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THE AUDITORY-EVOKED AROUSAL MODULATES MOTOR CORTEX EXCITABILITY

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Abstract—Arousal enhances the readiness to process sensory information and respond to it. Rapid increment of arousal, referred to as arousal reaction or startle, increases the level of attention and the chance of survival. Arousal reaction is known to originate from the brainstem ascending reticular activating system and to modulate neuronal activity throughout the central nervous system. In the present study we investigated the effect of arousal on the central motor system by synchronizing transcranial magnetic stimulation (TMS) with acoustically evoked N100 potential. Because of the widespread cortical distribution of N100 to a sudden acoustic stimulus it is thought to be related to arousal reaction. Eight healthy subjects participated in this study. TMS was focused on the primary motor cortex utilizing neuronavigation. Trains of four identical loud tones repeated at 1-s intervals were delivered to the right ear and TMS was randomly placed after one tone in the train. The motor-evoked potentials (MEPs) were measured from the contralateral first dorsal interosseous muscle. The MEPs evoked by TMS timed at N100 after the first tone in train were significantly ($p < .001$) larger in comparison with the control stimulation without a preceding sound or stimulation placed after the N100, i.e., 120% of the N100 interstimulus interval. Also, the MEPs following the second tone were significantly weaker ($p < .05$) when compared with the MEPs following the first tone. Our findings suggest that acoustic arousal reaction facilitates, not only the activation of sensory cortices, but also simultaneously the central motor system.

Key words: transcranial magnetic stimulation, neurophysiology, arousal, evoked potentials, auditory, N100.

INTRODUCTION

The ability to quickly reach the state of full alertness at the first sign of danger is one of the ultimate survival functions. Even in our civilized society, the daily performance depends on our ability to adjust the level of attention to the task at hand (Whyte, 1992). Arousal enhances the state of readiness to process sensory information and respond to it (Whyte, 1992). The rapid increment of arousal to a novel stimulus is referred to as arousal reaction or startle (Moruzzi and Magoun, 1949). The arousal reaction has been demonstrated to originate from the brainstem ascending reticular activation system (RAS) (Moruzzi and Magoun, 1949; Brown et al., 1991) and various neurotransmitters play a role in controlling the momentary level of arousal (Robbins, 1997). The arousal system contains two major networks: the first connects upper brainstem to the thalamus, activates thalamic relay neurons and thus modulates the transmission of information to the cortex. The second network that bypasses the thalamus and activates neurons in the lateral hypothalamic area, basal forebrain and throughout the cerebral cortex, promotes cortical activation during waking state (Saper et al., 2005).

Arousal reaction evoked by a novel sensory stimulus may have an immediate modulatory effect on the entire cortical mantle. The effect of a sudden sound on motor cortex excitability has been studied with transcranial magnetic stimulation (TMS) and transcranial electric stimulation (TES) (Barker et al., 1985; Furubayashi et al., 2000; Kühn et al., 2004; Fisher et al., 2004; Ilic et al., 2011). TES mainly directly activates pyramidal tract axons (D-wave), whereas TMS mainly activates cortical interneurons and these activate the pyramidal tract via synaptic connections (indirect waves, I-waves) (Amassian et al., 1987; Day et al., 1989; Di Lazzaro et al., 2004). A loud sound preceding the TMS by 30–50 ms has been shown to suppress the motor-evoked potentials (MEPs) in the hand muscles (Furubayashi et al., 2000; Kühn et al., 2004). The suppression occurred only with TMS and not with TES, which could indicate that the startle-evoked activation of RAS would transiently inhibit the motor cortex excitability (Furubayashi et al., 2000; Fisher et al., 2004). Recent studies have demonstrated that arousal elicited by stimuli with emotional content can affect the overall activation of the central motor system. For example, emotional music has been reported to modulate corticospinal motor tract excitability (Baumgartner et al., 2007). The effect on motor excitability is considered to be linked to the level of emotional

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Abbreviations: AEP, auditory-evoked potential; EEG, electroencephalography; EMG, electromyography; 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; TES, transcranial electric stimulation; TMS, transcranial magnetic stimulation.

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arousal instead of the valency (e.g. happiness or fear) of the emotion (Coombes et al., 2009).

The cortical analysis of auditory stimuli has barely started within the suppression time-frame of 30–60 ms found by Furubuayashi et al. The generally observed auditory response N100 (or N1) is an event-related potential (ERP) with peak latency between 50 and 150 ms depending on the individual (Näätänen and Picton, 1987). It is generated by different areas of the central nervous system (CNS) processing the physical aspects of the sensory stimulus before the conscious analysis of the stimulus (Näätänen and Picton, 1987; Näätänen et al., 2011). It has been demonstrated to comprise specific and widespread nonspecific components, and the generator of the latter is not known (Näätänen and Picton, 1987). Because of the widespread cortical distribution of N100 it is thought to be related to arousal reaction (Näätänen and Picton, 1987). High amplitudes of N100 have been demonstrated to correlate with faster reaction times (Karlin et al., 1971) suggesting that the startle reaction has an enhancing effect on the corticospinal motor system. However, after the once novel stimulus is repeated, the evoked cortical responses are suppressed (Fruhstorfer, 1971).

Repetition suppression (RS) (Grill-Spector et al., 2006) or habituation (Groves and Richard, 1970; Rankin et al., 2009) of the evoked responses to the repetitive stimuli of different sensory modalities is a widely studied phenomenon. After an acoustic stimulus is repeated, auditory-evoked potentials (AEPs) and especially the N100 wave decrease until reaching a fully habituated baseline (Fruhstorfer, 1971). The neuronal mechanism of habituation is not revealed yet but several theories, from repetition-induced facilitation of higher cortical processing areas to simple neuronal fatigue after the affected neurons have fired have been suggested (Grill-Spector et al., 2006).

In our previous study, we demonstrated RS of MEPs and cortical responses evoked by TMS and suggested that RS is a general cortical mechanism not limited to sensory processing (Löfberg et al., 2013). The aim of the present study was to investigate the effect of arousal on motor cortex excitability using TMS synchronized with the N100 evoked with a loud novel sound. We hypothesized that N100 time frame overlaps the strongest effect of the general arousal reaction that enhances the motor cortical excitability.

EXPERIMENTAL PROCEDURES

Subjects, equipment setup and study protocol

Eight right-handed healthy subjects (6 male and 2 female) aged 22–58 years were recruited. 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. All subjects underwent T1-weighted 3D MR-imaging with a Siemens Magnetom Avanto (Erlangen, Germany). Individual MR data were used for navigated transcranial magnetic stimulation (nTMS). The nTMS experiment was conducted with a figure-of-eight TMS-coil and biphasic pulse waveform (eXimia 3.2.2., Nexstim Oy, Helsinki, Finland). During nTMS, electromyography (EMG) was recorded with a system-integrated EMG-device. Surface EMG was measured from pre-gelled disposable Ag/AgCl electrodes attached to the right first dorsal interosseous (FDI) muscle. The MEPs were measured from the resting muscle EMG as peak-to-peak responses (Fig. 1). In addition, cortical responses to auditory stimuli were recorded with a 60-channel electroencephalography (EEG) amplifier (Nexstim Oy) at 1450 Hz. The EEG electrodes were referenced to an electrode placed on the right mastoid. For online analysis, the EEG was bandpass filtered between 1 and 40 Hz.

In the first step, we measured the hearing threshold for each subject by gradually decreasing the sound intensity until the subject could not hear the stimulus. The duration of the 800-Hz tone was 84 ms including 7-ms rise and fall times and the inter-stimulus interval (ISI) between the pulses was 1 s. Then, we measured the cortical N100 responses in the EEG during a common auditory habituation protocol (Näätänen and Picton, 1987). The tones were delivered to the right ear of the subject at 60 dB above the hearing threshold. The stimulation paradigm comprised 160 tones in 40 trains, 4 tones within a train. The inter-train interval (ITI) was set at 20 s while the ISI between the tones within a train was 1 s (Furubayashi et al., 2000; Löfberg et al., 2013). During the experiment, the subjects listened passively and watched a silent video. Neuroscan Stim Audio System P/N 1105 (Compumedics Neurocan, El Paso, Texas, USA) was used for auditory stimulation. From the cortical responses, we measured the N100 latency from the vertex electrode (Cz, Fig. 1) used later in the study.

Subsequently, the primary motor cortex area was mapped to locate the optimal cortical representation area of right hand FDI muscle by finding the highest amplitude MEP. Then, the resting motor threshold (rMT) intensity was determined at the mapped target with 50-μV amplitude limit for acceptable MEP (Rossini et al., 1994). Threshold hunting paradigm was used (Awiszus, 2003) applying Motor Threshold Assessment Tool (MTAT 2.0) with 20 stimuli (Awiszus and Borckardt, 2012). After this, we conducted a stimulation protocol with TMS using 120 stimuli at 120% of the rMT. The stimuli were given in trains of 4 stimuli with ISI of 1 s and ITI of 20 s, similar to that used in the auditory stimulation. EMG responses were recorded (Fig. 1). The subjects were instructed to keep their hands in rest and not to focus their attention on the stimulation or muscle contraction. During the experiment, the subjects watched a muted video.

As a last step, we combined the auditory stimulation protocol with TMS. The auditory stimulation was conducted as was previously described and TMS was randomly placed after one stimulus within the 4 stimulus train, such that the likelihood of a TMS occurring within a stimulus train was 80% with equal chance of TMS following any auditory stimulus within the train. The TMS was timed at the N100 latency of the subject or 1.2 times the latency. The two timings were recorded in separate sessions in randomized order. Each session