Case 14, DES (up to 6 mA) could not elicit a motor response from hand to finger at the nTMS hotspot at the cortex surface in the presumed hand knob. However, in the later phase of the tumor resection, direct subcortical stimulation of the cavity wall (3 mA) elicited a positive response from the contralateral thumb and wrist.

In Case 6, in which apparent presurgical deficits due to a giant tumor exists on the left frontal lobe and nTMS-MEP was not elicited.

Comparison of Motor Thresholds Between Hemispheres

In both the affected hemisphere (AH) and the unaffected hemisphere (UH), RMT (% machine output) or AMT (% machine output), latency (msec), and peak-to-peak amplitude (μV) of MEPs at hotspots for the contralateral APB muscle were measured (Table 4). In the presurgical nTMS study, the RMTs of AH were available from 11 of 14 patients. Among these 11 patients, the RMTs of AH (65.0 ± 15.7) and UH (61.4 ± 10.5) were not statistically different (p = 0.22, paired t-test). The RMTs of UH were constantly available from every examined patient, and there were no statistical differences among different timings of the examination (i.e., before surgery, 1 week after surgery, and 3 weeks after surgery) (p = 0.81, ANOVA).

On the other hand, the RMTs of AH were available from only 79% of patients at presurgical nTMS, 46% at 1 week after surgery, and 46% at 3 weeks after surgery. The availability of RMTs between AH and UH was not statistically different before surgery (p = 0.11, Fisher’s exact test), but significantly different at 1 week and 3 weeks after surgery (p < 0.01, Fisher’s exact test). Thus it can be said that after surgery, the cortical excitability of AH became compromised compared with UH.

Anatomical Evaluation and Predictive Value of Presurgical nTMS

From the 13 patients in whom hotspots were identified
Prognostic value of navigated TMS in recovery from motor deficits

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B). Next, the relationship between D HS-L and recoveries of at presurgical nTMS, D HS-L was measured (Fig. 2A and B). The relationship between D HS-L and better recovery was ascertained.

There were significant differences in the ratio of grip strengths between the 2 groups at 1 week and 3 months after surgery (p < 0.01, Welch’s t-test) and at 3 weeks after surgery (p < 0.05, Welch’s t-test). There were correlations between D HS-L and the ratio of grip strength at 1 week, 3 weeks, and 3 months after surgery (r = 0.74, 0.68, and 0.65, respectively). Thus, longer D HS-L in presurgical nTMS was a predictive value of better recovery from postsurgical deficits.

**Predictive Value of ioMEP Reduction**

From 11 patients in whom ioMEP for UH was available, 2 groups were defined according to whether ioMEP reduction was positive (n = 6) or negative (n = 5). The D HS-L values of the positive and negative groups were 10.1 ± 6.1 mm and 14.5 ± 10.6 mm, respectively, with no statistical difference between them (p = 0.35, Welch’s t-test). The positive and negative groups recovered the contralesional grip strengths at 3 months after surgery, up to 69% and 78%, respectively (Fig. 3B). There were no statistical differences between the 2 groups at 1 week, 3 weeks, and 3 months after surgery (p = 0.67, 0.50, and 0.66, respectively, Welch’s t-test). There were no correlations between ioMEP reduction and recovery of grip strength at 1 week, 3 weeks, and 3 months after surgery (r = -0.13, -0.22, and -0.14, respectively). In other words, although ioMEP monitoring is indispensable for the detection of neurological deficits during surgery, in the present study, ioMEP reduction was unsuitable for predicting recovery from postsurgical deficits.

**Predictive Value of Postsurgical nTMS-MEP**

From 12 patients for whom nTMS at 1 week after sur-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Preop</th>
<th>Postop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VPA 1600 mg</td>
<td>VPA 1600 mg</td>
</tr>
<tr>
<td>2</td>
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<td>VPA 800 mg</td>
</tr>
<tr>
<td>3</td>
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<td>PHT 300 mg, LEV 2000 mg, CLB 10 mg</td>
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<th>Case No.</th>
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<tr>
<td>14</td>
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**Table 2. Antiepileptic drugs in 14 patients**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Preop</th>
<th>Postop</th>
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<tr>
<td>1</td>
<td>VPA 1600 mg</td>
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<td>2</td>
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<td>4</td>
<td>ZNS 200 mg</td>
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<td>7</td>
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<td>LEV 2000 mg, PHT 3000 mg</td>
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<tr>
<td>14</td>
<td>None</td>
<td>VPA 800 mg</td>
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</table>

At presurgical nTMS, D HS-L was measured (Fig. 2A and B). Next, the relationship between D HS-L and recoveries of grip strengths was investigated. Regression curves at each point (i.e., 1 week, 3 weeks, and 3 months after surgery) were depicted on the scatterplot, and the coefficients of determination (R²) for these were 0.67, 0.71, and 0.73, respectively (Fig. 2C). Therefore, a credible correlation between D HS-L and better recovery was ascertained.

Subsequently, recoveries of adjacent and nonadjacent groups were compared. In the present study, cases in which distances were < 10 mm were defined as the adjacent group and cases in which distances were ≥ 10 mm were defined as the nonadjacent group. The D HS-L values of the adjacent group (n = 6) and the nonadjacent group (n = 7) were 4.6 ± 2.1 mm and 20.0 ± 5.9 mm, respectively, and there was a significant difference between them (p < 0.01, Welch’s t-test). At 3 months after surgery, the adjacent group and the nonadjacent group recovered up to 55% and 95%, respectively (Fig. 3A).

There were significant differences in the ratio of grip strength between the 2 groups at 1 week and 3 months after surgery (p < 0.01, Welch’s t-test) and at 3 weeks after surgery (p < 0.05, Welch’s t-test). There were correlations between D HS-L and the ratio of grip strength at 1 week, 3 weeks, and 3 months after surgery (r = 0.74, 0.68, and 0.65, respectively). Thus, longer D HS-L in presurgical nTMS was a predictive value of better recovery from postsurgical deficits.

**Predictive Value of Postsurgical nTMS-MEP**

From 12 patients for whom nTMS at 1 week after sur-

### Table 4. Change in nTMS parameters

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Timing of Examination</th>
<th>RMT, % Machine Output</th>
<th>AMT, % Machine Output</th>
<th>MEP, Negative Cases</th>
<th>Availability of RMT, %</th>
<th>Latency, msec</th>
<th>Amplitude, μV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected</td>
<td>Preop (n = 14)</td>
<td>65.0 ± 15.7 (n = 11)</td>
<td>87.5 ± 17.7 (n = 2)</td>
<td>Case 5 (n = 1)</td>
<td>79</td>
<td>21.8 ± 2.8</td>
<td>1089 ± 977</td>
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<tr>
<td></td>
<td>1 wk postop (n = 13)</td>
<td>76.7 ± 19.7 (n = 6)</td>
<td>92.5 ± 15 (n = 3)</td>
<td>Cases 1, 4, 5, 6 (n = 4)</td>
<td>46%</td>
<td>20.4 ± 2.7</td>
<td>774 ± 916</td>
</tr>
<tr>
<td></td>
<td>3 wks postop (n = 13)</td>
<td>72.1 ± 18.9 (n = 6)</td>
<td>95 ± 10 (n = 4)</td>
<td>Cases 1, 5, 6 (n = 3)</td>
<td>46%</td>
<td>21.3 ± 2.84</td>
<td>490 ± 743</td>
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<tr>
<td>Unaffected</td>
<td>Preop (n = 14)</td>
<td>61.4 ± 10.5 (n = 14)</td>
<td>64.6 ± 11.3 (n = 13)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 wk postop (n = 13)</td>
<td>61.9 ± 10.1 (n = 13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 wks postop (n = 13)</td>
<td>64.6 ± 11.3 (n = 13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.01, Fisher’s exact test, difference between hemispheres.
gery was available (excluding the case in which presurgical nTMS was negative [Case 6]), 2 groups were defined according to whether patients were nTMS-MEP positive (n = 9) or negative (n = 3). In both groups, contralesional grip strength was initially decreased immediately after surgery, and thereafter it recovered gradually throughout the postoperative course (Fig. 3C). It is noteworthy that the negative group consisted of the 3 cases closest to the lesion. The distances of the positive and negative groups were 16.6 ± 8.4 mm and 3.3 ± 1.4 mm, respectively, with a significant difference between them (p < 0.01, Welch’s t-test).

There was also a moderate correlation between positive nTMS-MEP and distance (r = 0.53). The positive and negative groups recovered grip strength at 3 months after surgery up to 89% and 43%, respectively, with a significant difference between them (p < 0.01, Welch’s t-test).

Illustrative Case

Case 9

History and Examination

A right-handed 24-year-old woman experienced frequent focal seizure of her left hand, which was heralded by vertigo for 2 months. She had no other neurological deficits before surgery; MMTs of UE and LE were all 5, FMA-UE was 66/66, and grip strength was 24.2/26.7. Her seizure was controlled by 1000 mg of levetiracetam. MRI demonstrated an enhancing brain tumor centered in the right precentral gyrus, which had a hypointense signal on T1-weighted images and a heterogeneous hyperintense signal on T2-weighted and FLAIR images (Fig. 4A). Methionine-PET showed high uptake in the MRI-enhanced lesion (tumor/normal tissue ratio 4.57). Presurgical nTMS showed a hotspot of contralesional APB muscle in the peritumoral edema, which was located on the medial side of the tumor, with a D_{HS-L} of 4.2 mm (Fig. 4B). The nTMS-MEP amplitude of the hotspot was 192 μV (Fig. 4E).

Operation

Removal of the brain tumor via right frontal craniotomy was performed. Tumor removal was guided by a navigation system based on ioMRI that was performed after incision.
of the dura mater. After the patient awoke from general anesthesia, motor eloquent area mapping was performed by DES using an Ojemann stimulator. Movements of the left hand and fingers were observed at the medial side of the tumor to be the same as presurgical nTMS results. Next, the medial border of the tumor was carefully removed while checking the patient’s motor function by DES. However, because a highly malignant tumor was suspected before surgery, resection of the tumor with sufficient margin had priority over preservation of the motor function.

After resection of the medial side of the tumor, movement of the patient’s left hand and wrist was deteriorated, and ioMEP from her left UE dropped to 0. After tumor removal in en bloc fashion, residual tumor spots on the cavity wall were checked with photodynamic diagnosis and then also removed. In the final stage of the operation, enhanced residual tumor was not detected by a second ioMRI, and then the operation was finished. Immediately after the surgery, paresis of the left UE was observed. The patient could lift her shoulder (MMT = 3), but distal extremity muscles including elbow, wrist, and fingers were flaccid (MMT = 0) (Fig. 4D).

Postoperative Course

Histopathological diagnosis of the tumor was anaplastic ependymoma (WHO Grade III), and therefore the patient underwent radiation therapy of 60 Gy for 30 days. The day after surgery, paresis of her left UE was slightly alleviated. At 1 week after surgery, proximal muscles (e.g., shoulder to elbow) showed gross movement; however, paresis of distal muscles (e.g., hand and fingers) was observed, and FMA-UE was 60/66. In particular, the weakness of the thumb was still evident at 3 weeks after surgery.

Postsurgical serial nTMS studies showed the expansion of the responsive area for contralateral APB (Fig. 4B). At 1 week after surgery, the responsive area was confined to a spot medial to the excised cavity. Then it expanded to a definite stretch at 6 weeks after surgery. Amplitudes of nTMS-MEPs were 63 μV at 1 week and 51 μV at 3 weeks after surgery. At 6 weeks after surgery, the nTMS-MEP amplitude recovered to 190 μV, which was almost the same as presurgical nTMS-MEP (Fig. 4E). The patient’s hand function was almost completely recovered at 3 months after surgery; MMTs of UE and LE were all 5/5 except thumb abduction, which was 4/5; FMA-UE was 66/66; and her left grip strength recovered to 22.0 (83% compared with before surgery). She returned to work as a server at a wedding hall. MR images at 6-month follow-up showed no signs of recurrence (Fig. 4C).

Discussion

Presurgical nTMS as a Decision Support Tool

In the present study, on the basis of anatomical evaluation of the presurgical nTMS results, the longer DHS-L correlated with better recovery. In other words, hotspots that are close to lesions (e.g., < 5 mm) should be regarded as a warning sign for the risk of residual postsurgical deficits. In such cases, to detect the neurological deterioration during surgery, precise mapping by DES and ioMEP under awake surgery is obviously advisable. When carefully deciding on a surgical plan, it must be considered whether patients accept the risk of deficits in exchange for a higher resection rate. For deliberate presurgical decision making that includes patients, the presurgical nTMS results would become desirable information.
Predictive Value of Postsurgical nTMS Compared With ioMEP Reduction

In the present study, the presence of nTMS-MEP at 1 week after surgery correlated well with better recovery. In previous reports about recovery after stroke, early post-stroke cortical excitability in response to TMS has been studied as a possible prognostic tool. From the systematic review by Hendricks et al., it is known that the presence of TMS-MEP at the acute stage after stroke has prognostic value with respect to motor recovery. Also, the presence of responses to TMS in the contralateral UE correlated well with the recovery of voluntary activity in distal muscles, but not as well with such activity in the proximal group.

On the other hand, in the present study, ioMEP reduction was not a direct prognostic predictor of recovery from deficits of hand function. In brief, ioMEP monitoring has reliable value for the ongoing status of neurological deficits during surgery; however, those deficits are potentially alleviated after the patients leave the operating room. Considering that, the presence of nTMS-MEP at 1 week after surgery had a good prognostic value of recovery from deficits; in other words, it is representative of the viability of the corticofugal pathway.

To the best of our knowledge, no previous report has shown the prognostic value of nTMS for recovery from neurological deficits after glioma removal. Although this study was conducted with a relatively small number of cases, we hope that accumulating the functional prognoses based on neurophysiological assessment will contribute to better surgical planning for patients with glioma.

Estimated Mechanisms of Recovery From Postsurgical Deficits

In the illustrative case, which showed marked recovery from severe deficits of hand function after surgery (Case 9), postsurgical serial nTMS studies showed expansion of the responsive area and re-enhancement of MEP along with motor function recovery. At 1 week after glioma removal, the responsive area was confined to a spot medial to the excised cavity, and the amplitude of MEP was small. Then, the responsive area expanded to a definite stretch, which correlated well with better recovery.
and the MEP amplitude was re-enhanced at 6 weeks after surgery concomitant with the recovery of thumb muscle abduction. These topographical and electrophysiological changes represent the postsurgical plasticity, which is consistent with the conception of use-dependent reorganization of cortical representation.44

From previous studies, it is known that substantial functional reorganization occurs in the primary motor cortex of adult primates following a focal ischemic infarct.44,57,58 Moreover, it is also known that the cortex has no fixed organization, but actually has a dynamic mosaic-like representation, with multiple and overlapping redundancies hierarchically organized.59 In addition, unmasking of perilesional latent networks,60 remodeling in cortical tissue,61 and recruitment of parallel networks within M162 are recognized as mechanisms of rapid compensation following damage of motor function.

Regarding remodeling after stroke, a recent in vivo 2-photon imaging study showed the extensive turnover of the dendritic spines and vascular remodeling in the peri-infarct cortex of mouse.63 In the mouse, peri-infarct dendrites were exceptionally plastic, manifested by a dramatic increase in the rate of spine formation that was maximal at 1–2 weeks (5 to 8-fold increases) and still evident 6 weeks after stroke.64 In this respect, it was estimated that rewired perilesional cortical networks contributed to recruitment of descending corticospinal volleys after surgical invasion, manifested by the re-enhancement of MEP at 6 weeks after surgery. Despite the promising finding presented here-in, additional investigations using pre- and postsurgical nTMS are needed to elucidate the mechanisms of functional reorganization after surgery for glioma removal.

**Similarity Between nTMS and DES**

According to the review by Takahashi et al.,65 in all 11 previous reports in which adult patients were examined with nTMS prior to surgery, results from presurgical nTMS correlated well with ioDES. In 81 patients described in 6 quantitatively evaluated studies, the mean distance between motor areas identified by nTMS and DES was 6.18 mm for the APB muscle. Also, using the realistic individual finite element method for simulations of the electric field distribution during presurgical nTMS and ioDES, stimulation areas in nTMS and DES showed overlap of up to 80%.45

In these previous reports, both presurgical nTMS and ioDES were mapped on the same presurgical MR image. On the other hand, other studies have shown that the surface of the brain is deformed by up to 20 mm after the skull is opened during neurosurgery, which could lead to substantial error in commercial image-guided surgery systems.66 In addition, the orientation of the coil affects both the strength and penetration depth of the electric field, and the field strongly depends on the direction of the sulcus, where the target neurons are located.67 Then the coil position that gives the strongest electric field in the target cortical region may deviate from the closest scalp location by a distance on the order of 1 cm.68

Considering the deformation of the brain surface after craniotomy and deviation of the electric field from the center of the coil, the exact distance might be difficult to compare between the 2 methods. To avoid the intraoperative misleading due to brain shift after craniotomy, our institution adopts updating ioMRI-guided neuronavigation, and the first ioMRI is taken after dural incision. Therefore, in the present study, coordinate comparison between presurgical nTMS and ioDES was not possible; in addition, the distance was not quantitatively studied on the same MR image. Despite these difficulties, results of the present study show that nTMS and DES were quite concordant. Furthermore, presurgical nTMS was useful for predicting the location of the motor area before surgery, especially when gyral structures were distorted due to large tumors (e.g., Cases 4, 5, 9, and 11).

**Difference Between nTMS and DES**

From the results of presurgical nTMS and DES, the appearances of positive responses were compared. In 2 cases of anaplastic astrocytoma in which tumors were located near the hand knob, MTs of presurgical nTMS for the APB muscle were extremely elevated and therefore MEP was elicited only under an activated condition (Cases 5 and 14). Concurrently, in these 2 cases, motor responses for contralateral UE were not found by ioDES on the cortical surface. As has been reported, an area invaded by a tumor has an increased impedance, which could justify an increase of stimulation intensity relative to neighboring healthy tissue, especially in cases in which gliomas infiltrate functional areas.64 Presumably, in these 2 cases, because the hand motor area was infiltrated by a tumor, DES might not evoke sufficient corticofugal descending impulse to activate muscles. In these situations, why could TMS excite MEP whereas ioDES could not? Two hypotheses that explain why TMS could elicit MEP are discussed below.

**Difference of Corticofugal Discharges Between nTMS and DES**

The generally accepted neurophysiological explanation for corticofugal discharges through the pyramidal tract is the D- and I-wave hypothesis. From classic research using an animal model, the response evoked by electrical stimulation of the motor cortex was recorded through an electrode inserted into the bulbary pyramid or cervical spinal cord of cats and primates.1,47 The response consisted of a stable early positive deflection (D wave) followed by a series of later positive deflections of variable latency and configuration (I waves, e.g., I1, I2, I3, I4).1,47 These deflections are called descending spinal volleys. It was suggested that the initial volley was produced by direct stimulation of the pyramidal tract axons (hence D = direct wave), whereas the later volleys were produced by trans-synaptic activation of the same pyramidal tract neurons (hence I = indirect wave). These D and I waves have been recorded not only in animal models, but also in human subjects, in a study using epidural motor cortex stimulation (EMCS) and epidural cervical electrodes implanted in patients with chronic neuropathic pain.39 In this previous study, anodal single square-wave monopolar EMCS generated D waves, suggesting direct activation of corticospinal fibers, whereas single square-wave bipolar EMCS generated more I waves, suggesting trans-synaptic activation of the corticospinal tract.39 Above all, TMS also
excites the pyramidal neurons directly or trans-synaptically, giving rise to D and I waves.\textsuperscript{10,11,69}

By using TMS and spinal epidural electrodes implanted in patients with intractable pain, Di Lazzaro et al. recorded the corticospinal volley of fully awake humans. They compared the difference of recruitment patterns of descending activity between different types of waveforms (i.e., monophasic and biphasic) and between different directions of stimulation (i.e., AP, PA, and lateral-medial in monophasic; AP-PA and PA-AP in biphasic). Among these, lateral-medial monophasic stimulation evoked a clear D wave, whereas AP-PA biphasic and PA monophasic stimulations tended to recruit more I waves than D waves, especially early \( I_1 \) wave at mild to intermediate stimulus.\textsuperscript{10} In particular, it is thought that the TMS pulse directly activates small interneurons in the primary motor cortex, which project to corticospinal tract neurons.\textsuperscript{35} Also, \( I_1 \) waves from Areas 2 and 6 are estimated to be possible sources of volley generation.\textsuperscript{35}

**The Difference of Spatial Expanse Between nTMS and DES**

In TMS, excitation is achieved by driving an intense pulse of current \( I(t) \) through a coil located above the head. The source of activation is the electric field \( E \) induced in the tissue, obtained from Faraday’s law:

\[
\nabla \times E = -\frac{\partial B}{\partial t},
\]

where the magnetic field \( B \) produced by the TMS coil is given by the Biot-Savart law:

\[
B(r, t) = \frac{\mu_0}{4\pi} \int_l (l(t) \times (r - r')) \, dl / |r - r'|^3
\]

The induced \( E \) is greatest near the coil and typically stimulates a cortical area of a few centimeters in diameter.\textsuperscript{60} According to Faraday’s law and the Biot-Savart law, the magnitude of the induced \( E \) is directly proportional to the current intensity \( I(t) \). The electric field beneath the coil was measured using a phantom head model filled with physiological saline. The electric field decreases linearly along with the distance from the coil. Compared with the electric field at a distance of 1.5 cm from the coil, the electric field decay of a Magstim figure-8 coil with an internal diameter of 70 mm was approximately 50% at 3 cm and 20% at 5 cm.\textsuperscript{59}

In brief, when TMS was performed with higher power output, brain tissue stimulated by the electrical field caused by TMS expanded both horizontally and tangentially. On the other hand, in DES, stimulation with a bipolar probe creates electric field lines between both poles in which the current density is homogeneous,\textsuperscript{64} and in this case bipolar stimulation produces focused electrical stimulation between electrodes. Therefore, it is estimated that the extent of stimulation by a bipolar probe is quite confined compared with TMS.

Thus we suggest that this difference of recruitment patterns due to expansion of induced electrical field results in the discrepancy of MEP inducibility between DES and TMS. Therefore, if the perilesional motor area is stimulated by nTMS with higher stimulation than the motor area in the UH, the pyramidal tract submerged beneath the brain tumor is possibly stimulated by summation of trans-synaptic impulses from the associated cortical area.

For example, in Cases 5 and 14, the presurgical AMT of AH was 25% and 66% higher than the RMT of UH, respectively. In these cases, it was estimated that nTMS-induced corticofugal discharges were more spatially summed. Simultaneously, in Cases 5 and 14, the motor responses of ioDES on the cortical surface were both negative. However, from the intraoperative findings, it was estimated that the pyramidal tracts for the contralateral hand ran adjacent to the tumor cavity. Thus we estimated that the positive response obtained by presurgical nTMS with a highly elevated MT indicated the existence of submerged or suppressed pyramidal tract adjacent to the tumor.

**Limitations of the Study**

There are limitations to the present study. First, this study was conducted with a relatively small number of cases. However, this was a prospective study of consecutive patients with glioma located within or adjacent to motor areas. Considering the novelty of this study and the rarity of cases, we believe that this article is quite valuable with this number of patients. Also, as shown in the scatterplots (Fig. 2C), there was impartiality of data and regression curves with decent coefficients of determination \( (R^2 > 0.5) \) were observed; thus we can say that these data are reliable enough to be valid. Nevertheless, to obtain better statistical evidence, the predictive value of nTMS should be validated with a larger number of cases.

Second, in our institution, neither magnetoencephalography, functional MRI, nor diffusion tensor imaging were used routinely for pre- and postsurgical motor mapping. For this reason, it was not possible to validate the difference of usefulness among these methods. Third, in this study, we have evaluated gross motor strength considering factors such as MMT and grip strength as measures of neurological recovery. For a more precise understanding of recovery from deficits, measures of dexterity such as pinch strength, performance in the Purdue pegboard,\textsuperscript{4} or the action reach arm test\textsuperscript{12,54} would be useful; thus we should conduct further studies using these measures.

**Conclusions**

The results of the present study demonstrate the predictive value of pre- and postsurgical nTMS in UE motor function recovery from postsurgical neurological deficits after glioma removal. The longer \( D_{\text{HS-1}} \), and positive nTMS-MEP at 1 week after surgery have prognostic values of better recovery from postsurgical neurological deficits.

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References


navigated transcranial magnetic stimulation compared to repeated intraoperative DCS mapping in awake craniotomy. 

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

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Supplemental Information

Previous Presentations

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