Cerebellar theta burst stimulation in stroke patients with ataxia

Sonia Bonnì, PsyD, PhD[a]
Viviana Ponzo[a]
Carlo Caltagirone, MD, PhD[a,b]
Giacomo Koch, MD, PhD[a,b]

[a] Non-invasive Brain Stimulation Unit, IRCCS Santa Lucia Foundation, Rome, Italy
[b] Department of Neuroscience, University of Rome "Tor Vergata", Rome, Italy

Correspondence to: Sonia Bonnì
E-mail: s.bonni@hsantalucia.it

Summary

Evidence for effective improvement of the symptoms of cerebellar stroke is still limited. Here, we investigated the effects of repetitive transcranial magnetic stimulation (rTMS) applied over the injured cerebellar hemisphere in six patients with posterior circulation stroke. We applied a two-week course of cerebellar intermittent theta burst stimulation (iTBS).
Before and after the iTBS treatment, paired-pulse TMS methods were used to explore: i) the functional connectivity between the cerebellar hemisphere and the contralateral primary motor cortex (M1), by means of the cerebellar brain inhibition (CBI) protocol; and ii) the intracortical circuits in the contralateral M1, by means of the short intra-cortical inhibition (SICI) and intra-cortical facilitation (ICF) protocols. Patients were also evaluated using the Modified International Cooperative Ataxia Rating Scale (MICARS). Cerebellar iTBS induced a decrease in CBI and an increase in ICF at an interstimulus interval of 15 msec. These neurophysiological changes were paralleled by a clinical improvement, shown by the MICARS posture and gait subscale scores. Cerebellar iTBS could be a promising tool to promote recovery of cerebellar stroke patients.

KEY WORDS: cerebellar stroke; theta burst stimulation; intracortical facilitation

Introduction

Patients affected by ischemic or hemorrhagic stroke present motor disturbances such as ataxia, intention tremor, axial latero-pulsion and dysarthria. Ataxia is a common impairment after posterior circulation stroke (PCS) involving the cerebellum or brainstem, and it restricts patients in their mobility and activities of daily living (Teasell et al., 2002).
Various strategies have been suggested to improve the symptoms of cerebellar stroke, but the evidence of their effectiveness is still limited (Kruger et al., 2007). Repetitive transcranial magnetic stimulation (rTMS) has recently been proposed as a potentially useful method for modulating the excitability of cerebello-thalamo-cortical (CTC) pathways, which could have a favorable effect on the cerebellar deficit (Koch, 2010). The current study was conducted to investigate the effects of a two-week course of cerebellar intermittent theta burst stimulation (iTBS) in a sample of six chronic stroke patients affected by PCS. This protocol is known to induce an increase in the excitability of the CTC pathways (Koch et al., 2008). Before and after the iTBS treatment we used paired-pulse TMS methods to explore: i) the functional connectivity between the affected cerebellar hemisphere and the contralateral motor cortex (M1), assessing cerebellar brain inhibition (CBI), and ii) the excitability of the contralateral M1, assessing short intra-cortical inhibition (SICI) and intra-cortical facilitation (ICF). In addition, all the patients were submitted to clinical evaluation: the Modified International Cooperative Ataxia Rating Scale (MICARS) was administered to investigate whether the iTBS protocol could improve symptoms of cerebellar dysfunction.

Materials and methods

Subjects

We recruited six patients (5 males and 1 female; mean age 45.2 years, SD 2.8; age range: 33-53 years) with a diagnosis of cerebellar stroke. The following conditions constituted exclusion criteria: increased intracranial pressure, contraindications to iTBS such as implanted pacemakers, a history of seizures, inability to provide written informed consent. All the patients underwent complete clinical and neuroradiological investigations (MRI) and were selected on the basis of clinical signs of cerebellar lesions. The patients' clinical and demographic features are summarized in table I (over). Cases 2 to 4 had cerebellar infarction while cases 1, 5 and 6 had hemorrhagic stroke. At the beginning and at the end of the iTBS treatment, all the patients underwent clinical evaluation (MICARS). CBI, SICI and ICF were measured before and after the end of the iTBS sessions.

The iTBS treatment consisted of 10 sessions, each lasting approximately three minutes, spread over two weeks (one session a day/5 days a week: Monday to Friday). It was performed at the same time every morning (11 a.m.) in each patient. iTBS was applied over the damaged lateral cerebellum to evaluate the hypothesis that this procedure is capable of inducing long-term potentiation of CTC pathways (Koch et al., 2008) and thereby of modulating the interconnected cortical areas and promoting favorable clinical and neurophysiological changes in stroke patients. During the treatment period, the patients were submitted to standard physical therapy protocols, held every other day in an outpatient setting. Given the limited number of PCS patients recruited for this study we decided not to include other control groups such as PCS patients treated with physical therapy or with iTBS alone. All the patients gave their informed consent to participate in the study. Experimental procedures were approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

Transcranial magnetic stimulation

Single- and paired-pulse TMS was delivered through a monophasic Magstim 200 stimulator (Magstim Co., Whitland, Dyfeld, UK) connected to a figure-of-eight coil (diameter 70 mm) placed tangentially over the left M1 in the optimal position (hot spot) for eliciting motor evoked potentials (MEPs) in the right first dorsal interosseous (FDI) muscle. We used a neuronavigation system (Softaxic, E.M.S., Bologna, Italy) to precisely position the coil over the left or right M1, using individual anatomical MRI data.

The resting motor threshold (RMT) was calculated as the lowest intensity evoking five MEPs of at least 50 μV in 10 consecutive trials (Rossini et al., 1994). The active motor threshold (AMT) was set at the lowest intensity able to produce MEPs < 200 μV in at least five out of ten trials when the subject performed a 10% of maximum contraction using visual feedback (Rothwell, 1997). Electromyographic activity was recorded from the contralateral FDI muscle, using two Ag-AgCl surface cup electrodes (9 mm) in a belly-tendon montage. Responses were amplified with a Digitimer D360 amplifier (Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK) through filters set at 20 Hz and 2 kHz, with a sampling rate of 5 kHz; they were then recorded by a computer using SIGNAL software (Cambridge Electronic Devices, Cambridge, UK).

We used a figure-of-eight coil (diameter 70 mm) connected to two Magstim 200 stimulators to apply paired-pulse TMS to investigate M1 intra-cortical circuits i.e. SICI and ICF. The magnetic stimuli had an almost monophasic pulse configuration. The coil was placed at the optimal position for eliciting MEPs from the contralateral FDI muscle. The handle of the coil pointed backward and was perpendicular to the presumed direction of the central sulcus, about 45° to the mid-sagittal line. The direction of the induced current was posterior to anterior and was optimal to activate the motor cortex transynaptically (Rothwell, 1997).

For testing SICI and ICF we used paired-pulse TMS with a conditioning stimulus (CS) preceding a test stimulus (TS) by different inter-stimulus intervals (ISIs): 1, 2, 3, 5, 7, 10 and 15 msec (Kujirai et al., 1993; Ziemann et al., 1996). The conditioning pulse was delivered randomly.

The CS was set at 80% of the AMT (Huang and Rothwell, 2004) while the intensity of the TS was adjusted to evoke an approximately 1 mV peak-to-peak MEP in the relaxed FDI muscle.

Cerebellar brain inhibition (CBI) was investigated in the FDI muscle by delivering cerebellar stimulation followed by M1 stimulation in a paired-pulse paradigm (Ugawa et al., 1995) to explore the connectivity between the affected cerebellar hemisphere and the contralateral motor cortex. We set the intensity for the motor cortical TS at the intensity required to elicit MEPs of 0.5-1 mV, with the muscle relaxed. The cerebellar CS randomly preceded the TS at different ISIs, ranging from 3 to 10 msec (3, 5, 10 msec). The intensity was set at 90% of the RMT obtained in the con-

Table I – Clinical and demographic characteristics of six cerebellar stroke patients.

Pat. n.	Age	Sex	Neuroradiological findings	Presenting signs and symptoms	Time from stroke
1	45 yrs	M	Hemorrhagic infarct in the territory of the right superior cerebellar artery	Right ataxic hemisyndrome, bilateral dysmetria, dysarthria	7 yrs
2	50 yrs	M	Ischemic lesion in the territory of the right anterior inferior cerebellar artery	Vertigo, ataxia, nystagmus	9 mths
3	53 yrs	M	Ischemic lesion in the territory of the left anterior inferior cerebellar artery	Dysarthria, nystagmus, left ataxic hemisyndrome	3 yrs
4	45 yrs	M	Bilateral ischemic lesion in the territory of the vertebral artery	Dysarthria, bilateral dysmetria, tetraparesis	2 yrs
5	45 yrs	M	Hemorrhagic infarct in the territory of the left posterior inferior cerebellar artery	Ataxia, dysmetria, anarthria, severe hypotonia	2 yrs
6	33 yrs	F	Hemorrhagic infarct in the territory of the left anterior inferior cerebellar artery	Ataxia, diplopia, dysarthria	3 yrs

tralateral motor cortex. Overall, eight responses were collected for each different ISI condition and 15 responses were collected following the TS alone, for a total of 39 stimuli.
iTBS was performed with a MagStim Super Rapid magnetic stimulator connected to a standard figure-of-eight flat coil (70 mm diameter) as in Huang et al. (2004, 2005) (3 pulses at 50 Hz repeated at a rate of 5 Hz; 20 trains of 10 bursts delivered at 8-sec intervals; total duration: 190 sec, 600 pulses). The stimulus intensity was 80% of the AMT. iTBS was applied over the lesioned cerebellum using the same scalp coordinates (1 cm inferior to and 3 cm left/right of the inion) (Del Olmo et al., 2007). The coil was positioned tangentially to the scalp, with the handle pointing superiorly.

Clinical assessment of motor dysfunction in cerebellar stroke

The MICARS (Schmahmann et al., 2009) was used to assess and monitor cerebellar motor functions. This validated semi-quantitative 120-point rating scale for the assessment of ataxia is based upon the International Cooperative Ataxia Rating Scale (Trouillas et al., 1997; Storey et al., 2004). MICARS subscales measure postural and gait disturbances, limb ataxia, dysarthria, and oculomotor disorders. Higher scores indicated higher levels of impairment. In the current study, the scale was administered by blinded raters before the start of the first stimulation session (pre-iTBS) and again after two weeks of stimulation (post-iTBS).

Statistical analysis

The effects of two weeks of iTBS on the CBI functional connections and on SICI/ICF were expressed as percentages of the mean peak-to-peak amplitude of the test stimulus. MEP size was analyzed by a two-way ANOVA with the within-subjects main factors TIME (pre-iTBS vs post-iTBS) and ISI (CBI= 3, 5, 10 msec; SICI/ICF= 1, 2, 3, 5, 7, 10, 15 msec). Duncan post-hoc comparisons were performed when required. For all statistical analyses, a p-value <0.05 was considered to be significant. The non-parametric Wilcoxon test was applied to mean MICARS total and sub-scale scores.

Results

Cerebellar brain inhibition

The intensity of the TS over the left M1 needed to produce a 1 mV MEP was 64.3±3.9% of maximal stimulator output. The two-way ANOVA performed on CBI values showed a significant TIME ($F(1,4)=10.3$; $p=0.03$) (Fig. 1) but not ISI ($F(2,8)=0.14$; $p=0.14$) main effect. The interaction between TIME and ISI was not significant ($F(2,8)=0.02$; $p=0.97$).

Intracortical inhibition and facilitation

At baseline the RMT for the left M1 was 48.5±3.1. The intensity of the TS over the left M1 needed to produce a 1 mV MEP was 63.6±3.8. The two-way ANOVA performed on SICI/ICF values showed significant TIME ($F(1,4)=7.31$; $p=0.50$) (Fig. 1) and ISI ($F(6,24)=3.38$; $p=0.014$) main effects and a significant TIME x ISIs interaction $F(1,4)=7.31$; $p<0.05$). Duncan post-hoc analysis showed that conditioned MEP amplitude increased at the 15-msec ISI ($p=0.005$) after two weeks of iTBS over the cerebellum (Fig. 2).

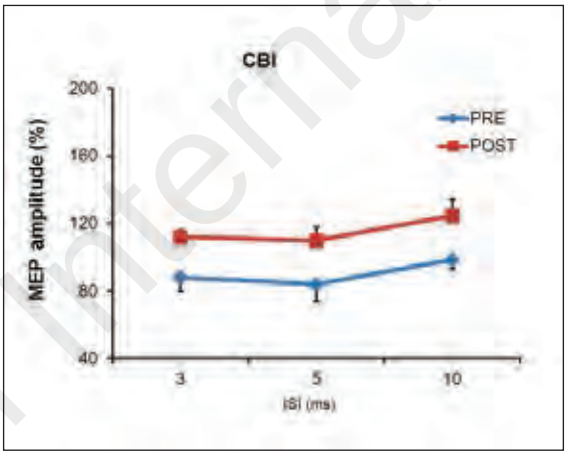

Figure 1 - Effects on cerebellar brain inhibition (CBI) of two weeks of treatment with iTBS applied over the cerebellum.
The MEP amplitude refers to the mean peak-to-peak amplitude size expressed as a percentage of the unconditioned test pulse.

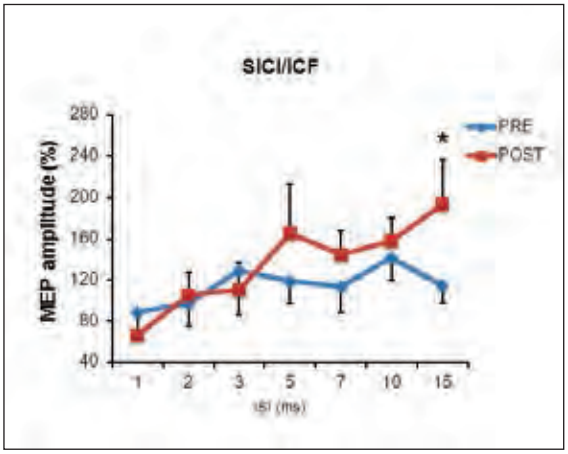

Figure 2 - Effects on short intracortical inhibition (SICI) and intracortical facilitation (ICF) of two weeks of treatment with iTBS applied over the cerebellum.
The MEP amplitude refers to the mean peak-to-peak amplitude size expressed as a percentage of the unconditioned test pulse. An increase in ICF at ISI=15 msec was observed. Error bars indicate S.E.M.; asterisks indicate $p<0.05$.

MICARS score

We used the MICARS test to determine the effects of the two weeks of iTBS treatment applied over the cerebellum in all the patients. The total and the subscale scores were tested pre-TBS and post-TBS. Mean MICARS total scores increased moderately after iTBS treatment (Table II) (Wilcoxon test p=0.03). We then subdivided the analysis considering the subscales separately. Of these four subscales, only the Posture and gait disturbances subscale was significant (Wilcoxon test p=0.02) (Fig. 3).

Table II – MICARS total scores recorded by six cerebellar stroke patients.

Pat. n.	MICARS score pre-iTBS	MICARS score post-iTBS
1	79	78
2	9	6
3	43	28
4	91	71
5	53.4	43.8
6	45	36
Mean±SD	53.4±13.0	43.8±12.1

Abbreviations: MICARS=Modified International Cooperative Ataxia Rating Scale; iTBS=intermittent theta burst stimulation; SD=standard deviation

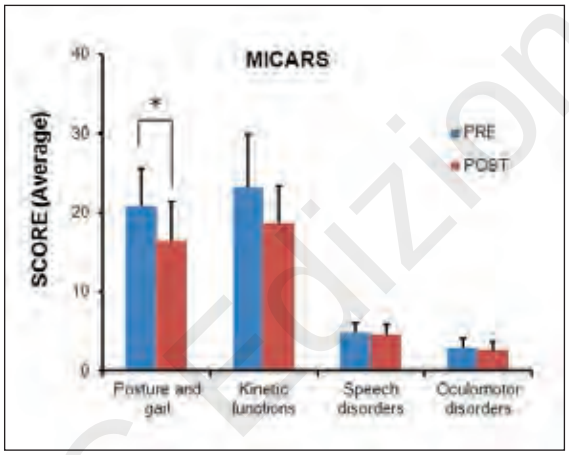

Figure 3 - MICARS scores obtained by patients pre- and post-treatment.
A significant clinical improvement post-treatment was observed in the posture and gait subscale scores. Error bars indicate S.E.M. Asterisks indicate a p-value < 0.05.

Discussion

Our data show that iTBS applied over the lateral cerebellum in PCS patients modulates the intra-cortical circuits in the contralateral motor cortex and modifies the functional cerebellar-motor connectivity. Moreover, these neurophysiological changes were coupled with a clinical improvement in ataxic gait and posture symptoms.
We hypothesize that these changes depend on long-lasting activation of the CTC pathways. The observed effects depend on the interaction between the affected cerebellum and the intact contralateral cortical circuits, which the remote stimulation may have rendered more efficient. The physiology of the CTC pathway activated by magnetic stimulation has recently been clarified (Koch, 2010). It has been proposed that cerebellar TMS activates the Purkinje cells of the superior cerebellum, resulting in inhibition of the dentate nucleus, which is known to exert a background tonic facilitatory drive onto the contralateral M1 through a synaptic relay in the ventral lateral thalamus (Daskalakis et al., 2004; Middleton and Strick, 2000). This in turn leads to inhibition of the contralateral M1, due to a reduction of the dentato-thalamo-cortical facilitatory drive (Ugawa et al., 1994, 1995). In our sample of patients, even though they were affected by PCS, CBI was normally evoked at baseline. After two weeks of cerebellar stimulation, this inhibitory interaction was found to be decreased. One possible interpretation is that an increase in the excitability of the cerebellar cortex could have led to a modulation of the inhibitory drive over the dentate nucleus favoring facilitation in the contralateral M1 (Koch, 2010). However, this interpretation remains rather speculative. Efferent pathways from the cerebellum are connected with both excitatory and inhibitory neurons in the M1. Therefore, it is difficult to determine which pathway might be more involved in mediating the effects of iTBS over the cerebellum.
We also found a critical modulation of ICF at ISI=15 msec. In our sample of cerebellar patients there was, at baseline, a defective efficacy of the ICF that is consistent with previous studies. Several studies found a similar loss of ICF in cerebellar stroke patients (Liepert et al., 1998, 2004; Restivo et al., 2002). Moreover, we previously demonstrated that in healthy subjects cerebellar iTBS was also effective in modulating ICF circuits in the contralateral M1 (Koch et al., 2008). In the present context, it was not surprising that cerebellar iTBS was able to modulate the ICF neuronal circuits, provoking an increase in ICF and its recovery. Indeed, our data reinforce the notion that 15 msec is a critical inter-stimulus interval in the study of intra-neuronal circuits mediating cerebello-thalamo-motor interactions.
These neurophysiological changes were coupled with a clinical improvement, as demonstrated by the decrease in the MICARS posture and gait subscale scores. Strong evidence suggests that the cerebellum plays a particular role in the generation of appropriate patterns of limb movements, dynamic regulation of balance, and adaptation of posture and locomotion (Bastian, 2011). The increase in ICF could be related to improvements in some aspects of locomotion such as gait speed (Vacherot et al., 2010). However, the mechanisms by which cerebellar iTBS improved the gait and posture remain obscure. Indeed, different aspects of locomotion are likely mediated by different cerebellar regions (Bastian, 2011). Therefore, the role of different cerebellar areas in controlling different gait and balance functions remains to be investigated in depth. These considerations apart, in our study we found an improvement in the patients' performance on the MICARS after

two weeks of iTBS coupled with physical therapy. It is important to note that two weeks of physical therapy alone are not able to induce a significant clinical improvement in the chronic phase of stroke (Kwakkel and Kollen, 2013), while in our study such an improvement was observed following two weeks of physical therapy coupled with cerebellar iTBS. This finding seems consistent with the findings of previous studies showing that motor improvements in chronic stroke patients are due not only to conventional therapy, but also to the application of rehabilitation programs, including innovative and adjunctive techniques such as constraint-Induced movement therapy (Smania et al., 2012) and robot-assisted therapy (Lo et al., 2010).

The current study presents some limitations. First, our sample was too small and heterogeneous in terms of the affected cerebellar hemisphere to allow the construction of a proper double-blind controlled trial that might have given more solid information concerning the clinical efficacy of cerebellar iTBS. Second, we used only one clinical scale (MICARS), which may not be sufficient and appropriate to detect all the complex clinical aspects of cerebellar dysfunction in stroke patients. Third, we did not collect gait analysis parameters, which would have allowed us to detail more specifically any changes in locomotion.

In conclusion, the current preliminary study suggests that modulating the excitability of the cerebellar-cortical network could promote functional recovery in patients with PCS. Future research may make it possible to clarify the mechanisms underlying the recovery process and may contribute to the identification and development of therapeutic strategies.

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