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Abstract

Cognitive control is thought to rely upon a set of distributed brain regions within frontoparietal cortex, but the functional contributions of these regions remain elusive. Here, we investigated the disruptive effect of transcranial magnetic stimulation (TMS) over the human prefrontal and parietal cortices in task preparation at different abstraction levels. While participants completed a task-switching paradigm that assessed the reconfiguration of task goals and response sets independently, TMS was applied over the left inferior frontal junction (IFJ) and over the left intraparietal sulcus (IPS) during task preparation. In experiment 1, TMS over the IFJ caused interference with the updating of task goals, while leaving the updating of response sets unaffected. In experiment 2, TMS over the IPS created the opposite pattern of results, perturbing only the ability to update response sets, but not task goals. Experiment 3 furthermore revealed that TMS over the IPS interfered with task goal updating when the pulses are delivered at a later point in time during preparation. This dissociation of abstract and action-related components not only reveals distinct cognitive control processes during task preparation, but also sheds new light on how prefrontal and parietal areas might work in concert to enable flexible and goal-oriented control of behavior.

Introduction

Task preparation has been shown to rely upon a set of distributed regions within frontoparietal cortex that are typically located around the inferior frontal junction (IFJ) and the intraparietal sulcus (IPS; see Ruge et al., 2013 for a review). Although the general involvement of these areas in preparatory control is well established, their respective contributions remain much debated.

Classical theories of cognitive control ascribe a superordinate role to the prefrontal cortex (PFC), which is thought to generate top-down signals to bias processing in posterior cortices (Bunge & Wallis, 2007; Fuster, 2008; Miller & Cohen, 2001; Passingham & Wise, 2012). This view is anatomically plausible given the PFC's rich connections with other association cortices, and is furthermore supported by chronometric evidence of prefrontal activity preceding parietal activity during task preparation in macaques (Crowe et al., 2013; Goodwin et al., 2012; Merchant et al., 2011) and humans (Brass et al., 2005; Jamadar et al., 2010). At the functional level, neuroimaging studies have revealed very similar properties of prefrontal and parietal areas in cognitive control (e.g., Woolgar et al., 2011). Nevertheless, several studies demonstrated dissociations, implicating a rather general role of the IPS in sensorimotor transformations, and a more specific contribution of the IFJ to the guidance of behavior on the basis of internal goals (e.g., Bunge et al., 2002; Hartstra et al., 2011; Philipp et al., 2012). Together, these findings indicate that the IFJ and the IPS may both represent upcoming task demands, but at different abstraction levels. While the IFJ may provide an initial representation of the general context of a task episode, the IPS might specify the resulting mappings of stimulus categories to effectors, thereby providing a more action-related task representation (Brass et al., 2004; 2005).

Despite support from diverse areas of inquiry, the evidence for this top-down view on preparatory control is still rather indirect and alternative ideas have been raised in the literature. For instance, it has been argued that the IPS constitutes the source rather than the target of task-related control signals (Bode & Haynes, 2009; Swaminathan & Freedman, 2012). Others have proposed that frontoparietal areas serve similar rather than hierarchically organized functions (Dehaene et al., 1998; Duncan, 2010). Correlational methods, such as functional neuroimaging, are insufficient to resolve this ambiguity, as they cannot reveal whether task-related brain activity in a given region is in fact necessary for the respective behavior (see Walsh & Cowey, 2000). Here, we sought to overcome this limitation by investigating the disruptive effect of transcranial magnetic stimulation (TMS) over the IFJ and the IPS at different levels of task preparation. TMS was applied over the left IFJ and over the left IPS while participants completed a modified task-switching paradigm that independently assessed updating of either abstract task goals or different response sets within a single task. According to top-down theories, prefrontal TMS should interfere only with the capacity to update task goals, but not response sets, whereas parietal TMS should yield the opposite interference pattern.

Materials and Method

Participants

The sample consisted of 45 right-handed males (mean age = 23.04; SD = 2.37; range = 19-28) that were divided across the three experiments (number of participants: experiment 1 = 14; experiment 2 = 14; experiment 3 = 17). All participants reported normal or corrected to normal vision and had no personal or family history of neurological abnormalities. An additional screening procedure

was conducted to exclude the presence of other TMS contraindications (see Rossi et al., 2009). All subsequent procedures were approved by the local ethics committee and written informed consent was received from all participants prior to participation.

Stimuli and tasks

We assessed abstract and action-related components of task preparation in separate block types using a modified version of the cued task-switching paradigm (see Philipp et al., 2012 for a similar procedure). *Task-Goal Blocks* (TGBs) required subjects to classify stimuli according to two different categorization rules (shape vs. color) that could repeat or alternate across trials. Half of these blocks were performed with the middle fingers (left and right) and the other half with the ring fingers (left and right). TGBs thus required an occasional reconfiguration of the relevant task goal, while the response set used for task implementation remained constant throughout the block. Conversely, *Response-Set Blocks* (RSBs) required subjects to apply only a single categorization rule throughout the entire block. Half of these blocks required categorization of color, and the other half categorization of shape. In these blocks, however, the response set (middle fingers vs. ring fingers) could repeat or alternate across trials. RSBs thus required an occasional update of the relevant implementation rules while the abstract goal of the task remained constant throughout the entire block. Note that in TGBs half of the trials were congruent (i.e., the target stimulus was associated with the same response in both tasks) and the other half incongruent (i.e., the target stimulus was associated with different responses in the two tasks). In RSBs, on the other hand, stimuli were always univalent because they were categorized only on the basis of one stimulus feature throughout the block. However, as congruency did

not interact with the stimulated brain region in any of the three experiments, data in TGBs were pooled across congruent and incongruent trials.

The trial structure of TGBs and RSBs is illustrated in Fig. 1. All stimuli were presented centrally on a black screen. Trials began with the presentation of a task cue for 100 ms. In TGBs, the words 'KLEUR' or 'VORM' (Dutch for 'color' and 'shape') were displayed (font = Arial, color = white; font size = 40) to instruct color or shape categorization respectively. In RSBs, the words 'MIDDEL' or 'RING' (Dutch for 'middle' and 'ring') instructed responses with the middle fingers or the ring fingers respectively. This was followed by a cue-target interval (CTI) of 500 ms during which a fixation cross (size = 0.5 cm, color = white) was shown. Thereafter a target stimulus was presented on the screen for 200 ms. Targets were either squares or circles (diameter = 2 cm), and presented in either blue or orange color (matched for luminance). After the target disappeared from the screen, participants were given a time window of 2800 ms to respond. Trials were separated by an intertrial interval of jittered duration (1700 – 2300 ms) during which a blank screen was presented. Subjects' responses were recorded with the buttons 'A', 'S', 'K', and 'L', of a QWERTY keyboard. Instructions emphasized speed and accuracy of performance equally.

The full combination of task goals and response sets resulted in four different blocks (i.e., TGB with middle fingers, TGB with ring fingers, RSB with color categorization, RSB with shape categorization; see Fig. 1). TGBs counted 36 trials during which both task goals were instructed equally often; RSB counted 36 trials during which both response sets were instructed equally often. Moreover, in each block, task goals or response sets were repeated in two thirds of all trials (repetition trials) and alternated in one third of all trials (switch trials). Stimulus presentation was counterbalanced to ensure that each target and each response occurred equally often across design cells and to guarantee

an equivalent frequency of stimulus repetitions and response repetitions across blocks and design cells.

Overall, participants performed two runs (corresponding to different stimulation sites see below), each of which contained all four blocks, resulting in a total of 288 experimental trials. The two runs were separated by a break of approximately 30 min. Block order was counterbalanced across subjects with the constraint that TGBs and RSBs always alternated (in order to minimize the effects of continuous influences such as fatigue). Within each participant, the block order was kept identical across the two runs. In advance of each block, participants received instructions and performed a practice block of six trials. In experiment 3, this procedure was modified. Each run consisted of four TGBs and all blocks were performed with the middle fingers (see section experiment 3 for details).

----------Figure 1 about here----------

TMS navigation

The positioning of the TMS coil was guided by a neuronavigation system in which target sites were located onto individual anatomical MR images acquired in a separate session prior to the TMS experiment. To identify coordinates of sub-regions within the prefrontal and parietal cortices that are implicated in task preparation, we conducted a quantitative meta-analysis of brain imaging studies using the activation-likelihood estimation (ALE)-method (Eickhoff et al., 2009; 2012). The ALE-method, as implemented in GingerALE software (brainmap.org/ale), provides a quantitative voxel-wise approach for meta-analyses of neuroimaging data. Its central concept is to treat foci of single studies as spatial probability distributions rather than as single coordinates. To

reveal statistically significant clustering of brain activity, ALE maps are generated by computing the voxel-wise concordance of activation across experiments and compared with a random distribution which is based on permutation tests. Studies for the meta-analysis were selected based on the following criteria: (i) fMRI was used as the brain-imaging method; (ii) coordinates were reported in a standardized stereotaxic space and statistical analyses were applied to the whole brain; (iii) study samples consisted of healthy adults; (iv) studies employed a cued task-switching paradigm and the analysis entailed at least one contrast of cue-related brain activation on switch trials compared with repetition trials. Altogether, we identified 45 studies including 817 participants that fulfilled these criteria and entered the 469 foci that were reported in the selected contrasts to the meta-analysis. The false discovery rate of the analysis was set to $p < 0.01$ and the cluster threshold to a minimum of 200 continuous voxels. This analysis revealed significant concordance of activation within bilateral frontolateral, insular, frontomedian, and intraparietal areas, closely corresponding to previous descriptions of frontoparietal areas that are involved in diverse types of cognitive demand (e.g., Cole & Schneider, 2007; Duncan, 2010). Most importantly for the given purpose, the two clusters with the greatest ALE-values were located within the left IFJ (MNI peak coordinate: -40, 4, 32), and the left IPS (MNI peak coordinate: -34, -56, 43). In a second step, these normalized coordinates were transformed into each individual's native space with a reversed normalization procedure, to allow the precise positioning of the TMS coil over the target region using the Brainsight frameless stereotaxic software (Rogue Research). Fig. 2 illustrates the location of both target sites within standardized and native coordinate spaces. The somatosensory leg area was chosen as control site because it is not involved in task preparation. To localize this area in each subject, the stimulator coil was placed over the inter-hemispheric midline and

moved caudally beyond the central sulcus. The resulting MNI coordinates (experiment 1: 0, -39, 76; experiment 2: -1, -39, 73; experiment 3: 0, -38, 71) confirmed close correspondence to anatomical locations of the somatosensory leg area reported in previous studies (e.g., Del Gratta et al., 2000; Ruben et al., 2001).

----------Figure 2 about here----------

TMS protocol

Repetitive TMS was delivered with a Magstim Rapid stimulator (Magstim Company, Whitland, UK) using a figure-eight coil (inner diameter = 70 mm). In each trial, a train of five TMS pulses was delivered at a frequency of 10 Hz and an intensity corresponding to 110% of each participant's resting motor threshold (mean output = 64.2 %, range = 56-65). Electromyographical recordings (BioSemi, Amsterdam, The Netherlands) were used to measure the resting motor threshold, defined as the minimum intensity necessary to induce motor-evoked potentials (MEPs) with a peak-to-peak amplitude > 50 μV in the first dorsal interosseus muscle of the right hand in at least five out of ten trials. In one run of four blocks, the coil was positioned over the target site (IFJ in experiment 1, and IPS in experiments 2 and 3); and in the other run over the control site (CTR). The sequence of the stimulation sites (target site vs. control site) was counterbalanced across subjects. In experiments 1 and 2, TMS trains were time-locked to the offset of the task cue and thus covered the first 400 ms of the CTI. The trains were applied after presentation of the task cue and before onset of a target stimulus in order to maximize interference with the processes involved in task preparation while avoiding non-specific effects upon perceptual processing of the cue or the initiation of a specific response. In experiment 3, we aimed at

probing the involvement of the IPS in the final stages of task goal updating (based on the results of experiments 1 and 2). Accordingly, in this experiment, the TMS trains were time-locked to the onset of the target stimulus. Moreover, to avoid stimulation during the response period, the number of pulses in each TMS train was reduced from five to three in experiment 3 (see Fig. 5 and section on experiment 3 for details).

Statistical analyses

Individual median reaction times (RTs) and percentages of errors were subjected to repeated-measures ANOVAs with the factors STIMULATION SITE (target site vs. control site), BLOCK TYPE (TGB vs. RSB), and TRANSITION (repetition vs. switch). Error trials and post-error trials (i.e., trials subsequent to errors) were removed from the RT analysis. To assess cognitive interference related to updating, we computed 'switch costs' (i.e., the performance difference between switch trials and repetition trials) separately for each block type and target site (see Monsell, 2003). In order to ensure a sufficient level of aggregation for each experimental condition, the data were pooled across left and right hand responses in all subsequent analyses. Based on our assumption that the IFJ is involved in the setting of task goals, and the IPS in the specification of action rules, we expected that TMS would have distinct effects on performance at the level of switch costs. While TMS over the IFJ should enhance switch costs in TGBs but not in RSBs, TMS over the IPS should produce the converse pattern with increased switch costs in RSBs but not in TGBs. Paired-samples *t*-tests were used to perform these planned comparisons between the switch costs in TGBs and in RSBs (one-tailed, $p < 0.05$ corrected for multiple comparisons using Bonferroni correction).

Results

Experiment 1: Selective role of the left IFJ in updating task goals

As expected, participants responded slower on switch trials than on repetition trials, as indicated by a significant main effect of TRANSITION ($F_{(1,13)}$ = 19.247, p = 0.001; repetition = 461 ms, switch = 523 ms). The other main effects of STIMULATION SITE and BLOCK TYPE were both non-significant as were all two-way interactions. Most importantly, there was a significant three-way interaction between STIMULATION SITE, BLOCK TYPE, and TRANSITION ($F_{(1,13)}$ = 5.239, p = 0.039). Planned comparisons revealed that, compared to TMS over the control site, stimulation of the IFJ increased switch costs in TGBs ($t_{(13)}$ = 2.813, corrected p = 0.015; switch costs: IFJ = 87 ms; CTR = 42 ms), but not in RSBs ($t_{(13)}$ = -.493, corrected p = 0.630; switch costs: IFJ = 52 ms; CTR = 63 ms). At the accuracy level, there was only a significant effect of TRANSITION, reflecting the presence of switch costs ($F_{(1,13)}$ = 26.16, p = .0001 ; repetition = 2.52% ; switch = 5.88%). All other main effects and interaction terms were non-significant (see Fig. 3 for an overview of the results).

Experiment 2: Selective role of the left IPS in updating response sets

Participants responded slower on switch trials than on repetition trials, as indicated by the significant main effect of TRANSITION ($F_{(1,13)}$ = 19.36, p = 0.001; repetition = 458 ms, switch = 504 ms). Moreover, a significant main effect of BLOCK TYPE was found, reflecting that RTs were slower in RSBs than in TGBs ($F_{(1,13)}$ = 6.06, p = 0.029; TBGs = 467 ms; RSBs = 495 ms). Importantly, however, the switch costs did not differ between block types or between stimulation sites (both F-values < 0.2). No other main effects or interaction terms were significant at the RT level (see Fig. 3 for an overview). The analysis

of error rates yielded a significant main effect of TRANSITION, reflecting the presence of switch costs ($F_{(1,13)}$ = 9.38, p = 0.009; repetition = 2.99%; switch = 5.73%). In addition, the main effect of STIMULATION SITE was significant, indicating increased error rates after IPS stimulation ($F_{(1,13)}$ = 7.30, p = 0.018; IPS = 5.51%; CTR = 3.21%). Importantly, this effect was further qualified by a significant three-way interaction between STIMULATION SITE, BLOCK TYPE, and TRANSITION ($F_{(1,13)}$ = 5.96, p = 0.030). Planned comparisons revealed that, compared to TMS over the control site, IPS stimulation enhanced switch costs in RSBs ($t_{(13)}$ = 3.13, corrected p = 0.008; switch costs: IPS = 5.84%, CTR = 1.09%), but not in TGBs ($t_{(13)}$ = -0.68, corrected p = 0.509; switch costs: IPS = 1.32%; CTR = 2.76%).

We conducted an additional follow-up analysis to further explore the specificity of the observed TMS effect in RSBs. Here we were interested in the specific types of errors that were consecutive to the IPS stimulation. Given that in RSBs the classification rule remained the same throughout the entire block (e.g., to respond with the left hand to a square and with the right hand to a circle), the selection of task goals and the selection of response sets are reflected independently in the choice of response hand and finger type respectively. As a consequence, we distinguished between three different types of errors. First, *set-selection errors* were defined as responses with the incorrect finger type of the correct hand. These errors should reflect a specific failure at the level of response-set selection, as the superordinate task rule, which determines the hand choice, was applied correctly. Second, *goal-selection errors* were defined as responses with the correct finger type of the incorrect hand. These errors indicate the converse type of failure, as they reflect selection of the adequate response set, but an incorrect application of the general categorization rule. Finally, *combination errors* were defined as responses with the incorrect finger

type of the incorrect hand. These errors reflect a simultaneous failure of both processing stages. Based on our prior assumption that IPS is involved in the specification of action rules, we expected TMS to specifically increase the frequency of set-selection errors when an update of the response set was required. To address this question, we analyzed the percentages of each error type separately using repeated-measures ANOVAs with the factors STIMULATION SITE and TRANSITION. The contribution of an error type to the observed TMS effect on the capacity to update response sets should be reflected in a significant interaction of the two factors. Given the explorative nature of this analysis and the specificity of the prediction tested here, the subsequent analyses are based on one-tailed significance tests without correction for multiple comparisons.

Combination errors hardly ever occurred throughout the entire experiment (only in 0.31% of repetition trials in blocks with control stimulation) and were thus not analyzed further. For goal-selection errors, there was a reliable effect of STIMULATION SITE ($F_{(1,13)}$ = 7.823, p = 0.015), reflecting a higher frequency with IPS stimulation (IPS = 2.96%; CTR= 1.68%). However, neither the effect of TRANSITION ($F_{(1,13)}$ = 0.02, p = 0.885) nor the interaction between STIMULATION SITE and TRANSITION reached significance ($F_{(1,13)}$ = 0.36, p = 0.561). This indicates that goal-selection errors, albeit more frequent with IPS stimulation, did not drive the modulation of switch costs observed in the main analysis. Finally, the analysis of set-selection errors yielded significant main effects of STIMULATION SITE ($F_{(1,13)}$ = 3.92, p = 0.035; IPS = 3.23%, CTR = 1.50%); and TRANSITION ($F_{(1,13)}$ =10.02; p= 0.0035; repetition = 0.70%; switch = 4.03%), and, most importantly, a significant interaction of the two factors ($F_{(1,13)}$ = 4.476, p = 0.027). As predicted, compared to the stimulation of the control site, TMS over the IPS increased the percentages of set-selection errors exclusively on switch trials ($t_{(13)}$ = 2.155, p = 0.025; IPS = 5.68%; CTR =

2.38%), and not on repetition trials ($t_{(13)}$ = 0.29, p = 0.388; IPS = 0.78%; CTR = 0.66%). This pattern of results corroborates the finding that TMS over the IPS increased switch costs in RSBs by enhancing the probability of responding with the no longer adequate response set when an update thereof was required.

----------Figure 3 about here----------

Comparison between experiments 1 and 2

Although the previous analyses yielded striking differences between the interference effects with prefrontal and parietal TMS, a claim of distinct functions requires a direct statistical comparison between the respective effects in a conjunctive analysis (see Nieuwenhuis et al., 2011). This is, however, complicated by the fact that TMS affected performance at the level of speed in experiment 1 and at the level of accuracy in experiment 2. We therefore computed inverse efficiency scores (IES) to obtain an integrated performance measure across the two experiments (see Townsend & Ashby, 1983). IES of all 28 participants were computed individually by dividing the RTs of each design cell by the percentage of correct responses. These scores were subjected to a repeated-measures ANOVA using STUDY as a between-subjects factor and STIMULATION SITE, BLOCK TYPE, and TRANSITION as within-subjects factors. A modulation of the respective TMS effects on switching performance by the stimulated target site should be reflected in a significant four-way interaction. The analysis yielded a significant main effect of TRANSITION, reflecting performance costs on switch trials compared with repetition trials ($F_{1,26}$ = 46.266, p = 0.0001; repetition = 474 ms; switch = 547 ms). In addition, there was a significant four-way interaction between STUDY, STIMULATION SITE, BLOCK TYPE, and TRANSITION ($F_{(1,26)}$ = 4.863, p = 0.036). All other main effects

and interaction terms were non-significant (see Fig. 4 for an illustration of the results). To specify the nature of this interaction, we conducted further post-hoc comparisons between the 'relative switch costs' (i.e., the difference in the magnitude of switch costs with stimulation of the target site and the control site) of the two experiments. In TGBs, relative switch costs were significantly larger in experiment 1 than in experiment 2 ($t_{(26)}$ = 2.450; corrected p = 0.019; IFJ = 50 ms; IPS = -13 ms). In RSBs, relative switch costs were numerically larger in experiment 2 than in experiment 1, yet this difference did not reach statistical significance ($t_{(26)}$ = 1.255; corrected p = 0.236; IFJ = 1 ms; IPS = 31 ms). The latter may reflect that the computation of IES increases the amount of error variance (Bruyer & Brysbaert, 2011).

----------Figure 4 about here----------

Experiment 3: Role of the IPS in the final stages of task goal updating

We conducted a third experiment to further elaborate on the role of the IPS in preparatory control. Given our assumption that this region translates abstract task goals into response sets, we had expected parietal TMS to cause interference with updating primarily in RSBs, which is precisely what was found in experiment 2. However, the complete absence of interference in TGBs was nevertheless unexpected to us because updating of task goals presumably also necessitates a recoding of the relevant SR rules, in addition to more abstract processes such as attention shifts between different stimulus dimensions. A possible explanation for this non-finding resides in the temporal dependence between abstract and action-related preparatory processes. The activation of response sets is typically assumed to take place upon completion of task goal setting (e.g., Rubinstein et al., 2001). Accordingly, it seems plausible that in

TGBs the CTI is used primarily for goal setting, and response-set activation might be postponed until the onset of the target stimulus. Under this assumption, TMS over the IPS may not have affected performance in TGBs because the critical processes took place outside the CTI after goal setting. This hypothesis was addressed in experiment 3. Its goal was to examine if TMS over the left IPS would interfere with task goal updating if the pulses were no longer time-locked to the task cue but instead to the target stimulus, i.e., when the translation of goals into SR rules is required (see Fig. 5 and methods section for details on the procedure).

----------Figure 5 about here----------

RTs and error rates were analyzed using repeated measures ANOVAs with the factors STIMULATION SITE (IPS vs. CTR) and TRANSITION (repeat vs. switch). An effect of the IPS stimulation on task goal updating should be reflected in a significant interaction between the two factors. The RT analysis revealed a significant main effect of TRANSITION ($F_{(1,16)}$ = 12.337, p = 0.003), reflecting increased RTs on switch trials compared with repetition trials (see Fig. 6 A). The main effect of STIMULATION SITE ($F_{(1,16)}$ = 0.285, p = 0.601) and the interaction term ($F_{(1,16)}$ = 0.548, p = 0.470) were both non-significant. The analysis of error rates revealed a significant main effect of TRANSITION ($F_{(1,16)}$ = 22.144, p < 0.001), reflecting the presence of switch costs, and a marginally significant main effect of STIMULATION SITE ($F_{(1,16)}$ = 3.594, p = 0.076). Most importantly, the interaction between the two factors was significant ($F_{(1,16)}$ = 9.918, p = 0.006; IPS = 5.6 %; CTR = 3 %; see Figure 5). To specify this interaction, we compared switch costs with stimulation of the IPS and stimulation of the control site, revealing that switch costs were indeed enhanced with IPS

stimulation ($t_{(16)}$ = 3.149; corrected p = 0.006; see Fig. 6 B). This result suggests that TMS over the IPS is also capable of causing interference with task goal updating, but the critical time window occurs later than with TMS over the IFJ, likely reflecting the delayed specification of response sets after goal setting.

----------Figure 6 about here----------

Discussion

In the present study, we investigated the disruptive effect of TMS over the IFJ and the IPS on abstract and action-related preparation processes in humans. In line with our predictions, TMS over the IFJ selectively interfered with the ability to update abstract rules for stimulus categorization. By contrast, TMS over the IPS interfered with the capacity to switch between different action rules within a given task. These findings are consistent with a top-down view on cognitive control in which the PFC biases processing in posterior areas in favor of task goals. Yet, given the increasing evidence that TMS impacts not only the stimulated target region but also functionally connected areas (Feredoes et al., 2011; Zandbelt et al., 2013; Zanto et al., 2011), our findings should be viewed as reflecting the existence of distinct networks for the setting of task goals and response sets, connected to the left IFJ and the left IPS respectively.

IFJ and the setting of task goals

Our finding that TMS over the IFJ interfered with the setting of new task goals is concordant with various theories of PFC function that consider goal representations within the lateral PFC as the source of top-down signals directed towards posterior cortices (e.g., Bunge, 2004; Fuster, 2008; Miller & Cohen,

2001; Passingham & Wise, 2012; Sreenivasan et al., 2014). Interestingly, these theories differ with regard to the representational depth that they ascribe to the PFC. For instance, Miller & Cohen (2001) proposed in their guided-activation theory that prefrontal activity reflects the maintenance of goals and the means for their achievement. Passingham & Wise (2012), on the other hand, emphasized the abstract nature of prefrontal goal representations and stressed that the means for their achievement are specified further downstream in the processing hierarchy. The dissociation of goal setting and rule activation in our study clearly favors a distinction between goal representations themselves and the representations of their behavioral implications.

This view is furthermore supported by recent work on the implementation of verbally instructed behavior. Hartstra et al. (2011) asked participants to implement different types of symbolic instructions (i.e., either mappings of stimuli to responses or mappings of different stimulus attributes) that were either new or practiced prior to the experiment. It was found that the left IFJ represented new instructions regardless of their type, whereas the bilateral intraparietal sulci were specifically involved in the preparation of stimulus-response (SR) mappings, regardless of their novelty. This indicates that rule-guided behavior might rely on the interplay between domain-general goal representations in the PFC and modality-specific brain areas in posterior cortices that are involved in rule implementation. Such a distinction is also in accord with recent single-cell recordings in macaque monkeys during visual categorization tasks (e.g., Crowe et al., 2013; Goodwin et al., 2012; Merchant et al., 2012). For instance, Goodwin et al. (2012) recorded simultaneously from neurons in the principal and intraparietal sulci and found that the former exhibited earlier and stronger coding of rule-dependent categories than the latter. Furthermore, Crowe et al. (2013) recently demonstrated that signals about upcoming task

rules are transmitted unidirectionally from prefrontal to parietal neurons, possibly reflecting a single-cell substrate of the transformation of abstract goals into specific action rules.

An open issue pertains to the exact mechanism through which the IFJ and its network exert control over novel task goals. One likely candidate is the top-down modulation of the preparatory activation levels in category-specific sensory cortices. Previous studies have shown that effective preparation is associated with regulatory adjustments in extrastriate visual areas that are implicated in processing task-relevant visual information (Wylie et al., 2006; Yeung et al., 2006). Connectivity analyses have identified the IFJ as source of such feature-based top-down modulations (Zanto et al., 2010; Baldauf & Desimone, 2014), and TMS over the IFJ results in diminished category selectivity in visual cortex, which is moreover predictive of subsequent performance impediment in a working-memory task (Lee & D'Esposito, 2012; Zanto et al., 2011). Accordingly, it is reasonable to assume that the IFJ is part of a neural network that facilitates updating of task goals via anticipatory adjustments in task-specific neural circuitries.

IPS and the activation of response sets

The results of experiments 2 and 3 shed new light on the contribution of the left IPS to preparatory control. In previous work, the IPS has been ascribed a prominent role in sensorimotor transformations (Andersen & Buneo, 2002; Cohen & Andersen, 2002), connecting cognitive, perceptual, and motor codes (Gottlieb, 2007). The left IPS in particular has been linked with motor aspects of cognition such as motor attention (Rushworth et al., 2001), effector choice (Cui & Andersen, 2007; 2011), and action intentions (Hamilton & Grafton, 2006). Based on these findings, it has been proposed that the left IPS constitutes the

top of the motor hierarchy, presumably via projections to the premotor cortex where, in turn, a specific motor program is selected (Davare et al., 2010; Rice et al., 2006; Taubert et al., 2010; Tunik et al., 2005; 2007). These considerations fit well with our conclusion that the IPS and its network are involved in the translation of abstract task goals into specific action rules to guide task implementation upon the appearance of a target stimulus. The results of experiment 3 further substantiated this view by indicating that TMS over this region can also cause interference with task goal updating, but that the critical time window occurs later than with IFJ stimulation, namely when the specification of response sets is required. This study also replicated our observation that parietal TMS affected performance at the level of accuracy. This is consistent with our view that the IPS and its network contribute to stages of preparation that are proximate to task implementation. Accordingly, TMS over this region may lead to direct confusion of response sets, resulting in inaccurate rather than delayed performance.

Applying TMS at different time points may generally offer a promising approach for future research to fully characterize the crosstalk between frontoparietal areas during task preparation. For instance, the IFJ and the IPS could both be stimulated at different timings within the same group of participants. Moreover, combining TMS with additional imaging methods may help to reveal the neural mechanisms that mediate behavioral effects of TMS (see Taylor et al., 2007; Feredoes et al., 2011; Higo et al., 2011; Zanto et al., 2011; 2013).

Implications for cognitive control of human behavior

Our findings have broad implications given that the distinction between abstract and action-related control components is applicable to a variety of

paradigms. For instance, Derrfuss et al. (2004; 2005) argued that interference in the classical Stroop task can similarly be decomposed into a task component (i.e., interference between the goals to name either the ink color or the meaning of a word) and a response component (i.e., interference between the respective responses associated with the ink color and word meaning of a given stimulus). In a similar vein, Rushworth et al. (2002), distinguished between an 'attentional set' and an 'intentional set' in order to differentiate cognitive conflict that is induced either by competing stimulus dimensions or by incompatible response-selection rules. Clearly, further research will be necessary to examine the transfer of our findings to other paradigms, yet it is tempting to consider that the interplay of abstract goals and response sets reflects a cardinal principle of cognitive control. This idea is supported by an existing body of research that points to the level of abstraction as a central characteristic in the neural architecture of cognitive control. Ever since the seminal experiment by Koechlin et al. (2003), numerous studies have indicated that the PFC is organized along a rostral-caudal gradient, with more anterior regions being involved in increasingly higher-order control functions (e.g., Badre & D'Esposito, 2007; Badre et al., 2010; Desmet et al., 2011; Kim et al., 2011; Nee & Brown, 2013). Our results thus corroborate the validity of distinguishing cognitive control functions based on their abstraction levels and furthermore highlight that such differences are not only relevant for the organization of the frontal lobe itself, but also for its interaction with other brain areas.

Conclusion

Our study shows that TMS over prefrontal and parietal cortices has dissociable effects on task preparation in humans. While TMS over the IFJ perturbed the capacity to update the general context of a task episode, TMS over

the IPS interfered with the specification of the resulting SR rules. These findings demonstrate that effective task preparation entails distinct types of cognitive control processes and elucidate how prefrontal and parietal cortices may interact in the pursuit of behavioral goals.

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Figure captions:

Figure 1: Single trial structure of the different block types employed in experiments 1 and 2. In Task Goal Blocks (left panel), stimuli were classified according to two different categorization rules (shape or color) that could repeat or alternate across trials. In the shape task, participants were instructed to respond with the left hand to a square, and with the right hand to a circle. In the color task, participants were instructed to respond with the left hand to a blue stimulus, and with the right hand to an orange stimulus. Half of the blocks were performed with the left and right middle fingers (**A**) and the other half with the left and right ring fingers (**B)**. In Response Set Blocks (right panel), stimuli were classified according to only one of the categorization rules, but the response set used for task implementation (middle fingers or ring fingers) could repeat or alternate across trials. Half of the blocks required color categorization (**C**), and the other half classification of shape (**D**).

Figure 2: Illustration of TMS navigation in experiment 1 (**A**) and experiment 2 (**B**), based on the results of a meta-analysis of 45 cued task-switching experiments. The upper panel displays the results of the meta-analysis overlaid on the template of the Montreal Neurological Institute. The peak coordinates of the meta-analysis, displayed in red in the lower panel, were used as a guide for positioning the coil over IFJ (-40, 4 30) and IPS (-34, -56, 43) by means of frameless stereotaxic neuronavigation. The coronal sections of the lower panel also display the position of the coil center, where the magnetic field is maximal, relative to the subject's skull (blue markers). Yellow spheres indicate the direction of the current flow (distance between two spheres = 1 cm). The average distance between the skull and the target site across participants was 2.36 cm in experiment 1, and 2.45 cm in experiment 2. Note that the application of TMS trains also affects the brain tissue between the skull and the target site.

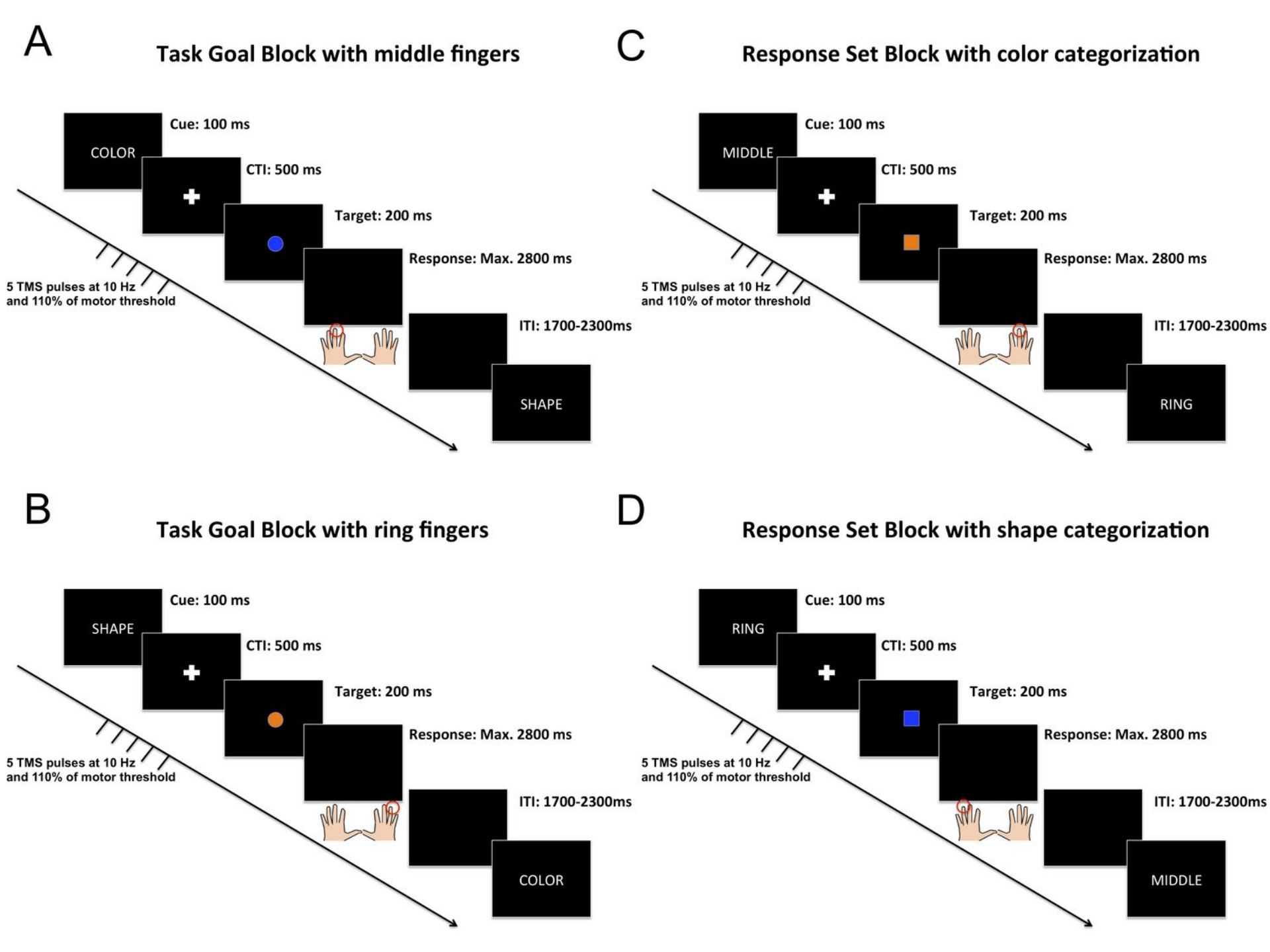
Figure 3: Reaction times (**A**) and error rates (**B**) of experiments 1 (left) and 2 (right) as a function of the target site, block type, and trial transition. Note: The displayed values are means and within-subject confidence intervals (calculated according to Loftus & Massen, 1994). Stars indicate significant differences between repetition and switch trials as well as differences in switch costs between target and control site stimulation.

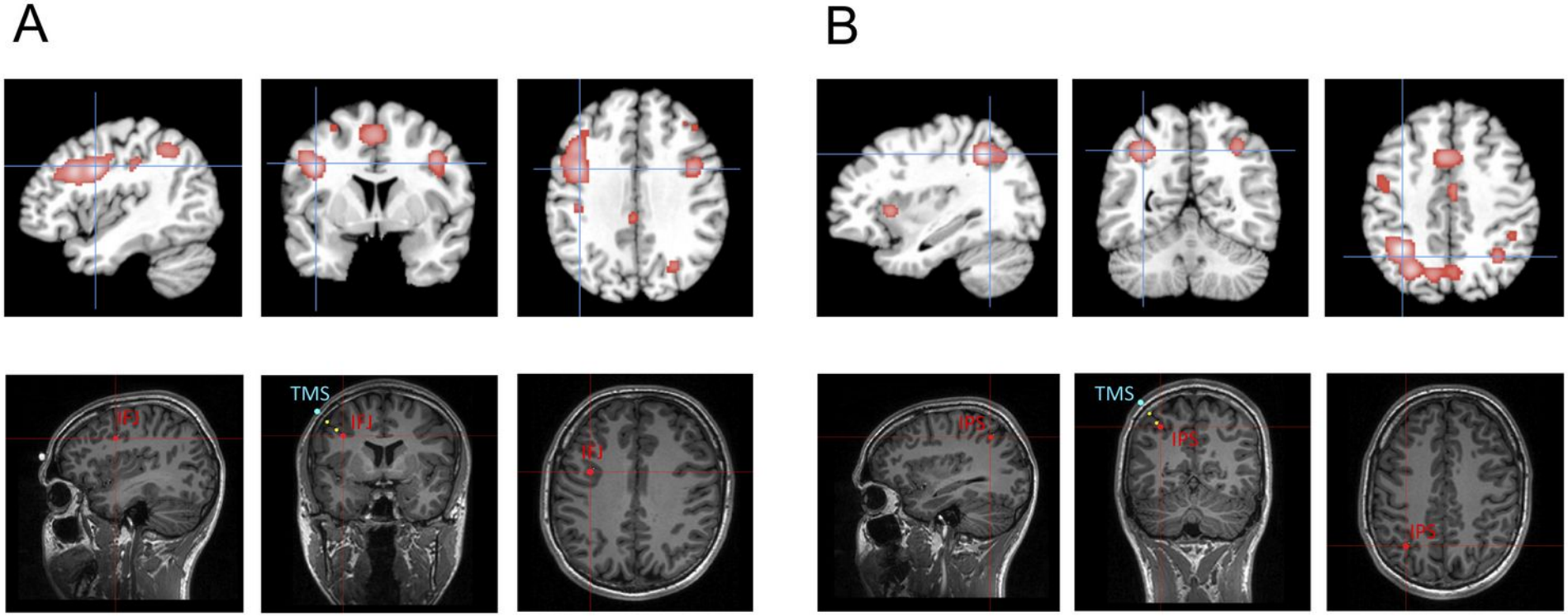
Figure 4: Pooled analysis of results across experiments 1 and 2. Performance on each block type is expressed as difference between switch trials and repetition trials using inverse efficiency scores (IES) to integrate speed and accuracy into a single measure. IES are computed by dividing the reaction time of a design cell by the percentage of correct responses. Note: The displayed values are means and standard errors. Stars indicate significant differences in switch costs between target site and control site stimulation.

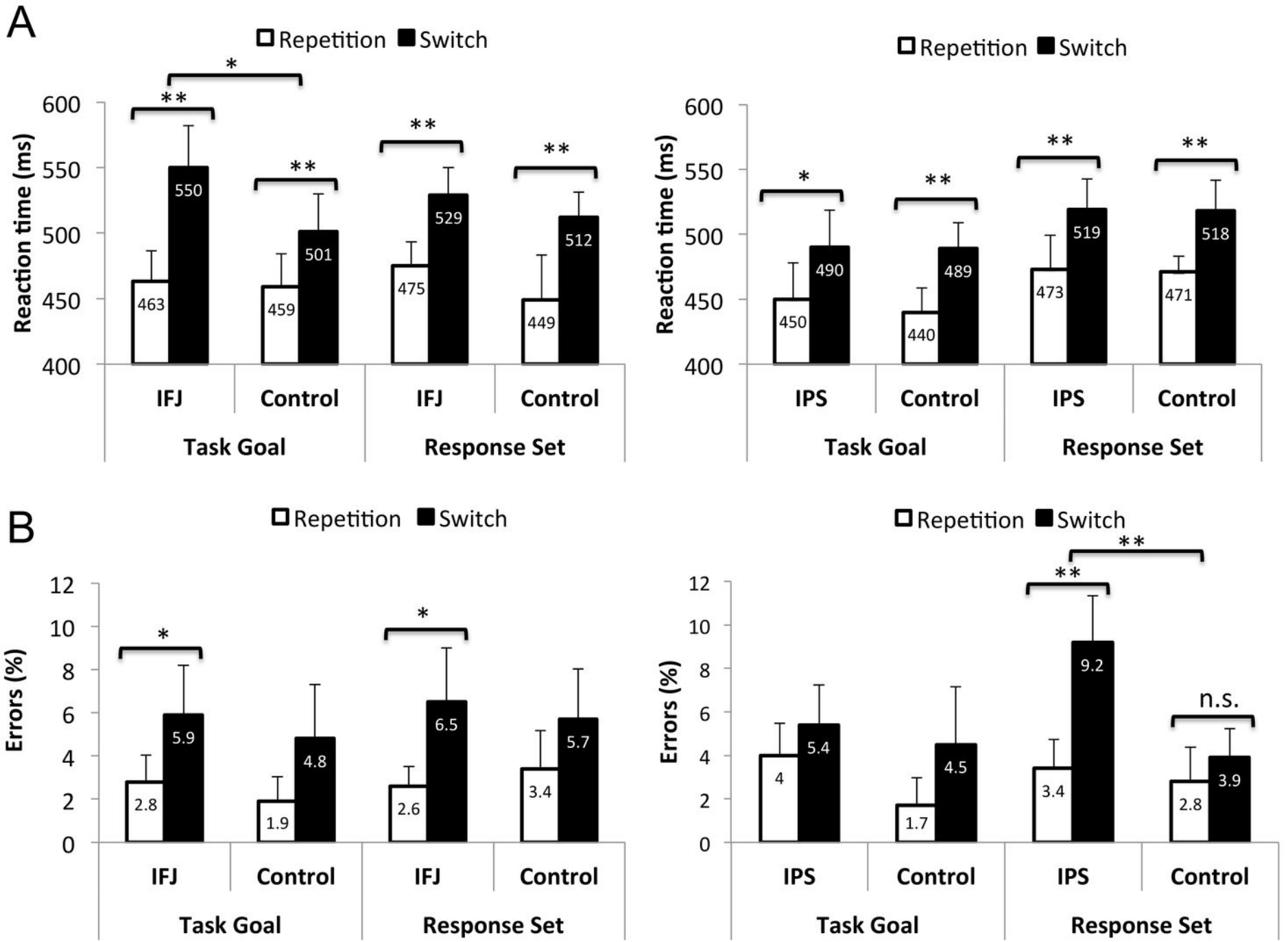
Figure 5: Illustration of the setup of experiment 3. Single-trial structure of the experimental paradigm (**A**). In this experiment, participants completed only TGBs using their left and right middle fingers throughout all blocks. The TMS

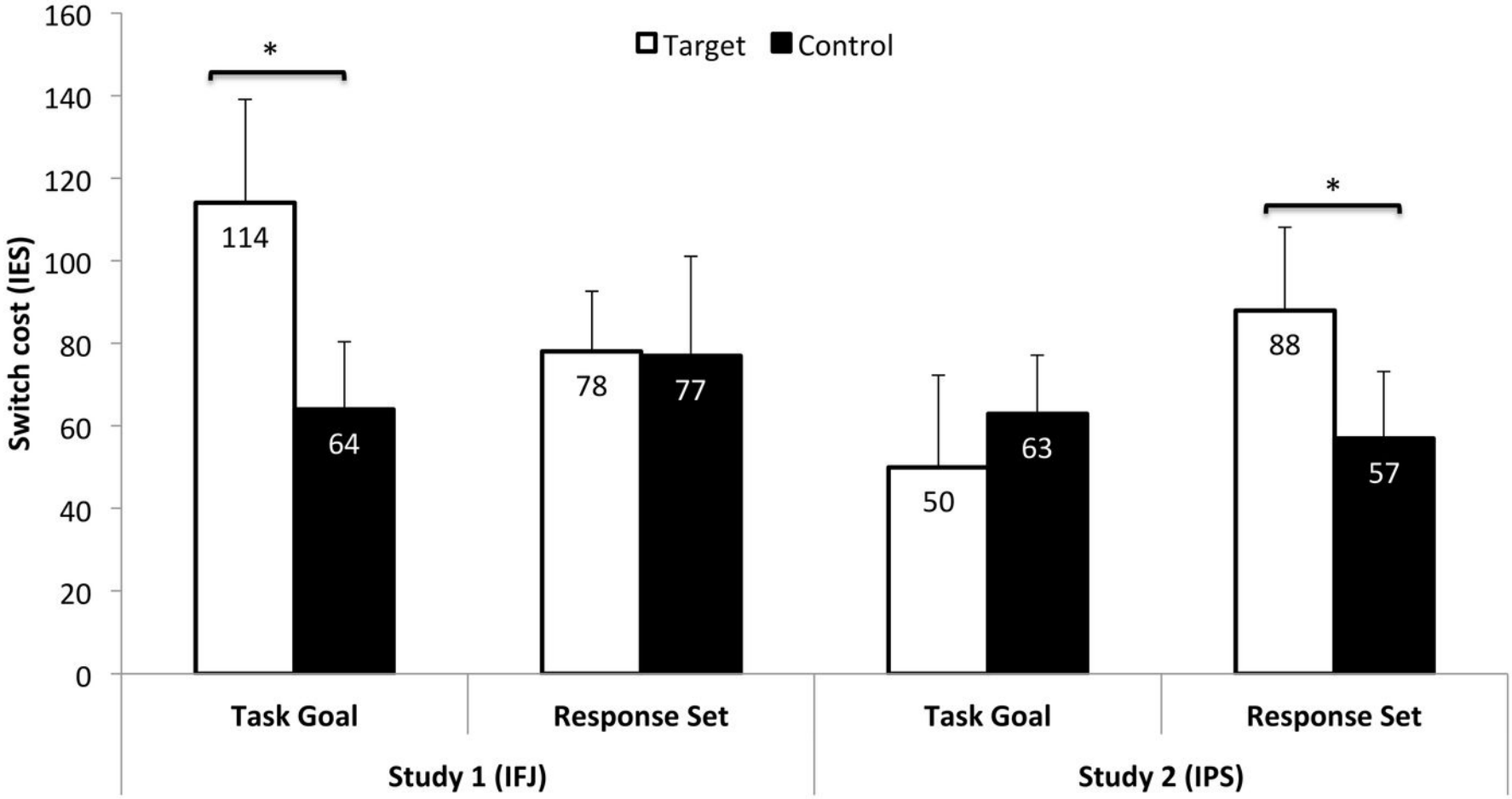
pulses were time-locked to the onset of the target stimulus to affect the final preparation stages. To avoid stimulation at the time of a response, the number of pulses was reduced to three pulses. Localization of the parietal target site (**B**) was identical as to experiment 2 (MNI coordinate: -34, -56, 43). The coronal sections of the lower panel also display the position of the coil center, where the magnetic field is maximal, relative to the subject's skull (blue markers). Yellow spheres indicate the direction of the current flow (distance between two spheres = 1 cm). The average distance between the skull and the target site was 2.41 cm across participants. Note that the application of TMS trains also affects the brain tissue between the skull and the target site.

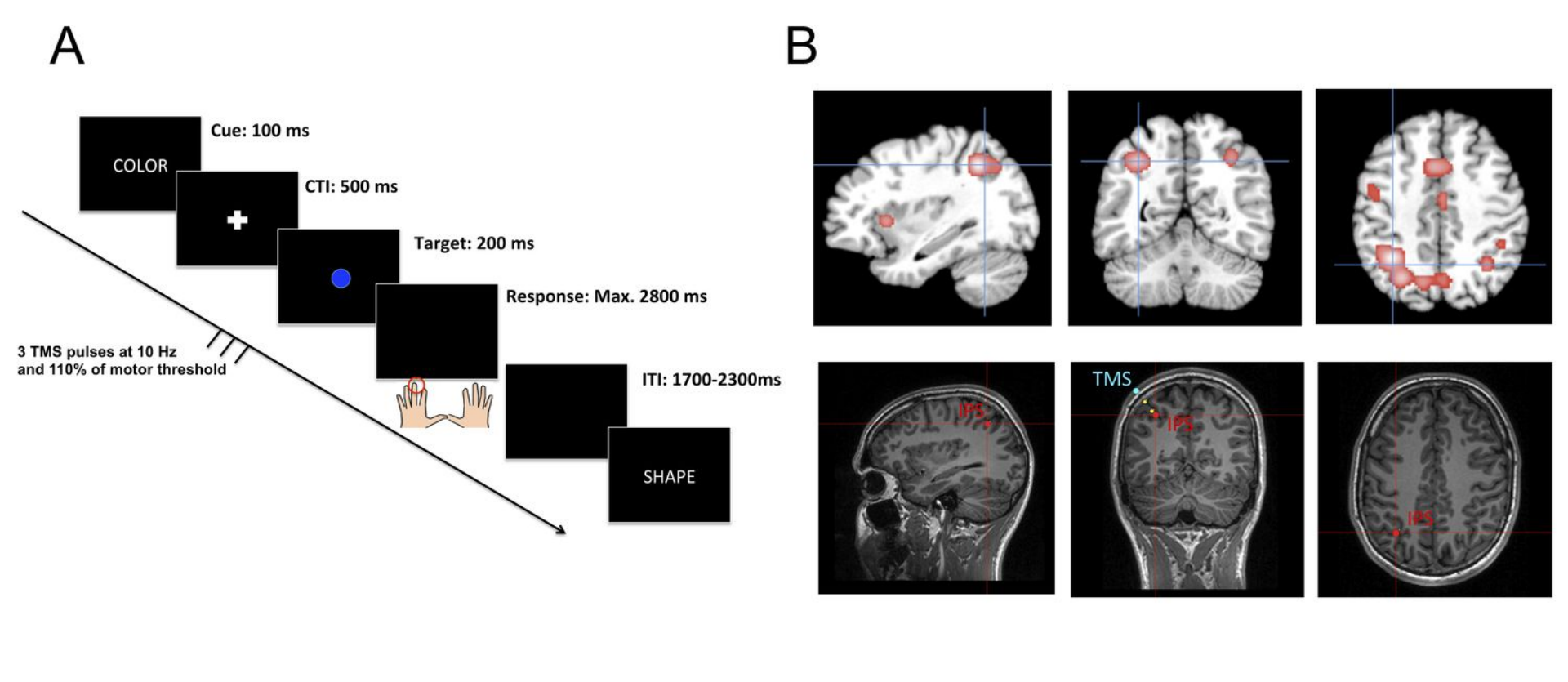
Figure 6: Reaction times (**C**) and error rates (**D**) of experiment 3 as a function of target site and trial transition. Stars indicate significant differences in switch costs with stimulation of the target site and stimulation of the control site. Note: The displayed values are means and within-subject confidence intervals (calculated according to Loftus & Massen, 1994).

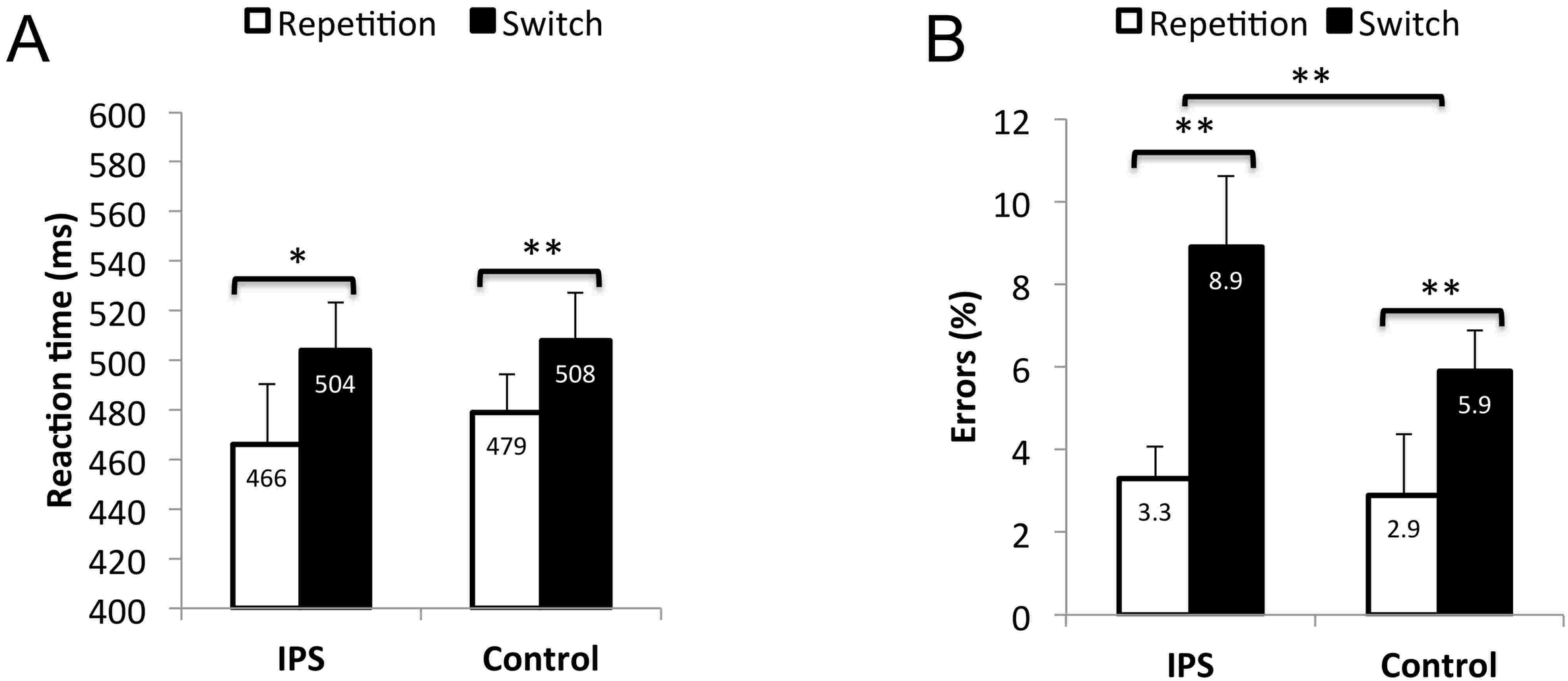

A
Task Goal Block with middle fingers
COLOR
Cue: 100 ms
CTI: 500 ms
Target: 200 ms
Response: Max. 2800 ms
5 TMS pulses at 10 Hz
and 110% of motor threshold
ITI: 1700-2300ms
SHAPE
B
Task Goal Block with ring fingers
SHAPE
Cue: 100 ms
CTI: 500 ms
Target: 200 ms
Response: Max. 2800 ms
5 TMS pulses at 10 Hz
and 110% of motor threshold
ITI: 1700-2300ms
COLOR
C
Response Set Block with color categorization
MIDDLE
Cue: 100 ms
CTI: 500 ms
Target: 200 ms
Response: Max. 2800 ms
5 TMS pulses at 10 Hz
and 110% of motor threshold
ITI: 1700-2300ms
RING
D
Response Set Block with shape categorization
RING
Cue: 100 ms
CTI: 500 ms
Target: 200 ms
Response: Max. 2800 ms
5 TMS pulses at 10 Hz
and 110% of motor threshold
ITI: 1700-2300ms
MIDDLE


A
B
IFJ
TMS
IFJ
IFJ
IPS
TMS
IPS
IPS


A
Repetition
Switch
Reaction time (ms)
600
550
500
450
400
*
**
463
550
459
501
475
529
449
512
IFJ
Control
IFJ
Control
Task Goal
Response Set
450
490
440
489
473
519
471
518
IPS
Control
IPS
Control
B
Errors (%)
12
10
8
6
4
2
0
2.8
5.9
1.9
4.8
2.6
6.5
3.4
5.7
4
5.4
1.7
4.5
3.4
9.2
2.8
3.9
n.s.


160
140
120
100
80
60
40
20
0
Switch cost (IES)
Target
Control
*
*
114
64
78
77
50
63
88
57
Task Goal
Response Set
Task Goal
Response Set
Study 1 (IFJ)
Study 2 (IPS)


A
COLOR
Cue: 100 ms
CTI: 500 ms
Target: 200 ms
Response: Max. 2800 ms
3 TMS pulses at 10 Hz
and 110% of motor threshold
ITI: 1700-2300ms
SHAPE
B
IPS
TMS
IPS
IPS


A
Repetition
Switch
Reaction time (ms)
600
580
560
540
520
500
480
460
440
420
400
*
**
504
508
466
479
IPS
Control
B
Repetition
Switch
Errors (%)
12
10
8
6
4
2
0
**
**
8.9
5.9
3.3
2.9
IPS
Control