JMD
https://doi.org/10.14802/jmd.19083 / J Mov Disord 2020;13(2):115-117
pISSN 2005-940X / eISSN 2093-4939

VIEWPOINT

Future of Tanscranial Magnetic Stimulation in Movement Disorders: Introduction of Novel Methods

Yoshikazu Ugawa,[1] Yasushi Shimo,[2] Yasuo Terao[3]

[1]Department of Neuro-Regeneration, Fukushima Medical University, Fukushima, Japan
[2]Department of Neurology, Juntendo University Nerima Hospital, Tokyo, Japan
[3]Department of Medical Physiology, Faculty of Medicine, Kyorin University, Mitaka, Japan

Transcranial magnetic stimulation (TMS) has been used as an important tool for basic research and clinical application for more than 30 years. Several review papers have been published concerning the validity of TMS in movement disorders.[1-6] Central motor conduction studies using single-pulse TMS have been proven to be useful for the differential diagnosis of movement disorders. On the other hand, several paired-pulse TMS techniques, such as short-interval intracortical inhibition, long-interval intracortical inhibition, intracortical facilitation (ICF), short-interval intracortical facilitation (SICF), and short-interval afferent inhibition, have also been shown to have possible clinical utility, but they have not been fully confirmed.[1] As a treatment tool, repetitive TMS (rTMS) is ranked as a possibly useful method, but further studies are needed to establish its genuine clinical utility.[2] rTMS over the cerebellum is a treatment option for movement disorders, but this should also be verified by large-scale randomized control trials.[3,4] A similar conclusion has been reached about the effects of cerebellar stimulation on essential tremor.[5,6]

Because there are several good review papers on the clinical utility of TMS as shown above, in this manuscript, we will present some examples of future TMS utilities: 1) confirmation of animal findings in humans; 2) utility of cerebellar stimulation; and 3) rTMS enhancement of rehabilitation effects.

CONFIRMATION OF ANIMAL FINDINGS IN HUMANS

Physiological findings previously shown in monkeys or other animals do not always hold true in the same way for humans. Physiological confirmation in humans has been frequently performed by functional neuroimaging studies. TMS has also been used for this purpose by producing virtual lesions with single-pulse TMS.[7] Another physiological method used for this purpose is the long-term effects induced by rTMS. This procedure is easier to perform than the virtual lesion method because, whereas the virtual lesion effect induced by single-pulse TMS is only transient, the effects of rTMS last for a certain period of time after stimulation. Hereafter, we provide one example of the use of rTMS to confirm physiological findings in humans.

Learning task

The task used in our study was originally devised to investigate the learning of sequential movements in monkeys,[8] and their findings have been replicated in human neuroimaging studies.[9,10] The most important finding from these studies was that the presupplementary motor area (preSMA) played a critical role in new sequence learning in the early stages of learning, whereas SMA played some role in speeding up performance of already learned sequential movements in the later stages. To physiologically con-

Received: November 1, 2019 **Revised:** December 2, 2019 **Accepted:** December 31, 2019
Corresponding author: Yoshikazu Ugawa, MD, PhD
Department of Neuro-Regeneration, Faculty of Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan / **Tel:** +81-24-547-1248 / **Fax:** +81-24-548-3797 / **E-mail:** ugawa-tky@umin.net

firm this finding in humans, we studied the effects of quadripulse stimulation (QPS) over the preSMA or SMA on performance in the sequential learning task in normal subjects.[11] The performance of a normal volunteer is presented in the video attached to this paper (Supplementary Video 1 in the online-only Data Supplement). The speed of learning a new sequence was bidirectionally affected by QPS5 or QPS50 over the preSMA but not by QPS over the SMA. In contrast, the performance speed of already learned movements was bidirectionally affected by QPS over the SMA but not by QPS over the preSMA. Neither the overlearned sequential learning task nor the simple reaction time task was affected by QPS over the preSMA or SMA. These findings support the functional differences between the SMA and preSMA, as previously demonstrated in monkeys.

UTILITY OF CEREBELLAR STIMULATION

Most cerebellar stimulation studies with TMS have used motor evoked potentials (MEPs) as a marker of changes in primary motor cortical excitability. The effect of cerebellar modulation on the primary motor cortex was investigated with a paired coil stimulation method. Namely, the conditioning stimulus was given by one coil placed over the cerebellum, after which a test stimulus was given by another coil placed over the primary motor cortex (M1). Comparing the MEP size obtained when both the conditioning and test stimuli were given with that when the test stimulus alone was given, we can estimate the effects of conditioning cerebellar stimulation on M1. The original paper used high-voltage electrical stimulation as cerebellar stimulation.[12] Research in ataxic patients using this electrical stimulation method has suggested that the cerebellar stimulation should activate Purkinje cells and suppress M1 through dentate-thalamus-cortical pathways.[13-16] This suppressive effect has been named cerebellar inhibition (CBI). Magnetic stimulation over the cerebellum also evoked a similar suppressive effect on M1.[17] After the invention of magnetic cerebellar stimulation that can be applied to patients without pain, CBI has been used for the pathophysiological analyses of ataxia.[18-21] This method revealed cerebellar involvement in disorders originally reported to have no cerebellar involvement, such as progressive supranuclear palsy (PSP).[22] Hereafter, we present one example of cerebellar involvement revealed by CBI.

Cerebellar studies in essential tremor

Several animal studies have suggested that the inferior olive is one of the tremor-generating sites. A few pathological investigations have reported cerebellar involvement in essential tremor (ET).[23-25] To confirm this finding in humans, we studied cerebellar function in patients with ET.[26] We revealed a reduction in CBI in ET, which suggested cerebellar efferent pathway dysfunction. We also found disruptions in the prism adaptation task, which has been shown to reflect the learning ability of the cerebellum. One of the future utilities of TMS must be to reveal unexpected functional abnormalities that cannot be detected by clinical neurological examination.

Cerebellar stimulation may be used as a diagnostic tool and as a treatment tool for some disorders. CBI is an example of a diagnostic tool, and its clinical utility can be established as shown above. As mentioned in the first part of this paper, its clinical utility as a treatment tool should be established by future large-scale randomized placebo-controlled studies.

rTMS ENHANCEMENT OF REHABILITATION EFFECTS

Many papers have reported the enhancement of rehabilitation effects when combined with rTMS procedures. One review paper on the rehabilitation of stroke patients concluded that rTMS should be a promising tool for stroke rehabilitation, but its effectiveness has not been proven with robust data.[27] Here, we describe one example: a clinical treatment trial of patients with paraparesis due to a spinal cord injury by inducing gait-like movements with self-controlled rTMS over the lumbar spinal cord.

Gait induction by rTMS over the lumbar spinal cord

We reported that rTMS over the lumbar spine can induce alternating leg movements similar to gait in normal subjects.[28] In this stimulation procedure, the pulses generated from the electromyogram of the patient's own upper limb muscles trigger the magnetic stimulator. The natural and physiological trigger pulses probably provide a kind of natural stimulation to the lumbar cord gait (locomotion) center, which produces gait-like alternating movements of both legs.

Based on the above reported results, we have recently applied this procedure to several patients with paraplegia or paraparesis in combination with usual rehabilitation. Because these are preliminary results, we will not show the actual data from this trial. Chronic paraplegic patients, one year or longer after the onset of acute spinal cord injury, were selected for this treatment trial because no additional functional recovery could be expected at this late stage of the injury by conventional rehabilitation. The patients showed some recovery of gait movement after the intervention. Some patients regained gait-like alternating movements in both legs, even without stimulation. Our impression is that the procedure enhanced the functional recovery compared with the usual rehabilitation alone. We are in the process of a clinical trial examining gait induction by rTMS in patients with spinal cord injury. We hope that our trial will reveal that rTMS over the lumbar spinal cord has genuine clinical usefulness by enhancing rehabilitation effects.

We have shown three examples of future directions for TMS in movement disorders. We may develop more applications in the future.

Supplementary Video Legend

Video 1. This is an example of the task performance of one normal subject. The hyperset included 5 sets in this experiment.

Supplementary Material

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.19083.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgments

None.

Author Contributions

Conceptualization: Yoshikazu Ugawa. Data curation: Yoshikazu Ugawa. Formal analysis: Yoshikazu Ugawa. Funding acquisition: Yoshikazu Ugawa. Investigation: Yasushi Shimo, Yasuo Terao, and Yoshikazu Ugawa. Writing—original draft: Yoshikazu Ugawa. Writing—review & editing: Yasuo Terao and Yasushi Shimo.

ORCID iD

Yoshikazu Ugawa https://orcid.org/0000-0002-8016-152X

REFERENCES

1. Latorre A, Rocchi L, Berardelli A, Bhatia KP, Rothwell JC. The interindividual variability of transcranial magnetic stimulation effects: implications for diagnostic use in movement disorders. Mov Disord 2019;34:936-949.
2. Latorre A, Rocchi L, Berardelli A, Bhatia KP, Rothwell JC. The use of transcranial magnetic stimulation as a treatment for movement disorders: a critical review. Mov Disord 2019;34:769-782.
3. França C, de Andrade DC, Teixeira MJ, Galhardoni R, Silva V, Barbosa ER, et al. Effects of cerebellar neuromodulation in movement disorders: a systematic review. Brain Stimul 2018;11:249-260.
4. Miterko LN, Baker KB, Beckinghausen J, Bradnam LV, Cheng MY, Cooperrider J, et al. Consensus paper: experimental neurostimulation of the cerebellum. Cerebellum 2019;18:1064-1097.
5. Shih LC, Pascual-Leone A. Non-invasive brain stimulation for essential tremor. Tremor Other Hyperkinet Mov (N Y) 2017;7:458.
6. Kang N, Cauraugh JH. Does non-invasive brain stimulation reduce essential tremor? A systematic review and meta-analysis. PLoS One 2017;12:e0185462.
7. Terao Y, Fukuda H, Ugawa Y, Hikosaka O, Hananjima R, Furubayashi T, et al. Visualization of the information flow through human oculomotor cortical regions by transcranial magnetic stimulation. J Neurophysiol 1998;80:936-946.
8. Hikosaka O, Rand MK, Miyachi S, Miyashita K. Learning of sequential movements in the monkey: process of learning and retention of memory. J Neurophysiol 1995;74:1652-1661.
9. Hikosaka O, Sakai K, Miyauchi S, Takino R, Sasaki Y, Pütz B. Activation of human presupplementary motor area in learning of sequential procedures: a functional MRI study. J Neurophysiol 1996;76:617-621.
10. Sakai K, Hikosaka O, Miyauchi S, Takino R, Sasaki Y, Pütz B. Transition of brain activation from frontal to parietal areas in visuomotor sequence learning. J Neurosci 1998;18:1827-1840.
11. Shimizu T, Hanajima R, Shirota Y, Tsutsumi R, Tanaka N, Terao Y, et al. Plasticity induction in the pre-supplementary motor area (pre-SMA) and SMA-proper differentially affects visuomotor sequence learning. Brain Stimul 2020;13:229-238.
12. Ugawa Y, Day BL, Rothwell JC, Thompson PD, Merton PA, Marsden CD. Modulation of motor cortical excitability by electrical stimulation over the cerebellum in man. J Physiol 1991;441:57-72.
13. Ugawa Y, Genba-Shimizu K, Rothwell JC, Iwata M, Kanazawa I. Suppression of motor cortical excitability by electrical stimulation over the cerebellum in ataxia. Ann Neurol 1994;36:90-96.
14. Ugawa Y, Hanajima R, Kanazawa I. Motor cortex inhibition in patients with ataxia. Electroencephalogr Clin Neurophysiol 1994;93:225-229.
15. Ugawa Y, Genba-Shimizu K, Kanazawa I. Suppression of motor cortical excitability by electrical stimulation over the cerebellum in Fisher's syndrome. J Neurol Neurosurg Psychiatry 1994;57:1275-1276.
16. Ugawa Y, Terao Y, Nagai C, Nakamura K, Kanazawa I. Electrical stimulation of the cerebellum normally suppresses motor cortical excitability in a patient with ataxia due to a lesion of the middle cerebellar peduncle. Eur Neurol 1995;35:243-244.
17. Ugawa Y, Uesaka Y, Terao Y, Hanajima R, Kanazawa I. Magnetic stimulation over the cerebellum in humans. Ann Neurol 1995;37:703-713.
18. Ugawa Y, Terao Y, Hanajima R, Sakai K, Furubayashi T, Machii K, et al. Magnetic stimulation over the cerebellum in patients with ataxia. Electroencephalogr Clin Neurophysiol 1997;104:453-458.
19. Iwata NK, Hanajima R, Furubayashi T, Terao Y, Uesugi H, Shiio Y, et al. Facilitatory effect on the motor cortex by electrical stimulation over the cerebellum in humans. Exp Brain Res 2004;159:418-424.
20. Iwata NK, Ugawa Y. The effects of cerebellar stimulation on the motor cortical excitability in neurological disorders: a review. Cerebellum 2005;4:218-223.
21. Kikuchi S, Mochizuki H, Moriya A, Nkatani-Enomoto S, Nakamura K, Hanajima R, et al. Ataxic hemiparesis: neurophysiological analysis by cerebellar transcranial magnetic stimulation. Cerebellum 2012;11:259-263.
22. Shirota Y, Hamada M, Hanajima R, Terao Y, Matsumoto H, Ohminami S, et al. Cerebellar dysfunction in progressive supranuclear palsy: a transcranial magnetic stimulation study. Mov Disord 2010;25:2413-2419.
23. Kuo SH, Wang J, Tate WJ, Pan MK, Kelly GC, Gutierrez J, et al. Cerebellar pathology in early onset and late onset essential tremor. Cerebellum 2017;16:473-482.
24. Louis ED, Kuo SH, Wang J, Tate WJ, Pan MK, Kelly GC, et al. Cerebellar pathology in familial vs. sporadic essential tremor. Cerebellum 2017;16:786-791.
25. Louis ED, Kerridge CA, Chatterjee D, Martuscello RT, Diaz DT, Koeppen AH, et al. Contextualizing the pathology in the essential tremor cerebellar cortex: a patholog-omics approach. Acta Neuropathol 2019;138:859-876.
26. Hanajaima R, Tsutsumi R, Shirota Y, Shimizu T, Tanaka N, Ugawa Y. Cerebellar dysfunction in essential tremor. Mov Disord 2016;31:1230-1234.
27. Dionísio A, Duarte IC, Patrício M, Castelo-Branco M. The use of repetitive transcranial magnetic stimulation for stroke rehabilitation: a systematic review. J Stroke Cerebrovasc Dis 2018;27:1-31.
28. Sasada S, Kato K, Kadowaki S, Groiss SJ, Ugawa Y, Komiyama T, et al. Volitional walking via upper limb muscle-controlled stimulation of the lumbar locomotor center in man. J Neurosci 2014;34:11131-11142.