学 位 論 文 の 要 旨

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学 位 論 文 名　Magnetic Stimulation and Movement-related Cortical Activity for Acute Stroke With Hemiparesis

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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.

論文審査及び最終試験又は学力の確認の結果の要旨

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論文審査の結果の要旨

脳卒中による運動機能障害に対し、機能回復のための様々な治療法が試みられているが、未だ確立されたものはない。反復経頭蓋磁気刺激（rTMS）は、体表から脳皮質を刺激し、皮質脊髄路や皮質間経路を介してニューロンの興奮性を増大あるいは抑制する方法で、脳卒中の他にもさまざまな脳疾患の治療法として期待されている。しかし、神経疾患の機能回復に至る詳細なメカニズムや脳卒中後機能回復のための至適なニューロン刺激方法は確立されていない。

申請者は急性期皮質下脳梗塞による不全片麻痺患者への rTMS の効果を運動機能検査と電気生理学的検査により評価した。20 名の急性期皮質下脳梗塞患者を rTMS 治療群 10 名と非治療群 10 名にランダムに振り分け、治療群には、非損傷側運動皮質に対して 1Hz 20 分間の rTMS を 5 日間実施した。治療効果は、運動機能については上肢の運動機能を示す Fugl-Meyer Assessment (FMA) 、手指の巧緻運動機能を示す Purdue pegboard test (PPT)および握力により評価した。また、電気生理学的側面からは、麻痺手の伸展運動に伴う脳電位（Movement-Related Cortical Potential: MRCP）を記録し、得られた MRCP 波形を 3 つの構成要素（BP, NS', MP）に分けて評価した。その結果、治療群では麻痺側の FMA と PPT に有意な改善が認められた。MRCP では、治療群において損傷側半球の運動野近傍の NS'と MP に電位増加が認められた。以上の結果から、低頻度 rTMS を非損傷側運動皮質に対して実施することにより、急性期脳卒中患者の運動機能が改善したと考えられた。そのメカニズムのひとつとして、非損傷側運動皮質への rTMS により損傷側半球への抑制性の入力が抑制され、損傷側半球の運動野と運動前野ニューロンの興奮性が高まることが神経機能回復につながることが示唆された。本研究は脳卒中後運動機能回復の新しい治療方法の開発につながる臨床的高い価値を有する研究であると判断し、博士(医学)の学位授与に値すると判断した。

最終試験又は学力の確認の結果の要旨

申請者は、脳卒中急性期患者に対し非損傷半球から低頻度 rTMS を行い運動機能回復に効果があることを示した。また電気生理学的に神経機能回復のメカニズムの一因を明らかにした。本研究は脳卒中後機能回復の新しい治療法として重要な研究である。関連領域の知識も十分であり学位授与に値すると判断した。（主査：秋山　恭彦）

申請者は、低頻度 rTMS を非損傷半球の損傷部位に対応する運動皮質に行うことにより運動機能の回復が早まることを運動機能および電気生理学的評価により示し、そのメカニズムを示唆する仮説を提唱することで至適なニューロン刺激方法や新しい治療法につながる研究成果を示した。実験に用いた方法への知識や関連領域の知識も十分であることが確認でき、学位授与に値すると判断した。（副査：廣田　秋彦）

申請者は、反復経頭蓋磁気刺激を急性期脳梗塞患者の非損傷側に行い、前向き研究で症状改善評価と脳電位検査による改善機序の考察を行った。新規治療法の可能性を提示した研究は価値があり、申請者は関連領域の知識も十分であり、学位授与に値すると判断した。（副査：長井　篤）

（備考）　要旨は、それぞれ４００字以内とする。