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Cortical mechanisms of unilateral voluntary motor inhibition in humans

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Abstract

While motor control is very often a goal-oriented event, little is known about the mechanisms underlying the termination of motor performance. To investigate what type of cortical activation underlies the muscle relaxation required to terminate the act, we performed single- and double-pulse transcranial magnetic stimulation (TMS) studies during voluntary muscle relaxation in nine normal volunteers. Subjects maintained a weak isometric contraction of the right first dorsal interosseous muscle (FDI), and either increased the level of contraction (Contraction), terminated the contraction (Relaxation), or maintained it (No-go) depending on a visual cue. Motor evoked potentials (MEP) and the silent period (SP) were recorded from the FDI during motor activity. To measure intra-cortical inhibition (ICI), we also performed double-pulse TMS, applying subthreshold conditioning stimuli at interstimulus intervals of 2 ms. When single-pulse TMS was given just prior to muscle relaxation (−21 to −70 ms), the MEP was reduced while the SP was unchanged. Intra-cortical inhibition was smaller just prior to the muscle relaxation. Unilateral voluntary muscle relaxation may not be associated with activation of the intracortical inhibitory system, but rather with the possible excitation of the corticospinal system, which can inhibit motoneurons disynaptically. These findings suggest that multiple inhibitory mechanisms act in diverse ways to achieve motor inhibition.

Keywords: Voluntary motor inhibition; Muscle relaxation; Transcranial magnetic stimulation; Reaction time paradigm; Silent period; Intra-cortical inhibition

1. Introduction

Normal motor behavior requires the orchestration of the activity of multiple muscle groups. To make the appropriate amount of muscle contraction at the correct time, the precise control of voluntary muscle relaxation is crucial. In some hyperkinetic movement disorders such as chorea, dystonia and tics, a key feature of the symptoms may be a deficit in voluntary movement inhibition. For example, abnormal cortical activation associated with muscle relaxation has been reported in dystonia (Yazawa et al., 1999; Oga et al., 2002). However, the cortical mechanism of motor inhibition is not yet clear.

Functional magnetic resonance imaging (fMRI), electroencephalography (EEG) and magnetoencephalography (MEG) studies in humans have shown that muscle relaxation is an active process requiring cortical activation (Terada et al., 1995; Rothwell et al., 1998; Toma et al., 1999, 2000). The presence of ''Bereitschaftspotential'' (Kornhuber and Deecke, 1965; Shibasaki et al., 1980) preceding self-paced muscle relaxation suggests that the muscle relaxation is associated with activity in cortical motor areas (Terada et al., 1995; Rothwell et al., 1998). A recent fMRI study showed that muscle relaxation can activate the primary motor cortex (MI), supplementary motor areas (SMAs) and pre-SMA (Toma et al., 1999).

In this regard, it is not yet understood how apparently similar M1 activation can lead to both muscle relaxation and contraction. Differences in the cortical inhibitory system underlying the activity in M1 may be crucial to understand motor inhibition. However, cortical mechanism of voluntary

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relaxation has been rarely studied by TMS (Begum et al., 2003; Buccolieri et al., 2004).

In the present study, we used single-and double-pulse transcranial magnetic stimulation (TMS) to investigate the dynamic changes of the excitatory and inhibitory neural circuits in M1 during the visual, paired-stimulus delayed reaction time task. The double-pulse TMS technique employed a subthreshold conditioning shock followed by a suprathreshold test shock within 1–5 ms. This allows the noninvasive assessment of the GABA-A receptor-mediated intra-cortical inhibition (ICI) system of M1 (Kujirai et al., 1993; Nakamura et al., 1997; Di Lazzaro et al., 1998; Fisher et al., 2002), which has been demonstrated in pharmacological studies (Ziemann et al., 1996; Werhahn et al., 1999).

2. Methods

2.1. Subjects

We studied nine right-handed healthy volunteers (seven males and two females, aged 23–43 years), including five authors (T.B., T.M., T.O., H.H. and T.S.). The Committee of Medical Ethics, the Graduate School of Medicine and the Faculty of Medicine of Kyoto University approved the experimental procedures, and all subjects gave their written informed consent before the procedure began.

2.2. Tasks

The subjects were seated comfortably in a chair with their right forearm supported by an armrest and the radial border of the right index finger attached to a force transducer. During the experiment, subjects were asked to fixate a dot on the center of a computer monitor placed 1 m in front of them. The subjects were asked to maintain constant pressure on the force transducer at 20–30% of the maximal voluntary contraction (MVC) of the right first dorsal interosseous (FDI) muscle. Before the experiment, subjects were trained to perform the task for 10–30 min with the aid of electromyogram (EMG) visual feedback.

The experimental paradigm is shown in Fig. 1. We used the delayed reaction time task, in which S1 informed the type of movement to be performed immediately after S2 (interstimulus interval (ISI): 2 s). During S1, either a green, red or yellow circle was randomly presented for 200 ms on the black background of the computer screen. These were each presented with the same probability. The colors indicated level of contraction (Contraction), terminated the contraction (Relaxation) or maintained it (No-go) tasks, respectively. A white rectangle then appeared for 200 ms (S2) at the same position as S1, which cued the subjects to perform the required task as quickly as possible. For the Contraction task, subjects were instructed to abruptly increase the level of FDI contraction upto the highest level and to maintain it for 1–2 s. For the Relaxation task, subjects were asked to relax the FDI for 1–2 s without any overt antagonist contraction and to return to the initial state of isometric contraction. For the No-go task, subjects maintained the same isometric contraction. Inter-trial interval from S2 to the next S1 was 5–7 s.

2.3. Recordings

Bipolar electromyograms were recorded from the right FDI, first volar interosseous (FVI) and extensor carpi radialis (ECR) muscles, using a pair of silver electrodes. The EMGs and the force transducer signals were amplified and filtered (bandpass 5–1000 Hz for EMGs and 0.01–1000 Hz for the force transducer (3000 Hz recordable), sampling rate: 10 kHz, Neuroscan, Neuroscan Co., Herndon, VA). Reaction times (RTs) for both the Contraction and Relaxation conditions were measured visually offline by the experimenter at the onset of the force transducer signal following S2 (Fig. 2).

2.4. Transcranial magnetic stimulation (TMS)

TMS was applied using a figure-of-eight shaped coil (outer diameter of each coil: 9 cm) connected to the Magstim 200 stimulator (Magstim Co., Whitland, UK) through the Bistim module (Magstim Co., Whitland, UK). When double-pulse stimulation was performed, two stimulators connected by the Bistim module (Magstim Co., Whitland, UK) were used. Stimulus intensities were expressed as a percentage of the maximum stimulator output. The coil was placed tangentially to the scalp at the optimal position (hotspot) and directed to elicit the maximum motor evoked potential (MEP) in the right FDI. The coil handle was held ∼45° to the midsagittal line (approximately perpendicular to the central sulcus). The active motor threshold (aMT) was determined as the minimum intensity necessary to induce visible MEPs in at least five out of ten trials in the contracting muscle (Rossini et al., 1988).

2.5. Experimental design

In Experiment 1, TMS was given at the hotspot for the right FDI muscle (left M1). The stimulus output was set to induce peak-to-peak MEP amplitude of approximately 1 mV during the FDI contraction in the recording condition. The TMS pulse was given during the task at 12 different time-intervals with regard to S2 (−500, −300, −200, −100, −50, 0, 50, 100, 200, 250, 300, and 400 ms) (Fig. 1). Ten trials were performed at each time interval for each of the three tasks. To avoid fatigue, the subject took a short rest every 10–15 min, resulting in an experiment that lasted approximately 1–2 h. We also included tasks without TMS in the session to measure the mean control RT (10 trials for each task). As a control, 10 MEPs and SPs were measured during weak contractions of the FDI muscle.

To evaluate the excitability of motor pathway, the peak-to-peak MEP amplitude was measured. To investigate the inhibitory system, the duration

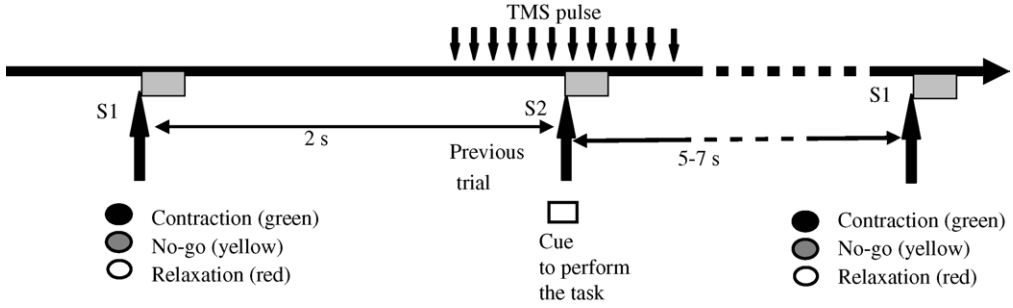

Fig. 1. Schematic diagram of Experiment 1. Subjects maintained a weak isometric contraction of the right first dorsal interosseous (FDI) muscle against the force transducer. Subjects were asked to respond after the second visual cue (S2) based on the color of the first cue (S1). Both S1 and S2 were presented for 200 ms. Responses to S2 included either the abrupt increase in the contraction of FDI (Contraction), the maintenance of the same contraction (No-go) or the complete termination of the muscle contraction (Relaxation). A TMS pulse was given at the right FDI hotspot during the task at random time-intervals from S2 (−500 to 400 ms). Inter-trial interval was 5–7 s.