Motor training strengthens corticospinal suppression during movement preparation

Pierre Vassiliadis[1,2]*, Gerard Derosiere[1], Julien Grandjean[1], Julie Duque[1]

[1] Institute of Neuroscience, Université catholique de Louvain, 1200, Brussels, Belgium.
[2] Center for Neuroprosthetics (CNP) and Brain Mind Institute (BMI), Swiss Federal Institute of Technology (EPFL), 1202, Geneva, Switzerland

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*** CORRESPONDENCE TO:**
Pierre Vassiliadis
Institute of Neuroscience
Université catholique de Louvain
53, Avenue Mounier
COSY- B1.53.04
B-1200 BRUSSELS
Belgium
Email: pierre.vassiliadis@uclouvain.be
Web: http://www.coactionslab.com

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Abstract

Motor training improves the efficiency of trained movements and modifies neural activity at rest and during motor execution. Training may also shape preparatory processes but the neural correlates and the potential behavioral relevance of changes at the level of action preparation remain unclear. In humans, transcranial magnetic stimulation (TMS) studies have shown that movement preparation is accompanied by a suppression of corticospinal (CS) excitability relative to a baseline measure; a phenomenon called preparatory suppression. Here, we trained participants to initiate quick movements in an instructed-delay reaction time (RT) task and investigated resting CS excitability as well as preparatory suppression over the practice blocks. We found that training speeds up motor initiation, with no repercussion on error rates. Moreover, training increased baseline CS excitability and deepened preparatory suppression. Importantly, training-related changes in preparatory suppression were correlated to behavioral improvements: the subjects who showed a stronger expansion of preparatory suppression were also those exhibiting larger gains in RTs. Finally, in line with previous data, we observed a trial-by-trial relationship between the amount of preparatory suppression and the subsequent RT: subjects responded faster on trials with more preparatory suppression. Strikingly though, such a dependency of RTs on preparatory suppression was tuned by the amount of training performed: while it was not evident early on, the link emerged during the later practice blocks. Overall, our data indicate that training induces changes in motor preparatory processes that are linked to an enhanced ability to initiate fast movements.

Significance statement

Any movement is preceded by a period of preparation which involves significant changes in the activity of the motor system, including a broad suppression of the corticospinal output pathway, commonly referred to as preparatory suppression in human studies. Whether training can alter such preparatory activity is unknown. Here, we show that motor training leads to a strengthening of preparatory suppression in an instructed-delay reaction time (RT) task, and that such change is related to a shortening of RTs. Moreover, at the single-trial level, we observed a dependency of RTs on preparatory suppression which developed over training: the stronger the preparatory suppression, the faster the RT. These results indicate that motor training can alter motor preparatory activity in a behaviorally-relevant manner.

1. Introduction

Motor training generally improves the speed and/or accuracy at which movements are selected, initiated and executed. A great deal of research has been devoted to unveiling the functional changes at the basis of such improvements (Krakauer et al., 2019). At the neural level, neuroimaging (*e.g.*, Wiestler and Diedrichsen, 2013; Wenger et al., 2017; Yokoi and Diedrichsen, 2019) and transcranial magnetic stimulation (TMS) studies (*e.g.*, Rosenkranz et al., 2007; Reis et al., 2008; Mawase et al., 2017) have shown that training is accompanied by a plastic reorganization of the motor cortex, potentially supporting the formation of new motor memories. Most noticeably, training was shown to amplify resting corticospinal (CS) excitability (*e.g.*, Christiansen et al., 2018) and to induce learning-specific changes of motor activity during movement execution (Krakauer et al., 2004; Steele and Penhune, 2010; Shmuelof et al., 2014). Interestingly, several animal studies have also reported learning-related modulations of motor activity during action preparation (Paz et al., 2003; Makino et al., 2017; Vyas et al., 2018, 2020) that could reflect an optimization of preparatory processes with training (Mawase et al., 2018). Yet, the neural underpinnings and the behavioral relevance of the effects of training on action preparation remain fundamentally unclear.

In humans, motor activity can be assessed by applying single-pulse TMS over the primary motor cortex (M1), eliciting motor-evoked potentials (MEPs), whose amplitude reflects the excitability of the CS output pathway (Derosiere and Duque, 2020). When applied during reaction time (RT) tasks at specific time points, TMS elicits MEPs that can be used to assess CS excitability changes associated with action preparation and initiation. Multiple TMS studies have revealed that CS excitability is often suppressed during action preparation when compared to a baseline

condition. This phenomenon, called preparatory suppression (or inhibition), has received growing interest in the last decades but its function remains largely unknown (*e.g.*, Greenhouse et al., 2015; Duque et al., 2017; Derosiere, 2018; Hannah et al., 2018). A prominent view in the field is that it assists action selection processes by preventing the release of premature or incorrect responses (Duque et al., 2010). This view is supported by studies showing that the amount of preparatory suppression scales with the complexity of selection processes (Klein et al., 2014; Duque et al., 2016). Interestingly, another hypothesis in the field is that preparatory suppression could reflect a form of neural inhibition easing action initiation (Greenhouse et al., 2015; Hasegawa et al., 2017). This proposition was supported by the results of a study showing a dependence of RTs on the amount of preparatory suppression on a trial-by-trial basis: the stronger the preparatory suppression, the faster the initiation of the ensuing movement (Hannah et al., 2018). Importantly, these hypotheses are not incompatible as they focus on different levels of control, which are both known to shape motor activity: while the choice hypothesis suggests that some suppression originates from processes that help select accurate actions at precise timings (*i.e.*, therefore reducing the error rate), the motor hypothesis entails that a fair amount of preparatory suppression is also generated by processes speeding up action initiation (*i.e.*, therefore reducing RTs).

In the present study, we investigated the impact of motor training on preparatory suppression. Subjects practiced an instructed-delay RT task in which they were required to respond as fast as possible with the left or right hand according to a visual cue. The choice aspects were clear-cut, as evident from the low error rates, even before training. Hence, in such task the selection requirements are so low that there is no need or room for improvement; subjects can only become more skilled at the motor level, by initiating their action faster. Based on this, we predicted that

RTs would decrease over the course of practice but that the error rates would remain marginal. Moreover, based on the motor hypothesis that preparatory suppression eases action initiation, we supposed that subjects may show deeper preparatory suppression at the end of training and that this change may be linked to the shortening of RTs. We also examined the dependence of RTs on preparatory suppression on a trial-by-trial basis, at early and late stages of training.

2. Materials and Methods

2.1. Participants

A total of fifteen right-handed healthy subjects participated in the present study (n= 15; 10 women; 22.4 ± 1.63 years old) and received a monetary compensation. Handedness was assessed via a shortened version of the Edinburgh Handedness inventory (Oldfield, 1971) and all subjects filled out a TMS safety questionnaire. In addition, participants were screened for any neurological or psychiatric condition, drug or alcohol abuse, or drug treatment that could influence their performance or their neural activity. The protocol was approved by the Ethics Committee of the Université Catholique de Louvain and required written informed consent, in compliance with the principles of the Declaration of Helsinki. We had to exclude one subject because we encountered a technical problem during the experiment; hence, analyses were run on the fourteen remaining subjects. Part of the data reported here has been exploited in a separate study (Vassiliadis et al., 2018). All of the data are expressed as mean ± SE.

2.2. Experimental set-up

All experiments were conducted in a quiet and dimly-lit room. Subjects were seated at a table in front of a 21-inch cathode ray tube computer screen to perform an instructed-delay choice reaction time (RT) task which was implemented with Matlab 7.5 (the Mathworks, Natick, Massachusetts, USA) using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997). The monitor was positioned about 60 cm in front of the subjects and its refresh rate was set at 100 Hz. The subjects' left and right forearms were semi-flexed with both hands resting palm-down on

a custom response device **(Fig. 1A)**. This device, composed of two pairs of metal edges fixed on a wooden platform (one for each hand) was used to record the subjects' responses during the task (*i.e.*, abduction of the left or right index finger from the outer to the inner metal edge; see Task section). It also provided us with a very precise measure of the RTs (precision = 1 ms), while controlling for the initial position of the index fingers. This set-up has been used in previously published work (Quoilin et al., 2016, 2018, 2019; Grandjean et al., 2019).

2.3 Task

The instructed-delay choice RT task consisted in a virtual "Rolling Ball" game (Quoilin et al., 2016) which required subjects to choose between abduction movements of the left or right index finger. In this task, participants were informed that the position of a preparatory cue (*i.e.*, a ball separated from a goal by a gap) indicated the movement side for the forthcoming response. If the ball was presented on the left side of the screen (with the goal appearing on the right), subjects had to prepare a left index finger response (to get ready to "shoot the ball into the goal") and if the ball was on the right side (goal appearing on the left), subjects had to prepare a right index finger response. Participants were explicitly told to withhold their response until the onset of a "Go" signal (*i.e.*, a bridge), which appeared 1000 to 1200 ms after the ball and remained on the screen until a finger movement was detected or for a maximum duration of 500 ms. When the bridge appeared on the screen, subjects had to respond as fast as possible to allow the ball to roll on it and to quickly reach the goal. Hence, in this task, the time needed for sensory processing and motor preparation are both strongly constrained, and most of the RT can be assumed to result from action initiation (Haith et al., 2016). Note that each block included some catch trials in which the bridge

did not appear (5% of all trials). Subjects were required not to respond on these trials and were penalized if they did so. Hence, the presence of these trials allowed us to make sure participants would wait for the bridge onset before initiating their response. Each trial ended with a feedback screen displaying a score (see below) presented for 500 ms. Trials were separated by the presentation of a blank screen lasting for a duration that varied between 2050 and 2300ms. The variable delays in the task were sampled from uniform distributions to induce temporal uncertainty and therefore reduce anticipation that could emerge with the repetition of trials.

The feedback score reflected the subjects' performance on the current trial. Overall, the feedback procedure encouraged subjects to respond as quickly as possible while remaining accurate. On correct trials, scores ranged from 1 to 100 points and were displayed in green. Participants were informed that the score was inversely proportional to the RT: the faster the response, the higher the score. The RT was defined as the time interval between the onset of the bridge and the time when the index finger left the outer metal edge of the response device. In order to homogenize the score across subjects, scores on correct trials were individualized according to RTs measured during a familiarization session just before the main experiment (see Vassiliadis et al., 2018; Grandjean et al., 2019 for more details on how the score on correct trials was computed). Incorrect responses were penalized with negative scores displayed in red. They involved responses occurring too early, referred to as "anticipation errors" (penalized by 75 points), responses occurring too late, referred to as "time-out errors" (penalized by 50 points), responses provided with the incorrect hand (penalized by 20 points), referred to as "choice errors" and responses provided on catch trials (penalized by 12 points), referred as "catch errors". Anticipation errors consisted in responses provided either before the bridge onset or after its onset but with a RT

smaller than 100 ms. Time-out errors consisted in responses provided more than 500 ms after the bridge onset. When subjects succeeded not to respond on a catch trial, they were rewarded by +12 points. The total score was displayed at the end of each block.

2.4 TMS Protocol

Monophasic TMS pulses were delivered through one or two small figure-of-eight shaped coils (wing internal diameter: 35 mm), each connected either to a Magstim 200² magnetic stimulator (Magstim, Whitland, Dyfed, UK) or a Magstim Bistim² magnetic stimulator. The use of each TMS machine for the stimulation of each hemisphere was counterbalanced between subjects. Notably, TMS pulses could be triggered in one (*i.e.*, single-coil TMS) or in the two coils (*i.e.*, double-coil TMS) eliciting MEPs in one or in both hands, respectively. Importantly, in double-coil trials, a 1-ms interval separated the onset of the two pulses, eliciting MEPs in both hands at a near simultaneous time (Algoet et al., 2018; Grandjean et al., 2018; Vassiliadis et al., 2018; Quoilin et al., 2019). This interval was used to avoid direct electromagnetic interference between the two coils (Cincotta et al., 2005), while preventing transcallosal interactions that would occur between motor areas with longer delays (Ferbert et al., 1992; Hanajima et al., 2001).

During the experiment, each TMS coil was placed tangentially over one primary motor cortex (M1) with the handle pointing backward and laterally at a 45° angle away from the midline, approximately perpendicular to the central sulcus **(Fig. 1C)**. For each M1, the optimal scalp position to elicit a contralateral MEP in the first dorsal interosseous muscle (FDI) was identified and marked on a cap placed on the subject's scalp to provide a reference mark throughout the

experiment (Duque et al., 2014; Derosiere et al., 2017a, 2017b). The FDI muscle was the prime-mover in our instructed-delay RT task. The resting Motor Threshold (rMT) was determined at this "hotspot" for each M1. It was defined as the minimal TMS intensity required to evoke MEPs of a 50 μV amplitude in the relaxed FDI muscle in at least 5 out of 10 consecutive stimulations. Across participants, the rMTs equalled 41.7 ± 5.05 % and 40.8 ± 6.39 % of the maximum stimulator output for the left and the right FDI, respectively. For each hemisphere, the intensity used throughout the experiment was set at 115 % of the individual rMT (Derosiere et al., 2019). Note that for all participants, stimulating the hotspot for the FDI also elicited reliable MEPs in the abductor digiti minimi (ADM), a pinkie abductor muscle which, contrary to the FDI, was not directly involved in the RT task (i.e., task-irrelevant muscle). Using this protocol, we were therefore able to assess training-related CS excitability changes both in the prime-mover and in a task-irrelevant muscle.

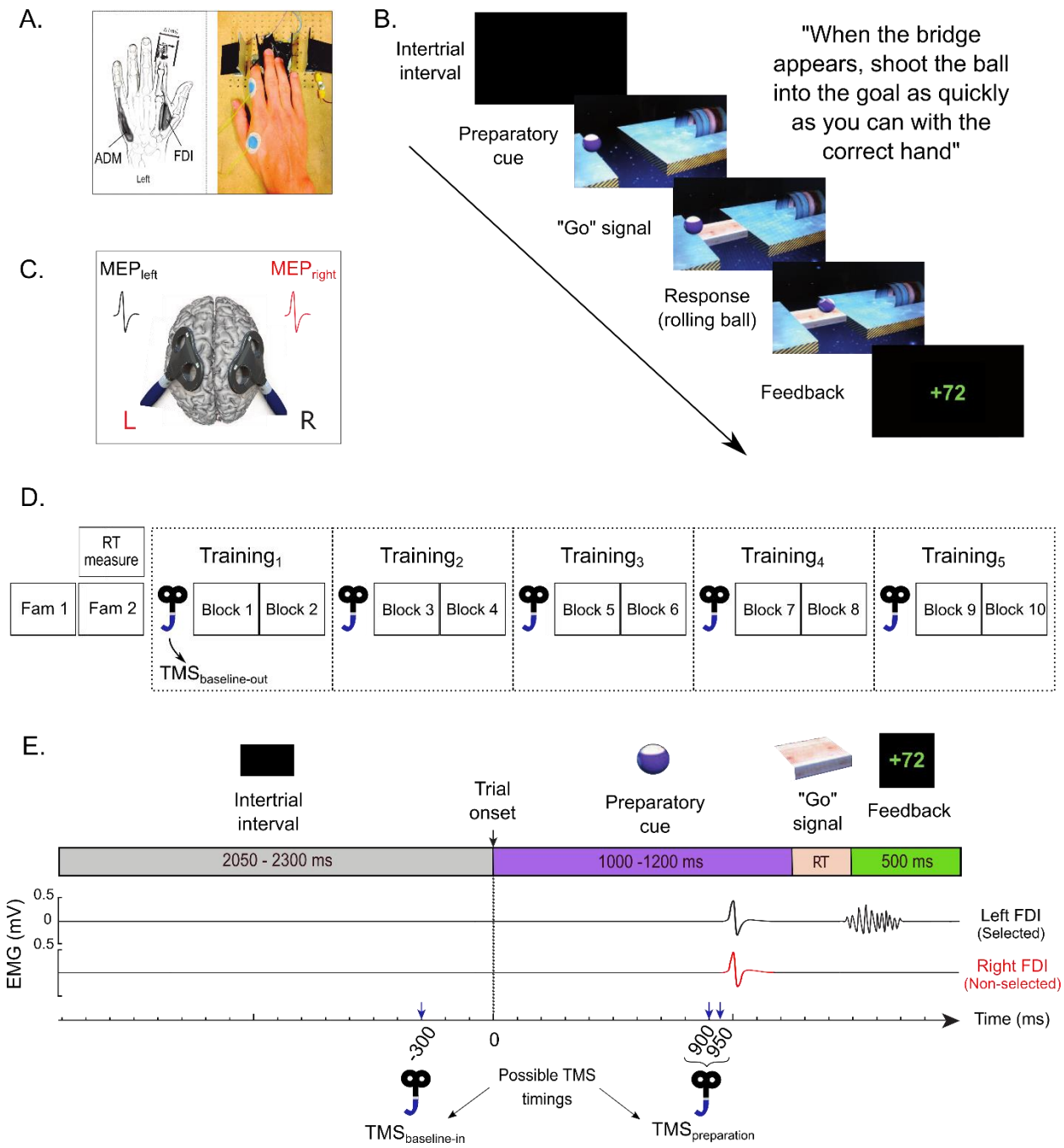

Figure 1. A, The response device. Index finger responses were recorded using a home-made device positioned under the left (graphic representation) and right (photographic representation) hands. Note that electrodes are only shown for the first dorsal interosseous (FDI) on the photo but were also placed over the abductor digiti minimi (ADM) in this study. **B, "Rolling Ball" task.** Subjects were asked to choose between responding with the left or right index finger according to

the position of a ball (Preparatory cue) appearing on the left or right part of the screen (left in the current example). They had to wait until the onset of a bridge ("Go" signal) to release their response as quickly as possible. The ball then rolled on the bridge (when the subjects answered correctly) to reach a goal located on the other side of the gap. A feedback reflecting how fast and accurate the subjects concluded each trial. **C, TMS protocol.** Two figure-eight-shaped coils were placed over the subject's primary motor cortex (M1), eliciting MEPs in the left and/or right FDI and ADM. **D, Time-course of the experiment.** After two familiarization blocks (Fam1 & Fam 2, see methods), subjects executed ten blocks of forty trials during which MEPs were elicited at $TMS_{baseline\text{-}in}$ or $TMS_{preparation}$ (see 1E). The effect of training was assessed by comparing five sets of data ($Training_1$ to $Training_5$), each involving MEPs pooled over two consecutive blocks. MEPs were also elicited outside the blocks ($TMS_{baseline\text{-}out}$) at five points in time, before block 1 and after blocks 2, 4, 6 and 8, categorized as $Training_1$ to $Training_5$, similar to the MEPs elicited during the blocks. Comparing these data sets allowed us to consider potential training-related changes in resting CS excitability outside the context of the task. **E, Time course of a trial**. Trials were separated by a blank screen (intertrial interval; 2050 to 2300 ms) and always started with a preparatory cue appearing for a variable delay period (1000 to 1200 ms). Then, a "Go" signal was presented and remained on the screen until a response was detected, hence for the duration of the reaction time (RT). The feedback was presented at the end of each trial for 500 ms. TMS pulses occurred either during the intertrial interval (300 ms before the beginning of the trial; $TMS_{baseline\text{-}in}$), or during the delay period (900 or 950 ms after the preparatory cue onset, timings pooled; $TMS_{preparation}$). In double-coil trials, motor-evoked potentials (MEPs) were elicited in the first dorsal interosseous (FDI) and abductor digiti minimi (ADM, not represented here) of both hands

at a near simultaneous time (1 ms delay); in single-coil trials, MEPs were elicited in the left or right hand. The figure displays a left hand trial with double-coil TMS at $TMS_{preparation}$.

2.5 Experimental procedure

The experiment started with two familiarization blocks during which subjects performed the "Rolling Ball" task for the first time. The first block did not involve any TMS and allowed participants to become acquainted with the basic features of the task (Familiarization 1, 20 trials). The second block involved TMS, exactly as in the main experiment, and enabled subjects to get used to the stimulations while performing the task (Familiarization 2, 40 trials). This second familiarization block also served to compute the median RT for each subject, which was used to individualize the scores on correct trials according to the initial performance.

Then, subjects performed the "Rolling Ball" task for a total of 400 trials divided in 10 blocks. Hence, subjects were provided with a large amount of trials to practice the task. Each experimental block involved an equal combination of single- and double-coil trials. These trials occurred in a random order so that subjects could not anticipate the type of pulse (single or double) they would face next. Importantly, given that both techniques produce equivalent MEPs (Grandjean et al., 2018; Vassiliadis et al., 2018), these data were considered regardless of the protocol used to elicit them. Moreover, in double-coil trials, half of the trials involved a pulse over left M1 first whereas the other half involved a pulse over the right M1 first (1 ms delay). Again, we assembled these data because the order of stimulation does not influence the amplitude of double-coil MEPs (Grandjean et al., 2018; Vassiliadis et al., 2018). In summary, MEPs obtained

in each hand were evaluated regardless of the type of stimulation (single- or double-coil TMS) and the order of stimulation in double-coil trials (left-right or right-left).

TMS could occur in three different settings. First of all, some TMS pulses were applied outside the blocks ($TMS_{baseline\text{-}out}$) while subjects were relaxing with the eyes open; at this time, the amplitude of MEPs reflects baseline CS excitability at complete rest. $TMS_{baseline\text{-}out}$ pulses were applied every other block at five different points in time, starting before block 1 and ending after block 8 **(Fig. 1D)**. Each time point involved 10 double-coil (i.e. 10 pulses on both M1) and 10 single-coil (5 pulses on each M1) pulses, allowing us to collect 15 MEPs in each hand at each of the 5 different stages of the experiment. Then, among the TMS pulses that fell within the blocks **(Fig. 1E)**, some occurred during the inter-trial interval (blank screen), 300 ms before the beginning of the trial (*i.e.*, 1750 to 2000 ms after the blank screen onset). The MEPs recorded at this time provided us with another baseline measure of CS excitability, when subjects were at rest but engaged in the task ($TMS_{baseline\text{-}in}$; Labruna et al., 2011). In each block, $TMS_{baseline\text{-}in}$ occurred in 4 double-coil (4 for both M1) and 4 single-coil trials (2 for each M1), allowing us to collect a total of 6 baseline MEPs per block in each hand. Finally, in order to assess preparatory suppression during training, TMS was also applied 900 or 950 ms after the onset of the preparatory cue ($TMS_{preparation}$). Since no difference was found between MEPs recorded at these two timings in our previous analysis on the same dataset (Vassiliadis et al., 2018), these data were pooled together. $TMS_{preparation}$ occurred in 16 double-coil (16 for both M1) and 16 single-coil trials (8 for each M1), allowing us to collect a total of 24 preparatory MEPs per block in each hand. Notably, half of these MEPs fell in trials requiring a left hand response, while the other half occurred in right hand trials. Hence, MEPs could either fall in a hand that was selected for the forthcoming response ($MEP_{selected}$;

e.g., left MEPs preceding a left index finger response) or in a hand that was non-selected ($MEP_{non-selected}$; *e.g.*, left MEPs preceding a right index finger response).

2.6 Data processing and statistical analyses

The purpose of the study was threefold: (1) to characterize training-related changes in preparatory suppression in a basic instructed-delay RT task, (2) to assess whether such modulation, if any, is correlated to training-related improvements in RTs and (3) to evaluate, at a trial-by-trial level, the dependency of RTs on the level of preparatory suppression and assess if this link is modified by training. To do so, the behavior and MEPs were evaluated according to the block within which they were elicited and data from two consecutive blocks were pooled together. In this way, given the 10 blocks, we obtained five data sets reflecting five different training stages ($Training_{STAGE}$ = $Training_1$ to $Training_5$; **Fig. 1D)**.

Statistical analyses were carried out with Matlab 2018a (the Mathworks, Natick, Massachusetts, USA) and Statistica 10 (StatSoft Inc., Tulsa, Oklahoma, USA). All data were systematically tested for the sphericity assumption using Maunchley's tests. The Greenhouse–Geisser (GG) correction was used for sphericity when necessary. Post-hocs comparisons were always conducted using the Fisher's Least Significant Difference (LSD) procedure. The significance level was set at $p \leq 0.05$.

2.6.1 RTs and errors

Left and right hand RTs were assessed by considering the time elapsed between the onset of the "Go" signal and the moment at which the responding index finger quitted the outer metal edge of the response device. Trials in which subjects made any type of error were removed from the data set for the analysis of RTs. As a result, an average of 35 left and 34 right hand trials remained for each subject at any given $\text{Training}_{\text{STAGE}}$. We computed the mean RT for left and right hand responses separately and then averaged these data together. We choose this two-step method to make sure that left and right hand RTs would have the same weight in the averaged data for each $\text{Training}_{\text{STAGE}}$, regardless of the number of errors in each hand. Besides, we also assessed the accuracy of motor responses over the course of training. To do so, we computed, for each $\text{Training}_{\text{STAGE}}$, the amount of anticipation, time out and catch errors as well as the overall error rate. For each of these variables, we expressed the number of incorrect trials in percentage of the total amount of trials, regardless of the responding hand. Choice errors were not analysed because they were really rare (4 choice errors across all subjects).

For the statistical analysis of RTs and errors (*i.e.*, anticipation, time out, catch and global errors), we used one-way analyses of variance for repeated measures (ANOVA_{RM}) with the factor $\text{Training}_{\text{STAGE}}$ (Training_1 to Training_5).

2.6.2 MEP amplitudes

MEP data were obtained by recording electromyography (EMG) activity bilaterally from surface electrodes (Neuroline, Medicotest, Oelstykke, Denmark) placed over the FDI and ADM.

On each trial, EMG data were collected for 1000 ms starting 300 ms before the TMS pulse. The EMG signals were amplified (x1000), bandpass filtered online (10-500Hz; NeuroloLog; Digitimer), and digitalised at 2000 Hz for offline analysis. MEP data were collected with Signal (Signal 3.0, Cambridge, UK) and analyzed with custom Signal scripts. Trials with background EMG activity (root mean square computed from -250 to -50 ms before the TMS pulse) exceeding 3 standard deviations (SD) around the mean were discarded for the analyses (1.46 ± 0.32 % removal). This was done to prevent contamination of the MEP measurements by significant fluctuations in background EMG (Duque et al., 2014; Klein et al., 2016). In addition, for each muscle and each TMS_{TIMING}, we excluded MEPs with peak-to-peak amplitude exceeding 3 SD around the mean (1.88 ± 0.21 % removal).

MEP data were processed and analyzed separately for the FDI and ADM muscles. For the analysis of MEPs elicited at $TMS_{baseline\text{-}out}$ and $TMS_{baseline\text{-}in}$, we averaged separately left and right hand MEPs for each $Training_{STAGE}$ before computing the mean of these averaged data, similarly as for the RT data. Moreover, for the analysis of MEPs at $TMS_{preparation}$, we first removed the trials in which subjects made a mistake (10.78 ± 1.81 % removal). We then grouped left and right hand MEPs according to whether they corresponded to a $MEP_{selected}$ or $MEP_{non\text{-}selected}$. Again, within these categories, we computed the average of the separate means of left and right hand MEPs for each $Training_{STAGE}$. As mentioned in the introduction, MEPs are typically suppressed at $TMS_{preparation}$ relative to baseline, a process referred to as preparatory suppression (or inhibition; Duque et al., 2017).

For the statistical analysis of MEPs, we first considered the data elicited at rest. To do so, we used a two-way $ANOVA_{RM}$ with TMS_{TIMING} ($TMS_{baseline\text{-}out}$ or $TMS_{baseline\text{-}in}$), and $Training_{STAGE}$ ($Training_1$ to $Training_5$) as within-subject factors. Then, we considered MEPs elicited at $TMS_{preparation}$. These MEPs were expressed as a percentage of MEPs at $TMS_{baseline\text{-}in}$ to take into account possible fluctuations in resting CS excitability along with training (Duque et al., 2017). First, we tested whether these percentage MEP amplitudes show a significant suppression (*i.e.*, reflecting preparatory suppression) at the beginning of the experiment. To do so, t-tests were used to compare the percentage MEPs elicited at $Training_1$ to a constant value of 100%. Then, we analyzed all percentage MEP amplitudes at $TMS_{preparation}$ by means of a two-way $ANOVA_{RM}$ with the factors $MEP_{SELECTION}$ ($MEP_{selected}$ or $MEP_{non\text{-}selected}$) and $Training_{STAGE}$ ($Training_{1,}$ to $Training_5$). This ANOVA was also run on absolute MEP amplitudes.

2.6.3 Correlation between training-related changes in RTs and preparatory suppression

In a further analysis, we examined whether the RT reduction occurring along with practice correlates to training-related changes in preparatory suppression. To address this question, we computed ratios reflecting training-related changes in RTs and MEPs ($TMS_{preparation}$; expressed in percentage of baseline). Based on the RT data, we realized that the subjects' behavior improved substantially during the first practice stage ($Training_1$ to $Training_3$) but then, RTs remained quite stable later on (from $Training_3$ to $Training_5$; see Result section). For this reason, we considered ratios for these two phases of training separately, providing us with an indication of early ($Training_{ratio\text{-}early}$: $Training_3/Training_1$) and late ($Training_{ratio\text{-}late}$: $Training_5/Training_3$) training-related changes in RTs and MEPs ratios. We then examined the correlation between these two sets

of RT and MEP $\text{Training}_{\text{ratios}}$ by using least squares linear regressions. Notably, MEP $\text{Training}_{\text{ratios}}$ were computed based on the data obtained in both the FDI and the ADM; separate analyses were run on these data.

2.6.4 RT dependency on preparatory suppression

Another primary goal here was to evaluate whether the speed at which subjects respond depends on the strength of preparatory suppression during the ongoing trial and whether this dependency may consolidate with training. To address this point, we selected the MEPs elicited at $\text{TMS}_{\text{preparation}}$ and here again, expressed them as a percentage of $\text{TMS}_{\text{baseline-in}}$. We only used the double-coil trials, to consider a homogeneous set of data, with preparatory MEPs falling in both hands systematically. For each of these trials, we extracted the RT of the selected response, as well as the MEPs recorded from the FDI and ADM muscles in both the selected ($\text{MEP}_{\text{selected}}$) and non-selected ($\text{MEP}_{\text{non-selected}}$) hands. Hence, for each trial, we obtained one RT measure linked to four different MEPs.

We first examined the overall dependence of RTs to preparatory suppression, regardless of the $\text{Training}_{\text{STAGE}}$. To do so, we pooled the trials from all 10 blocks together and sorted them according to the amplitude of MEPs within each trial. Given that there were four MEPs in each trial, we repeated this procedure four times, providing us with four different orderings of the trials according to the $\text{MEP}_{\text{selected}}$ or $\text{MEP}_{\text{non-selected}}$, in the FDI or ADM. Within each arrangement, trials were then grouped into 6 consecutive percentile bins (MEP_{BIN}: $\text{MEP}_{\text{BIN-1}}$ = 0 to 16.7%, $\text{MEP}_{\text{BIN-2}}$ = 16.7 to 33.3% … $\text{MEP}_{\text{BIN-6}}$ = 83.3 to 100% of the data). $\text{MEP}_{\text{BIN-1}}$ always contained the trials

with the stronger preparatory suppression whereas the MEP_{BIN-6} included the trials with the weaker preparatory suppression. We then computed the mean RT of trials within each MEP_{BIN}, separately for left and right hand responses (12 trials per condition on average and never less than 9 trials), and then averaged the RTs across response sides. Hence, following this method, we obtained six average RT values (i.e. one for each MEP_{BIN}) for each of the trial arrangements based on the four MEP types. These RT data were analysed using four separate $ANOVA_{RM}$ with the factor MEP_{BIN} (MEP_{BIN-1} to MEP_{BIN-6}).

In a second analysis, we examined the impact of training on this MEP-RT dependency. To do so, the trials were separated into two equal parts according to whether they were acquired at the early stage of training (blocks 1-5; $Training_{early}$) or at a later stage (blocks 6-10; $Training_{late}$). Again, for each of these two $Training_{STAGE}$, the trials were sorted according to the amplitude of the corresponding MEPs. Here, we focused on the FDI MEP data as this is where we found a significant MEP-RT dependency in the global analysis (i.e., in the non-selected FDI; see Result section). Then, trials were split into 3 consecutive percentile bins (MEP_{BIN} : MEP_{BIN-1} = 0 to 33.3%, MEP_{BIN-2} = 33.3 to 66.6%, MEP_{BIN-3} = 66.6 to 100% of the data), with MEP_{BIN-1} containing the trials with the strongest preparatory suppression. Here, we only used 3 bins instead of 6 bins to allow a sufficient number of MEPs per condition at each $Training_{STAGE}$. Next, similarly to the initial analysis, we computed the mean RT of trials within each MEP_{BIN}, separately for left and right hand responses (12 trials on average and never less than 9 trials), and then averaged the RTs across response sides; one subject had to be excluded from the analysis because the number of remaining trials was insufficient in one MEP_{BIN}. These RT data were analyzed using a two-way

ANOVA$_{RM}$ with the factors MEP$_{BIN}$ (MEP$_{BIN-1}$ to MEP$_{BIN-3}$) and Training$_{STAGE}$ (Training$_{early}$ or Training$_{late}$).

3. Results

3.1. RTs and errors

Fig. 2A shows the evolution of RTs as training progressed. Visually, it appears clearly that RTs decreased over the $\text{Training}_{\text{STAGES}}$. Consistently, the ANOVA_{RM} revealed a significant influence of $\text{Training}_{\text{STAGE}}$ on the RT data ($F_{(4,52)} = 4.31$, $p = 0.0043$). In particular, post-hoc tests showed that RTs measured from Training_3 to Training_5 were significantly shorter than the RTs at Training_1 (all $p < 0.004$). In contrast, the error rate remained stable over the blocks ($F_{(4,52)} = 0.82$, $p = 0.52$, **Fig. 2B**). More specifically, we did not observe any modification of the percentage of anticipation ($F_{(4,52)} = 1.12$, $p = 0.36$), time out (GG-corrected $F_{(2.50,32.50)} = 0.90$, $p = 0.44$) or catch errors ($F_{(4,52)} = 1.73$, $p = 0.16$). These behavioral data indicate that practicing the task over the blocks enabled subjects to respond more quickly while maintaining the same level of accuracy.

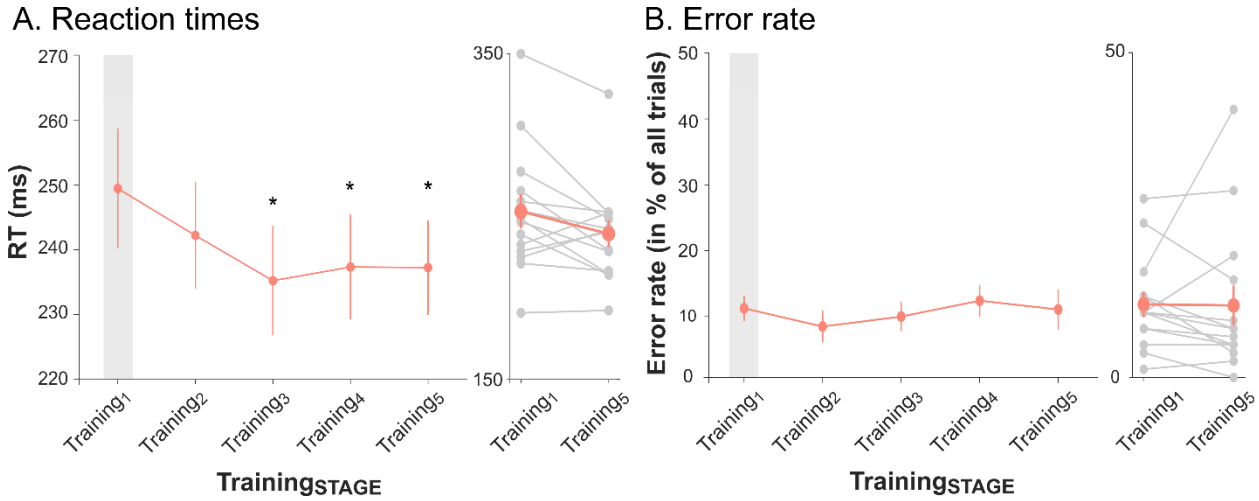

Figure 2. Evolution of Reaction times (RTs) and error rate throughout training. The mean RTs (**A**, in ms) and error rate (**B,** in % of all trials) are represented for each $\text{Training}_{\text{STAGE}}$,

regardless of the responding hand. Stars denote a significant difference between a given $Training_{STAGE}$ and $Training_1$ ($p < 0.05$). Individual data for $Training_1$ and $Training_5$.

3.2. MEP amplitude

First, we evaluated the effect of training on MEPs acquired at rest, either outside the blocks ($TMS_{baseline\text{-}out}$**)** or within them ($TMS_{baseline\text{-}in}$), separately for the FDI and ADM muscles. First, as apparent on **Fig. 3**, MEPs were generally larger in the FDI when compared to the ADM muscle. This was expected given that the TMS 'hotspot' was determined based on MEPs elicited in the FDI and not the ADM (see Methods section). Still, past studies indicate that this method can provide us with a reliable measure of CS excitability changes occurring in a task-irrelevant effector (Vassiliadis et al., 2018; Quoilin et al., 2019). As evident on **Fig. 3A,** FDI MEPs were generally larger at $TMS_{baseline\text{-}in}$ (1.81 ± 0.17 mV) than at $TMS_{baseline\text{-}out}$ (1.32 ± 0.18 mV). Consistently, the factor TMS_{TIMING} was significant ($F_{(1,13)} = 29.17$, $p < 0.001$), indicating that FDI MEP amplitudes were significantly larger when assessed in the context of the task compared to when subjects were fully at rest, as observed in previous studies (Labruna et al., 2011; Derosiere et al., 2015). Interestingly, the $ANOVA_{RM}$ also revealed a significant effect of $Training_{STAGE}$ on baseline FDI MEPs ($F_{(4,52)} = 5.94$, $p < 0.001$). As such, MEPs recorded at $Training_2$ to $Training_5$ were larger than those obtained at $Training_1$ (all $p < 0.03$). Importantly, this training effect on MEP amplitudes occurred independently of the TMS_{TIMING}: there was a parallel increase in the amplitude of FDI MEPs elicited at $TMS_{baseline\text{-}out}$ and $TMS_{baseline\text{-}in}$ over the course of training (*i.e.*, the $Training_{STAGE}$ x TMS_{TIMING} interaction was not significant: $F_{(4,52)} = 0.16$, $p = 0.96$). Finally, this training-related increase in resting CS excitability was not limited to the FDI, prime-mover in the task, but extended

to the ADM muscle **(Fig. 3B)**, which was task-irrelevant (TMS_{TIMING}: $F_{(1,13)}$= 17.77, p = 0.001, $Training_{STAGE}$: $F_{(4,52)}$ = 5.65, p < 0.001). This effect also occurred regardless of whether MEPs were elicited outside or within the blocks (TMS_{TIMING} x $Training_{STAGE}$: GG-corrected $F_{(2.25,29.23)}$ = 1.19, p = 0.32).

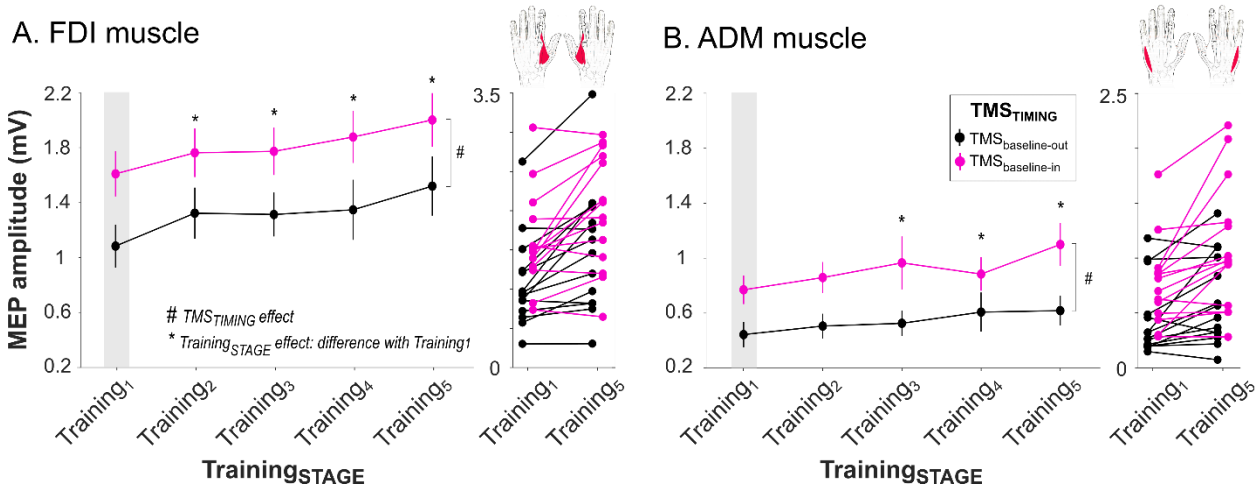

Figure 3. Evolution of baseline MEPs throughout training. MEP amplitudes (in mV) elicited at $TMS_{baseline\text{-}out}$ (black) and $TMS_{baseline\text{-}in}$ (pink) in the FDI **(A)** and ADM **(B)** muscles at the different $Training_{STAGES}$. Hash signs indicate a TMS_{TIMING} effect. Stars denote a significant difference between a given $Training_{STAGE}$ and $Training_1$ (p < 0.05). Individual data for $Training_1$ and $Training_5$ are also displayed.

Second, we analyzed the effect of training on MEPs elicited during action preparation (*i.e.*, at $TMS_{preparation}$). In a first step, we expressed these data in percentage of the MEPs obtained at $TMS_{baseline\text{-}in}$, as shown on **Fig. 4A** and **4B** for the FDI and ADM muscles, respectively. As evident on **Fig. 4A**, percentage FDI MEPs were initially suppressed at $Training_1$ (MEPs smaller than 100 %), consistent with the presence of preparatory suppression in the prime-mover (FDI), whether

selected for the forthcoming response ($MEP_{selected}$: 74.85 ± 4.08 %; t = -6.16, p < 0.0001) or not ($MEP_{non\text{-}selected}$: 76.56 ± 4.21 %; $t_{(13)}$= -5.57, p < 0.0001). Notably, preparatory suppression was also initially observed in the task-irrelevant ADM but only when the probed hand was non-selected for the forthcoming movement ($MEP_{non\text{-}selected}$: 78.70 ± 4.53%, $t_{(13)}$= -4.70, p < 0.001) and not when it was selected ($MEP_{selected}$: 93.77 ± 4.95%, $t_{(13)}$= -1.26, p = 0.23). More interestingly, preparatory suppression became more prominent over the course of training. Consistently, the $ANOVA_{RM}$ revealed a significant decrease in percentage MEP amplitudes over the $Training_{STAGES}$ for the FDI ($F_{(4,52)}$ = 2.63, p = 0.045) and the ADM ($F_{(4,52)}$ = 3.30, p = 0.017). This change became significant from $Training_4$ in the FDI (*i.e.*, $Training_4$: p = 0.044 when compared to $Training_1$) and from $Training_5$ in the ADM (*i.e.*, $Training_5$; p = 0.0011). It did not depend on the hand within which MEPs were elicited. That is, the effect could be observed whether MEPs were obtained from a hand that was selected for the forthcoming response or non-selected, consistent with the absence of significant $Training_{STAGE}$ x $MEP_{SELECTION}$ interaction, neither for the FDI ($F_{(4,52)}$ = 0.35, p = 0.84), nor for the ADM (GG-corrected $F_{(2.23,28.99)}$ = 2.14, p = 0.13). Notably though, we did observe an effect of $MEP_{SELECTION}$ for the ADM ($F_{(1,13)}$ = 6.53, p = 0.024). As such, percentage MEPs were generally larger in the selected than in the non-selected hand in this task-irrelevant muscle, as clearly displayed on **Fig. 4B**. Such an effect was not found for the FDI ($MEP_{SELECTION}$: $F_{(1,13)}$ = 0.43, p = 0.52). Hence, these data suggest that training induced a global decrease in preparatory activity (i.e., reflecting a strengthening of preparatory suppression), when expressed with respect to resting MEPs elicited during the inter-trial interval, at $TMS_{baseline\text{-}in}$. Because these latter MEPs rather showed an increase in their amplitude along with training (similarly as MEPs at $TMS_{baseline\text{-}out}$), the question remains as to whether preparatory MEPs would show any change at all when considered in absolute value.

To address this question, we ran another set of $ANOVA_{RM}$ on absolute MEP amplitudes (rather than percentage values) at $TMS_{preparation}$, both for the FDI (**Fig. 4C**) and the ADM (**Fig. 4D**). Interestingly, when considering these data, we did not observe any fluctuation of preparatory MEPs over the $Training_{STAGES}$, neither for the FDI ($F_{(4,52)} = 1.05$, $p = 0.39$), nor for the ADM (GG-corrected $F_{(2.33,30.31)} = 1.08$, $p = 0.36$). The only effect here concerned the factor $MEP_{SELECTION}$, which was significant for the ADM ($F_{(1,13)} = 4.80$, $p = 0.047$) but not the FDI ($F_{(1,13)} = 1.49$, $p = 0.24$), supporting the presence of a higher task-irrelevant preparatory activity in a selected compared to a non-selected hand. Again, the interactions were not significant for the FDI ($Training_{STAGE}$ x $MEP_{SELECTION}$: $F_{(4,52)} = 0.81$, $p = 0.53$) and ADM muscles (GG-corrected $F_{(1.55,20.10)} = 2.00$, $p = 0.17$). In conclusion, the analysis of our MEP data indicate that a basic instructed-delay choice RT task repeated over several blocks of trials can elicit training-related changes in CS excitability. Overall, there seems to be an increasing differentiation between the baseline level of CS excitability, which is growing stronger over time, even outside of the context of the blocks, and the absolute level of preparatory activity, which remains stable over the blocks, as reflected in a strengthening of preparatory suppression along with training. These CS excitability changes occur in parallel with an improvement in response speed and a maintenance of response accuracy.

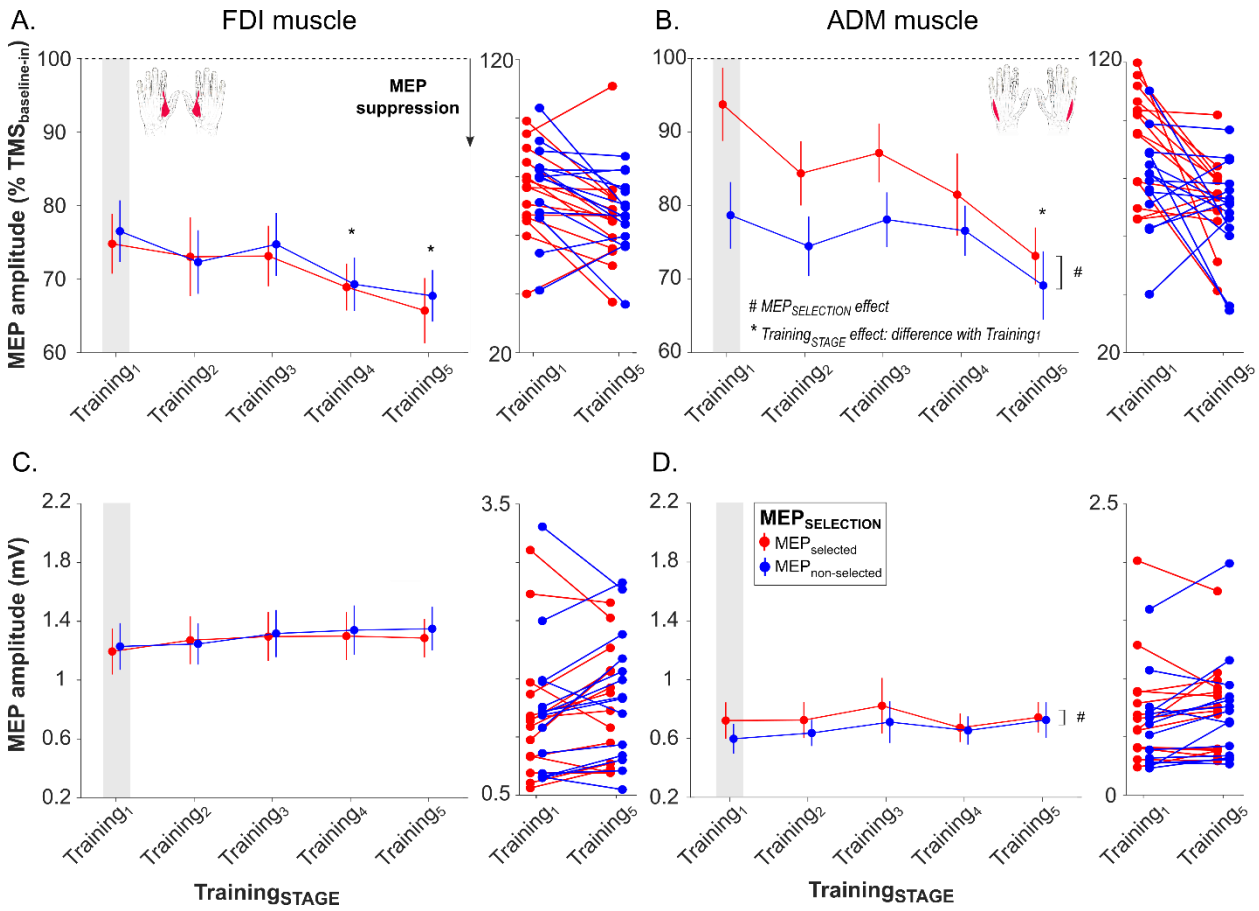

Figure 4. Evolution of preparatory MEPs throughout training. Normalized MEP amplitudes recorded at $TMS_{preparation}$ (in percentage of MEPs elicited at $TMS_{baseline\text{-}in}$) elicited in the FDI **(A)** and ADM **(B)** muscles at the different $Training_{STAGES}$. Absolute MEP data (in mV) are represented for the FDI **(C)** and ADM **(D)** muscles. Hashes indicate a TMS_{TIMING} effect. Stars denote a significant difference between a given $Training_{STAGE}$ and $Training_1$ ($p < 0.05$). Individual data for $Training_1$ and $Training_5$ are also displayed.

As reported above, training on the RT task induced an increase in preparatory suppression, with deeper MEP suppression observed at later stages of training. However, because RTs were also reduced by the training, one may argue that the training-related modulation in preparatory

suppression were due to changes in the delay between the TMS pulse and the movement onset ($Delay_{TMS\text{-}TO\text{-}MOVE}$). Importantly though, in the present study, changes in RTs do not directly translate into equivalent changes in the $Delay_{TMS\text{-}TO\text{-}MOVE}$. As such, the latter variable also includes the delay between the TMS pulse and the "Go" signal ($Delay_{TMS\text{-}TO\text{-}GO}$) which was variable in the current experiment (see Methods).

However, because the TMS pulse fell on average closer to movement onset at $Training_5$ (399.68 ± 8.47 ms) than $Training_1$ (419.80 ± 10.08 ms, $t_{(13)} = -2.98$, $p = 0.011$), we performed an additional analysis to control for a potential bias of the $Delay_{TMS\text{-}TO\text{-}MOVE}$ on our MEP preparatory measures. To do so, we conducted a response-locked analysis whereby we divided the percentage FDI MEPs at $TMS_{preparation}$ (regardless of the $Training_{STAGE}$) according to the $Delay_{TMS\text{-}TO\text{-}MOVE}$ in 5 consecutive bins of trials ($Delay_{BIN} = Delay_{BIN\text{-}1}$= 0 to 20%, $Delay_{BIN\text{-}2}$= 20 to 40%, …, $Delay_{BIN\text{-}5}$= 80 to 100% of the $Delay_{TMS\text{-}TO\text{-}MOVE}$ data). This allowed us to run an $ANOVA_{RM}$ on the preparatory MEP data depending on the factors $Delay_{BIN}$ and $MEP_{SELECTION}$. Importantly, this analysis did not reveal any effect of $Delay_{BIN}$ ($F_{(4,52)} = 1.14$; $p = 0.35$), nor was there any significant $MEP_{SELECTION}$ x $Delay_{BIN}$ interaction ($F_{(4,52)} = 0.32$; $p = 0.87$; **Fig. 5**). These results suggest that MEPs elicited preceding a "Go" signal are quite unaffected by the delay separating the TMS pulse from the movement onset. Hence, training-related changes in the $Delay_{TMS\text{-}TO\text{-}MOVE}$ are unlikely to be responsible for the strengthening of preparatory suppression observed along with practice in the current study.

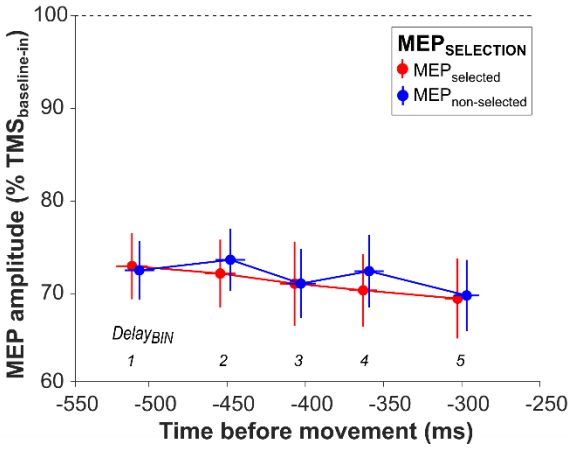

Figure 5. Preparatory suppression according to time before movement onset. Normalized MEP amplitudes recorded at $TMS_{preparation}$ (in percentage of MEPs elicited at $TMS_{baseline\text{-}in}$) are represented for each $Delay_{BIN}$ in a selected (red) or non-selected (blue) FDI muscle.

3.3 Correlation between training-related changes in RTs and preparatory suppression

As described in the previous sections, training on the RT task involved excitability changes in the motor system and improvements in RTs. In a subsequent analysis, we evaluated whether individual changes in RTs were correlated to modifications in preparatory suppression in selected and non-selected muscles. We did so for the early ($Training_{ratio\text{-}early}$: $Training_3/Training_1$) and late phase of practice ($Training_{ratio\text{-}late}$: $Training_5/Training_3$). Interestingly, we found that the individual RT changes observed at $Training_{ratio\text{-}early}$ could be in part predicted by the change in preparatory suppression observed in the selected **(Figure 5A;** $r^2 = 0.29$, $p = 0.049$**)** and non-selected FDI **(Fig. 5B;** $r^2 = 0.44$, $p = 0.0092$), such that the subjects showing a greater reinforcement of preparatory suppression also showed larger improvements in RTs. Importantly, this correlation was not observed at $Training_{ratio\text{-}late}$ neither for the selected ($r^2 = 0.013$, $p = 0.69$) nor for the non-selected

effectors (r^2 =0.20, p = 0.11), suggesting that later modulations in preparatory suppression did not further influence RTs. This relation was not present for the ADM muscle, neither at $Training_{ratio-early}$ (r^2 = 0.20, p = 0.78 and r^2 = 0.20, p = 0.11 for selected and non-selected ADM, respectively), nor at $Training_{ratio-late}$ (r^2 = 0.074, p = 0.35 and r^2 = 0.13, p = 0.21). Notably, we also checked whether these correlations could be observed with MEPs elicited at $TMS_{baseline-in}$ but this was not the case (all r^2 <0.078; all p>0.33). Altogether, these results suggest that the ability to improve RTs with training is linked to an early deepening of preparatory suppression in the prime-mover.

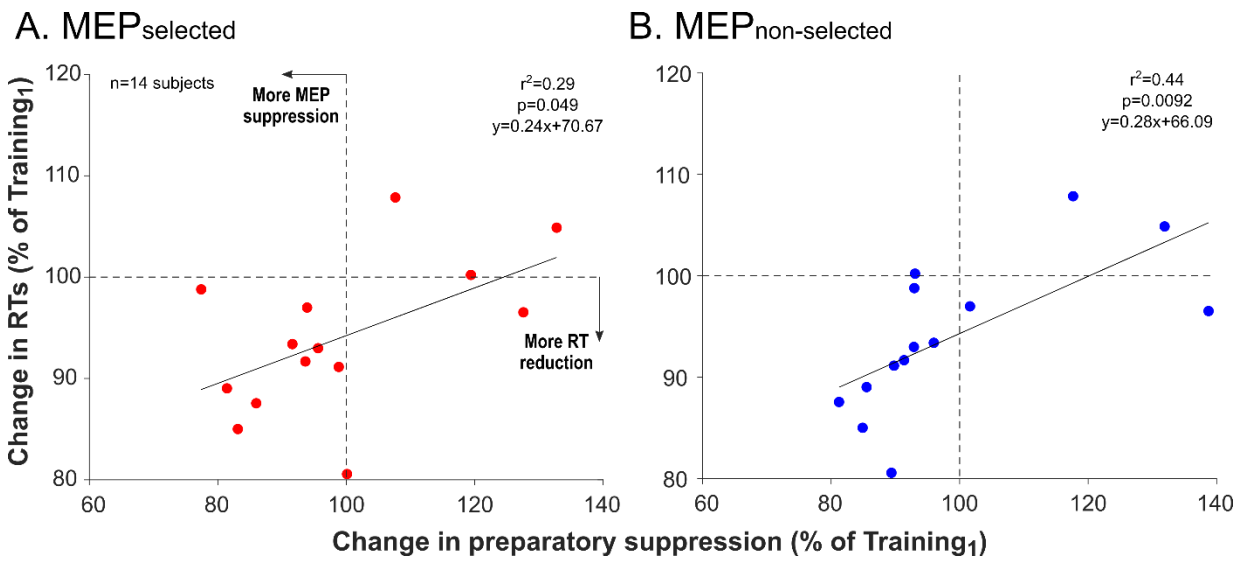

Figure 6. Correlation between early training-related changes in preparatory suppression and RTs. Changes in RTs as a function of changes in preparatory suppression during the early $Training_{stage}$ in the selected **(A)** and non-selected FDI muscle **(B)**. For this analysis, changes in RTs and MEPs were assessed by computing percentage ratios between the values obtained at $Training_3$ and $Training_1$.

3.4. RT dependency on preparatory suppression

In another set of analyses, we asked whether the speed at which subjects provided their responses depended on the amount of preparatory suppression manifest preceding their initiation. Initially, we assessed this MEP-RT dependency regardless of the $Training_{STAGE}$, by considering data from all blocks together. We did not observe any relationship between RTs and MEPs obtained in the selected hand, whether these MEPs were obtained from the FDI (main effect of MEP_{BIN}: GG-corrected $F_{(2.53,32.89)} = 0.56$, $p = 0.62$; **Fig. 6A)** or the ADM (GG-corrected $F_{(2.35,30.58)} = 0.19$, $p = 0.86$). However, we did find a link between RTs and MEPs recorded from the non-selected hand. That is, the greater the strength of preparatory suppression observed in the non-selected hand was, the shorter the RTs were. Consistently, the $ANOVA_{RM}$ run on RTs revealed that this dependency was particularly true for the prime-mover (**Fig. 6B**), with a significant effect of the factor MEP_{BIN} on RTs for the FDI ($F_{(5,65)} = 3.36$, $p = 0.0092$). For this effector, post-hoc tests revealed that RTs in MEP_{BIN-1} (i.e. strongest preparatory suppression) were systematically shorter than those in MEP_{BIN-6} ($p = 0.0015$). In fact, RTs at MEP_{BIN-6} were also longer than those measured at MEP_{BIN-2}, MEP_{BIN-3} and MEP_{BIN-5} (all $p < 0.02$). The ADM showed a similar trend but here the effect of the factor MEP_{BIN} on RTs was not significant ($MEP_{non\text{-}selected}$; $F_{(5,65)} = 1.84$, $p = 0.12$). Hence, preparatory suppression in the non-selected (non-responding) hand appears as a predictor of the speed at which the upcoming response will be released after the "Go" signal. The lower this activity, the faster the response, consistent with previous observations (Hannah et al., 2018).

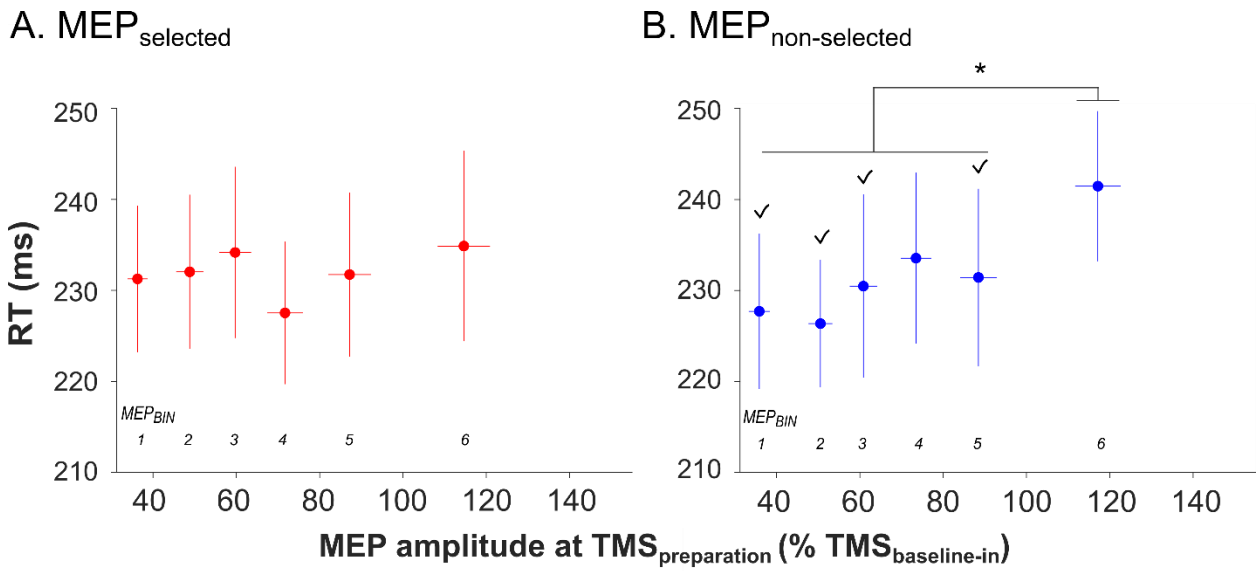

Figure 7. MEP-RT relationship in the FDI muscle. Averaged RTs as a function of the preceding preparatory activity in a selected **(A)** or non-selected FDI **(B)** muscle. For this analysis, the MEP data were divided in 6 MEP_{BIN} of increasing amplitude and the RTs corresponding to each MEP_{BIN} were averaged. The ticks highlight MEP_{BINS} that were significantly different from $MEP_{BIN\text{-}6}$ ($p<0.05$)

Then, we aimed at evaluating how practicing the task influences this MEP-RT dependency. In other words, we wanted to assess if training alters the dependency of RTs to preparatory suppression. To do so, we first focused on the dependency of RTs to non-selected FDI MEPs, which showed the strongest global effect, as described above. To do so, we split all the trials in two groups, according to the $Training_{STAGE}$ ($Training_{early}$ or $Training_{late}$) at which they occurred (**Fig. 8A**). This allowed us to investigate whether the effect of MEP_{BIN} on RTs is function of the $Training_{STAGE}$. The $ANOVA_{RM}$ performed on these RT data revealed a main effect of the $Training_{STAGE}$ ($F_{(1,12)} = 13.84$, $p = 0.0029$): RTs were overall shorter at $Training_{late}$ than $Training_{early}$. This result is consistent with the main analysis on RTs showing that response times

become faster over the blocks (**Fig. 2A**). Yet, the $ANOVA_{RM}$ performed on these RT data did not reveal any MEP_{BIN} x $Training_{STAGE}$ interaction ($F_{(2,24)} = 2.73$, $p = 0.085$).

However, a concern we had with the analysis above was that the MEP_{BINS} were not equivalent at $Training_{early}$ and $Training_{late}$, precluding us from considering RTs for comparable MEP amplitudes at the early and late training stages. That is, as evident on **Fig. 8A** and as described earlier in the section on MEP amplitudes, the percentage MEP values were globally smaller at the late stage of the experiment compared to the early one (see **Fig. 4A**). To account for this bias in the current analysis, we corrected the MEP_{BINS} by discarding extreme values in the $Training_{early}$ and $Training_{late}$ data distributions in steps of 1 % for each subject. Based on this procedure, the MEP_{BINS} became similar once we had removed the highest 4 % MEP values at $Training_{early}$ and the lowest 4% values at $Training_{late}$. This left us on average with 11 trials per bin with never less than 8 trials in one bin. When considering these adjusted data, the RTs remained different between the two $Training_{STAGES}$: RTs were shorter at the late than at the early training stage, even when considering only trials that were matched for the MEP amplitudes ($Training_{STAGE}$: $F_{(1,12)} = 12.86$, $p = 0.0037$). Hence, the training-related shortening of RTs was also evident when comparing trials with equivalent levels of preparatory suppression. This suggests that part of the training-related shortening of RTs was independent of changes in preparatory suppression. The $ANOVA_{RM}$ run on these adjusted data also revealed a significant MEP_{BIN} x $Training_{STAGE}$ interaction ($F_{(2,24)} = 4.15$, $p = 0.028$, see **Fig. 7B**). Interestingly, while RTs were comparable in all MEP_{BINS} at $Training_{early}$ (all bin comparison $p > 0.27$), indicating no initial dependency of RTs on percentage MEP values, a link emerged at $Training_{late}$: responses were faster in trials showing the strongest preparatory suppression. That is, RTs in MEP_{BIN-1} (i.e. strongest preparatory suppression) were shorter than in

the two other bins ($p = 0.011$ and $p = 0.0001$ when compared to MEP_{BIN-2} and MEP_{BIN-3}, respectively). Importantly, this effect of training on the MEP-RT dependency was not observed when RTs were sorted according to the selected FDI. More specifically, we found no MEP_{BIN} x $Training_{STAGE}$ interaction on RTs organized according to the selected FDI, neither before ($F_{(2,24)} = 0.28$, $p = 0.76$) nor after MEP correction ($F_{(2,24)} = 0.22$, $p = 0.81$). In conclusion, our data indicate that RTs depend on preparatory suppression in the non-selected prime-mover and that this link emerges mainly after a period of practice, at $Training_{late}$. Interestingly, these results suggest that the dependency of RTs on preparatory activity reported in single-neuron studies (Churchland et al., 2006; Afshar et al., 2011; Michaels et al., 2015; Hasegawa et al., 2017) and more recently in TMS work (Hannah et al., 2018) may have been mainly shaped by data considered at a later training stage.

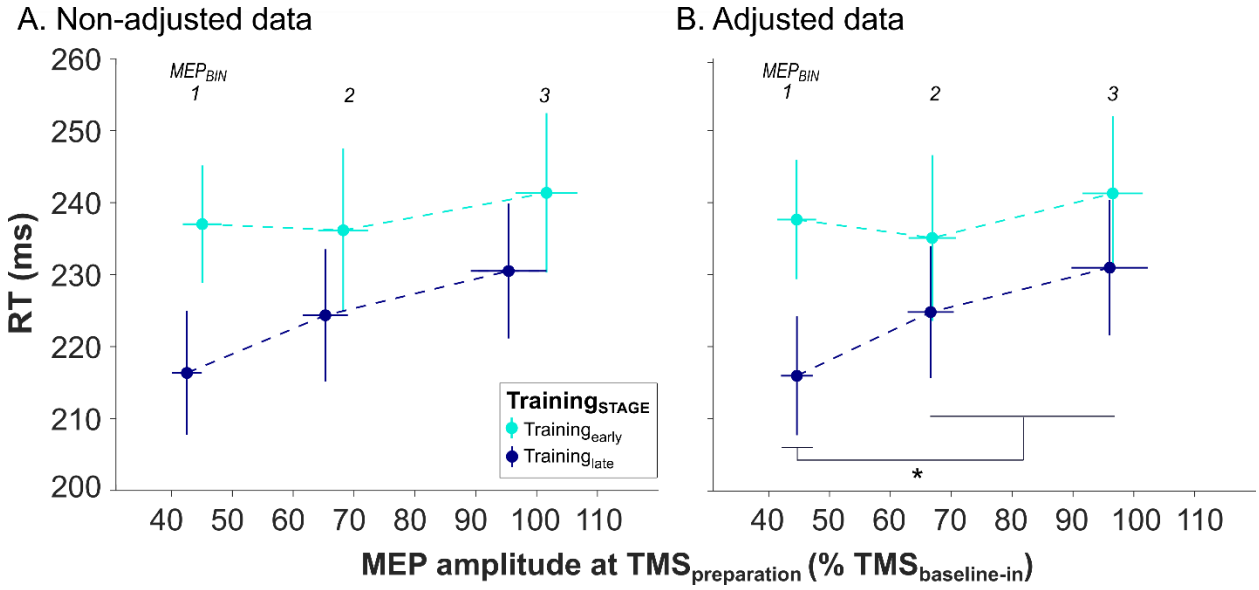

Figure 8. Effect of training on the MEP-RT dependency. Averaged RTs as a function of the preceding preparatory activity in a non-selected FDI muscle at $Training_{early}$ (light blue) and $Training_{late}$ (navy blue) before **(A)** and after MEP correction **(B)**. For this analysis, trials were

divided in 3 MEP_{BIN} of increasing amplitude and the RTs corresponding to each MEP_{BIN} were averaged. Note that correction was performed to compare RTs associated with preparatory MEPs of similar amplitude. Stars denote a significant difference between RTs corresponding to MEP_{BIN-1} and to the two other MEP_{BINS} at $Training_{late}$ ($p < 0.05$).

4. Discussion

Training speeded up RTs while errors remained low. Moreover, CS excitability became larger at rest and preparatory suppression was stronger after training. Interestingly, subjects who showed the strongest RT improvements at the early stages of training were also those displaying the largest initial strengthening in preparatory suppression. Finally, we found that RTs were generally faster in trials where preparatory suppression was deeper. Yet, this dependency was not present early on during training, but only emerged at a late stage, once subjects were faster to respond in the task.

Training reduced RTs

Subjects became faster at responding over the course of training. RTs reflect the sum of the time required for processing the imperative cue, for preparing the motor command and for initiating the action (Haith et al., 2016; Derosiere et al., 2019) and, in theory, training may impact any of these sensory-motor components. Consistently, previous studies have shown that RT improvements can result from both faster sensory processing (Clark et al., 2015) and more efficient motor preparation (Mawase et al., 2018). Yet, in an instructed-delay task, the time needed for sensory processing and motor preparation is strongly constrained and most of the RT is assumed to reflect the time needed for action initiation (Haith et al., 2016). Hence, the RT gains reported here are likely to reflect a reduction in initiation time. Our findings therefore suggest that, in addition to speeding up sensory processing and motor preparation, training can also boost action initiation. This reduction of initiation time did not lead to an increase in error rates, which remained low throughout practice.

Training increased resting CS excitability and deepened preparatory suppression in a behaviorally-relevant way

Practicing the task led to a significant increase in baseline CS excitability, consistent with former studies showing that movement repetition increases resting excitability of motor representations involved in the task (*e.g.*, Pascual-Leone et al., 1995; Butefisch et al., 2000; Duque et al., 2008; Christiansen et al., 2018). Yet, our data reveal that this increase in CS excitability is not limited to the prime-mover (i.e. FDI), but extends to task-irrelevant muscles too (i.e. ADM). Accordingly, a recent study showed that motor learning leads to a reorganization of both trained and untrained representations in M1 (Raffin and Siebner, 2019). While this broad increase in CS excitability does not seem to be ubiquitous across studies (Muellbacher et al., 2001; Bologna et al., 2015), different factors may influence the breadth of cortical plasticity, including the type of movement executed (Muellbacher et al., 2001), the duration of training (Classen et al., 1998) and the mechanical constrains applied on the untrained effectors (Raffin and Siebner, 2019). Still, our findings favor the view that motor training, even in very simple tasks, is associated with a broad functional reorganization in M1, affecting both trained and untrained motor representations.

Preparatory suppression was present from the first blocks and was overall broad, concerning the prime-mover and task-irrelevant muscles, in both the selected and non-selected hands (Labruna et al., 2019). Most importantly, preparatory suppression became stronger over the course of practice and this effect concerned all the investigated effectors. Hence, training appears to strengthen a form of suppression that broadly impacts the CS system. A plausible source for such a broad preparatory suppression is the fronto-basal ganglia (BG) network (Duque et al., 2012;

Greenhouse et al., 2015; Aron et al., 2016). Interestingly, multiple nodes of this network appear to be sensitive to motor training. For instance, disruption of the prefrontal cortex prevents training-related RT gains (Filmer et al., 2013). Besides, motor learning deficits in Parkinson's disease patients are partly reversed by deep brain stimulation of the subthalamic nucleus (which is part of the BG; Carbon and Eidelberg, 2006; Mure et al., 2012; de Almeida Marcelino et al., 2019). Hence, one may hypothesize that plasticity in the fronto-BG network mediated the strengthening of preparatory suppression we observed with practice.

The strengthening of preparatory suppression resulted from an increased differentiation between baseline levels of CS excitability, which grew stronger, and absolute levels of preparatory activity, which remained stable over time. Based on this sole finding, one could propose that changes in baseline excitability are key to RT improvements, which may appear in line with the inverse relationship between baseline CS excitability and RTs described recently (Greenhouse et al., 2017). Yet, we found that training-related changes in baseline excitability did not predict RT gains. What was predictive instead was the change in relative CS excitability, as measured during action preparation. The subjects who showed the strongest strengthening in preparatory suppression at the early stages of training were those who became fastest, consistent with animal studies showing that behavioral improvements in motor learning tasks are associated with changes in normalized preparatory activity (Paz et al., 2003; Mandelblat-cerf et al., 2009; Vyas et al., 2018). This finding is also in line with the idea that efficient action preparation relies on dynamical shifts of neural activity from a baseline state to a preparatory state (Churchland et al., 2012). From this dynamical point of view, training may allow tuning the dynamics of preparatory activity, bringing it closer to an optimal state for action initiation (Vyas et al., 2018). In this line, strengthening of

preparatory suppression would facilitate action initiation by allowing excitatory inputs targeting the selected motor representation to better stand out against a quiescent background, ultimately speeding up RTs (Hasbroucq et al., 1997; Greenhouse et al., 2015; Hasegawa et al., 2017).

Interestingly, at the group level, training-related changes in preparatory suppression appeared later than changes in RTs. This observation is in line with previous motor adaptation studies showing that changes in preparatory activity often lag behavioral changes (Wise et al., 1998; Paz et al., 2003). However, at the individual level, a majority of subjects already exhibited a strengthening of preparatory suppression at early training stages which was related to their RT improvement (**Fig. 6**). This suggests that behaviorally-relevant changes in preparatory suppression occurred earlier than what would have been assumed based on group averages.

Training strengthened the dependency of RTs to preparatory suppression

Another key finding of the present study is that RTs depended on the foregoing amount of preparatory suppression. That is, stronger levels of suppression were predictive of faster initiation times in the very same trials. This is coherent with the view that action preparation is an essential part of motor behavior, with relative changes in preparatory activity/suppression being a key determinant of the efficiency of ensuing action initiation (Hasegawa et al., 2017; Hannah et al., 2018). Notably though, we found such relationship when considering the non-selected prime-mover but not the selected one, possibly because MEPs in the latter effector reflect many overlapping inputs during response preparation (Duque and Ivry, 2009), an aspect that may have precluded us from observing a trial-by-trial link with behavior.

Most importantly, we found that this relationship between preparatory suppression and response speed depended on training. In the early stage of training, the amount of preparatory suppression was, in fact, not predictive of RTs. The relationship only emerged at later stages, suggesting that the relative contribution of preparatory suppression to the RT was modified by training. One potential explanation for this effect is that rapid action initiation depends on many different factors, of which the respective weight may vary with practice. At early stages, many brain regions indeed contribute to action initiation (Makino et al., 2017), and the relative contribution of preparatory suppression may be then limited. Yet, over training, the network involved gets narrower and the pattern of activity leading to action initiation becomes both temporally and spatially stereotyped across trials (Wiestler and Diedrichsen, 2013; Makino et al., 2017). This functional reorganization may give more weight to preparatory suppression in initiation processes. Alternatively, the emergence of a relationship between our discrete measure of preparatory suppression and behaviour might be the result of an increased temporal stereotypy of preparatory processes occurring with training (Makino et al., 2017), causing the TMS pulse to fall at a more similar stage of action preparation in each trial. This would increase the chance of observing a relationship, independently of the contribution of preparatory suppression to RTs. All in all, our findings indicate that the relationship between preparatory activity and RTs previously described in animals (*e.g.*, Michaels et al., 2015; Hasegawa et al., 2017) and humans (Hannah et al., 2018) may not be an immutable feature of how movements are generated by the motor system, but may instead depend on one's proficiency in outputting a given behavior.

Conclusion

The present study shows that a simple training paradigm can lead to improvements in action initiation that are accompanied by a strengthening of a broad form of CS suppression. We speculate that these changes could rely on functional modifications in a fronto-BG network. Moreover, our results support the view that one function of preparatory suppression is to facilitate action initiation. These findings have implications for the rehabilitation of patients suffering from impaired action initiation such as in cerebellar ataxia (Battaglia et al., 2006) or Parkinson's disease (Mure et al., 2012).

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