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Effect of Cerebellar Stimulation on Gait and Balance Recovery in Patients With Hemiparetic Stroke
A Randomized Clinical Trial

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IMPORTANCE Gait and balance impairment is associated with poorer functional recovery after stroke. The cerebellum is known to be strongly implicated in the functional reorganization of motor networks in patients with stroke, especially for gait and balance functions.

OBJECTIVE To determine whether cerebellar intermittent θ-burst stimulation (CRB-iTBS) can improve balance and gait functions in patients with hemiparesis due to stroke.

DESIGN, SETTING, PARTICIPANTS This randomized, double-blind, sham-controlled phase IIa trial investigated efficacy and safety of a 3-week treatment of CRB-iTBS coupled with physiotherapy in promoting gait and balance recovery in patients with stroke. Thirty-six patients with consecutive ischemic chronic stroke in the territory of the contralateral middle cerebral artery with hemiparesis were recruited from a neuro-rehabilitation hospital. Participants were screened and enrolled from March 2013 to June 2017. Intention-to-treat analysis was performed.

INTERVENTIONS Patients were randomly assigned to treatment with CRB-iTBS or sham iTBS applied over the cerebellar hemisphere ipsilateral to the affected body side immediately before physiotherapy daily during 3 weeks.

MAIN OUTCOMES AND MEASURES The primary outcome was the between-group difference in change from baseline in the Berg Balance Scale. Secondary exploratory measures included the between-group difference in change from baseline in Fugl-Meyer Assessment scale, Barthel Index, and locomotion assessment with gait analysis and cortical activity measured by transcranial magnetic stimulation in combination with electroencephalogram.

RESULTS A total of 34 patients (mean [SD] age, 64 [11.3] years; 13 women [38.2%]) completed the study. Patients treated with CRB-iTBS, but not with sham iTBS, showed an improvement of gait and balance functions, as revealed by a pronounced increase in the mean (SE) Berg Balance Scale score (baseline: 34.5 [3.4]; 3 weeks after treatment: 43.4 [2.6]; 3 weeks after the end of treatment: 47.5 [1.8]; $P < .001$). No overall treatment-associated differences were noted in the Fugl-Meyer Assessment (mean [SE], baseline: 163.8 [6.8]; 3 weeks after treatment: 171.1 [7.2]; 3 weeks after the end of treatment: 173.5 [6.9]; $P > .05$) and Barthel Index scores (mean [SE], baseline: 71.1 [4.92]; 3 weeks after treatment: 88.8 [2.1]; 3 weeks after the end of treatment: 92.2 [2.4]; $P > .05$). Patients treated with CRB-iTBS, but not sham iTBS, showed a reduction of step width at the gait analysis (mean [SE], baseline: 16.8 [4.8] cm; 3 weeks after treatment: 14.3 [6.2] cm; $P < .05$) and an increase of neural activity over the posterior parietal cortex.

CONCLUSIONS AND RELEVANCE Cerebellar intermittent θ-burst stimulation promotes gait and balance recovery in patients with stroke by acting on cerebello-cortical plasticity. These results are important to increase the level of independent walking and reduce the risk of falling.

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Supplemental content

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Gait and balance impairment owing to limb deficit after stroke is one of the main determinants associated with poorer functional recovery.[1] Because gait is a critical determinant of independent living, improvement of walking function is one of the major goals of stroke rehabilitation.[2] Balance dysfunctions have substantial impact on functional independence and overall recovery.[3] However, rehabilitation of gait in patients with stroke still lacks of advanced well-defined rehabilitation protocols. The contralesional cerebellum is strongly implicated in functional reorganization of the motor network after stroke when recovery takes place.[4,5] In animal models of stroke, the stimulation of cerebellar-cortical networks was found to improve functional recovery.[6,7] Notably, functional magnetic resonance imaging studies showed that activity in contralesional cerebellum positively correlates with gait recovery in patients with stroke.[8] Patients often have to relearn simple motor strategies, a mechanism that is supposed to be actively controlled by the cerebellum.[9] These types of cerebellar-mediated motor learning can be potentiated by simultaneous application of noninvasive brain stimulation methods,[10] especially for gait and balance functions.[11] In particular, the neural activity of the cerebellum can be strongly activated by means of cerebellar intermittent θ-burst stimulation (CRB-iTBS),[12] a novel form of repetitive transcranial magnetic stimulation (TMS) that mimics protocols inducing long-term potentiation in animal models.[13-16] On the basis of this background, we hypothesized that CRB-iTBS coupled with physiotherapy (PT) could improve gait and balance recovery in patients with stroke by enhancing motor relearning and promoting favorable cortical reorganization.

Key Points

Question Is it possible to enhance gait and balance recovery in patients with hemiparesis due to stroke by using noninvasive cerebellar stimulation?

Findings In this randomized clinical trial that included 34 patients with ischemic stroke, cerebellar magnetic stimulation coupled with physiotherapy vs sham stimulation improved gait and balance functions by promoting cerebello-cortical plasticity.

Meaning Cerebellar magnetic stimulation may be an effective, low-cost, and noninvasive strategy to promote gait and balance recovery in patients with stroke.

Methods

Inclusion and Exclusion Criteria

Among 52 patients assessed for eligibility, 36 (13 women [36.1%]; mean [SD] age, 64 [11.3] years) were recruited for the study between March 2013 and June 2017 at the Santa Lucia Foundation IRCCS (**Table**). Inclusion criteria included (1) first ever chronic ischemic stroke (ie, at least 6 months after the stroke event); (2) hemiparesis due to left or right subcortical or cortical lesion in the territory of the middle cerebral artery; and (3) residual gait and balance impairment. Exclusion criteria were (1) history of seizures; (2) severe general impairment or concomitant diseases; (3) patients older than 80 years; and (4) treatment with benzodiazepines, baclofen, and antidepressants.

Trial Design and Treatments

We investigated safety and efficacy of 3 weeks of daily CRB-iTBS coupled with PT on motor recovery in a randomized, double-blind, sham-controlled phase IIa study. Clinical efficacy was assessed by the Berg Balance Scale (BBS), the Fugl-Meyer Assessment (FMA), and the Barthel Index (BI). Locomotion assessment was performed with gait analysis. We combined TMS and electroencephalogram (EEG) to determine the patterns of cortical reorganization over the posterior parietal cortex (PPC) and the primary motor cortex (M1) of both affected and unaffected hemisphere.[17] The PPC was selected being a key area of the broad fronto-parietal network involved in voluntary control of gait and balance.[18-20] Each patient performed 1 session per day of conventional PT. Physiotherapy consisted of exercises designed to promote recovery of voluntary motor and balance functions, including muscle stretching, active-assisted mobilizations, progressive neuromuscular facilitation training balance exercises, and gait training,[21] lasting 90 minutes including rest periods between exercises. During gait training, the therapist (A.M.C.) was positioned behind the patient to support hip and trunk stability. Cerebellar intermittent θ-burst stimulation was carried out using a Magstim Rapid magnetic biphasic stimulator connected with a figure-8 coil with a 70-mm diameter (Magstim Company). Before each daily PT session, 2 runs of CRB-iTBS were applied over the contralesional lateral cerebellum, spaced by an interval of 5 minutes.[12] For each stimulation session, in total, we delivered 1200 pulses over the lateral cerebellum, contralateral to the affected hemisphere.[13-16] Cerebellar intermittent θ-burst stimulation intensity was set at 80% of the active motor threshold,[22] adjusted according to the individual scalp-to-cortex distance.[23] The coil was positioned tangentially to the scalp, with the handle pointing superiorly.[24] A neuronavigation system (SofTaxic; EMS) coupled with a Polaris Vicra infrared camera was used to ensure that in each patient, CRB-iTBS was applied over the same spot across different sessions. The statistical analysis plan is available in Supplement 1, and the trial protocol is available in Supplement 2.

This study was reviewed and approved by the local institutional ethical committee on January 25, 2013, and was conducted in compliance with the Declaration of Helsinki,[25] Good Clinical Practice, and applicable regulations. All patients provided written informed consent. After the trial was completed, the trial was registered late on March 7, 2018, in the ClinicalTrials.gov site following an initial failed attempt to get approval for the European Clinical Trials Database platform through the Italian regulatory authority. We decided to register the trial to get a public registration into an internationally recognized site, in agreement with current standard scientific and ethical responsibilities and in agreement with editorial policies of most peer-reviewed international journals. Registration was completed after patient recruitment started but before data analysis began.

Randomization and Blinding

Patients were randomly assigned to 2 age-matched groups treated either with CRB-iTBS treatment (18 patients; 6 women

Table. Demographic and Clinical Information of Patients

Patient No./Sex/Age, y	Group	Stroke Lesion	AH	Time From Stroke, mo	NIHSS Score	RMT[a]	
						AH	UH
1/M/70	CRB-iTBS	F-P	Right	78	3	87	57
2/M/55	CRB-iTBS	CN	Right	6	4	96	75
3/F/44	CRB-iTBS	T-INS	Right	14	7	MEP−	56
4/F/79	CRB-iTBS	INS-T-P-CN	Right	10	6	89	81
5/F/61	CRB-iTBS	F-P	Left	13	7	MEP−	54
6/M/70	CRB-iTBS	F-P	Right	16	10	MEP−	71
7/F/74	CRB-iTBS	CN, CR	Right	6	9	MEP−	75
8/M/62	CRB-iTBS	F-INS, P-O, PUT	Right	6	10	MEP−	86
9/M/62	CRB-iTBS	F-T-P	Left	7	4	50	46
10/M/67	CRB-iTBS	F-T-P	Right	24	5	58	71
11/M/75	CRB-iTBS	F-T-P, BG	Right	29	7	62	59
12/M/77	CRB-iTBS	CN, LN	Right	6	5	71	66
13/M/56	CRB-iTBS	CR, SC	Right	7	5	MEP−	69
14/M/73	CRB-iTBS	O-T, CN	Left	7	7	82	75
15/M/49	CRB-iTBS	CN, CR	Left	6	4	65	52
16/M/58	CRB-iTBS	CR, IC	Left	6	5	80	89
17/M/45	CRB-iTBS	LN, SC	Left	6	9	MEP−	58
18/F/40	Sham iTBS	SC, CR	Left	7	4	63	72
19/M/59	Sham iTBS	F-T-P	Right	7	10	MEP−	56
20/M/64	Sham iTBS	CR, EC	Left	6	8	60	56
21/M/54	Sham iTBS	F-T-P, LN, IC	Right	13	4	60	49
22/M/64	Sham iTBS	F-P, INS, CR, BG	Left	12	8	MEP−	56
23/M/58	Sham iTBS	F-T-P	Right	5	2	59	86
24/F/50	Sham iTBS	CN	Right	7	7	MEP−	65
25/F/70	Sham iTBS	F-T, INS	Left	6	7	66	74
26/M/61	Sham iTBS	F-T-P	Left	77	11	MEP−	84
27/F/51	Sham iTBS	CN	Left	13	11	81	56
28/M/76	Sham iTBS	CN, LN	Left	6	3	MEP−	90
29/F/81	Sham iTBS	LN	Right	6	5	51	50
30/F/71	Sham iTBS	CN	Right	7	6	MEP−	65
31/M/71	Sham iTBS	CN	Right	6	4	MEP−	68
32/M/75	Sham iTBS	CN, LN	Right	6	7	54	52
33/F/78	Sham iTBS	CR, CN	Right	6	9	62	58
34/M/81	Sham iTBS	F-T-P	Left	7	10	68	60

Abbreviations: AH, affected hemisphere; BG, basal ganglia; CN, capsular nucleus; CR, corona radiata; CRB-iTBS, cerebellar intermittent θ-burst stimulation; EC, external capsula; F, female; F-T-P-O, fronto-temporal-parietal-occipital; IC, internal capsula; INS, insula; iTBS, intermittent θ-burst stimulation; LN, lenticular nucleus; M, male; MEP−, not motor-evoked potentials; NIHSS, National Institutes of Health Stroke Scale; PUT, putamen; RMT, resting motor threshold; SC, semioval center; UH, unaffected hemisphere.

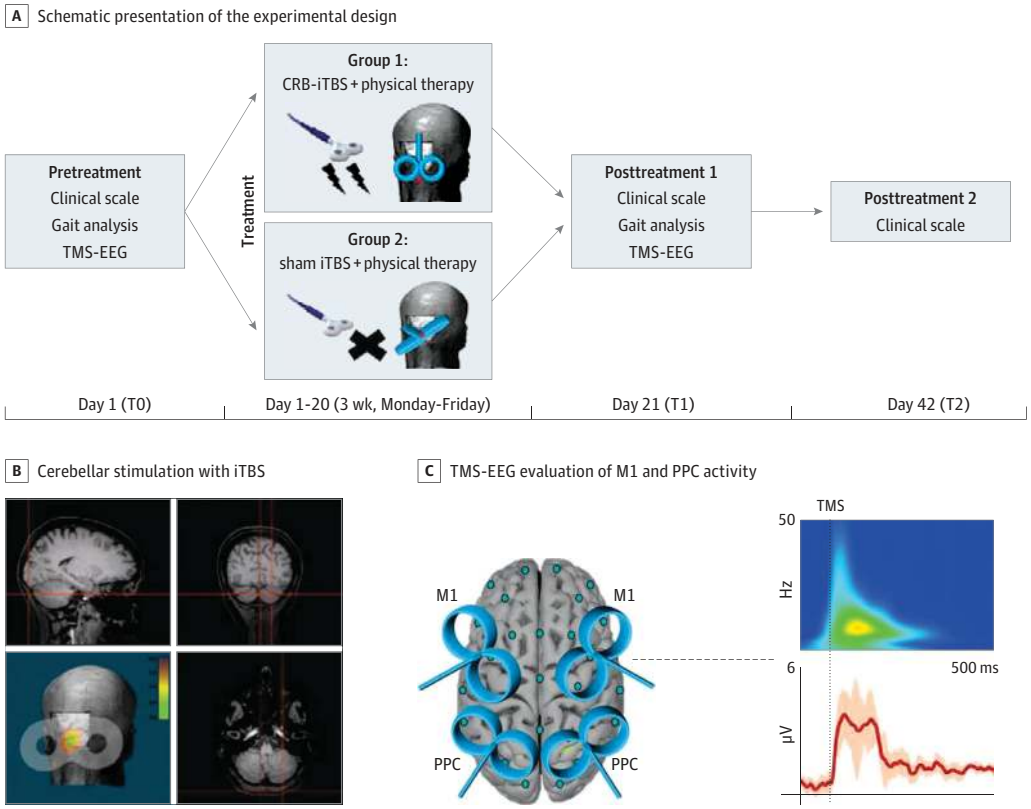
[a] Measured with biphasic transcranial magnetic stimulation pulses.

[33.3%]; mean [SD] age, 63 [11] years) or sham iTBS (18 patients; 7 women [38.9%]; mean [SD] age, 65 [12] years) coupled with PT (**Figure 1**). The randomization algorithm used the minimal sufficient balancing method to prevent imbalances in baseline age and stroke severity. Clinical scores, locomotion analysis, and cortical activity were assessed at baseline (T0) and after 3 weeks of treatment (T1). A further clinical evaluation was performed again after 3 weeks from the end of the treatment (T2). Each evaluation was performed by a clinician (G.K. or F.S.) (for clinical rating) or by a neurophysiologist (V.P. or M.I.) (for gait analysis and TMS/EEG recordings) who was blinded to the experimental condition of the patient. We used a power analysis to determine the necessary sample size, based on previously published work on cortical plastic changes induced by cerebellar TBS protocols,[13,14,17] considering 80% power and a 95% CI, we calculated that 32 patients would be needed.

Locomotion Analysis

Patients were asked to walk at their comfortable speed while wearing comfortable shoes within a rectangle (6 m × 2.5 m) formed by optoelectronic bars placed on the ground in our laboratory (Optogait; Microgate). Half of the electronic bars contained an infrared light emitter (each 1.04 cm), and the other half contained a receiver at the same distance. The frequency of emission and detection was 100 Hz. This instrumentation allowed to measure spatiotemporal gait parameters such as step

Figure 1. Experimental Design and Methods



Clinical evaluation, gait analysis, and transcranial magnetic stimulation (TMS) with electroencephalogram (EEG) were performed at baseline (T0), after 3 weeks of treatment (T1), and 3 weeks after the end of treatment (T2) (A). The treatment consisted of 3 weeks of daily cerebellar intermittent θ-burst stimulation (CRB-iTBS) or sham iTBS preceding the physiotherapy session. θ-Burst stimulation was applied over the cerebellum contralateral to the hemisphere affected by the stroke in the territory of the middle cerebral artery (B). Cortical activity was evaluated with TMS-EEG over primary motor cortex (M1) and posterior parietal cortex (PPC) of both affected and unaffected hemispheres (C) in terms of oscillatory activity (right upper panel, C) and TMS-evoked potentials (right lower panel, C).

length, step width, speed, stance, and swing percentages during steps performed by affected and unaffected leg (ie, when the affected or unaffected leg are in stance phase and the other in swing phase, respectively).

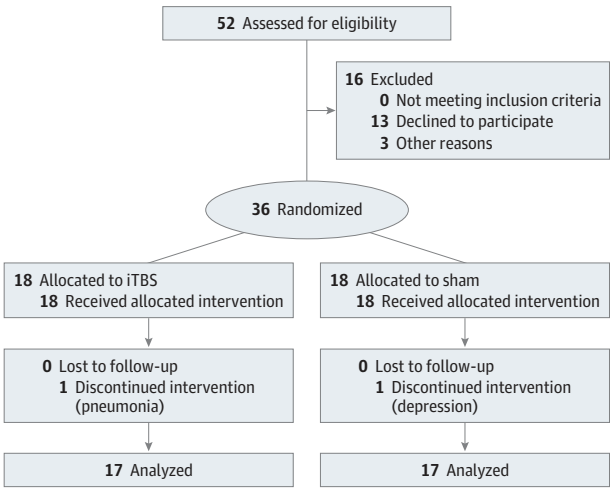
Analysis of Cortical Activity

Analysis of cortical activity was performed with TMS-EEG. During the entire session, patients were seated on a dedicated, comfortable armchair in a soundproofed room. Each session consisted of 80 TMS single pulses applied at a random interstimulus interval of 2 to 4 seconds over M1 and PPC of both the hemispheres (320 pulses in total).[17] The intensity of stimulation was set at 90% of the resting motor threshold.[22] When resting motor threshold was not recordable in the affected hemisphere owing to the lack of any motor-evoked potentials response, TMS was set at the same value of the unaffected hemisphere. Transcranial magnetic stimulation–EEG data were analyzed offline with Brain Vision Analyzer (Brain Products GmbH). To evaluate the effects of the CRB-iTBS treatment, the single-pulse TMS-evoked responses were evaluated with 2 approaches: (1) a spatiotemporal-domain analysis to assess cortical evoked activity and (2) a time/frequency-domain analysis to evaluate the cortical oscillatory activity. Spatiotemporal-domain analysis was conducted on a time window lasting from 100 milliseconds before to 500 milliseconds after a single TMS pulse. To assess the TMS-evoked global cortical response, we performed a global mean field power (GMFP) analysis, computed as the SD of the signal across all the electrodes on the scalp. For each patient and each stimulation site, the first 4 peaks (ie, P1, P2, P3, P4) of the GMFP waveform were detected within 300 milliseconds following the TMS pulse. To evaluate changes in the oscillatory domain, we applied a time/frequency decomposition based on Morlet wavelet (parameters c = 3; 41 linear 1-Hz steps from 4 to 45 Hz) on the entire EEG epoch. Spectral power was subsequently extracted for the θ (4-7 Hz), α (8-13 Hz), β (14-30 Hz), and γ band (31-45 Hz) and averaged in a time window lasting from 20 milliseconds to 300 milliseconds, where the TMS-evoked cortical activity was visible.[26] Transcranial magnetic stimulation–evoked spectral power, separately for each frequency band, was averaged among each channel to assess the global oscillatory activity.

Outcomes

For efficacy analyses, the primary end point was change from baseline in BBS score[27] for the assessment of gait and balance

Figure 2. CONSORT Flow Diagram for Randomization of Patients With Stroke Enrolled in the Study



iTBS indicates intermittent θ-burst stimulation.

functions at T1. Secondary end points were changes from baseline in total scores of the FMA[28] and the BI,[29] change from baseline in locomotion assessed with gait analysis, and change from baseline in cortical activity recorded with TMS-EEG at T1.[17]

Statistical Analysis

Clinical scales (BBS, FMA, and BI scores) were separately analyzed with repeated-measures mixed analysis of variance with a between-individual factor group (CRB-iTBS and sham iTBS) and a within-individual factor time (T0, T1, and T2). Gait analysis of step length, step width, speed, stance, and swing percentages for the affected and the unaffected leg was separately performed with repeated-measures mixed analysis of variance with a between-individual factor group and a within-individual factor time. Transcranial magnetic stimulation–evoked cortical activity was averaged within each GMFP peak time window. To evaluate the treatment effects on cortical excitability, we used a repeated-measures mixed analysis of variance with between-individuals factor group and within-individuals factors hemisphere, time, and peak separately for each stimulation site. Repeated-measures mixed analysis of variance with between-individuals factor group and within-individuals factors hemisphere and time was performed to evaluate the treatment effects on oscillatory activity, separately for each frequency and stimulation site. Correlation between clinical, behavioral, and neurophysiological data were tested with Pearson coefficient.

Results

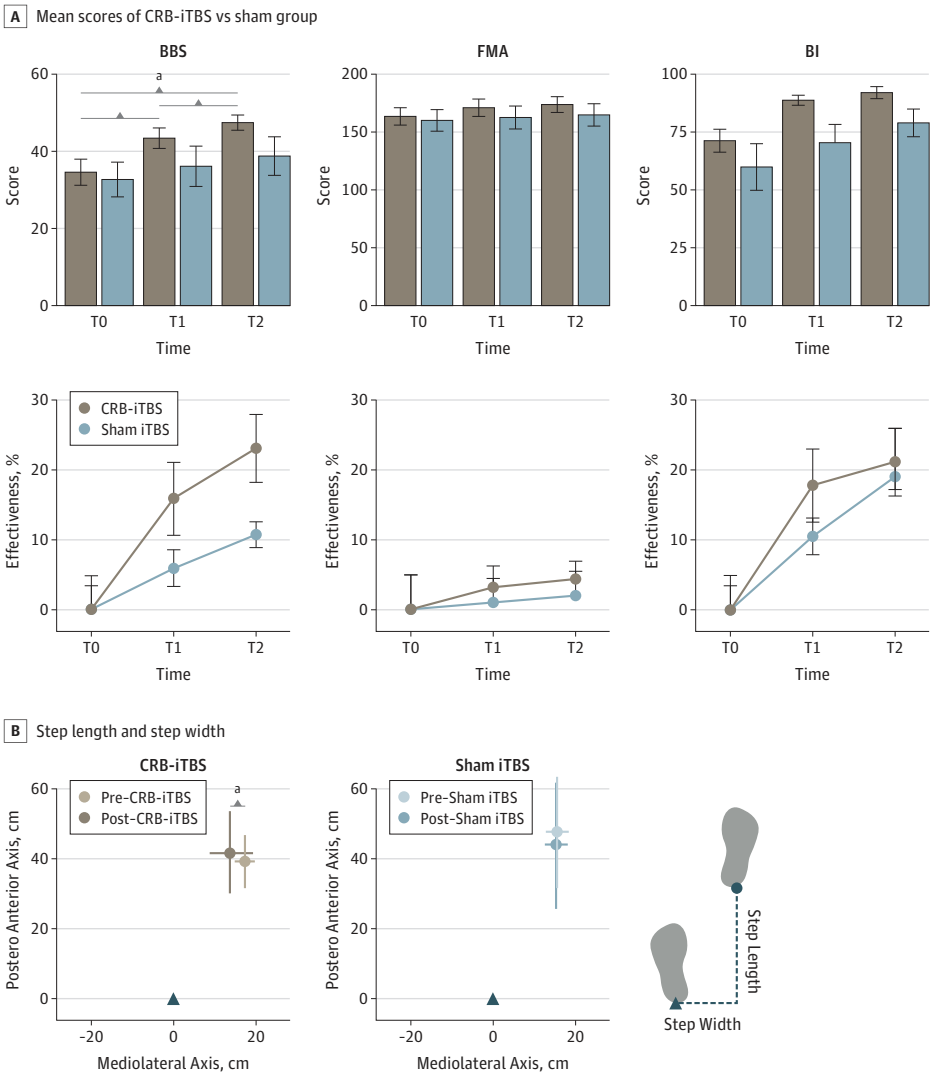
The procedure was well tolerated, and no significant adverse effects were reported in either group. The 2 groups did not differ at baseline level (T0) in age, sex, lesion side, number of months from the stroke event, and severity of stroke as assessed by National Institutes of Health Stroke Scale. Two patients discontinued during the treatment period and 34 patients (mean [SD] age, 64 [11.3] years; 13 women [38.2%]) completed treatments (**Figure 2**). The effective training time was similar between groups. We found that 3 weeks of CRB-iTBS coupled with PT resulted in an increase of BBS score compared with sham iTBS (group × time interaction, $F_{2,60} = 3.73$; $P = .03$; $\varepsilon = 0.111$). Post hoc analysis revealed that BBS score increased in the CRB-iTBS at T1 compared with T0 ($P < .001$), at T2 compared with T0 ($P < .001$), and at T2 compared with T1 ($P = .04$) (mean [SD], T0: 34.5 [3.4]; T1: 43.4 [2.6]; T2: 47.5 [1.8]) (**Figure 3**A). No differences were observed for the sham iTBS group (mean [SD], T0: 32.8 [4.9]; T1: 36.1 [5.2]; T2: 38.8 [4.8]). Post hoc analysis also showed a significant difference at T2 between the 2 groups ($P < .05$). The analysis of effectiveness showed that BBS score improved by 15.8% (T1) and 23.1% (T2) in the CRB-iTBS group and by 5.8% (T1) and 10.3% (T2) in the sham iTBS group (Figure 3A). We did not find any differences on FMA and BI scores between the 2 groups. Specifically, the analysis of FMA scores revealed a mild increase at T1 and T2 similarly for both the CRB-iTBS and sham iTBS groups ($F_{2,60} = 13.73$; $P < .001$; $\varepsilon = 0.314$). Also for the BI scores, we found a similar mild increase in the 2 groups after 3 weeks of treatment ($F_{2,40} = 19.94$; $P < .001$; $\varepsilon = 0.499$) both at T1 and T2 compared with T0 (T0 vs T1, $P < .001$; T0 vs T2 post hoc, $P < .001$) and at T2 compared with T1 (T1 vs T2, $P < .05$). The analysis of effectiveness revealed that, compared with baseline, FMA scores improved by 2.3% (T1) and 3.3% (T2), whereas BI scores improved by 12.6% (T1) and 18.1% (T2) in the 2 groups.

The instrumented gait analysis showed that step width, measured during the step of unaffected limb, was significantly reduced in the CRB-iTBS group ($F_{1,14} = 7.794$, $P < .01$) (mean [SD], CRB-iTBS, T0: 16.8 [4.8]; T1: 14.3 [6.2] cm; sham iTBS, T0: 16.8 [4.0], T1: 15.7 [2.5] cm) (Figure 3B). A similar trend was observed during the steps performed with the affected limb, but the higher variability made this result not significant (mean [SD], CRB-iTBS, T0: 15.9 [4.3], T1: 14.1 [5.4] cm; sham iTBS, T0: 15.8 [2.5], T1: 17.1 [2.7] cm). No group-specific effects were observed for step length or stance percentage duration.

After 3 weeks of treatment, the M1-GMFP amplitude evaluated over the affected hemisphere was higher for both groups ($F_{1,26} = 6.669$; $P < .05$; $\varepsilon = 0.204$) (**Figure 4**A). In contrast, the PPC-GMFP (P3) evaluated over the affected hemisphere was significantly higher only for the CRB-iTBS group ($F_{3,78} = 3.148$; $P < .05$; $\varepsilon = 0.108$; P3 post hoc $P < .001$) (Figure 4A). No effects were detectable when stimulating the unaffected hemisphere. When stimulating M1, we found a general increase of β activity evoked over the affected hemisphere for both CRB-iTBS and sham iTBS groups ($F_{1,26} = 4.568$; $P = .04$; $\varepsilon = 0.149$; post hoc $P = .05$) (Figure 4B). On the other hand, when we tested PPC oscillatory activity, we found that 3 weeks of CRB-iTBS treatment enhanced the oscillatory activity evoked over affected hemisphere in the θ range of frequency ($F_{1,26} = 6.226$; $P < .05$; $\varepsilon = 0.193$; post hoc $P < .001$) and not in the other frequency bands (Figure 4B). No effects were observed after sham iTBS, nor when stimulating the unaffected hemisphere.

The correlation analysis revealed that posttreatment BBS changes correlated with step width ($r = -0.517$; $P = .03$) and with PPC-GMFP ($r = 0.496$; $P = .04$) (Figure 4C), indicating that

Figure 3. Clinical Scores and Gait Analysis



Berg Balance Scale (BBS), Fugl-Mayer Assessment (FMA), and Barthel Index (BI) mean scores and effectiveness for the cerebellar intermittent θ-burst stimulation (CRB-iTBS) and sham iTBS group at baseline (T0), 3 weeks after treatment (T1), and 3 weeks after the end of the treatment (T2) (A). Patients who underwent CRB-iTBS coupled with physiotherapy showed a significant increase in BBS score after the TBS treatment (T1), which was still significant at T2. B, Step length (vertical lines) and step width (horizontal lines) in the CRB-iTBS and sham iTBS group, before (upper plots) and after (below plots) the 3-week cerebellar TBS treatment. Triangles and circles respectively depict the start and the final point from which the step is measured. Patients who underwent CRB-iTBS coupled with physiotherapy showed a significant reduction of the step width after the TBS treatment. Error bars indicate standard error of the mean. [a]*P* < .05.

a greater increase in gait and balance functions was associated with more pronounced reduction of step width and to a larger increase of TMS-evoked PPC cortical activity.

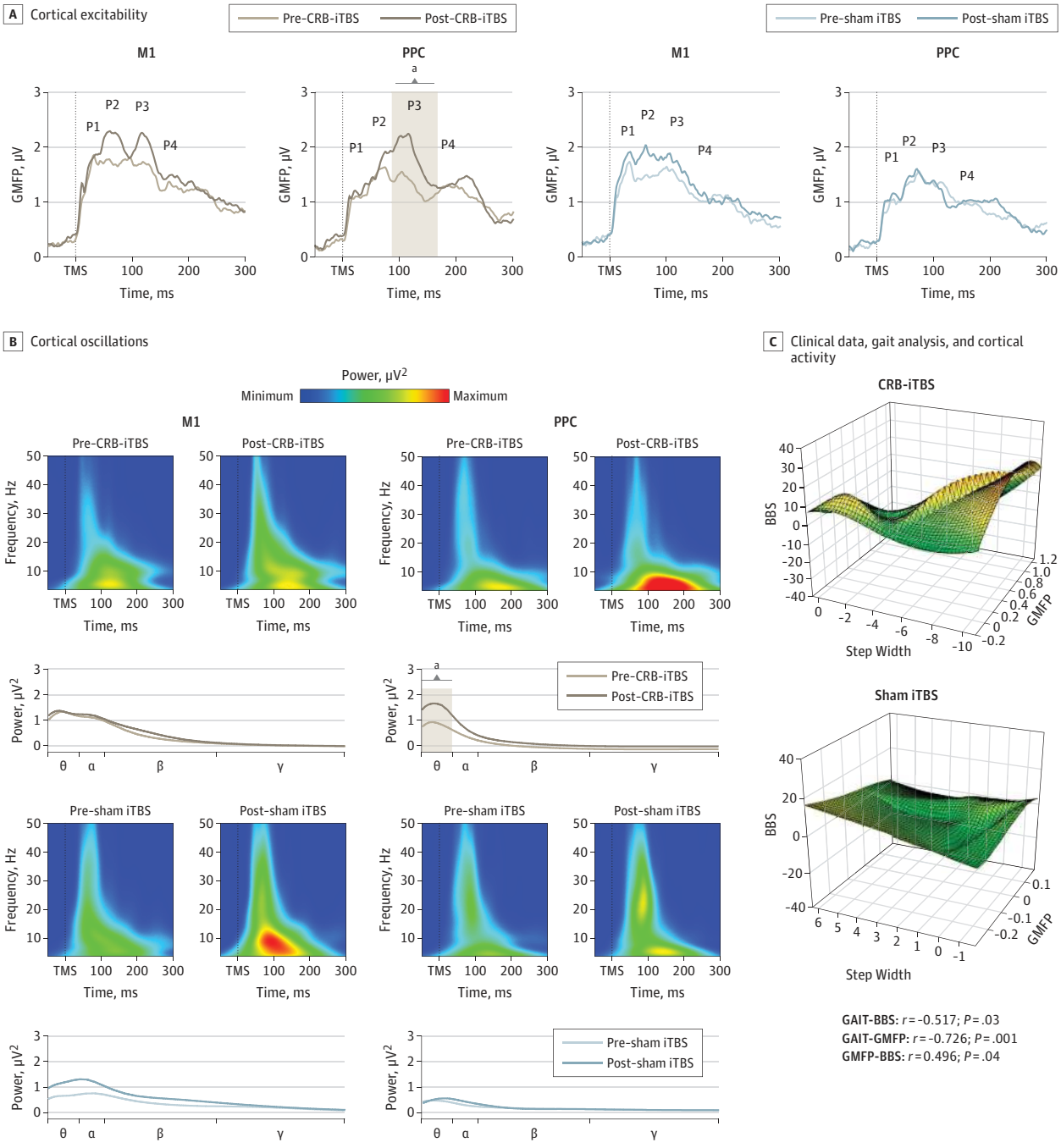
Discussion

Our study shows that CRB-iTBS coupled with PT improves gait and balance functions in patients with hemiparesis due to stroke, as demonstrated by the increase in BBS score and by the reduction of step width provided by the gait analysis. Importantly, these changes were paralleled by an enhancement of neural activity in the PPC of the affected hemisphere as measured by TMS-EEG.

From a clinical point of view, we found that CRB-iTBS coupled with PT increased BBS score from 35 to 47 points, passing from a level in which patients need assistance for walking to a level of independent walking. Notably, this increase in the BBS score indicates also a significant reduction of the risk of falling, passing from a medium fall risk to a low fall risk.[27] This result is relevant for several reasons. First, we were able to improve gait in a sample of patients with chronic stroke. This is important since walking functions tend to decline more at 6 months from stroke onset after a transient initial improvement, and such deficit is associated with long-term disability and reduced quality of life.[9] Second, such improvement was achieved in a relatively short period of training (3 weeks), showing that CRB-iTBS can be useful to design fast, low-cost, and effective protocols for gait rehabilitation.

From a behavioral point of view, the TBS-induced reduction of step width was due to a decrease of the step of unaffected limb. Owing to the lack of gait stability, the gait pattern of individuals after stroke differs from that of healthy individuals.[30,31] Indeed, a larger step width in individuals after stroke has been explained as a compensation for the larger body sway in the frontal plane.[32] Therefore, the reduction of step width should be considered a clear sign of the improvement of gait stability in patients in the CRB-iTBS group. On the other hand, the lower increase in walking speed can be seen as a strategy to improve gait stability.[33]

Figure 4. Cortical Activity



Global mean field power (A) and oscillatory activity (B) evoked from the affected hemisphere–primary motor cortex (M1) and affected hemisphere–posterior parietal cortex (PPC) of the cerebellar intermittent θ-burst stimulation (CRB-iTBS) and sham iTBS group. Light brown and dark brown lines depict the activity evoked before and after the 3-week cerebellar TBS treatment, respectively. Light blue and dark blue lines depict the activity evoked before and after the sham iTBS, respectively. Patients who underwent CRB-iTBS coupled with physiotherapy showed a significant increase of PPC neural activity (A) and θ oscillations (B) after the TBS treatment.
C, 3-Dimensional plots of the correlations between step width (x-axis), cortical activity (global mean field power, y-axis) and Berg Balance Scale (BBS, z-axis) in the CRB-iTBS and sham iTBS group. Patients receiving CRB-iTBS with the highest recovery at the BBS (y-axis) were the ones who showed a greater reduction of step width (x-axis) and stronger PPC global mean field power (GMFP) (z-axis). TMS indicates transcranial magnetic stimulation. P1, P2, P3, and P4 indicate the first 4 peaks of the global mean field power waveform. [a]$P < .05$.

Despite the dramatic consequences on the daily activities, the precise mechanism underlying balance impairment after stroke is still unclear. Oscillatory activity is enhanced in sensorimotor area and PPC while participants voluntarily tracked a target speed on an active treadmill and during simulated walking.[34-36] Along the same lines, a recent study used continu-

ous TBS to disrupt the activity of the PPC, decreased the complexity of body sway and its variability, supporting the involvement of this area in the control of body balance.[19] Taken together, these studies demonstrate that PPC is crucially involved during the integration of sensorimotor inputs in nonsimplistic motor commands. In agreement with this background, our data demonstrate that the induction of cerebellar plasticity by means of iTBS was indeed associated with relevant changes in the neural activity of the contralateral PPC, likely through the activation of cerebello-thalamo-cortical pathways targeting parietal-frontal networks.[17] In the present study, the 3-week CRB-iTBS protocol could have promoted long-term potentiation at the level of the cerebellar cortex[36] with an effect on the interconnected PPC of the contralateral lesioned hemisphere.[18] Notably, cerebellar output influences not only M1 but also premotor, prefrontal, and parietal areas such as the PPC.[37] The potentiation of PPC activity was observable not only in terms of TMS-evoked activity but also of cortical θ oscillations, probing the state of the thalamo-cortical circuits. One possibility is that cerebellar iTBS could have modulated γ-aminobutyric acid–ergic activity at thalamic or cortical level.[17] At this regard, it has been proposed that cerebellar TBS exerts its effects likely by impinging on specific set of interneurons dependent on aminobutyric acid–ergic activity,[13] which plays a key role in driving mechanisms of brain plasticity during post-stroke recovery.[38] Thus, the long-term potentiationlike mechanism induced by the CRB-iTBS could have reinforced the cerebello-thalamo-cortical interactions cycling at low-frequency range, responsible for spatial-motor learning required for movement execution. Indeed, we argue that CRB-iTBS could have contributed to the better clinical improvement by promoting cerebellar-dependent mechanism of motor learning.

We also found a general enhancement of M1 activity in both groups. These effects are likely due to the course of coupled 3 weeks of daily PT, independently from the CRB-iTBS treatment. Moreover, we did not observe any neurophysiological changes in the unaffected hemisphere, in agreement with the notion that CRB-iTBS is able to potentiate specifically the neural activity of the contralateral parieto-frontal network.[17]

The novelty of our results lies in the novel multimodal approach we used, consisting of combining TMS, EEG, gait analysis, and clinical scores. Accordingly, patients who had a greater increase of PPC activity showed a higher score in the BBS score and a stronger reduction of the step width in the gait analysis. So far, TMS measures in patients with stroke derived mostly from motor-evoked potentials analysis, a well-known index of cortico-spinal excitability. However, motor-evoked potentials cannot be recorded from the lesioned hemispheres in a large percentage of patients with stroke.[39] In our sample, motor-evoked potentials were not recordable for the purposes of evaluating cortico-spinal excitability and intracortical activity in more than 50% of the cases, making such measurement not reliable. In this view, TMS-evoked EEG response was assessed in all patients and therefore represents important markers of the state of cortex in patients in absence of any motor response.

Limitations

We acknowledge some limitations of the present study. Because our sample includes patients with stroke in both hemispheres, we could not take into account the influence of laterality. In addition, the relatively low number of recording electrodes did not allow us to perform any brain source analysis. Moreover, a relevant concern is owing to the fact the TMS-EEG was applied on the hand representation of M1, while clinical changes were mostly observed in gait and balance functions. Therefore, this could explain the lack of specific effects for M1-TMS-EEG. Finally, we are aware of the fact that our study is limited by the relatively low sample size.

Conclusions

In conclusion, we provide novel evidence that combining CRB-iTBS with traditional PT is an effective strategy to promote gait and balance recovery by engaging successful cerebello-cortical reorganization in patients with ischemic stroke.

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