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INVOLVEMENT OF SMAP IN THE INTENTION-RELATED LONG LATENCY STRETCH REFLEX MODULATION: A TMS STUDY

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Abstract—When our movement is perturbed by environmental forces, the Long Latency Stretch Reflex (LLSR), generated by a transcortical loop through the primary motor cortex (M1), is the fastest reaction adapted according to our prior intent. We investigated the involvement of the caudal part of the Supplementary Motor Area (SMAp) in this intention-related LLSR modulation. Subjects were instructed either to not react (i.e. to 'let-go') or to resist a mechanical perturbation extending the wrist and Transcranial Magnetic Stimulation (TMS) was used to transiently inactivate SMAp, either at the time of the LLSR generation (TMS was applied 50 ms before the perturbation), or at the end of the preparation period (TMS was applied 150 ms before the perturbation). The effect of SMAp transient inactivation on the LLSR modulation was compared to the effect of transient inactivation of M1 or of a Control area. Compared to the Control condition, the intention-related LLSR modulation decreased when TMS was applied either over SMAp or over M1 50 ms before perturbation occurrence, suggesting that SMAp, as M1, is involved in the LLSR modulation. Moreover, the LLSR modulation also decreased when TMS was applied over SMAp 150 ms before the perturbation, indicating that anticipatory processes taking place in SMAp participate to the LLSR modulation. In addition, TMS applied over SMAp elicited Motor-Evoked Potentials (MEPs) whose latency and shape were similar to MEPs evoked by TMS over M1, suggesting that they are due to direct corticospinal projections from SMAp. Interestingly, the SMAp MEPs amplitude was modulated depending on the subject's intention to resist or to let-go. Taken together these results strongly favor the idea that, during the expectation of a perturbation, SMAp is the seat of anticipatory processes that are specific to the subject's intent and that preset M1 in order to adapt the LLSR to this intention.

Key words: Supplementary Motor Area proper, TMS, stretch reflex, Motor-Evoked Potentials, primary motor cortex.

INTRODUCTION

Following a movement perturbation, the induced muscle stretch causes a series of reflex contractions (that form the stretch reflex) on the stretched muscles (Jaeger et al., 1982; Lee and Tatton, 1982; Gielen et al., 1988), and among others the Long Latency Stretch Reflex (LLSR), starting around 50–60 ms after movement perturbation. Contrary to the short latency stretch reflex, the LLSR adapts to cognitive factors such as the subject's prior intent, given the environmental constraints (Hammond, 1956; Rothwell et al., 1980; Bonnet, 1983; MacKinnon et al., 2000; Kimura et al., 2006). As a result, the reaction to movement perturbations can be fast and well adapted according to a prior intention, allowing the movement to reach its goals despite transient environmental forces' perturbations. Nowadays, it is widely accepted that the LLSR is generated by a rapid transcortical loop (Phillips, 1969; for reviews, see: Marsden et al., 1983; Matthews, 1991), presumably through the primary motor cortex (M1) (MacKinnon et al., 2000; Tsuji and Rothwell, 2002; Spieser et al., 2010). Moreover, M1 has been shown to be involved in the LLSR amplitude modulation (Abbruzzese et al., 1985; Bonnard et al., 2004; Kimura et al., 2006; Spieser et al., 2010). In Kimura et al. (2006) study, Transcranial Magnetic Stimulation (TMS) was used to transiently interrupt M1 activity at the moment of the reflex generation, while the LLSR amplitude varied as a function of the dynamical context in which the subject realized the task. To this aim, they used the Silent Period caused by TMS as an indicator of M1 inhibition duration and applied TMS over M1 50 ms before perturbation occurrence at an intensity sufficient to induce a Silent Period of at least 100 ms. They showed that this temporary inactivation of M1 led to the suppression of the reflex modulation, indicating that M1 is essential to the LLSR modulation. More recently, the cortical mechanisms involved were probed using combined EEG–TMS (Spieser et al., 2010). In this study, subjects were asked either to resist or not to react (i.e. to ''let-go'') to a passive wrist extension and

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Abbreviations: ANOVA, analysis of variance; dPMC, dorsal premotor cortex; ECR, extensor carpi radialis; ERPs, Event-Related Potentials; FCR, flexor carpi radialis; LLSR, Long Latency Stretch Reflex; M1, primary motor cortex; MEPs, Motor-Evoked Potentials; SMAp, Supplementary Motor Area proper; TMS, Transcranial Magnetic Stimulation.

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Event-Related Potentials (ERPs) evoked either by a TMS applied over M1 during the perturbation expectation or by the perturbation itself were recorded. The results showed that both the ERPs obtained in response to TMS during the perturbation expectation and the ERPs evoked by the perturbation itself were modulated according to subject's intention, suggesting that anticipatory processes preset the primary sensorimotor cortex activity in order to adapt its early reaction to the subject's intention.

In the present study, we tested the hypothesis that the Supplementary Motor Area (SMA), and specifically its caudal part called SMA *proper* (SMAp), is involved in those anticipatory processes presetting M1 activity. Indeed, M1 receives multiple afferences, particularly from SMAp and dorsal and ventral premotor cortices (Luppino et al., 1993). It has thus been proposed that those networks, upstream to M1, influence its dynamical state. The hypothesis of SMAp involvement in the LLSR amplitude modulation has been proposed by several authors (Tanji and Taniguchi, 1978; Tanji et al., 1980; Hummelsheim et al., 1986; Dick et al., 1987; Alexander and Crutcher, 1990). In studies from Tanji and collaborators (Tanji and Taniguchi, 1978; Tanji et al., 1980), monkeys had to prepare either to resist or let-go a mechanical perturbation. During the preparation to the perturbation, the authors showed a discharge modulation of some SMAp neurons after the instruction occurrence. Moreover, over the 201 neurons showing such a modulation, 94 showed an early modulation (as soon as 140 ms after the instruction) that differed as a function of the instruction. In another monkey study (Hummelsheim et al., 1986), a conditioning train stimulation of SMAp applied before elbow displacement (between -30 and -12 ms) has been shown to decrease the response of some M1 neurons to the perturbation. The authors thus proposed that SMAp could be involved in the LLSR amplitude modulation. Finally, regarding studies in Humans, a recent fMRI experiment showed that SMAp, as well as M1, was activated from the very beginning of the preparation to a mechanical perturbation (de Graaf et al., 2009). Nevertheless, this study revealed no difference in the BOLD signal of SMAp when the subject intended to resist or to let-go, therefore a specific involvement of SMAp in the LLSR modulation could not be established.

Thus, SMAp seems to be part of the sensorimotor network involved in the anticipation to a motor perturbation. However, its specific involvement in the LLSR modulation has not been clearly established in Humans. In the present experiment, SMAp involvement in the intention-related LLSR modulation was investigated by transiently inactivating SMAp: subjects were asked either to let-go or to resist a mechanical perturbation while TMS was applied over SMAp either 50 or 150 ms before perturbation occurrence. As in the study by Kimura et al. (2006), the 50-ms delay served to evaluate the impact of SMAp inactivation at the time of the LLSR generation. Indeed, applying TMS 50 ms before perturbation occurrence inactivated SMAp at least until the end of the LLSR generation (occurring approximately between 20 and 70 ms after the perturbation). The longer 150-ms delay allowed evaluation of the impact of SMAp inactivation at the end of the preparation period, but prior to the generation of the LLSR. For comparison, the effect of M1 transient inactivation at the same delays on the LLSR modulation was also tested. Moreover, as a Control condition, TMS was also applied over a non-involved area (right Brodmann area 19).

An additional interest of this experiment was to determine if muscular responses, i.e. a Motor-Evoked Potential (MEP) and/or a Silent Period, can be systemically elicited by a single-pulse TMS applied over SMAp and, if so, whether these responses are modulated by the subject prior intention. Indeed, only a few studies have used single-pulse TMS to stimulate SMAp, and even fewer via a precise neuronavigation system. However, it has been shown using neuronavigation that MEPs followed by a Silent Period can be elicited by stimulating non-primary motor areas (Teitti et al., 2008; Vaalto et al., 2010). In those studies, the authors reported that MEPs could be easily evoked by applying TMS over the superior frontal gyrus, and principally over Brodmann area 6 (Teitti et al., 2008), presumably corresponding to the dorsal premotor cortex (dPMC) (Teitti et al., 2008; Vaalto et al., 2010). The observed MEPs were compared to those elicited by M1 stimulation, and results showed that MEPs evoked by applying TMS over dPMC were similar in both shape and latency to MEPs obtained by TMS over M1. This suggests that MEPs evoked by dPMC stimulation reflect direct corticospinal projections originating from this area. Similarly to dPMC, SMAp is known to send direct corticospinal fibers since corticospinal projections both on motoneurons and on spinal interneurons have been observed in monkeys (Dum and Strick, 1991). In Humans, such projections have not yet been observed but are strongly suspected (for a recent study, see Chen et al., 2013), and would be coherent with what is known across phylogenetic evolution (Nakajima et al., 2000).

EXPERIMENTAL PROCEDURES

Subjects

This study was conducted on eight right-handed healthy subjects (five females and three males, mean age: 30). No subjects had previous neurological disease or contraindications to TMS. All gave their informed consent and the study was approved by the ethics committee (CPP Sud Méditerranée I).

Experimental set up

The subject sat in a comfortable armchair, facing a computer screen, on which the instructions appeared. His/her right forearm and hand were in a semi-pronation position and attached in a manipulandum allowing flexion/extension movements of the wrist in the horizontal plane (for more details, see Spieser et al., 2010). The manipulandum axis was equipped with