

Probing preparatory inhibition bilaterally with double-coil TMS

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Excitability of the corticospinal pathway can be investigated non-invasively in humans by applying transcranial magnetic stimulation (TMS) over the primary motor cortex (M1), eliciting motor-evoked potentials (MEPs) in targeted contralateral muscles. The amplitude of MEPs elicited in muscles of the contralateral limb (often the hand) is a precious indicator of corticospinal excitability (CSE) at the time of stimulation (Duque et al., 2017). Comparing MEP amplitudes in different conditions have helped to characterize the corticospinal correlates of various neural processes (Klein et al., 2012; Cos et al., 2014; Derosiere et al., 2015, 2017a, 2017b; Derosière et al., 2015; Zénon et al., 2015; Algoet et al., 2018) including those underlying action preparation (Duque et al., 2010, 2012, 2013, 2014, 2016, Klein et al., 2014, 2016; Quoilin and Derosiere, 2015; Wilhelm et al., 2016; Quoilin et al., 2016, 2018; Vassiliadis et al., 2018). During action preparation recent TMS studies have revealed that the motor output pathway shows profound inhibitory changes, even during the planning of simple finger movements (Bestmann & Duque, 2016; Duque, Greenhouse, Labruna, & Ivry, 2017). As such, MEPs are strongly suppressed preceding motor responses, indicating that the excitability of the corticospinal pathway is largely inhibited when the motor system prepares a behavior (Duque, et al., 2017).

To date, these studies have exploited a classical single-coil TMS protocol, stimulating one hemisphere (e.g. the right hemisphere) and registering MEPs in the contralateral hand (e.g. the left hand). Hence, in most experiments, the MEP data have only provided researchers with half of the story, increasing the probability of seeing data being misinterpreted. This occurs because applying TMS over both M1 in separate blocks doubles the duration of the experiment, making it impossible to fit all the conditions in a single session. Thus, so far, it has been assumed that differences in the strength of preparatory inhibition between conditions in which the target muscle (e.g. left index agonist) is either selected (e.g. left index response) or non-selected (e.g. right index response) for the forthcoming movement are due to the distinct function of the left index finger muscle in these two situations (Duque et al., 2010, 2014; Labruna et al., 2014). Yet, there is a substantial confound here because besides the function (selected vs. non-

selected), conditions also differ in regard to the hand being cued for the response (left or right). Hence, left MEP differences in preparatory inhibition between left and right hand movement trials may be due to the use of the non-dominant vs dominant hand and not to the distinct function of the targeted muscle in these trials.

We recently showed that, in the resting state, double-coil stimulation of the two M1 with a 1 ms inter-pulse interval (double-coil_{1ms} TMS) elicits MEPs in both hands that are comparable to MEPs obtained using single-coil TMS (Grandjean et al., 2017a, 2017b, 2018). In the present study (Vassiliadis et al., 2018), we intended to evaluate whether MEPs elicited with double-coil_{1ms} TMS are equivalent to single-coil MEPs when elicited during action preparation in an instructed-delay choice reaction time task where subjects have to inhibit a cued response until an imperative signal is displayed. We thus aimed at assessing if the inhibitory mechanisms extensively described in this type of task (Duque et al., 2017) are faithfully reproduced when using a double-coil_{1ms} protocol. To do so, we compared the amplitude as well as the coefficient of variation (CV) of MEPs produced by double-coil_{1ms} or single-coil TMS during action preparation.

We observed that MEPs were suppressed (smaller amplitude) and often less variable (smaller CV) during the delay period compared to baseline as previously reported (Klein-Flügge et al., 2013; Duque et al., 2017). Importantly, these effects were equivalent whether single-coil or double-coil_{1ms} TMS was used. This result supports the absence of any neural interactions between the two corticospinal volleys with the double-coil_{1ms} method and suggests that double-coil_{1ms} TMS is a reliable tool to assess CSE, not only when subjects are at rest, but also when they are involved in a task.

The advantages of double-coil_{1ms} TMS are manifold. First, the number of MEPs that can be collected in a given amount of time is doubled. This is a crucial aspect as it gives the opportunity to test more conditions within the same duration than could be done with a regular single-coil method. Second, MEPs are elicited in both hands at a near simultaneous time, meaning that CSE excitability can be probed bilaterally on each trial. Hence, dominant and non-dominant hand MEPs are elicited in the exact same conditions during the task (Duque et al., 2013). This obviously increases the signal to noise ratio in a significant way. Third, the acquisition of MEPs in both hands allows researchers to make direct comparisons between bilateral MEPs on a single-trial basis and to develop new measures such as indexes reflecting

the ratio between CSE changes occurring in the two hands. In fact, one may be interested in studying the impact of various task parameters (e.g. instruction, presence of reward, sensory evidence, level of urgency, effort required etc.) on the relationship between bilateral MEP amplitudes and CVs. Hence, the present technique opens new horizons in the study of how both hemispheres interact in various task settings (Verleger et al., 2009; Klein et al., 2016).

Lay abstract:

Transcranial magnetic stimulation (TMS) allows stimulating targeted cortical areas non-invasively in humans. When applied over primary motor cortex (M1), TMS can yield electrical responses in contralateral hand muscles, called motor-evoked potentials (MEPs). Comparing MEPs in different contexts has allowed to identify various neural processes, including the occurrence of motor inhibition during action preparation, a phenomenon called preparatory inhibition. So far, most studies have probed preparatory inhibition by focusing on MEPs elicited in one hand following single-coil TMS over contralateral M1. Here, we show that preparatory inhibition can be reliably probed bilaterally, by applying double-coil TMS pulses over both M1.

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