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A novel approach for monitoring writing interferences during navigated transcranial magnetic stimulation mappings of writing related cortical areas

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HIGHLIGHTS

- Proposed setup to be used with nTMS mappings of writing related cortical areas.
- Pen for writing integrated into EMG of nTMS system was developed.
- On-line monitoring of EMG and pen related activity from hand muscles during writing.
- Application of chronometric TMS design and patterned protocol of rTMS.
- Stopping and slowing during writing was elicited by mapping premotor cortices.

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ABSTRACT

Background: It has recently been shown that navigated repetitive transcranial magnetic stimulation (nTMS) is useful in preoperative neurosurgical mapping of motor and language brain areas. In TMS mapping of motor cortices the evoked responses can be quantitatively monitored by electromyographic (EMG) recordings. No such setup exists for monitoring of writing during nTMS mappings of writing related cortical areas.
New method: We present a novel approach for monitoring writing during nTMS mappings of motor writing related cortical areas.
Comparison with existing method(s): To our best knowledge, this is the first demonstration of quantitative monitoring of motor evoked responses from hand by EMG, and of pen related activity during writing with our custom made pen, together with the application of chronometric TMS design and patterned protocol of rTMS.
Results: The method was applied in four healthy subjects participating in writing during nTMS mapping of the premotor cortical area corresponding to BA 6 and close to the superior frontal sulcus. The results showed that stimulation impaired writing in all subjects. The corresponding spectra of measured signal related to writing movements was observed in the frequency band 0–20 Hz. Magnetic stimulation affected writing by suppressing normal writing frequency band.

Abbreviations: APB, abductor pollicis brevis; DCS, direct cortical stimulation; CS, central sulcus; EMG, electromyography; FFT, fast Fourier transform; fMRI, functional magnetic resonance imaging; LLR, long latency response; M1, primary motor cortex; MEP, motor evoked potential; nTMS, navigated transcranial magnetic stimulation; PSD, power spectral density; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SFS, superior frontal sulcus.

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Conclusion: The proposed setup for monitoring of writing provides additional quantitative data for monitoring and the analysis of rTMS induced writing response modifications. The setup can be useful for investigation of neurophysiologic mechanisms of writing, for therapeutic effects of nTMS, and in preoperative mapping of language cortical areas in patients undergoing brain surgery.

1. Introduction

Transcranial magnetic stimulation (TMS) is often used in mapping eloquent brain cortices (motor and language related cortical areas) in patients undergoing neurosurgical operation (Forster et al., 2011; Picht et al., 2013; Krieg et al., 2014). The majority of studies used TMS mapped language cortical areas by rTMS to interfere with a specific language function (Gough et al., 2005; Romero et al., 2006; Papagno et al., 2009; Whitney et al., 2011; Sliwinska et al., 2015). Other language studies applied different stimulation protocols at distinct time points during a task to perturb intrinsic neural activity in the stimulated area (chronometric fashion): (a) single, double, or triple pulse protocols (Amassian et al., 1989; Coslett and Monsul, 1994; Devlin et al., 2003; Mottaghy et al., 2003; Schuhmann et al., 2009; Schuhmann et al., 2011; Sliwinska et al., 2012; Wheat et al., 2013; de Graaf et al., 2014), rTMS (Rösler et al., 2014; Sollmann et al., 2014), (b) patterned protocols of rTMS (Deletis et al., 2014; Rogić et al., 2014). Anatomo-functional network underlying writing was studied in lesion studies of pure agraphia (Exner, 1881; Anderson et al., 1990; Tohgi et al., 1995), in healthy subjects in neuroimaging studies (Sugihara et al., 2006; Planton et al., 2013; Segal and Petrides, 2012), and intraoperatively in patients by direct cortical stimulation (DCS) (Roux et al., 2014; Roux et al., 2009; Scarone et al., 2009; Magrassi et al., 2010). Neurophysiologic mechanisms of writing, as an expressive modality of language, have not been satisfactorily studied by TMS. So far, TMS has only been used for testing therapeutic effects of rTMS on writing in patients with aphasia following stroke in overall language functions (Kakuda et al., 2011; Ren et al., 2014), in patients with Parkinson's disease presenting with deficits in writing (Randhawa et al., 2013), and in focal hand dystonia patients (Kimberley et al., 2015).

Classical neuroanatomical and neuropsychological models of writing distinguish central (language) processes from peripheral (motor) processes (Friedman and Alexander, 1989; Roeltgen, 2003). Direct cortical electrical stimulation was used to study neural substrates of the writing function in patients, in order to detect these areas during removal of brain tumors, as well as to reduce postoperative writing deficits in patients. Electrical stimulation of specific cortical areas elicited specific writing impairments confirming the crucial involvement of the left frontal and superior parietal regions in writing. Language interferences during writing were generated by stimulation of the left superior temporal gyrus and supramarginal gyrus (Roux et al., 2014); different patterns of writing impairments while stimulating the superior parietal gyrus (Magrassi et al., 2010); difficulties in motor aspects of writing while stimulating the supplementary motor area (Scarone et al., 2009); pure cessation of writing (Roux et al., 2009) while stimulating premotor cortices corresponding to BA 6 (the middle frontal gyrus) and close to the superior frontal sulcus.

Due to scarce TMS studies in writing (mainly testing therapeutic effects of rTMS) we wanted to develop an optimal methodological setup for future TMS studies investigating the interferences of TMS on central and peripheral writing processes applying different stimulation protocols at distinct time points during a writing task. Therefore, the aim of the present study was to propose a novel setup which employs synchronous recording of individual's writing performance combined with navigated transcranial magnetic stimulation (nTMS). Our group developed a writing pen integrated into the amplifier of nTMS system which can provide measures of hand writing frequency, as well as digital documentation of writing errors, in addition to monitoring of motor evoked responses (MEPs) from the hand muscles by electromyographic recordings (EMG). Furthermore, chronometric TMS design and our modified patterned protocol of rTMS (Rogić et al., 2014) was applied during writing for the first time. For the purpose of this pilot study, we mapped the left premotor cortical area corresponding to BA 6 and close to the superior frontal sulcus (later termed as: BA6 and cSFS), and the left M1 for the hand muscle during participant's writing of a dictation task.

Our results showed that lower stimulation intensities (RMT intensity or intensities 25% above the RMT intensity) over the left BA6 and cSFS generated blocking of writing in all subjects without visible hand movements, and MEPs from the hand muscle in the EMG signal. We could not determine the latency onset of these MEP responses due to pre-stimulus EMG activity. When applying higher stimulation intensities blocking of writing occurred with hand movements and MEPs in the EMG signal. Stimulation of the M1 for hand muscle elicited writing interferences related to movements of the hand and fingers. Analysis of the pen signal showed the suppression of normal hand writing frequency band (0–20 Hz) during blocking of writing.

2. Materials and methods

2.1. Subjects

The experimental setup was tested on four healthy volunteers (two males and two females; age range 23–43 years) having no neurological disorders. All participants were right handed dominant. The Edinburgh Handedness Inventory (Oldfield, 1971) was used to assess the hand dominance. All of them were native Croatian speakers. The ethical committee of the School of Medicine University of Split, Croatia approved the experimental procedures of the study in accordance with the declaration of Helsinki.

2.2. Experimental setup

2.2.1. Writing pen – electromyography (EMG)–tablet interface

The photo sensitive electronic circuit consist of silicon NPN phototransistor BPW40 (Telefunken electronic, Frankfurt am Mein, Germany) and 0.6 W 680 Ω resistor. Due to its water clear epoxy, the phototransistor is sensitive to visible and near infrared radiation. When the BPW 40 is illuminated with the light from the LCD display of ACER tablet (Iconia Tab 10, A3-A20/A3-A20FHD) it starts to conduct with voltage rise to 100 mV, which can be detected on the single channel of the 6-channel EMG amplifier module integrated into the nTMS system. When the phototransistor is not in direct contact with LCD display it stops to conduct and voltage on EMG is around 20 mV. Reaction distance of phototransistor on LCD display is approximately 5 mm. The 9 V battery was used as power supply for the pen in order to additionally suppress disturbances from electronic equipment (such as: 50 Hz from AC source, off-set from op amps) and environment (such as: thermal noise). One meter cable with DIN 42802 connector (ARVO-Kabel GmbH, Germany) was used for interface with EMG amplifier.