Neuroscience 233 (2013) 64–71

COMPARING THE AFTER-EFFECTS OF CONTINUOUS THETA BURST STIMULATION AND CONVENTIONAL 1 HZ RTMS ON SEMANTIC PROCESSING

S. BRÜCKNER, M. KIEFER AND T. KAMMER *

Department of Psychiatry, University of Ulm, Germany

Abstract—Our aim was to evaluate continuous theta burst stimulation (cTBS) as a tool to induce temporary impairment (virtual lesion) in semantic processing. Four groups with 20 subjects each were stimulated. In the three experimental groups the stimulation site was the left superior temporal cortex. Stimulation was either 1 Hz repetitive transcranial magnetic stimulation (rTMS) at 100% resting motor threshold (RMT) or cTBS, with intensities of 80% or 90% active motor threshold (AMT). The TMS-control group was stimulated at the right medial prefrontal cortex with 1 Hz rTMS. After stimulation subjects accomplished a lexical decision task with a duration of about 20 min. In an additional fifth group the lexical decision task was performed without TMS. Reaction times were not influenced by cTBS applied with 80% AMT, but prolonged for about 80 ms with 90% AMT compared to the no stimulation condition. An increase of 140 ms was found after 1 Hz rTMS. The effect lasted for the whole task, but declined from the first to the second half of the experiment. The direct comparison of cTBS and 1 Hz rTMS suggests that both stimulation patterns can induce virtual lesions in the left superior temporal cortex and impair semantic processing. We suppose that cTBS could replace 1 Hz rTMS in this field since the application is faster and it is more comfortable to the subjects.

Key words: transcranial magnetic stimulation, theta burst stimulation, left superior temporal cortex, lexical decision, stimulation intensity, semantic processing.

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) has been established as a tool to induce ‘virtual lesions’ in a cortical region in order to explore the specific function of the stimulated cortex area (Pascual-Leone et al., 1999). Initially, the inhibitory effect of 1 Hz rTMS has been established for the motor cortex (Wassermann et al., 1996; Chen et al., 1997; Siebner et al., 1999; Fitzgerald et al., 2002; Plewnia et al., 2003). This inhibitory effect was successfully transferred to other cortical regions. In the visual cortex several studies (Boroojerdi et al., 2000; Brighina et al., 2002; Fierro et al., 2005) showed raised phosphene thresholds in normal subjects after 1 Hz rTMS of a mid-occipital stimulation site. In the language domain, stimulation of the anterior temporal lobe led to increased reaction times in synonym judgment (Lambon Ralph et al., 2009) and semantic association (Pobric et al., 2010). Applied to the left prefrontal cortex, 1 Hz rTMS impaired generating verbs by prolonged response latencies (Shapiro et al., 2001). Stimulation of Wernicke’s area impaired word processing (Knecht et al., 2002) and picture–word-verification (Dräger et al., 2004).

With the introduction of a new stimulation pattern, the theta burst stimulation (TBS, Huang et al., 2005), an inhibitory effect was found in the motor cortex for the continuous application of 600 pulses (continuous TBS). The attenuation of motor-evoked potential (MEP) amplitudes seems similar to conventional 1 Hz rTMS. However, stimulation intensity was much lower (80% of active motor threshold (AMT) for continuous theta burst stimulation (cTBS), compared to 100% of resting motor threshold (RMT) for 1 Hz rTMS), and total duration of stimulus train was much shorter (40 s for cTBS compared to 15–20 min for 1 Hz rTMS); thus the application is much more comfortable for the participants compared with conventional rTMS.

cTBS was successfully applied to non-motor cortical areas. Franca et al. (2006) showed increased phosphene thresholds after the stimulation of the visual cortex. Applied over the frontal eye field, both cTBS and 1 Hz rTMS had inhibitory effects on saccade triggering (Nyffeler et al., 2006).

The aim of our study was to compare the after-effects of conventional 1 Hz rTMS with those of cTBS at various stimulation intensities in a lexical decision task (word/pseudoword decision) to investigate whether cTBS is suitable to also modulate higher cognitive functions such as language comprehension. The lexical decision task has been shown to involve several aspects of linguistic processing such as orthographic, phonological, and semantic processes (Kiefer, 2002; Fujimaki et al., 2009; Dilkina et al., 2010; Kiefer and Martens, 2010). We stimulated a region within the left posterior superior and the middle temporal cortex to analyze the impact of the virtual lesion on a lexical-decision-task. This region,

*Corresponding author. Address: Department of Psychiatry, University of Ulm, Leimgrubenweg 12, D-89075 Ulm, Germany. Tel: +49-731-500-61544; fax: +49-731-500-61512.
E-mail address: thomas.kammer@uni-ulm.de (T. Kammer).
Abbreviations: AMT, active motor threshold; ANOVA, analysis of variance; cTBS, continuous theta burst stimulation; MEP, motor-evoked potential; RMT, resting motor threshold; RT, reaction time; rTMS, repetitive transcranial magnetic stimulation.

0306-4522/12 $36.00 © 2013 Published by Elsevier Ltd. on behalf of IBRO.
http://dx.doi.org/10.1016/j.neuroscience.2012.12.033

which is considered to be part of Wernicke's language area, contributes to several linguistic processes known to contribute to lexical decision performance: Posterior superior and middle temporal cortex activity has been related to semantic (Hoffmann et al., 2011) and phonological (Hickok and Poeppel, 2007) processing. In particular, besides other functions (e.g., Kiefer et al., 2008), this region has been suggested to serve as a semantic convergence zone subserving the activation of word meaning (Jung-Beeman, 2005), multisensory and amodal semantic integration (Beauchamp et al., 2004), or semantic selection (de Zubicaray et al., 2001). Hence, posterior temporal cortex is a good candidate region to study the effect of cTBS on linguistic processing during a lexical decision task.

EXPERIMENTAL PROCEDURES

Subjects

Altogether 101 healthy subjects participated in the study (mean age 24.45 years; range 19–33 years; 50 men) after giving written informed consent. They all were right-handed and had no metallic implants, no prior history of neurological or psychiatric disorders, in particular no epileptic fit, and no drug abuse or alcoholism. One subject had to be excluded due to excessive errors in the task. Subjects were paid for participation. The study was approved by the Ethics Committee of the University of Ulm.

Stimulation procedure

Eighty participants were divided into four stimulation-groups with 20 subjects in each group (10 men, 10 women). Subjects sat in a comfortable chair while they were stimulated with a MagVenture Magpro X100 stimulator (Farum, Denmark) with the standard biphasic pulse form, using a figure-of-eight-coil, MC-B70. Coil position in relation to the head was monitored and registered continuously in all six degrees of freedom (three rotational and three translational) with the frameless stereotactic positioning system BrainView (V2, Fraunhofer IPA, Stuttgart, Germany, cf. Kammer et al., 2007). Brain anatomy of the individual subjects (T1-weighted MPRAGE sequence, resolution $1 \times 1 \times 1$ mm) was measured on a Siemens Allegra MR-scanner (3 T). Posterior temporal cortex (3 experimental groups) or Brodmann-area 9 (TMS-control group) were labeled with a white spot (see Fig. 1) using the segmentation tools from BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands). For posterior temporal cortex, the posterior part of the left superior temporal sulcus was identified where the course of the sulcus changed from horizontal to upward. At this spot left superior and middle temporal gyri in the posterior part (Brodmann areas 22 and 21) are stimulated. For the control site, the right medial prefrontal cortex (Brodmann area 9), we applied Talairach-coordinates ($x = 15$, $y = 35$, $z = 50$). Coil's handle was oriented upward and rotated about 30° to posterior at posterior temporal cortex.

Prior to the experiment RMT or AMT, respectively, was determined in the right abductor pollicis brevis muscle with electrophysiological recording (cf. Cárdenas-Morales et al., 2011). RMT was used to scale intensity for 1 Hz rTMS (Chen et al., 1997), AMT scaled intensity for cTBS (Huang et al., 2005). cTBS for a total of 600 pulses was delivered to participants' posterior temporal cortex in the first group at 80% and in the second group at 90% of individual AMT (mean first group 20.8%, second group 24.0% of maximum stimulator output). In the third group the same area was stimulated with conventional 1 Hz rTMS for 20 min, for a total of 1200 pulses. Low-frequency stimulation was delivered with 100% of individual RMT (mean 35.8% of maximum stimulator output). In the fourth group stimulation of Brodmann-area 9 of the right hemisphere was used for TMS-control (1 Hz rTMS for 20 min, 100% RMT, mean 36.0% of maximum stimulator output). We chose 20 min of 1 Hz stimulation in order to maximize the inhibitory effect (cf. Maeda et al., 2000). RMT and AMT were determined for the right abductor pollicis brevis muscle with stimulation of the left M1 hot spot following standard protocols (cf. Cárdenas-Morales et al., 2011).

To control for possible nonspecific TMS-effects and as a general baseline, an additional group of 20 subjects (10 men) passed the behavioral task without any TMS (group nostim). Participants in the four stimulation groups and the group without TMS stimulation did not differ significantly with regard to age.

Behavioral task

Immediately after stimulation the participants performed a lexical-decision-task. One hundred German words and 100 pseudowords of comparable word length (6 letters on average) were presented randomized on a computer monitor, using ERTS (BeriSoft Cooperation, Frankfurt, Germany). In order to increase semantic processing the pseudowords were generated by transposing a vowel in a real word (e.g., "Apful" instead of "Apfel" [apple], cf. Dilkina et al., 2010). None of the real words used as templates for the pseudowords were taken as a word-stimulus. The 200 stimuli were presented in four blocks with 50 presentations each, with a total duration of about 20 min.

At the beginning of each trial a break symbol (###) was presented for 1500 ms. Then a fixation cross was shown for 500 ms, followed by 400 ms presentation of the stimulus. Then a black screen was shown lasting 2000 ms as response time period. The participants had to decide as fast and as accurately as possible whether the presented stimulus was a real word or not by pressing one of two buttons (two alternative forced choice task). The time from the beginning of the stimulus-presentation until the button-press was measured as reaction time (RT). If no response was given within the response interval, the trial was labeled as a false response. The participants passed a practice phase with 16 trials before rTMS to make sure that they understood the task correctly.

Data analysis

For RT analysis, mean RT of the correct responses calculated for words and pseudowords, respectively. Responses faster or slower than two standard deviations of the individual's means of each stimulus type were defined as outliers and not entered into data analysis (5.01% of the data set).

Separate repeated-measures analyses of variance (ANOVAs) on reaction times and error rates were performed in STATISTICA (version 8, StatSoft GmbH, Hamburg, Germany). Post-hoc analyses were applied using planned *t*-tests.

RESULTS

All subjects tolerated rTMS well and no adverse effects have been reported.

Reaction times

Data were subjected to a repeated measures ANOVA with the between-factor group (nostim, TMS control, 1 Hz rTMS, cTBS 80%, cTBS 90%) and the within-factor stimulus type (word, pseudoword). A significant