doi:10.1093/brain/aws182 Brain 2012: 135; 3426–3439 | 3426

BRAIN
A JOURNAL OF NEUROLOGY

Theta burst stimulation reduces disability during the activities of daily living in spatial neglect

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Left-sided spatial neglect is a common neurological syndrome following right-hemispheric stroke. The presence of spatial neglect is a powerful predictor of poor rehabilitation outcome. In one influential account of spatial neglect, interhemispheric inhibition is impaired and leads to a pathological hyperactivity in the contralesional hemisphere, resulting in a biased attentional allocation towards the right hemifield. Inhibitory transcranial magnetic stimulation can reduce the hyperactivity of the contralesional, intact hemisphere and thereby improve spatial neglect symptoms. However, it is not known whether this improvement is also relevant to the activities of daily living during spontaneous behaviour. The primary aim of the present study was to investigate whether the repeated application of continuous theta burst stimulation trains could ameliorate spatial neglect on a quantitative measure of the activities of daily living during spontaneous behaviour. We applied the Catherine Bergego Scale, a standardized observation questionnaire that can validly and reliably detect the presence and severity of spatial neglect during the activities of daily living. Eight trains of continuous theta burst stimulation were applied over two consecutive days on the contralesional, left posterior parietal cortex in patients suffering from subacute left spatial neglect, in a randomized, double-blind, sham-controlled design, which also included a control group of neglect patients without stimulation. The results showed a 37% improvement in the spontaneous everyday behaviour of the neglect patients after the repeated application of continuous theta burst stimulation. Remarkably, the improvement persisted for at least 3 weeks after stimulation. The amelioration of spatial neglect symptoms in the activities of daily living was also generally accompanied by significantly better performance in the neuropsychological tests. No significant amelioration in symptoms was observed after sham stimulation or in the control group without stimulation. These results provide Class I evidence that continuous theta burst stimulation is a viable add-on therapy in neglect rehabilitation that facilitates recovery of normal everyday behaviour.

Keywords: hemispatial neglect; neurorehabilitation; activities of daily living; repetitive transcranial magnetic stimulation; interhemispheric rivalry

Abbreviations: ADL = activities of daily living; CBS = Catherine Bergego Scale; TBS = theta burst stimulation; TMS = transcranial magnetic stimulation

Received February 10, 2012. Revised May 25, 2012. Accepted June 6, 2012. Advance Access publication July 24, 2012

Introduction

Stroke is one of the main causes of acquired disability in adults and its prevalence is expected to further increase over the next two decades (World Health Organization, 2003). Thus, the development of appropriate, specific interventions for restoring or optimizing functioning after stroke should be one of the major objectives of the healthcare system. A particularly disabling syndrome after stroke is spatial neglect, generally defined as the failure to detect, respond or orient to the stimuli located in the portion of space contralateral to the lesion (Heilman *et al.*, 1993). Spatial neglect is common, occurring in up to 43% of patients suffering from an acute right-hemispheric stroke (Ringman *et al.*, 2004) and is an independent predictor of poor outcome in terms of post-stroke functional independence (Stone *et al.*, 1992; Di Monaco *et al.*, 2011). Patients with spatial neglect have a slower functional progress during rehabilitation and need longer hospitalization periods (Cherney *et al.*, 2001; Buxbaum *et al.*, 2004; Gillen *et al.*, 2005). Furthermore, they have a decreased likelihood of being discharged home, resulting in increased costs for the healthcare system (Paolucci *et al.*, 2001; Wee and Hopman, 2008). Hence, there is a compelling need for effective and specific interventions for neglect rehabilitation, with the goal of improving patients' outcome not only in terms of functional recovery, but also in the activities of daily living (ADL) and in their participation in society.

In recent years, several treatment options for spatial neglect have been developed (Kerkhoff and Schenk, 2012), such as training of visual and tactile exploration (Weinberg *et al.*, 1979; Pizzamiglio *et al.*, 1992), caloric vestibular stimulation (Rubens, 1985), optokinetic stimulation (Karnath, 1996; Kerkhoff *et al.*, 2006), trunk rotation (Karnath *et al.*, 1991), spatiomotor or visuo-spatiomotor cueing (Kalra *et al.*, 1997), transcutaneous mechanical muscle vibration (Karnath *et al.*, 1993), transcutaneous electrical neural stimulation (Vallar *et al.*, 1995) and prismatic adaptation (Frassinetti *et al.*, 2002). A recent review of several neurorehabilitation techniques concluded that the existing evidence for the effectiveness of these approaches in reducing spatial neglect symptoms is mixed (Cappa *et al.*, 2011). Class I evidence characterizes controlled trials with masked or objective assessment of the outcome, conducted in a representative population, and with equivalent relevant characteristics (or an appropriate statistical adjustment of the latter) across treatment groups at baseline. Moreover, Class I trials also require allocation concealment, a clear definition of the primary outcome(s) and of the inclusion/exclusion criteria, an appropriate accounting for dropouts and a low number of crossovers between initially planned treatment groups (French and Gronseth, 2008). According to Cappa *et al.* (2011), Class I evidence exists only for visual exploration training (Weinberg *et al.*, 1977) and for spatiomotor or visuo-spatiomotor cueing (Kalra *et al.*, 1997). Although these techniques may ameliorate performance in clinical testing, a Cochrane Review reported that there is insufficient evidence of a positive impact on the disability in ADL and for a persistence of the effects after intervention (Bowen and Lincoln, 2007).

Non-invasive brain stimulation such as repetitive transcranial magnetic stimulation (TMS) or transcranial direct current stimulation is a new approach to treat spatial neglect (Cazzoli *et al.*, 2010; Utz *et al.*, 2010; Hesse *et al.*, 2011).

The rationale underlying the use of these non-invasive approaches to the treatment of spatial neglect is based on the interhemispheric rivalry model by Kinsbourne (1987, 1993). According to this model, a lesion to the attentional network of one hemisphere leads to a deficient transcallosal inhibition on the contralateral, intact homologue. This results in a pathological hyperactivity of the contralesional hemisphere, biasing visuospatial attention towards the ipsilesional side of space and thus resulting in spatial neglect.

Evidence for the validity of altered interhemispheric inhibition mechanisms as an explanatory model of spatial neglect comes from different lines of research, such as animal models (Sprague, 1966; Payne and Rushmore, 2004; Rushmore *et al.*, 2006; Valero-Cabré *et al.*, 2006; Palmer *et al*., 2012), functional MRI (Corbetta *et al*., 2005; He *et al*., 2007; Carter *et al*., 2010), clinical observations (Vuilleumier *et al*., 1996) and TMS (Koch *et al*., 2008, 2012). Thus, the application of inhibitory, non-invasive brain stimulation can potentially reduce the pathological hyperactivity in the contralesional, intact hemisphere and ameliorate symptoms of spatial neglect (Cazzoli *et al*., 2010; Utz *et al*., 2010; Hesse *et al*., 2011).

A promising repetitive TMS protocol that has been shown to induce inhibitory effects on behaviour that outlast the stimulation period is continuous theta burst stimulation (TBS) (Huang *et al.*, 2005; Nyffeler *et al.*, 2006). These effects are hypothesized to involve the induction of durable plasticity (after effects) via mechanisms similar to long-term potentiation and long-term depression (Cooke and Bliss, 2006; Huang *et al.*, 2007, 2011; Ridding and Rothwell, 2007). Of particular relevance to neurorehabilitation is evidence that repeated application of continuous TBS trains on a single day disproportionately prolongs the stimulation after-effects on cortical excitability. For instance, whereas a single continuous TBS train applied over the frontal eye field delayed saccade triggering in an oculomotor paradigm for up to 30 min, four trains of continuous TBS yielded an after-effect lasting up to 10 h (Nyffeler *et al.*, 2006). A similar prolongation of the after-effects by means of the application of repeated continuous TBS trains was also recently shown for the motor cortex (Goldsworthy *et al*., 2012). This prolongation resembles the phenomena observed in animal models in which repeated stimulation application enhanced the lifetime of activity-dependent synaptic plastic changes (Bliss and Gardner-Medwin, 1973; Abraham *et al.*, 1993, 2002).

In a proof of concept study, we used repeated application of continuous TBS trains on a single day to attempt to ameliorate spatial neglect symptoms in 11 patients who suffered right-hemispheric stroke (Nyffeler *et al.*, 2009). Our results demonstrated that the application of four continuous TBS trains applied over the contralesional, intact posterior parietal cortex yielded a significant increase in the number of perceived left visual targets in a visual perception task for up to 32 h.

The primary aim of the present study was to investigate whether the repeated application of continuous TBS trains can ameliorate spatial neglect in the ADL, in a randomized, double-blind, sham-controlled design. For this purpose, we applied—in addition to a battery of neuropsychological tests—the Catherine Bergego

Scale (CBS) (Azouvi *et al.*, 1996), which specifically quantifies the severity of spatial neglect in several ADL. Furthermore, we aimed to assess whether the stimulation after-effects could be prolonged for several weeks by the application of a greater number of continuous TBS trains. To this end, we applied eight continuous TBS trains over two consecutive days and assessed the effects over weeks.

Materials and methods

Patients

The study inclusion criteria for the patients with spatial neglect were as follows. Patients had to have suffered a first (i.e. no previous history of cerebral damage) ischaemic or haemorrhagic lesion to the right hemisphere and exhibit left-sided spatial neglect on clinical judgement and on clinical testing at admission. Every patient underwent a neurological examination and a cognitive function screening. The latter included three classes of neuropsychological tests for spatial neglect: a cancellation task [Star cancellation test (Wilson *et al.*, 1987); Random letter cancellation test (Weintraub and Mesulam, 1988); or Bells test (Gauthier *et al.*, 1989)], a line bisection task [Line bisection task (Schenkenberg *et al.*, 1980); Line bisection test (Wilson *et al.*, 1987); or Complex line bisection test (Butter *et al.*, 1988)], and a drawing task [copy and/or spontaneous; Rey-Osterrieth complex figure test, copy (Osterrieth, 1944); Five-point test (Regard *et al.*, 1982); Figure copying test (Morris *et al.*, 1989); Copy drawing test (Halligan *et al.*, 1991); or Clock drawing test]. The administered paper–pencil tests, the applied cut-off scores and the results at admission are summarized in Supplementary Table 1. The presence of spatial neglect was determined on the basis of deficits in at least two out of three classes of paper–pencil tests and on the clinical judgement of the clinician. Moreover, all patients had to have normal or corrected-to-normal visual acuity and an intact central 30° of their visual field, as assessed by perimetry (Octopus Perimetry or Goldman Kinetic Perimetry, Octopus Perimeter 101, Haag-Streit International). The selection of patients with spared central (i.e. within 30°) visual field enabled us to better interpret the results in terms of spatial neglect and avoid confounding effects of hemianopia or quadrantanopia. However, visual field defects in patients suffering from spatial neglect are common (e.g. Vallar and Perani, 1986) and they may exacerbate spatial neglect symptoms (e.g. Doricchi and Angelelli, 1999; but see also Halligan *et al.*, 1990). Thus, one should be aware that the effects of continuous TBS application in a group of spatial neglect patients who are not selected with respect to visual field defects might theoretically have a different outcome.

Exclusion criteria for the application of TMS were based on the internationally accepted safety guidelines for TMS application (Rossi *et al.*, 2009), which include an assessment of the history of epilepsy, prior head trauma, drug and alcohol abuse and major psychiatric disorders.

Twenty-four right-handed patients (seven females; 14 with ischaemic, 10 with haemorrhagic brain lesions) were included in the study between April 2009 and June 2011 and were randomly allocated to one of three groups: continuous TBS followed by sham, 'continuous TBS, then sham' group; sham followed by continuous TBS, 'sham, then continuous TBS' group; and 'no stimulation' control group. Their mean age was 58 years [standard error of the mean (SEM) = 2.25 years] and the mean interval between stroke onset and beginning of testing was 26.63 days (SEM = 4.44 days). The study was performed in the subacute stage for all patients. Age and latency between stroke onset and the beginning of testing were not significantly different between the three groups: [$F(2,21) = 0.038$, $P = 0.887$; and $F(2,21) = 3.23$, $P = 0.06$, respectively].

The present study was carried out in accordance with the principles of the latest version of the Declaration of Helsinki and was approved by the Ethical Committee of the State of Bern.

Lesion analysis

Lesion mapping and overlap analyses were performed on high-resolution structural MRI data of the patients using the MRIcron software (Rorden *et al.*, 2007), in order to map the locations of the damaged cortical areas and to calculate the volume of the lesion. We used the same procedure as applied by Karnath *et al.* (2002, 2004). Diffusion-weighted scans were used when an MRI sequence was conducted within the first 48 h post-stroke. Otherwise, a T_2-weighted scan acquired 48 h post-stroke was used as the basis for the lesion analyses. The boundary of the lesions was delineated directly on the individual MRI image for every transverse slice. Both the scan and the lesion shape were then mapped into approximate Talairach space using the spatial normalization algorithm provided by SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Mapping of the lesions was performed by a collaborator who was naive to the patients' test results and clinical presentation.

The overlap of the patients' individual cerebral lesion mappings is presented in Fig. 1.

The mean lesion volume was 61.9 cm^3 (SEM = 9.35 cm^3) in the 'continuous TBS, then sham' group, 122.72 cm^3 (SEM = 31.14 cm^3) in the 'sham, then continuous TBS' group and 57.99 cm^3 (SEM = 20.19 cm^3) in the 'no stimulation' control group. Although the lesion volume in the 'sham, then continuous TBS' group was greater compared to the other groups, the mean lesion volume across the three groups was not significantly different [ANOVA with 'Group' as the between-subjects factor; $F(2,21) = 2.69$, $P = 0.091$].

Neuropsychological tests and assessment of the activities of daily living

In the Subtask of the Vienna test system (Peripheral Perception; Dr G. Schuhfried GmbH), patients were asked to respond to light bands appearing in the visual field periphery while their attention was engaged in a central tracking task (see for details Nyffeler *et al.*, 2009). Overall, 15 left-sided and 15 right-sided light bands were presented, in random order and at unpredictable time intervals. Omissions were defined as the absence of reaction to the light bands during 9 s. Reaction times were defined as the time needed to press the foot pedal in response to the light bands.

In the random shape cancellation test (Weintraub and Mesulam, 1988), patients were presented with an unstructured array of geometric shapes and were asked to mark a particular target. There were 30 targets on the left side and 30 targets on the right side of the paper sheet, symmetrically located with respect to the horizontal and vertical axes, whereas non-target shapes were irregularly distributed. Left-sided omissions were defined as the target shapes on the left side of the paper sheet that were not marked by the patients.

The two part picture test (Brunila *et al.*, 2003) is a picture scanning test, representing coloured line drawings of two room interiors, one on the left and one on the right side, containing 10 target objects each. Patients were asked to name and to point at every object they saw on the picture. Left-sided omissions were defined as the target objects on the left side of the paperboard that were not named by the patients.

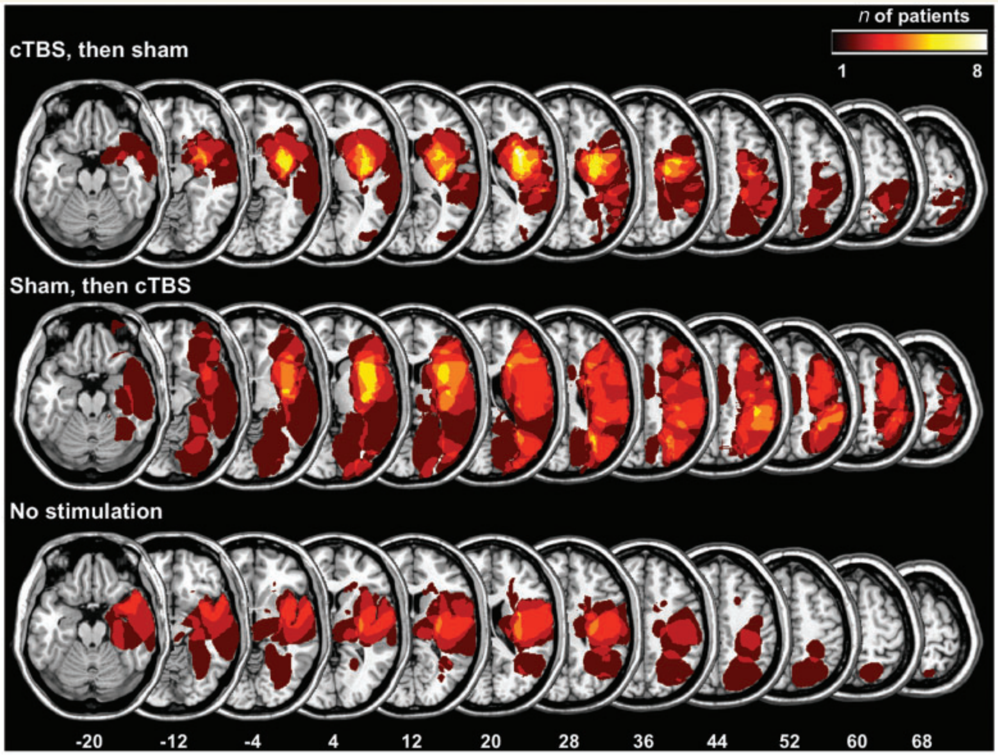

Figure 1 Overlap map showing the degree of involvement of each individual voxel normalized to the MNI template in the lesions of the three groups of spatial neglect patients. The map is presented as 2D axial renderings on the MNI 'representative' brain in 8 mm ascending steps. The *z*-position of each axial slice in the Talairach stereotaxic space is presented at the bottom of the figure. cTBS = continuous TBS.

The Munich reading texts (Kerkhoff *et al.*, 1992) are six 180-word texts (parallel versions A–F) in German, with easy linguistic structure and short sentences. The versions of the texts were administered alphabetically, one for each of the assessment time-points. The patients were requested to read aloud the text as quickly and as accurately as possible. During reading, patients were not allowed to use any aid. Left-sided reading errors were defined as any error or letter/word omission on the left side of the paper sheet.

The CBS (Azouvi *et al.*, 1996) is a valid and reliable scale (Schädler *et al.*, 2009) intended to assess the presence and severity of spatial neglect in the ADL. The scale includes 10 questions to observers, targeting different domains of the ADL. Raters are asked to score the performance of the patients in a particular domain of the ADL from 0 (no neglect) to 3 (severe neglect). Performance on the ADL was assessed by four independent raters who were responsible for the care of each particular patient in the neurorehabilitation setting, i.e. nurses, physiotherapists, occupational therapists and neuropsychologists. The raters were all trained in the use of the CBS and blind with respect to which of the three groups each patient had been allocated.

To evaluate possible negative effects of continuous TBS application on left-hemispheric functions such as language, we administered the 'short aphasia checklist' (kurze Aphasie-Check-Liste; Kalbe *et al.*, 2002), a standardized and sensitive screening tool for language impairment, to a subset of patients after continuous TBS application.

Continuous theta burst stimulation and sham protocol

Continuous TBS was applied by means of a MagPro X100 stimulator (Medtronic Functional Diagnostics) connected to a round coil with 60 mm outer radius (Magnetic Coil Transducer MC-125). Continuous TBS was delivered with the same protocol described previously (Nyffeler *et al.*, 2008, 2009; Cazzoli *et al.*, 2009*a*, *b*). In brief, the continuous TBS protocol comprised 801 pulses, delivered in a continuous train and consisting of 267 bursts. Each burst contained three pulses at 30 Hz, repeated at 6 Hz. The total duration of one single, continuous TBS train was 44 s. Overall, eight continuous TBS trains were applied over 2 days. Four continuous TBS trains were applied on Day 1 (two continuous TBS trains with an interval of 15 min, the third and the fourth train 60 and 75 min after the first continuous TBS train, respectively; see Nyffeler *et al.*, 2009) and four continuous TBS trains on Day 2 (same time intervals as for Day 1). Continuous TBS was applied over P3, according to the International 10–20 EEG System. This site overlies the posterior parietal cortex in proximity of the intraparietal sulcus (Hilgetag *et al.*, 2001). The coil was held tangentially to the scalp, with the handle pointing posteriorly, the current flowing clockwise as viewed from above. The patients were asked to close their eyes during continuous TBS application. Continuous TBS was delivered at 100% of patients' individual resting motor threshold.

Sham was applied with the same protocol as described above, except for the use of a sham coil (Magnetic Coil Transducer MC-P-B70).

Experimental procedures

The timelines of the experimental procedures in the three groups of patients are schematically depicted in Fig. 2. For illustrative purposes, we define five exemplary weeks numbered from 0 to 4, with 7 days numbered from 1 to 7.

For the 'continuous TBS, then sham' group, baseline assessment started during Day 3 of Week 0. During Day 3, neuropsychological assessments took place and the CBS forms were handed over to the raters. The raters were asked to observe the patients during the period going from Day 3 to Day 7 of Week 0 and to fill it out at the end of the week. Continuous TBS application (Nyffeler *et al.* 2008, 2009; Cazzoli *et al.*, 2009*a*, *b*) was performed on Day 1 and Day 2 of Week 1, as described above. Neuropsychological assessment after continuous TBS application (postcontinuous TBS) took place on Day 3 of Week 1. On the same day, the CBS forms for the evaluation after continuous TBS application were handed over to the raters. Sham application was performed on Day 1 and Day 2 of Week 2 according to the continuous TBS protocol. Neuropsychological assessment (post sham) and CBS evaluations were carried out as described above. Finally, a follow-up assessment was performed on Day 3 of Week 3 with the same evaluation procedure as used in the previous weeks.

For the 'sham, then continuous TBS' group the same experimental procedure as above was applied, except for the reversed order of continuous TBS and sham application, in a crossover design (Fig. 2). Moreover, a second follow-up assessment time point (Week 4) was introduced to enable us to assess the patients in this group for 2 weeks after continuous TBS application, as was the case in the 'continuous TBS, then sham' group. The assessment of the 'no stimulation' control group was exactly the same as in the 'continuous TBS, then sham' group.

Concerning the CBS evaluation, each patient was rated in most cases (i.e. in 85% of cases) by the same four people who were responsible for her/his care (i.e. nurses, physiotherapists, occupational therapists and neuropsychologists) in the neurorehabilitation setting. To evaluate inter-rater agreement between the four raters, we calculated intraclass correlation coefficients (Shrout and Fleiss, 1979) based on the CBS scores of each time point (i.e. from Week 0 to Week 4) and corresponding *F*-statistics (testing the null hypothesis of no agreement). The mean intraclass correlation coefficient was of 0.789 (coefficients of the single time points ranging from 0.675 to 0.853, all significant at $P < 0.05$), indicating substantial agreement (Landis and Koch, 1977).

All patients included completed the study protocol (i.e. there were no dropouts). Moreover, all patients were assessed with all tests included in the study protocol, with the following exceptions. Three patients included in the control group could not be assessed with the Subtask of the Vienna Test System (Peripheral Perception), due to differences in the equipment of the clinics participating in the present study. One patient in the 'sham, then continuous TBS' group was not tested at all assessment time points with the two part picture test. The data of the patient in this particular test were thus excluded from the analysis. The 'short aphasia checklist' was administered to a subgroup of five patients undergoing continuous TBS.

During the study, all patients were also undergoing full neurorehabilitation therapy including 1 h neuropsychological training (visuospatial exploration training, and attention and concentration training), 1 h of occupational therapy and 1 h of physiotherapy per day.

Data analysis

For the Subtask of the Vienna Test System (Peripheral Perception), the number of omitted left-sided or right-sided visual targets was computed for every patient and every assessment time-point. Moreover, the mean reaction time to the left-sided and to the right-sided visual targets was calculated.

For every CBS assessment time-point, the scores given by the raters were averaged for each of the 10 questions. The 10 values were then averaged, resulting in one value per patient and assessment time-point.

For the paper–pencil assessment, the number of left-sided omissions (random shape cancellation test and two part picture test) and the number of left-sided reading errors (Munich reading texts) were computed for every patient and every assessment time-point.

To exclude the possibility that baseline differences before the intervention were responsible for the different outcomes observed in each group, we compared baseline performance (i.e. Week 0) of the three groups on all the above-mentioned parameters by means of multiple independent, univariate ANOVAs with 'Group' as the between-subjects variable (levels: continuous TBS, then sham; sham, then continuous TBS; no stimulation).

The effects of continuous TBS, sham or 'no stimulation' were assessed for each group by means of repeated-measures ANOVAs, with

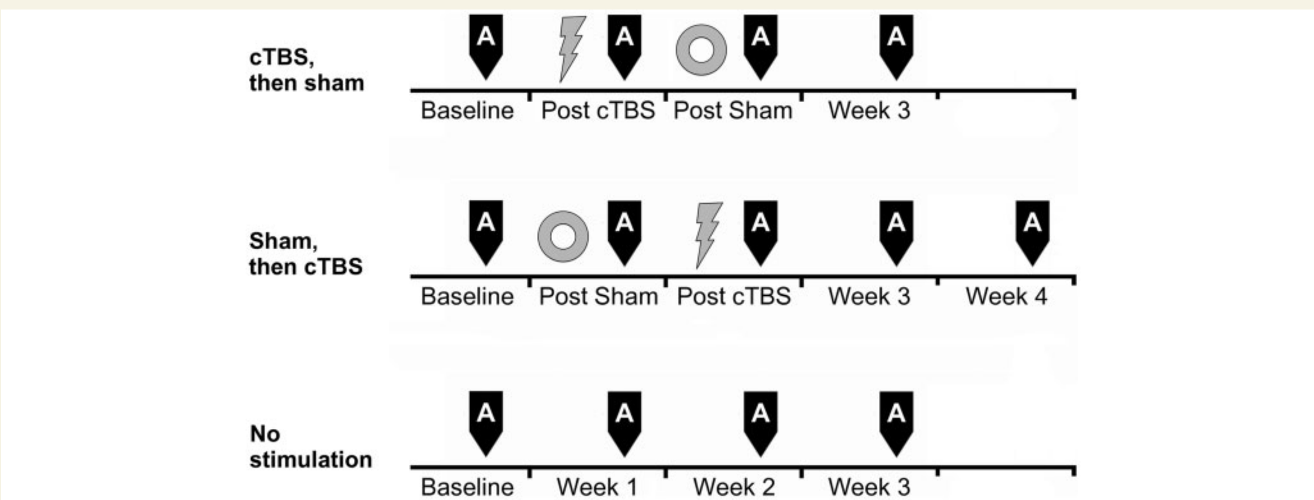

Figure 2 Schematic representation of the time line of the experimental procedures in the three groups of patients with neglect. Arrows with an 'A' indicate assessment time-points, bolt signs represent continuous TBS stimulation, and round signs depict sham stimulation. cTBS = continuous TBS.

'Time' as a within-subject variable (four levels: baseline, post continuous TBS, post sham, Week 3, Week 4 only for the 'sham, then continuous TBS' group). *Post hoc* testing was performed by means of Fisher's least significant difference-corrected *t*-tests and was week-to-week (i.e. Week 0 versus Week 1, Week 1 versus Week 2, etc.).

To further evaluate whether the continuous TBS application would yield a significantly greater spatial neglect amelioration than during the same time period in the control group, we also performed statistical testing between groups applying standardized pre–post differences (Becker, 1988; Grawe and Braun, 1994), which are commonly used to evaluate treatment efficacy (Lambert and Ogles, 2004). The scores are standardized by calculating the pre–post difference and dividing it by the standard deviation of the pre-test. The two following comparisons were tested by means of *t*-tests for independent samples (two-tailed): (baseline–post continuous TBS) in the 'continuous TBS, then sham' group versus (baseline–Week 1) in the 'no stimulation' control group; and (post sham post continuous TBS) in the 'sham, then continuous TBS' group versus (Week 1–Week 2) in the 'no stimulation' control group. Moreover, to assess whether this amelioration would still be present at a later time course, we performed statistical testing on the standardized pre–post differences resulting from the subtraction (baseline–Week 3) between the two groups undergoing continuous TBS (i.e. the 'continuous TBS, then sham' group and the 'sham, then continuous TBS' group) and the 'no stimulation' control group, by means of *t*-tests for independent samples (two-tailed).

Pearson's correlations were used to test for associations between age, neglect severity and lesion volume and the change in the CBS after continuous TBS [(CBS score post continuous TBS − CBS score pre continuous TBS) $\times -1$].

The transformed scores of the 'short aphasia checklist' were computed for every patient pre and post continuous TBS application and statistically compared by means of a *t*-test for paired samples.

Results

Continuous TBS and sham protocols were well tolerated by all patients, without any side effects (such as pain, vertigo, dizziness, headache or paraesthesia). There was no significant difference in the 'short aphasia checklist' scores pre and post continuous TBS application [pre continuous TBS: mean = 34.9, SEM = 0.86 points; post continuous TBS mean = 36.2, SEM = 0.96 points; $t(4) = -1.307$, $P = 0.261$, two-tailed]; that is, continuous TBS had no detrimental effect on language functioning. The patients did not report any particular sensation during or after the continuous TBS or sham application.

Continuous theta burst stimulation significantly improves neglect in the activities of daily living as measured by the Catherine Bergego Scale

The baseline values of neglect severity as measured on the ADL (CBS score) were equivalent across the three groups [$F(2,21) = 1.680$, $P = 0.21$].

In the 'continuous TBS, then sham' group, there was a significant reduction over time of neglect severity [$F(3,21) = 8.635$, $P < 0.001$]. Neglect severity was significantly reduced by the application of continuous TBS (i.e. baseline versus post continuous TBS, $P = 0.006$) but not of sham stimulation (i.e. post continuous TBS versus post sham, $P = 0.11$).

A significant reduction of neglect severity over time was also found in the 'sham, then continuous TBS' group [$F(4,28) = 11.858$, $P < 0.001$]. Neglect severity was significantly reduced by the application of continuous TBS (i.e. post sham versus post continuous TBS, $P = 0.002$) but not by sham stimulation (i.e. baseline versus post sham, $P = 0.625$).

In the 'no stimulation' control group, there was no significant reduction of neglect severity over time [$F(3,21) = 2.118$, $P = 0.128$]. Mean CBS scores in the three groups of patients are shown in Fig. 3.

The test on the standardized pre–post differences revealed a significantly greater reduction of spatial neglect severity after continuous TBS application in both the 'sham, then continuous TBS' group (mean = 0.961, SEM = 0.253) and in the 'continuous TBS, then sham group' (mean = 0.865, SEM = 0.296) compared with the same time periods in the 'no stimulation' control group (mean = 0.087, SEM = 0.052; and mean = 0.105, SEM = 0.170) [$t(14) = -3.384$, $P = 0.004$; and $t(14) = -2.222$, $P = 0.043$, respectively]. The reduction of spatial neglect severity from baseline was still significantly greater at Week 3 in both the 'sham, then continuous TBS' group (mean = 1.409, SEM = 0.242) and in the 'continuous TBS, then sham' group (mean = 1.113, SEM = 0.317) compared with the 'no stimulation' control group (mean = 0.359, SEM = 0.131) [$t(14) = -3.813$, $P = 0.002$; and $t(14) = -2.196$, $P = 0.045$, respectively].

To elaborate on the ameliorative effects of continuous TBS on spatial neglect as measured by the ADL, Fig. 4 depicts the single CBS values pre and post continuous TBS application of the patients in the 'continuous TBS, then sham' group and in the 'sham, then continuous TBS' group. The mean percentage change in the CBS score between pre and post continuous TBS application corresponded to −37.35% (SEM = 11.64%) in the 'continuous TBS, then sham' group and to −36.95% (SEM = 8.54%) in the 'sham, then continuous TBS' group. There was no significant difference between the two groups [one-way ANOVA with 'Group' as the between-subjects factor; $F(1,14) = 0.001$, $P = 0.978$].

There was no significant correlation between the change in the CBS score after continuous TBS and the age of the patients ($r = 0.060$, $P = 0.825$, two-tailed), the severity of spatial neglect in the baseline ($r = 0.335$, $P = 0.205$, two-tailed), or the lesion volume ($r = -0.207$, $P = 0.442$, two-tailed).

Continuous theta burst stimulation significantly improves the detection of left-sided visual targets in the subtask of the Vienna Test System

The baseline values of the number of omitted left-sided and right-sided visual targets were equivalent across the three groups [$F(2,18) = 0.949$, $P = 0.406$; $F(2,18) = 0.503$, $P = 0.613$].

In the 'continuous TBS, then sham' group, there was a significant reduction of the number of omitted left-sided visual targets over time [$F(3,21) = 16.062$, $P < 0.001$]. Left-sided omissions

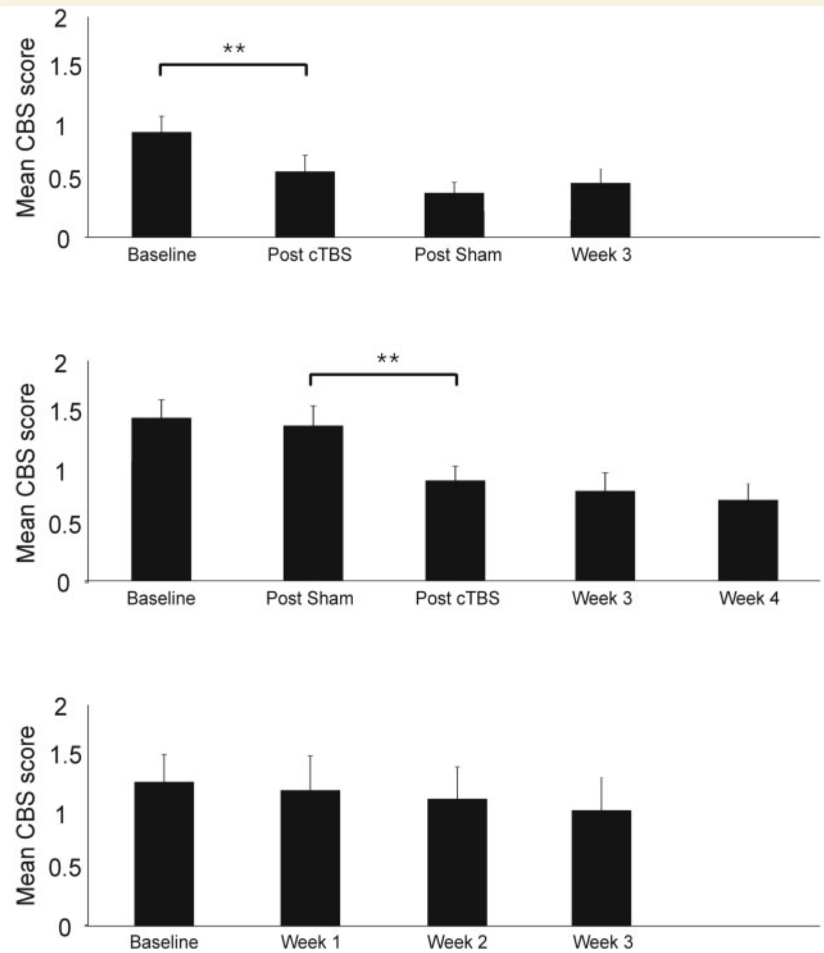

Figure 3 Mean CBS score in the 'continuous TBS, then sham' group (*top*), the 'sham, then continuous TBS' group (*middle*), and the 'no stimulation' control group (*bottom*). Error bars indicate the standard error of the mean (SEM). Asterisks depict significant *post hoc* tests at $^{**}P < 0.01$. cTBS = continuous TBS.

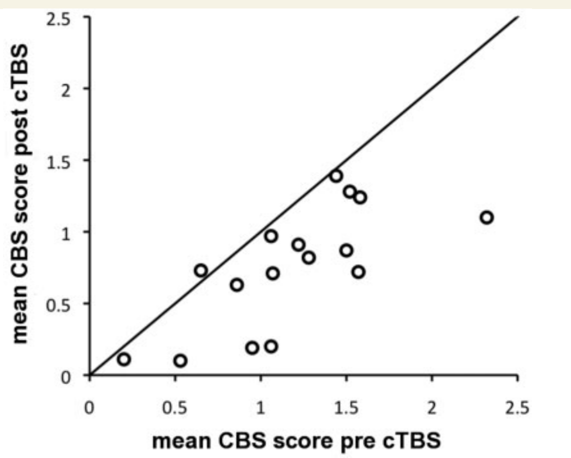

Figure 4 Single values of the CBS scores in the 16 spatial neglect patients pre (*x*-axis) and post (*y*-axis) continuous TBS application. The diagonal line represents no change. Values below the line indicate amelioration (CBS score decrease), values above the line deterioration (CBS score increase). cTBS = continuous TBS.

were significantly reduced after continuous TBS (i.e. baseline versus post continuous TBS, $P < 0.001$) but not after sham stimulation (i.e. post continuous TBS versus post sham, $P = 0.423$).

In the 'sham, then continuous TBS' group, there was also a significant reduction of the number of omitted left-sided visual targets over time [$F(4,28) = 6.477$, $P < 0.001$]. Again, left-sided omissions were significantly reduced after continuous TBS (i.e. post sham versus post continuous TBS, $P = 0.046$), but not after sham stimulation (i.e. baseline versus post sham, $P = 0.592$).

In the 'no stimulation' control group, there was no significant reduction of the number of omitted left-sided visual targets over time [$F(3,12) = 1.276$, $P = 0.327$].

The test on the standardized pre–post differences revealed a significantly greater reduction in the number of omitted left-sided visual targets after continuous TBS application in both the 'sham, then continuous TBS' group (mean = 0.833, SEM = 0.206) and in the 'continuous TBS, then sham' group (mean = 0.880, SEM = 0.189) compared with the same time periods in the 'no stimulation' control group (mean = 0.165, SEM = 0.128; and mean = −0.031, SEM = 0.058) [$t(11) = -2.364$, $P = 0.038$; and $t(11) = -3.670$, $P = 0.004$, respectively]. The reduction in the number of omitted left-sided visual targets from baseline was still significantly greater at Week 3 in both the 'sham, then continuous TBS' group (mean = 1.089, SEM = 0.312) and in the 'continuous TBS, then sham' group (mean = 1.157, SEM = 0.260) compared with the 'no stimulation' control group (mean = 0.156, SEM = 0.070) [$t(11) = -2.309$, $P = 0.041$; and $t(11) = -2.957$, $P = 0.013$, respectively].

There was no significant change over time in the number of omissions of right-sided visual targets in any of the three groups ['continuous TBS, then sham': $F(3,21) = 0.635$, $P = 0.600$; 'sham, then continuous TBS': $F(4,28) = 0.953$, $P = 0.449$; 'no stimulation': $F(3,12) = 1.265$, $P = 0.331$].

Figure 5 shows the mean number of omitted visual targets presented on the left and on the right side in the three groups.

The baseline values of the mean reaction times for the left-sided and the right-sided visual targets were equivalent across the three groups [$F(2,18) = 1.190$, $P = 0.327$; $F(2,18) = 0.238$, $P = 0.791$].

In the 'continuous TBS, then sham' group, patients detected left-sided visual targets significantly faster over time [$F(3,21) = 11.403$, $P < 0.001$]. Mean reaction times to left-sided visual targets were significantly decreased after continuous TBS (i.e. baseline versus post continuous TBS, $P = 0.003$), but not after sham stimulation (i.e. post continuous TBS versus post sham, $P = 0.26$).

In the 'sham, then continuous TBS' group, patients also detected left-sided visual targets significantly faster over time [$F(4,28) = 10.499$, $P < 0.001$]. Mean reaction times to left-sided visual targets were significantly decreased after continuous TBS (i.e. post sham versus post continuous TBS, $P = 0.008$) but not after sham stimulation (i.e. baseline versus post sham, $P = 0.866$).

In the 'no stimulation' control group, mean reaction times to left-sided visual targets were not significantly decreased over time [$F(3,12) = 1.276$, $P = 0.327$].

Additionally, in the 'continuous TBS, then sham' group, patients also detected right-sided visual targets significantly faster over time [$F(3,21) = 7.818$, $P = 0.001$]. Mean reaction times to right-sided visual targets were significantly decreased after continuous TBS (i.e. baseline versus post continuous TBS, $P = 0.002$), but not after sham stimulation (i.e. post continuous TBS versus post sham, $P = 0.932$). In the other two patient groups, there was no significant change over time in the mean reaction times to the right-sided visual targets ['sham, then continuous TBS': $F(4,28) = 2.232$, $P = 0.091$; 'no stimulation': $F(3,12) = 0.291$, $P = 0.831$].

Figure 6 shows the mean reaction times for the left and the right side in the three groups.

In summary, patients showed a better and faster detection of left-sided visual targets after continuous TBS, without a detrimental effect on the detection of right-sided visual targets.

Continuous theta burst stimulation significantly improves neglect in the paper–pencil assessment

There were no significant differences between the baseline values of three groups in either the two part picture test [$F(2,20) = 2.066$, $P = 0.153$], or the Munich reading texts [$F(2,21) = 2.375$,

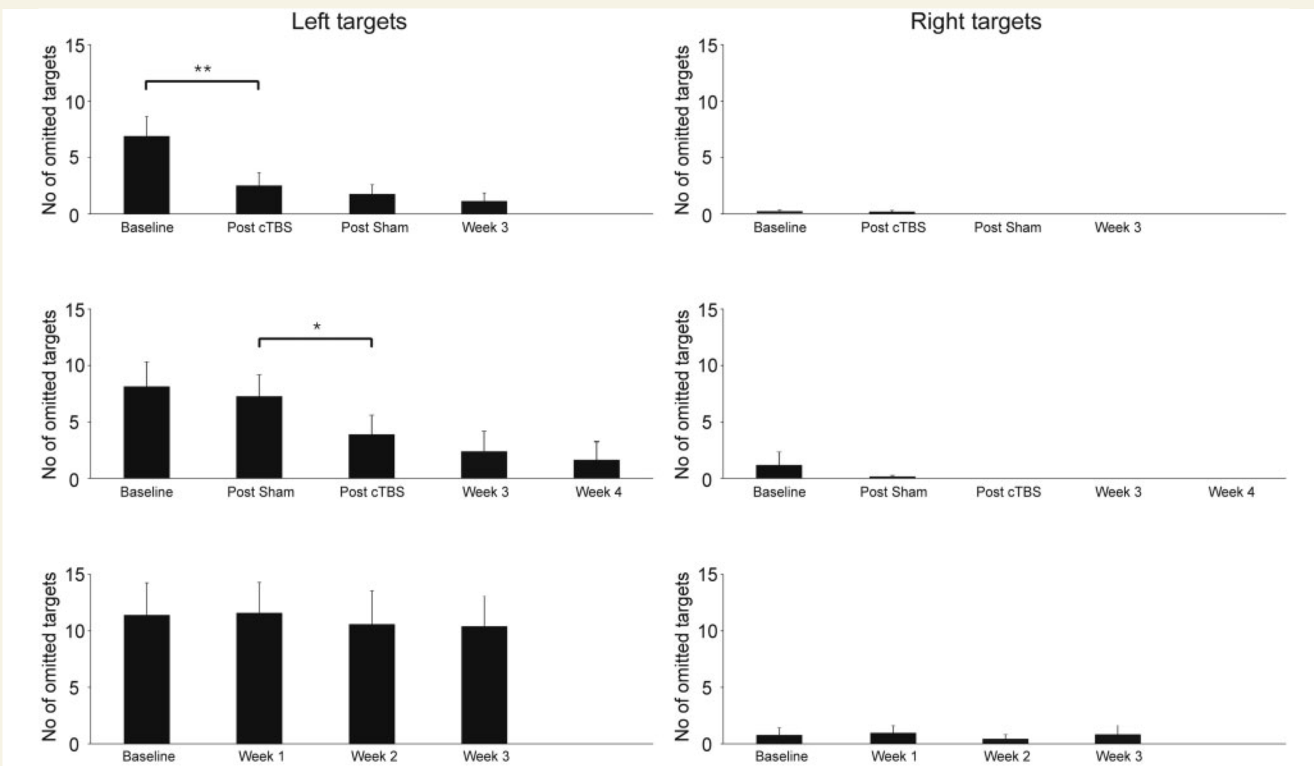

Figure 5 Mean number of left- and right-sided omitted visual targets in the subtask of the Vienna Test System (Peripheral Perception) in the 'continuous TBS, then sham' group (*top*), the 'sham, then continuous TBS' group (*middle*), and the 'no stimulation' control group (*bottom*). Error bars indicate the standard error of the mean (SEM). Asterisks depict significant *post hoc* tests at $^{**}P < 0.01$ or $^{*}P < 0.05$. cTBS = continuous TBS.

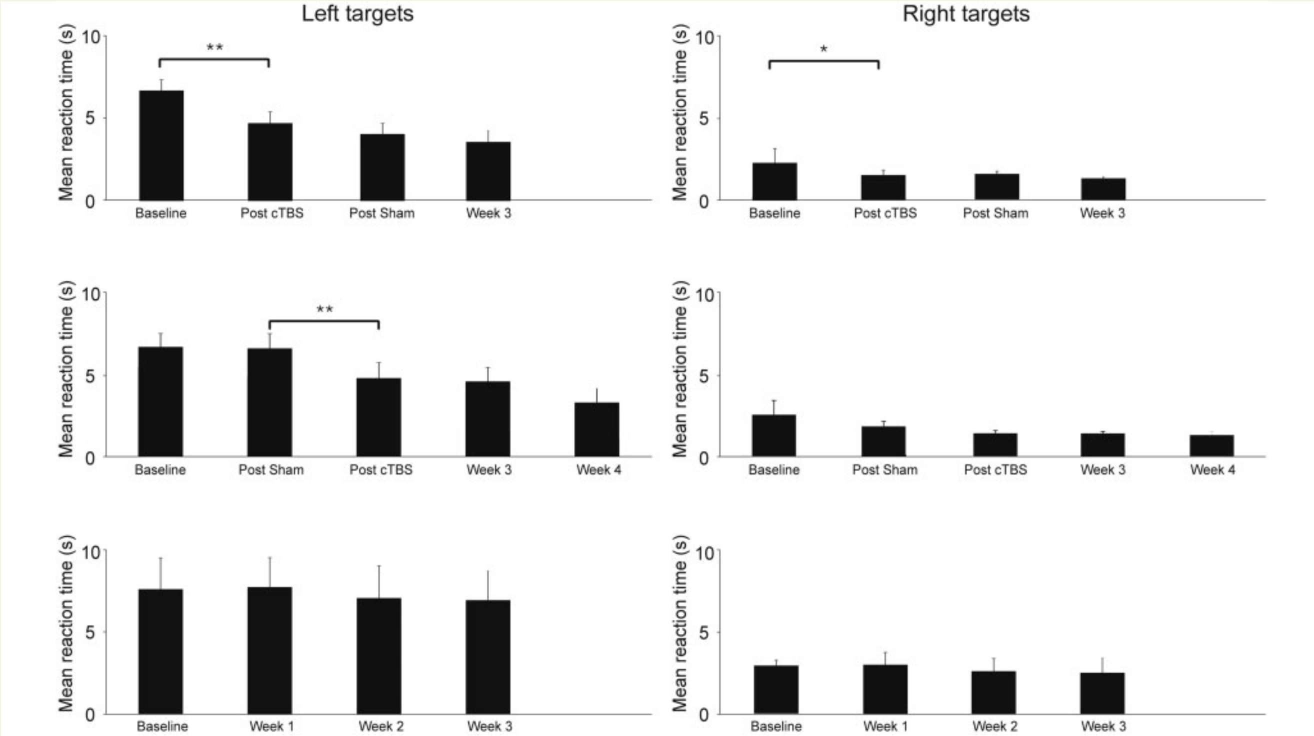

Figure 6 Mean reaction times for the left- and right-sided visual targets in the subtask of the Vienna Test System (PVT) in the 'continuous TBS, then sham' group (*top*), the 'sham, then continuous TBS' group (*middle*), and the 'no stimulation' control group (*bottom*). Error bars indicate the standard error of the mean (SEM). Asterisks depict significant *post hoc* tests at $^{**}P < 0.01$ or $^{*}P < 0.05$. cTBS = continuous TBS.

$P = 0.118$]. Baseline values on the random shape cancellation test revealed significant differences between the groups [$F(2,21) = 4.171$, $P = 0.030$]. At baseline, the 'continuous TBS, then sham' group omitted significantly fewer left-sided targets in the random shape cancellation test than the 'sham, then continuous TBS' group ($P = 0.009$), but not than the 'no stimulation' control group ($P = 0.111$).

'Continuous theta burst stimulation, then sham' group

In the 'continuous TBS, then sham' group, there was a significant reduction of left-sided omissions over time in both the random shape cancellation test [$F(3,21) = 9.097$, $P < 0.001$] and in the two part picture test [$F(3,21) = 7.929$, $P = 0.001$]. Left-sided omissions were significantly reduced after continuous TBS (i.e. baseline versus post continuous TBS; random shape cancellation test, $P = 0.003$; two part picture test, $P < 0.001$), but not after sham stimulation (i.e. post continuous TBS versus post sham; random shape cancellation test, $P = 0.501$; two part picture test, $P = 0.824$). No significant reduction in left-sided reading errors was found over time in the Munich reading texts [$F(3,21) = 2.252$, $P = 0.112$].

The results of the three paper–pencil tests for the 'continuous TBS, then sham' group are presented in Fig. 7.

The test on the standardized pre–post differences revealed a significantly greater reduction in the number of left-sided omissions after continuous TBS application in the 'continuous TBS, then sham' group in the random shape cancellation test (mean = 0.691, SEM = 0.186) and in the two part picture test (mean = 0.781, SEM = 0.273) compared with the same time period in the 'no stimulation' control group (random shape cancellation test: mean = 0.038, SEM = 0.200; two part picture test: mean = 0.026, SEM = 0.062) [$t(14) = -2.394$, $P = 0.031$; and $t(14) = -2.698$, $P = 0.017$, respectively]. In the Munich reading texts, there was no significant difference in the pre–post differences concerning left-sided reading errors between the 'continuous TBS, then sham' group after continuous TBS application (mean = 0.484, SEM = 0.315) and the 'no stimulation' control group in the same time period (mean = −0.003, SEM = 0.036) [$t(14) = -1.534$, $P = 0.147$]. The reduction of left-sided omission from baseline to Week 3 in the three paper–pencil tests was not significantly greater in the 'continuous TBS, then sham' group (random shape cancellation test: mean = 1.001, SEM = 0.274; two part picture test: mean = 0.827, SEM = 0.292; Munich reading texts: mean = 0.484, SEM = 0.328) than in the 'no stimulation' control group (random shape cancellation test: mean = 0.393, SEM = 0.273; two part picture test: mean = 0.340, SEM = 0.142; Munich reading texts: mean = 0.274, SEM = 0.176) [$t(14) = -1.570$, $P = 0.139$; $t(14) = -1.496$, $P = 0.157$; $t(14) = -0.563$, $P = 0.582$; respectively].

'Sham, then continuous theta burst stimulation' group

In the 'continuous TBS, then sham' group, there was a significant reduction of left-sided omissions over time in the random shape cancellation test [$F(4,28) = 19.697$, $P < 0.001$], in the two part

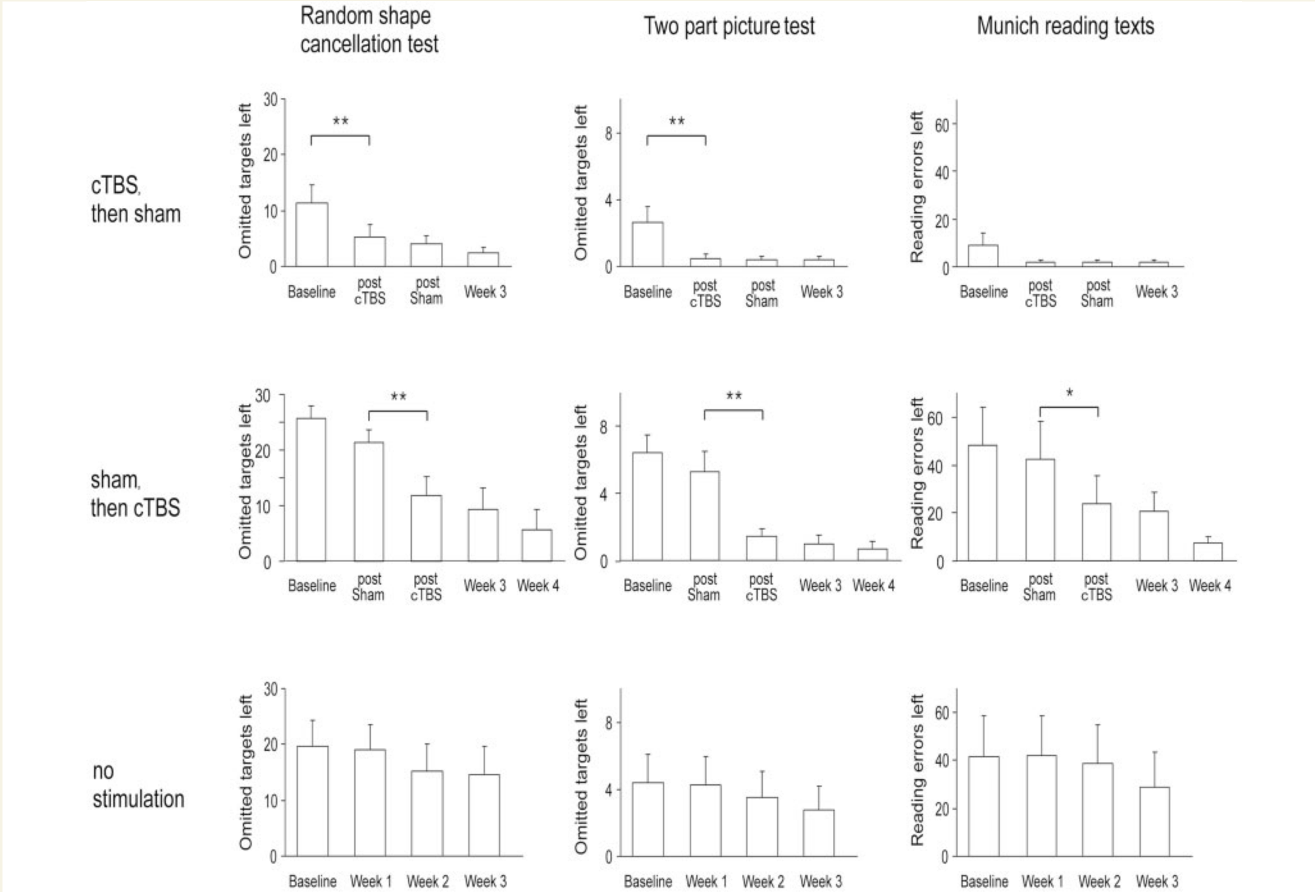

Figure 7 Results in the paper–pencil assessment of the 'continuous TBS, then sham' group (*top row*), the 'sham, then continuous TBS' group (*middle row*), and the 'no stimulation' control group (*bottom row*). Random shape cancellation test (*left column*), two part picture test (*middle column*), and Munich reading texts (*right column*). Error bars indicate the standard error of the mean (SEM). Asterisks depict significant *post hoc* tests at $**P < 0.01$ or $*P < 0.05$. cTBS = continuous TBS.

picture test [$F(4,24) = 26.573$, $P < 0.001$] and in the Munich reading texts [$F(4,28) = 6.054$, $P = 0.001$]. Left-sided omissions were significantly reduced after continuous TBS (i.e. post sham versus post continuous TBS; random shape cancellation test, $P = 0.002$; two part picture test, $P < 0.001$; Munich reading texts, $P = 0.04$), but not after sham stimulation (i.e. baseline versus post sham; random shape cancellation test, $P = 0.112$; two part picture test, $P = 0.133$; Munich reading texts, $P = 0.57$).

The results of the three paper–pencil tests in the 'sham, then continuous TBS' group are presented in Fig. 7.

The test on the standardized pre–post differences revealed a significantly greater reduction in the number of left-sided omissions after continuous TBS application in the 'sham, then continuous TBS' group in the random shape cancellation test (mean = 1.358, SEM = 0.314) and in the two part picture test (mean = 1.168, SEM = 0.276) compared with the same time period in the 'no stimulation' control group (random shape cancellation test: mean = 0.324, SEM = 0.217; two part picture test: mean = 0.154, SEM = 0.108) [$t(14) = -2.708$, $P = 0.017$; and $t(13) = -3.599$, $P = 0.003$, respectively]. In the Munich reading texts, there was no significant difference in the pre–post differences concerning left-sided reading errors between the 'sham, then continuous TBS' group after continuous TBS application (mean = 0.421, SEM = 0.210) and the 'no stimulation' control group in the same time period (mean = 0.066, SEM = 0.029) [$t(14) = -1.670$, $P = 0.117$]. The reduction in the number of left-sided omissions from baseline was still significantly greater at Week 3 in the 'sham, then continuous TBS' group in both the random shape cancellation test (mean = 2.407, SEM = 0.545) and in the two part picture test (mean = 1.886, SEM = 0.249) compared with the 'no stimulation' control group (mean = 0.393, SEM = 0.273; and mean = 0.340, SEM = 0.142; respectively) [$t(14) = -3.302$, $P = 0.005$; and $t(13) = -5.559$, $P < 0.001$, respectively]. The reduction of left-sided reading errors in the Munich reading texts from baseline to Week 3 was not significantly greater in the 'sham, then continuous TBS' group (mean = 0.615, SEM = 0.223) than in the 'no stimulation' control group (mean = 0.274, SEM = 0.176) [$t(14) = -1.198$, $P = 0.251$].

'No stimulation' control group

In the 'no stimulation' control group, there was no significant reduction in left-sided omissions over time in the random shape cancellation test [$F(3,21) = 1.823$, $P = 0.174$] or in the Munich reading texts [$F(3,21) = 2.216$, $P = 0.116$]. In the two part picture test, there was a significant reduction over time of left-sided omissions [$F(3,21) = 3.441$, $P = 0.035$]. However, week-to-week *post hoc* testing revealed no significant comparisons. The results of the three paper–pencil tests in the 'no stimulation' control group are depicted in Fig. 7.

Discussion

The present study shows, for the first time, that non-invasive brain stimulation yields a substantive improvement of spatial neglect in the ADL, which persists for at least 3 weeks. Application of continuous TBS over the undamaged posterior parietal cortex improved the ability of neglect patients to attend to and act upon the contralesional, left space during spontaneous everyday behaviour. The observed improvement in spatial neglect was demonstrated using a double-blind, sham-controlled crossover design that also included a control group without stimulation. Therefore, the effects were specific to continuous TBS and not due to non-specific factors or conventional rehabilitation therapy. Unlike all prior studies that have assessed the impact of interventions by using neuropsychological tests or behavioural batteries such as the Behavioural Inattention Test (Wilson *et al.*, 1987), the impact of continuous TBS on spatial neglect was determined using the CBS, which stresses the observation of spontaneous behaviour during the ADL, rather than putting the patient into a test situation.

Measuring the effects of continuous TBS with the CBS has several advantages. First, behavioural assessment can reveal difficulties that neglect patients may only show during complex everyday behaviour with higher cognitive demands or multitasking (Bowen *et al.*, 1999). Moreover, fluctuations in the severity of neglect symptoms due to different attentional and emotional factors may occur (Vuilleumier and Driver, 2007). Since neuropsychological tests are conducted in a very restricted time frame, their results may be influenced by these fluctuations, whereas the behavioural observation conducted over several days may be more reliable in this respect. These differences may explain why the assessment of everyday behaviour has been shown to be more sensitive in detecting neglect than single paper–pencil tests (Azouvi *et al.*, 2006). In the present study, the significant improvement of spatial neglect in the ADL after continuous TBS application was reflected by the reduced CBS scores, which were determined during a period of 5 days for each assessment time-point.

In line with the improvement in the ADL, a specific and significant amelioration of spatial neglect after continuous TBS application was also observed in the Subtask of the Vienna Test System (PVT) and in neuropsychological tests closely reflecting everyday activities such as visual exploration and visual search. The observed amelioration in the spatial neglect tests after the continuous TBS application over the undamaged posterior parietal cortex is in line with non-invasive brain stimulation studies applying single pulse TMS (Oliveri *et al.*, 1999), low frequency ($\leqslant$1 Hz) repetitive TMS (Brighina *et al.*, 2003; Shindo *et al.*, 2006; Koch *et al.*, 2008; Song *et al.*, 2009; Lim *et al.*, 2010), cathodal transcranial direct current stimulation (Sparing *et al.*, 2009), or continuous TBS (Koch *et al.*, 2012). This convergence of results strongly suggests that the reduction of the pathological hyperactivity of the undamaged posterior parietal cortex, which also results in a decreased interhemispheric inhibition from the undamaged towards the damaged hemisphere, is a central mechanism leading to spatial neglect amelioration (He *et al.*, 2007; Grefkes and Fink, 2011).

Which approach of non-invasive brain stimulation should be preferentially employed to ameliorate spatial neglect is still an open question. In general, studies using non-invasive brain stimulation such as 1 Hz TMS or transcranial direct current stimulation apply daily stimulation over 2 weeks to ameliorate neglect (Cazzoli *et al.*, 2010; Utz *et al.*, 2010; Hesse *et al.*, 2011). As a further interesting development, Koch *et al.* (2012) combined the conventional approach of stimulation over 2 weeks with the newer approach of applying two consecutive continuous TBS trains the same day (Nyffeler *et al.*, 2009). A significant improvement in the Behavioural Inattention Test after continuous TBS application was reported up to 2 weeks, whereas no significant effect was observed in the sham group. In the present study, we applied a higher number of train repetitions per day (four trains), but for fewer days (2 days). The advantage conferred by this approach is revealed by the prolongation of the behavioural improvements up to 3 weeks. In our previous study (Nyffeler *et al.*, 2009), the behavioural effects of four continuous TBS trains at the same day lasted up to 32 h. Additionally, in contrast to Koch *et al.* (2012), who applied 20 trains of continuous TBS, the total number of applied continuous TBS trains in our study was only eight trains per patient. Whether the efficacy of continuous TBS can be further enhanced by adding more days of stimulation or more trains per day is an important question for future work (Schambra and Marshall, 2012). The results from the present study suggest that the latter approach—allowing a lower total number of applied continuous TBS trains—might be particularly promising for the clinical application.

The magnitude of the mean improvement in ADL functions after continuous TBS was statistically equivalent in the two stimulation groups (37.35% in the 'continuous TBS, then sham' group versus 36.95% in the 'sham, then continuous TBS' group). The ability of our continuous TBS protocol to deliver a reliable mean improvement in ADL functions across the two stimulation groups is particularly striking. It is nonetheless important to consider factors that could potentially influence the effects of continuous TBS on neglect symptoms. First, even though the mean lesion volumes were statistically equivalent across the three groups of patients, the 'sham, then continuous TBS' group was associated with a numerically larger mean lesion volume than the other two groups. Importantly however, this difference did not have consequences on the baseline neglect severity, because our assessment revealed that the impairment was comparable in all three groups. Furthermore, the mean lesion volume did not correlate with the continuous TBS effect, i.e. the amelioration of neglect after continuous TBS application did not depend on lesion volume. The present study also showed no significant correlations between the amelioration of spatial neglect on the level of the ADL after continuous TBS application and initial severity of spatial neglect or age of the patients. Advancing age is an important issue because it is a predictor of poorer functional and cognitive outcome after stroke (Klimkowicz-Mrowiec *et al.*, 2006; Nys *et al.*, 2007), probably due to a decline in synaptic plasticity (Petcu *et al.*, 2008; Cramer *et al.*, 2011). Since spatial neglect is more common in older than in younger stroke patients (Ringman *et al.*, 2004; Gottesman *et al.*, 2008), it is noteworthy that in our patient sample, with a fairly broad age range (from 32 to 76 years), all but one patient improved in the ADL after continuous TBS.

In conclusion, the present study provides Class I (French and Gronseth, 2008) evidence to demonstrate that continuous TBS over the contralesional posterior parietal cortex can induce a specific and long-lasting improvement of spatial neglect on the level of the ADL. These results suggest that continuous TBS is a promising and viable add-on therapy in neglect rehabilitation that facilitates recovery of normal everyday behaviour.

Acknowledgements

The authors would like to thank the staff of the Division of Cognitive and Restorative Neurology, Department of Neurology, Inselspital, Bern University Hospital, and of the Center of Neurology and Neurorehabilitation, Department of Internal Medicine, Luzerner Kantonsspital. The authors would like to thank the Editors and two anonymous Reviewers for their thoughtful and constructive comments on previous versions of the manuscript.

Funding

This work was supported by the Swiss National Science Foundation (3200B0-116074/1, PBBEP3_134978 to D.C.); and the Ernst Göhner Foundation.

Supplementary material

Supplementary material is available at *Brain* online.

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