The Causal Role of the Lateral Prefrontal Cortex for Task-order Coordination in Dual-task Situations: A Study with Transcranial Magnetic Stimulation

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Abstract

■ Dual tasks are characterized by the requirement for additional task-order coordination processes that schedule the processing order of two temporally overlapping tasks. Preliminary evidence from functional imaging studies suggests that lateral pFC (lPFC) activation correlates with implementing these task-order coordination processes. However, so far, it is unclear whether the lPFC is also causally involved in coordinating task order during dual-task performance and which exact mechanisms are implemented by this brain region. In this study, we addressed these open issues by applying online TMS during a dual-task situation. For this purpose, participants performed a dual task in fixed-order blocks with a constant order of tasks and in random-order block, in which the order of tasks varied randomly and thus demands on task-order coordination were increased. In Experiment 1, TMS of the lPFC compared with control TMS conditions impaired dual-task performance in random-order blocks, whereas performance in fixed-order blocks was unaffected by TMS. In Experiment 2, we tested for the specificity of the lPFC TMS effect on task-order coordination by applying TMS over the preSMA. We showed that preSMA TMS did not affect dual-task performance, neither in fixed-order nor in random-order blocks. Results of this study indicate that the lPFC, but not the preSMA, is causally involved in implementing task-order coordination processes in dual-task situations. ■

INTRODUCTION

In everyday life, we often perform two (or more) tasks simultaneously. Usually, in these multitasking situations severe performance decrements emerge compared with situations in which we perform the same tasks separately. This is shown in different dual-task (DT) paradigms, such as psychological refractory paradigm, in which participants perform two temporally overlapping choice RT tasks and which usually leads to increased processing times and/or error rates compared with single-task situations (Schubert, 1999; Pashler, 1994). The resulting DT costs can be explained by the assumption of a central bottleneck, which requires that central processing stages in the two tasks are processed serially (e.g., Pashler, 1994, and many others). Although the nature of the bottleneck is still a matter of debate and is subjected to structural and/or strategic reasons, we assume in line with other accounts (Schubert, 2008; Luria & Meiran, 2003, 2006; Sigman & Dehaene, 2006; Logan & Gordon, 2001; Meyer & Kieras, 1997; De Jong, 1995) that bottleneck processing requires additional cognitive control processes that schedule the serial processing order of the two tasks and temporally coordinate both task processing streams along the central bottleneck.

Studies employing the fMRI method (Stelzel, Kraft, Brandt, & Schubert, 2008; Szameitat, Lepsien, von Cramon, Sterr, & Schubert, 2006; Schubert & Szameitat, 2003; Szameitat, Schubert, Müller, & Von Cramon, 2002; D'Esposito et al., 1995) as well as lesion studies (Leclercq et al., 2000; Baddeley, Della Sala, Papagno, & Spinnler, 1997; McDowell, Whyte, & D'Esposito, 1997) give rise to the assumption that the lateral pFC (lPFC) plays a crucial role for implementing these task-order coordination processes. However, although the former can only provide correlational evidence for the association of a given brain region with a specific cognitive function (Logothetis, 2008), causal conclusions based on the latter are limited due to different restraints such as a lack in lesion focality (Rorden & Karnath, 2004). Therefore, even despite the evidence from neuroimaging and lesion studies, it is not yet clear whether or not the lPFC has a causal role for task-order coordination in DTs with overlapping task processing. Additionally and equally important, it is still an open question which exact processes are implemented by the lPFC to regulate the processing order of two temporally overlapping tasks. So far, different mechanisms of task-order coordination have been identified (Kübler, Reimer, Strobach, & Schubert, 2018) that operate on different timescales and subserve different

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functions for regulating task order (for an elaborate characterization, see Task-order Coordination and the lPFC section). However, it is not clear for which of those mechanisms the lPFC is recruited. In this study, we used transcranial magnetic stimulation (TMS), a noninvasive brain stimulation method, to address these open issues and to investigate the causal and functional role of the lPFC for task-order coordination in DTs.

Task-order Coordination and the lPFC

Evidence for the involvement of the lPFC in task-order coordination processes comes from neuroimaging studies applying DTs consisting of two temporally overlapping choice RT tasks. In an fMRI study by Szameitat et al. (2002; see also Stelzel et al., 2008), participants performed DT blocks in which they responded to an auditory and a visual stimulus that were presented one after the other with variable, that is, randomly changing, order. Importantly, participants were instructed to respond to both stimuli according to the order of their presentation. Neural activation was contrasted between these random-order blocks and fixed-order blocks, in which both tasks were presented with a constant stimulus order, for example, always the visual stimulus first and the auditory stimulus second. As a result, the authors found increased fMRI activation in a frontoparietal network, including the left lPFC with focal activation peaks close to the inferior frontal junction (IFJ) during random-order compared with fixed-order blocks. The IFJ is located at the intersection point of the precentral sulcus (PrCS) and the inferior frontal sulcus (IFS) and has also been shown to be consistently involved in other cognitive control tasks, such as the task switching, the Stroop, or the *n*-back paradigm (Brass, Derrfuss, Forstmann, & von Cramon, 2005; Derrfuss, Brass, Neumann, & von Cramon, 2005; Derrfuss, Brass, & von Cramon, 2004). In addition, on a behavioral level, the performance of DT trials with changing order compared with fixed order was accompanied by prolonged RTs for both tasks.

These results, that is, increased IFJ activation and prolonged RTs in random-order blocks compared with fixed-order blocks, are in line with the assumption that task-order coordination processes regulating the processing order are involved in DT blocks with varying task order but not in blocks with fixed order. In fixed-order blocks, as the order of tasks remains constant, participants can employ the same scheduling strategy for every trial throughout the entire block. Contrarily, in random-order blocks, the order of tasks varies unpredictably from trial to trial, and participants have to match the task processing order to the order of stimulus presentation. This requires that, across the entire block, participants need to monitor the order of stimuli and to schedule the processing order accordingly. According to several authors (Stelzel et al., 2008; Szameitat et al., 2002), the increased demands on task-order coordination processes during random-order compared with fixed-order blocks result in the additional recruitment of the IFJ, leading to increased neural activation.

Further evidence for the involvement of the lPFC in task-order coordination comes from a related line of research that investigates task coordination on a more fine-grained trial-by-trial level. In an event-related fMRI study, Szameitat et al. (2006) presented a DT consisting of an auditory and a visual choice RT task with varying stimulus order. The presentation of trials with randomly varying stimulus order allowed the authors for distinguishing between two different types of DT trials: same-order trials and different-order trials (see also Luria & Meiran, 2003, 2006; De Jong, 1995). In same-order trials, the task order was the same as compared with the previous trial, for example, in both trials the visual task was performed first and the auditory task was performed second. On the contrary, in different-order trials, the order of tasks was reversed relative to the preceding trial, for example, in the previous trial the visual task was performed first and the auditory task was performed second, but in the next trial the auditory task was performed first and the visual task was performed second. The authors analyzed fMRI activity for both trial types and found increased activation in regions of the left IFJ in different-order trials compared with same-order trials, which was accompanied by increased RTs in different-order compared with same-order trials.

According to Szameitat et al. (2006), trial-specific task-order coordination processes occur in different-order but not in same-order DT trials: In more detail, in different-order trials participants prepare the task order in the current DT trial according to a memory presentation of the task order in the previous trial. Because the stimulus order and thus task-order in different-order trials are reversed relative to the previous trial, participants need to overcome the prepared task order and to adapt the current task order to the correct stimulus order. This explains the additional processing demands in different-order compared with same-order trials and the related IFJ activation. Note that in same-order trials, participants can rely on the task order primed by the previous trial when performing the current trial because task order is repeated.

Although earlier fMRI studies provided rather correlative evidence for the involvement of the lPFC in task-order coordination, the first aim of the current study was to test for a potential causal role of the IFJ in task-order coordination by applying online TMS. Furthermore, we aimed to disentangle possible TMS effects on task-order coordination mechanisms, which can be revealed by a comparison of random-order and fixed-order blocks and task-order coordination mechanisms, which are observable when contrasting same-order and different-order trials. In addition, we wanted to test the specificity of potential TMS effects in the IFJ region by comparing these effects with those resulting from

stimulating an alternative control region; as a candidate control region, we focused on the preSMA in Experiment 2, because the preSMA had recently been shown to be involved in bottleneck processing in DTs (Soutschek, Taylor, & Schubert, 2016).

TMS and Rationale of This Study

We applied online TMS because it allowed us to interfere with cortical information processing in narrowly circumscribed brain regions with high temporal resolution (Bestmann, 2008; Hallett, 2007; Pascual-Leone, Walsh, & Rothwell, 2000). By inducing an electrical field by means of electromagnetic induction, TMS can transiently and reversibly disturb cognitive functions implemented by the stimulated brain site and disrupt participants' task performance, which allows for causal inferences about the targeted brain region (Miniussi, Harris, & Ruzzoli, 2013; Siebner, Hartwigsen, Kassuba, & Rothwell, 2009). Recently, TMS had also been shown to provide reliable findings about different brain regions that are causally linked to the implementation of various cognitive control processes (Taylor, Nobre, & Rushworth, 2007; Chambers et al., 2006; Rushworth, Hadland, Paus, & Sipila, 2002).

In the current study, we presented participants with a DT consisting of an auditory and a visual choice RT task that overlapped in time and applied TMS. The DTs were presented in fixed-order and random-order blocks with the instruction to respond to the tasks in the order of stimulus presentation (Stelzel et al., 2008; Szameitat et al., 2002). Trials within the random-order blocks were further subdivided in same-order and different-order trials (Szameitat et al., 2006). We assessed DT performance under different conditions of TMS by measuring RTs and error rates, that is, the percentage of incorrect responses. Additionally, the accuracy of task-order coordination performance was assessed by analyzing the rates of task-order reversal trials. Note that, in task-order reversal trials, participants' task-order processing is reversed to the presented stimulus order, which reflects nonsuccessful task-order coordination.

We applied an order cue that informed participants about the order of stimuli in the upcoming trial. The logic behind presenting this order cue was to temporally separate task-order coordination from other mechanisms that may be involved in the processing of the DT (but not, specifically, in coordinating task order), such as perceptual or response selection processes (De Jong, 1995). We administered TMS after the presentation of the order cue and before the presentation of the first stimulus to exclusively interfere with task-order coordination but leave these other processes undisturbed. To control for effects of TMS on the cue processing (which might confound the impact of TMS on task-order coordination), we administered an additional control task. In this control task, participants were instructed to respond to the order of stimuli as it was indicated by the instructional order cue. Thus, instead of processing a DT in the correct order, participants were required to process the order cue and indicate its identity with corresponding button presses. As we only changed the instruction for participants in the control task but applied the same stimulus material, demands on visual processing of the order cue should be comparable between the DT and the control task. Hence, if TMS indeed interferes with cue processing, we should find impaired performance in the control task after stimulation. If, alternatively, TMS does not disturb performance in the control tasks, we can infer that stimulation has no effects on processing the order cue.

EXPERIMENT 1

In Experiment 1, we investigated the effects of IFJ TMS on task-order coordination relative to two control TMS conditions (no TMS and vertex TMS). We compared the effect of IFJ TMS on trials in fixed-order blocks and on same-order trials, as well as on different-order trials in random-order blocks. If the IFJ is causally linked to task-order coordination processes that are required in random-order blocks to adjust one's processing order to a changing stimulus order, TMS of the IFJ should result in decreased DT performance relative to control TMS conditions in both same-order and different-order trials; in other words, TMS of the IFJ should lead to slower RTs in random-order blocks compared with the control TMS conditions. In fixed-order blocks, however, demands on task-order coordination are reduced as participants can employ the same scheduling strategy on every single trial. Therefore, TMS of the IFJ should have no effect on the performance in fixed-order blocks. Alternatively, if the IFJ is causally involved in task-order coordination processes that are specific for different-order trials, that is, when the order of tasks changes relative to the preceding trial and memory-based preparation has to be overcome in the current trial, IFJ TMS should result in impaired DT performance compared with control TMS conditions only in different-order trials. In same-order trials and in trials of fixed-order blocks, there is no requirement to change the task order compared with the previous trial. Therefore, TMS of the IFJ should have no effect on the DT performance in these trials. To investigate whether any potential effects of IFJ TMS on task-order coordination are specific for this brain region, we conducted Experiment 2 in which we stimulated the preSMA, a brain region that has been recently shown to be involved in bottleneck processing (Soutschek et al., 2016).

Methods

Participants

Twenty healthy participants (12 women; mean age = 27.3 years, *SD* = 3.2 years) were invited to take part in

the experiment after obtaining written informed consent. To determine an appropriate sample size, we conducted an a priori power analysis using the G*Power program (Faul, Erdfelder, Lang, & Buchner, 2007). For this analysis, we estimated a medium effect size of $f = 0.24$. With an α error probability of .05 and a power ($1 - \beta$ error probability) of .80, the analysis yielded a required sample size of $N = 15$. Note that this number of participants is similar to sample sizes in comparable studies using noninvasive brain stimulation methods in DT situation with temporally overlapping component tasks (Soutschek et al., 2016; Strobach, Soutschek, Antonenko, Floel, & Schubert, 2015). Bearing in mind that this a priori power analysis may underestimate the required sample size and to account for any potential dropout, we decided to invite 20 participants to guarantee sufficient power for analyses. Participants were paid 10 euros per hour for their participation. The experimental protocol conformed to the declaration of Helsinki as well as to common safety guidelines for TMS studies (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). Approval of the local ethics committee was obtained before the commencement of the study. All participants were right-handed, were German native speakers, and had normal or corrected-to-normal vision. For four participants, neuronavigation (see below) failed as a result of technical problems. Those four participants' data could not be included in the analyses. Another participant reported adverse effects of TMS (rapid heartbeat) before commencing the control task (see below), and thus, only her data from the DT blocks could be used for analyses.

Apparatus and Stimuli

Participants performed a DT consisting of an auditory and a visual choice RT task (for a similar DT situation, see Stelzel et al., 2008). Stimuli for the auditory task consisted of three sine wave tones with a frequency of 250, 500, or 1000 Hz presented for 100 msec via headphones. Participants were instructed to respond to the low-, middle-, and high-pitched tones by pressing the keys "Y," "X," and "C" of a QWERTZ keyboard with the ring, middle, and index fingers of their left hand, respectively (note that, in contrast to the more common QWERTY keyboard, on the QWERTZ keyboard the response keys "Y," "X," and "C" are aligned next to each other from left to right). For the visual task, one of three digits ("1," "5," or "9") was presented centrally on a computer screen and subtended approximately 0.52° × 0.31° of the visual angle at a viewing distance of 80 cm. Visual stimuli remained visible for 100 msec, and participants responded to the digits in ascending order by pressing the keys "," (comma), "." (period), and "-" (dash) of a QWERTZ keyboard with the index, middle, and ring finger of their right hand, respectively.

Design and Procedure

Each DT trial started with the presentation of a central fixation cross (0.42° × 0.42°) for 1200 msec (Figure 1), followed by a centrally presented instructional order cue (0.52° × 0.31°), indicating the presentation order of both stimuli in the upcoming trial. This procedure was used so that participants execute task-order coordination processes before target presentation and, thus, temporally isolate them from other cognitive processes that are necessary for performing both component tasks (De Jong, 1995). The instructional cue lasted for 100 msec and was either the letter "T" or the letter "Z" in trials in which the tone task was presented first or the digit task was presented first, respectively. The cue target interval (CTI) was set to 600 msec. After the CTI, both target stimuli were presented for 100 msec each with a constant SOA of 200 msec. After the presentation of both target stimuli, the screen was cleared for a response period of 2900 msec, resulting in a total trial time of 5000 msec. Participants were instructed to react as fast and as accurately as possible to both stimuli according to the order of their presentation.

Participants performed the DT in two types of blocks. In fixed-order blocks, the presentation order of both stimuli remained constant throughout the entire block. On half of the fixed-order blocks, the auditory stimulus was presented first, on the other half of the fixed-order blocks, the visual stimulus was presented first. In random-order blocks, the presentation order of both stimuli varied randomly from trial to trial and unpredictably to participants. The instructional order cue was

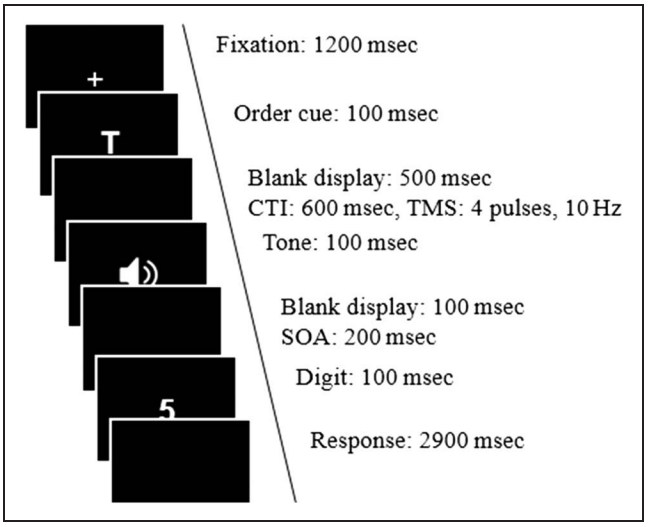

Figure 1. The time course for an exemplary DT trial in which the tone task was presented as the first task. Following a fixation cross an instructional order cue provides information of the presentation order of both stimuli in the upcoming trial. On TMS trials, four TMS pulses were administered with a frequency of 10 Hz during the CTI. After the CTI, both stimuli were presented for 100 msec with an SOA of 200 msec. The maximum time for both responses was set to 2900 msec.

presented in both block types. Fixed-order blocks consisted of 40 trials. Thirty-six of these trials were regular DT trials with two stimuli that required two responses. To discourage the usage of a response grouping strategy (Pashler & Johnston, 1989), the remaining 10% of the trials within fixed-order blocks were catch trials, in which the first task was omitted and only the second task was presented (Luria & Meiran, 2003). Random-order blocks consisted of 36 trials; in half of these trials the auditory stimulus was presented first, and in the other half the visual stimulus was presented first. Additionally, on 18 trials, the order of stimuli was repeated compared with the preceding trial, whereas on the remaining 18 trials, stimulus order was reversed relative to the previous trial.

The experimental session consisted of a practice phase and an experimental phase. The practice phase started with four single-task blocks, which were followed by two fixed-order and two random-order practice blocks. In the subsequent experimental phase, half of participants performed four fixed-order blocks and eight random-order blocks in the following sequence of blocks: two fixed-order blocks, four random-order blocks, two fixed-order blocks, and four random-order blocks. The remaining participants performed the same blocks in the reversed order. Subsequently, participants conducted a control task (see below).

TMS Procedure

TMS was applied with the eXimia Navigated Brain Stimulation System (Nexstim) using a focal bipulse figure-eight coil with a mean winding diameter of 50 mm and an outer winding diameter of 70 mm. Coil positioning over the IFJ was guided by neuronavigation software employing a Polaris Spectra 3D Optical tracking unit (NDI) that enables the recording of the real-time position and orientation of the TMS coil with respect to the participant's head with an accuracy below .035 mm. This procedure is based on a coil specific 3-D model, individual's structural MR images, and the stimulator parameters. Using this system, stimulation was applied to the IFJ, whereas the distance between the target area and the peak electric field was recorded for every TMS pulse. Structural T1 scans for each participant were acquired with a 3.0-T Siemens Magnetom Trio scanner using a 32-channel radiofrequency head coil beforehand.

TMS was administered in half of the trials of each block excluding catch trials and the first trial of each block. Stimulation was applied in trains of four pulses with a frequency of 10 Hz and an intensity of 110% of the individual's motor threshold (M = 37.6%), starting with cue offset and lasting for 300 msec (for a similar TMS protocol in a study on cued task switching, see Muhle-Karbe, Andres, & Brass, 2014). Stimulation was applied during the CTI to exclusively interfere with task-order coordination processes, but not with Task 1 or Task 2 processing. Note that with the last impulse delivered 200 msec before the presentation of the first stimulus and the perturbing effects of individual TMS pulses typically lasting for 80–120 msec (Miniussi et al., 2013; Bestmann, 2008), any TMS effects on stimulus processing, which should only occur after presentation of the first stimulus, are rather unlikely. Moreover, due to the short-lasting effect of online TMS (Rossi et al., 2009; Siebner et al., 2009) and the total trial duration of 5000 msec, carryover effects of stimulation on subsequent trials can be excluded. Coil position was varied blockwise, and TMS was applied either to the IFJ or to the vertex. In addition to trials without stimulation, vertex TMS was chosen as a second control condition to rule out that any observed effects may have been caused by confounding nonneural effects of TMS (Jung, Bungert, Bowtell, & Jackson, 2016). The IFJ TMS site was located at the junction between the IFS and the inferior part of PrCS based on the individual's structural brain scan (Derrfuss, Brass, von Cramon, Lohmann, & Amunts, 2009). The PrCS was defined as the first major sulcus anterior and running parallel to the central sulcus, and the IFS was defined as the first major sulcus located dorsal to the anterior ascending ramus of the Sylvian fissure and approximately running in a posterior–anterior direction. An average distance of 1.81 mm (SD = 1.04 mm) between the individual IFJ TMS site and the peak electric field was estimated throughout the entire experiment based on the real-time estimation of the electric field induced on the cortical surface by TMS. The vertex was located at the Pz electrode position according to the international 10–20 system. The coil was orientated in anterior direction perpendicular to the inferior prefrontal sulcus and the medial longitudinal fissure for the IFJ TMS site and the vertex, respectively, resulting in TMS pulses with a posterior–anterior initial current direction. Coil position between both target areas was changed after every second random-order block in a row of four random-order blocks, which guaranteed an equal distribution of TMS trials between both the IFJ TMS and vertex TMS conditions. Half of the participants started the experimental session with the TMS coil positioned over the IFJ TMS site, and the other half started the session with the coil positioned over the vertex.

Control Task

As TMS was applied after the presentation of the instructional order cue, potential effects of stimulation could, theoretically, also be explained by interference with the processing of the instructional order cue instead of disturbed task-order coordination. To exclude this confound, after finishing DT blocks, participants performed a control task to assess any effects of TMS on the processing of the instructional cue. For this purpose, participants were presented two random-order blocks consisting of 36 trials. Instead of responding to both target stimuli,

participants were instructed to indicate the order of tasks as signaled by the instructional cue presented at the beginning of each trial. Participants responded to trials in which the tone task was presented first by pressing the "C" key with their left index finger and to trials on which the digit task was presented first by pressing the "," key with their right index finger. As in the DT blocks, a train of four TMS pulses with a frequency of 10 Hz and an intensity of 110% of the motor threshold was applied in half of the trials after the offset of the instructional cue. The coil position was changed after the first block, with half of the participants performing the first block with the coil positioned over the IFJ TMS site and the second block with the coil positioned over the vertex TMS site. For the other half of the participants, the order of the coil positioning was reversed.

Statistical Analysis

For the DT, we analyzed median RTs and error rates separately for the first task (Task 1, RT1) and the second task (Task 2, RT2). As an additional measure, we analyzed task-order reversal rates (trials on which participants' response order was reversed compared with stimulus order). For these analyses, trials with grouped (interresponse interval = RT2 − RT1 + SOA < 200; Miller & Ulrich, 2008) or omitted responses (M = 4.4%) were excluded from the data set and, exclusively for the RT analyses, trials with erroneous responses (M = 8.0%) and task-order reversals (M = 2.2%). For the control task, RTs and error rates were analyzed. ANOVAs and subsequent paired-sample t tests (two-tailed) as planned comparisons were calculated. A significance threshold of 5% was used for all analyses. The p values of the ANOVAs were adjusted according to the Greenhouse–Geisser correction when necessary.

Results

Task 1

The first analysis tested the effect of IFJ TMS on Task 1 performance in fixed-order, same-order, and different-order trials. Participants' median RT1 and error rates were analyzed using a 3 × 3 ANOVA with the within-subject factors Trial Type (fixed-order trials, same-order trials, different-order trials) and TMS (no TMS, vertex TMS, IFJ TMS). If our hypothesis holds true and IFJ TMS distinctively modulates performance on the different trial types, we should find a significant interaction of the factors trial type and TMS.

The significant main effect of the factor Trial Type, $F(2, 30) = 7.03$, $p < .01$, $\eta_p^2 = .32$, revealed an increase in RT1 from fixed-order trials (M = 811 msec) to different-order trials (M = 889 msec), $t(15) = 2.58$, $p = .02$, indicating the occurrence of task-order coordination processes. The significant main effect of TMS, $F(2, 30) = 5.62$, $p = .02$, $\eta_p^2 = .27$, revealed that TMS over the IFJ increased RT1 (M = 882 msec) compared with no TMS (M = 837 msec), $t(15) = 2.22$, $p = .04$, and vertex TMS (M = 819 msec), $t(15) = 2.55$, $p = .02$.

Most importantly, this TMS effect was modulated by the factor Trial Type, $F(4, 60) = 2.67$, $p = .04$, $\eta_p^2 = .15$, suggesting that IFJ TMS had distinctive effects in fixed-order, same-order, and different-order trials. Pairwise comparisons revealed no differences between TMS conditions for the fixed-order trials (all ps > .50; see Figure 2). For the same-order trials, IFJ TMS resulted in increased RT1 (M = 890 msec) relative to no TMS

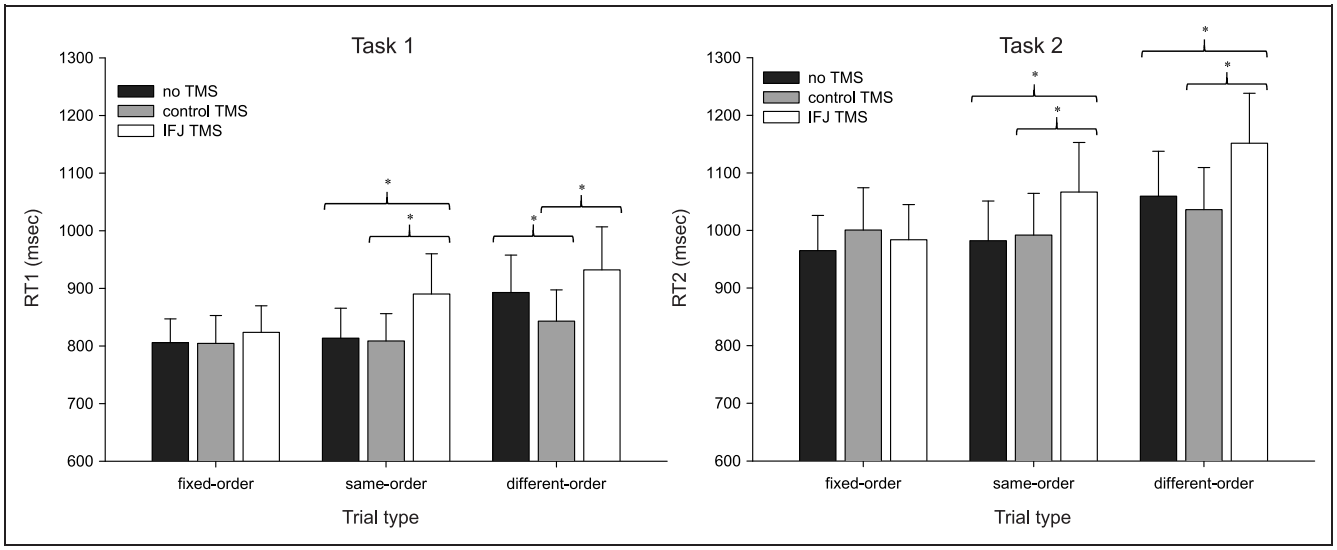

Figure 2. Mean RTs for Task 1 and Task 2 as a function of trial type and TMS conditions for Experiment 1. Error bars reflect the *SEM*. Asterisks indicate significant differences between TMS conditions. Left: RTs for Task 1, right: RTs for Task 2.

(M = 814 msec), $t(15) = 3.01$, $p < .01$, and vertex TMS (M = 809 msec), $t(15) = 2.92$, $p = .01$. Vertex and no TMS conditions did not differ, $t(15) = 0.35$, $p = .73$. A similar pattern was detected for different-order trials: RT1 after IFJ TMS (M = 932 msec) was, by trend, prolonged in comparison to no TMS (M = 893 msec), $t(15) = 1.77$, $p = .09$, and significantly slowed compared with vertex TMS (M = 843 msec), $t(15) = 2.85$, $p = .01$. Additionally, RT1 in different-order trials was approximately 49 msec faster after vertex TMS compared with no TMS, $t(15) = 2.30$, $p = .04$, which can be explained by unspecific TMS effects attributable to increased alertness due to acoustic stimulation or aversiveness (Marzi et al., 1998; Nikouline, Ruohonen, & Ilmoniemi, 1999).

For the error rate in Task 1, we did not find any significant effects of the factors trial type, $F(2, 30) = 1.34$, $p = .28$, $\eta_p^2 = .08$, and TMS, $F(2, 30) = 1.17$, $p = .32$, $\eta_p^2 = .07$, nor of their interaction, $F(4, 60) = 2.06$, $p = .10$, $\eta_p^2 = .12$ (for error rates, see Table 1).

Taken together, data of Task 1 showed that TMS of the IFJ results in impaired DT performance in random-order blocks, whereas it has no effect on trials in fixed-order blocks. This was indicated by significant differences in RT1 between the IFJ TMS condition and both control TMS conditions in same-order trials, as well as a significant RT difference in different-order trials after IFJ TMS compared with control TMS and a respective trend for the comparison between IFJ TMS and no TMS.

Task 2

To test whether IFJ TMS also disrupts performance on Task 2, we analyzed participants' median RT2 and error rates using the same 3 × 3 ANOVA as for the analysis of the Task 1 data. Again, the significant effect of Trial Type on RT2, $F(2, 30) = 7.35$, $p < .01$, $\eta_p^2 = .33$, indicated the occurrence of task-order coordination processes. Furthermore, we found a significant main effect of TMS, $F(2, 30) = 6.09$, $p = .02$, $\eta_p^2 = .29$, indicating increased RT2 after IFJ TMS (M = 1067 msec) compared with no TMS (M = 1002 msec), $t(15) = 2.88$, $p = .01$, and vertex TMS (M = 1010 msec), $t(15) = 2.34$, $p = .02$.

More importantly and similar to RT1, the significant interaction Trial Type × TMS, $F(4, 60) = 4.14$, $p = .02$, $\eta_p^2 = .21$, suggested that TMS effects differed between the different trial types. In fixed-order trials, IFJ TMS did not increase RT2 compared with both control TMS conditions (both ps > .55). In same-order trials, RT2 was prolonged after IFJ TMS (M = 1067 msec) compared with no TMS (M = 982), $t(15) = 2.95$, $p = .01$, and vertex TMS (M = 993 msec), $t(15) = 3.33$, $p < .01$. No difference was found between both the no TMS and vertex TMS conditions, $t(15) = 0.63$, $p = .54$. Also in different-order trials, IFJ TMS resulted in increased RT2 (M = 1151 msec) compared with no TMS (M = 1059 msec), $t(15) = 4.12$, $p = .001$, and vertex TMS (M = 1036 msec), $t(15) = 2.91$, $p = .01$, whereas the latter two conditions did not differ, $t(15) = 0.75$, $p = .46$.

Regarding error data in Task 2, we found a significant main effect of the factor TMS, $F(2, 30) = 4.43$, $p = .02$, $\eta_p^2 = .23$, indicating an unspecific TMS effect (see Table 1): For all trial types, the error rate was reduced in the no TMS condition (M = 4.46%) compared with the IFJ TMS condition (M = 6.60%), $t(15) = 2.65$, $p = .02$, and the vertex TMS condition (M = 5.73%), $t(15) = 2.25$, $p = .04$. Both, the IFJ and vertex TMS conditions did not differ, $t(15) = 1.12$, $p = .28$. The effect of Trial Type, $F(2, 30) = 2.19$, $p = .13$, $\eta_p^2 = .13$, and the interaction of Trial Type × TMS, $F(4, 60) = 0.28$, $p = .89$, $\eta_p^2 = .02$, did not reach significance.

In summary and similar to Task 1, data from Task 2 show that TMS of the IFJ results in disrupted DT

Table 1. Mean Rates of Errors for Task 1 and Task 2 in Percentage (and Standard Deviation) from Experiment 1 and Experiment 2 as a Function of Trial Type and TMS Condition

	Trial Type					
	Fixed-order Trial		*Same-order Trial*		*Different-order Trial*	
TMS Condition	*Task 1*	*Task 2*	*Task 1*	*Task 2*	*Task 1*	*Task 2*
Experiment 1						
No TMS	2.43% (2.46%)	3.65% (3.72%)	3.47% (2.78%)	4.43% (3.94%)	5.38% (4.36%)	5.30% (4.34%)
Control TMS	4.51% (6.72%)	4.86% (4.81%)	3.82% (3.19%)	5.73% (5.78%)	3.13% (4.04%)	6.60% (6.24%)
IFJ TMS	3.13% (3.35%)	4.86% (3.72%)	6.08% (5.85%)	7.29% (7.58%)	5.20% (6.49%)	7.64% (6.37%)
Experiment 2						
No TMS	3.70% (6.03%)	5.86% (8.04%)	3.70% (4.07%)	6.02% (6.52%)	9.03% (7.52%)	9.34% (7.38%)
Control TMS	3.40% (3.51%)	4.01% (4.49%)	6.17% (7.89%)	7.25% (5.88%)	6.64% (6.95%)	8.03% (6.73%)
preSMA TMS	5.71% (11.45%)	7.87% (16.09%)	4.17% (7.40%)	7.56% (9.13%)	6.48% (6.94%)	10.49% (10.85%)

performance in same-order and different-order trials compared with control TMS conditions. In fixed-order trials, however, IFJ TMS does not affect DT performance.

Task-order Reversals

We analyzed task-order reversal rates as an additional measure for task-order coordination processes. On average, participants responded to both tasks in a reversed order compared with stimulus presentation on 2.20% of all trials. The percentage of task-order reversals was, thus, rather low (see Table 2), most probably due the usage of the instructional order cue at the beginning of each trial. Despite this low rate of task-order reversals and the thereby reduced statistical power, which should be kept in mind as caveat, we conducted a 3 × 3 ANOVA with the within-subject factors Trial Type (fixed-order trials, same-order trials, different-order trials) and TMS (no TMS, vertex TMS, IFJ TMS). This ANOVA revealed a significant main effect of the factor Trial Type, $F(2, 30) = 7.93$, $p < .01$, $\eta_p^2 = .35$, indicating that participants adhered to the correct task order with different success in different trial conditions: Task-order reversal rate increased from fixed-order trials ($M = 0.55\%$) to same-order trials ($M = 2.23\%$), $t(15) = 2.03$, $p = .03$, and from same-order trials to different-order trials ($M = 4.05\%$), $t(15) = 2.22$, $p = .02$. The effect of the factor TMS was not significant, $F(2, 30) = 1.97$, $p = .16$, $\eta_p^2 = .12$.

However, there was a tendency for a significant interaction between the factors trial type and TMS, $F(4, 60) = 2.27$, $p = .07$, $\eta_p^2 = .13$. A closer inspection of the data revealed that this interaction is mostly driven by the fact that in same-order trials participants produced more task-order reversals after IFJ TMS ($M = 3.30\%$) relative to the vertex TMS condition ($M = 1.39\%$), $t(15) = 2.55$, $p = .02$. There was also a tendency for an increased task-order reversal rate compared with the no TMS condition ($M = 2.00\%$); however, this comparison just failed significance, $t(15) = 1.89$, $p = .07$. In different-order trials, task-order reversal rate was significantly increased after IFJ TMS ($M = 4.69\%$) compared with no TMS ($M = 3.13\%$), $t(15) = 2.26$ $p = .04$, and numerically higher after IFJ TMS compared with vertex TMS ($M = 4.34\%$); however, this trend failed to pass the statistical threshold, $t(15) = 1.18$, $p = .25$. On fixed-order trials, IFJ TMS did not increase task-order reversal rates compared with control conditions.

Control Task

To control for a possible confounding influence of TMS on cue processing, we analyzed participants' performance in the control task, which was conducted after the DT blocks. For that purpose, we analyzed participants' median RTs by using a 2 × 3 ANOVA with the within-subjects factors Trial Type (same-order trials, different-order trials) and TMS (no TMS, vertex TMS, IFJ TMS). The main effect of Trial Type, $F(1, 14) < 1$, $p = .43$, $\eta_p^2 = .05$, did not reach significance, neither did the main effect of TMS, $F(2, 30) < 1$, $p = .80$, $\eta_p^2 = .02$, nor the interaction between Trial Type and TMS, $F(4, 60) < 1$, $p = .67$, $\eta_p^2 = .03$. A similar pattern was found for the error data. A 2 × 3 ANOVA with the within-subject factors Trial Type (same-order trials, different-order trials) and TMS (no TMS, vertex TMS, IFJ TMS) did not reveal a significant effect of Trial Type, $F(1, 14) < 1$, $p = .84$, $\eta_p^2 < .01$, TMS, $F(2, 28) < 1$, $p = .46$, $\eta_p^2 = .05$, nor Trial Type × TMS, $F(2, 28) = 2.28$, $p = .12$, $\eta_p^2 = .14$. Altogether, RT and error data of the control task provide no evidence for significant effects of IFJ TMS on the processing of the instructional cue. RT and error data of the control task can be found in Table 3.

Table 2. Mean Rates of Task-order Reversals in Percentage (and Standard Deviation) from Experiment 1 and Experiment 2 as a Function of Trial Type and TMS Condition

	Trial Type		
TMS Condition	*Fixed-order Trial*	*Same-order Trial*	*Different-order Trial*
Experiment 1			
No TMS	0.78% (1.34%)	2.00% (3.73%)	3.13% (3.92%)
Control TMS	0.69% (1.90%)	1.39% (2.59%)	4.34% (5.27%)
IFJ TMS	0.17% (0.70%)	3.30% (4.67%)	4.69% (5.14%)
Experiment 2			
No TMS	0.15% (0.45%)	0.62% (0.98%)	3.63% (2.86%)
Control TMS	0.15% (0.66%)	1.23% (1.71)	2.01% (2.49%)
preSMA TMS	0.46% (1.07%)	0.62% (1.52%)	2.01% (3.41%)

Table 3. Mean RTs in Milliseconds and Mean Error Rates in Percentage (and Standard Deviation) of the Control Task from Experiment 1 and Experiment 2 for Each, Depending on the TMS Condition

	Trial Type			
	Same-order Trial		*Different-order Trial*	
TMS Condition	*RT (msec)*	*Error Rate (%)*	*RT (msec)*	*Error Rate (%)*
Experiment 1				
No TMS	509 (104)	5.86 (6.99)	502 (127)	4.01 (5.97)
Control TMS	516 (133)	4.32 (8.64)	506.24 (135)	5.56 (6.87)
IFJ TMS	503 (90)	4.94 (7.83)	507.93 (98)	2.47 (4.75)
Experiment 2				
No TMS	553 (275)	1.17 (2.33)	541 (253)	3.80 (3.23)
Control TMS	540 (224)	5.26 (10.71)	538 (235)	4.90 (8.45)
preSMA TMS	539 (221)	5.26 (8.58)	523 (245)	4.09 (6.64)

Discussion

Experiment 1 revealed that TMS over the IFJ results in impaired performance in DT situations with random task order: RTs in both component tasks were increased after IFJ TMS relative to control conditions in same-order and different-order trials, whereas RTs in trials in fixed-order blocks were unaffected by the TMS manipulation. Note that even for the case of Task 1 in different-order trials, RT1 was numerically and by trend larger for the IFJ TMS condition compared with the no TMS condition.[1] These results are in line with the assumption that the IFJ is causally involved in the implementation of task-order coordination processes in random-order blocks. More specifically, the IFJ seems to be recruited for implementing coordination processes that are necessary in DTs with random task-order, such as matching the processing order to a constantly changing normative task order (Stelzel et al., 2008; Szameitat et al., 2002). Importantly, we found an effect of IFJ TMS in both same-order and different-order trials, suggesting that the IFJ is not involved in implementing task-order processes that are specific for different-order trials, that is, when the order of tasks changes relative to the preceding trial.

Two potential counterargumentations need to be addressed. First, one might argue that the reported effects can also be explained by impaired processing of the task stimuli due to TMS rather than interference with task-order coordination. However, this argumentation is rather unlikely, as the effects of individual TMS pulses typically last for 80–120 msec (Miniussi et al., 2013; Bestmann, 2008), and in our paradigm, the time interval between the last TMS impulse and stimulus presentation lasted 200 msec. Furthermore, if TMS had interfered with stimulus processing, we should have also found TMS effects in fixed-order blocks because demands on stimulus processing do not differ between both block types. As this was not the case, we conclude that TMS of the IFJ interfered with task-order coordination and not with the processing of the target stimuli. According to a second argumentation, TMS of the IFJ might have, theoretically, impaired the processing of the order cue rather than task-order coordination. However, we demonstrated that TMS did not affect performance in a control task, in which participants had to indicate the order of stimuli as it was indicated by the instructional order cue. This result suggests that TMS of the IFJ did not interfere with the cue processing. Nevertheless, one might, theoretically, argue that demands on cue stimulus processing and stimulus identification might differ between the DT and the control task due to different instructions and responses on the presented order cue in the DT and the analog stimulus in the control task. However, we used the same stimulus material in both task situations, and earlier studies suggested that manipulations of stimulus material (e.g., stimulus degradation: Frowein & Sanders, 1978; stimulus contrast: Pachella & Fisher, 1969; similarity between stimuli: Shwartz, Pomerantz, & Egeth, 1977) rather than task instructions (Spijkers & Walter, 1985; Sanders, 1980) affect the early processing stages during the perception of visual stimuli (for an overview, see Sanders, 1990). Thus, as the stimulus material was physically identical for both tasks, we assume that that the demands on stimulus cue identification are similar across the DT and the control task situations. Consequently, there would be no reason to assume that TMS has affected stimulus processing in the one but not the other situation.

EXPERIMENT 2

The aim of Experiment 2 was to test whether or not the causal function for task-order coordination as shown in

Experiment 1 is specific for the IFJ. For that purpose, during a DT with fixed-order and random-order of the component tasks, we applied TMS over the preSMA, which has recently been associated with bottleneck processing (Soutschek et al., 2016). The preSMA was chosen as the site of stimulation because this brain region, in addition to the IFJ, shows increased neural activation during DTs with variable task-order (Szameitat et al., 2002; see also Schubert & Szameitat, 2003) and evidence from single-cell and lesion studies in primates (Shima & Tanji, 1998; Tanji & Shima, 1994) as well as from neurophysiological studies on humans (Nachev, Kennard, & Husain, 2008; Kennerley, Sakai, & Rushworth, 2004) suggests that the preSMA is pivotal for the sequencing of multiple motor actions and the updating of complex motor plans. Applying TMS on the preSMA in a DT with the same procedure and protocol as in Experiment 1 allows us to investigate if the IFJ should be regarded as a specific region for task-order coordination or if also other brain regions are causally related to task-order coordination.

Methods

Participants

In analogy to Experiment 1, 20 healthy participants (13 women; mean age = 23.6 years, *SD* = 3.9 years) were invited to take part in the experiment after obtaining written informed consent. All participants were right handed, were German native speakers, and had normal or corrected-to-normal vision. One participant was excluded from analysis due to poor DT performance (less than 50% of correct trials). For another participant, neuronavigation could not be performed reliably. Data of the remaining 18 participants were included in analyses.

Apparatus and Stimuli

Apparatus and stimuli were the same as in Experiment 1.

Design and Procedure

The procedure and design were the same as in Experiment 1.

TMS Procedure

The TMS procedure was similar to the one employed in Experiment 1, with four TMS pulses applied during the CTI with an intensity of 110% of the individual's motor threshold (*M* = 39.9%) and a frequency of 10 Hz. TMS was applied either to preSMA or to the vertex to test whether the preSMA is causally involved in task-order coordination processes. As in Experiment 1, a neuronavigated approach was used to validate coil position over the preSMA in real time throughout the entire experiment. Again, structural brain scans for each participant were acquired beforehand. The preSMA TMS site was located on the midline, approximately 1 cm anterior to intersection of the verticofrontal line and the outer cortex surface (Mayka, Corcos, Leurgans, & Vaillancourt, 2006; Muessgens, Thirugnanasambandam, Shitara, Popa, & Hallett, 2016). An average distance of 1.00 mm (*SD* = 0.55 mm) between the individual preSMA TMS site and the peak electric field was estimated throughout the whole experiment. As in Experiment 1, the vertex was located at the Pz electrode position according to the international 10–20 system. The average distance between the vertex and preSMA TMS site amounted to 48.46 mm (*SD* = 8.14 mm). The coil was orientated in anterior direction perpendicular to the medial longitudinal fissure for both the preSMA TMS site and the vertex, respectively.

Statistical Analysis

Statistical analyses were similar to those in Experiment 1. For these analyses, trials with omitted or grouped responses (*M* = 8.1%) were excluded from the data set and, exclusively for the RT analyses, task-order reversal trials (*M* = 1.2%) and trials with erroneous responses (*M* = 9.0%).

Results

Task 1

In the first analysis, we tested whether the preSMA is recruited for the implementation of task-order coordination processes in the current DT situation. Participants' median RT1 and error rate were analyzed with a 3 × 3 ANOVA with the within-subject factors Trial Type (fixed-order trials, same-order trials, different-order trials) and TMS (no TMS, vertex TMS, preSMA TMS). Most importantly, the analysis of RT1 revealed no effect of the factor TMS, $F(2, 34) = 0.54$, $p = .56$, $\eta_p^2 = .03$, nor of its interaction with the factor Trial Type, $F(4, 68) = 0.52$, $p = .55$, $\eta_p^2 = .03$, suggesting that preSMA TMS had neither a general nor a trial-specific effect on DT performance. The only significant effect was found for the factor Trial Type, $F(2, 34) = 9.33$, $p = .001$, $\eta_p^2 = .35$, indicating the occurrence of task-order coordination processes (see Table 4).

The analysis of error rate in Task 1 (Table 1) did not reveal any significant effects, neither of the factor Trial Type, $F(2, 34) = 2.43$, $p = .10$, $\eta_p^2 = .13$, TMS, $F(2, 34) < .01$, $p = 1.00$, $\eta_p^2 = .00$, nor of their interaction Trial Type × TMS, $F(4, 68) = 1.70$, $p = .16$, $\eta_p^2 = .09$. In summary, Task 1 data provided no evidence that preSMA TMS modulates DT performance.

Task 2

As for RT1, we analyzed RT2 and error rates using a 3 × 3 ANOVA with the within-subject factors Trial Type (fixed-order trials, same-order trials, different-order trials)

Table 4. Mean RTs in Milliseconds (and Standard Deviation) for Task 1 and Task 2 as a Function of Trial Type and TMS Conditions for Experiment 2

	Trial Type		
TMS Condition	*Fixed-order Trial*	*Same-order Trial*	*Different-order Trial*
Task 1			
No TMS	861 (259)	851 (301)	967 (420)
Control TMS	852 (254)	903 (375)	937 (328)
preSMA TMS	872 (268)	872 (310)	975 (367)
Task 2			
No TMS	992 (274)	994 (320)	1100 (373)
Control TMS	994 (291)	1075 (455)	1165 (410)
preSMA TMS	1045 (334)	1029 (363)	1130 (405)

and TMS (no TMS, vertex TMS, preSMA TMS). In this analysis, neither the factor TMS, $F(2, 34) = 1.60$, $p = .22$, $\eta_p^2 = .09$, nor the interaction Trial Type × TMS, $F(2, 34) = 1.22$, $p = .31$, $\eta_p^2 = .07$, was significant. Again, only the effect of the factor Trial Type was significant, $F(2, 34) = 11.92$, $p < .001$, $\eta_p^2 = .41$, indicating the occurrence of task-order coordination.

Regarding the error rate in Task 2, the effect of the factors Trial Type, $F(2, 34) = 1.41$, $p = .26$, $\eta_p^2 = .08$, as well as TMS, $F(2, 34) = 1.20$, $p = .31$, $\eta_p^2 = .07$, were not significant. Neither was the effect of their interaction, $F(2, 34) = 0.43$, $p = .79$, $\eta_p^2 = .03$. To summarize, similar to data on Task 1, we found no significant effects of preSMA TMS on DT performance in Task 2.

Task-order Reversals

Similar to Experiment 1, task-order reversal rates were rather low ($M = 1.17\%$, see Table 2). To test for effects of preSMA TMS on DT accuracy, task-order reversal rates were analyzed using a 3 × 3 ANOVA with the within-subject factors trial type (fixed-order trials, same-order trials, different-order trials) and TMS (no TMS, vertex TMS, preSMA TMS). We found a significant main effect of the factor Trial Type, $F(2, 34) = 19.10$, $p < .001$, $\eta_p^2 = .53$. The task-order reversal rate increased from fixed-order trials ($M = 0.26\%$) over same-order trials (0.82%), $t(17) = 2.50$, $p = .02$, to different-order trials ($M = 2.54\%$), $t(17) = 4.32$, $p < .001$, indicating that participants were able to adjust their task order to the stimulus order with different success across different trial types. The factor TMS did not reach significance, $F(2, 34) = 0.70$, $p = .51$, $\eta_p^2 = .04$. The significant interaction of Trial Type and TMS, $F(4, 68) = 3.29$, $p = .02$, $\eta_p^2 = .16$), suggested different effects of TMS on task-order reversals for each trial type. However, this significant interaction was mainly driven by an unspecific TMS effect in different-order trials. Compared with no TMS ($M = 3.63\%$), task-order reversal rate was reduced after preSMA TMS ($M = 2.01\%$), $t(17) = 2.15$, $p = .05$, and by trend after vertex TMS ($M = 2.01\%$), $t(17) = 1.98$, $p = .06$. Both TMS conditions did not differ significantly, $t(17) = 0.00$, $p = 1.00$. No other pairwise comparison revealed significant differences (all ps > .10). In summary, preSMA TMS compared with vertex and no TMS did not modulate DT accuracy as measured by task-order reversal rates.

Control Task

Median RTs as well as error rates of the control task were analyzed employing a 2 × 3 ANOVA similar to the related analysis in Experiment 1. For both RTs and error rates (see Table 3), these analyses revealed no significant effects (all ps > .27), suggesting that preSMA TMS did not affect the processing of the instructional order cue.

Comparison across Experiments

We demonstrated that TMS of the preSMA compared with control conditions does not modulate DT performance at all. Therefore, to assess whether this result pattern can be distinguished from the IFJ TMS result pattern of Experiment 1, we conducted a between-experiment analysis. For that purpose, we calculated a repeated-measures ANOVA with the within-subject factors Task (Task 1, Task 2), Trial Type (fixed-order trials, same-order trials, different-order trials), and TMS (no TMS, vertex TMS, TMS) as well as Experiment (Experiment 1, Experiment 2) as a between-subject factor on participants' median RTs from Experiments 1 and 2. Most importantly, this analysis revealed a significant interaction of the factors Trial Type, TMS, and Experiment, $F(4, 128) = 2.66$, $p = .036$, $\eta_p^2 = .08$, indicating that the effect of TMS on

RTs in same-order trials and different-order trials differed between both experiments. Thus, we can confirm that, although we found an effect of the IFJ TMS on DT performance in same-order and different-order trials in Experiment 1, we did not find similar effects in Experiment 2 when applying preSMA TMS. No other interaction including the between-subject factor Experiment was significant (all $ps > .10$).

Discussion

In Experiment 2, we showed that stimulation of the preSMA has no effect on the implementation of task-order coordination: Compared with IFJ TMS, preSMA TMS did not affect DT performance, neither in trials of fixed-order blocks nor in same-order and different-order trials of random-order blocks. Together with the findings of a subsequent cross-experiment analysis, these results indicate the specificity of the TMS effects for the IFJ compared with other brain regions and emphasize its dominant role for coordinating task order in DT situations.

GENERAL DISCUSSION

The aim of this study was to investigate the causal and functional role of the IFJ for implementing task-order coordination processes in DT situations. For this purpose, we applied online TMS during a DT with fixed and random order of the component tasks. In Experiment 1, TMS of the IFJ compared with control TMS conditions resulted in impaired DT performance in same-order and different-order trials in random-order blocks as reflected in increased RTs for Task 1 and Task 2. Performance in trials in fixed-order blocks was unaffected by IFJ stimulation. Additionally, in a control task, we showed that stimulation did not affect cue identification, suggesting that the TMS effects on DT performance are most probably not attributable to interference with cue processing due to TMS. In Experiment 2, we showed that preSMA TMS had no effect on DT performance, neither in fixed-order nor in random-order blocks. This pattern of results was confirmed in a combined analysis of both experiments emphasizing the specific role of the IFJ for task-order coordination. In summary, the data of both experiments are in line with the assumption that the IFJ is causally involved in implementing task-order coordination processes in DT situations with varying order of the component tasks.

Prior evidence for the potential involvement of the IFJ in implementing task-order coordination in DTs stems from fMRI studies (Stelzel et al., 2008; Szameitat et al., 2002, 2006) as well as studies testing neurological patients suffering from brain damage (Baddeley et al., 1997; McDowell et al., 1997). However, based on the fMRI method, only correlational conclusions about the IFJ and its role for task-order coordination can be drawn (Logothetis, 2008). Furthermore, evidence from lesion studies can only be interpreted with caution. Because brain lesions are usually not restricted to a narrowly circumscribed brain region (like the IFJ) but instead affect vast cortical as well as subcortical areas (Rorden & Karnath, 2004), impairments in task-order coordination in neurological populations can also point to a potential influence of brain damage beyond the IFJ. As TMS is characterized by high spatial (and temporal) resolution and as it is able to interfere with neural information processing, the current study allows for overcoming these issues by providing evidence that the IFJ is indeed causally involved in the execution of task-order coordination.

In addition to testing its causal role, a further aim of the study was to specify the functional contribution of the IFJ for task-order coordination. We showed that stimulation of the IFJ impaired DT performance in trials in random-order blocks, that is, in same-order and different-order trials, but not in trials in fixed-order blocks. Thus, based on our results, we conclude that the IFJ is recruited for task-order control processes that are necessary to adjust the processing order of the to-be-performed tasks to the permanently varying stimulus order: In random-order blocks, participants are instructed to respond to both tasks according to the order of stimulus presentation. As a result, in each trial, participants have to judge the order of stimuli based on their temporal onsets and then adjust the processing order of the respective tasks accordingly. But how, exactly, can this adjustment be realized? According to cognitive models on task-order coordination (Kübler et al., 2018; Luria & Meiran, 2003, 2006), task-order in DT situations is regulated by a higher order control structure, the task-order set, which contains information about the specific processing order of the two tasks. When performing a DT trial, participants have to monitor the order of stimuli and implement the appropriate order set, that is, the order set that matches the stimulus order, which then schedules the processing of the component tasks. Note that if participants would not use this higher order representation and, instead, would simply rely on control processes on the level of the component tasks, we should find a performance benefit for different-order trials compared with trials in which the order is repeated relative to the previous trial (i.e., same-order trials). This is so, as in different-order trials, the first task of the current trial was the second task in the preceding trial resulting in a local task repetition despite a global change in task order. However, the finding that performance in different-order trials is impaired compared with same-order trials indicates that participants indeed take global order information, as it is represented by the task-order set, into account when performing DTs with variable order. The current results suggest that the IFJ is relevant for selecting and activating the appropriate task-order set in random-order blocks, when participants have to switch between different task-orders. As a result, TMS of the IFJ results in impaired DT performance in this block type. In fixed-order blocks, when participants know the

task order in each trial in advance, there is no additional need for the IFJ to implement these task-order coordination processes, and thus, TMS has no effect on DT performance.

As an alternative, one could argue that the IFJ is causally involved in the monitoring of and the decision about the stimulus order rather than implementing the appropriate order set accordingly. Note that in the applied paradigm information about the stimulus order was given by the instructional order cue at the beginning of each trial. Importantly, however, TMS of the IFJ had no effect on the performance in the control task. In this control task, participants were instructed to respond to the order of stimuli (as it was indicated by the instructional order cue). Thus, instead of responding to both target stimuli in a specific order, participants were only required to monitor the information given by the instructional cue and to make a decision about the stimulus order. Consequently, in both tasks participants had to employ the same monitoring processes for retrieving the information given by the instructional order cue. Importantly, as IFJ TMS did not affect performance in this control task, it is rather unlikely that the IFJ is recruited for monitoring and decisional processes with respect to the stimulus order.

The current findings are in line with findings of recent fMRI studies suggesting that the IFJ plays a crucial role for the implementation of cognitive control in different experimental paradigms (Muhle-Karbe et al., 2016; Brass et al., 2005; Derrfuss et al., 2004, 2005). For example, in their fMRI study on task switching, Braver, Reynolds, and Donaldson (2003) contrasted single-task blocks, in which participants only performed one of two choice RT tasks, with mixed blocks, in which participants had to constantly switch between two different choice RT tasks. As a result, they reported focal activation peaks within the lPFC closely located to the IFJ during trials in mixed blocks compared with trials in single-task blocks, which led them to conclude that the IFJ plays an important role for the selection and representation of specific task information (i.e., the task set) during task switching. Similar results have also been found for other cognitive control tasks such as the Stroop paradigm (for an overview, see Brass et al., 2005). Importantly, the results of our study expand these findings. Whereas in the work by Braver et al. (2003) participants had to shift between different tasks and select different task sets on a trial-by-trial basis, in the current study participants had to switch between different task orders and activate different task-order sets accordingly. Thus, by applying TMS in random-order DT blocks, we showed that the IFJ is not only recruited for implementing specific task information but also for selecting and activating task-order information that is specified by the task-order set.

The current results are also in line with data of Strobach et al. (2015). In this study, the authors intended to improve DT performance by applying transcranial direct current stimulation (tDCS) over the lPFC during fixed-order and random-order DT blocks as well as single-task blocks. Although stimulation did not affect performance in the single task, the authors showed that anodal tDCS over the left lPFC compared with sham stimulation resulted in improved performance (i.e., speeded RTs for both tasks) during DT blocks. An additional analysis revealed that this improvement was mainly evident in random-order compared with fixed-order blocks, which, according to the authors, provides preliminary evidence for a causal role of the lPFC in task-order coordination. However, several methodological characteristics of tDCS prevent a conclusive interpretation of these earlier findings. Compared with online TMS, tDCS is characterized by poor temporal as well as spatial resolution (Filmer, Dux, & Mattingley, 2014; Nitsche et al., 2008; Antal, Nitsche, & Paulus, 2006). In our study, we were able to circumvent these shortcomings because online TMS produces temporally highly focused effects (Sparing & Mottaghy, 2008) and can be used to interfere with neural information processing to a specific point in time on a trial-to-trial basis. Furthermore, TMS is characterized by a higher spatial resolution relative to tDCS (Priori, Hallett, & Rothwell, 2009); therefore, compared with Strobach et al. (2015), the current findings allow for a precise localization of brain regions with a causal role for task-order coordination.

Furthermore, we observed similar effects of IFJ TMS on performance in both same-order and different-order trials. This suggests that the IFJ's function in task-order coordination is not restricted to different-order trials, in which the task order changes relative to the previous trial (Szameitat et al., 2006), because in this case we should have observed selective effects of IFJ TMS in different-order trials compared with same-order trials. In recent studies (Kübler et al., 2018; Schubert, 2008; see also Hirsch, Nolden, & Koch, 2017), it was argued that performance differences between same-order and different-order trials reflect memory-based processes of task-order preparation. More specifically, task-order on a current trial is prepared in accordance with the task order in the previous trial. However, when the task order changes in different-order trials, the prepared task order has to be overcome, which results in additional processing demands compared with same-order trials. The data of the current study, however, indicate that the stimulation of the IFJ does not modulate these task-order coordination processes, which are specific for different-order trials. Instead, as we found equal effects of IFJ TMS on same-order and different-order trials, our results suggest that TMS of the IFJ interferes with task-order coordination processes during random-order blocks (i.e., for same-order and different-order trials alike), which are required for the active adjustment of the processing according to the sequence of stimuli.

It is important to note that, in addition to task-order coordination, the IFJ may implement further processes in DT situations. For example, evidence from DT studies

using neuroimaging (Dux, Ivanoff, Asplund, & Marois, 2006) as well as noninvasive brain stimulation (Filmer, Mattingley, & Dux, 2013) suggests that the IFJ may also play an important role for executing response selection-related processes. Importantly, however, the aim of the current study was to investigate the causal relation between the IFJ and task-order coordination processes. For this purpose, TMS was applied during the CTI, that is, after the presentation of an instructional order cue and before the display of both target stimuli. The purpose of presenting this order cue was to temporally isolate task-order coordination processes from other processes that are crucial for performing the component tasks, such as perceptual or response selection-related processes (De Jong, 1995). Because of this temporal isolation, we were able to interfere with task-order coordination processes by applying TMS without impairing these other processes. Thus, the current findings do not contradict the findings of Dux et al. (2006) and Filmer et al. (2013). Instead they indicate that, in addition to response selection, the IFJ is also recruited for executing task-order coordination processes.

In contrast to the stimulation of the IFJ, TMS of the preSMA did not modulate task-order coordination processes in DT situations. This was indicated by the results of Experiment 2, according to which preSMA TMS did not affect DT performance, neither in trials from fixed-order blocks nor in trials from random-order blocks. This suggests that the preSMA does not play a causal role for task-order coordination. Nevertheless, the preSMA seems to be involved in implementing other processes relevant for DT processing as indicated by its increased BOLD response during DT situations (see Schubert & Szameitat, 2003; Szameitat et al., 2002). According to Soutschek et al. (2016), the preSMA contributes to resolving conflict between two tasks by inhibiting Task 2 processing, rather than implementing task-order coordination. This was shown by the fact that in that study preSMA TMS during the presentation of Task 2 results in faster RT2 compared with control conditions but leaves Task 1 performance undisturbed. The current findings do not contradict these findings of Soutschek et al. (2016). Instead, they extend these findings by indicating that the role of the preSMA is rather limited to resolving conflict between the two tasks and that it seems not to be involved in processes regulating task order in a DT situation. This is so because, in this study, we applied TMS during the CTI and not during Task 2 processing, as in the study of Soutschek et al. (2016), to exclusively interfere with the task-order coordination processes. As preSMA TMS did not affect DT performance, we conclude that the state of this brain region does not contribute to the implementation task-order coordination processes albeit it still may be causally involved in other processes required during DTs.

The results of our study add important insights to the field of DT research. A common finding from DT research is that RTs and error rates are usually increased in DT situations compared with situations in which only one of the two tasks is processed. A vast body of evidence indicates that these DT costs can be attributed to the serial processing at the response selection stage (Pashler, 1994)—although processing on perception and motor-related stages is usually carried out in parallel. This serial processing constitutes a bottleneck in the processing of temporally overlapping tasks. So far, DT research has mostly focused on questions considering basic attributes of this bottleneck (Koch, Poljac, Müller, & Kiesel, 2018). For example, on the one hand, a plethora of behavioral studies have tried to locate the central bottleneck within the stream of information processing or have investigated whether the bottleneck is structural (Pashler, 1994) or strategic (Logan & Gordon, 2001; Meyer & Kieras, 1997) in nature. On the other hand, multiple imaging studies aimed at pinpointing the bottleneck to certain brain structures (Spence, 2008; Dux et al., 2006; Marois & Ivanoff, 2005). More recent approaches in DT research examine how the cognitive system and the human brain deal with the additional requirements imposed by bottleneck processing. More specifically, as two tasks that have to be performed closely in time and compete for access to the bottleneck stage, the requirement for additional control processes arises that reduce resulting interference between the two temporally overlapping tasks (Schubert, 2008).

The findings of this study are consistent with views that active control processes, that is, task-order coordination processes, regulate the processing order of two tasks. These processes must be assumed in addition to a rather passive first-come, first-served principle suggested by classical response selection bottleneck models (De Jong, 1995; Pashler, 1994). Although the latter suggests a rather passive mechanism of deciding which task is processed first or second based on the arrival time of the tasks at the bottleneck (Strobach, Hendrich, Kübler, Müller, & Schubert, 2018), the former mechanism requires active monitoring and control processes. In line with recent accounts on task scheduling in DT situations (Szameitat et al., 2006; Luria & Meiran, 2003), these task-order coordination processes rely on order representations containing the sequence information of two task sets (instead of only one task representation). Importantly, by applying TMS we demonstrated that the lPFC is causally involved in task-order coordination in DT situations, supposedly by implementing the selection and activation of these higher order task-order representations. This adds to the findings from earlier studies assuming a similar function of the lPFC for maintaining and switching between representations of single tasks (Muhle-Karbe et al., 2014; Brass et al., 2005; Braver et al., 2003; Dove, Pollmann, Schubert, Wiggins, & Von Cramon, 2000). These order control processes complement other control mechanisms resolving conflict between two temporally overlapping tasks during DT processing on a more local level, for example, processes involved in the inhibitory

control of one task stream during the ongoing processing of another task stream or resolving perceptual interference between the stimuli of the two tasks, and are associated with brain regions beyond the lPFC (Soutschek et al., 2016; Stelzel, Brandt, & Schubert, 2009; Jiang, 2004; Herath, Klingberg, Young, Amunts, & Roland, 2001). Taken together, these findings are in line with models assuming that interference processing in complex task situations such as DTs relies on multiple control mechanisms that are implemented by a number of different brain regions (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). Operations executed by these brain regions allow for the monitoring and detection of information signaling potential interference as well as the appropriate and flexible adaptation of the cognitive system to different task demands. As indicated by our findings, among these brain regions, the lPFC seems to play a crucial role in regulating the sequence of two competing actions.

Conclusion

In this study, we investigated the causal role of the IFJ for task-order coordination by applying TMS in a DT with fixed and random order of the component tasks. We demonstrated that stimulation of the IFJ compared with control TMS conditions resulted in impaired DT performance in random order but not in fixed-order blocks. No such effect was found after preSMA TMS. These results indicate that the IFJ is causally involved in task-order coordination processes that are required to select and implement the appropriate processing order of two temporally overlapping tasks in DTs with variable task order.

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Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethics standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval of the local ethics committee (Humboldt-Universität zu Berlin Department of Psychology) was obtained before the commencement of the study.

Note

1. Please note that a conjoined ANOVA combining both types of trials (same-order and different-order trials) provided evidence on a significance level with $p < .05$ that TMS over the IFJ affected task-order coordination processes in different-order trials to the same extent as in same-order trials . For that purpose, we analyzed RT1 using an ANOVA with the within-subject factors Trial Type (same-order trials, different-order trials) and TMS (no TMS, vertex TMS, IFJ TMS). In addition to the significant effect of the factor Trial Type, $F(2, 30) = 11.97$, $p < .01$, $\eta_p^2 = .44$, this analysis revealed a significant main effect of the factor TMS, $F(2, 30) = 8.52$, $p = .01$, $\eta_p^2 = .36$. Importantly, the interaction of the factors TMS and Trial Type did not reach significance, $F(2, 30) = 1.96$, $p = .16$, $\eta_p^2 = .12$, indicating a similar effect of IFJ TMS on same-order and different-order trials. These results are consistent with the assumption that stimulation of the IFJ results in impaired performance in random-order blocks irrespective of the specific trial type.

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