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Transcranial magnetic stimulation for the treatment of vestibular decompensation

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Abstract. *Transcranial magnetic stimulation for the treatment of vestibular decompensation***.** *Objectives*: Low-frequency repetitive transcranial magnetic stimula-tion (LFrTMS) is a non-invasive and potentially potent tool for neuromodulation in the central nervous system. This case study reports on the therapeutic efficacy of LFrTMS for patients with dynamic vestibular decompensation.
Methodology: Three patients participated, each of which experienced vestibular decompensation from vestibular neuritis. They complained of dizziness even after completing >six months of vestibular rehabilitation education. LFrTMS was administered over the contra-lesional vestibular cerebellum for five consecutive days. Objective instability and subjective symptoms were evaluated with a stabilometer and self-reported questionnaires, respectively.
Results: Postural instability of all patients was ameliorated from day 5 to one month after treatment, but subjective symptoms of patients with anxiety did not change.
Conclusion: This report suggests the utility of LFrTMS targeted at the vestibular cerebellum for the treatment of chronic dynamic vestibular decompensation for patients with minimal anxiety.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive and potentially potent tool for neuromodulation in the central nervous system. In the present case study, we examined the therapeutic efficacy of low-frequency rTMS (LFrTMS) for the treatment of chronic dizziness from vestibular decompensation (VDC), as there is no promising treatment for intractable dynamic VDC to date. Unilateral vestibular hypofunction is recovered through two stages, namely, static vestibular compensation (VC) and dynamic VC.[1] Static VC is completed within approximately one week after the onset of vestibular impairment, while the symptoms at rest, such as vertigo and nausea, disappear. Dynamic VC follows, with symptoms including movement-related dizziness disappearing within a few months, which is achieved by compensation from the vestibular cerebellum-related network (Figure 1).[1] In general, unilateral hypofunction is treated with vestibular rehabilitation and medication(s), while hypofunction is compensated by the vestibular cerebellum-related network (Figure 1).[1] However, certain patients remain symptomatic for years, with these patients having dynamic VDC. For such patients, rTMS over the vestibular cerebellum-related network is a reasonable treatment because a number of reports has demonstrated the benefits of the rTMS of the cerebrum or the cerebellum for intractable chronic symptoms, such as tinnitus, cerebellar ataxia, unsteadiness resulting from central nervous system disease, upper limb dysfunction after stroke and psychoses.[2-7] It has also been demonstrated that the cerebellum is suitable for neuromodulation because of its high plasticity[8] and given that rTMS non-invasively induces neuromodulation in the cerebellum.[7] To the best of our knowledge, however, no researchers have used rTMS to modulate the vestibular cerebellum, which is a deep region of the cerebellum.

LFrTMS has been shown to inhibit neuronal activity and be effective for patients with depression and rehabilitation after stroke.[2,3] Multiple lines of evidence indicate that depressed patients show

Conflicts of interest. There are no conflicts of interest for any of the authors.

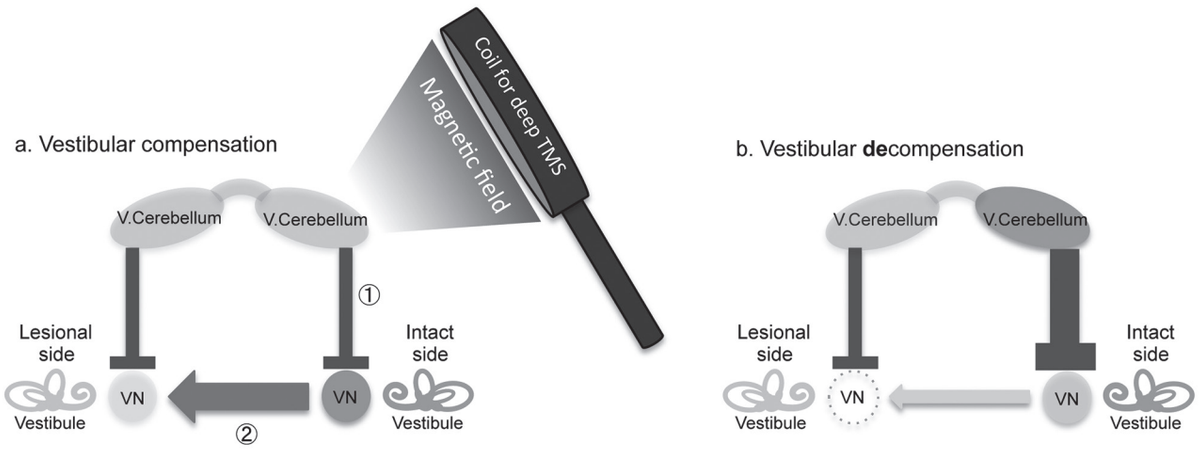

Figure 1

Schematic presentation of vestibular compensation and decompensation in the chronic stage. Deeper colour and thicker lines indicate more activity. The vestibular cerebellum-related network compensates for hypofunction of the unilateral peripheral vestibule. (a) The vestibular cerebellum (V.Cerebellum) essentially inhibits the ipsilateral VNs in the brainstem (1). In the compensated state, sufficient excitatory information (2) from the contralesional VNs restores the activity of the VNs on the lesional side. The coil used in the present study was designed specifically to repetitively stimulate a deeper region than a conventional eight-figure or circular coil, while its maximum stimulation takes place under the coil centre. The magnetic field generated by the TMS coil is naturally strongest at the surface of the coil and decreases as it goes deeper. (b) In the decompensated state, excessive activity of the vestibular cerebellum causes excessive inhibition of healthy VNs, with an insufficient amount of sensory information from the contralesional VNs entering the VNs on the lesional side.

hypoactivity in the left dorsolateral prefrontal cortex. Generally, high-frequency rTMS, which can enhance neuronal activity, when applied over the left prefrontal cortex, is used for treating depression; additionally, LFrTMS, to the right of the prefrontal cortex improves depressive symptoms via inhibition of the non-lesional prefrontal cortex.[2] With respect to rehabilitation after stroke, inhibition of hyperactivity of the non-lesional hemisphere over the primary motor area using LFrTMS, combined with occupational therapy, improves motor function of the affected upper limb, for which the beneficial effect is thought to be attributable to increased neural activation in the lesional hemisphere, caused by reduced interhemispheric inhibition from the non-lesional hemisphere.[3]

The exact mechanism of dynamic VC remains unknown, but a possible mechanism is suggested as follows. Dynamic VC is achieved by sensory inputs from the contralesional vestibular neurons (VNs) in the brainstem to the lesional VNs (Figure 1a).[1] On the other hand, the vestibular cerebellum essentially inhibits the ipsilateral VNs.[9] In a study of the interaction between the cerebellum and cerebrum, LFrTMS of the cerebellum was found to decrease the inhibitory activity of the cerebellum against the cerebrum.[7] Therefore, for patients with chronic dynamic VDC (Figure 1b), we hypothesized that LFrTMS to the contralesional hyperactive vestibular cerebellum would help mitigate the excessive inhibition of non-lesional VNs, thus restoring sufficient information from the contralesional to the lesional VNs to promote dynamic VC (Figure 1a). In turn, we investigated the therapeutic efficacy of LFrTMS targeting the contralesional cerebellum (centring on the vestibular cerebellum) of patients in combination with vestibular rehabilitation.

Case report

Eligible patients (1) were aged ≥20 years, (2) had unilateral vestibular hypofunction confirmed by tests for gaze nystagmus, spontaneous nystagmus, positional nystagmus, positioning nystagmus and head shaking nystagmus, and caloric tests as assessed with electronystagmography, (3) had been experiencing vestibular hypofunction for ≥six months, and (4) complained of dizziness, even after completing a five-day vestibular rehabilitation education programme and continuing the self-administered home-based vestibular exercise with periodic supervision by medical staff for >six months, with the effect proving effective based

on published criteria.[10] In brief, the programme comprised repeated training involving seven programmes of vestibule-ocular reflexes, as well as eight static and five dynamic programmes of vestibule-spinal reflexes. Ultimately, three patients (Cases 1-3) with intractable VDC, as caused by unilateral vestibular neuritis, participated in this study. Cases 1-3 were aged 51, 77, and 66 years, while the duration of their current VDC symptoms was 22, 41 and 16 months, respectively. All patients provided written informed consent for participation, while this study was approved by the ethics committee of the Kyorin University School of Medicine.

LFrTMS was administered using the MagPro R30 therapy system and Cool-125 (Magventure, Inc., Denmark). Cool-125 is a specially designed coil, which can stimulate a deeper region than a conventional eight-figure coil (3.5 cm vs. 2 cm at the centre of the coil), while its maximum stimulation takes place under the coil centre (Figure 1a), which differs from an ordinary circular coil in that maximum stimulation takes place under the rim of the coil. For stimulating the ventricular cerebellum, the centre of the coil was moved rightwards/leftwards off the midpoint by 3 cm along a line between the inion and the right/left mastoid process.[11] Treatment was standardized at a stimulation intensity of 80-120%, relative to the patient's resting motor threshold. The resting motor threshold is defined as the minimum TMS intensity at the motor cortex in order to produce a motor-evoked potential in the abductor pollicis brevis, which is the common way of calibrating and normalizing TMS intensity for individuals. LFrTMS was applied at 1 Hz for 15 min every day for five days. At the beginning of the first day, the stimulation intensity was set to 80% of the motor threshold, increasing by 10% every 15 s to ensure tolerability. From the next day, the intensity was set to the maximum intensity of the previous day, minus 10%, then increased 10% every 15 s while ensuring tolerability, although the maximum intensity was not allowed to exceed 120%. The stimulation intensity for Case 1 was weaker than that for the others because he presented with muscle-twitching discomfort on the back of his neck during treatment. The maximum stimulation intensities for each patient from days 1 to 5 were as follows: Case 1 = 80, 90, 100, 110 and 120% of motor threshold; Case 2 = 100, 120, 120, 120 and 120%; and Case 3 = 110, 120, 120, 120 and 120%. Patients, who were hospitalized for the five consecutive days of treatment, were also trained to perform vestibular rehabilitation during the trial.

The Japanese version of the Dizziness Handicap Inventory (DHI) was used to evaluate subjective effects. To evaluate postural stability objectively and quantitatively, patients stood on the platform of a stabilometer with their eyes closed, with the sway area of the path described by the centre of foot pressure for 60 s measured. This reflected the fact that the sway area with eyes closed has been demonstrated to be a useful component for following up vestibular patients with chronic peripheral disease, although the length of sway with eyes, whether open or closed, and the sway area with eyes open are not appropriate for follow-up.[12] To prevent patients from learning how to maintain stability on the stabilometer during repetitive measurements after starting LFrTMS, the sway area with eyes closed was only measured at pretreatment, five days after the beginning of the treatment, and one and three months after completion of LFrTMS. Frequent meetings with an attending physician was also found to influence subjective symptoms. To minimize this possibility, after completing the LFrTMS, subjects were only seen at one and three months after treatment. Therefore, we only evaluated DHI at the same time as measuring the sway area with eyes closed. To evaluate anxiety, the State-trait Anxiety Inventory (STAI) was used. The anxiety level, as determined by the STAI, was categorized as normal, very low, low, high or very high. We also obtained data for DHI, the sway area and the STAI before, one month after, and three months after a five-day vestibular rehabilitation education programme, which had been conducted before LFrTMS administration.

No side effects were observed as a consequence of stimulation over the vestibular cerebellum with LFrTMS, except for muscle-twitching discomfort in Case 1 on the first day of the treatment. No subject experienced nausea, dizziness or vertigo, which could have been induced by direct stimulation of the vestibular nerve and VNs in the brainstem during the application of LFrTMS. In all cases, the sway area with eyes closed decreased from day 5 to one month after LFrTMS treatment; that is, instability decreased objectively during this period (Figure 2). Moreover, the sway area with eyes closed, as measured one month after LFrTMS treatment, was

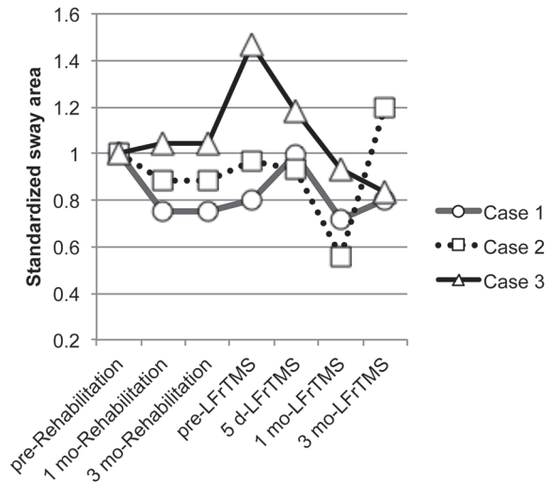

Figure 2

Changes in objective postural stability. The sway area of the centre of foot pressure as measured with eyes closed was assessed prior to (pre) or at five days, one month, or three months after a five-day vestibular rehabilitation education programme (rehabilitation) alone, and after the rehabilitation plus application of LFrTMS. For all patients, VDC improved from day 5 to one month post-treatment.

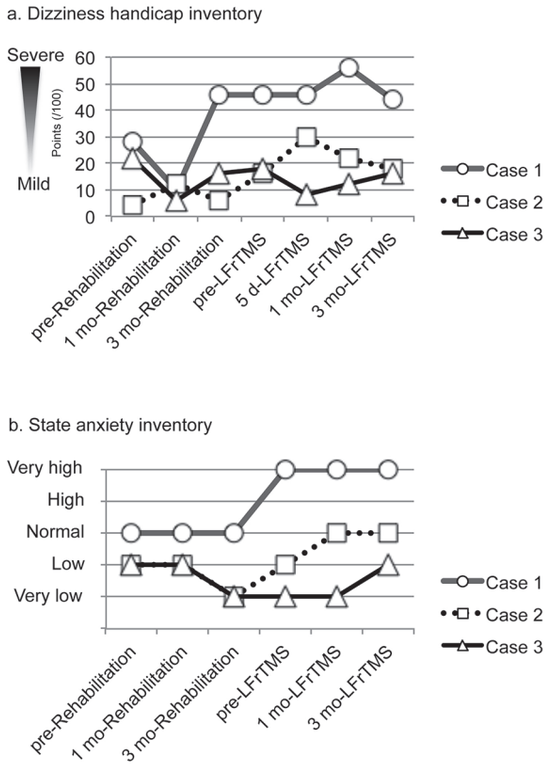

Figure 3

Changes in subjective symptoms measured prior to (pre) or at various times after a five-day vestibular rehabilitation education programme and the application of LFrTMS. (a) A change in the subjective symptom of "dizziness" was evaluated with the DHI, a 25-item self-reported questionnaire. The highest possible score is 100, with a higher score indicating more dizziness. (b) A change in psychological factors, such as an anxiety state, was evaluated with the STAI. These subjective factors did not change in parallel with an improvement in the objective factor, i.e., the sway area with eyes closed, one month after treatment. Cases 1-3 in Figure 3 are the same as those in Figure 2.

better than that at one month and three months after the five-day vestibular rehabilitation education programme. In particular, Cases 2 and 3, who were given more intense stimulation than Case 1, exhibited greater improvement at five days or one month after LFrTMS treatment compared with Case 1. Such an improvement had never been observed in these individuals during the period when rehabilitation alone was applied (Figure 2). The sway area with eyes closed for Case 1 returned to the pretreatment level. For Case 2, the area worsened three months after initial treatment, but the patient did not complain about any associated aggravation (Figure 3a; Cases 1-3 in Figure 3 are the same as those in Figure 2). For Case 3, the area was still decreasing after three months. The anxiety level of Case 1 remained very high during the course of the study, while Case 2 exhibited low anxiety at pretreatment, but had a normal level of anxiety at one and three months after treatment (Figure 3b). The DHI score for the two patients with anxiety did not improve during the course of treatment (Figure 3a). Case 3 had a very low anxiety level, with the DHI score improving during the course of treatment. When asked about their condition at the outpatient clinic, none of the subjects reported any improvement in VDC symptoms from the beginning of LFrTMS to three months after treatment, although they all reported some improvement >six months after treatment, based on a simple question asked by the physician at an ordinary outpatient clinic, namely: "How is your dizziness these days?" The STAI did not change in parallel with the change in the sway area with eyes closed.

Discussion

Potential of LFrTMS in the treatment of chronic VDC

Our results demonstrate that a therapeutic intervention based on our hypothesis had a positive effect on objective parameters for one month,

although the subjective symptoms of patients with anxiety did not improve. While there were only three subjects in this case study, the pattern of decreasing sway area with eyes closed from day 5 to one month after treatment was identical for the three subjects, with such substantial changes not observed during the five-day vestibular rehabilitation education programme (Figure 2). Moreover, such changes in vestibule-related function and symptoms have not been observed with rTMS over the cerebral cortex, even when applied for four to six weeks.[13] In particular, Cases 2 and 3, who were given more intense LFrTMS stimulation than Case 1, exhibited more substantial treatment responses after LFrTMS than Case 1. These findings suggest that objective improvement in postural instability may be attributable to treatment with LFrTMS over the vestibular cerebellum. Furthermore, the subjective symptoms may be affected by the severity of anxiety, while application of LFrTMS to the cerebellum may not improve anxiety.

The positive objective effect (i.e., a decrease in the sway area with eyes closed) disappeared less than three months after initial treatment for Cases 1 and 2. Similar limitations of the persistence of the rTMS effect have also been observed for tinnitus, for which the effects were found to disappear in a few weeks,[4] which is consistent with the neuromodulatory effect of LFrTMS. For Case 3, however, the effect lasted for three months. Potential explanations for this difference include the shorter duration of VDC and/or stronger stimulation for Case 3. In this regard, LFrTMS could be a therapeutic option for VDC if conventional treatment fails (e.g., six months after disease onset). More intense stimulation could maintain positive neuronal modulation for a longer period and ultimately have a positive effect on subjective symptoms. To achieve this without excessive inhibition of the normal cerebellar function, one possible strategy is to apply a maintenance LFrTMS session one month after treatment, as reported for treatment of depression.[5] Additionally, considering that Case 3, who had limited anxiety, had a better result, management of the psychological aspect could have enhanced the positive effect as suggested previously.[14] One possible option for improving the psychological aspect is to apply Acceptance and Commitment Therapy, with which it is possible to increase the patient's acceptance of certain aspects of chronic distress, which may be difficult to alter.[15]

Subjects reported that their symptoms improved >six months after treatment at an ordinary outpatient clinic, although the positive objective effect for Cases 1 and 2 disappeared three months after treatment. This suggests that the present protocol could have additional positive effects on a vestibular rehabilitation programme if continued for a period longer than that assessed in the present study. Subjects reported subjective improvements an unexpectedly long time after treatment, but we did not evaluate this aspect comprehensively. A longer evaluation programme with multiple kinds of questionnaires about subjective symptoms is needed in future studies. The use of other questionnaires, such as the Situational Vertigo Questionnaire or International Physical Activity Questionnaire, could evaluate aspects of treatment effects other than those evaluated with DHI.

One other issue regarding this approach is that there is currently no validated quantitative reference value for evaluating dynamic VC. In the present study, the sway area with eyes closed was used for the purposes of quantitative analysis. However, other outcome measures, such as three-dimensional gait analysis, computerized posturography and dynamic visual acuity, will be useful in future work.

Mechanisms inducing the positive objective effect

Our hypothesis that LFrTMS would promote dynamic VC, thereby leading to the present protocol, was based on the mechanism of VC, as suggested by animal studies (Figure 1),[1] while the mechanisms of VC and VDC in humans are not fully understood. The ability to stimulate deeper brain structures is achieved at the expense of inducing a wider electrical field spread. The magnetic field generated by the coil that we used is greatest at the surface of the coil, but decreases as it goes deeper, as shown in Figure 1a. Therefore, Purkinje cells in the cerebellar hemisphere are likely to be the most inhibited by the coil used in this study because they are the nearest structure to the coil, which could also decrease the sway area with eyes closed. For example, Shimizu et al. found that LFrTMS over the cerebellum improved the steadiness of patients with spinocerebellar ataxia, although they used much wider and shallower stimulation (i.e., stimulation was applied over the right, left and middle superficial cerebellar cortex), as well as an ordinary circular coil with 10 pulses at <0.2 Hz for

21 days.[6] They were also unable to determine the mechanism by which rTMS produces this effect. The subjects in this study did not complain of vestibule-related symptoms during the present LFrTMS application, although such symptoms typically appear as a consequence of direct stimulation of VNs and the vestibular nerve. Thus, our results suggest that there was little effect of LFrTMS on VNs and the vestibular nerve.

Considering that the vestibular cerebellum has direct functional connectivity with VNs, while the cerebellar hemisphere was the most widely inhibited region by LFrTMS (Figure 1), the positive objective effects seen in this study may be attributable to neuromodulation via the application of LFrTMS to both of these cerebellar regions.

The mechanism of VC is not completely understood, while the cerebellum is a multifunctional complex structure. To further elucidate the effects of LFrTMS on the vestibular cerebellum-related network and VC, a neuroimaging study using functional magnetic resonance imaging and multi-channel electroencephalograms could be used to assess changes in vestibular cerebellum-related network activity after LFrTMS. In addition, a neuronavigation system should facilitate more accurate and focal stimulation of the targeted area.

Conclusions

The results of this preliminary case study suggest the utilization of LFrTMS, when targeted at the vestibular cerebellum, for the treatment of chronic dynamic VDC for patients with minimal anxiety. Further well-designed studies with a larger sample size will be needed to confirm the therapeutic efficacy of LFrTMS, as well as standardize the stimulation parameters for the treatment of chronic dynamic VDC.

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