

Cortical and subcortical interactions during action reprogramming and their related white matter pathways

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The right inferior frontal gyrus (rIFG) and the presupplementary motor area (pre-SMA) have been identified with cognitive control—the top-down influence on other brain areas when nonroutine behavior is required. It has been argued that they “inhibit” habitual motor responses when environmental changes mean a different response should be made. However, whether such “inhibition” can be equated with inhibitory physiological interactions has been unclear, as has the areas’ relationship with each other and the anatomical routes by which they influence movement execution. Paired-pulse transcranial magnetic stimulation (ppTMS) was applied over rIFG and primary motor cortex (M1) or over pre-SMA and M1 to measure their interactions, at a subsecond scale, during either inhibition and reprogramming of actions or during routine action selection. Distinct patterns of functional interaction between pre-SMA and M1 and between rIFG and M1 were found that were specific to action reprogramming trials; at a physiological level, direct influences of pre-SMA and rIFG on M1 were predominantly facilitatory and inhibitory, respectively. In a subsequent experiment, it was shown that the rIFG’s inhibitory influence was dependent on pre-SMA. A third experiment showed that pre-SMA and rIFG influenced M1 at two time scales. By regressing white matter fractional anisotropy from diffusion-weighted magnetic resonance images against TMS-measured functional connectivity, it was shown that short-latency (6 ms) and longer latency (12 ms) influences were mediated by cortico-cortical and subcortical pathways, respectively, with the latter passing close to the subthalamic nucleus.

connectivity | diffusion-weighted imaging | inhibition | transcranial magnetic stimulation | cognitive control

We humans can engage in a complex repertoire of behaviors geared toward often far-removed goals. We have to override reflexive and habitual reactions to orchestrate behavior in accordance with our intentions. The mechanisms that allow us to act in this way are commonly referred to as “cognitive control processes,” and their functions include controlling, and often preventing, lower level or more automatic sensory, memory, and motor operations (1). In the control of action, a network involving the presupplementary motor area (pre-SMA) and right inferior frontal gyrus (rIFG) has been commonly identified as crucial for the adaptation of actions to changes in the environment (2–10), a process we refer to as “action reprogramming” (6). The precise contributions of these regions, however, remain unknown. For example, at a cognitive level, the rIFG has been suggested to be involved in the inhibition of an incorrect motor program (2, 7). However, whether this cognitive inhibition is also reflected at a physiological level remains subject to investigation (8). Moreover, how each individual node of the cortical network exerts its influence and interacts with other nodes is unknown. Some authors have argued that interactions among cortical regions during action reprogramming occurs via direct cortical routes (11, 12), whereas others have argued for the involvement of subcortical routes, particularly via the subthalamic nucleus (STN) (2, 3, 13). However,

the relative contributions of these different routes, particularly at the millisecond time scale during which these control processes take place, remain unclear.

In the present study, we use a combination of techniques to characterize the interaction among different cortical regions during action reprogramming and to study the underlying anatomical networks involved. We use paired-pulse transcranial magnetic stimulation (ppTMS) to characterize the interactions between rIFG and pre-SMA with primary motor cortex (M1) during normal action selection and action reprogramming. We then use a combination of ppTMS and diffusion-weighted (DW) MRI to investigate the anatomical networks that support these interactions. Furthermore, we use repetitive TMS (rTMS) (14) to interfere briefly with pre-SMA functioning, allowing us to make some claims about causality and direction of influence during frontal cortical interactions. We show that during action reprogramming, rIFG and pre-SMA have, respectively, inhibitory and facilitatory influences on M1. Different anatomical networks support these interactions. At short latencies, the influence of rIFG and pre-SMA occurs via relatively direct cortical routes, whereas influence at longer latencies occurs via a route through subcortical structures, including STN. Although only rIFG directly inhibited M1, pre-SMA is identified as a crucial node in the network because interfering with its activity leads to a breakdown of rIFG/M1 interactions.

Results

The ppTMS approach makes it possible to measure causal functional interactions among brain areas during different cognitive states. In the present investigation, it was used to measure the causal influence of rIFG or pre-SMA on M1 corticospinal excitability. A test TMS pulse is delivered over M1, and the amplitude of the motor-evoked potential (MEP) in the electromyographic signal recorded from a hand muscle involved in the task [right first dorsal interosseus (FDI)] is measured to quantify M1 excitability. On some trials, the M1 test pulse is preceded by a conditioning pulse applied over rIFG or pre-SMA (ppTMS). The conditioning pulse can modulate the amplitude of the MEP elicited by the test pulse over M1. Changes in M1 excitability attributable to the conditioning pulse can be quantified by calculating the ratio [ppTMS MEP amplitude/single-pulse (sp) TMS MEP amplitude].

A total of 29 (15 female) right-handed volunteers participated in 1 or more of the 74 TMS experiments using various versions of a task modeled on the paradigm developed by Isoda and Hiko-

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which has the primary role in the making of right hand movements). Independent sample *t* tests revealed a significant difference between switch and stay trials for left hand response trials at 175-ms SOA [$t(18) = -2.438$; $P = 0.025$; switch < stay] and for right hand response trials at 175-ms SOA [$t(18) = -3.472$; $P = 0.003$; switch < stay] (Fig. 2A). One-sample two-tailed *t* tests of the MEP ratios against baseline (MEP ratio of 1.0) showed that the right hand FDI MEPs were significantly inhibited in left hand response switch trials [trials on which subjects prepared a right hand response but had to switch to making a left hand response, $t(9) = -3.563$; $P = 0.006$] and significantly facilitated in right hand response stay trials [$t(9) = 3.189$; $P = 0.011$] at 175 ms after center cue color onset. Although the effects were clearest for the right hand, contralateral to the stimulated M1, there was evidence of inhibition being exerted even when subjects were switching away from a prepared left hand movement (SI Text Section 3). In summary, rIFG stimulation during action reprogramming unveils an inhibitory influence of rIFG on the M1 that controls the hand that must be stopped. During normal action selection on stay trials, however, rIFG exerts a facilitatory influence over the M1 that corresponds to the responding hand.

The exact same task and parallel procedure were used by Mars et al. (12) to investigate interactions between pre-SMA and M1 during action reprogramming. To compare influences exerted by pre-SMA and rIFG on M1 excitability during action reprogramming, we conducted an ANOVA on FDI switch trial MEP ratios from the current rIFG/M1 experiment and the previous pre-SMA/M1 experiment (12) with the within-subjects factors hand (left vs. right) and SOA (75, 125, and 175 ms) and the between-subjects factor “area” (pre-SMA vs. rIFG). The ANOVA revealed a significant between-subjects effect of area [$F(1,19) = 6.410$; $P = 0.02$] and a significant within-subjects effect of SOA [$F(2,38) = 8.049$; $P = 0.002$], a significant area × hand interaction [$F(1,19) = 4.640$; $P = 0.044$], and an area × SOA interaction [$F(2,38) = 3.398$; $P = 0.047$]. This indicates that although both areas, pre-SMA and

rIFG, seem to exert an influence on M1 excitability during action reprogramming, the influence differs in time course and character (Fig. 2A and B). Whereas pre-SMA, on switch trials, facilitates the unexpected and unprepared but correct response 125 ms after instruction cue onset, rIFG inhibits the prematurely activated but incorrect response 175 ms after cue onset (SI Text Section 2).

Effects at Different IPLs and Associated White Matter Pathways. The aim of the next pair of experiments (performed on a single group of 16 participants in a counterbalanced order) was to investigate interactions between rIFG and M1 [“rIFG/M1 interpulse latency (IPL) experiment”] and interactions between pre-SMA and M1 [“pre-SMA/M1 IPL experiment”] at different latencies. Although the earlier experiments had investigated pre-SMA/M1 and rIFG/M1 interactions at different time points following visual cue onset, the interval between the conditioning and test pulses was always fixed. By contrast, in the current experiments, TMS was delivered at the postvisual cue time point of maximum interaction (125 ms for pre-SMA and 175 ms for rIFG) with variable interpulse latencies (IPLs = 3, 6, 9, 12, and 18 ms). We hypothesized that different pathways might mediate interactions between pre-SMA and M1 and between rIFG and M1 occurring at different IPLs. To relate patterns of functional connectivity to the anatomical white matter tracts by which they were mediated, we correlated individual differences in ppTMS effect sizes with individual differences in diffusion-weighted MRI (DW-MRI)-derived fractional anisotropy (FA) (SI Text Sections 5 and 6). Hence, the second aim of these experiments was to localize pathways mediating interactions between pre-SMA/M1 and rIFG/M1 connectivity during action reprogramming within the brain’s white matter.

To test whether pre-SMA and M1 functional connectivity differed significantly from functional connectivity between rIFG and M1, we conducted an ANOVA with the within-subjects contrasts of hand (left vs. right), “IPL” (3, 6, 9, 12, and 18 ms), and area (pre-SMA vs. rIFG). The ANOVA showed a main effect of area

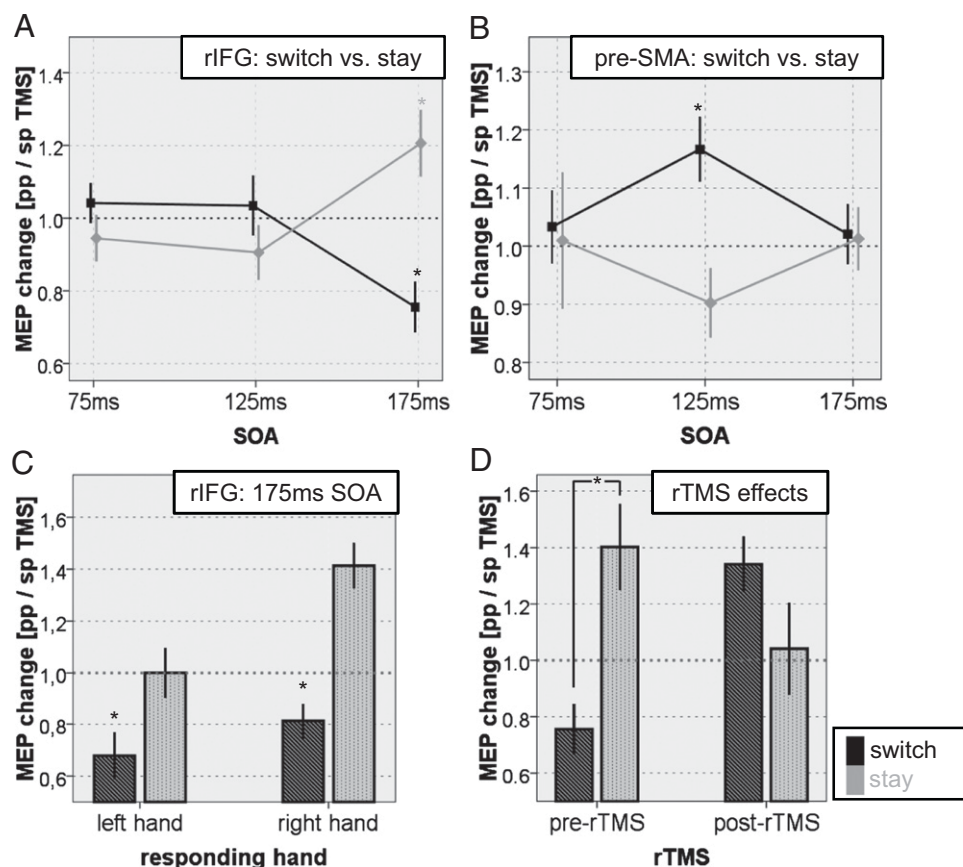


Fig. 2. Time course of frontal/M1 interactions. ppTMS and spTMS MEP ratios are plotted for each SOA between central fixation color change and TMS delivery. (A) MEP ratios for switch (gray) and stay (black) trials shown for rIFG/M1 interactions pooled over both hands. (B) Similar information for pre-SMA data from Mars et al. (12), adapted with permission of the Society for Neuroscience. (C) rIFG/M1 interactions separately for trials in which right and left hand responses were executed. Asterisks indicate significant inhibition compared with the single-pulse baseline. (D) rIFG/M1 interactions before and after 15 min of 1-Hz TMS over pre-SMA.

stimulation as seed masks and the clusters as waypoints for multi-fiber probabilistic tractography (17). This allowed us to estimate the areas that had a high probability of interconnection, via the area of correlated FA, with the area of conditioning pulse application, either pre-SMA or rIFG. We used a mask of right pre-SMA as a seed mask for tractography via the clusters significantly correlated with TMS effects in the pre-SMA/M1 IPL experiment and a rIFG seed mask for tractography via the clusters significantly correlated with TMS effects in the rIFG/M1 IPL experiment. Clusters significantly correlated with TMS effects in the pre-SMA/M1 experiment with an IPL of 6 ms generated tracts within dorsomedial frontal and parietal white matter connecting pre-SMA and premotor areas with motor and parietal areas. However, tracts derived from clusters significantly correlated with TMS effects in the pre-SMA/M1 experiment with an IPL of 12 ms connected pre-SMA with ventral and dorsal premotor areas; areas in the rIFG, M1, and parietal areas; and subcortical areas in the vicinity of STN. Similarly, clusters significantly correlated with TMS effects in the rIFG/M1 experiment with an IPL of 6 ms generated tracts connecting rIFG with M1 and temporoparietal areas, whereas tracts derived from clusters significantly correlated with TMS effects at an IPL of 12 ms connected ventral premotor cortex with more anterior areas in rIFG, adjacent ventrolateral prefrontal cortex, medial frontal cortex and pre-SMA; M1 and areas in the parietal lobe; and STN.

The evidence that longer latency pathways might be mediated by the basal ganglia, including STN, is important because it has been argued that STN is a particularly critical part of the circuit for action inhibition (2, 3) and that a pathway running from the striatum via the globus pallidus and STN might be critical for learning when to withhold actions that are unrelated to reward (18). Because tractography only provides probabilistic evidence about the existence of interconnections among brain regions, it might be argued that only limited importance can be ascribed to the evidence that any single FA region is likely to be connected to STN. We therefore quantified the number of tracts derived from all FA clusters correlated with the rIFG and pre-SMA 12-ms IPL effects that reached a region of interest (ROI) for STN, defined as a box sized $10 \times 10 \times 10$ mm, centered at MNI coordinates ($x = \pm 10, y = -15, z = -5$) (2) and compared them with the numbers of tracts derived from FA clusters correlated with rIFG and pre-SMA 6-ms IPL effects (Fig. 4); an ANOVA on the tractography-derived voxels within the ROI with the within-subjects contrast of IPL (6 ms, 12 ms) and area (rIFG, pre-SMA) revealed a significant effect of IPL [$F(1,15) = 252.084; P < 0.001$] and of area [$F(1,15) = 12.108; P = 0.003$]. To investigate further whether there was a significantly greater chance of tracts ending up in STN at 6- or 12-ms IPLs, we performed paired-samples t tests. These confirmed that tractography derived from rIFG 12-ms IPL clusters reached the STN ROI significantly more often than tractography derived from rIFG 6-ms IPL clusters [$t(15) = 10.236; P < 0.001$] and that tractography derived from pre-SMA 12-ms IPL clusters reached the STN ROI significantly more often than tractography derived from pre-SMA 6-ms IPL clusters [$t(15) = 11.767; P < 0.001$]. The observed differences were still significant after correcting for the number of clusters revealed in each condition.

Influence of Pre-SMA Interference on rIFG/M1 Interactions. The first experiments, which manipulated the time between visual cue presentation and TMS, demonstrated that pre-SMA/M1 interactions were modulated at 125 ms, which is before the time (175 ms) at which rIFG/M1 interactions were initially significantly modulated. The aim of the final experiment was to investigate whether functional interactions between rIFG and M1 depend on activity in pre-SMA. Activity in cortical areas can be decreased by a 15-min period of 1-Hz rTMS (14). We compared functional connectivity between rIFG and M1 at an SOA of 175 ms after cue onset before and after such a transient disruption of pre-SMA. An ANOVA on the pre-SMA rTMS data with “pre/post” and trial type (switch, stay) as within-subjects factors shows a significant trial type \times pre/post interaction [$F(1,7) = 11.918; P = 0.011$]. Paired-samples t tests among MEP ratios revealed a significant difference

between rIFG/M1 interactions on switch and stay trials [$t(7) = -4.134; P = 0.004$; stay > switch] only before rTMS application. This difference disappeared or, if anything, was even reversed after 15 min of 1-Hz rTMS over pre-SMA (switch > stay; $P > 0.15$). These results suggest that although rTMS over pre-SMA did not significantly change behavioral performance (SI Text), it did change the pattern of interactions between rIFG and M1. Identical rTMS over a parietal control site (electrode position Pz) did not induce any change in rIFG/M1 functional connectivity (SI Text).

Discussion

In the current set of studies, we investigated the interactions among regions of the human brain during a behavior that is one of the hallmarks of cognitive control, the adaptation of a planned movement to suit a change in the environment. We focused first on how regions in the frontal lobe influence M1 when a prepared action must be inhibited and an alternative selected. The rIFG has a preeminent role in a network for action inhibition because it inhibits M1 corticospinal activity during action reprogramming 175 ms after a visual cue, indicating that a change in action is needed (SI Text Section 2). It has previously been suggested that rIFG might exert its influence over other brain areas by inhibiting physiological activity (8), but this has been difficult to test empirically. The current results support this claim. At 175 ms, the timing of rIFG's effect in the current experiments is reminiscent of the timing of changes in synchrony recorded in this area during action inhibition (8). Despite the evidence that rIFG induces inhibition at a physiological level when cognitive control is needed, it should also be emphasized that the part of rIFG we investigated here (SI Text Section 1) exerted an excitatory influence on M1 corticospinal activity during routine action selection on “stay” trials. That rIFG might have such a facilitatory influence over action selection when action selection proceeds in a routine fashion has received less emphasis in neuroimaging experiments.

In contrast, pre-SMA's influence is earlier, at 125 ms, and its direct effect is to facilitate the M1 associated with the correct action on switch trials (12). There is evidence that pre-SMA plays a critical role in inhibiting actions in stop signal RT tasks (19, 20) at a behavioral level, but this was previously difficult to reconcile with an absence of evidence of direct physiological inhibition of M1 (12). The results of the final rTMS experiments reported here allow us to reconcile these positions. Consistent with previous suggestions that there is an increase in functional connectivity between rIFG and pre-SMA during action inhibition (5), we investigated rIFG/M1 interactions before and after a transient interruption of pre-SMA functioning. Interruption of pre-SMA rather than rIFG was chosen because the earlier paired-pulse experiments showed

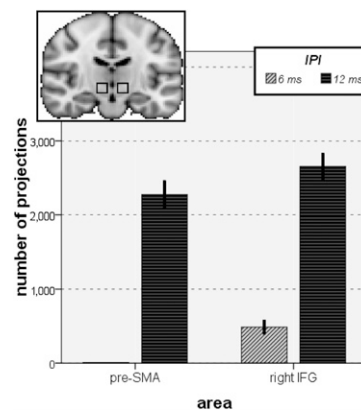


Fig. 4. Bars show the number connections from probabilistic diffusion tractography that passed through the STN ROIs (Upper). Tracts were derived from clusters of significant correlation between FA and TMS effect size in the IPL experiments (pre-SMA, Left; rIFG, Right) and the two different IPLs (light gray = 6 ms, dark gray = 12 ms). It can be seen that tracts were significantly more likely to pass through or near STN at the 12-ms IPL only.

that pre-SMA effects precede those of rIFG. Following pre-SMA inactivation, the rIFG/M1 interactions broke down, indicating a role for pre-SMA in mediating rIFG/M1 interactions. The current findings thus suggest a route by which pre-SMA activity may result in inhibition of M1. Other researchers have also argued that medial frontal cortical activity is a determinant of lateral frontal activity when cognitive control must be asserted (11, 21).

It has been repeatedly suggested that interactions between frontal and motor areas during action inhibition involve a subcortical route (2, 3, 22). However, the IPLs of 6 or 8 ms used in previous ppTMS studies made it unlikely that the effects were mediated by such a route (12, 23). To investigate this issue further, the present experiment assessed pre-SMA/M1 and rIFG/M1 interactions using a range of IPLs and looked for correlations between TMS effect sizes and white matter integrity. Not only did we look at the location of regions of white matter correlation, but we used tractography to examine whether the regions were likely to be interconnected with STN. At short latencies, there was evidence only for cortical route mediation of pre-SMA/M1 and rIFG/M1 interactions. However, at longer latencies of 12 ms, additional routes that include STN are taken. These results provide direct evidence that there are multiple routes involved in frontal/M1 interactions during action inhibition: a subcortical route being used at longer latencies and a direct cortical route.

Together, these results provide direct evidence concerning the existence, timing, physiological nature, and causal direction of interactions in a network of frontal cortical regions during a key component of cognitive control: action reprogramming. In addition, the study provided information about two major sets of anatomical pathways that might mediate such interactions.

Methods

Participants and Experimental Setup. Twenty-two participants (10 female) participated in the 28 rIFG/M1 experiments, 16 (10 female) in the 32 IPL and DW-MRI experiments and 11 (3 female) in the 14 rTMS experiments. All participants had no personal or familial history of neurological or psychiatric disease, were right handed, gave written informed consent, were screened for adverse reactions to TMS and risk factors by means of a safety questionnaire, and received monetary compensation for their participation. During the TMS experiments, 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 movement. The experimental procedures were approved by local research ethics committees, and the experiments were conducted in accordance with the Declaration of Helsinki. Experiments were controlled using a personal computer running Windows XP (Microsoft Corporation) and Presentation 0.53 (Neurobehavioral Systems, Inc.).

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TMS Parameters. In all rIFG/M1 ppTMS experiments, TMS pulses were delivered on 30 of 180 trials per block. There were two types of TMS trials. On half of the TMS trials, spTMS trials, a single TMS “test pulse” was delivered over the left M1 representation of the right FDI. The intensity of this TMS test pulse was such that a MEP of 1–1.5 mV was evoked in the relaxed contralateral FDI. On the other half of the trials, ppTMS trials, the M1 test pulse was preceded by a “conditioning pulse” over the rIFG. The intensity of the preceding conditioning pulse was set at 110% of the resting motor threshold (RMT, defined as the minimum stimulator output required to elicit a 50- μ V MEP in 5 of 10 trials) of the left FDI muscle (right M1), and the IPL was 8 ms (23, 24). Several studies have used similar interhemispheric TMS coil configuration and conditioning and test pulse intensities, because the size of the head precludes placing two TMS coils over frontal and M1 areas in the same hemisphere in some participants and an interhemispheric configuration produces similar results, albeit with a slightly higher intensity conditioning pulse, to an intrahemispheric configuration (16, 23). We hypothesized that the preceding conditioning pulse would change the MEP amplitude elicited by the test pulse, depending on the type of the trial (switch vs. stay trial) and the time after center cue color onset (75, 125, or 175 ms) (Fig. 1B). TMS pulses were delivered through two 50-mm diameter figure-of-eight coils directly connected to two high-power Magstim 200 MonoPulse machines (The Magstim Company) (Fig. 1C). The location for the conditioning coil was determined using an MRI-aligned frameless stereotaxic neuronavigation system (Brainsight; Rogue Research, Inc.). When testing the influence of pre-SMA interference on rIFG/M1 interactions, 15 min of 1-Hz rTMS [900 pulses at 90% RMT through a 70-mm diameter figure-of-eight coil connected to a biphasic Magstim Super Rapid stimulator (The Magstim Company)] was applied over pre-SMA. PpTMS was used to investigate functional connectivity between rIFG and M1 at 175-ms SOA and with 8-ms IPL both at baseline and after the rTMS (the order of baseline and post-rTMS testing sessions was counter-balanced across subjects). A similar rTMS protocol was used over Pz in a control experiment. These procedures were repeated for all subsequent TMS experiments except for details described in the relevant sections.

DW-MRI and White Matter Pathways. DW-MRI data were acquired for all participants using a 3.0-T Siemens Trio MR scanner. White matter FA values for each subject were calculated and regressed against each subject’s MEP ratio in the rIFG/M1 IPL experiment and pre-SMA/M1 IPL experiment for right hand responses with 6- and 12-ms IPLs in a four-regressor multiple regression analysis (additional analyses are found in *SI Text*).

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