Brain Stimulation 8 (2015) 945–952

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Joint Contribution of Left Dorsal Premotor Cortex and Supramarginal Gyrus to Rapid Action Reprogramming

Gesa Hartwigsen [a,b,*], Hartwig R. Siebner [b,c,d]

[a] Department of Psychology, Christian-Albrechts-University Kiel, Olshausenstrasse 62, 24118 Kiel, Germany
[b] Department of Neurology, Christian-Albrechts-University Kiel, Arnold-Heller-Str. 3, 24105 Kiel, Germany
[c] Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Kettegaard Allé 30, 2650 Hvidovre, Copenhagen, Denmark
[d] Department of Neurology, Copenhagen University Hospital Bispebjerg, Bispebjerg Bakke 23, 2400 København NV, Denmark

ARTICLE INFO

Article history:
Received 12 December 2014
Received in revised form
28 April 2015
Accepted 29 April 2015
Available online 29 May 2015

Keywords:
Transcranial magnetic stimulation
Parietal cortex
Virtual lesion
Compensation
Non-invasive brain stimulation
Interaction

ABSTRACT

Background: The rapid adaptation of actions to changes in the environment is crucial for survival. We previously demonstrated a joint contribution of left dorsal premotor cortex (PMd) and left supramarginal gyrus (SMG) to action reprogramming. However, we did not probe the contribution of PMd to the speed and accuracy of action reprogramming and how the functional relevance of PMd changes in the presence of a dysfunctional SMG.

Objective: This study further dissociated the unique contribution of left PMd and SMG to action reprogramming. Specifically, we tested whether the critical contribution of PMd during action reprogramming depends on the functional integrity of SMG.

Methods: Adopting a condition-and-perturb repetitive transcranial magnetic stimulation (rTMS) approach, we first transiently conditioned left SMG with 1 Hz offline rTMS and then perturbed PMd activity with online rTMS whilst human subjects performed a spatially-precued reaction time task.

Results: Relative to sham rTMS, effective online perturbation of left PMd significantly impaired both the response speed and accuracy in trials that were invalidly pre-cued and required the subject to reprogram the prepared action. Moreover, the disruptive effect of rTMS over left PMd on response speed became stronger after SMG had been conditioned with offline rTMS.

Conclusions: These results corroborate the notion that left PMd and SMG jointly contribute to rapid action reprogramming. Moreover, the strong virtual lesion effect observed with rTMS over PMd suggest that this area represents a key node for both the suppression of activation based on the precue and response activation based on the response target.

Introduction

The ability to flexibly adjust prepared motor plans to environmental changes is often referred to as action reprogramming. During action reprogramming, one is required to rapidly discard a prepared action plan and replace it with an appropriate alternative. Previous studies have demonstrated that several frontal and parietal cortical areas contribute to the efficient reprogramming of actions [1–5]. For instance, it was shown that left dorsal premotor cortex (PMd) is preferentially involved in non-routine stimulus-response mapping [6,7] or more indirect stimulus-response mapping based on arbitrary relations between cue and action [8,9]. To further elucidate the role of left hemispheric areas in motor updating, several previous studies applied repetitive transcranial magnetic stimulation (rTMS) over parietal and premotor regions

Conflict of interest: H.R.S. has received honoraria as speaker from Lundbeck A/S, Valby, Denmark, Biogen Idec, Denmark A/S, Genzyme, Denmark and MerckSerono, Denmark, honoraria as editor from Elsevier Publishers, Amsterdam, The Netherlands and Springer Publishing, Stuttgart, Germany, and travel support from MagVenture, Denmark.

This work was supported by the Volkswagenstiftung (grant no. I/79-932 to HRS). GH was supported by the Deutsche Forschungsgemeinschaft (HA 6314/1-1). HRS was supported by the Bundesministerium für Bildung und Forschung (01GO0511 'NeuroImageNord') and is supported by a Grant of Excellence sponsored by The Lundbeck Foundation Mapping, Modulation & Modeling the Control of Actions (ContAct) (R59 A5399).

* Corresponding author. Department of Psychology, Christian-Albrechts-University Kiel, Olshausenstrasse 62, D-24114 Kiel, Germany. Tel.: +49 431 880 4872; fax: +49 431 880 1829.
E-mail address: hartwigsen@psychologie.uni-kiel.de (G. Hartwigsen).

http://dx.doi.org/10.1016/j.brs.2015.04.011

prior to or during spatially pre-cued reaction time tasks [1,10–12]. These studies provided evidence for an essential contribution of left supramarginal gyrus (SMG) and PMd to motor reprogramming. Specifically, online perturbation of left SMG with high-frequency rTMS prolonged response speed when subjects had to reprogram their actions in response to visuo-spatial cues [12]. Low-frequency offline rTMS of left PMd, on the other hand, has been shown to improve action reprogramming in a spatially pre-cued reaction time task by reducing the number of errors in invalidly pre-cued trials [13]. Moreover, the individual decrease in error rate after rTMS conditioning of left PMd correlated with a stronger task-related coupling between PMd and SMG.

We recently combined low-frequency offline rTMS over PMd with subsequent online perturbation over SMG to probe the functional interaction and compensation between these regions during action reprogramming [14]. We found that the response accuracy of invalidly pre-cued trials was significantly decreased with online perturbation of left SMG. Additionally, the response speed in these trials was delayed when online rTMS over SMG was preceded by offline conditioning of left PMd with low-frequency offline rTMS. This study implicated that the contribution of left SMG to efficient action reprogramming depended on the functional integrity of left PMd.

While the above cited studies demonstrated a joint functional contribution of PMd and SMG to action reprogramming, none of the previous experiments directly perturbed activity in left PMd during action reprogramming. It is thus less clear how critically PMd contributes to the speed and accuracy of action reprogramming and how the functional contribution of PMd changes in the presence of a dysfunctional SMG.

This study was designed as a mirror experiment to our previous study [14]. To further elucidate the role of left PMd and SMG during action reprogramming, we thus adopted a condition-and-perturb approach combining low-frequency rTMS conditioning of left SMG with subsequent online perturbation of left PMd. We reasoned that both PMd and SMG are key regions for non-routine responses that require the integration of conflicting information during action reprogramming. Our design allowed us to test two alternative hypotheses on the contribution of SMG and PMd to action reprogramming.

Based on the previous studies described above [12,14] one might expect that SMG but not PMd would be critical for accurate action reprogramming. Hence, SMG should contribute to the switching of motor plans, by suppressing the release of a prepared but incorrect response triggered by an invalid precue. Moreover, both SMG and PMd might be critically involved in efficient rapid stimulus-response mapping requiring the initiation of the correct response [13–16]. If this were the case, we would not expect any disruptive effects of online rTMS over left PMd on the accuracy of invalidly pre-cued trials. However, offline conditioning of left SMG should limit the brain's ability to compensate for the disruptive effect of PMd rTMS on stimulus-driven response activation. Therefore, after offline rTMS of left SMG, subsequent online rTMS of left PMd should delay the speed of responding to the unprepared target stimulus. Alternatively, intact PMd function might be critical for both the speed and accuracy of action reprogramming. If this were the case, online perturbation of PMd should impair both the accuracy and response speed in invalidly pre-cued trials.

Materials and methods

Subjects

16 volunteers (8 females, mean age = 24.2 years, range = 21–29 years) with no history of neurological disorders or head injury participated in the experiment. All subjects were right-handed (laterality index of ≥90%) according to the Edinburgh Handedness Inventory [15]. During the experiments, subjects were equipped with earplugs. Written informed consent was obtained before the experiment. The study was performed according to the guidelines of the Declaration of Helsinki and approved by the local Ethics Committee.

Experimental design and task

The study design is illustrated in Fig. 1. After a training session of validly pre-cued trials, we conditioned activity in left SMG or vertex (control condition) with 1 Hz offline rTMS (i.e., TMS before a task) in two separate sessions (Fig. 1A and C). Subsequently, participants performed a spatially pre-cued reaction time task. The task required spatially congruent button presses in response to a visually presented right- or left-sided target. Subjects were instructed to prepare for the response indicated by the directional precue (S1) that validly predicted the correct position of the target stimulus (S2) in 75% of all trials (Fig. 1B). The task consisted of 2×240 trials, including 2×180 trials with right valid or left valid precues and 2×60 trials with right invalid and left invalid precues with an inter-trial interval of 1 s.

Online rTMS consisted of a 4-pulse burst of 10 Hz rTMS with an interstimulus interval of 100 ms. Each burst started 20 ms after the presentation of the target stimulus (Fig. 1C and D). Subjects were instructed to respond as quickly and accurately as possible. Stimulus presentation and response recording was obtained with E-PRIME (Psychology Software Tools Inc., Pittsburgh, PA).

Transcranial magnetic stimulation

We used neuronavigated TMS (TMS-Navigator, Localite, Sankt Augustin, Germany) based on the registered individual T1-weighted MR image for coil positioning and maintaining its exact position throughout the experiment (see Supplementary Information for more details). The coil was placed tangentially on the surface of the head. The handle pointed at 45° to the sagittal plane, with the second phase of the biphasic pulse inducing a posterior-to-anterior current flow. Stimulation intensity was set to 90% of individual resting motor threshold of the right first dorsal interosseus muscle for both conditioning and perturbing rTMS. Both rTMS protocols were within the published safety limits [16].

Each participant received a total of 1800 stimuli of 1 Hz offline rTMS for 30 min either over left SMG or vertex in two sessions that were applied in counterbalanced order at least five days apart. Online rTMS perturbation consisted of a four-pulse train of effective or sham 10 Hz rTMS that was applied over left PMd 20 ms after the onset of S2 (Fig. 1D). Effective and sham rTMS trials were equally frequent (50% each) and pseudo-randomly intermingled. Sham online rTMS was given through an additional coil which was placed over the first coil at an angle of 90°. Stimulation intensity was set 15% higher for sham as compared to effective online rTMS to produce a comparable acoustic stimulus without effectively stimulating the brain.

Relating task performance to the variation in response speed

We explored the differential effects of rTMS over SMG and PMd on efficient and accurate action reprogramming within the theoretical framework of a dual-process model to determine effect size as a function of response speed (Fig. 2A for a schematic illustration). Dual-process models have been previously used to capture stimulus-response compatibility effects in conflict tasks [14,17,18]. According to the dual-process model, it can be assumed that invalidly pre-cued trials are characterized by two competing

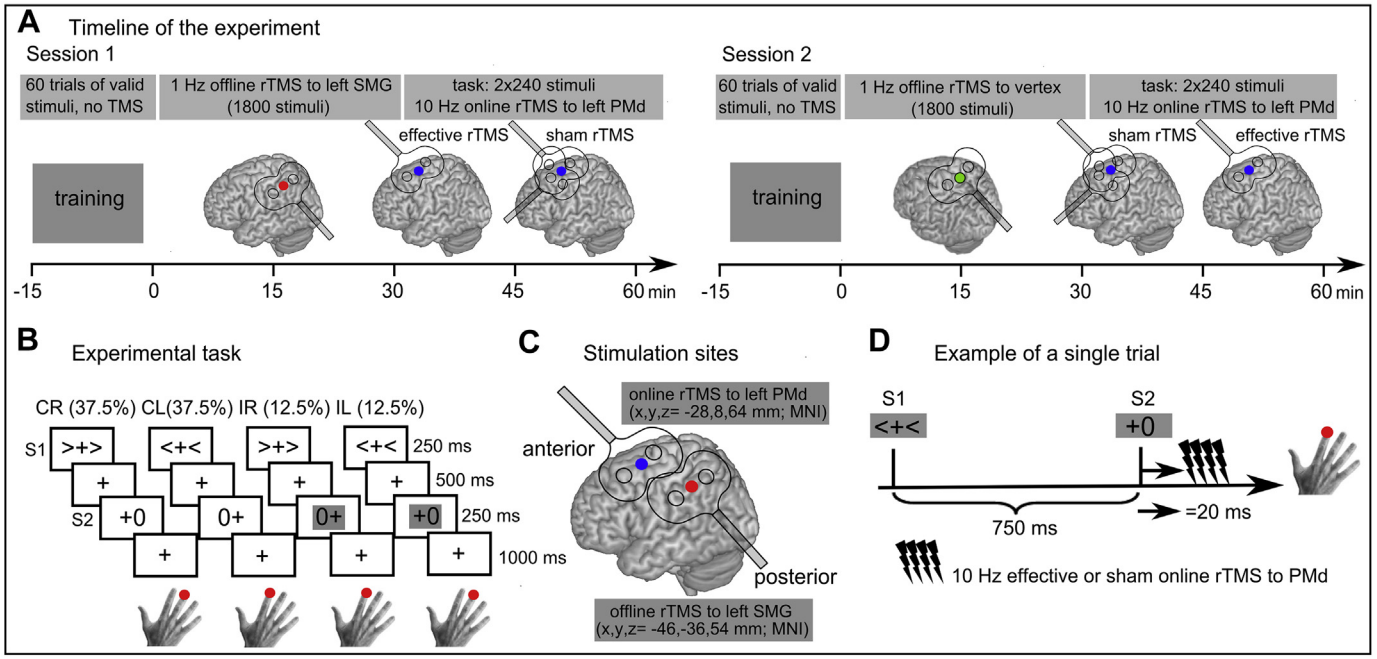

Figure 1. Experimental design. **A**. The experiment consisted of two sessions which were performed at least five days apart in counterbalanced order. In both sessions, 1 Hz conditioning rTMS was applied either to left supramarginal gyrus (SMG, in red) or vertex (in green). During the experimental task, effective or sham 10 Hz online rTMS was applied to left dorsal premotor cortex (PMd, in blue). **B**. Subjects performed a visually pre-cued two-choice reaction time task. A directional precue (S1) appeared for 250 ms on the screen and indicated the probable position of a target stimulus (S2). 750 ms after S1, S2 appeared for 250 ms. Subjects were instructed to prepare for the response indicated by S1 that validly predicted the correct target position in 75% of the trials. Participants made spatially compatible button presses with their right index finger (left-sided target) or middle finger (right sided target) according to the position of S2. The order of event types was pseudo-randomized. **C**. Stimulation sites for left SMG and PMd were taken from our previous study [14] (SMG: $x, y, z = -46, -36, 54$ mm; PMd: $x, y, z = -28, 8, 64$ mm; within MNI space). **D**. 20 ms after the onset of S2, a four-pulse train of 10 Hz rTMS was applied to left PMd. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

processes that converge at the level of response activation processes. A direct response activation route would be activated by the invalid precue (S1) whereas the controlled processes of stimulus-response translation (i.e., deliberate response decision processes) would be activated by the target stimulus (S2) [14,17,18]. One critical assumption of the dual-process model is that the selective suppression of direct stimulus activation (i.e., suppression of the response triggered by the invalid precue S1) takes some time to build up and may vary from trial to trial. Hence, interference effects (i.e., activation of the direct response based on the invalid precue) are more effectively controlled by selective suppression when subjects make slow as opposed to faster responses [19].

We constructed delta plots which capture changes in task performance as a function of response speed [17–19]. For details on the construction of the delta plots and other data analyses, please refer to the Supplementary Information.

Results

Effects of conditioning and perturbing rTMS on the response speed in invalidly precued trials

The effects of conditioning (offline) and perturbing (online) rTMS on task processing were analyzed separately for correct and incorrect responses (i.e., error trials) to investigate whether conditioning rTMS of SMG and perturbing rTMS of PMd differentially affected reaction times (RTs) and error rates (ERs). in validly precued trials, effective relative to sham online rTMS significantly decreased RTs independent of the offline rTMS site (main effect of online rTMS; $F_{1,15} = 9.97$; $P = 0.007$; Fig. 3A). This effect was reversed in invalidly pre-cued trials: Relative to sham rTMS, effective rTMS of PMd significantly delayed reaction times when subjects had to update their action plans independent of the type of offline rTMS (main effect of online rTMS; $F_{1,15} = 6.59$; $P = 0.02$; Fig. 3B). The perturbing effect of online rTMS depended on the type of offline rTMS conditioning (interaction between offline rTMS and online rTMS; $F_{1,15} = 6.58$; $P = 0.022$). Offline rTMS of left SMG sensitized the ipsilateral PMd to the acute disruptive effects of high-frequency online rTMS on response initiation, leading to a further delay in task performance. Mean RTs were significantly prolonged with effective relative to sham online rTMS to PMd after offline 1 Hz rTMS of SMG (post-hoc paired t-test: $t_{15} = 4.72$; $P = 0.0001$) but not vertex ($P = 0.12$). There was also a trend towards delayed RTs for effective online rTMS of PMd ($t_{15} = 1.87$; $P = 0.081$) but not sham rTMS ($P = 0.71$) when preceded by offline rTMS of SMG as compared to the vertex (Fig. 3B).

Analysis of the validity effect, the increase in RTs for invalidly as opposed to validly pre-cued trials, further substantiated the joint disruptive effect of rTMS over SMG and PMd (Fig. 3C). The RT cost for invalidly pre-cued trials revealed significantly delayed RTs after effective relative to sham online rTMS of PMd independent of the type of offline conditioning (main effect of online rTMS: $F_{1,15} = 11.39$; $P = 0.004$). The combined disruption of both PMd and SMG further prolonged RTs as evidenced by a significant interaction of the type of conditioning rTMS with the type of perturbing rTMS ($F_{1,16} = 5.62$; $P = 0.032$, Fig. 3C). This interaction again showed that conditioning offline rTMS targeting left SMG increased the disruptive effect of online perturbation over left PMd. Consequently, the RT-difference between invalidly and validly pre-cued trials was enhanced when effective vs. sham online rTMS to PMd was preceded by offline rTMS of left SMG ($t_{15} = 5.02$; $P = 0.0001$) but not offline rTMS over vertex (0.13). However, the effect of effective online perturbation was not significantly stronger when preceded by offline rTMS of SMG as compared to the vertex

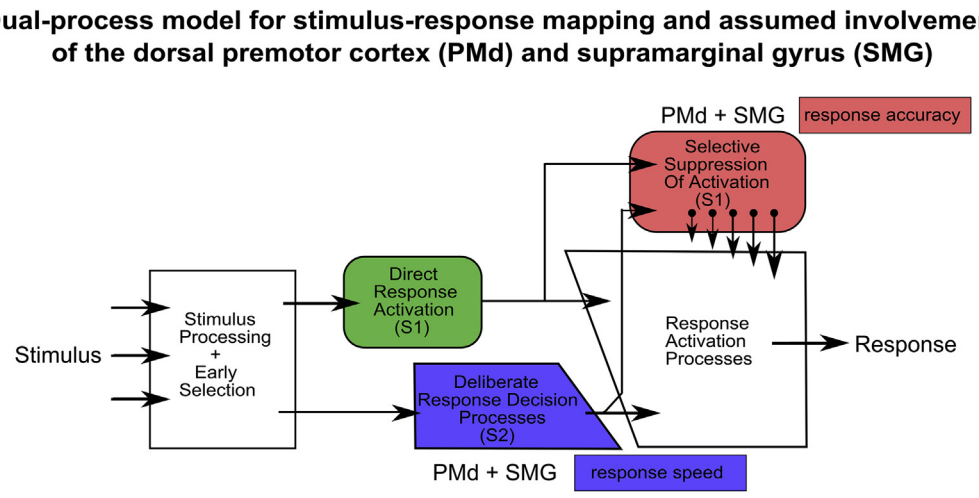

Figure 2. Joint contribution of left SMG and PMd during action reprogramming. Illustration of the dual-process model for stimulus-response mapping in trials with conflicting information. The increasing size of the arrows for selective inhibition represents the operation dynamics for this process. Note that suppression is not initiated immediately after signal onset but takes time to build up. Left PMd and SMG are critical nodes for both the direct response activation that determines response accuracy in invalidly pre-cued trials and deliberate response decision processes that contribute to the response speed. S1: invalid precue, S2 target stimulus.

($P = 0.12$), and there was no difference for perturbing sham rTMS after offline rTMS of SMG as compared to vertex ($P = 0.75$) (Fig. 3C).

Online rTMS over left PMd decreases the accuracy in invalidly pre-cued trials

Analyses of ERs only included errors of commission as errors of omission were negligible (<5% of all error trials). Here, we did not find any effects of rTMS on validly pre-cued trials (Fig. 4A). However, effective online rTMS of PMd significantly interfered with the rapid online updating of motor plans when the prepared response based on an invalid precue had to be inhibited and replaced by the appropriate response triggered by the target stimulus: This was reflected by a main effect of online rTMS in the ANOVA ($F_{1,15} = 7.53$; $P = 0.015$; Fig. 4B). The detrimental effect of effective online rTMS on the ability to suppress the prepared but inappropriate response was not influenced by the type of offline rTMS. There was no significant interaction between online and offline rTMS and no main effect of offline rTMS. The validity effect on error rates also showed that effective online rTMS impaired the inhibition of the prepared invalid response regardless of the type of offline rTMS (main effect of online rTMS: $F_{1,15} = 8.57$; $P = 0.01$; Fig. 4C).

rTMS-induced changes in speed and accuracy as a function of response speed

First, we constructed delta plots within the theoretical framework of a dual-process model (Fig. 2 for illustration of the model) and assessed the effects of conditioning and perturbing rTMS on the change in RT interference effects with a three-factorial repeated measures ANOVA and the slope of the RT delta plots as dependent variable. This ANOVA showed an overall increase in the RT cost for invalidly pre-cued trials after effective relative to sham online rTMS of PMd across all slope segments and both offline rTMS conditions (main effect of online rTMS: $F_{1,7} = 6.38$; $P = 0.039$; Fig. 5A). Moreover, there was a significant interaction between the type of online rTMS and slope segment ($F_{2,14} = 7.27$; $P = 0.007$). During sham online rTMS of PMd, the slopes of the RT delta plots were negative for the latest quartile, showing a weaker validity effect of the precue on RTs at slower response times. This relationship between the validity effect and response speed was inverted by effective online rTMS over PMd. Now the validity effect on RTs was more pronounced at slower response times. Accordingly, post-hoc *t*-tests showed that effective online rTMS of PMd was associated with a stronger increase in the RT slopes than sham online rTMS for the middle and latest quartiles (quartile 2–3: $t_{15} = 3.50$; $P = 0.003$; quartile 3–4: $t_{15} = 3.44$; $P = 0.004$), but not for the earliest quartile (quartile 1–2: $P = 0.31$).

Relative to offline rTMS over the vertex, offline rTMS over left SMG further increased the RT cost for invalidly pre-cued trials with increasing response time when left PMd was perturbed with effective online rTMS (Fig. 5A). Accordingly, we found a three-way interaction between the type of offline rTMS, type of online rTMS, and the slope segment ($F_{2,14} = 3.93$; $P = 0.045$). The sensitizing effect of offline 1 Hz rTMS over left SMG on the response delay induced with online rTMS of left PMd was further substantiated by post-hoc pair-wise comparisons. When preceded by offline rTMS of SMG, effective online rTMS of PMd significantly increased the slope for the later slope segments compared to sham online rTMS of PMd, with the strongest effect on the middle quartile (quartile 2–3: $t_7 = 5.16$; $P = 0.001$), providing evidence for a strong virtual lesion effect after combined disruption of SMG and PMd. There was also a similar trend for the latest slope (quartile 3–4: $t_9 = 2.59$; $P = 0.036$) which did not survive the Bonferroni–Holm correction. In contrast, after offline rTMS of the vertex, effective online rTMS vs. sham online rTMS of PMd tended to increase the slope for the latest segment only (quartile 3–4: $t = 2.53$; $P = 0.04$). This effect did not survive the Bonferroni–Holm correction.

We also constructed delta plots for accuracy. The relative increase in error rates for incorrectly pre-cued trials as opposed to correctly pre-cued trials was higher for fast responses. This speed–accuracy relationship is illustrated in the delta plots for accuracy (Fig. 5B). Accordingly, the three-factorial ANOVA showed a main effect of slope segment ($F_{2,15} = 6.01$; $P = 0.013$). This was caused by an overall increase in the slopes for the earlier compared with the later RT quartiles across all rTMS conditions (quartile 1–2 vs. quartile 2–3: $t_{15} = 4.32$; $P = 0.0001$; quartile 1–2 vs. quartile 3–4: $t_{15} = 4.50$; $P = 0.0001$). The overall accuracy was significantly decreased after effective relative to sham online rTMS of PMd across all slope segments and both offline rTMS conditions (main effect of online rTMS: $F_{1,7} = 5.02$; $P = 0.042$). However, this adverse effect of online rTMS on accuracy across all slope segments was not modulated by the type of offline rTMS.

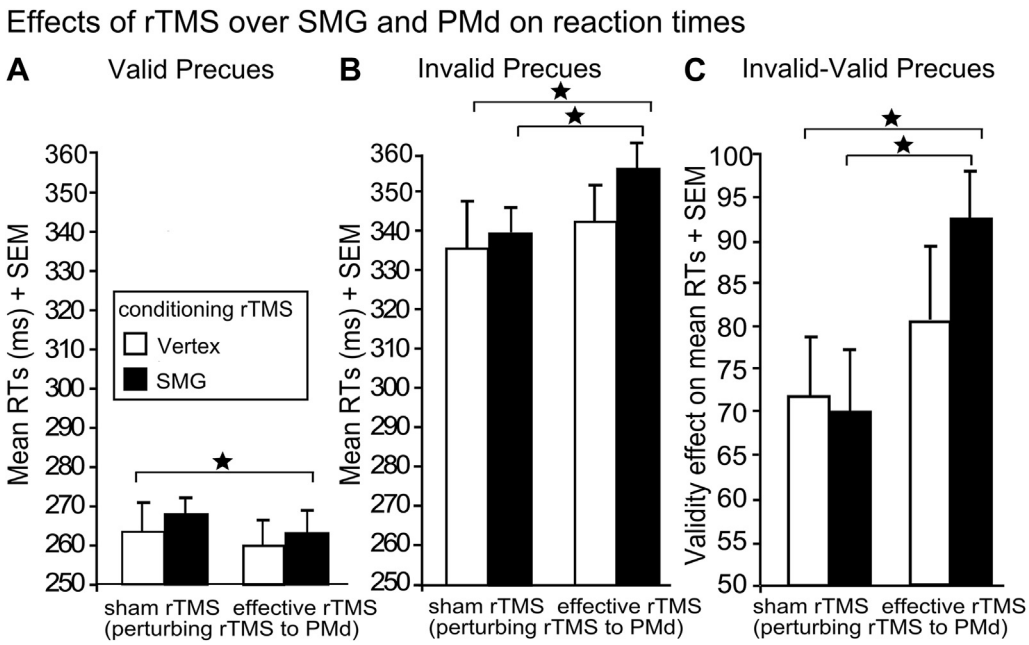

Figure 3. The disruptive effects of rTMS on mean reaction times (RTs) for the different trial types. Panel **A** displays the significant main effect of online rTMS on validly pre-cued trials. Panels **B** and **C** show the significant main effect of online rTMS and the significant two-way interaction between offline and online rTMS on (B) invalidly pre-cued trials and (C) the validity effect (i.e., the difference between invalidly and validly pre-cued trials). Note that for illustrating purposes, the different rTMS conditions are shown separately in all panels although the main effect of online rTMS was pooled across the factor offline rTMS. Error bars represent onefold standard error from the mean (SEM). $^{*}P < 0.05$; two-tailed.

Discussion

This study addressed the functional contribution of left PMd and SMG to rapid action reprogramming by means of a condition-and-perturb rTMS approach. Specifically, we were interested in elucidating the role of left PMd in the switching of motor plans. Mirroring our previous study that targeted left PMd with offline rTMS and left SMG with online rTMS [14], we first conditioned SMG with low-frequency offline rTMS and then transiently perturbed task-related activity in ipsilateral PMd with high-frequency online rTMS while subjects performed a task that required the rapid updating of motor plans. This allowed us to investigate whether conditioning and perturbing rTMS over both areas had similar effects on action reprogramming.

Our results demonstrate for the first time that left PMd critically contributes to both the deliberate response decision processes based on the target stimulus and the switching of motor plans that requires the suppression and release of a prepared but incorrect

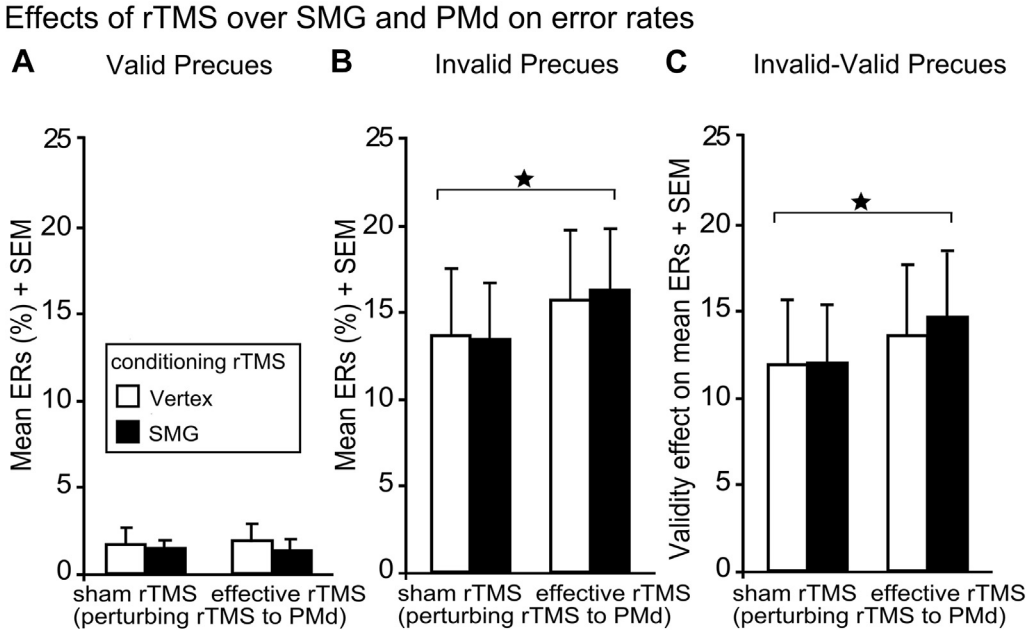

Figure 4. The disruptive effects of rTMS on mean error rates (ERs) for the different trial types. Panel **A** illustrates the absence of any modulating effect of rTMS on validly pre-cued trials. Panels **B** and **C** show the significant main effect of online rTMS on (B) invalidly pre-cued trials and (C) the validity effect (i.e., the difference between invalidly and validly pre-cued trials). Note that for illustrating purposes, the different rTMS conditions are shown separately in all panels although the main effect of online rTMS was pooled across the factor offline rTMS. Error bars represent onefold standard error from the mean (SEM). $^{*}P < 0.05$; two-tailed.

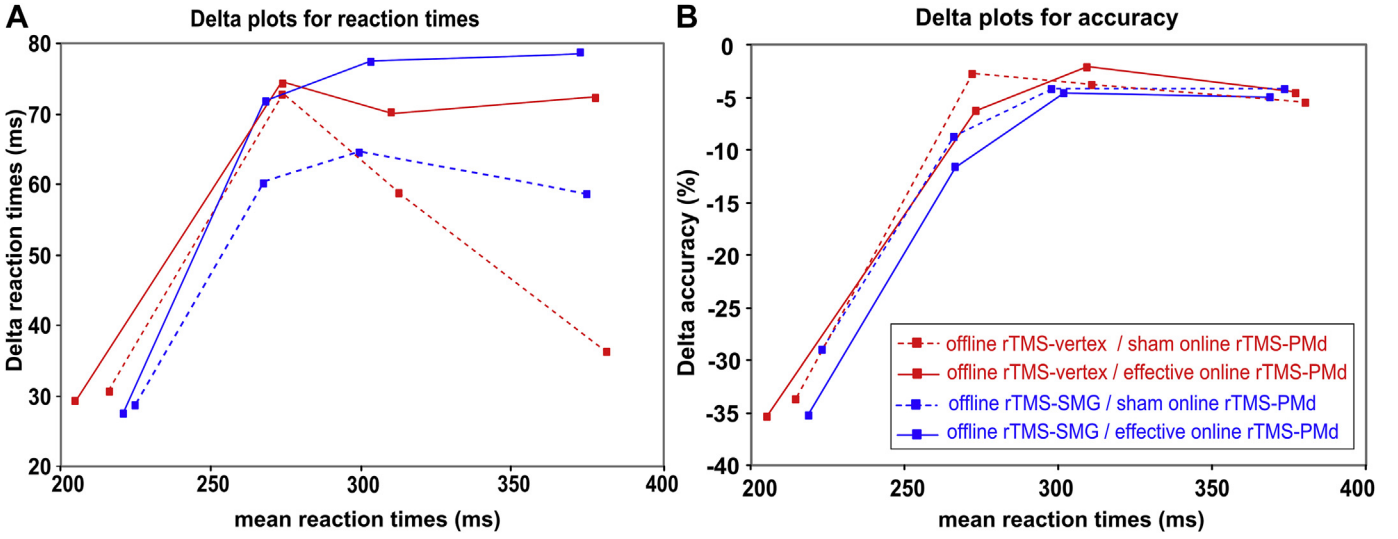

Figure 5. Delta plots for the different rTMS conditions. The delta plots illustrate the interference effect of invalidly pre-cued trials as a function of response speed for the validity effect. **A**. Relative increase in reaction times (in ms) for invalidly as compared to validly pre-cued trials. **B**. Relative decrease in accuracy (in %). The four data points of each curve represent the mean data for equally sized RT quartiles (0–25%, 26–50%, 51–75%, 76–100%).

response based on an invalid precue. This was evidenced by our finding of significantly impaired speed and accuracy in invalidly pre-cued trials with online perturbation of PMd. Similar effects were obtained for the validity effect (i.e., the response cost for invalidly pre-cued trials), quantified as difference in response times between invalidly and validly pre-cued trials. These results provide novel evidence for a critical role of left PMd in non-routine stimulus-response mapping [6,7]. The virtual lesion effect of premotor online rTMS on response speed during action reprogramming was further increased when the left SMG was conditioned with offline rTMS. The observation that offline rTMS to SMG augmented the online lesion effect of premotor rTMS indicates that both areas jointly contribute to the updating of motor plans.

The observed impaired response accuracy in invalidly pre-cued trials with online perturbation of PMd in the present study mirrors our previous findings of significantly decreased accuracy with online perturbation of left SMG during the same task [14]. Together, these results suggest that left SMG and PMd represent two critical nodes for the selective suppression of the inappropriate response (Fig. 6A). A focal perturbation over either of these key nodes was already sufficient to significantly decrease behavioral accuracy, showing that the non-lesioned area was not able to compensate for a focal online perturbation of the respective other area.

Offline rTMS of SMG did not augment the adverse effect of online rTMS of PMd on response accuracy. Accordingly, offline rTMS of left PMd did not enhance the detrimental effect of online rTMS over SMG on response accuracy during the same task in our previous study [14]. This might indicate that the observed increase in error rates after perturbation of one critical node had already reached a ceiling level. A possible alternative explanation for the absence of a disruptive effect of conditioning rTMS over either SMG or PMd on the behavioral accuracy might be the critical timing of the rTMS-induced interference. Hence, it is possible that the behavioral accuracy of action reprogramming is only impaired when a virtual lesion directly interferes with the switching process (i.e., during online rTMS), resulting in a stronger acute interference effect. Indeed, online perturbation was applied immediately after the onset of the target stimulus in our study. Future studies might explore the critical timing and compensatory potential of both areas during the switching of motor plans with dual-site online approaches and focal mini-coils that would allow for the simultaneous application of online perturbation over both network nodes. This might provide insights into the direction of the information flow between both nodes.

A second key result of our study was that the disruptive effect of perturbing online rTMS over PMd was increased when left SMG was preconditioned with low-frequency offline rTMS, indicating that the functional significance of one area for successful action reprogramming depends, at least to some extent, on the functional integrity of the other [14]. These findings demonstrate that both SMG and PMd are key regions for the integration of conflicting information. This was further substantiated by our observation that during sham rTMS of PMd, the validity effect for reaction times was stronger for faster response times, whereas the validity effect became more pronounced for slower response times during effective rTMS of PMd (Fig. 5A). The change in the slopes of the RT delta plots suggests that effective online rTMS interfered with deliberate response decision processes [17] that capture controlled processes of stimulus-response mapping based on the target stimulus which are required for correct responses [19]. Accordingly, rTMS of PMd delayed the response speed in our study, with its strongest impact on relatively slow but correct responses. Note that the disruptive effect of PMd rTMS on deliberate response activation processes was stronger after left SMG had been conditioned with offline rTMS (Fig. 6A). The stronger virtual lesion effect on the response speed after combined rTMS over both left SMG and PMd relative to unifocal perturbations of either area observed in our study replicates and extends the results of our previous study [14] that conditioning left PMd with low-frequency rTMS sensitized left SMG to the disruptive effects of high-frequency online perturbation.

Beyond the observation that PMd and SMG represent critical nodes for action reprogramming, the present study further demonstrates that the disruptive effects of acute online perturbation over PMd on response speed differed from the conditioning effects of premotor offline rTMS (Fig. 6A). We found that online rTMS perturbation of left PMd was already sufficient to significantly delay the speed of successful action reprogramming, as evidenced by a main effect of online rTMS on invalidly pre-cued trials and the validity effect. In contrast to the present findings, we did not observe any significant delay in response speed with offline conditioning of left PMd in our previous study unless left SMG was

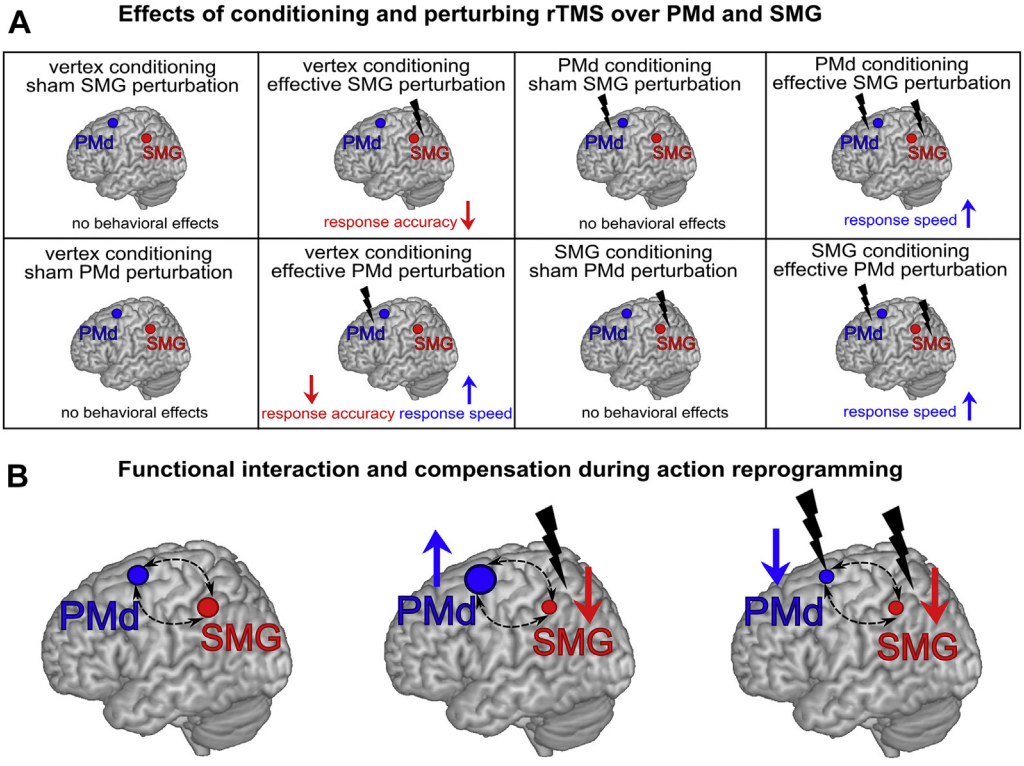

Figure 6. **A**. Illustration of the behavioral effects of conditioning or perturbing TMS over left SMG and PMd during action reprogramming based on our previous study [14] (top row) and the current experiment (bottom row). **B**. Schematic illustration of the synergistic interaction between left SMG and PMd during efficient action reprogramming. Left panel. Left PMd and SMG are critical nodes for the response speed of invalidly precued trials. The functional interaction between both nodes is indicated by the dotted arrows. Middle panel. Conditioning left SMG with offline rTMS decreases the functional contribution of this area to trials that require action reprogramming (indicated by the small circle). In turn, the contribution of left PMd is enhanced as indicated by the large circle. The up-regulation of region B may help to maintain task performance. Right panel. If left PMd function is additionally perturbed with online rTMS, the relative contribution of both areas is decreased (indicated by the small circles) and response speed is impaired.

additionally disrupted with online rTMS. This is in line with the observation from previous studies that online rTMS over a homolog cortical site can unmask an offline lesion effect by blocking compensatory processes [20]. Our findings imply that the relative impact of premotor online perturbation on task processing was stronger than the effect of offline conditioning applied in our previous study (Fig. 6A). A stronger local virtual lesion effect after online perturbation relative to offline rTMS over the same cortical area is not surprising given that the acute rTMS-induced disruption during task performance should leave the system no time to develop adaptive plasticity [21].

Our findings challenge the general notion that response speed might be easier to affect by rTMS than accuracy. In contrast, our results rather indicate that the effects of rTMS on response speed and accuracy during action reprogramming strongly depend on the timing of the applied rTMS protocol. With online rTMS over PMd alone, we observed disruption of both the speed and accuracy in trials that required the reprogramming of actions. The disruptive effects of online rTMS on the speed but not accuracy were further increased after conditioning rTMS was applied over left SMG. Other studies reported a TMS-induced modulation of task accuracy but not speed with different unifocal offline or online rTMS protocols and various cognitive tasks including action reprogramming [12,14], visual motion detection [22] or working memory and language [23–26]. Together, the previous and present results suggest that the TMS-induced behavioral modulation is strongly influenced by the task-induced brain state (see also Ref. [27]).

In sum, our findings provide further causal evidence for a joint functional contribution of left PMd and SMG to action reprogramming. The proposed mechanisms for the functional interaction between both nodes are summarized in Fig. 6B. We show that PMd is a key area for both the suppression of the prepared but incorrect response and the initiation of the correct response. Moreover, rTMS of left SMG further sensitized left PMd to the disruptive effect of online rTMS, indicating that conditioning one critical node within a network with offline rTMS can increase the disruptive effect of online rTMS over another important key area within the same network.

Appendix. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.brs.2015.04.011.

References

[1] Chambers CD, Bellgrove MA, Gould IC, et al. Dissociable mechanisms of cognitive control in prefrontal and premotor cortex. J Neurophysiol 2007;98(6):3638–47.
[2] Forstmann BU, Jahfari S, Scholte HS, Wolfensteller U, van den Wildenberg WP, Ridderinkhof KR. Function and structure of the right inferior frontal cortex predict individual differences in response inhibition: a model-based approach. J Neurosci 2008;28(39):9790–6.
[3] Mars RB, Klein MC, Neubert FX, et al. Short-latency influence of medial frontal cortex on primary motor cortex during action selection under conflict. J Neurosci 2009;29(21):6926–31.
[4] Neubert FX, Mars RB, Buch ER, Olivier E, Rushworth MF. Cortical and subcortical interactions during action reprogramming and their related white matter pathways. Proc Natl Acad Sci U S A 2010;107(30):13240–5.
[5] Verbruggen F, Aron AR, Stevens MA, Chambers CD. Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. Proc Natl Acad Sci U S A 2010;107(31):13966–71.

[6] Dassonville P, Lewis SM, Zhu XH, Ugurbil K, Kim SG, Ashe J. The effect of stimulus-response compatibility on cortical motor activation. Neuroimage 2001;13(1):1–14.
[7] Iacoboni M, Woods RP, Mazziotta JC. Bimodal (auditory and visual) left frontoparietal circuitry for sensorimotor integration and sensorimotor learning. Brain 1998;121(Pt 11):2135–43.
[8] Hoshi E, Tanji J. Differential involvement of neurons in the dorsal and ventral premotor cortex during processing of visual signals for action planning. J Neurophysiol 2006;95(6):3596–616.
[9] Pirulli C, Fertonani A, Miniussi C. Is neural hyperpolarization by cathodal stimulation always detrimental at the behavioral level. Front Behav Neurosci 2014;8:226.
[10] Buch ER, Mars RB, Boorman ED, Rushworth MF. A network centered on ventral premotor cortex exerts both facilitatory and inhibitory control over primary motor cortex during action reprogramming. J Neurosci 2010;30(4):1395–401.
[11] O'Shea J, Johansen-Berg H, Trief D, Gobel S, Rushworth MF. Functionally specific reorganization in human premotor cortex. Neuron 2007;54(3):479–90.
[12] Rushworth MF, Ellison A, Walsh V. Complementary localization and lateralization of orienting and motor attention. Nat Neurosci 2001;4(6):656–61.
[13] Ward NS, Bestmann S, Hartwigsen G, et al. Low-frequency transcranial magnetic stimulation over left dorsal premotor cortex improves the dynamic control of visuospatially cued actions. J Neurosci 2010;30(27):9216–23.
[14] Hartwigsen G, Bestmann S, Ward NS, et al. Left dorsal premotor cortex and supramarginal gyrus complement each other during rapid action reprogramming. J Neurosci 2012;32(46):16162–71.
[15] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.
[16] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009;120(12):2008–39.
[17] Ridderinkhof KR. Micro- and macro-adjustments of task set: activation and suppression in conflict tasks. Psychol Res 2002;66:312–23.
[18] Forstmann BU, van den Wildenberg WP, Ridderinkhof KR. Neural mechanisms, temporal dynamics, and individual differences in interference control. J Cogn Neurosci 2008;20(10):1854–65.
[19] Ridderinkhof KR, Scheres A, Oosterlaan J, Sergeant JA. Delta plots in the study of individual differences: new tools reveal response inhibition deficits in AD/HD that are eliminated by methylphenidate treatment. J Abnorm Psychol 2005;114:197–215.
[20] Sack AT, Camprodon JA, Pascual-Leone A, Goebel R. The dynamics of interhemispheric compensatory processes in mental imagery. Science 2005;308(5722):702–4.
[21] Hartwigsen G, Siebner HR. Probing the involvement of the right hemisphere in language processing with online transcranial magnetic stimulation in healthy volunteers. Aphasiology 2012;26(9):1131–52.
[22] Ruzzoli M, Marzi CA, Miniussi C. The neural mechanisms of the effects of transcranial magnetic stimulation on perception. J Neurophysiol 2010;103(6):2982–90.
[23] Hartwigsen G, Golombek T, Obleser J. Repetitive transcranial magnetic stimulation over left angular gyrus modulates the predictability gain in degraded speech comprehension. Cortex 2014 Sep 18. pii: S0010-9452(14)00290-1. http://dx.doi.org/10.1016/j.cortex.2014.08.027 [Epub ahead of print].
[24] Kohler S, Paus T, Buckner RL, Milner B. Effects of left inferior prefrontal stimulation on episodic memory formation: a two-stage fMRI-rTMS study. J Cogn Neurosci 2004;16(2):178–88.
[25] Lauro LJ, Pisoni A, Zerboni H, Papagno C. The neural correlates of abstract versus concrete words: evidence from an rTMS study. Brain Lang 2007;103:146–7.
[26] Deschamps I, Baum SR, Gracco VL. On the role of the supramarginal gyrus in phonological processing and verbal working memory: evidence from rTMS studies. Neuropsychologia 2014;53:39–46.
[27] Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev 2013;37(8):1702–12.