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Theta-burst stimulation of the left hemisphere accelerates recovery of hemispatial neglect



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ABSTRACT

Objective: Cortico-cortical circuits originating from the posterior parietal cortex (PPC) of the intact left hemisphere (LH) may become hyperexcitable in patients with hemispatial neglect due to a right hemispheric (RH) stroke.

Methods: In the current randomized, double-blind, sham-controlled study, we investigated safety and efficacy of continuous theta-burst stimulation (cTBS) in 10 sessions over 2 weeks applied over the intact PPC of the LH in subacute ischemic stroke patients. Severity of neglect was assessed through the standardized Behavioral Inattention Test (BIT). We also measured, by means of bifocal transcranial magnetic stimulation (TMS), how cTBS modified the excitability of the parieto-frontal functional connections in the intact LH.

Results: We found that 2 weeks of cTBS, but not sham cTBS, were effective in improving neglect symptoms as measured by BIT score. BIT scores improved by 16.3% after 2 weeks of cTBS and 22.6% at 1 month follow-up. We also found that hyperexcitability of LH parieto-frontal circuits was reduced following treatment with real but not sham cTBS.

Conclusion: These findings suggest that a 2-week course of cTBS over the LH PPC may be a potential effective strategy in accelerating recovery from visuospatial neglect in subacute stroke patients, possibly counteracting the hyperexcitability of LH parieto-frontal circuits.

Classification of evidence: This study provides Class III evidence that left posterior parietal cortex theta-burst stimulation improves hemispatial neglect for up to 2 weeks after treatment. *Neurology*® 2012;78:24-30

GLOSSARY

AG = angular gyrus; **AMT** = active motor threshold; **ANOVA** = analysis of variance; **BIT** = Behavioral Inattention Test; **BIT-B** = behavioral scale of the Behavioral Inattention Test; **BIT-C** = conventional scale of the Behavioral Inattention Test; **CS** = conditioning stimulus; **cTBS** = continuous theta-burst stimulation; **FDI** = first dorsal interosseous; **IPL** = inferior parietal lobule; **IPS** = intraparietal sulcus; **ISI** = interstimulus interval; **LH** = left hemisphere; **M1** = primary motor cortex; **MEP** = motor evoked potential; **MNI** = Montreal Neurological Institute; **PPC** = posterior parietal cortex; **RH** = right hemispheric; **RMT** = resting motor threshold; **TMS** = transcranial magnetic stimulation; **TS** = test stimulus.

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Supplemental data at www.neurology.org

Supplemental Data



Podcast



CME



Hemispatial neglect is a common and disabling syndrome following unilateral stroke, particularly to the right hemisphere (RH).¹⁻³ Although recovery from neglect is an important aim in stroke rehabilitation, it is generally agreed that the current cognitive rehabilitation is unsatisfactory.⁴

One influential proposal about the mechanisms contributing to neglect has invoked inter-hemispheric rivalry or competition.⁵⁻⁷ From this perspective, the RH lesions that typically induce left hemispatial neglect may lead to pathologic overexcitability of LH circuits, due to release from inhibitory rivalry.^{7,8} Moreover, recent anatomic and functional neuroimaging studies have potentially implicated altered patterns of cortico-cortical connectivity at the basis of neglect.^{9,10} According to this background, we recently demonstrated that the excitability of parieto-frontal cortical circuits of the LH is higher in neglect patients than in other stroke patients.¹¹ Moreover, we showed that a single session of rTMS applied over the left PPC is able

From the Laboratory of Clinical and Behavioural Neurology (G.K., S.B., V.G., G.B., B.B., F.L., V.V., M.B., C.C.), Santa Lucia Foundation IRCCS; Stroke Unit (G.K.), Policlinico Tor Vergata; and Department of Neuroscience (C.C.), University of Rome Tor Vergata, Rome, Italy.

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to transiently normalize this overexcitability and to improve neglect,¹¹ providing further implications for possible treatment.¹¹⁻¹⁴

Here, we aimed to investigate whether this approach may be useful in promoting clinical recovery from neglect. We used a TBS protocol, which has proven to be effective in inducing powerful long-lasting changes in the excitability of the stimulated cortex.¹⁵ A recent study showed that left PPC cTBS may increase the number of perceived left visual targets in patients with neglect for several hours.¹⁶ Therefore, here we tested the potential “therapeutic” effect of this intervention when applied repeatedly for 2 weeks in patients with poststroke neglect. To evaluate changes in clinical scores associated with neglect we used the BIT,¹⁷ a comprehensive battery that consists of both conventional (e.g., cancellation, bisection, and drawing tests) and behavioral (e.g., picture scanning, telephone dialing, menu, and article reading) tests. We choose the BIT battery measure as the primary outcome of the treatment. We also aimed to verify whether a 2-week course of PPC cTBS was effective in normalizing the overexcitability of left parieto-frontal connections previously described in these patients.¹¹

METHODS Subjects. Twenty consecutive patients with RH subacute ischemic stroke and affected by hemispatial neglect, as confirmed by radiologic (CT or MRI) and clinical examination, were enrolled in the study since January 2008 until June 2010 (table e-1 on the *Neurology*[®] Web site at www.neurology.org). All subjects were right-handed, according to the Edinburgh inventory.¹⁸ All had had an ischemic stroke and were admitted to the neurorehabilitation unit of the Santa Lucia Foundation for a period of standard physical and cognitive therapy following an ischemic stroke. They all underwent a standard clinical neurologic and neuropsychological examination to assess any sensory or motor deficits, language disorders, or cognitive impairment, and critically the presence or absence of left neglect. Patients were randomly assigned to real or sham left PPC cTBS: 10 were assigned to real cTBS, and the remaining 10 to sham cTBS. Two patients (1 of each group) were not able to perform all the TBS sessions and were discarded from the study. The 2 groups did not differ in gender, mean age ($p = 0.09$), duration of illness ($p = 0.27$), or baseline BIT scores ($p = 0.84$), and had similar stroke location (table e-1). Patients were unaware of their group assignment; all were only told that they had been enrolled in rehabilitation treatment for their spatial attention deficits (figure 1). Therapists were also blinded in respect to the type of intervention. The 4-week rehabilitation program consisted of 20 sessions of 45 minutes each, held 5 days per week, performed at the same time for each patient in the afternoon. The conventional therapy was based on computerized visuospatial scanning train-

ing that included both saccadic (the patient is required to seek a stimulus presented at randomly selected points on the screen) and attention and concentration training (detection and identification of stimuli presented on the right side of the screen, then seeking for their counterparts on the left side among a variety of distracting stimuli). Additionally, some paper-and-pencil tasks aimed at improving visual scanning in the course of reading and writing were used. The patients were also treated with standard programs for motor rehabilitation when necessary. To provide an overview of brain lesions in the patients treated with TBS, the damage evident in CT or MRI (as available clinically) was reconstructed for each patient and plotted using MRIcro software (www.sph.sc.edu/comd/rorden/micro.html) and a graphics tablet (WACOM Intuos A6), by a neurologist who was blind to the TMS results and the clinical scores when plotting the lesions. A T1-weighted template comprising 12 axial slices was used to demarcate lesions for every patient (figure e-1).

Standard protocol approval, registration, and patient consent.

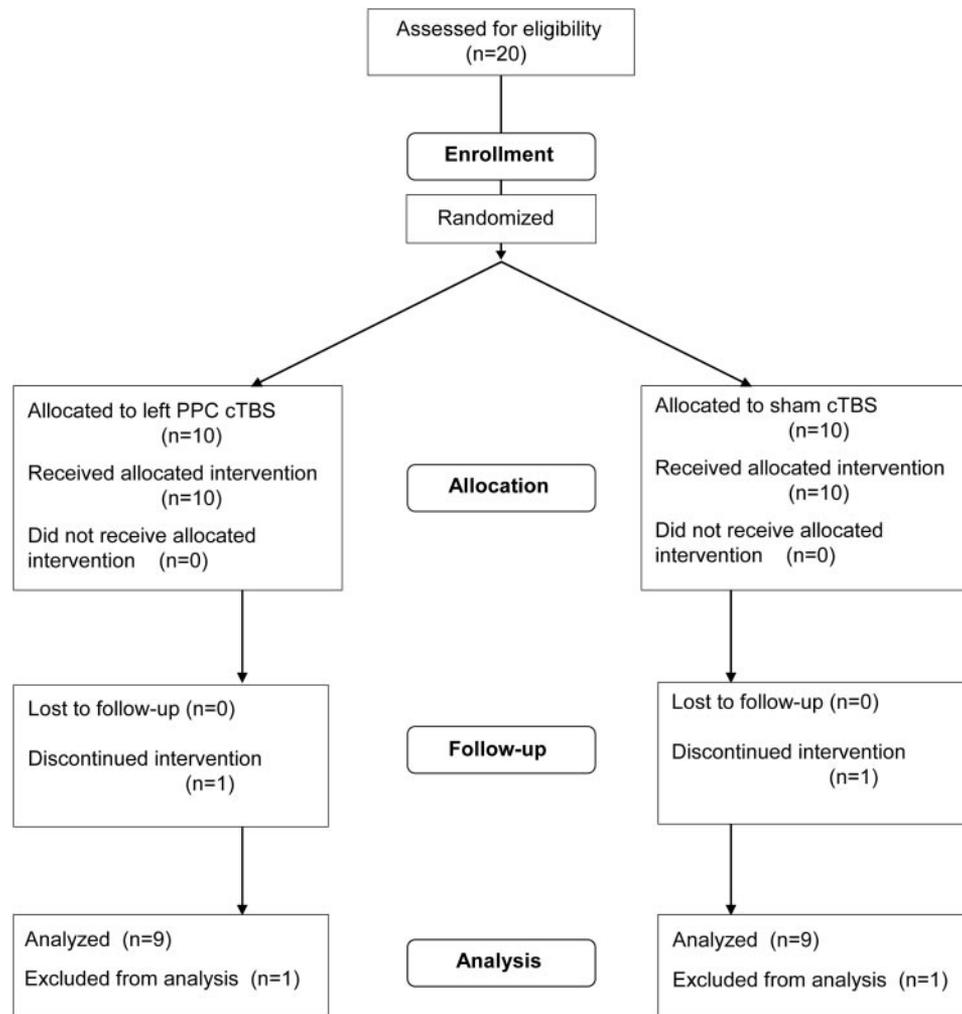
All patients gave informed consent for participation in the study. Experimental procedures were approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

cTBS. A MagStim Super Rapid magnetic stimulator (Magstim Company, Whitland, Wales, UK), connected with a figure-of-eight coil with a diameter of 70 mm, was used to deliver cTBS. In every session, 3-pulse bursts at 50 Hz repeated every 200 msec for 40 s were delivered at 80% of the active motor threshold (AMT) over the left PPC (600 pulses).¹⁵ Every day 2 sessions of left PPC cTBS were applied with an interval of 15 minutes.^{16,19} Stimulation lasted for 10 days (5 days per week, Monday to Friday), and was applied daily at the same hour every morning (11 AM) to all patients. We used a neuronavigation system (Softaxic, E.M.S., Bologna, Italy) to precisely position the coil over the left PPC, using individual anatomic MRI; this technique has been described in detail previously.²⁰⁻²² The individual coordinates of each stimulation site were normalized a posteriori into the Montreal Neurological Institute (MNI) coordinate system and averaged. To target the left PPC, the coil was positioned in the angular gyrus (AG) in the posterior portion of the inferior parietal lobule (IPL), close to a posterior part of the adjoining intraparietal sulcus (cIPS).²⁰⁻²² The center of the coil was positioned tangentially to the skull with the handle pointing downward and slightly posteriorly.^{20,22} Sham stimulation was delivered with the coil angled at 90°, with only the edge of the coil resting on the scalp. Stimulus intensity, expressed as a percentage of the maximum stimulator output, was set at 80% AMT for the FDI, inducing the same acoustic sensation as for real TBS.

Clinical assessment of visuospatial neglect.

Hemispatial neglect was assessed with the BIT, a battery of tests for evaluation of spatial deficits which includes both conventional (BIT-C) and behavioral scales (BIT-B). The conventional tests are line crossing, letter cancellation, star cancellation, figure and shape copying, line bisection, and representational drawing. The behavioral tests reflect aspects of daily life activities, and are picture scanning, telephone dialing, menu reading, article reading, telling and setting the time, coin sorting, address and sentence copying, map navigation, and card sorting. The cutoff scores for the conventional and behavioral tests are 129 (0–146, maximum score 146) and 67 (0–81, maximum score 81), respectively. Patients were classified as having neglect when their score was below the cutoff score in either or both the BIT-C and BIT-B. Evaluation of BIT was performed by blinded raters 1 hour before

Figure 1 CONSORT 2001 flow diagram



cTBS = continuous theta-burst stimulation; PPC = posterior parietal cortex.

starting the first session of stimulation (pre cTBS), the Monday following the 2 weeks of stimulation (post cTBS), and again 4 weeks after the beginning of the stimulation period. Testing sessions required approximately 2 hours per patient.

PPC-M1 functional connectivity in the intact left hemisphere. In the same patients, we also assessed changes of the functional connections between the left PPC and ipsilateral primary motor cortex (M1) before, after 2 weeks of cTBS, and after 4 weeks from the beginning of the treatment. We used a paired-pulse TMS technique with 2 high-power Magstim 200 machines (Magstim Co., Whitland, Dyfed, UK)^{11,20-22} connected to the stimulating coil. A first test stimulus (TS) was applied over the hand motor area of the intact LH and was defined as the site where stimulation elicited the largest motor evoked potentials (MEPs) from the contralateral right first dorsal interosseous (FDI) muscle. The intensity of the TS was adjusted to evoke an MEP of approximately 1 mV peak-to-peak amplitude in the relaxed FDI muscle. To best activate the ipsilateral PPC-M1 connection, a conditioning stimulus (CS) was applied over the left PPC at an intensity of 90% of the ipsilateral resting motor threshold (RMT).²⁰⁻²³ The interstimulus interval (ISI) between the CS and TS was set at 4 msec. In each block 2 conditions were randomly intermingled: TS alone (MEP) and CS + TS (condi-

tioned MEP). Twenty responses were collected for the test stimulus alone and 20 responses for conditioned MEPs (total number of trials: 40). Measurements were made on each individual trial and the mean peak-to-peak amplitude of the conditioned MEP was expressed as a percentage of the mean peak-to-peak amplitude of the unconditioned test pulse. We used a neuronavigation system (Softaxic, E.M.S., Bologna, Italy) to precisely position the coil over the PPC site, using individual MRI volumes as anatomic reference; this technique has been previously described in detail.^{11,20-23}

Data analysis. A repeated-measures analysis of variance (ANOVA) was performed between the values of total BIT scores, with group (cTBS vs sham) as between-subject main factor and time (pre cTBS vs post cTBS vs 2 weeks post cTBS) as within-subject main factor. Additional ANOVA analyses were performed on each subtest of the BIT, with the same group (cTBS vs sham) as between-subject main factor and time (pre cTBS vs post cTBS vs 2 weeks post cTBS) as within-subject main factor. If a significant effect was observed, single comparisons were performed by *t* tests for post hoc analysis. Separate ANOVAs with group (cTBS vs sham) as between-subject main factor and time (pre cTBS vs post cTBS) as within-subject main factor were also performed on the left PPC-M1 functional connections. The ef-

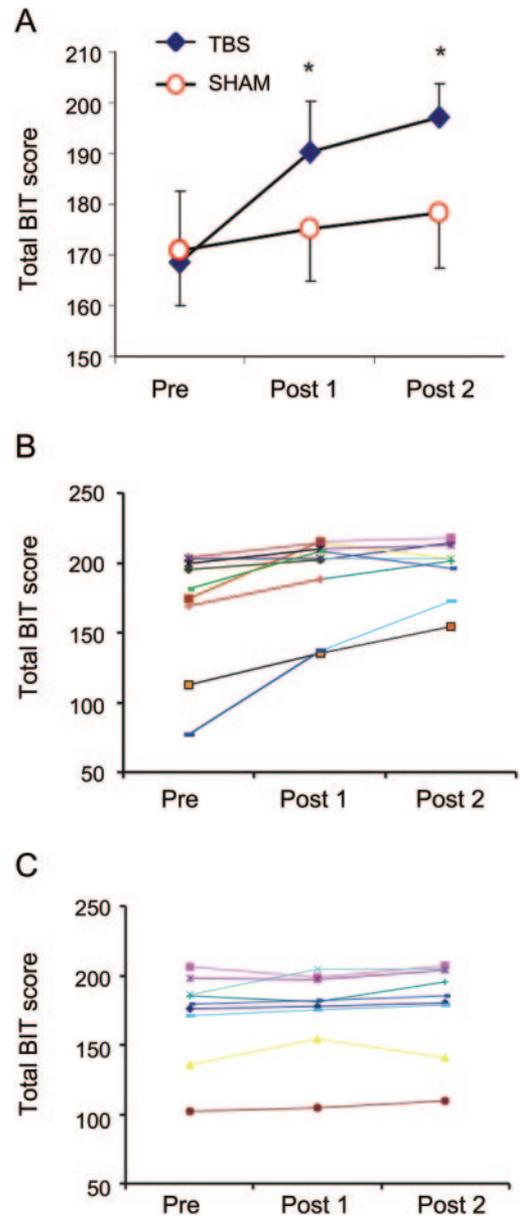
fects of paired stimulation of PPC on the size of MEPs recorded from the contralateral FDI in response to M1 TMS were analyzed as the percentage of the mean peak-to-peak amplitude of the unconditioned test M1 pulse. The same analyses were performed on RMT and 1 mV MEP thresholds. For all statistical analyses, a p value < 0.05 was considered to be significant.

RESULTS BIT scores. No significant adverse effect was reported. We found that cTBS over the left PPC induced an improvement in visuospatial neglect measured by total BIT scores in comparison to sham cTBS, as revealed by ANOVA analysis showing an effect of time main factor ($F_{2,32} = 14,54; p < 0.001$) as well a group \times time interaction ($F_{2,32} = 6,78; p < 0.05$). Post hoc analyses showed that improvements of the total BIT scores were evident for the cTBS group immediately after the end of the 2 weeks treatment and at follow-up 2 weeks later (all $p < 0.05$) (figure 2A). The individual values for the total BIT scores in the different conditions are reported for completeness in figure 2, B and C. The same analyses performed on each subtest of the BIT revealed that among the BIT-C scales, cTBS induced an improvement of the letter cancellation task (time main factor: $F_{2,32} = 16,22; p < 0.001$; group \times time interaction: $F_{2,32} = 8,12; p < 0.001$), and of the drawing task (time main factor: $F_{2,32} = 13,86; p < 0.001$; group \times time interaction: $F_{2,32} = 7,46; p < 0.05$) (table 1). Among the BIT-B scales, there were improvements of the picture scanning task (time main factor: $F_{2,32} = 15,22; p < 0.001$; group \times time interaction: $F_{2,32} = 6,97; p < 0.05$) and of the menu reading task (time main factor: $F_{2,32} = 12,68; p < 0.001$; group \times time interaction: $F_{2,32} = 9,22; p < 0.001$) (table 2).

Functional connectivity. At baseline RMT for left M1 did not differ between the cTBS group and the sham group ($36.8 \pm 8.1\%$ vs $38.2 \pm 6.1\%$ maximal stimulator output). The intensity of TS over the left M1 needed to produce a 1 mV MEP was $52.2 \pm 12.1\%$ of maximal stimulator output. The corresponding values for the sham group were $53.3 \pm 8.3\%$. Following real or sham cTBS there were no significant changes for both RMT and 1 mV MEP thresholds (figure 3, A and B).

Real but not sham cTBS was effective in reducing the excitability of the parieto-frontal functional connections in the intact LH¹¹ as shown by the ANOVA analyses (time main factor: $F_{2,32} = 6,29; p < 0.05$; group \times time interaction: $F_{2,32} = 3,68; p < 0.05$). Post hoc analysis showed that the excitability of PPC-M1 functional connection was reduced following real but not sham cTBS, as measured after the end of the cTBS treatment and at follow-up 2 weeks later (all $p < 0.05$) (figure 3C).

Figure 2 Behavioral Inattention Test (BIT) scores



(A) BIT scores obtained in the 2 groups of neglect patients before, at the end of the 2 weeks treatment period (Post 1), and 2 weeks later (Post 2). Individual total BIT scores measured for each patient in the theta-burst stimulation (TBS) group (B) and in the sham group (C) before and after the 2 weeks of stimulation. Asterisks indicate p values < 0.05 .

DISCUSSION In previous proof of principle studies, noninvasive brain stimulation methods have been shown to improve unilateral spatial attention by modulation of cortical excitability.^{24,25} A few studies consistently demonstrated that single or repeated sessions of low frequency inhibitory rTMS or transcranial direct current stimulation applied over the left PPC of the intact hemisphere were able to reduce visuospatial neglect.^{11-12,25-27} Crucially, in these studies the evaluation of neglect improvement was based

Table 1 Scores of the conventional BIT-C subtests

	Line crossing	Letter cancellation	Star cancellation	Figure and shape copying	Line bisection	Representational drawing
TBS pre	32.67 ± 5.15	30.00 ± 6.96	41.78 ± 14.75	2.22 ± 1.64	5.89 ± 2.39	2.11 ± 0.64
TBS post 1	35.44 ± 1.13	31.56 ± 7.06	42.22 ± 11.50	2.89 ± 1.76	6.44 ± 1.67	2.67 ± 0.50 ^a
TBS post 2	35.44 ± 1.01	34.78 ± 7.05 ^a	46.89 ± 7.96	2.78 ± 1.86	7.22 ± 1.99	2.33 ± 0.71
Sham pre	35.25 ± 0.96	28.75 ± 9.60	41.25 ± 13.67	2.25 ± 0.50	7.50 ± 2.38	2.00 ± 0.82
Sham post 1	34.95 ± 0.88	29.00 ± 8.21	41.50 ± 13.30	2.50 ± 1.29	7.75 ± 0.50	2.50 ± 1.00
Sham post 2	35.45 ± 0.65	29.50 ± 8.35	48.00 ± 5.72	2.75 ± 1.50	6.50 ± 2.52	2.75 ± 0.50

Abbreviations: BIT-C = conventional scale of the Behavioral Inattention Test; TBS = theta-burst stimulation.

^a Significant differences at post hoc *t* tests ($p < 0.01$) in comparison with pre treatment scores.

on heterogeneous and isolated tests such as the line bisection task,¹²⁻¹⁴ the clock drawing task,¹³ chimerical objects task,¹¹ and line cancellation tasks.¹⁴ Here, for the first time we assessed the effects of the novel cTBS protocol to verify the global impact of this procedure by measuring standardized conventional and behavioral assessments. Apart from an overall global improvement in the total BIT scores, we found improvements for some subtests of both the BIT-C and BIT-B scales. While standard cognitive therapies for neglect lead to some clinically significant improvement after 20–40 sessions²⁸⁻³⁰ over a duration of 4–12 weeks, we were able to accelerate clinical recovery after just 2 weeks of treatment. Indeed, we demonstrated that cTBS may be effective in improving not only standard tests, but may also extend to more general behavioral aspects of the syndrome, that are usually not directly addressed by standard cognitive therapy. However, the overall improvement obtained in the total BIT score was 16.3% after 2 weeks of cTBS and 22.6% at 1 month follow-up. Therefore, such partial improvement of neglect could not likely boost independence of the activities of daily living remarkably. At this regard, it is important to notice that in our group of patients treated with TBS, a stronger improvement was observed in those patients who were more severely affected at baseline. Therefore, it is possible that TBS could induce a more

pronounced and clinically relevant effect if applied to selected population of more affected patients. Yet, we did not observe any significant side effect and therefore the overall risk-benefit ratio of this procedure could be favorable in terms of clinical improvement even in milder patients. Increasing the number of daily sessions of TBS over the contralesional PPC may be a further effective strategy to improve neglect by means of rTMS. A recent study demonstrated that while 2 trains of cTBS increase the number of perceived stimuli in the left hemifield for up to 8 hours, 4 sessions result in a much longer-lasting effect, with an improvement of visual neglect that may last up to 36 hours.¹⁶ Therefore, other studies are needed to evaluate whether such multiday session approach may be even more effective in inducing a global improvement of visuospatial neglect, when treatment has a duration of at least 2 weeks. Indeed, the current TBS approach could also be used in association with other rehabilitative methods such as prism adaptation³¹⁻³³ or optokinetic stimulation^{29,34-36} to further increase the relative benefit of the different therapies. Notably, in the current study all patients were getting standard cognitive rehabilitation, and therefore, as designed, the study cannot distinguish between the effects of TBS alone and the effects of TBS plus rehabilitation. Furthermore, it remains to be established whether TBS

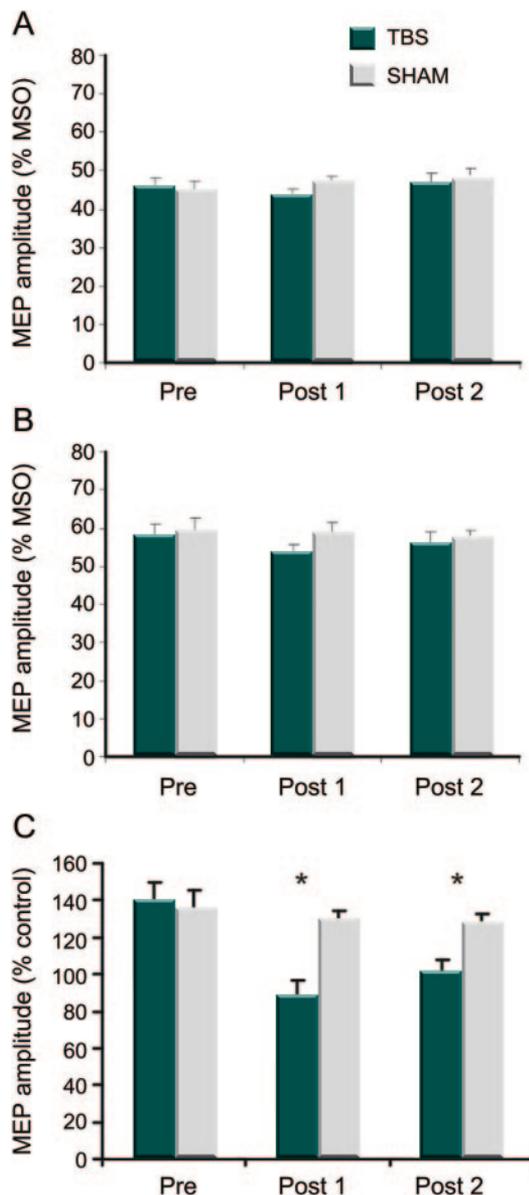
Table 2 Scores of the behavioral BIT-B subtests

	Picture scanning	Telephone dialing	Menu reading	Article reading	Telling and setting the time	Coin sorting	Address and sentence copying	Map navigation	Card sorting
TBS pre	3.00 ± 2.62	7.22 ± 2.44	5.75 ± 3.49	4.56 ± 4.25	7.78 ± 1.55	6.00 ± 2.75	6.78 ± 2.59	7.44 ± 2.59	5.22 ± 2.66
TBS post 1	4.78 ± 2.70 ^a	8.89 ± 0.31	8.33 ± 1.89 ^a	6.78 ± 3.68	8.78 ± 0.42	7.00 ± 1.89	7.11 ± 3.31	8.22 ± 2.72	6.00 ± 1.41
TBS post 2	5.22 ± 2.35 ^a	8.78 ± 0.63	8.33 ± 1.33 ^a	6.78 ± 3.68	9.00 ± 0.00	7.44 ± 1.83	7.22 ± 2.94	8.56 ± 2.45	7.56 ± 2.01
Sham pre	3.75 ± 2.63	7.25 ± 0.96	7.50 ± 3.00	8.75 ± 0.50	4.50 ± 5.20	4.75 ± 4.03	7.75 ± 2.50	6.75 ± 2.87	6.75 ± 1.50
Sham post 1	5.75 ± 0.88	8.75 ± 8.21	8.50 ± 13.30	6.00 ± 1.29	6.25 ± 0.50	5.25 ± 1.00	6.75 ± 0.50	8.50 ± 0.50	6.00 ± 0.50
Sham post 2	6.00 ± 2.71	8.75 ± 0.50	8.50 ± 1.00	6.50 ± 3.00	6.50 ± 4.36	4.75 ± 4.03	6.75 ± 4.50	9.00 ± 0.00	6.75 ± 1.50

Abbreviations: BIT-B = behavioral scale of the Behavioral Inattention Test; TBS = theta-burst stimulation.

^a Significant differences at post hoc *t* tests ($p < 0.01$) in comparison with pre treatment scores.

Figure 3 Effects of 2 weeks treatment with theta-burst stimulation (TBS) or sham stimulation on the excitability of the primary motor cortex (M1) of the left intact hemisphere



(A) Data obtained for the resting motor thresholds. (B) Data obtained for the 1 mV motor evoked potential amplitude thresholds. (C) Effects of 2 weeks treatment with TBS or sham stimulation on the posterior parietal cortex-M1 functional connection of the left intact hemisphere. Asterisks indicate $p < 0.05$.

could be more effective if applied immediately before or during the different sessions of cognitive rehabilitation. Another limitation of the current study is that we did not assess the impact of cTBS on global scales of functioning such as the FIM and on other cognitive functions through detailed neuropsychological testing.

The clinical improvement observed with BIT scores was paralleled by a long-lasting decrease in the excitability of the LH parieto-frontal functional connections, providing further evidence that visuospatial attention can be improved by the rebalancing of hemispheric activity through noninvasive TMS.^{11,24,25,37} In the current study, we studied parieto-frontal functional connectivity with a recently developed bifocal TMS approach^{20,21} and found that the previously described hyperexcitability of the LH parieto-frontal circuits¹¹ can be significantly counteracted by 2 weeks of TBS over the LH. Importantly, the reduction of the hyperexcitability was evident even at the follow-up measures, 2 weeks after the end of the “therapeutic” sessions, demonstrating that TBS can be a potentially effective approach able to induce long-lasting changes in the excitability of the LH parieto-frontal circuits. Our data provide direct evidence that by counteracting the disinhibition of circuits involving the left PPC we may effectively improve some aspects of visuospatial neglect. We hypothesized that lesions in the RH may induce changes in the cortico-cortical excitability of corresponding specific areas and circuits in the nonlesioned hemisphere, through a mechanism of locally reduced transcallosal inhibition.^{11,38} However, it is known that neglect may originate from several cortical and subcortical sites apart from the right PPC, such as the prefrontal and temporal lobes.^{8,39} Therefore it remains to be investigated whether the current approach could be similarly effective when neglect occurs following lesions of cortical or subcortical regions that do not directly involve the right PPC.³⁹ Finally, it has to be considered that our interpretation based on unbalanced transcallosal inhibition could account only for some aspects of visuospatial neglect, given that the complexity of neglect signs likely involves the concomitant dysfunction of other cortical circuits within the RH.⁴⁰

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by G.K., G.K. and C.C. conceived the study. G.K. wrote the manuscript. S.B., G.B., V.G., M.B., B.B., and V.V. performed the TMS experiments and collected the behavioral data.

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DISCLOSURE

Dr. Koch, Dr. Bonni, V. Giacobbe, G. Bucchi, Dr. Basile, Dr. Lupo, and Dr. Versace report no disclosures. Dr. Bozzali serves as Senior Associate Editor for the *Journal of Alzheimer's Disease* and receives research support from the Italian Ministry of Health. Dr. Caltagirone reports no disclosures.

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