学 位 論 文 の 要 旨

氏名　松浦　晃宏

学位論文名	Magnetic Stimulation and Movement-related Cortical Activity for Acute Stroke With Hemiparesis
発表雑誌名 （巻，初頁～終頁，年）	European Journal of Neurology (in press)
著者名	Akihiro Matsuura, Keiichi Onoda, Hiroaki Oguro, Shuhei Yamaguchi

論 文 内 容 の 要 旨

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive tool, which can facilitate functional motor recovery. Low-frequency rTMS in the contralesional hemisphere can improve motor performance in patients with stroke. However, the neurophysiological mechanisms for the functional improvement after rTMS is largely unknown in clinical population, although one study reported increased peripheral motor evoked potential of paretic hand after rTMS, which provided an indirect evidence of changes in cortical excitability.

Movement-related cortical potential (MRCP) is a gradually-developed negative electrical potential recorded on the scalp. Since MRCP carries excellent temporal information of neural activity related to movement execution, it would provide direct evidence of temporally defined neural activity over the movement-related cortical areas associated with motor recovery modified by rTMS in stroke patients. The aim of this study was to investigate whether low frequency rTMS to the contralesional hemisphere of patients with acute stroke-induced subcortical lesion could facilitate functional motor recovery, and to clarify the changes in neuronal activity of movement-related cortices associated with motor recovery after rTMS.

MATERIALS AND METHODS

Study design and patient population

We studied 20 patients aged 43 to 89 years (mean 73.5) with first-ever acute ischemic stroke. The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects. The timing of the study entry was 9.6 days (4 ~ 21 days) after stroke onset. Following the entry, patients were randomly assigned to two groups; real rTMS group (n=10) and sham rTMS group (n=10). Both real and sham rTMS were performed for 5 consecutive days. The pre- and post-rTMS assessments for motor functions and MRCP measurement were performed 24 hours before and after the whole rTMS session.

rTMS procedures

The coil was placed tangentially over the motor cortex of the unaffected hemisphere at the optimal location to elicit maximal contraction of the contralateral extensor carpi radialis (ECR) muscle. We performed the stimulation at a rate of 1 Hz for 20 min (1,200 pulses) per day. Sham rTMS was performed by placing the coil perpendicularly to the scalp.

MRCP recording and measurement

Patients were instructed to perform self-paced extension of the affected wrist at irregular intervals between 7 and 10s. Electroencephalogram (EEG) data were measured at FC3, FCz, FC4, C3, Cz, and C4 (international 10–20 system). The surface electromyogram (EMG) was recorded from a pair of electrodes placed over the ECR muscle for determining the onset of movement. A total of 80–100 EEG artifact-free epochs were collected and averaged offline for MRCP analysis. MRCP was divided into three components of Bereitschaft potential (BP, 2.0 - 0.5s before the movement onset), negative slope (NS', 0.5 - 0.05s before the movement onset), and motor potential (MP, negative peak around the movement onset).

Motor function tests

Motor impairment of the upper extremity was evaluated using the FMA, Purdue pegboard test (PPT), and grip strength before and after rTMS sessions in a blinded fashion.

Statistical analysis

The MRCP data were subjected to repeated measures analysis of variance (ANOVA) using time (pre-rTMS and post-rTMS) and anterior-posterior electrode site (FC and C) and lateral electrode site (ipsilesional and contralesional) as within-subject factors and group (rTMS group and sham group) as a between-subjects factor. The lateral electrodes were organized as a function of electrode site over the ipsilesional (i.e., FCi, Ci) or contralesional (i.e., FCc, Cc) hemisphere. A level of $P < 0.05$ was accepted as statistically significant. Pearson correlation coefficient was used to assess associations between the MRCP and motor function data.

RESULTS AND DISCUSSION

Behavioral data

The real rTMS group showed larger improvement of both FMA and PPT scores compared to the sham group (FMA: $F(1,18) = 17.6$, $p = 0.001$; PPT: $F(1,18) = 7.77$, $p = 0.012$). The interaction of group and time for grip strength was not significant. In summary, FMA and PPT scores of the affected limb were improved by rTMS.

Electrophysiological data

For MP, there was a significant interaction of group, time and lateral electrode site (F

(1,18) = 4.43, p = 0.049), which showed a larger negative increase of MP in the real rTMS group compared to the sham group over the ipsilesional hemisphere. We then analyzed the interaction of group and time for each electrode site. There were significant interactions for MP at FCi (F (1,18) = 10.61, p = 0.004), whereas no interactions were observed in other electrode sites. Thus, increased negativity of MP by rTMS was observed only over the ipsilesional cortex.

NS' amplitude showed similar changes as MP amplitude. The ANOVA showed a significant interaction of group, time and lateral electrode (F (1,18) = 4.54, p = 0.047), indicating increased mean amplitude of ipsilesional NS' by rTMS. For each electrode site, there were significant interactions for NS' at FCi (F (1,18) = 10.38, p = 0.005), whereas no interactions were observed in other electrode sites. Thus, increased NS' by rTMS was also evident over the ipsilesional cortex. On the other hand, the interaction of group and time for BP was not significant, indicating that BP amplitude was not modified by rTMS intervention.

Since MP component is generated in the motor cortex, it was assumed that activity of the motor cortex was primarily enhanced by contralesional inhibitory rTMS. In addition to MP, the mean amplitude of NS' was also increased over the same region. The generator source of NS' is located in the premotor and motor areas. Thus, the activation of the premotor region by contralesional rTMS also seems to contribute to enhancing motor function recovery. This electrophysiological study provided the evidence that the rTMS effect on cortical activity was clearly lateralized to ipsilesional hemisphere and the function recovery was attributed not only to activity change of the motor cortex but also to that in premotor stage of movement execution as indexed by increased NS' amplitude.

Relationship between motor recovery and electrophysiological data

We found that the increase of MP amplitude at FCi was correlated with the increase of FMA score (r = -0.595, p = 0.006). The increase of NS' amplitude at FCi was also correlated with the increase of FMA score (r = -0.616, p = 0.004). There were no significant correlations of the changes of MP and NS' at other electrode sites with FMA score change.

This study demonstrated that low-frequency rTMS to the contralesional motor cortex improved motor function of the affected upper limb, as assessed with FMA and PPT scores associated with increased MRCP amplitude. Although the validity of the interhemispheric competition model is still in dispute, it is plausible that low-frequency rTMS can weaken the influence of abnormal transcallosal inhibition from the contralesional motor cortex, and restore the balance between two hemispheres.

CONCLUSION

Our study demonstrated that low-frequency rTMS to the contralesional motor cortex facilitates early recovery of paretic limbs in patients with acute stroke through enhancing neuronal reorganization of motor and premotor areas of the ipsilesional hemisphere.