MRI can Predict the Response to Therapeutic Repetitive Transcranial Magnetic Stimulation (rTMS) in Stroke Patients

Abstract

**Background:** Previous studies suggest that purposeful modulation of excitability by up regulation in primary motor area (M1) in the lesioned hemisphere or down regulation of excitability in M1 intact hemisphere can influence function in the paretic hand.

**Objectives:** 1- To determine if magnetic resonance imaging (MRI) delineation of lesion has an impact on the modality and site of rTMS stimulation, and 2- To determine whether MRI can predict the degree of recovery of motor function after rTMS treatment.

**Methods:** A total of 60 ischemic stroke patients were recruited. Physical examination, mini mental state examination, activities of daily living assessment, motor subscale of the activity index (AI) and fine hand movement assessment were performed initially and then 2 weeks later (after the end of therapeutic course), then at 4, 8, and 12 weeks. MRI was performed for all patients and used to localize the site and extent of lesion. The patients were divided to 3 group consisting of 20 patients each: group 1 received repetitive rTMS 5hz at 90% motor threshold for 2.5min on the infarcted hemisphere, group 2 received rTMS 1hz at 110% motor threshold for 2.5min on the intact hemisphere, and group 3 received sham stimulation. All patients received standard physical therapy following each rTMS session.

**Results:** Patients with total anterior circulation stroke demonstrated on MRI showed no significant improvement when compared to those with partial anterior circulation, lacunar or posterior circulation strokes. The patients with cortical strokes experienced less improvement when compared with those with subcortical strokes especially with 1 hz stimulation to intact hemisphere.

**Conclusion:** MRI can help predict the response to rTMS for stroke rehabilitation and assist the clinician choose the mode and site of rTMS application.

**Keywords:** Acute ischemic stroke, transcranial magnetic stimulation, activities of daily living, motor cortex, excitability

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**Functional imaging has shown that presence of neural activation in the affected primary motor area (M1) of the affected hemisphere might be a marker of motor recovery.** Secondary motor areas of both hemispheres may assist in recovery based on findings from experiments using transcranial magnetic stimulation (TMS). Other studies have shown that following a motor stroke, transcallosal connections are disrupted resulting in an excess inhibitory drive from the unaffected M1 to the lesioned M1. This inhibition correlates negatively with the degree of recovery in chronic stroke patients. Accordingly, the development of therapeutic strategies of brain stimulation is based on the hypothesis that either increasing activity in the lesioned hemisphere or decreasing activity in intact hemisphere could be beneficial for stroke recovery. Purposeful modulation of excitability by up regulation in M1 lesioned hemisphere or down regulation of excitability in M1 intact hemisphere can influence function in the paretic hand.

Repetitive transcranial magnetic stimulation (rTMS) can modulate regional brain excitability in a painless, non invasive manner by cortical stimulation causing a direct effect of neuronal depolarization at the site of application. Studies have shown that 1 Hz stimuli depress cortical excitability, and stimuli of 5 Hz or more at suprathreshold intensities increase cortical excitability. The changes in cortical excitability persist beyond the stimulation period. A non-invasive technique may help guide the choice of the site and mode of therapeutic brain stimulation by identifying the extent of M1 involvement and the integrity of alternative pathways in the affected and intact hemisphere. MRI can provide supply high resolution information about lesion location and extent. We determined if MRI delineation of lesion has an impact on the choice of modality and site of rTMS stimulation lesion, and whether MRI appearance can predict the degree of recovery of motor function after rTMS treatment.

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Methods

A total of 60 ischemic stroke patients were recruited from Ain Shams University Hospital and Ain Shams University Specialized hospital. Recruitment and follow up of patients took place between February 2007 and January 2008. An informed consent was taken from all patients.

- **Inclusion criteria:** 1. Acute ischemic stroke. 2. Anterior or posterior circulation ischemic strokes. 3. Onset of symptoms at least 2 months before recruitment. 4. Age>18 years. 5. Mini mental state examination (MMSE) score of 24 or greater, with no receptive aphasia, visuospatial neglect, nor anosognosia; and 6. Presence of residual motor disability in the hand that is graded as mild to moderate on the activity index (AI) scale.

- **Exclusion criteria:** 1. Hemorrhagic stroke; 2. Venous infarction; 3. History of seizures; and 4. Presence of metallic devices or pacemakers.

A detailed history and physical examination including full neurological examination and MMSE was performed. Additional assessments included a) Activities of daily living assessment by AI, and b) Motor system assessment by: Motor subscale of the AI.

**Imaging studies**

MRI of the brain was performed in all patients using a 1.5- Tesla scanner (General Electric GE, Milwaukee, Wisconsin) with a gradient strength and echo-planar capabilities. The images were reviewed for:

- Site of stroke: either total anterior circulation stroke (TACS), partial anterior circulation stroke (PACS), posterior circulation stroke (POCS), and lacunar stroke (LACS).
- Presence or absence of cortical involvement.
- Presence and extent of leukoaraiosis: 4 grades (no lesion, focal lesions, beginning of confluence, and diffuse lesions).

**Physical therapy**

Standard physical therapy was undertaken for all patients according to the discretion of the treating physician and physical therapist. In addition, a individually tailored rehabilitation protocol was devised in concordance with the methods used in the EXCITE trial.
TMS sessions
A DANTEC Magnetic Stimulator MagLite Denmark MC-B70 machine was used. The patients were randomly assigned by sealed envelops, into one of three groups to receive ten repetitive transcranial magnetic stimulation sessions over a 2 week period.

Group 1
- 20 patients received 5 Hz stimulation rTMS at 80-90% of the motor threshold for 2.5 minutes continuously, resulting in a total dose of 750 pulses/session and 7500 pulses/therapeutic course.
- Stimulation was done at the area of abductor pollicis brevis (APB) in the primary motor area of the lesioned hemisphere contralateral to the paretic hand.

Group 2
- 20 patients received 1 Hz stimulation rTMS at 110-120% of the motor threshold for 2.5 minutes continuously resulting in a total dose of 150 pulses/session and 1500 pulses/therapeutic course.
- Stimulation was done at the area of APB in the primary motor area of the unaffected hemisphere ipsilateral to the paretic hand.

Group 3
- 20 patients received sham stimulation rTMS for 2.5 minutes continuously.
- Stimulation done at the area of APB in the primary motor area of the unaffected hemisphere ipsilateral to the paretic hand but the coil was angled away from the head to reproduce the same noise of the stimulation and some local sensation.

Follow up
Clinical follow-up was performed at 2 weeks later (after the end of therapeutic course), then at 4, 8, and 12 weeks following treatment.

Statistical Analysis
SPSS (Statistical Package for the Social Sciences) version 13 was used to perform Pearson chi-square test, ANOVA, and oneway ANOVA tests to compared findings within and between groups. Pearson correlation coefficient test was computed.

Results
The demographics and clinical characteristics of the study population were compared. No significant differences were identified between the three patient groups in regards to age, gender, cardiovascular risk factors, duration of stroke, and side of lesion. The analysis of the MRI brain findings showed that there was no significant difference between the three patient groups regarding the stroke type, extent of leukoaraiosis, and the prevalence of cortical involvement (Table 1).

<table>
<thead>
<tr>
<th>MRI analysis</th>
<th>Group 1 (%)</th>
<th>Group 2 (%)</th>
<th>Group 3 (%)</th>
<th>Total (%)</th>
<th>Difference between groups (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PACS</td>
<td>17 (85%)</td>
<td>9 (45%)</td>
<td>8 (40%)</td>
<td>34 (56.7%)</td>
<td>NS (0.117)</td>
</tr>
<tr>
<td>TACS</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
<td>3 (5%)</td>
<td>NS (0.564)</td>
</tr>
<tr>
<td>LACS</td>
<td>1 (5%)</td>
<td>8 (40%)</td>
<td>8 (40%)</td>
<td>14 (23.3%)</td>
<td>NS (0.071)</td>
</tr>
<tr>
<td>POCs</td>
<td>2 (10%)</td>
<td>4 (20%)</td>
<td>3 (15%)</td>
<td>9 (15%)</td>
<td>NS (0.717)</td>
</tr>
<tr>
<td>Cortical involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (50%)</td>
<td>6 (30%)</td>
<td>6 (30%)</td>
<td>22 (36.7%)</td>
<td>NS (0.317)</td>
</tr>
<tr>
<td>No</td>
<td>10 (50%)</td>
<td>14 (70%)</td>
<td>14 (70%)</td>
<td>38 (63.3%)</td>
<td></td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td></td>
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<td></td>
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<tr>
<td>No lesion</td>
<td>6 (30%)</td>
<td>5 (25%)</td>
<td>8 (40%)</td>
<td>19 (31.7%)</td>
<td>NS (0.692)</td>
</tr>
<tr>
<td>Focal lesion</td>
<td>7 (35%)</td>
<td>12 (60%)</td>
<td>7 (39%)</td>
<td>26 (43.3%)</td>
<td>NS (0.382)</td>
</tr>
<tr>
<td>Beginning confluence</td>
<td>6 (30%)</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
<td>11 (18.3%)</td>
<td>NS (0.307)</td>
</tr>
<tr>
<td>Diffuse lesion</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>2 (10%)</td>
<td>4 (6.7%)</td>
<td>NS (0.779)</td>
</tr>
</tbody>
</table>

Abbreviations used: LACS: Lacunar stroke; NS: Not significant; PACS: Partial anterior circulation stroke; POCs: Posterior circulation stroke; TACS: Total anterior circulation stroke, § = Chi-square test.
Localization of ischemic stroke and response to rTMS

- Ischemic stroke subtype (figures 2, 3)
Patients with TACS had significantly lower initial and 12 week AI scores relative to other stroke subtypes (table 2). There was however, no significant difference in the AI scores between other stroke subtypes (fig. 4).

- Cortical involvement and response to rTMS
Subjects with cortical involvement (fig.3) (22 patients) had lower AI scores initially and at 12 weeks follow up compared with those without cortical involvement (fig.6). The difference was statistically significant at both time points of ascertainment (p=0.006 and p=0.022 respectively). On individual group analysis, group 1 cases with and without cortical involvement had significant improvement between the initial and the 2 week follow up AI score (p=0.001 and p=0.012 respectively). Group 2 patients without cortical involvement had significant improvement in their AI scores across the same 2 time intervals (p<0.0001) and between the 2 and 4 week assessment points (p=0.005), while group 2 patients with cortical involvement had no significant improvement between the 2 time intervals (p=0.113, and p=0.363, respectively).

- Leukoaraiosis and response to rTMS
Although the mean AI scores (initial and at 12 week follow up after rTMS) for patients with diffuse leukoaraiosis were less than those with less severe leukoaraiosis (figure 7), the difference was not statistically significant (initial AI: p=0.406; 12 week follow AI: p=0.441) (fig.8)

Discussion:
In the current study, MRI findings correlated with recovery following rTMS. Patients with TACS and/or severe leukoaraiosis had worst initial AI scores and did not demonstrate any improvement on follow up evaluation after rTMS. This finding...
ing is consistent with the findings reported by Khedr et al.2005,15 who found that patients with massive infarcts do not improve following rTMS. Patients with other types of stroke subtypes (PACS, LACS, and POCS) showed improvement without any clear difference in response. Our findings suggest that rTMS can improve functional impairment in selected patients with anterior and posterior circulation strokes. Our results also demonstrate that determining the size of lesion and presence or absence of cortical involvement by MRI can be more predictive of the response to rTMS than only the anatomical site of the lesion.

Since the benefit of rTMS is mediated by modulating cortical excitability, it was crucial to examine the differential effects of rTMS in patients with and without severe cortical involvement. A recent fMRI study showed that application of 1 Hz rTMS to the unaffected M1 in stroke patients resulted in a decrease in the activity of the unaffected hemisphere and was associated with an improvement in the motor function of the paretic hand16 However this study did not differentiate between cortical or subcortical involvement. Our results showed that cases with cortical involvement who received contralesional inhibitory rTMS did not show evidence of significant improvement contrary to cases without cortical involvement. However, patients with and without cortical involvement who received ipsilesional stimulatory rTMS showed a significant improvement following rTMS. Possibly restoring interhemispheric balance with contralesional low frequency rTMS requires an intact ipsilesional cerebral cortex. The suggested explanation from fMRI studies may be that overall brain activation in patients with cortical involvement in response to paretic hand movement is lower17

Another important factor in determining the ability of the brain to recover its impaired functions is the integrity of the brain parenchyma not affected by stroke4 In our study, the extent of leukoaraiosis was assessed by MRI. The results suggested that as the severity of leukoaraiosis increased, there was a tendency for the severity of functional impairment to increase. Therefore, patients with marked loss of integrity of the brain parenchyma tend to have less motor recovery. Similarly, O’Sullivan et al.18, 2004 showed that MRI findings correlated with executive functions in patients with leukoaraiosis.

We can conclude from our study that MRI can help in predicting the response to rTMS and help in selecting the
site and mode of brain rTMS. If the initial MRI of the brain demonstrates extensive infarctions, or severe leukoaraiosis, the patient is less likely to respond to rTMS. If the patient has cortical involvement on MRI, then inhibitory rTMS to MI of the intact hemisphere will not be effective, but such therapy can be effective in patients with subcortical lesions. The best response to rTMS is obtained in patients with either PACS, POCS and lacunar infarctions especially in patients presenting with residual motor function.

References