RESEARCH ARTICLE

Modulation of short intra-cortical inhibition during action reprogramming

**Franz-Xaver Neubert · Rogier B. Mars ·
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Abstract Actions are selected in the context of environmental demands and internal goals. Since both change continuously it is often necessary to inhibit a prepared action plan in favour of an alternative, a process we refer to as action reprogramming. Previous studies have established that a frontal/basal ganglia network exerts top-down control over the primary motor cortex (M1) during action reprogramming. The current study focuses on the role of M1 itself during action reprogramming. Participants were asked to perform a behavioural task that required them to either execute a prepared response or to reprogram an alternative response. Paired-pulse TMS was used to investigate short-interval intra-cortical inhibition (SICI) during these action execution and action reprogramming trials. Normal action execution was associated with sustained SICI in the M1 during both trials in which the contralateral hand was to respond and trials in which the ipsilateral hand was to respond. In contrast, reprogramming towards an alternative action was associated with a progressive release of SICI in M1 involved in the execution of the novel response. This release started 125 ms after the cue telling the participants to reprogram their action. This time point is consistent with previous results showing a facilitatory influence of the pre-supplementary motor area (pre-SMA) on the M1 at the same delay. Hence, SICI might be a potential candidate mechanism through which frontal lobe areas could influence primary motor cortex output.

Keywords SICI · Cognitive control · Action reprogramming · Inhibition · TMS

Introduction

Decisions are made in the context of internal goals and environmental demands. As both change continuously we have to be able to quickly inhibit an ongoing action plan in order to select and execute a more appropriate alternative movement when the environment calls for it. The neural basis of this 'action reprogramming' has been the subject of extensive research in recent years. A network of brain regions has been consistently implicated in action reprogramming, including the pre-SMA, the right inferior frontal gyrus (rIFG), and the subthalamic nucleus (STN) (Aron et al. 2007; Mars et al. 2007; Coxon et al. 2009; Hikosaka and Isoda 2010; Neubert and Klein 2010). Studies in patients revealed that both a lesion to pre-SMA and a lesion to rIFG can impair stopping performance (Aron et al. 2003; Nachev et al. 2007), and neuroimaging studies have shown these two regions to be more active during response inhibition than during normal action execution in stop-signal tasks (Aron and Poldrack 2006; Duann et al. 2009).

As a target of influence coming from these two areas, M1 is likely to be a site of convergence for processes underlying response selection, response inhibition or action reprogramming. Indeed, the motor system is largely

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influenced by preparatory and inhibitory processes associated with action selection and reprogramming (Bestmann et al. 2008; Sinclair and Hammond 2008; Stinear et al. 2009). In a series of paired-pulse transcranial magnetic stimulation (ppTMS) experiments, we have recently started to quantify the impact of pre-SMA and rIFG on M1 during action reprogramming. We have shown that pre-SMA exerts a facilitatory influence on corticospinal excitability during action reprogramming (Mars et al. 2009), while rIFG exerts an inhibitory influence on M1 excitability, but at a later time point than the pre-SMA (Neubert et al. 2010). The rIFG effect has been examined in the context of different reprogramming tasks and shown to be robust (Buch et al. 2010). In addition, we have identified the white matter pathways mediating the influence of pre-SMA and rIFG on M1. We found evidence for both direct cortico–cortical routes and relatively indirect routes running via the STN being involved in mediating top-down control over M1 (Neubert et al. 2010). Hence, the fronto-basal ganglia network (Aron et al. 2007; Mars et al. 2007; Hikosaka and Isoda 2010) that has been suggested to play a crucial role in response inhibition and action reprogramming might influence behaviour by modulating excitability of M1 (Mars et al. in press).

An open question is how processes intrinsic to M1, the target of these frontal lobe influences, develop during action reprogramming. Paired-pulse transcranial magnetic stimulation (ppTMS) over M1 can be used to study M1 intrinsic inhibitory process. A single, supra-threshold TMS pulse over M1 induces a current flow within the underlying tissue, causing depolarization and firing of neurons in the cortex. The firing of corticospinal neurons, in turn, produces a motor-evoked potential (MEP) in the EMG recorded from the muscle represented in the M1 region underlying the TMS coil. When this pulse is preceded by 1–5 ms by a subthreshold "conditioning" pulse, the resulting MEP is generally inhibited (Kujirai et al. 1993). This so-called short-interval intra-cortical inhibition (SICI) has proven particularly useful for studying inhibitory neurophysiological mechanisms within M1 during the preparation (Sinclair and Hammond 2008) and stopping (Coxon et al. 2006) of responses. In the current study, we examine SICI during the execution and reprogramming of actions using the same paradigm as used in the ppTMS studies described elsewhere (Mars et al. 2009; Neubert et al. 2010).

Methods

Participants

Sixteen healthy volunteers (age range 18–30 years, mean age ± standard deviation [SD] = 22.4 ± 3.41, 8 women)

with no personal or familial history of neurological or psychiatric disease participated in one of the two experiments investigating action reprogramming in M1. The experiments were approved by the Oxfordshire Research Ethics Committee and conducted in accordance with the declaration of Helsinki. All participants were right handed and gave written informed consent. They were all screened for adverse reactions to TMS and risk factors by means of a safety questionnaire.

Experimental setup

Participants were seated in a darkened room and wore a tight-fitting EEG cap, on which TMS sites were marked, and earplugs to protect against TMS noise. A chin rest was used to minimize head movements. Responses were recorded using a keyboard.

Behavioural task

The task was modelled on the paradigm developed by Isoda and Hikosaka (2007) and required participants to respond with the left or right index finger in response to visual stimuli presented on a 17 inch computer screen ~85 cm in front of them (see Fig. 1c). Each trial began with the presentation of a central white fixation square (4.7° width) followed, 1,000 ms later, by the presentation of two flanker stimuli, one on each side of the white central square (6° width) (see Fig. 1a). On each trial, one of the flanker squares was green, the other one was red, with trialwise random assignment of colour to side of display. After a variable delay of 450–600 ms (uniform distribution, see Fig. 1b), the white central square turned either red or green, instructing the subjects to respond with the index finger on the side corresponding to the flanker of the same colour. The critical manipulation imbedded in the task was that the central cue repeatedly turned the same colour for a series of between three and seven consecutive trials (uniform distribution). This afforded participants the opportunity to prepare a movement in the period between the onset of the two flanker squares and the onset of the centre colour cue. However, after taking the same colour for a series of trials, the centre cue changed. This manipulation meant that there were two types of trials: stay trials, in which the fixation square turned into the same colour as in the previous trial, thus allowing the participants to perform the already prepared response, and switch trials, in which the fixation square turned into a different colour as in the previous trial, thus requiring participants to inhibit an already prepared response and to reprogram their actions. It is noteworthy that trials requiring action reprogramming were not announced by a distinct instructional cue. Moreover, the participants were not even told that some trials would
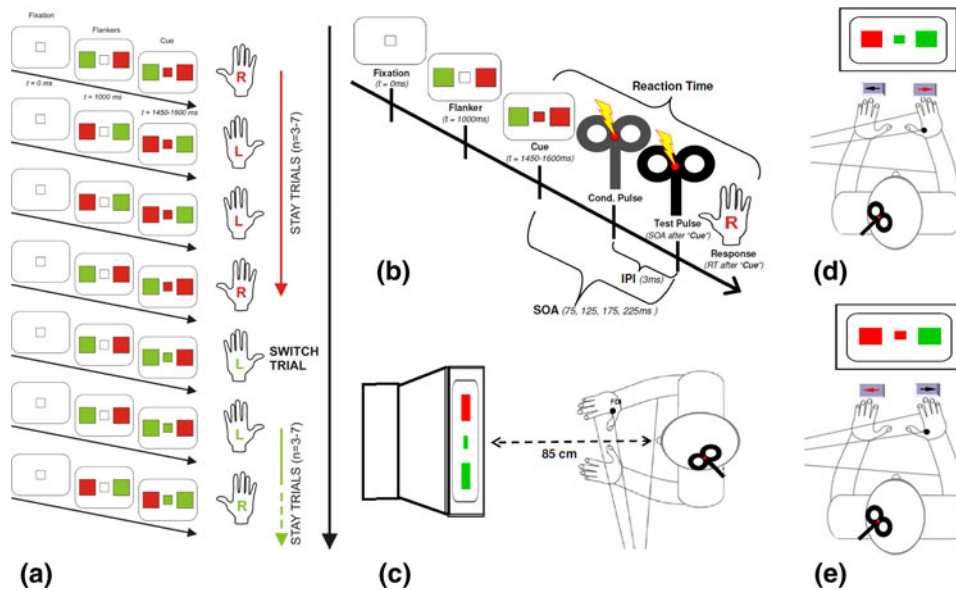
Fig. 1 a The behavioural task was modelled on the paradigm developed by Isoda and Hikosaka (Isoda and Hikosaka 2007) and required participants to respond with the *left* or *right* index finger in response to visual stimuli presented on a computer screen. Each trial started with the presentation of two peripheral flankers (*red* and *green*, sides random). A centre cue taking the colour of one of the flankers appeared 450–600 ms later. Participants had to respond with the finger of the hand on the side of the congruent flanker colour. The centre cue took the same colour for trains of 3–7 trials. Hence, on each trial, participants could prepare a movement based on their knowledge of the identity of the centre cue on the previous trial. However, after taking the same colour for a series of trials, the centre cue colour changed. This manipulation meant that there were two types of trials: stay trials, in which the fixation square turned into the same colour as in the previous trial, thus allowing the participants to execute the already prepared response, and switch trials, in which the fixation square turned into a different colour to the previous trial, thus requiring participants to inhibit an already prepared response and to reprogram their action plans. **b** Time course of a single trial:

Following at 1 s fixation, the flankers appeared. After 450–600 ms (uniform distribution), the central fixation square took the colour of one of the two flankers, indicating the required response to the participants. During the response period, at either 75, 125, 175 or 225 ms following the centre colour cue onset the test TMS pulse could be delivered. On half of the TMS trials, this pulse was preceded by a conditioning pulse applied through the same coil 3 ms earlier. **c** Schematic representation of the setup, with the TMS coil placed over *left* M1. **d**–**e** TMS was always applied to the left M1 and MEPs were always recorded from the *right* FDI during *left-hand* and *right-hand* responses (correct response indicated by *red arrow* button). Note that the *left-hand* response trials in the SWITCH EXPERIMENT always served as the "switch away" condition (*grey lines* in Fig. 3a), and the right-hand response trials always served as the "switch towards" condition (*black lines* in Fig. 3a). In the STAY EXPERIMENT, the *left-hand* response trials served as the "stay with the non-recorded hand" condition (*grey lines* in Fig. 3b) and the *right-hand* response trials always served as the "stay with the *recorded* hand" condition (*black lines* in Fig. 3b)

require inhibition or reprogramming behaviour. Rather, switch trials violated an implicit expectation that was built up during the previous train of stay trials. Stimuli were pseudo-randomly generated, and a different stimulus order was used for each block.

Custom software written in Presentation (version 0.53, Neurobehavioral Systems, Albany, CA, USA) controlled the experiment. Before the actual experiment, participants were familiarised with the task in one behavioural training block (without TMS pulses, 30 trials) and with the whole experimental setup including TMS pulses in a second training block (with TMS pulses, 30 trials). To be able to study SICI patterns during action reprogramming and action execution, we had to run two separate experimental sessions involving different participants using the same behavioural task and experimental setup. This was necessary because obtaining an adequate number of trials for both switch and stay trials at each stimulus onset

asynchrony (SOA) with both hands and both single and paired pulses would have resulted in the participants receiving a very large number of TMS pulses and an exceedingly long experiment. Hence, two separate experimental sessions had to be conducted to investigate SICI during (1) action reprogramming and inhibition of prepared responses (subsequently called the "SWITCH EXPERIMENT") and (2) execution of prepared responses (subsequently referred to as "STAY EXPERIMENT"), respectively. The behavioural paradigm was exactly the same in both experiments, including the same proportion of switch trials and stay trials. However, in the SWITCH EXPERIMENT, TMS was given and MEPs were recorded mostly on switch trials to measure SICI during action reprogramming. In the STAY EXPERIMENT, TMS was exclusively given on stay trials to measure SICI during action execution. Analysis of EMG data concentrated on peak-to-peak amplitudes of the MEPs measured on switch trials in the SWITCH EXPERIMENT and on

stay trials in the STAY EXPERIMENT, respectively. The participants did not know about this difference. In this paper, we refer to the type of experiment with UPPER CASE LETTERS and to the type of trials with lower case letters. Eight participants (3 women, mean age = 22.3 ± 3.45 SD) participated in the "SWITCH EXPERIMENT". Eight participants (5 women, mean age = 22.6 ± 3.58 SD) participated in the "STAY EXPERIMENT". The "SWITCH EXPERIMENT" consisted of seven experimental blocks. The "STAY EXPERIMENT" consisted of five experimental blocks. Each block contained 32 switch and 160 stay trials. Reaction times (RTs) were recorded, defined as the time interval between the onset of centre square colour and the index finger response button press.

Transcranial magnetic stimulation (TMS)

TMS pulses were delivered through a single 70-mm-diameter figure-of-eight coil connected via a BiStim module to two high-power Magstim 200 MonoPulse machines (The Magstim Company, Whitland, UK). The magnetic pulse was monophasic, with a rise time of ∼100 μs, decaying back to zero over ∼800 μs. TMS was delivered over the left M1, with the coil placed tangentially to the scalp (see Fig. 1c), inducing posterior-to-anterior current flow perpendicular to the central sulcus. TMS pulses were delivered on some trials to investigate M1 intrinsic inhibitory processes during action execution and action reprogramming. There were two types of TMS trials. On half of the TMS trials, so-called "single-pulse" trials, a single TMS test pulse was delivered over the centre of gravity of the M1-representation of the right-hand first dorsal interosseus muscle (FDI). The centre of gravity of the M1-representation of the FDI was defined as the scalp site at which the largest mean MEP amplitude from a train of five single pulses was elicited. The intensity of this TMS test pulse was adjusted so that an MEP of 1–1.5 mV was evoked in the relaxed, contralateral FDI. This resulted in an intensity of 48.37% (SEM ± 2.4) of the maximum stimulator output in the SWITCH EXPERIMENT and 44.87% (SEM ± 2.2) for the STAY EXPERIMENT. On the other half of the TMS trials, so-called "paired-pulse" trials, the test pulse was preceded by a "conditioning pulse" by 3 ms. The intensity of the test pulse was exactly the same as in "single-pulse trials". The intensity of the preceding "conditioning pulse" was set at 80% of the resting motor threshold (RMT) of the same FDI muscle. RMT is defined as the TMS pulse intensity necessary to evoke an MEP of 50 μV in the completely relaxed muscle with 50% probability (5 out of a series of 10 trials). Average RMT was 42.62% (±2.8) of maximum stimulator output in the SWITCH EXPERIMENT and 42.25% (±2.1) in the STAY EXPERIMENT. Stimulator intensity and interval between conditioning and test pulse (inter-pulse interval, IPI, 3 ms)

were chosen based on the literature on short-interval intracortical inhibition (Sohn et al. 2002; Reis et al. 2008). TMS was delivered 75, 125, 175 or 225 ms after onset of the centre colour cue (stimulus onset asynchrony, SOA) during SWITCH EXPERIMENTS and 75, 125 and 175 ms in STAY EXPERIMENTS (see Fig. 1b). TMS pulses were not delivered at the longest interval, 225 ms SOA, in the STAY EXPERIMENTS, as this time point was too close to the actual responses in stay trials (median RT in stay trials was 288.3 ms as compared with 372.1 ms on switch trials).

During "SWITCH EXPERIMENTS", pulses were almost exclusively delivered during switch trials (32 TMS trials on switch trials and 4 TMS trials on stay trials). In the "STAY EXPERIMENTS", TMS was exclusively delivered during stay trials. The presence or absence of the TMS pulse(s) or any pulse-related signals—such as the sounds associated with the discharge or the tactile sensation on the scalp—could not serve as pre-cue indicating trial identity, because the pulses were only applied after the switch or stay cue had already occurred, i.e. 75 ms after cue onset at the earliest. There were no indicative signals (such as arming of the MagStim units) before centre cue colour onset. The capacitors of the MagStim machines recharge directly after the TMS pulse delivery. Also even if the participants were able to use the presence of the TMS pulses as a cue to trial identity, this cannot have influenced the MEP, which is the direct result of the pulse itself and occurs within 20 ms of the pulse, a delay which is purely the result of the central and peripheral motor conduction times. However, in the SWITCH EXPERIMENTS, we delivered a small number of pulses on stay trials, preventing the subjects from detecting any relationship between trial type and TMS application. Hence, in every block, TMS was delivered on 36 out of 192 trials (SWITCH EXPERIMENT: 32 TMS trials on switch trials and 4 TMS trials on stay trials, only switch trials were analysed; STAY EXPERIMENT: 36 TMS trials on stay trials). For the SWITCH EXPERIMENTS, a total of 14 TMS trials per hand (left vs. right hand), SOA (75, 125, 175, 225 ms) and pulse type (single vs. paired) were delivered and used for the analysis. For the STAY EXPERIMENT, a total number of 15 TMS trials per hand, SOA (75, 125, 175 ms) and pulse type were delivered and analysed. TMS trials were presented at least 7 s apart, to ensure that pulses on adjacent trials did not influence each other. In each block, TMS trials were distributed evenly with respect to response hand, SOA and pulse number (single- or paired-pulse TMS).

Electromyographic (EMG) recordings

MEPs were recorded from right-hand FDI using two surface Ag–AgCl electrodes in belly-tendon montage. Hence, the two electrodes were placed on the FDI muscle belly and the second metacarpo-phalangeal joint. An earth electrode

was placed on the right elbow (over the posterior border of the ulna ~ 5 cm distal of the olecranon). EMG responses were band-pass filtered between 10 and 1,000 Hz, with an additional 50-Hz notch filter, sampled at 5,000 Hz, and recorded using a CED 1902 amplifier, a CED micro 1401 Mk.II A/D converter and a PC running Spike2 (Cambridge Electronic Design, Cambridge, UK).

Analysis

For the analysis of the difference between action reprogramming (SWITCH EXPERIMENT) and action execution (STAY EXPERIMENT) in M1, we concentrated on a between-session and hence between-subject design: We analysed MEP data from the switch trials in the SWITCH EXPERIMENT (32 out of 36 TMS trials) and the stay trials in the STAY EXPERIMENT (all 36 TMS trials).

Trials with (a) incorrect, (b) pre-mature (RT <150) responses, (c) trials in which the response occurred before TMS delivery, (d) trials in which the test pulse failed to elicit a reliable MEP (amplitude <0.1 mV), and (e) trials in which participants pre-contracted the FDI muscle prior to application of the TMS pulse (EMG amplitude >0.1 mV in the 80 ms before the pulse) were discarded from the analysis. This was necessary because we wanted to ensure sufficient quality of the MEP data (exclusion category c, d and e), and we wanted to focus the MEP analysis on trials in which the participants were able to successfully reprogram or execute a prepared response, respectively (exclusion category a and b). Following this pre-processing, on average 2.9 (SEM $\pm$ 0.19) trials (of a total of 14 trials per condition, i.e. 21%) in the SWITCH EXPERIMENT and 3.3 ($\pm$0.243) trials (of a total of 15 trials, i.e. 22%) in the STAY EXPERIMENT were excluded. To elucidate whether the above-mentioned exclusion criteria had led to a systematic bias in trial rejection, we carried out two ANOVAs on the number of discarded trials in the SWITCH EXPERIMENT and the STAY EXPERIMENT, respectively with the within-subjects factors of "hand" (responding hand: left vs. right), "pulse" (number pulses delivered: single vs. paired pulse) and "SOA" (75, 125, 175, 225 ms in the SWITCH EXPERIMENT and 75, 125, 175 ms in the STAY EXPERIMENT). Additionally, in order to compare the number of rejected trials for every condition in both experiments, we carried out another ANOVA with the within-subjects factors of "hand", "pulse" and "SOA" and the between-subject factor "experiment" (experimental session: SWITCH VS. STAY EXPERIMENT). None of these three ANOVAs showed significant within- or between-subject effects or interactions (all $P > 0.14$). We also carried out 14 paired-samples t tests comparing the number of discarded trials in the single-pulse and paired-pulse TMS trials for each condition of SOA (75, 125, 175, 225 ms in the SWITCH EXPERIMENT and

75, 125, 175 ms in the STAY EXPERIMENT) and hand (left- vs. right-hand responses). None of these t tests showed significant effects (all $P > 0.3$). We also carried out 12 independent samples t tests to compare the number of removed trials for each condition of (1) number of pulses (single vs. paired-pulse TMS), (2) responding hands (left vs. right hand) and (3) SOA (75, 125, 175 ms). None of these t tests reached significance (all $P > 0.2$). This is important as a significant difference in the number of removed trials between the SWITCH and the STAY EXPERIMENTS could limit the comparability of SICI between the two experiments. Thus, we can conclude that there was no bias in the number of removed trials by condition and, hence, the removal of trials cannot explain any of the experimental effects reported in the present paper.

To account for differences in coil placement between experimental blocks, MEP sizes were median normalized within each block. Analyses of MEPs were carried out on the mean of the normalized MEP amplitudes in each condition. To quantify the effect of the subthreshold conditioning pulse on the MEP elicited by the supra-threshold test pulse (SICI effect), we calculated the ratio [paired-pulse TMS MEP amplitude/single-pulse TMS MEP amplitude]. Analyses of both behavioural and EMG data were conducted using ANOVA tests, using repeated measures where possible. Significant effects were identified based on Huynh–Feldt corrected ANOVA values, using SPSS 16.0. Post hoc two-sided t tests were used to further investigate significant effects in the ANOVAs.

Even though trials with excessive pre-contraction of the right FDI muscle were discarded from the analyses, an additional analysis was performed on the remaining trials to ensure that none of the reported MEP effects were caused by systematic differences in muscle contraction between conditions. The ANOVAs conducted on the MEP amplitudes were repeated for the values of the root mean square (RMS) of the background EMG in the 80-ms interval before the application of the TMS pulses. None of the main effects and interactions significant in the MEP data reached significance when analysing the RMS. Therefore, MEP amplitude effects were not confounded with differences in FDI background contraction.

Results

Behavioural results

ANOVAs on median RTs for correct trials and on error rates (incorrect responses/total number of trials) with "trial type" (switch vs. stay) as a within-subject factor and "experiment" (SWITCH VS. STAY EXPERIMENT) as a between-subject factor showed a main effect of "trial type"

($F_{1,14} = 57.804$, $P < 0.001$ for RTs; $F_{1,14} = 39.814$, $P < 0.001$ for error rates). Behavioural effects did not differ between the two EXPERIMENTS, as indicated by the absence of any main effect of *"experiment"* or interaction between *"experiment"* and *"trial type"* (all $P > 0.2$). Post hoc paired-samples t tests confirmed subjects were significantly slower on switch trials than on stay trials (RT: 372.1 ms on switch vs. 288.3 ms on stay trials, $t_{15} = 7.070$, $P < 0.001$) and made significantly more mistakes (error rate 20.3% on switch trials vs. 2.1% on stay trials, $t_{15} = 6.526$, $P < 0.001$; see Fig. 2a and b). These effects of slower and more inaccurate performance on switch trials can be measured as switching costs. RT switching costs are defined as the ratio [median RT in switch trials]/[median RT in stay trials]. RT switching cost was 1.36 (i.e. performance slowed down by 36% in switch trials). An independent samples t test comparing behavioural measures (RTs on switch trials, RTs on stay trials, RT switch costs, error rate, error rate in switch trials, error rate in stay trials) did not yield any significant differences ($P > 0.5$) between the SWITCH and STAY EXPERIMENT. Overall, these results confirmed the effectiveness of the task manipulation, showing that participants prepared their response and hence needed to reprogram their action on switch trials and that these effects were similar in the two EXPERIMENTS.

It has been observed that switching costs can outlast a switch trial and slow down performance in subsequent stay trials (Wylie and Allport 2000). Paired-samples t tests comparing median RTs in stay trials of different positions in a row of stay trials following a switch revealed a significant difference between the first and the second stay trial ($t_7 = 3.012$, $P = 0.02$), the first and the third stay trial ($t_7 = 2.733$, $P = 0.029$), and the first and the fifth stay trial ($t_7 = 2.792$, $P = 0.027$), indicating that subjects were slower on the first stay trial following the switch trial as compared with subsequent stay trials (see Fig. 2f). However, paired-samples t tests comparing median RTs on switch trials to median RTs of different stay trials in a row (1st to 7th stay trial) showed, that subjects were always significantly slower on switch trials as compared with any kind of stay trials (all $P \leq 0.016$).

Similarly, RTs in switch trials depended on the number of stay trials that preceded a switch. An ANOVA comparing median RTs in switch trials following 3–7 stay trials revealed a significant within-subjects effect of "number of stay trials preceding switch" ($F_4 = 5.132$, $P = 0.003$). Paired-samples t tests comparing median RTs in switch trials following a different number of stay trials revealed a significant difference between switch after three stay trials and switch after five stay trials ($t_7 = -2.614$, $P = 0.035$), and a significant difference between switch after three stay trials and switch after seven stay trials ($t_7 = -4.913$,

$P = 0.002$), indicating that subjects were slower on switch trials following a longer series of stay trials as compared with switch trials following only three stay trials (see Fig. 2e). This suggests that the cost of switching reflected mainly processes related to response selection and reprogramming rather than subjects' expectations of switching; expectations of switching should increase as the number of stay trials increased. But also note that the slight although non-significant tendency towards slower RTs in the 4–7th stay trials after the switch trial as compared with the first 3 stay trials after the switch trial (see Fig. 2f and previous paragraph) indicates that subjects might become more cautious if switch trials became more likely. This would suggest that both processes, increasing switching costs with increasing numbers of stay trials in a row, on the one hand, and subject's expectations of switching, on the other hand, play a role in reprogramming. Most importantly, however, paired-samples t tests comparing median RTs on stay trials to median RTs of different switch trials (switch after 3–7 stay trials) showed that subjects were always significantly faster on stay as compared with any kind of switch trials (all $P \leq 0.015$).

The experimental paradigm relies on the fact that participants prepared a response based on the centre cue colour changes witnessed in the previous trials. Hence, 'switch' and 'stay' trials were defined on the basis of whether the central fixation cue took the same colour ('stay') or a different colour ('switch') as the previous trial, independently of which hand was actually used. An alternative way to classify 'switch' and 'stay' trials would be to classify them according to whether the hand used to make the response was the same ('motor stay') or different ('motor switch') as in the previous trial. In order to rule out that participants solved the task in this manner, we analysed the behavioural data with the trials sorted according to these criteria. Analysed in this way, there was no effect of condition (motor switch or stay) on RT or on error rate (both $P > 0.25$, see Fig. 2c, d).

As already mentioned, we studied action reprogramming and action execution in two separate experiments applying TMS mostly on switch trials in the SWITCH EXPERIMENT and on stay trials in the STAY EXPERIMENT. To elucidate whether participants overtly or covertly detected a relationship between trial type and TMS application, we further analysed the behavioural data. If TMS had actually served as a pre-cue indicating trial identity, we would expect to see a behavioural benefit. An independent samples t-test comparing RTs and error rates in switch trials between the SWITCH and STAY EXPERIMENT did not yield any significant differences (all $P > 0.5$). An independent samples t-test comparing RTs and error rates in stay trials between the two experimental sessions (switch and stay) did not yield any significant differences (all $P > 0.2$). Moreover, a

Fig. 2 Show behavioural data from the paired-pulse TMS experiments. **a** Median RTs and **b** *error rates* in action reprogramming and action execution trials. Median RTs **c** and *error rates* **d** in motor switch and motor stay trials (trials in which the responding hand switched or stayed with respect to the previous trials, respectively, regardless of any change in *cue colour*). **e** Median RTs of action execution trials (stay) and reprogramming trials (switch) following 3–7 action execution trials in a row. **f** Median RTs for the action reprogramming trial ("switch", "0") and the successive action execution ("stay") trials following reprogramming
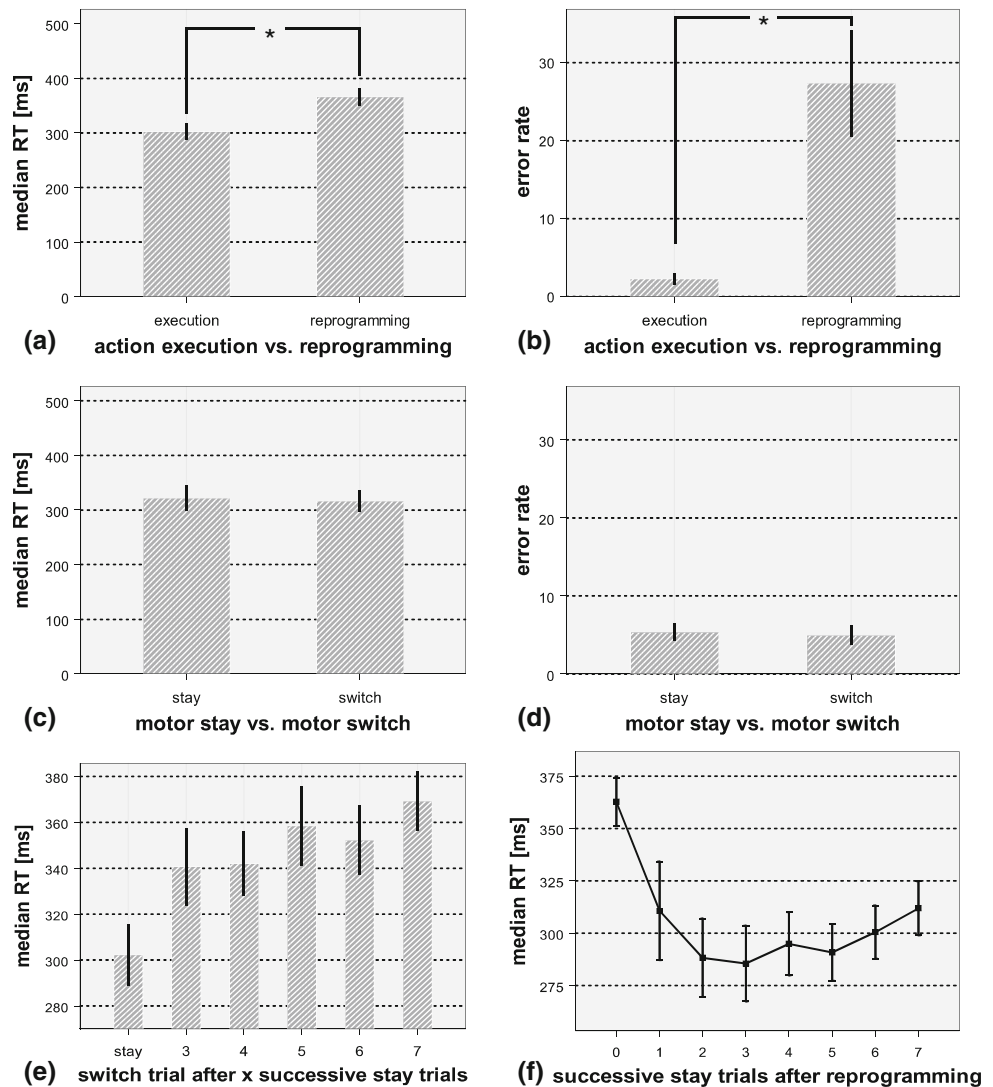
paired-samples *t*-test comparing RTs and error rates in the STAY EXPERIMENT in those stay trials *with* TMS application with RTs and error rates in stay trials *without* TMS application did not yield any significant differences (all $P > 0.15$). This indicates that TMS serving as a pre-cue did not actually lead to behavioural benefits in switch and stay trials in the SWITCH and STAY EXPERIMENT, respectively.

Also, the SICI TMS protocol used in this study might have caused a disruption in processing within M1 and hence a behavioural impairment in switching. Four paired-samples *t* tests comparing RTs and error rates of stay trials *with* TMS and *without* TMS within the SWITCH EXPERIMENT on the one hand (2 paired-samples *t* tests comparing RTs and error rates) and within the STAY EXPERIMENT on the other hand (2 paired-samples *t* tests) did not reveal any significant differences (all $P > 0.15$). This indicates that TMS did not have an effect on the behavioural measures RT and error rate during stay trials. Four independent samples

t tests comparing RTs and error rates in *switch trials* between the SWITCH and STAY EXPERIMENT and also comparing RTs and error rates in the stay trials between SWITCH and STAY EXPERIMENTS did not yield any significant differences (all $P > 0.2$). This indicates that TMS did not change RTs or error rates during switch and stay trials.

In summary, behavioural results indicate that our paradigm was effective in eliciting action reprogramming behaviour (cf. Mars et al. 2009; Neubert et al. 2010) and that these effects are not due to any confounding factors.

M1 excitability during switch and stay trials

In order to elucidate the time course of M1 corticospinal excitability during action reprogramming, single-pulse FDI MEPs from switch trials in the SWITCH EXPERIMENT were analysed with an ANOVA with within-subjects factors of *"hand"* (left vs. right hand) and *"SOA"* (75, 125, 175 and

225 ms) revealed a significant *"hand"* by *"SOA"* interaction ($F_{3,21} = 6.916$, $P < 0.001$). Post hoc t tests on single-pulse TMS MEPs between right- and left-hand responses revealed a significant difference at 225 ms SOA ($t_7 = -3.388$, $P = 0.012$. right > left). Post hoc t tests on single-pulse TMS MEPs between different time points revealed a significant difference between 75 and 225 ms after cue onset, in right-hand response trials ($t_7 = -3.863$, $P = 0.006$; 75 ms MEP < 225 ms MEP; i.e. increase in excitability over time) as well as between 125 and 225 ms SOA in right-hand responses ($t_7 = -5.351$, $P < 0.001$; 75 ms MEP < 225 ms MEP). We also found a strong but non-significant difference in left-hand responses between 175 and 225 ms SOA ($t_7 = 1.945$; $P = 0.93$; 175 ms MEP > 225 ms MEP, i.e. decrease in excitability over time). This is interesting, as it could suggest that both processes, inhibition of the prepared but inappropriate response and facilitation of the unprepared but required response occur at about the same time, just before the average response time of the stay trials (278.3 ms) and could therefore indicate that both processes are relevant for successfully reprogramming action plans. However, the effects of inhibition of the prepared but inappropriate response were not significant. Moreover, our SICI results (as discussed elsewhere) suggest that SICI plays a major role in the process of facilitating corticospinal excitability of the unprepared but required response.

To elucidate the time course of M1 excitability in action execution trials, we conducted an ANOVA on single-pulse FDI MEPs in the STAY EXPERIMENT with the within-subjects factors "hand" and "SOA" (75, 125 and 175 ms) and obtained a significant "hand" effect ($F_{1,7} = 12.763$, $P = 0.009$) and a significant effect of "SOA" ($F_{1,7} = 19.193$, $P = 0.002$). Post hoc t tests revealed a significant difference between left- and right-hand responses for the MEPs 175 ms ($t_7 = -3.404$, $P = 0.011$. right > left) after cue onset, and significant differences in FDI MEPs in right-hand response trials between time points 75 ms and 125 ms SOA ($t_7 = -2.436$, $P = 0.045$; 75 ms MEP < 125 ms MEP, i.e. increase in excitability over time) and between 75 and 175 ms SOA ($t_7 = -3.767$, $P = 0.007$; 75 ms MEP < 175 ms MEP).

Intra-cortical inhibition on switch trials

To ascertain whether some processes affecting M1 corticospinal excitability during action reprogramming are reflected in SICI, we analysed FDI MEP data from single-pulse and paired-pulse TMS trials in switch trials (see Fig. 3a). An ANOVA on the MEPs for every condition with *"pulse"*, *"SOA"* and *"hand"* as within-subjects factors revealed significant main effects of *"pulses"* ($F_{1,7} = 8.127$, $P = 0.025$), *"SOA"* ($F_{3,21} = 4.239$, $P = 0.031$) and

significant *"SOA"* × *"pulses"* ($F_{3,21} = 8.495$, $P = 0.023$) and *"SOA"* × *"hand"* ($F_{1,7} = 6.205$, $P = 0.008$) interactions. An ANOVA on the paired-pulse/single-pulse TMS ratios with within-subjects contrasts of *"SOA"* and *"hand"* revealed a significant effect of *"hand"* ($F_{1,7} = 23.596$, $P = 0.002$).

Post hoc two-tailed one-sample t tests of the MEP ratios against a baseline of 1.0 revealed that the presence of a conditioning pulse resulted in a significant inhibition of right-hand FDI MEPs in left-hand response trials 75 ms ($t_7 = -4.112$, $P = 0.005$), 175 ms ($t_7 = -2.858$, $P = 0.024$) and 225 ms ($t_7 = -4.994$, $P = 0.002$) after centre cue colour onset and in right-hand response trials 75 ms ($t_7 = -3.383$, $P = 0.012$) after centre cue colour onset. Post hoc paired-samples t tests on the MEP ratios revealed significant differences between left- and right-hand responses 175 ms ($t_7 = -3.007$, $P = 0.02$), and 225 ms ($t_7 = -2.642$, $P = 0.033$) after centre cue colour onset. Paired-samples t tests between the MEP ratios at different time points during action reprogramming revealed significant differences in right-hand response trials between 75 and 125 ms ($t_7 = -3.247$, $P = 0.014$), and 75 and 175 ms ($t_7 = -4.438$, $P = 0.003$), indicating that the observed difference in MEP ratios between left- and right-hand responses was mostly due to a release from inhibition of the unprepared, but correct, right-hand response in right-hand response trials.

SICI release seemed to be behaviourally relevant. SICI release ([paired-pulse/single-pulse TMS ratios in right-hand trials]−[paired-pulse/single-pulse TMS ratios in left-hand trials]) is an index of how much the M1 representing the response the subject is switching towards is released as compared with the M1 representing the response the subject is switching away from. We found a significant correlation between SICI release and RT switch costs ([median RTs at switch trials]/[median RTs at stay trials]) at 225 ms SOA (Pearson correlation = −0.736, $P = 0.037$, see Fig. 3c).

We have shown that switch costs increased with the number of stay trials preceding the switch trial (see "Behavioural results" above). In order to test whether there was a difference in SICI patterns during action reprogramming for switch trials after a small number of stay trials as compared with switch trials after a larger number of stay trials, we analysed the TMS data in the SWITCH EXPERIMENT with respect to the stay trials preceding the switch trial and binned the data to compare SICI patterns during switch trials following a row of 3–4 stay trials with switch trials following a row of 5–7 stay trials. To elucidate whether SICI differed in switch trials depending on whether the subjects had to switch after 3 to 4 as compared with 5 to 7 stay trials an ANOVA on paired-pulse/single-pulse TMS MEP ratios with the within-subjects factors
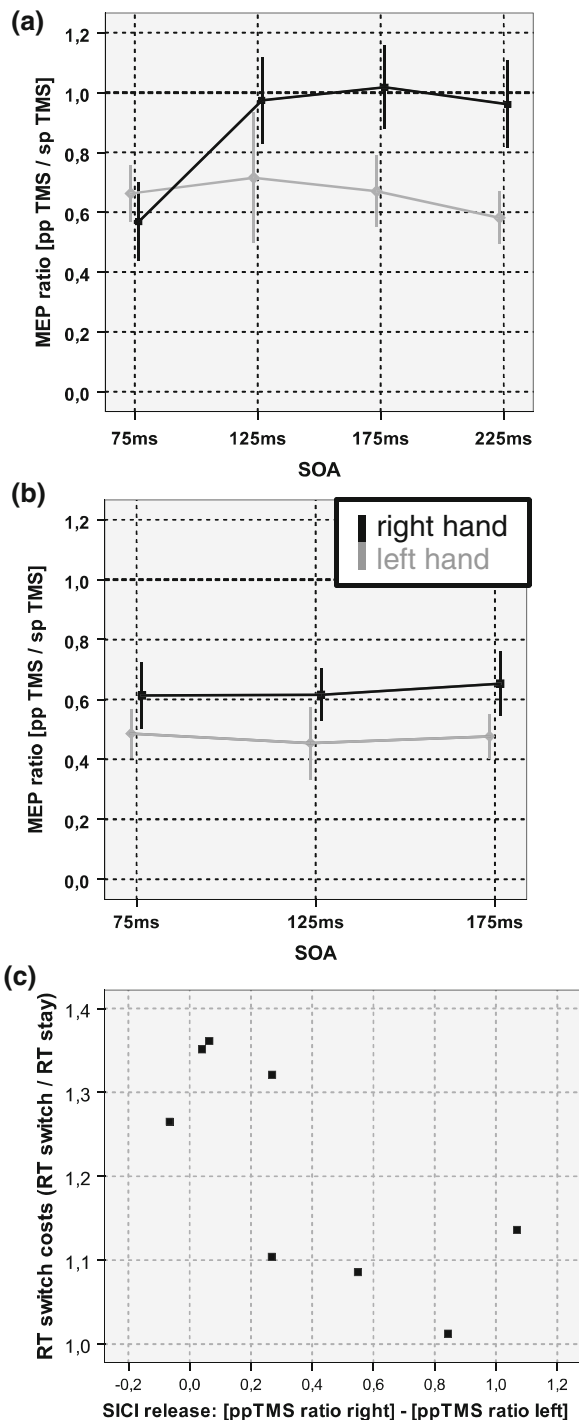
Fig. 3 Paired-pulse TMS data for the STAY and the SWITCH EXPERIMENT. Paired-pulse TMS data are plotted as a ratio of [paired-pulse TMS MEP/single-pulse TMS MEP] and for different stimulus onset asynchronies (SOA). TMS was always applied to the *left* M1, and MEPs were always recorded from *right-hand* FDI. **a** TMS MEP ratios at four time points after the cue onset in reprogramming trials. Trials in which participants had prepared a *left (right)*-hand response but were required to switch to a *right (left)-hand* response are shown in *black (grey)*. **b** TMS MEP ratios at three time points after cue onset in action execution trials. **c** Correlation between the release of SICI in switch trials [SICI$_{switch\ towards}$ − SICI$_{switch\ away}$] and the RT switching costs [median RT in switch trials/median RT in stay trials]

Intra-cortical inhibition on stay trials

To investigate changes in SICI associated with the execution of an already prepared response, we analysed single- and paired-pulse MEPs in the stay trials and calculated MEP ratios (see Fig. 3b). An ANOVA on the single and paired-pulse trial MEPs for every condition with within-subjects contrasts of "*pulse*", "*SOA*" and "*hand*" revealed significant effects of "*pulse*" ($F_{1,7} = 15.498$, $P = 0.008$), "*SOA*" ($F_{2,14} = 14.124$, $P = 0.007$), "*hand*" ($F_{1,7} = 21.459$, $P = 0.004$). An ANOVA on the paired-pulse/single-pulse TMS ratios with within-subjects contrasts of "*SOA*" and "*hand*" revealed a significant effect of "*hand*" ($F_{1,7} = 9.951$, $P = 0.02$). This "*hand*" effect indicates that a difference in SICI between the responding and the non-responding hand at all SOAs could be important for the selection of movements in stay trials. Post hoc two-tailed one-sample t tests of the MEP ratios against a baseline of 1.0 (i.e. 100%) revealed significant inhibition of right-hand FDI MEPs in left-hand response trials 75 ms ($t_7 = -6.844$, $P < 0.001$), 125 ms ($t_7 = -4.687$, $P = 0.002$) and 175 ms ($t_7 = -7.560$, $P < 0.001$) after the cue onset and in right-hand response trials 75 ms ($t_7 = -5.057$, $P = 0.002$), 125 ms ($t_7 = -4.596$, $P = 0.002$) and 175 ms ($t_7 = -3.231$, $P = 0.014$) after the centre cue colour onset.

Switch trials versus stay trials

To test whether SICI differed depending on whether the subjects were just executing the action they had prepared or whether they had to update their prediction, reprogram their action plan and inhibit the prepared, but incorrect, response, an ANOVA on paired-pulse/single-pulse TMS MEP ratios with the within-subjects factors "*hand*", "*SOA*" (75, 125 and 175) and the between-subject factor "*condition*" (switch vs. stay) was conducted. We found a main effect of "*hand*" ($F_{1,14} = 22.152$, $P < 0.001$) and a significant "*condition*" × "*SOA*" interaction ($F_{2,28} = 3.532$, $P = 0.045$), indicating that the time course of SICI change differed between switch and stay trials. Post hoc independent samples t tests, not assuming equal variances, revealed a significant difference between switch and stay

"*hand*", "*SOA*" (75, 125, 175 and 225 ms) and "*number of stay trials*" (3–4 vs. 5–7) was conducted. However, we did not find any significant effects (all $P > 0.16$). Post hoc paired-samples t tests comparing MEP ratios for each condition of hand and SOA between the two types of switch trials (switch after 3 to 4 vs. 5 to 7 stay trials), not assuming equal variances, revealed no significant differences (all $P > 0.18$).

trials for left-hand response trials at 75 ms SOA ($t_{14} = -4.129$, $P = 0.001$, stay > switch) and for right-hand response trials at 125 ms SOA ($t_{14} = 2.746$, $P = 0.017$, switch > stay) and at 175 ms SOA ($t_{14} = -3.980$, $P = 0.003$, switch > stay), showing relatively less SICI of the prepared but wrong response early (i.e. 75 ms after cue onset) in the time course of action reprogramming but not action execution and later on (i.e. 125 and 175 ms after cue onset) SICI release of the correct response is stronger during action reprogramming than during action execution. This is interesting as it could suggest that relatively early (125 ms after cue onset) strong releases of SICI-indexed processes are necessary for switching from a prepared and automatic response to an alternative one. Action reprogramming may be accomplished by inducing a general release from inhibition in the representations associated with both possible response, together with even stronger release of SICI-indexed inhibition of the unexpected, but correct, alternative response than occurs for the prepared, but wrong, response. This is then followed by an increase in inhibition of the prepared, but wrong, response.

Discussion

The present experiments aimed at investigating processes within M1 during action reprogramming by means of SICI. Significant SICI (i.e., [paired-pulse TMS MEP amplitude/single-pulse TMS MEP amplitude] ratios significantly smaller than 1.0 or 100%) was present during normal action execution throughout all SOAs probed, i.e. at 75, 125 and 175 ms. This significant SICI within the left M1 was present both in left- and right-hand responses although it was slightly, but significantly smaller in the latter. In contrast, during action reprogramming, we observed, in general, a greater release from SICI-indexed inhibition at later SOAs to the point of complete SICI disappearance (i.e. no significant difference from baseline 1.0) in the left M1 if the right hand was previously unprepared and now needed to be selected. SICI first differed between the two reprogrammed responses (i.e. switch to the left vs. switch to the right hand) 125 ms following the cue signalling the need to reprogram the response. This release of SICI was behaviourally relevant. Participants with a greater release of SICI during action reprogramming showed lower switching costs (see Fig. 3c).

During action execution trials (stay trials), the fact that left M1 SICI was smaller in right-hand response trials as compared with left-hand response trials already at 75 ms SOA (see Fig. 3b) could be interpreted as indicating the appropriate response was represented already 75 ms after the central colour cue onset, because it had been prepared even before cue onset. Surprisingly, we found no evidence

for a progressive release of left M1 SICI in right-hand response trials through the successive SOA periods in the stay trials. Such a progressive release to the point of complete disappearance of SICI was only observed during action reprogramming in the hemisphere controlling the unprepared but correct response (see Fig. 3a). In these action reprogramming trials, we did not find clear evidence for a progressive increase in SICI in the hand that was initially prepared but needed to be inhibited, although we did find a trend towards a decrease in general M1 excitability.

Previous studies looking at general corticospinal excitability and SICI during stop-signal inhibition found suppression of corticospinal excitability and an increase in SICI in the M1 that had to be inhibited (Coxon et al. 2006). However, our results indicate that not the increase in SICI in the hand that was to be inhibited but the release of SICI in the unprepared but correct hand plays a main role in action reprogramming; this suggests a fundamental difference between pure response inhibition (e.g. in stop-signal paradigms) and action reprogramming.

For example, pure response inhibition of prepared actions in stop-signal paradigms has been shown to be muscle unspecific and could be observed in nearby hand and even distant leg muscles not involved in the pre-prepared action (Coxon et al. 2006; Badry et al. 2009). This however would be inappropriate in the case of action reprogramming as a complete inhibition of all motor outputs would prevent the reprogramming towards the alternative response. Also, action reprogramming is more complicated, entailing a balance between the participant's expectancy and preparation of the upcoming response, which is correct on the majority of stay trials and the need to override the prepared response and select and execute the alternative response on switch trials. We did not find any significant differences in SICI patterns between switch trials after a shorter number of stay trials (three and four stay trials) and switch trials after a bigger number of stay trials (five to seven stay trials). However, this does not necessarily mean that SICI patterns do not vary with the number of stay trials preceding a switch. It has been shown that corticospinal excitability varies with the amount of uncertainty about an upcoming response (Bestmann et al. 2008). SICI is a likely candidate generating these uncertainty related trial-by-trial fluctuations in M1 excitability (although see Van Elswijk et al. 2007 for a failure to find any SICI modulation by expectancy even in the presence of modulations of single-pulse MEPs). Hence, it could still be that SICI patterns would also vary with the amount of uncertainty or the expectation of an upcoming switch trial. Unfortunately, as our experiment was not designed to detect these subtle differences in SICI patterns, we were not able to test this hypothesis. Further research on

variations in SICI with uncertainty and expectation is needed to fully answer this question.

On the other hand, our results showed that in trials in which prepared responses could be executed there was no SICI modulation over the SOAs probed and hence no progressive release in SICI. Although there is a small but significant difference between SICI for the responding and SICI for the non-responding hand, significant inhibition is present in both hands throughout the time course of response selection. SICI has indeed been shown to be constantly present in motor preparation paradigms, even at time points just before a response might have to be executed (van Elswijk et al. 2007), even though expectancy strongly modulates corticospinal excitability per se, as indicated by single-pulse TMS (van den Hurk et al. 2007; van Elswijk et al. 2007; Bestmann et al. 2008). This is interesting as it could indicate another fundamental difference in the neuronal mechanisms of action selection between (1) normal prepared action execution, on the one hand, and (2) rapid action reprogramming, on the other hand. Hence, at least in terms of SICI action, reprogramming shows remarkable differences from (a) complete response inhibition and from (b) normal action execution and should therefore not be perceived as a composite of normal action selection and action inhibition but a separate and probably more complex neuronal process.

TMS was always applied over the left M1, and MEPs were always recorded from the right FDI during left-hand and right-hand responses. In order to obtain SICI effects in "switch towards" and "switch away trials", we applied TMS in the SWITCH EXPERIMENT to the left M1 (note that all our participants were right handed) during switch to the "left-hand response trials" and during "switch to the right-hand response trials", respectively. Hence, the left-hand response trials in the SWITCH EXPERIMENT always served as the "switch away" condition, and the right-hand response trials always served as the "switch towards" condition. We did the same in the STAY EXPERIMENT. However, note that our results represent SICI effects during action reprogramming and action execution only in the M1 of the dominant hemisphere (left M1 in right handers) and that right M1 SICI might reveal subtle quantitative differences (Ilic, Jung, Ziemann, 2003). Further research on right hemispheric SICI during action reprogramming and action execution needs to be carried out.

Interestingly, the results obtained from paired-pulse studies looking at pre-SMA/M1 and rIFG/M1 interactions using the exact same paradigm show that the SICI release starts when the facilitatory effects of pre-SMA on M1 are maximum (Mars et al. 2009), but before rIFG inhibitory influences are present (Neubert et al. 2010). Consistent with a role of pre-SMA in facilitating the correct response, its facilitatory influence was most pronounced, which is

strongest and most specific in time, on M1 representing the hand to which the switch had to be made (Mars et al. 2009). Although there was a greater facilitation of M1 corresponding to the hand that would ultimately respond, it was noticeable that the pre-SMA also facilitated the other M1 too. There was also evidence that the other M1 showed a significant release from SICI-indexed inhibition in the present experiment too. The relatively greater SICI-indexed inhibition in the M1 corresponding to the hand that was prepared, but which should not be used to respond on switch trials is most apparent after the point that rIFG is known to exert an inhibitory influence over M1 in this paradigm (Neubert et al. 2010). This suggests that pre-SMA initiates the updated action plan by releasing SICI of the unprepared but correct response whereas rIFG inhibits the inappropriate action (probably, by processes other than SICI). Similar suggestions have been made based on functional imaging results (Coxon et al. 2009). The influence of the frontal cortex on the M1 may occur via sub-cortical routes, such as via the STN and pallidum (Frank 2006; Neubert et al. 2010).

It is a little surprising that we did not find evidence for an increase in SICI in the hand that was to be inhibited, but strong evidence for the release of SICI in the unprepared but correct hand playing the main role in action reprogramming. However, it is important to point out that this lack of increase in SICI during switch trials in the hand that was to be inhibited does not necessarily mean that the incorrect response is not inhibited at the level of M1, merely that SICI is not the responsible factor. In fact, the single-pulse TMS data showed a strong although non-significant tendency towards an increase in inhibition of corticospinal excitability during "switch away" trials. It is important to point out that SICI is only one method for studying processes intrinsic to M1. SICI at the inter-pulse interval employed in this study has been suggested to result from a suppression of the I_1-wave, generated through the depolarization of axons synapsing directly onto corticospinal neurons, by the conditioning pulse (Reis et al. 2008) and might be dependent on γ-aminobutyric acid (GABA)-A receptor-mediated inhibition in the cortex (Ziemann et al. 1996). Conversely, SICI at a shorter inter-pulse interval of $\sim$1.5 ms and longer interval intra-cortical inhibition (LICI) have been suggested to be of different origins (possibly GABA-B receptor-mediated inhibition in the case of LICI) (Vallssole et al. 1992; Fisher et al. 2002). However, the role of the processes underlying these measures, as well as intra-cortical facilitation (Kujirai et al. 1993), has been less well studied in action reprogramming. The present study focused on SICI because this has been implicated particularly in response inhibition (Sohn et al. 2002; Coxon et al. 2006). Therefore, inhibition of the incorrect response might occur via different mechanisms,

for example via different inhibitory inter-neurons or even via direct inhibitory projections onto pyramidal neurons bypassing M1 inter-neurons. Our data however only suggest that the facilitation of the unprepared but correct response occurs via a release of 3-ms SICI. Further research needs to clarify whether increases in other inhibitory mechanisms such as direct inputs from distant brain areas, different SICI inter-neuron populations (stimulated at different inter-pulse intervals), and LICI are causing this possible inhibition of M1 excitability.

In conclusion, the present results identify the nature of changes in SICI-indexed processes in M1, which can be related to the successive facilitatory and inhibitory inputs that it receives from pre-SMA and rIFG, respectively during action reprogramming (Mars et al. 2009; Neubert et al. 2010). The combination of facilitation and inhibition leads to a progressive release of SICI-indexed inhibition in the representation of the movement that will ultimately be made.

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