Clinical effects of non-invasive cerebellar magnetic stimulation treatment combined with neuromotor rehabilitation in traumatic brain injury. A single case study.

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Summary

Multimodal treatments are emerging as effective approaches for motor recovery in traumatic brain injury (TBI). Various evidence has demonstrated that repetitive transcranial magnetic stimulation (rTMS) may improve outcomes in people with motor disorders. Behavioral gains from rTMS protocols may be maximized when brain stimulation is coupled with carefully designed occupational/physical therapy. We present the case of a 25-year-old man with chronic TBI (a bilateral cortico-subcortical parieto-occipital lesion) who underwent three weeks of cerebellar intermittent theta burst stimulation (iTBS), a form of rTMS, combined with neuromotor rehabilitation. The Fugl-Meyer Assessment (FMA), Berg Balance Scale (BBS), Jebsen-Taylor Hand Function Test, and accelerometer gait analysis were administered before and after treatment. The results showed improvements in balance performance (BBS: T0=47; T1=53; +10.72%), motor recovery (FMA: T0=93/100; T1=96/100; +3.00%), step length (T0=50.4±7.2; T1=53.8±2.2 cm, p<0.001), and walking speed (T0=0.87±0.06; T1=0.91±0.04 m/sec, p<0.001). Combined cerebellar rTMS and neuromotor rehabilitation seems to be a promising treatment for motor and balance dysfunctions in TBI patients.

KEY WORDS: cerebellar cortex, physical therapy, rehabilitation, transcranial magnetic stimulation, traumatic brain injury.

Introduction

The signs and symptoms after traumatic brain injury (TBI) include cognitive, behavioral and sensory-motor disabilities that reduce the patient’s quality of life and necessitate long-term care. Standard rehabilitation approaches that target functional recovery following focal brain damage have limited utility in severe TBI (Demirtas-Tatlidede et al., 2012). Neuromodulation techniques, designed to improve functional outcomes in TBI patients by enhancing adaptive plasticity, are a promising treatment option in this setting (Villamar et al., 2012; Pape et al., 2006). Behavioral gains from repetitive transcranial magnetic stimulation (rTMS) protocols may be maximized when brain stimulation is coupled with carefully designed occupational/physical therapy. Recent experimental studies highlighted the fact that the cerebellum plays a key role in the reorganization of motor networks after TBI. In particular, deep cerebellar nuclei are involved in somesthetic reflex behaviors; they also assist the cerebral cortex in transforming sensory signals into motor-oriented commands, acting via the cerebello-thalamo-cortical (CTC) projections (Luft and Buitrago, 2005). We recently investigated the possibility of modulating the plasticity of the primary motor area (M1) via the CTC pathway by means of rTMS of the contralateral cerebellum (Koch et al., 2008). Different forms of theta burst stimulation (TBS) applied over the cerebellum induce bidirectional plastic changes that modulate different intracortical circuits within the contralateral M1. Intermittent TBS (iTBS), a protocol known to induce mechanisms of long-term potentiation, was found to be effective in improving ataxic gait and posture symptoms in patients with cerebellar stroke (Bonni et al., 2014). An approach based on the use of cerebellar neuromodulation tools in combination with neuromotor rehabilitation has never been tested in TBI in the chronic phase. Here we present a single case study in which we tested the effects of three weeks of iTBS applied over the lateral cerebellum coupled with neuromotor training (NT) in a patient with TBI.
Clinical case

In July 2010, a 25-year-old man with TBI following an accident in May 2010, which had resulted in a two-month comatose state, was admitted to the IRCCS Santa Lucia Foundation (SLF) for neurorehabilitation of moderate sensory-motor hemiplegia of the right side. In January 2014 (43 months after TBI) he agreed, with informed consent, to take part in the study protocol. The study received prior approval from the independent ethics committee of the SLF. Magnetic resonance imaging showed the presence of multiple areas of T2-FLAIR hyperintensity, localized bilaterally in the cortico-subcortical parieto-occipital junction and in the anterior frontal cortex with left hemispheric prevalence and in the right frontal and temporal cortex. The patient presented with a slight motor deficit on the right side as assessed using the Fugl-Meyer Assessment scale (FMA motor score = 201/212) and an abnormal increase in muscle tone in the right limbs, assessed by modified Ashworth scale (shoulder adductor=1+; elbow flexor =1+; wrist flexor=0; hip adductor=2; knee extensor=1+; ankle planter flexor=1); he also showed altered light touch sensitivity on the right side (FMA light touch sensory score =4/8), and difficulties in maintaining balance both statically and dynamically as assessed using the Berg Balance Scale (BBS) (score=47/56).

Materials and methods

For three weeks, the patient underwent, at the same time each morning (5 days per week, Monday to Friday), two sessions of iTBS applied over the right lateral cerebellum with a five-minute pause between the two sessions. Immediately after iTBS the patient performed a 45-minute NT session. In order to monitor the effect of iTBS-NT on motor recovery several clinical scales and gait analysis (GA) were administered by blinded raters before (T0) and after the treatment (T1).

Cerebellar intermittent theta burst stimulation

A MagStim Super Rapid magnetic stimulator (Magstim Company, Witland, Wales, UK), connected to a figure-of-eight coil with a diameter of 70 mm, was used to deliver iTBS. This consisted of 20 trains of stimuli with an inter-train pause of 8 seconds. Each train consisted of 10 bursts repeated at 5 Hz (200 milliseconds between each burst); each burst consisted of 3 pulses at 50 Hz (20 milliseconds between each pulse). Overall, 600 pulses were delivered in 190 seconds; the stimulus intensity was set at 80% of the active motor threshold (AMT). iTBS was applied over the right cerebellum (1 cm inferior to and 3 cm right of the inion) (Théoret et al., 2001). AMT was set at the lowest intensity able to produce a motor evoked potential <200 μV in at least five out of ten trials in which the subject performed a 10% of maximum contraction using visual feedback (Rossini et al., 1996).

Electromyographic activity was recorded from the contralateral first dorsal interosseous muscle, using two Ag-AgCl electrodes in a belly tendon montage, amplified with a Digitimer D360 amplifier (Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK) through filters set at 20 Hz and 2 kHertz, with a sampling rate of 5 kHz; the electromyography was then recorded using SIGNAL software (Cambridge Electronic Devices, Cambridge, UK).

Neuromotor training

The NT was designed to promote recovery of voluntary motor function of the right side and recovery of static and dynamic balance through: i) progressive neuromuscular facilitation training for the right limbs (Kraft et al., 1992); ii) tactile and proprioceptive discrimination training; iii) motor control exercises for the trunk; iv) proprioceptive training of load modulation in orthostatic position and during gait.

Clinical assessment

The FMA (for the right side) (Fugl-Meyer et al., 1975), the BBS (Berg et al., 1995), the Jebsen-Taylor Hand Function test (JHFT) (for the right side) (Jebsen et al., 1969), and GA were used to assess the effects of the combined rTMS-NT. We calculated the percentage of change between T0 and T1 applying the following formula \[ \text{([T1 score − T0 score]/total scale score x 100)} \] for clinical scores. The GA system was an optoelectronic device consisting of a rectangle (6 m x 1.5 m) made up of infrared light-emitting and receiving bars (forming an infrared matrix with each cell measuring 1.04 x 1.04 cm²) and a wireless tri-axial accelerometer located at L2-L3 level (Optogait® with the inertial unit Gyko, Microgate, Italy; sampling frequency=200 Hz). The optoelectronic bars provided information on spatiotemporal gait parameters, whereas root mean square acceleration values along the three body axes provided information about trunk stability during walking. The patient was asked to walk back and forth four times along a 6-m walkway and we analyzed the complete steps performed in the central sensorized part (4 m long) of this walkway. The number of recorded and analyzed steps was 56 at T0 and 44 at T1. Spatiotemporal data were analyzed by SPSS 17.0 using an unpaired t-test to compare steps performed at T0 vs steps performed at T1.

Results

The FMA score increased (T0=201/212; T1=204/212; +1.41%) in relation to motor recruitment in the lower limb (T0=28/34; T1=30/34; +5.90%) and upper limb (T0=65/66; T1=66/66; +1.51%). The BBS score showed an increase after combined rTMS-NT (T0=47/56; T1=53/56; +10.72%). The JHFT execution time decreased after combined rTMS-NT (T0=11.28 sec; T1=10.70 sec; −5.14%) (Table I). In the JHFT a negative percentage is predictive of a better outcome. As for the GA, at T1 the walking speed increased (T0=...
0.87±0.06 vs T1=0.91±0.04 m/sec, p<0.001), due to an increase in right step length (T0=50.4±7.2 vs T1=53.8±2.2 cm, p<0.001) (Fig. 1). Indeed, no significant effect was found for left step length (p=0.103). Despite the increase in speed, trunk accelerations did not increase (p>0.05, along all three axes).

Discussion

Motor and cognitive recovery after severe TBI is greatest in the first few weeks until the tenth week, when it reaches its maximum limit. After the tenth week there tends to be no further motor recovery, with motor performance remaining almost stationary (Hart et al., 2014).

In the present case, we found that a three-week treatment with cerebellar iTBS combined with NT was able to improve motor and balance functions almost four years after TBI. We suggest that modulation of the cerebellar circuits involved in motor learning and motor control might have facilitated motor recovery and balance performance in this patient. Upper and lower limb motor improvements could be explained by the role of the cerebellum in movement execution and motor control and its connections with the M1 through the CTC pathway (Groiss and Ugawa, 2013). At the end of three weeks of combined treatment the patient showed enhanced motor performance of the impaired lower limb. The motor recovery of the lower limb was reflected in improvements observed in the gait parameters (i.e. gait speed and right step length) and in static and dynamic balance. Balance improvement may result from direct modulation of cerebellar areas. Although it is known that midline regions of the cerebellum play a role in the control of static balance and locomotion, the lateral cerebellum also contributes to bipedal locomotion control and adjustment of locomotor pattern in novel contexts or when strong visual guidance is required. Morton and Bastian (2006) have suggested that the cerebellum plays a role in the generation of appropriate patterns of limb movements, dynamic regulation of balance, and adaptation of posture and locomotion through practice. We can suppose that in our patient, the lateral cerebellum stimulation coupled with neuromotor exercises engaged the motor networks involved in these abilities and optimized the effects of a standard treatment. Finally, the acquisition of new gait movement patterns may be due to the cerebellar motor learning function. Lateral por-

Table I - Motor assessment pre-treatment (T0) and post-treatment (T1).

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>T1</th>
<th>Improvement</th>
<th>Maximal score</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMA</td>
<td>201</td>
<td>204</td>
<td>+1.41%</td>
<td>212</td>
</tr>
<tr>
<td>BBS</td>
<td>47</td>
<td>53</td>
<td>+10.72%</td>
<td>56</td>
</tr>
<tr>
<td>JHFT (time in sec)</td>
<td>11.28</td>
<td>10.70</td>
<td>-5.14%</td>
<td>56</td>
</tr>
<tr>
<td>FMA UE (motor)</td>
<td>65</td>
<td>66</td>
<td>+1.51%</td>
<td>66</td>
</tr>
<tr>
<td>FMA UE (sensory)</td>
<td>10</td>
<td>10</td>
<td>0%</td>
<td>12</td>
</tr>
<tr>
<td>FMA LE (motor)</td>
<td>28</td>
<td>30</td>
<td>+5.90%</td>
<td>34</td>
</tr>
<tr>
<td>FMA LE (sensory)</td>
<td>10</td>
<td>10</td>
<td>0%</td>
<td>12</td>
</tr>
<tr>
<td>FMA (passive motion and pain)</td>
<td>88</td>
<td>88</td>
<td>0%</td>
<td>88</td>
</tr>
</tbody>
</table>

Abbreviations: FMA=Fugl-Meyer Assessment scale; BBS=Berg Balance Scale; JHFT=Jebsen-Taylor Hand Function Test; UE=upper extremity; LE=lower extremity.
tions of the cerebellar hemispheres, ventrolateral regions of the deep cerebellar nuclei, the mediodorsal nucleus of the thalamus and the cortical areas 9 and 46 are thought to be components of a cerebral-cerebellar circuit which interconnects neo-cerebellar regions and the prefrontal cortex. This circuit is active during the learning of new motor sequences (Middleton and Strick, 2000). Cerebellar iTBS could likely have enhanced the above-mentioned interconnected brain areas (Oliveri et al., 2005).

Although our results refer to a single case, they provide initial, preliminary evidence supporting the efficacy of an approach that combines non-invasive cerebellar brain stimulation tools and neurorehabilitation in motor and balance recovery in chronic TBI. Further studies, in larger samples and including more neurophysiological measurements, are needed to investigate the effects of this combined approach in driving cortico-cortical reorganization and to characterize the neurophysiological mechanisms involved in motor and balance function recovery in TBI in the chronic phase.

References


