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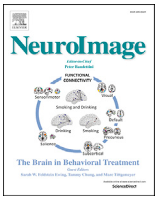

Improving visuo-motor learning with cerebellar theta burst stimulation: Behavioral and neurophysiological evidence

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ABSTRACT

The cerebellum is strongly implicated in learning new motor skills. Theta burst stimulation (TBS), a form of repetitive transcranial magnetic stimulation, can be used to influence cerebellar activity. Our aim was to explore the potential of cerebellar TBS in modulating visuo-motor adaptation, a form of motor learning, in young healthy subjects. Cerebellar TBS was applied immediately before the learning phase of a visuo-motor adaptation task (VAT), in two different experiments. Firstly, we evaluated the behavioral effects of continuous (cTBS), intermittent (iTBS) or sham TBS on the learning, re-adaptation and de-adaptation phases of VAT. Subsequently, we investigated the changes induced by iTBS or sham TBS on motor cortical activity related to each phase of VAT, as measured by concomitant TMS/EEG recordings. We found that cerebellar TBS induced a robust bidirectional modulation of the VAT performance. More specifically, cerebellar iTBS accelerated visuo-motor adaptation, by speeding up error reduction in response to a novel perturbation. This gain of function was still maintained when the novel acquired motor plan was tested during a subsequent phase of re-adaptation. On the other hand, cerebellar cTBS induced the opposite effect, slowing the rate of error reduction in both learning and re-adaptation phases. Additionally, TMS/EEG recordings showed that cerebellar iTBS induced specific changes of cortical activity in the interconnected motor networks. The improved performance was accompanied by an increase of TMS-evoked cortical activity and a generalized desynchronization of TMS-evoked cortical oscillations. Taken together, our behavioral and neurophysiological findings provide the first-time multimodal evidence of the potential efficacy of cerebellar TBS in improving motor learning, by promoting successful cerebellar-cortical reorganization.

1. Introduction

Learning new motor skills is crucial in everyday life, allowing us to adapt to novel external environmental demands. Newly learned motor abilities are formed and coded by a large cortical-subcortical network involving mainly the cerebellum (Ramnani, 2006; Ito, 2006). This notion is supported by studies in patients with cerebellar lesions, showing a pronounced impairment in their ability to learn new motor skills. These patients are particularly impaired in adapting to novel perturbations (Smith et al., 2005; Criscimagna-Hemminger et al., 2010) revealing that the activity of the cerebellum is crucial during the feedforward process required for successful motor adaptation (Imamizu et al., 2000).

Visuo-motor adaptation task (VAT) evaluates a specific form of motor learning, which refers to the error reduction occurring in response to a novel perturbation (Krakauer, 2009). During the initial training, when the perturbation is brought into the task, the direction of the movement is initially skewed and the subject is not able to reach accurately the target. After few trials, the movement becomes progressively more accurate and the directional errors smaller. In this phase, lasting several trials, the subjects continue to adapt to the external perturbation, improving constantly their performance until they are able to adjust well their motor performance to the novel condition. Thus, new internal models are formed or modified (learning phase). This improvement is then

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Abbreviations

TBS	theta burst stimulation
VAT	visuo-motor adaptation task
iTBS	intermittent theta burst stimulation
cTBS	continuous theta burst stimulation
TMS	transcranial magnetic stimulation
tDCS	transcranial direct current stimulation
LTP	long-term potentiation
LTD	long-term depression
AMT	active motor threshold
RMT	resting motor threshold
EEG	electroencephalography
MRI	magnetic resonance imaging
TEP	TMS-evoked potential
TRSP	TMS-related spectral perturbation

maintained when the performance is tested again in a second session (re-adaptation phase). Such after-effects represent a memory trace of the newly formed internal models and the level of achieved adaptation, which normally decays with time. Moreover, in this case the performance is also influenced by the ability of quickly selecting the appropriate internal model. In fact, during successive experiences with the same perturbation, the previously acquired internal models need to be retrieved proficiently in order to achieve faster re-adaptation, resulting in precise movement planning and small directional errors (Kitago et al., 2013; Moisello et al., 2015). Finally, when subjects are reintroduced to a condition where the visual transformation is removed, an error in the opposite direction to the perturbation is observed with this fading over subsequent trials (de-adaptation phase). The magnitude of this aftereffect is influenced by the retention of the acquired visuomotor transformation.

Non-invasive brain stimulation provides the unique opportunity to modulate cerebellar functions. Recent evidence showed that anodal transcranial direct current stimulation (tDCS), which usually enhances neural activity, is able to boost the learning rate when applied over the lateral cerebellum during a VAT (Galea et al., 2011). Similar results were obtained applying anodal tDCS in other VA tasks (Block and Celnik, 2013; Cantarero et al., 2015; Hardwick and Celnik, 2014), involving locomotor adaptation (Jayaram et al., 2012), or saccade adaptation (Panouillères et al., 2015). Thus, it has been hypothesized that cerebellar tDCS could restore functions in patients with cerebellar-related disorders (Grimaldi et al., 2014). However, recent studies highlighted the absence of evidence for cerebellar tDCS-induced effects on motor learning (Verhage et al., 2017; Steiner et al., 2016), thereby questioning the potential of this technique in the context of upcoming clinical applications.

Cerebellar transcranial magnetic stimulation (TMS) is another reliable method to investigate cerebellar functions (Grimaldi et al., 2014) when the stimulation threshold, current direction and stimulation site are precisely defined (Ugawa et al., 1995; Del Olmo et al., 2007). Several pieces of evidence show that the neural activity of the cerebellum can be strongly modulated by means of a specific form of repetitive TMS, defined theta burst stimulation (TBS) (Koch, 2010). TBS has been originally tested in the human primary motor cortex (M1) as a form of repetitive TMS mimicking protocols inducing in animal models long-term potentiation (LTP) or long-term depression (LTD) in the hippocampus (Huang et al., 2005). In animal models, TBS patterns also induce forms of LTP and LTD in the cerebellum, both at the mossy fiber - granule cells synapse and at the parallel fiber - Purkinje Cell synapse (D'Angelo, 2014). TBS has been applied in humans over the posterior cerebellum (lobules VII-VIII) (Del Olmo et al., 2007; Koch et al., 2008; Popa et al., 2010), which is a key node of a cerebello-thalamo-cortical pathway involved in sensory–motor tasks (O'Reilly et al., 2010; Stoodley, 2012; Koch, 2010). While continuous TBS (cTBS) induces long-lasting inhibition of the posterior lateral cerebellum, intermittent TBS (iTBS) exerts the opposite effect, increasing cerebellar excitability, as shown by remarkable changes occurring in neural activity of interconnected parieto-frontal networks (Koch et al., 2008, 2010; Casula et al., 2016; Halko et al., 2014; Rastogi et al., 2017).

Moreover, cerebellar TBS has also been tested in the context of various motor tasks, being able to modulate saccadic eye movement adaptation (Colnaghi et al., 2011, 2017a; 2017b), eye blink classical conditioning (Hoffland et al., 2012; Monaco et al., 2014) and body sway (Colnaghi et al., 2017c).

These studies demonstrate the efficacy of TBS in modulating cerebellar activity, supporting its potential use for clinical applications. Our group recently provided evidence that cerebellar TBS can be used in the field of movement disorders and stroke recovery with very encouraging results (Koch et al., 2009, 2014; 2018; Brusa et al., 2012, 2014; Bonnì et al., 2014).

Here we investigated the effects of cerebellar TBS in modulating visuo-motor adaptation in healthy subjects. We hypothesized that cerebellar cTBS would slow the learning rate of the VAT, while cerebellar iTBS would enhance it, and that such modulations would also be evident in the subsequent re-adaptation phase. Moreover, starting from recent evidence that cerebellar TBS modulates the neural activity of interconnected cortical areas (Casula et al., 2016), and a wide range of cognitive functions, by enhancing the temporal complexity of distributed brain networks (Farzan et al., 2016), we explored the neurophysiological correlates (in terms of cortical excitability and oscillatory activity changes) of the behavioral changes induced by cerebellar TBS on visuo-motor adaptation, by using a novel TMS and electroencephalography combined approach (TMS-EEG).

2. Materials and methods

2.1. Participants

Thirty-six healthy subjects (20 females, mean age: 26.2 ± 3.9 years) took part in Study 1 (see below) and twelve healthy subjects (6 females, mean age 25.6 ± 2.9 years) were enrolled for Study 2 (see below). All subjects were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971), with normal or corrected-to-normal vision and did not report TMS exclusion criteria (Rossi et al., 2009).

2.2. Study design

This study was approved by the local IRB and conducted according to the Declaration of Helsinki. All subjects provided written informed consent. In Study 1 performed with a between-subjects design, the participants were randomly assigned to three age-matched groups, receiving iTBS ($n = 12$), cTBS ($n = 12$) or sham TBS ($n = 12$) over right cerebellum before the learning phase of VAT. In Study 2, performed with a within-subject design, twelve participants (different from those recruited in Study 1) underwent two experimental sessions in which they received iTBS or sham TBS over right cerebellum before the learning phase of VAT. Each session was planned at least 1 week apart and the session order was counterbalanced among participants. Specifically, six subjects were first tested with iTBS and then Sham, whereas in the others six the order of the two conditions was reversed. TMS-EEG recordings were performed before the task (baseline), after the learning phase and after the re-adaptation phase. Fig. 1 depicts the experimental design for both the studies.

2.3. Visuomotor adaptation task (VAT)

Participants sat in a chair about 70 cm away from a computer screen (size: 37 cm × 24 cm) on which the task was presented and were asked to hold with right hand a joystick (low profile contactless joystick, APEM 9000 Series, RS Components) fixed to a table. Due to a shield that

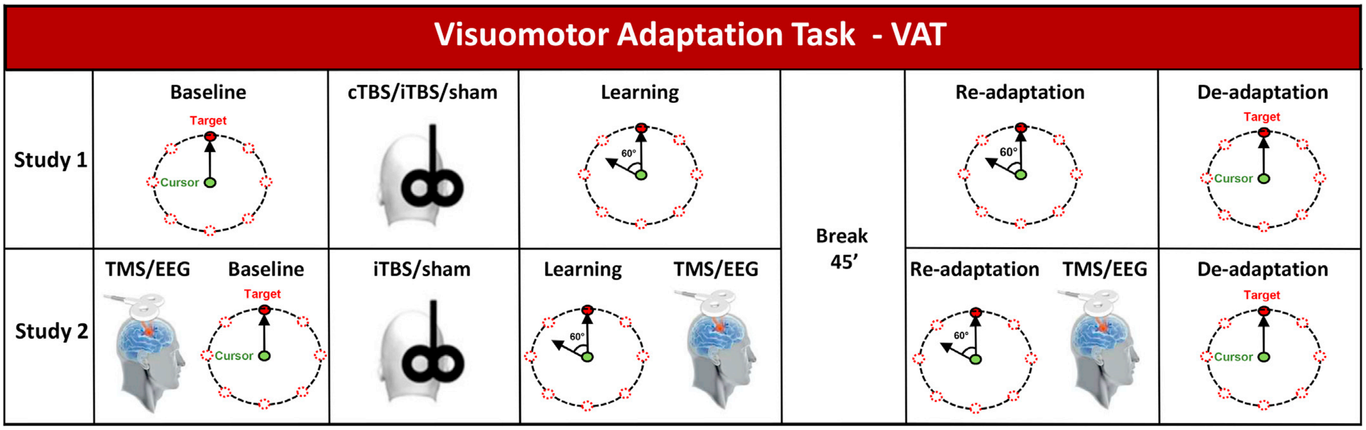

Fig. 1. Schematic representation of the study design. The visuo-motor adaptation task (VAT) was composed of four phases: baseline, learning, re-adaptation and de-adaptation. In the baseline and de-adaptation phases, the movements of the green cursor followed the exact path of the joystick movement. For the learning and re-adaptation phases, the movement of the green cursor was rotated by 60° counterclockwise relatives to the joystick movement. The red target was presented randomly to one of 8 equidistant positions located on the dashed line circle. TBS was delivered over right cerebellum, before the learning phase of VAT. In Study 1, the participants were randomly assigned to receive iTBS, cTBS or sham TBS, whereas in Study 2, the participants received iTBS or sham TBS in two separate sessions and TMS-EEG recordings were performed at baseline, after the learning and the re-adaptation phases.

covered the joystick, the subjects were not able to see their hand during the task, but were able to control it. With the movements of the joystick (sampling rate: 60 Hz), a green cursor (diameter: 0.3 cm) was moved on the computer screen. The goal of the task was to follow a red target (diameter: 0.3 cm) initially presented at the centre of the screen that quickly jumped to one of eight equidistant positions, separated by 45° located at the perimeter of a visible circle (radius: 4.6 cm). The red target was presented in the centre of the screen for 750 ms, and then jumped to a randomly selected peripheral position and stayed in this location for a further 750 ms. Targets were presented pseudorandomly so that every set of eight consecutive trials included one of each of the target positions.

Each trail started with the green cursor in the centre of the screen. Participants were instructed to move toward the red target and back in a single and straight motion without correcting for initial errors, and were reminded to move as quickly as possible in response to the cue. They did not have to stop on the target but were instructed to pass through it and then to release the joystick so that the green cursor could return to the centre of the screen, before the next trial.

The task was composed of four phases: baseline, learning, re-adaptation and de-adaptation. During the baseline, all participants performed 48 trials in which the direction of movement of the green cursor matched the movement of the joystick. After a 1-min break, a learning phase began. During this period, the relationship between the movement of the joystick and the cursor was altered so that the cursor moved with a -60° deviation relative to the joystick (152 trials). Participants were not told that a deviation would occur, but they were warned that they could find something different in the learning phase and it was important to continue to make straight, striking motions as in the baseline phase. After the learning phase, the participants took a 45-min break. Subsequently, a re-adaptation phase was performed by each subject, that was retested with the same -60° deviation (152 trials). Finally, a de-adaptation phase (152 trials) was conducted in which the veridical relationship between cursor and target (i.e., the angular deviation) was restored and returned to the baseline.

2.4. *Theta burst stimulation (TBS)*

TBS protocols were carried out using a Magstim Rapid stimulator (Magstim Company, Whitland, UK) and a 70 mm figure-of-eight coil. TBS stimulation intensity was set at 80% of the active motor threshold (AMT), defined as the lowest intensity which evoked at least five out of ten MEPs with an amplitude $> 200\ \mu$ V peak-to-peak in the first dorsal interosseous (FDI) muscle during 10% of maximum contraction (Rothwell, 1997).

The cTBS protocol consisted of three-pulse bursts at 50 Hz repeated every 200 ms for 40 s, whereas in the iTBS protocol a 2 s train of TBS was repeated 20 times, every 10 s for a total of 190 s (Huang et al., 2005). TBS was applied over the lateral cerebellum, i.e. 1 cm inferior and 3 cm right to the inion (Koch et al., 2008). The coil was positioned tangentially to the scalp, with the handle pointing superiorly; for sham TBS, it was angled away so that no current was induced in the brain (Koch et al., 2009). More specifically, in Study 1 sham TBS was delivered with continuous pattern in the half of the subjects, whereas the others received it with intermittent pattern. In Study 2 all the subjects received sham TBS with an intermittent pattern.

2.5. *TMS/EEG recordings*

In the TMS-EEG recordings, a Magstim Rapid stimulator connected to one booster module and a standard figure-of-eight shaped coil with an outer winding diameter of 70 mm (Magstim Company, Whitland, UK) were used. Eighty single TMS pulses were applied at an inter-stimulus interval of 2–4 s with a random variation of 20%. The intensity of stimulation was set at 90% of the resting motor threshold (RMT). The TMS coil was positioned over the left M1. To ensure the same stimulation conditions during the entire experiment and across each recording session, coil positioning and orientation on the optimal hotspot were constantly monitored by means of the Softaxic neuronavigation system (EMS, Bologna, Italy), coupled with a Polaris Vicra infrared camera (NDI, Waterloo, Canada) (Carducci and Brusco, 2012). In order to mask the click and avoid possible auditory responses during TMS-EEG recordings, each participant wore in-ear plugs which continuously played a white noise, that reproduced the specific time-varying frequencies of the TMS click. The volume of the white noise was set for each participant, until the participant was sure that he/she could no longer hear the TMS click. A TMS-EEG equipment (BrainAmp 32MRplus, BrainProducts GmbH) was used to record the cortical activity from 64 TMS-compatible Ag/AgCl pellet electrodes mounted on the cap according to the 10–20 international system. EEG signal was bandpass filtered at 0.1–1000 Hz and the sampling frequency was 5000 Hz.

3. Data processing and statistical analysis

3.1. Behavioral analysis

Behavioral data were analyzed on a trial-by-trial basis using semi-automated-in-house code written in MATLAB. We calculated the movement error as the angular difference between a straight line from the start position to the target and the position of the cursor at peak velocity. For each VAT phase, we clustered the trials into contiguous blocks of 8 trials (Epochs).

Thus, baseline phase consisted of 6 Epochs, while learning, re-adaptation and de-adaptation phases consisted of 19 Epochs each. The automated calculation of angular error was checked by the operator trial-by-trial. Individual trials exceeding over the 2 standard deviations of the mean of each epoch were rejected (about 5% of trials).

Considering the experimental designs, characterized by repeated measures for each subject, and the data error distribution (slightly positively skewed), Generalized Linear Mixed Models (GLMMss) for Gamma distributed data and with log link-function were applied for the two studies. In detail, GLMMs were performed for baseline and VAT phases (learning, re-adaptation, de-adaptation) with averaged angular error as dependent variable and Session order (iTBS, Sham) -when present-, Stimulation Groups (sham, cTBS, iTBS), Epochs and Stimulation Groups × Epochs interaction as independent variables (fixed effect).

We also analyzed motor adaptation data by fitting with exponentials curves the individual angular errors within each VAT phase (Huang et al., 2011; Krakauer et al., 2005; Joundi et al., 2012). Thus, following the within-block outlier rejection described above, individual trials in each session for every subject were fitted with a single exponential function:

$$y = C1 * \exp(-rate * x) + C_0$$

where C1 and C_0 are constants, x is the trial number, and y is the error. The 'rate' variable provided an index for "adaptation" in terms of rate of error reduction. When an interaction was found, post hoc tests with Sidak adjustments were then used to evaluate group differences in each VAT phase, with significant p value set at <0.05.

3.2. TMS-evoked cortical activity analysis

TMS-EEG data were analyzed off-line with BrainVision Analyzer 2 and EEGLAB 13.4.4 (Delorme and Makeig, 2004), running in a MATLAB environment. As first step of data processing, the TMS artifact induced by pulse delivery was removed using a cubic interpolation for a conservative interval from −1 to 10 ms after the pulse. Subsequently, the identification of artifacts unrelated to TMS (e.g. eye blinks, muscle activity) was made using independent component analysis (INFOMAX ICA) applied to the continuous EEG signal. Identified components were then visually inspected in terms of scalp distribution, frequency, timing, amplitude and then removed. The continuous EEG signal was average re-referenced, downscaled (1000 Hz), and then band-pass filtered (1 and 80 Hz, Butterworth zero phase filters, with a 50 Hz notch filter). Signal was then segmented into epochs starting 1 s before the TMS pulse and ending 1 s after it. Afterwards, all the epochs were visually inspected and those with excessively noisy EEG were excluded from the analysis.

In first instance, we analyzed the cortical response to TMS in the time and spatial domains with the aim to characterize and quantify the spread of activation over the whole cortex in terms of cortical excitability, related to different phases of VAT. At this aim, we analyzed TMS-evoked potentials (TEPs) starting 100 ms before and ending 500 ms after the TMS pulse. All epochs were baseline corrected to a time period of 100 ms recorded before TMS delivery. To assess the global cortical activation induced by TMS applied over M1, four windows of interest were defined starting from the TEPs waveform, established on previous studies (e.g., Casula et al., 2016). Therefore, TEPs analysis was performed for each phase of VAT, within the following time windows after TMS pulse: 20–50 ms (P1), 50–80 ms (P2), 80–130 ms (P3), and 130–200 ms (P4).

At the same time, we investigated the TMS response in the frequency domain related to VAT phases to understand the functional specificity of brain rhythms in the visuo-motor learning. At this regard, to evaluate TMS-evoked oscillatory activity we performed a time/frequency analysis in epochs starting 1 s before to 1 s after the TMS pulse. A time/frequency decomposition based on a complex Morlet wavelet was applied in a frequency range from 2 to 45 Hz, then a TMS-related spectral perturbation (TRSP) was computed as:

$$TRSP(f,t) = \frac{1}{n}\sum_{k=1}^{n} |F_k(f,t)|^2$$

Where, for n trials, the spectral estimate F was computed at trial k, at frequency f and time t (Casula et al., 2018). TRSP provides a mixed response that captures both the phase-locked and non-phase locked oscillations following TMS (i.e., evoked and induced oscillations). We chose to evaluate the TRSP because this procedure enhances the signal-to-noise ratio of both phase-locked and non-phase-locked event-related EEG responses, thereby allowing a better and clear description of possible TMS-related transient and non-stationary modulations of oscillatory activity (Pellicciari et al., 2017). TRSP analysis was performed from 20 to 250 ms after TMS in four frequency bands: theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz) and gamma (30–45 Hz). TEPs and TRSP analysis were conducted with a non-parametric bootstrapped statistic, as implemented in EEGLAB toolbox (Delorme and Makeig, 2004). For each electrode, we performed multiple dependent t-tests comparing two surrogate distributions (of two conditions) constructed randomly by bootstrapping the original distributions for 3000 times. Then, to avoid the occurrence of false positives, we applied a False Discovery Rate correction. This correction is widely used in EEG analysis and is based on the Holms-Bonferroni correction. In brief, all of the p-values resulting from the two conditions comparison, are first sorted from the smallest to largest and assigned an index j. These p-values are singularly corrected with the Holms-Bonferroni method, so that each p-value has a critical threshold computed as 0.05/j. Then, following the FDR correction, the last significant threshold calculated using Holms-Bonferroni correction is applied as a common threshold for all the p-values. Once the significant electrodes are computed, to further reduce the occurrence of false positives, we considered as significant only the electrodes with at least one neighboring significant electrode. This means that an isolated electrode resulting significant after the bootstrapping FDR-corrected procedure, was excluded from the analysis.

4. Results

4.1. Study 1

Considering the experimental design of Study 1, GLMMs were applied with Epochs repeated within each subject, and with Epoch, Group, Epoch × Group interaction as fixed effects. Performances measured by the mean error across the baseline epochs did not show any significant difference between Groups ($F(2,198) = 0.157$, $p = 0.855$) and across Epochs ($F(5,198) = 1.30$, $p = 0.264$), and no interaction between Groups and Epochs ($F(10,198) = 1.23$, $p = 0.277$). For the learning phase, we found a significant Stimulation Group effect ($F(2,627) = 212.66$, $p < 0.001$) and a significant interaction between Stimulation Group and Epochs ($F(36,627) = 3.34$, $p < 0.001$). Finally, a significant Epochs effect was observed ($F(18,627) = 96.45$, $p < 0.001$). Similarly, during the re-adaptation phase we found a significant Group effect ($F(2,627) = 254.45$, $p < 0.001$), a significant Epochs effect ($F(18,627 = 40.05$, $p < 0.001$), and a significant interaction between Group and Epochs ($F(36,627) = 3.24$, $p < 0.001$).

Post hoc revealed a significantly increased mean angular error for cTBS respect to sham group in both learning ($p < 0.001$) and re-adaptation phases ($p = 0.001$). On the contrary a significant decrease of mean angular error was observed for iTBS respect to sham group, in both learning ($p < 0.001$) and re-adaptation phases ($p < 0.001$). Additionally, a significant decreased mean angular error was observed when we compared iTBS and cTBS groups, in both learning ($p < 0.001$) and re-adaptation phases ($p < 0.001$). During de-adaptation phase, we found a significant Epoch effect ($F(18,627) = 82.75$, $p < 0.001$) but we did not find any significant Stimulation Group effect ($F(2,627) = 0.750$, $p = 0.473$) or interaction ($F(36,627) = 0.65$, $p = 0.947$).

Furthermore, we evaluated the motor adaptation by fitting curves to each subject's individual trials estimating the rate of error reduction. Fig. 2A shows the average of individual exponential curves overlaid on the mean ± SEM trial blocks. The ANOVA of error rate reduction between groups (iTBS, cTBS, sham) showed a significant difference in learning ($F(2,33) = 14.24$, $p < 0.001$) and re-adaptation ($F(2,33) = 26.93$, $p < 0.001$) phases. Then, multiple comparison test demonstrated a significant higher rate of error reduction for the iTBS respect to both sham and cTBS group in learning (iTBS vs sham: $t(22) = 3.07$, $p = 0.005$; iTBS vs cTBS: $t(22) = 4.31$, $p = 0.003$) and re-adaptation (iTBS vs sham: $t(22) = 4.43$, $p = 0.0002$; iTBS vs cTBS: $t(22) = 4.31$, $p < 0.001$). No significant difference between groups was found for de-adaptation phase ($p > 0.05$) (Fig. 2B).

4.2. Study 2

4.2.1. Behavioral performance

Considering the within-subjects design of the Study 2, GLMMs were applied with Epoch X Group repeated measures within subject and with Session order, Epoch, Group, Epoch X Group as fixed effects. There was no significant difference in mean error in the baseline epochs between Stimulation Groups ($F(1,131) = 2.70$, $p = 0.103$), across Epochs ($F(5,131) = 1.34$, $p = 0.253$), across Session order ($F(1,131) = 1.57$, $p = 0.213$) and no interaction between Groups and Epochs ($F(5,131) = 0.88$, $p = 0.498$). In the learning phase, GLMM showed an iTBS-induced modulation effect on the ability to adapt to the visuo-motor rotation. In fact, the iTBS Stimulation Group significantly decreased angular error within this VAT phase (Stimulation Group effect: $F(1,417) = 160.31$, $p < 0.001$; Epochs effect: $F(18,417) = 76.28$; $p < 0.001$). In addition, also Session order ($F(1,417) = 14.35$, $p < 0.001$) and interaction between Stimulation Group and Epochs ($F(18,417) = 13.70$; $p < 0.001$) were found significant. In the re-adaptation phase, we observed an iTBS-induced modulation effect as highlighted by a significant Stimulation Groups effect ($F(1,417) = 179.69$, $p < 0.001$). A significant Epochs effect was also observed ($F(18,417) = 14.97$, $p < 0.001$). Moreover, we observed a significant trend in the interaction between Stimulation Groups and Epochs ($F(18,417) = 1.48$, $p = 0.092$), while no significant effect was observed for Session order ($F(1,417) = 1.24$, $p = 0.266$). During de-adaptation phase, we found significant Stimulation Groups ($F(18,417) = 6.26$, $p = 0.013$) and Epoch ($F(18,417) = 35.59$, $p < 0.001$) but no the interaction Groups X Epoch ($F(18,417) = 1.28$, $p = 0.200$) and Session order effect ($F(1,417) = 2.26$, $p = 0.133$).

Fitting curves analysis estimating the rate of adaptation is shown in Fig. 3A. Subjects showed a higher adaptation rate after iTBS protocol respect to sham in both learning ($t(22) = 2.08$, $p = 0.04$) and re-adaptation phases ($t(22) = 2.19$, $p = 0.03$), but not in de-adaptation phase ($t(22) = 0.90$, $p = 0.37$) (Fig. 3B).

4.2.2. TMS-evoked cortical excitability

After cerebellar iTBS, we observed a significant difference in late component of TEP (P4), between baseline and learning phase. Specifically, TEPs were higher after learning phase with a specific topographical change in the right fronto-parietal electrodes ($p < 0.01$) (Fig. 4A). A similar cortical pattern persisted also comparing learning and re-

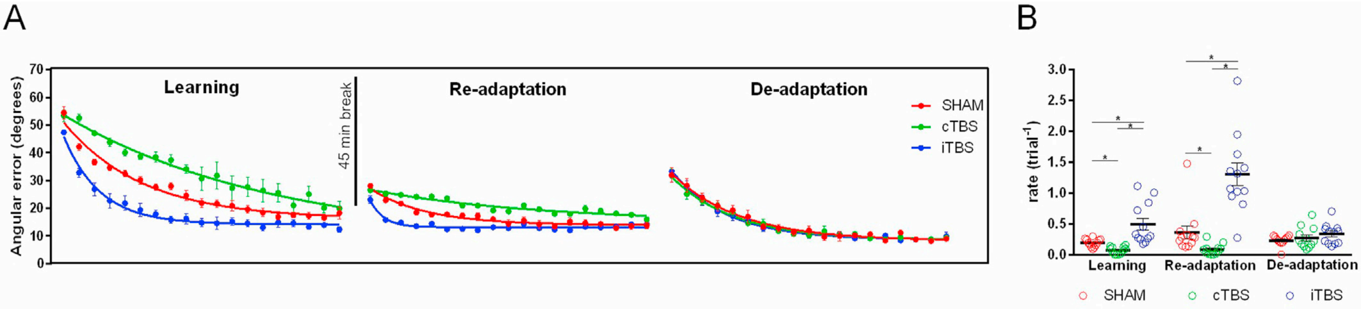

Fig. 2. Study 1. A) Curve fitting analysis of the single exponential adaptation curves for each VAT phase overlaid on mean ± SEM absolute error of each epoch for iTBS (blue), cTBS (green) and sham (red) group. B) Scatterplot of individual adaptation rate. iTBS (blue) group showed significantly higher rate of adaptation than sham (red) and cTBS (green) group in the learning and re-adaptation phases but no difference during de-adaptation. *$p < 0.05$.

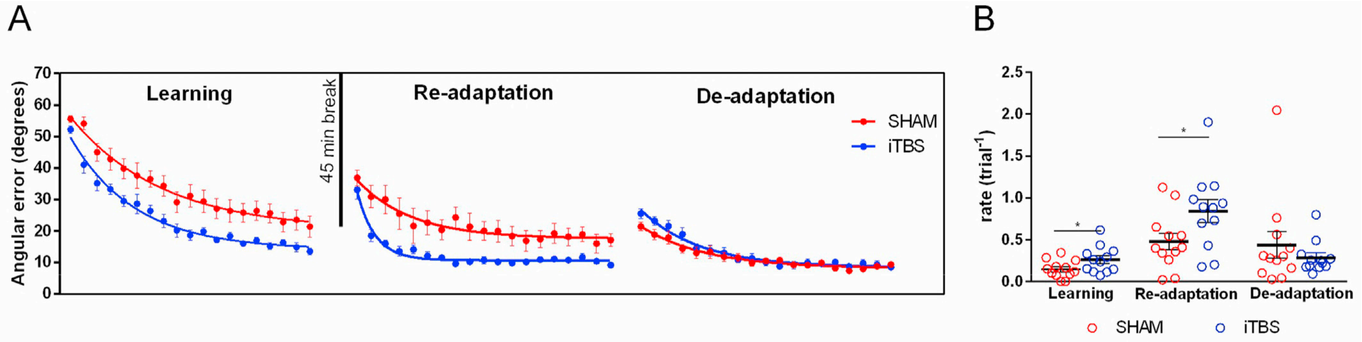

Fig. 3. Study 2. A) Curve fitting analysis of the single exponential adaptation curves for each VAT phase overlaid on mean ± SEM absolute error of each epoch in the same subjects after iTBS (blue) and sham (red) protocol. B) Scatterplot of individual adaptation rate. iTBS (blue) group showed significantly higher rate of adaptation than sham (red) in the learning and re-adaptation phases, but no difference during de-adaptation. *$p < 0.05$.

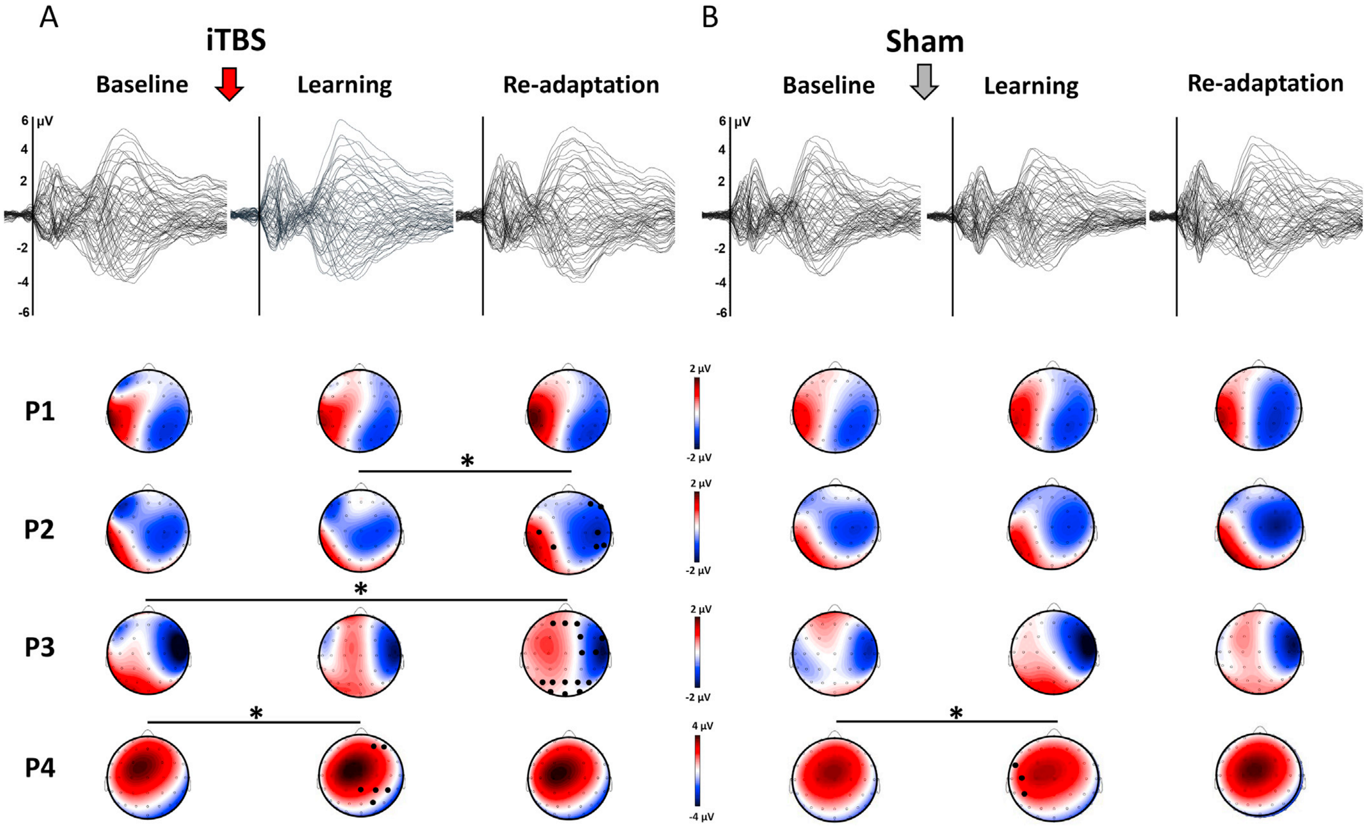

Fig. 4. Study 2. TMS-evoked potentials (TEPs) waveform with topographic scalp maps of the four mean peaks (P1, P2, P3 and P4) for each VAT phase (baseline, learning and re-adaptation). A) iTBS and B) Sham TBS were delivered before the learning phase of VAT. Black lines indicate when significant differences in the direct comparison among each VAT phase were detected, whereas black dots indicate a significant change of TEPs amplitude. $*p < 0.01$.

adaptation phase, with an excitability increase in the early TEP component (P2), localized bilaterally over the motor cortices ($p < 0.01$). Moreover, a widespread modulation of cortical excitability in the middle component of TEPs (P3) was observable when baseline and re-adaptation phases were compared, with a TEPs amplitude increase over the left and middle fronto-central electrodes ($p < 0.01$), paralleled by a contralateral decrease in several right fronto-central electrodes ($p < 0.01$) and bilaterally over the parietal-occipital sites ($p < 0.01$). Finally, when we compared baseline and learning phase after sham TBS, a local increase over the left motor cortex ($p < 0.01$) was observed in late TEPs component (P4). No difference was detected between baseline and re-adaptation phase ($p > 0.05$), as well as between learning and re-adaptation phase ($p > 0.05$) (Fig. 4B).

4.2.3. TMS-evoked cortical oscillations

Cerebellar iTBS resulted in a decrease of TMS-evoked cortical oscillations in the theta and beta frequency bands when tested after the learning phase. A decrease in TMS-evoked theta activity was evident over frontal electrodes ($p < 0.05$) and a more focused decrease in TMS-evoked beta activity over the left motor cortex ($p < 0.05$). Similar oscillatory patterns were detected after the re-adaptation phase, with a decrease of TMS-evoked cortical oscillations in theta, alpha and beta frequencies, over frontal, parietal and occipital electrodes, more evident ipsilaterally to TBS-stimulated cerebellum ($p < 0.05$) (Fig. 5A). After sham TBS, a widespread increase of TMS-evoked gamma activity was observed both in learning and re-adaptation phase as compared to baseline (all ps $<$ 0.05). No further effects were revealed after sham TBS (all ps $>$ 0.05) (Fig. 5B).

5. Discussion

We show here that cerebellar TBS is able to exert a robust bidirectional modulation of the VAT performance. Our results indicate that cerebellar iTBS accelerates visuo-motor adaptation by speeding up error reduction in response to a novel perturbation. This gain of function is still maintained when the novel acquired motor plan is tested during a subsequent phase of re-adaptation. On the other hand, cerebellar cTBS induces the opposite effect, slowing the rate of error reduction. This decreased rate of learning is still maintained in the re-adaptation phase. Moreover, cortical investigations show that the induction of LTP-like plasticity, by means of cerebellar iTBS, results in changes of cortical activity in the interconnected motor networks. The improved performance is accompanied by an increase of TMS-evoked cortical activity and a generalized desynchronization of TMS-evoked cortical oscillations. Taken together, our behavioral and neurophysiological data provide the first-time multimodal evidence of the potential efficacy of cerebellar TBS in improving motor learning, by promoting successful short-term cerebellar-cortical reorganization.

In the VAT, visual feedback is rotated from actual arm movement and the participants learn to adapt to these deviations by changing the angle of their movement. Functional magnetic resonance imaging (fMRI) investigations have demonstrated that the cerebellum plays an essential role in adaptation to visuo-motor rotation (Celnik, 2015). We believe that cerebellar iTBS could have improved VAT performance by promoting cerebellar-dependent mechanism of motor learning. In particular, we found that cerebellar TBS resulted in remarkable changes that were evident immediately after the early trials of the learning phase, when individuals were exposed to a novel visuomotor transformation during reaching. Over subsequent trials, subjects were able to adapt to the

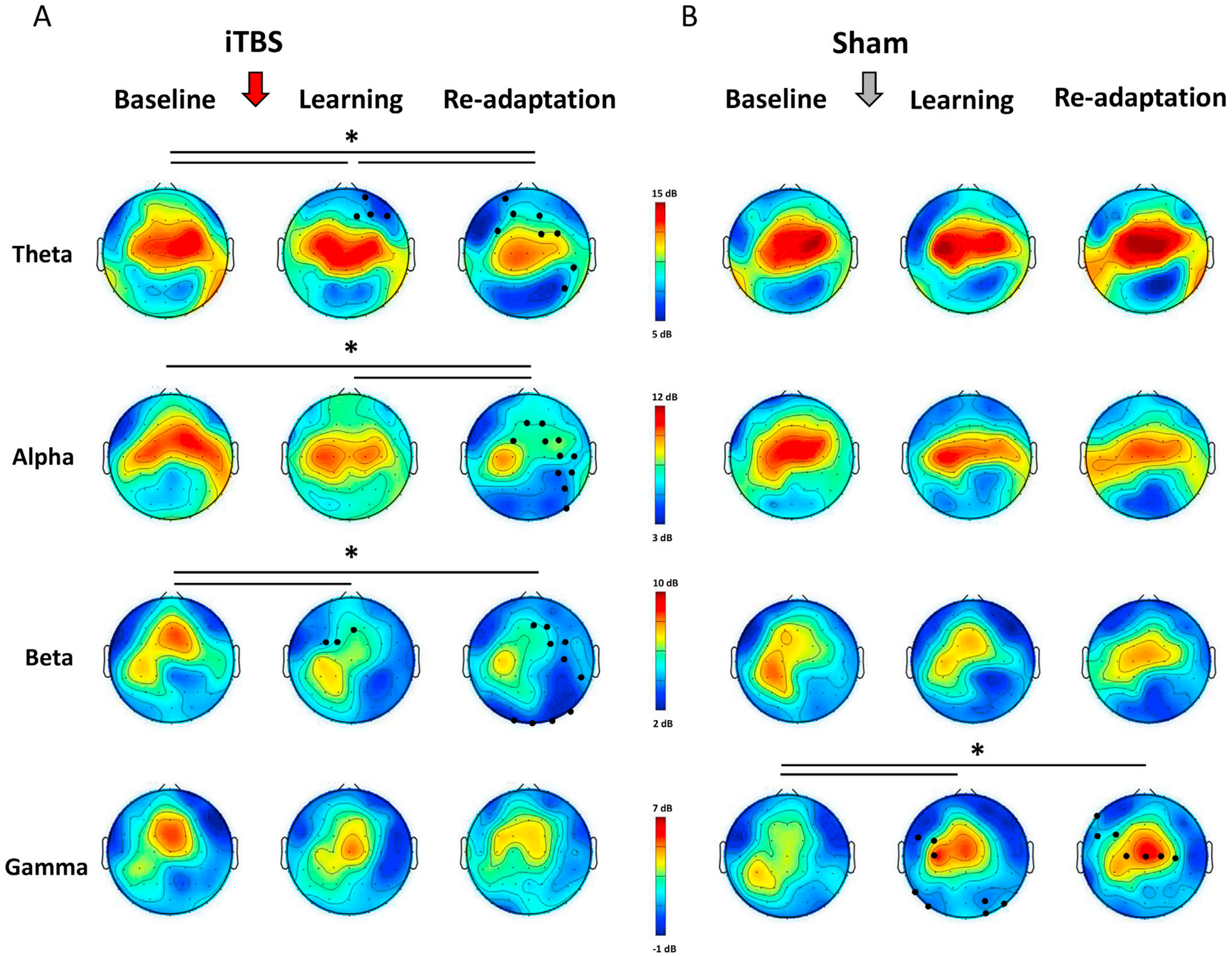

Fig. 5. Study 2. Topographic scalp maps of TMS-evoked oscillations in theta, alpha, beta and gamma band for baseline, learning and re-adaptation phases. A) iTBS and B) Sham TBS were delivered before the learning phase of VAT. Black lines indicate when significant differences in the direct comparison among each VAT phase were detected, whereas black dots indicate a significant change in the TMS-evoked cortical oscillations. $^*p < 0.05$.

perturbation and gradually reduce the error at different speed, depending on the TBS protocol adopted. This error reduction process can be interpreted as the acquisition of a novel visuomotor transformation that was influenced by cerebellar TBS. This hypothesis has been previously supported by studies performed in healthy subjects showing that anodal tDCS of the cerebellum was able to increase the rate of adaptive learning (Galea et al., 2011; Jayaram et al., 2012). Moreover, the effects of TBS were evident in the re-adaptation and de-adaptation phases of the task. These findings suggest that the effects were not transient, probably affecting the memory component of the task. This is in agreement with previous studies in which cerebellar TBS was able to modulate memory component of the eye blink classical conditioning (Monaco et al., 2014).

Our TMS/EEG data demonstrate that the induction of cerebellar plasticity by means of iTBS was associated with relevant changes in the neural activity of the contralateral M1, likely through the activation of cerebello-thalamo-cortical pathways (Caligiore et al., 2017). Although this mechanism has been mainly investigated by means of MEPs from M1 stimulation (Daskalakis et al., 2004; Koch et al., 2008; Reis et al., 2008; Ugawa et al., 1995), we recently demonstrated that it occurs in a similar manner over the posterior parietal cortex by combining TMS with EEG (Casula et al., 2016). In this view, the cerebellum could possibly control, with similar mechanisms, different cortical areas involved in complex motor and cognitive processes, such as learning novel complex motor skills (D'Angelo, 2014). In the present study, cerebellar iTBS could have promoted synaptic changes at the level of the cerebellar cortex (Koch, 2010; Casula et al., 2016; D'Angelo, 2014) with an effect on the interconnected M1. TBS is thought to stimulate the superficial layers of the cerebellar cortex. The effects of cTBS are NMDAR-dependent and are likely to involve LTP or LTD at specific synaptic connections of the granular and molecular layer, which could effectively take part in cerebellar motor learning (Colnaghi et al., 2017b). Here, we tracked for the first time, by means of TMS-EEG, the cortical changes related to learning and re-adaptation phases of VAT. A first neuronal correlate of adaptive motor learning was observable in the increase of cortical activation over the left M1, independently from cerebellar TBS. These findings are strongly in accordance with previous evidence that reported changes in task-related neuronal activity observed in M1 during motor adaptation (Wise et al., 1998).

On the other hand, boosting cerebellar activity with iTBS resulted in clear and widespread changes of TMS-evoked cortical activity related to different VAT phases. Specifically, an increased TMS-evoked cortical activity was evident after the learning phase over fronto-parietal brain regions. The pattern of cortical activation varied when the re-adaptation process was achieved, showing an increased activity over the sensorimotor cortices, likely related to the formation of a motor memory (Galea and Celnik, 2009). Thus, the increased cortical activation observed in VAT phases after cerebellar iTBS could suggest a specific role of cerebellum in motor learning (Della Maggiore et al., 2009; Krakauer et al., 2011). In a more specific manner, modulating the cerebellum could have triggered changes in the excitation-inhibition balance that characterize the cerebello-thalamo-cortical pathway (Koch et al., 2008), facilitating the learning and determining the re-adaptation in VAT.

Moreover, we observed a region-specific shift in the power of TMS-evoked cortical oscillations in all frequency bands, after cerebellar iTBS. Specifically, we found a decrease in the power of TMS-evoked oscillations ranging from theta to beta frequencies (4–30 Hz), after both learning and re-adaptation phases, mainly evident in the motor and prefrontal cortices. The modulation of oscillatory neural activity could represent a physiological mechanism underlying the faster adaptation induced by iTBS. Cerebellar iTBS could have activated low-threshold local interneurons and indirectly modulated dentate nucleus (Casula et al., 2016) with a consequent facilitatory effect on M1 during VAT (Farzan et al., 2016). According to previous evidence, the functional reduction of TMS-evoked cortical oscillations in fronto-central areas could reflect a gradual disengagement of not relevant neural resources to perform more effectively the task (Gentili et al., 2015). Our data are consistent with the idea that the cerebellum plays a critical role in promoting learning of new motor tasks, an issue that could be relevant in rehabilitative process for patients that have to re-learn simple motor strategies actively controlled by the cerebellum (Celnik, 2015).

We acknowledge some limitations of the present study. Firstly, the neurophysiological data were collected after each phase of VAT, allowing just to infer some neural correlates of visuo-motor learning. Additionally, in Study 2 we observed a significant effect of Session order in learning phase of VAT, that could point towards a learning/repetition effect. However, our results highlight in any case a relevant interaction between Stimulation Group and Epochs, that allow us to support the role of a specific cerebellar stimulation (i.e., iTBS) for inducing improvement of visuo-motor adaptation.

In addition, it is possible that the auditory or somatosensory sensation due to single-pulse TMS could have contribute to our TEPs. However, we tend to exclude that this could have affected the TMS-evoked cortical response. In fact, we used an ad-hoc masking noise able to cover the frequencies of the TMS click. As regards the somatosensory contribution, there is no direct evidence, to the best of our knowledge, that modulation of cerebellar activity can alter activity in the primary somatosensory cortex. Additionally, even if this was the case, EEG signals following stimulation in the cranio-facial region are difficult to obtain. Clear potentials have been observed only when stimulating branches of the trigeminal nerve with needle electrodes (Leandri et al., 1985; Zhu et al., 2017). Considering that when applying TMS on M1 stimulation of a nerve trunk does not occur, and that density of tactile receptors is much smaller on the scalp than in the facial area, it is very unlikely that TMS delivered over M1 induces a specific response on contralateral somatosensory areas. Finally, when a visuo-motor task is performed, a dynamic interplay between explicit and implicit learning should be considered. Cerebellum has been hypothesized to play a critical role in implicit learning, anticipating the sensory consequences of an action. However, it cannot be excluded that the cerebellum could provide some form of error signal, used by explicit learning for reducing the search space of aiming direction (Bond and Taylor, 2015). In particular, several studies have shown that explicit motor strategies contribute to learning in the contest of delayed error feedback (Brudner et al., 2016) and may promote long-term retention (Morehead et al., 2015). Nevertheless, in our task the termination of reaching movement and resultant visual feedback were simultaneous, allowing us to hypothesize a main involvement of implicit learning (Bond and Taylor, 2015; Kalmbach et al., 2009).

In conclusion, our data confirmed the initial hypothesis that by increasing the neural activity of the cerebellum is possible to improve motor learning in healthy subjects, and allow us to further support the role of cerebellar iTBS as an effective strategy to promote recovery of motor dysfunctions after brain injury (Koch et al., 2018).

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Author contribution statement

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Romina Esposito: Data curation; Investigation, Formal analysis.

Caterina Motta: Data curation; Methodology, Investigation, Software, Formal analysis, Writing-Original draft preparation, Reviewing and Editing.

Elias Paolo Casula: Data curation; Investigation, Formal analysis, Software, Reviewing and Editing.

Francesco Di Lorenzo: Investigation.

Sonia Bonnì: Investigation, Funding acquisition.

Alex Martino Cinnera: Investigation.

Viviana Ponzo: Data curation.

Michele Maiella: Data curation.

Silvia Picazio: Investigation.

Martina Assogna: Investigation.

Fabrizio Sallustio: Investigation.

Carlo Caltagirone: Supervision.

Maria Concetta Pellicciari: Methodology, Data curation; Investigation, Formal analysis, Writing-Original draft, Reviewing and Editing.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.116424.

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