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Cortical mechanisms underlying stretch reflex adaptation to intention: A combined EEG–TMS study

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ABSTRACT

During voluntary motor acts, potential perturbations due to transient external forces are counteracted very quickly by short- and long-latency stretch reflexes (SLSR and LLSR, respectively). The LLSR, presumably linked to a transcortical loop, can be modulated by the subjects' intention. Here, we used combined TMS–EEG to study cortical mechanisms involved in this intention-related modulation both before and during the reaction to a mechanical perturbation. Subjects had to prepare for a brisk wrist extension under the instruction either to 'resist' the perturbation or to 'let-go'. Following the perturbation, the early cortical evoked activity (45–75 ms) was greater in the 'let-go' condition; moreover, its amplitude was negatively correlated with the LLSR amplitude, regardless of condition. After 100 ms the pattern reversed, the late evoked activity (presumably linked to the voluntary reaction) was greater in the 'resist' condition. The early and late evoked activities also differed in their topography. Therefore, the cortical mechanisms involved in the intention-related LLSR modulation differ from those involved in the voluntary reaction. In addition, in response to a single-pulse TMS delivered during the expectation of the mechanical perturbation, the TMS-evoked N100 amplitude decreased when subjects intended to 'let-go', suggesting anticipatory decreased activity of intracortical inhibitory sensorimotor networks. Taken together, these results support the idea that anticipatory processes preset the sensorimotor cortex so as to adapt its early reaction to the perturbation relative to the subjects' intention.

Introduction

During voluntary motor acts, potential perturbations due to transitory changes in external forces are counteracted very quickly by the stretch reflex (Lee and Tatton, 1982; Jaeger et al., 1982; Gielen et al., 1988). Indeed, an involuntary muscle stretch causes a rapid muscle contraction due to the short-latency stretch reflex (SLSR), which is of spinal origin, followed by the long-latency stretch reflex (LLSR) which starts around 50 ms after the perturbation (Jaeger et al., 1982; MacKinnon et al., 2000). Following these reflex responses, the voluntary muscle contraction begins around 90 ms after the initial stretch (MacKinnon et al., 2000; Mutha et al., 2008; Pruszynski et al., 2008). While the origin of the LLSR has been debated for a long time, nowadays the transcortical loop hypothesis is widely accepted (Phillips, 1969; for reviews, see: Marsden et al., 1983; Matthews, 1991). Whereas both the SLSR and the LLSR amplitudes are modulated by the perturbation characteristics such as speed, force, magnitude, etc. (Calancie and Bawa, 1985; Lewis et al., 2006), the LLSR amplitude is also modulated by cognitive factors such as the subject's intention (Hammond, 1956; Rothwell et al., 1980), the planned force modulation (Kimura et al., 2006), and the movement goal (Pruszynski et al., 2008). This cognitive reflex modulation often allows the subject to realize his/her motor intention despite movement perturbations. As early as 1956, Hammond showed that the LLSR is greater when the subject is asked to 'resist' a mechanical perturbation than when he/she is instructed to 'let-go'. Interestingly, this intention-related LLSR modulation does not occur if the instruction is given simultaneously with the perturbation, suggesting that an anticipatory presetting is necessary to modulate the LLSR (Colebatch et al., 1979). A recent study has shown that intracortical sensorimotor networks contribute to the LLSR modulation in a forthcoming forces-dependent manner by showing that transcranial magnetic stimulation (TMS) applied over the primary motor cortex (so that the silent period caused by it coincided with the reflex response) disrupts reflex gain modulation (Kimura et al., 2006). However, the cortical mechanisms involved during the expectation of and the reaction to the perturbation remain poorly understood. The present study was aimed to investigate these mechanisms.

Concerning the cortical mechanisms involved in the reaction to the perturbation, several studies have identified early cortical event-related potentials (ERPs), which are doubtlessly related to the LLSR. For instance, several authors described ERPs following a wrist extension and concluded that the evoked activity around 55 ms

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following the muscle stretch is directly related to the LLSR transcortical loop (Abbruzzese et al., 1985; MacKinnon et al., 2000). This early evoked activity is presumably generated in the primary motor cortex (MacKinnon et al., 2000; Seiss et al., 2002). It remains unclear, however, whether it is modulated according to the subject's intention. While MacKinnon et al. (2000) did not observe intention-related modulation of the early cortical evoked activity, Abbruzzese et al. (1985) reported that a smaller early ERP amplitude was associated with an increased LLSR when the subjects were instructed to resist the perturbation.

Regarding the cortical mechanisms involved during the perturbation expectation, in monkeys the instruction indicating the animal how to react to the perturbation (pushing or pulling) modified the activity of precentral cortex neurons in a specific way (Evarts and Tanji, 1974; Evarts and Tanji, 1976; Tanji and Evarts, 1976). Moreover, these anticipatory specific modulations of neuronal activity have been related with those of the early cortical response to the perturbation. In humans, using fMRI, both the primary motor and somatosensory cortices were shown to be engaged in the preparation of a reaction to a mechanical perturbation from the very beginning of the expectation phase albeit that the BOLD level was not modified in an instruction-dependent fashion (de Graaf et al., 2009). fMRI, however, may be blind to subtle changes in the neuronal population's activity since global metabolic changes occur with both excitatory and inhibitory processes.

In view of the above, we hypothesized that intention-related modulation of the cortical response to a perturbation is related to anticipatory cortical mechanisms. Here, subjects were asked either to 'let-go' or to 'resist' to a brisk mechanically induced wrist extension. We investigated the cortical response to the perturbation as well as anticipatory cortical mechanisms during the expectation thereof using combined EEG–TMS. The latter mechanisms were investigated by analyzing the cortical response to a single-pulse TMS applied over the primary motor cortex in a time window in which the perturbation might occur (in this case, the perturbation was delayed relative to TMS). We focused on the N100 TMS-evoked potential which is thought to represent inhibitory intracortical processes (Nikulin et al., 2003; Bender et al., 2005; Kičić et al., 2008; Bonnard et al., 2009).

Materials and methods

Subjects

Ten healthy subjects (five females), aged 23 to 43 years, participated in this study. They gave their consent after being informed about the nature and procedure of the experiment. Care was taken to screen for any history of seizures or neurosurgery. This study was approved by the local ethical committee (CPP Sud Méditerranée I).

Experimental setup

The subjects were comfortably seated in an adjustable armchair in front of a screen. Their right forearm and hand were in a semiprone position attached to a pneumatic manipulandum, allowing only flexion and extension of the wrist in the horizontal plane (for more details, see de Graaf et al., 2009). The angle between the upper arm and the forearm was approximately 110°. The manipulandum axis was equipped with pneumatic jacks connected to a source of compressed air (5 bars) and controlled by a Labview interface. This setup allowed for the application of external forces on the wrist in the flexion or extension direction (see Fig. 1, upper right panel). In the present study, only perturbations inducing brisk wrist extensions were used.

Stereotactic TMS

We used a Magstim 200 stimulator (Magstim Company, Whitland, UK) that generates a monophasic magnetic field of up to 1.7 T, which was connected to a coplanar figure-of-eight coil with external loop diameter of 9 cm. The coil was maintained in the desired position by a custom-made coil holder system consisting of a knee joint which was connected to a sliding system in the horizontal plane (see Fig. 1, upper left panel). In this way, the coil could be optimally placed and directed, while maintaining its position stable throughout the experiment. The stimulation system was connected to a neuronavigation device (Navigation Brain System, Nexstim, Helsinki, Finland), which used an anatomical MRI of each subject to guide stimulation in a precise manner. The system calculates an estimate of the electric field induced in the cortex by the TMS pulse in real time and projects it onto the subject's anatomical MRI (see Fig. 2, upper left panel). Using this neuronavigation system, the coil was placed so as to stimulate the anterior bank of the left central sulcus at the location of the omega that corresponds to the cortical representation of the right hand in the primary motor cortex (Rumeau et al., 1994; Yousry et al., 1997; Sastre-Janer et al., 1998). The handle was pointing backward and laterally approximately 45° with respect to the midline to have the current direction perpendicular to the central sulcus. Around this position, we then optimized coil location so that stimulation evoked the strongest MEP (motor evoked potential) in the flexor carpi radialis (FCR, wrist flexor). The stimulation intensity was set just above the active motor threshold to evoke a clear MEP for all trials, without inducing a movement. The mean active motor threshold was $49 \pm 9\%$ of the maximum stimulator output (mean $\pm$ standard deviation), and the mean intensity stimulation was $54 \pm 10\%$ of the maximum stimulator output (around 110% of active motor threshold). To limit the subjects hearing the click induced by the coil discharge, they wore earplugs and headphones which delivered white noise (the intensity of the white noise was adjusted for each subject to be as loud as possible without being unpleasant). Previous studies established that this experimental procedure strongly attenuates the auditory evoked potentials due to the TMS click (Paus et al., 2001; Nikulin et al., 2003; Esser et al., 2006).

Experimental protocol

Before the experiment, subjects came to practice the experimental task and to have their optimal spot for TMS identified. The experiment consisted in 4 sessions of 80 trials preceded by a training session of 40 trials. Between sessions, the subjects had a few minutes of rest. The different events occurring in a trial are shown in Fig. 1 (lower panel).

Preceding each trial, the subject put his/her wrist in a light flexion. The trial started with the appearance of a fixation cross, and the manipulandum simultaneously applied a small force in the wrist extension direction during which he/she had to maintain the wrist in the initial flexed position. After 3 s, the instruction cue appeared for 500 ms; a red circle instructed the subject to resist the perturbation (RES condition), and a green circle instructed him/her to 'let-go' the hand and to follow the perturbation-induced movement (LGO condition). In both conditions, the subject had to prepare for the perturbation without changing his/her ongoing EMG activity (as for example by cocontracting the muscles when preparing to resist). The absence of cocontraction was visually checked online by an experimenter and further verified by offline analysis of the EMG activity recorded during the preparation period. The perturbation occurred at variable delays after the instruction cue presentation (3, 3.5, 4, or 4.5 s) and consisted of a 40.5-N force that was applied during 150 ms causing a brisk wrist extension. About 1.5 s after the perturbation, the manipulandum passively returned the hand in its initial flexed position and the next trial began.