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REPETITION SUPPRESSION IN THE CORTICAL MOTOR AND AUDITORY SYSTEMS RESEMBLE EACH OTHER – A COMBINED TMS AND EVOKED POTENTIAL STUDY

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Abstract—Repetition suppression (RS) in cortical sensory systems optimizes the size of neuronal ensemble reacting to repetitive stimuli such as sounds. Recently RS has also been demonstrated to occur with mental imaging of movement. We studied the existence of RS in the motor system using transcranial magnetic stimulation (TMS). Six healthy subjects participated in this study. TMS was focused on the primary motor cortex with neuronavigation and RS was studied by measuring the motor-evoked potentials from the contralateral first dorsal interosseous muscle. At the same time, we measured TMS-induced cortical responses using electroencephalography (EEG). For a comparison baseline, we evaluated RS by recording EEG responses to sounds with the same stimulation protocol as with TMS. Each stimulus train included four identical stimuli repeated at 1-s intervals, and the stimulation trains were repeated at 20-s intervals. The response amplitude was reduced significantly ($p < .01$) after the first stimulus in all stimulus trains. This suggests that RS may be a general mechanism for adaptation of neuronal population responses in the human cortex.

Key words: transcranial magnetic stimulation, neurophysiology, repetition suppression, evoked potentials.

INTRODUCTION

Repetition suppression (RS) (Grill-Spector et al., 2006) or habituation (Groves and Richard, 1970; Rankin et al., 2009) of auditory-evoked potentials (AEPs) and the initial startle reaction have been widely studied (Fruhstorfer, 1971; Näätänen and Picton, 1987). As the stimulus is repeated, AEPs and especially the N100 responses at 100 ms after any sound decrease in amplitude and habituate (Fruhstorfer, 1971). RS is an essential factor in controlling the visual memory (Desimone, 1996), level of arousal and sensory memory trace of acoustic surroundings (Näätänen and Picton, 1987). Impairment of RS has been demonstrated, e.g., in schizophrenia (Moriwaki et al., 2009) and in age-associated memory impairment (Soininen et al., 1995).

The neuronal mechanisms of RS and arousal control are not yet resolved (Rankin et al., 2009) though multiple models have been suggested, including the neuronal fatigue model, the sharpening model and the facilitation model (Grill-Spector et al., 2006). The fatigue model explains the RS with simple suppression of neuronal response to a repeated stimulus via adaptation (Miller and Desimone, 1994), while according to the sharpening model the size of the neuron population which responds to a stimulus is optimized as the stimulus is repeated (Wiggs and Martin, 1998). The facilitation model suggests that cortical areas upstream from the primary receiving cortex start processing the repeated stimulus faster and the required neuronal firing-time in receiving cortex shortens (Friston, 2005). Although all of these models have gained support, the fatigue model fails to explain the performance enhancing effect of repetition (Grill-Spector et al., 2006).

Recently, RS has been demonstrated to occur also during mental imaging of movement (Hohlefeld et al., 2011). Blood-oxygen-level-dependent contrast suppression has been shown during repetition of hand gestures in functional MRI (Hamilton and Grafton, 2009). Although these studies suggest that RS could have a role in motor control, they do not provide undeniable evidence of causal relation between neuroimaging data and cortical motor output.

Transcranial magnetic stimulation (TMS) is a non-invasive method for direct cortical stimulation (Barker et al., 1985). It enables examination of causality between artificial activation of a cortical area e.g., muscle contraction recorded in the periphery (Barker, 1991). If a weaker or conditioning TMS stimulus is given 1–300 ms prior to the test stimulus, the effect of the test stimulus is facilitated or inhibited depending on the inter-stimulus interval (ISI) (Di Lazzaro et al., 2004; Ferreri et al., 2011). Long-term modulation of cortical excitability can be induced with repetitive transcranial magnetic stimulation (rTMS). High-frequency rTMS is known to increase the cortical excitability, but the evidence of the inhibitory effect of low-frequency rTMS

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Abbreviations: AEP, auditory-evoked potential; EEG, electroencephalography; EMG, electromyography; EOG, electro-oculogram; FDI, first dorsal interosseous; ISI, inter-stimulus interval; ITI, inter-train interval; MEP, motor-evoked potential; nTMS, navigated transcranial magnetic stimulation; rMT, resting motor threshold; RS, repetition suppression; rTMS, repetitive transcranial magnetic stimulation; TMS, transcranial magnetic stimulation.

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on excitability still remains controversial (Fitzgerald et al., 2006). The mechanism behind rTMS is thought to be the modulation of interneuron circuits of the cortex (Fitzgerald et al., 2006). Brasil-Neto et al. have demonstrated postexercise decrement of motor-evoked potentials (MEPs) with 0.3-Hz TMS after a 30-s voluntary contraction of the target muscle. The responsible mechanism was suggested to be central fatigue in the motor pathways (Brasil-Neto et al., 1994).

Our aim was to study with TMS whether the output of central motor network is optimized by RS. We hypothesized that RS could be a part of motor control mechanisms. This would indicate that RS is a general mechanism of the brain for adapting cortical responses to both internal and external stimuli.

EXPERIMENTAL PROCEDURES

Subjects, equipment setup and study protocol

Six right-handed healthy subjects (five male and one female) aged 22–58 years participated in the study. The study was conducted in accordance with the Declaration of Helsinki and all procedures were conducted with the adequate understanding and with consent of the subjects. Each subject was scanned beforehand with a Siemens Magnetom Avanto (Erlangen, Germany) 1.5 T scanner to receive T1-weighted high-resolution 3D MR-images for the navigated transcranial magnetic stimulation (nTMS) (Ruohonen and Karhu, 2010) (Fig. 1).

We measured RS of the cortical N100 responses with electroencephalography (EEG) (Näätänen and Picton, 1987). For this, the hearing threshold for each subject was determined by gradually decreasing the sound intensity until the subject could not hear it anymore. The duration of each 800-Hz tone was 84 ms including 7-ms rise and fall times and the ISI between the pulses was 1 s. Then, we utilized a standard protocol in studying auditory habituation. Tones were delivered to the subject's right ear at 60 dB above the hearing threshold. The paradigm comprised of 160 tones (800 Hz) in 40 trains, four tones within a train. The inter-train interval (ITI) was 20 s while the ISI between the tones within a train was 1 s (Furubayashi et al., 2000). The subjects listened passively and watched a silent video to occupy their attention. Neuroscan Stim Audio System P/N 1105 was used for auditory stimulation. During the auditory habituation study, EEG was recorded with a 60-channel TMS compatible EEG device (Nexstim Oy, Helsinki, Finland). The EEG was recorded with a 1450-Hz sampling frequency and 16-bit precision and 350-Hz hardware low-pass cut-off. The EEG electrodes were referenced to an electrode placed on the right mastoid. Vertical electro-oculogram (EOG) was recorded from electrodes placed above and below the right eye. Ag/AgCl-electrodes were used with EEG.

The nTMS setup consisted of a navigation system, a stimulator and a figure-of-eight TMS-coil with biphasic pulse-form (Nexstim Oy, Helsinki, Finland). During nTMS, electromyography (EMG) was recorded to store muscle activity online with a system-integrated EMG-device at a 3-kHz sampling rate. EMG was measured from pre-gelled disposable Ag/AgCl electrodes attached to the right first dorsal interosseous (FDI) muscle. The TMS-induced MEPs were measured from the resting muscle EMG as peak-to-peak response between the highest positive and negative deflection from the baseline (Fig. 1).

After the auditory experiment, the primary motor cortex area was comprehensively mapped to locate the optimal cortical representation area of FDI muscle (Fig. 1) by finding the highest amplitude MEP. A compound muscle action potential with amplitude greater than 50 μV was taken as a reliable EMG response (Rossini et al., 1994). The resting motor threshold (rMT) intensity was determined for each subject at the mapped stimulus

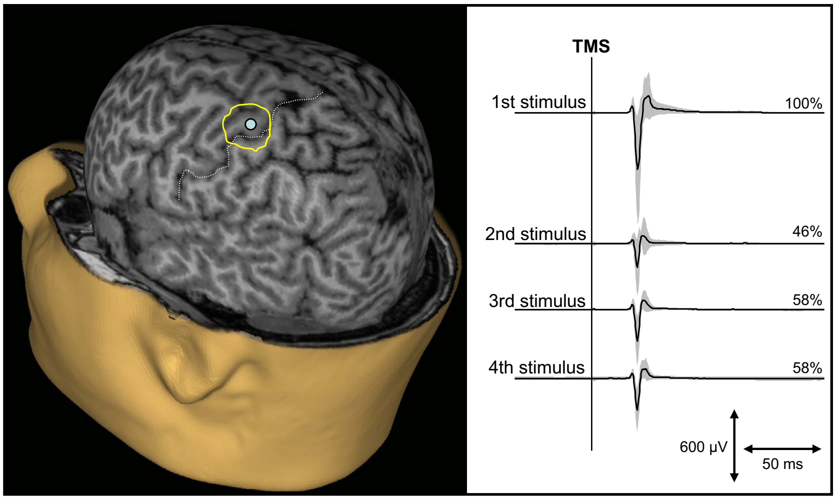

Fig. 1. The right hand representation area on the left hemisphere was mapped using neuronavigated TMS. The location inducing the highest amplitude motor-evoked potential (MEP) in one subject that is represented as a turquoise circle, and the mapped area is outlined with a yellow line. White-dashed line indicates the central sulcus. On the right, average MEP responses (black line) within the stimulation train are presented for the same subject. The gray area represents standard deviation of the repeated MEPs. Percentages on the right are the normalized MEP amplitudes with respect to the mean of first MEPs within the stimulus trains. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)