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. 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. 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. rTMS over the cerebellum is a treatment option for movement disorders, but this should also be verified by large-scale randomized control trials. A similar conclusion has been reached about the effects of cerebellar stimulation on essential tremor. 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. 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, and their findings have been replicated in human neuroimaging studies. The most important finding from these studies was that the pre-supplementary 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-
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. 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. Research in ataxic patients using this electrical stimulation method has suggested that the cerebellar stimulation should activate Purkinje cells and suppress M1 through dentate-thalamocortical pathways. This suppressive effect has been named cerebellar inhibition (CBI). Magnetic stimulation over the cerebellum also evoked a similar suppressive effect on M1. 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. This method revealed cerebellar involvement in disorders originally reported to have no cerebellar involvement, such as progressive supranuclear palsy (PSP). 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). To confirm this finding in humans, we studied cerebellar function in patients with ET. 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. 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. 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.

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**Author Contributions**

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