Different facets of object-use pantomime: online TMS evidence on the role of the supramarginal gyrus

Abstract

Background. A key question in apraxia research is which specific cognitive processes in pantomiming the parietal cortex supports. The manipulation-based hypothesis and the technical-reasoning hypothesis ascribe different roles to the inferior parietal lobule (IPL).

Objective. We elucidated the role of the left supramarginal gyrus (SMG, i.e., part of IPL) during the processing of different aspects of object-use pantomime.

Methods. Thirty-one healthy participants matched pantomimes with the corresponding object (PO) or the corresponding situation (PS) during online transcranial magnetic stimulation (TMS) interference applied to left SMG, compared to a control stimulation (vertex). Notably, the object corresponding to a given pantomime was explicitly not shown in the PS task, excluding the possibility to analyse a physical object. Matching an object to the corresponding situation (OS) served as a control task.

Results. TMS interference with left SMG significantly affected response times for both investigated pantomime tasks (PO and PS); the effect in the PO task significantly correlated with the PS task. As expected, no TMS effect was observed in the control task (OS).

Conclusion. Left SMG does not only establish a link between pantomime and a manipulable object but is also involved in pantomime recognition and comprehension. That TMS interfered with both pantomime tasks supports the manipulation-based hypothesis, assuming that the IPL recruits stored gesture engrams whenever pantomimes are processed.

1. Introduction

1.1. Pantomime of object-use in apraxia

Apraxia is a motor-cognitive disorder with a prevalence ranging from 30 to 50% in patients with left hemisphere stroke (Dovern et al., 2012). Apraxia can manifest in diverse deficits of gesture imitation, actual object-use, and pantomiming the use of objects (Wheaton & Hallett, 2007). In contrast to imitations of intransitive gestures that can be either meaningless or meaningful (Achilles et al., 2019), transitive, i.e., object-related gestures, are *per se* meaningful. Notably, pantomiming the use of objects is considered a transitive gesture.

Shedding light on these cognitive processes may speak to the two prevailing hypotheses and, thereby, the role of the parietal cortex in i) the manipulation-based hypothesis and ii) the technical reasoning hypothesis that will be outlined as followed.

1.2. Theoretical background on pantomime of object-use

The *manipulation-based hypothesis*, or 'gesture engram theory', postulates that information about learned object-use gestures is represented in the parietal cortex as 'manipulation knowledge', and thus linked to real object-use (Buxbaum, 2017). In this framework, sensorimotor representations of learned object-use actions are presumed to be stored in the parietal cortex (Buxbaum & Kalenine, 2010) and automatically triggered when seeing an object (Bach et al., 2014; Buxbaum, 2001).

In contrast, the *technical reasoning hypothesis* assumes that object use relies on the online processing of object properties by a mental simulation of the action based on mechanical knowledge (Osiurak & Badets, 2016). Arguments for the *technical reasoning hypothesis* stem from correlations of pantomime performance with tasks probing actual object-use and sequential mechanical problem solving (Goldenberg & Hagmann, 1998; Jarry et al., 2013).

Furthermore, mechanical problem solving was shown to predict the performance of tool-use pantomime in patients (Lesourd et al., 2017).

However, pantomime was also found to correlate with gesture recognition (Tarhan et al., 2015), supporting the idea of a communicational aspect of pantomimes (Goldenberg, 2001; Goldenberg et al., 2007). Along these lines, impaired pantomime could also be regarded as a form of deficient non-verbal communication rather than an impaired motor skill (Goldenberg, 2017).

1.3. Neural correlates of pantomime of object-use

While the cognitive processes underlying pantomimes are much debated, there is broad agreement about the neural basis of pantomime. Voxel-based lesion-symptom mapping studies (VLSM) in large patient populations found a strong association of lesions of the left inferior parietal lobule (IPL), in particular the supramarginal gyrus (SMG), with a deficient pantomime of object-use (Dressing et al., 2018; Hoeren et al., 2014; Kalenine et al., 2010; Schmidt et al., 2022; Sperber et al., 2019; Watson & Buxbaum, 2015; Weiss et al., 2016). A systematic review revealed that deficient pantomime was most frequently associated with lesions located in the parietal cortex (50%), followed by posterior temporal (22%) and frontal regions (14%), further supported by a meta-analysis of functional imaging studies (Niessen et al., 2014). Thus, an extensive left-lateralized fronto-temporo-parietal network supports object-use pantomimes, with the parietal cortex as a crucial hub (for a comprehensive literature review, also see (Vingerhoets, 2014)). More precisely, the SMG is considered a central node in the ventro-dorsal action processing stream that integrates semantic information about objects from ventral areas (Garcea et al., 2016; Kristensen et al., 2016). Notably, the left ventro-dorsal stream is supposed to process skilled object-use and long-term action representation, including object-use pantomime (Binkofski & Buxbaum, 2013; Hoeren et al., 2014; Rizzolatti & Matelli, 2003).

1.4. Prior TMS studies and online TMS interference

Transcranial magnetic stimulation (TMS) can interfere with neuronal activity by exposing the brain tissue to a rapidly changing magnetic field. TMS thus allows investigating the involvement of a specific brain area in a given task. Using this technique, differential roles of parietal and temporal regions in diverse action-/object-processing tasks have been unraveled, overall supporting an important role of the parietal cortex in object-use pantomime and action knowledge. In particular, tasks requiring the processing of functional/semantic aspects of objects were disturbed by TMS over temporal regions (Andres et al., 2013; Ishibashi et al., 2011), while TMS over the parietal cortex (IPL/SMG) led to selective effects for tasks probing the manipulation of objects, action processing, and hand positioning (Andres et al., 2013; Andres et al., 2017; Ishibashi et al., 2011; Kuhnke et al., 2020).

In the present study, we aimed at using online TMS interference (Tscherpel et al., 2020) in order to probe the relevance of the left SMG in pantomime tasks. In contrast to the more widely used offline approach of repetitive TMS, in which TMS is applied before task performance and which predominately makes use of long-lasting after-effects (Rossini et al., 2015), we here used a different TMS approach, i.e., online TMS interference, in which TMS is applied during task-performance utilising immediate effects. A simplified mechanistic view assumes that online TMS invariably interferes with the neural activity of the stimulated brain area by directly depolarising neural tissue, and thereby inducing noise into the fine-tuned neural processing (Rossi et al., 2009; Rossini et al., 2015; Walsh & Cowey, 2000). Thus, it is well established that online TMS interferes with the neural activity of the area underneath the

TMS coil (Gerloff, Cohen, et al., 1998; Gerloff, Corwell, et al., 1998; Pascual-Leone et al., 1991; Schluter et al., 1998). Notably, in contrast to offline rTMS, behavioral and neural effects of online TMS are transiently and time-locked to the stimulation period without relevant after-effects (Rossini et al., 2015; Walsh & Cowey, 2000). Here, the term interference predominately refers to the interference with neural processing as established in the TMS literature (see review Rossini 2015). Therefore, interference evoked by the stimulation of a specific region allows to conclude the involvement of this region in a given task. However, the direction of the evoked behavioral response, i.e., improvement or deterioration of task performance, does not necessarily determine the characteristics of the applied TMS protocol or the role of this region since the specific effects of online TMS are known to be influenced by several factors like timing of stimulation onset, stimulation intensity, or brain states and network configurations (Davare et al., 2007; Foltys et al., 2001; Jahanshahi & Rothwell, 2000; Li et al., 2015; Silvanto et al., 2008; Walsh & Cowey, 2000; Zrenner et al., 2018).

1.5. Aim and hypothesis of the current study

We here investigated the role of the left SMG in processing different facets of object-use pantomime that have not been addressed before with online TMS in healthy participants. We developed two experimental tasks requiring the matching of object-use pantomimes to the corresponding object (PO task) or the corresponding situation (PS task). A contextual matching task, in which participants had to match objects with the corresponding situation (based on semantic knowledge, OS task, see **Figure 1**), and a control stimulation over the vertex (sham) were used to account for general TMS-induced effects. We hypothesized that stimulation over the SMG would reveal *no* differential TMS effect for the OS task, as such tasks rather draw upon ventral stream areas (Kalenine & Buxbaum, 2016). According to previous studies using similar stimuli (Vingerhoets et al., 2013) and comparable tasks and methods (Andres et al., 2013; Andres et al., 2017), a TMS-induced effect over the left SMG was expected for the PO task. Therefore, the main focus of this present work was on the novel PS task, in which the situation corresponding to the pantomime was shown, but *not* the pantomime-related object. Thus, online TMS interference over the left SMG in the PS task could not be explained by disrupting the processing of object-related physical features as postulated by the technical reasoning hypothesis. Such interference in the PS task would instead suggest that the stimulation disturbs the activation of sensorimotor representations stored in the parietal cortex needed for "recognizing and understanding" the pantomime, supporting the manipulation-based hypothesis.

2. Material and methods

2.1. Participants

Thirty-one healthy right-handed participants gave written informed consent to this TMS experiment. One participant dropped out of the experiment due to discomfort during the stimulation (painful facial muscle twitching), and one had to be excluded from the analyses due to non-adherence to the instructions given. Data from 29 participants were initially processed, but four participants were discarded from the final analyses, as described in section 2.6. Thus, the reported results stem from data of 25 participants. All participants had no history of neurological or mental disorders and no contraindications for TMS (Rossi et al., 2009). The study was conducted under the Declaration of Helsinki and approved by the local ethics committee. Participants received 10 Euro per hour as compensation.

2.2. Tasks and stimuli

The experiment featured three tasks: the pantomime-object (PO), the pantomime-situation (PS), and the object-situation (OS) task (**Figure 1**). In each task, participants had to decide whether two photographs, presented simultaneously, portrayed a match or mismatch. The photos of the PO task showed a pantomime (upper picture) and an object (lower picture). In the PO task, participant had to judge whether the pantomime depicted corresponded to the object shown or not (match/mismatch). The photos of the PS task also showed a pantomime (upper picture), while the lower picture depicted a situation/setting, which corresponded to the pantomimed action (e.g., drinking from a glass – bar). However, the pantomime-related object itself was explicitly *not* shown (here: no glass present at the bar). Participants had to decide whether the pantomime was typical for the situation shown or not (match/mismatch) in the PS task. Lastly, the stimuli of the OS task (control task) consisted of an object shown in the upper part and a situation/setting in the lower part. Participants were asked to judge whether the object and the situation matched or not, i.e., whether the object relates to the given situation/setting (**Figure 1**). Participants indicated their decision (match/ mismatch) by pressing one of two buttons (green/red) with their *left* index finger and then always had to return to the starting point with equal distance to each button. The ipsilateral left hand was used to minimize any confounding effects of motor execution during stimulation of the left SMG. Pressing the response button terminated stimuli presentation. Participants were instructed to respond as fast and as accurately as possible. Before starting the experiment, participants were familiarized with the tasks but without stimulation. Practice trials consisted of 60 stimuli, i.e., 20 per task, that did not appear in the actual TMS experiment.

2.3. Creation and selection of stimuli

First, we created a list of suitable stimuli pairs, while selected objects had to be (i) recognizable by the corresponding pantomime, (ii) transportable to the photo studio, and (iii) picture taking of a corresponding setting/situation feasible. Initially, we obtained 56 stimuli pairs that met these criteria. A picture for each pantomime was taken from two angles, and pictures of the objects and setting/situation were taken in duplicate (same, but not identical object, situation/setting). Thus, 336 pictures were created (56x2 pantomimes, 56x2 objects, 56x2 settings/situations), and consecutively, paired as matches and mismatches for the three tasks, leading to a total of 672 paired stimuli (336 matches, 336 mismatches). Pantomimes were performed for right-handed usage. All stimuli underwent a two step-piloting procedure. First, based on the performance of 10 healthy participants, ambiguous stimuli were adapted or removed from the set and the remaining set was piloted again by different 10 participants. Note that the 20 participants, who piloted the stimuli, did not participate in the main experiment (see **Suppl.** for stimuli piloting and selection of stimuli, **Suppl. Table 1**).

2.4. Experimental procedure and design

The study employed a within-subject cross-over design, i.e., each participant underwent a verum (left SMG) and a control stimulation (vertex, i.e., sham condition) during the same session. In the course of the TMS experiment, a total of 64 paired stimuli per stimulation condition (verum/control) per task (PO, PS, OS) were presented, leading to a total of 384 stimuli, presented in eight blocks (4 verum, 4 control) with 16 trials (8 matches, 8 mismatches) per task (3 tasks) per block (8 x 16 x 3 = 384 stimuli, see **Suppl. Table 1** for the stimuli list and **Figure 2b** for the block set-up). As described above, we created two sets (altered duplicates), and their presentation during verum or control stimulation was randomized to rule out any potential set-related differences. The order of the blocks was pseudo-randomized, allowing no more than two blocks with the same stimulation condition in a row. Within one block, the letters 'wait for next task', displayed for 10 seconds, indicated a transition from one task to the next, while the task order was also pseudo-randomized. A maximum of three of a kind (match/mismatch) occurred in series to avoid within-task habituation. A break was implemented after each block to change stimulation sites and allow the participant a short rest. Each stimulus was followed by a white cross on a black background indicating the ongoing experiment. The inter-stimulus interval (ISI) was jittered (5 to 6 seconds) to prevent anticipation of the stimuli onset (see **Figures 2b and 2c**). We used the software Presentation® (Version 9.9, Neurobehavioral Systems, USA, http://neurobs.com) for the randomization, triggering the TMS machine, visual presentation of the stimuli, and recording the response times and accuracy.

2.5. Transcranial magnetic stimulation

We applied online repetitive transcranial magnetic stimulation (rTMS) using a MagStim Super Rapid^2 stimulator (The Magstim Co. Ltd, Whitland, United Kingdom) equipped with a figure-of-eight Air Film Coil. Trains of 5 rTMS pulses of 10Hz (400ms duration) were delivered 250 ms after the onset of stimuli presentation (see **Figure 2c**). Online TMS interference has the advantage that it directly, simultaneously, and transiently interferes with the cognitive processing during the task without relevant carry-over effects (Pascual-Leone et al., 2000), allowing alternations of control and verum stimulation within the same participant and one session. Please also see introduction (1.4.). We piloted the stimulation regimen with a fixed maximal stimulator output (MSO), set to 65% according with previous studies targeting the SMG (Andres et al., 2013; Andres et al., 2017). Due to significant discomfort in some of the piloting participants with the fixed MSO, we decided to set the TMS intensity to 120% of the individual resting motor threshold (rMT), but limited it to 65% MSO for the experiment. The rMT was assessed via motor evoked potentials by singe-pulse TMS over the left primary motor cortex (M1) and EMG recording from the first dorsal interosseous muscle (FDI) of the right hand using an algorithm provided by the TMS Motor Threshold Assessment Tool 2.0 (Awiszus, 2003), which performs parameter estimation by sequential testing.

As target area within the left SMG, we selected the MNI coordinate x = -60, y = -34, and z= +46, see **Figure 2a**.), which was also used in the TMS studies by Andres and colleagues investigating manipulation of objects (Andres et al., 2013; Andres et al., 2017). The MNI coordinate was warped into single-subject space to target the coordinate in the individual participant. To this end, the inverse normalization transform computed for the T1-MRI scans of each subject in SPM 12 software (Wellcome Trust Centre for Neuroimaging, University College London, UK) implemented in MATLAB Version R2014b was performed and the coordinate marked in MRIcron (www.sph.sc.edu/comd/rorden/MRicron). These individually transformed targets were then loaded into the neuro-navigation software used to guide the TMS coil and ensure ensuring stimulation over the target coordinate (BrainSight V.2.0.7; Rogue Research Ltd; Montreal, Canada). As control stimulation, the same TMS paradigm was administered over the parieto-occipital vertex with the coil inclined at a 45° angle upwards to avoid the induction of a current flow on brain tissue (Andres et al., 2013; Andres et al., 2017; Tscherpel et al., 2020). Ear plugs were worn during the entire experiment to attenuate the noise of the TMS.

2.6. Data analysis

Despite the 60 practice trials used for training before the experiment (see 2.2.), we observed a strong incipient learning effect in the main experiment, presumably because we had used different stimuli in the training session. It can be assumed that the familiarization with the new experimental stimuli led to faster processing for those stimuli that had been shown in previous trials of the main experiment, facilitating the association between presented objects, pantomimes, and situations and thus resulting in decreasing response times also at the beginning of the main experiment.

However, stable performance at the group level is mandatory for unambiguously detecting the effects of online TMS. Therefore, we defined stable task performance in a given block at the group level when the reduction of the mean RT from the previous to the current block was less than 5% of the overall mean RT at the group level. As this criterion was met for the first two blocks (RTs difference from first to second block 106ms, i.e., 10.6% deviation from the overall mean of 1004ms, and difference from second to third block 63ms, i.e., 6.2% deviation from the overall mean), we discarded these first two blocks from further analyses.

Besides, to ensure robust effects, we excluded participants from the analyses when less than 50% of the conducted trials (per task per stimulation, i.e., <32/64 trials) remained after eliminating the error trials and first two blocks. This criterion was met in four participants. Thus, data of 25 participants entered the final analyses and are presented here. Response accuracy rate (AR, % of correct responses) and response times (RTs in ms) of correct trials were analysed.

We conducted a 3 x 2 repeated-measures analysis of covariance (ANCOVA) with TASK (PS, PO, OS) and STIMULATION (left SMG, Vertex) as within-subject factors and stimulation intensity (maximal stimulator output, MSO) as a co-variate to account for the individual stimulation intensity applied. Two ANCOVAs were separately calculated for AR and mean RT of correct trials. For post-hoc comparisons of the significant effects, subsidiary two-sample t-tests were conducted, with a level of significance at $p < 0.05$, corrected for multiple comparisons using false discovery rate (FDR, (Benjamini & Hochberg, 1995)). Further, the difference in RTs between vertex and SMG stimulation of each task were calculated and correlated using Spearman's rank approach.

3. Results

3.1. Participants and stimulation intensities

Thirteen of the 25 participants (52%) were female; the mean age (± standard deviation) was 28.1 ± 3.9 years, ranging from 20 to 37 years. The rMT of the participants was 51.2 ± 8.2% on average (range: 36 to 76% MSO), and the mean stimulation intensity applied in the experiment was 59.1 ± 5.7% MSO, ranging from 44 to 65%. Please note that when 120% rMT exceeded 65% MSO, we applied 65% MSO as stimulation intensity (see methods section 2.5.), which was the case in seven participants (**Suppl. Table 2**).

3.2. TMS interference on the experimental tasks

For accuracy rates, the ANCOVA revealed no significant effects (TASK $F_{(2,48)}=0.33$, $p=0.72$; STIMULATION $F_{(1,24)}=1.679$, $p=0.21$ and TASK x STIMULATION $F_{(2,48)}=0.05$, $p=0.95$, see also **Table 1** for the ARs).

The ANCOVA performed on the mean RTs of correct trials showed no significant effect of STIMULATION ($F_{(1,23)}=0.03$, $p=0.88$), but a significant main effect of TASK ($F_{(2,46)}=4.9$, $p=0.01$). Post-hoc tests revealed significant RT differences between all three tasks (PO vs. PS: $p_{FDR}<0.01$, PS vs. PS: $p_{FDR}<0.01$, PO vs. OS $p_{FDR}=0.02$) with the longest RT in the PS task (mean RT 1015ms), followed by the PO task (943ms), and the shortest RT in the OS task (923ms, **Table 1**).

Notably, the ANCOVA also yielded a significant interaction effect of TASK x STIMULATION ($F_{(2,46)}=4.27$, $p=0.02$). Post-hoc t-tests indicated a significant reduction of the mean RT in the verum (left SMG) compared to the control stimulation (vertex) condition for the PO task, with a mean reduction of 23ms (p_{FDR}=0.03, FDR corrected for multiple comparisons) as well as for the PS task with a mean RT reduction of 64ms (p_{FDR}=0.04, **Table 1** and **Figure 3**). The RT-differences between the two stimulation conditions did not differ significantly between the two pantomime tasks (PO and PS; p=0.35). Notably, there was no significant RT difference between the stimulation conditions for the control task (OS). Therefore, the significant TASK x STIMULATION interaction was driven by a differential stimulation effect on the two pantomime tasks (PS, PO), but not on the control task (OS).

3.3. Correlations between tasks

RT changes induced by TMS interference with SMG significantly correlated in the PO and the PS tasks (Spearman's correlation coefficient PO/PS r=0.42, p=0.04). As expected, neither the PO and the OS task (p=0.87) nor the PS and the OS task (p=0.25, **Table 2**) correlated. Moreover, in none of the tasks, TMS interference correlated with the stimulation intensity (MSO) applied, ruling out a mere intensity-based mechanism. Instead, this supports that the TMS-induced changes impact task-specific cognitive processes.

4. Discussion

Using online TMS interference, the current study aimed to investigate the role of the left parietal cortex, particularly the involvement of the left SMG, in the processing of object-use pantomimes. To this aim, a novel task of matching pantomimes to the corresponding situation (PS task) was adopted, in addition to the more common task of matching pantomimes to the corresponding object (PO task) and a control task of matching objects to the corresponding situation (OS task).

4.1. *TMS inference over the SMG with the tasks*

4.1.1. *Object-situation task (OS)*

TMS applied over the left SMG did not influence the control task of matching objects to situations probing contextual, semantic knowledge. This finding met our expectations, as semantic knowledge was previously shown to be processed in more ventral areas (Canessa et al., 2008; Jung & Lambon Ralph, 2021; Kalenine & Buxbaum, 2016). Furthermore, in line with our results, a previous study showed no effect of TMS over the left SMG on a contextual task (Andres et al., 2013). Therefore, current results confirm that action and semantic knowledge draw on distinct neural networks.

4.1.2. *Pantomime-object task (PO)*

The current data showed a differential effect of online TMS over the left SMG compared to the control stimulation over the vertex for the PO task, confirming the involvement of the left IPL in tasks requiring the matching of hand postures and the corresponding objects as revealed by functional imaging studies (Kleineberg et al., 2018; Vingerhoets et al., 2013) and transcranial direct current stimulation (tDCS) in healthy participants (Evans et al., 2016). Further, TMS interference was reported for the SMG in the planning of goal-oriented hand-object interactions (Tunik et al., 2008). Notably, previous studies that applied TMS over the same coordinate as in the current study showed a causal involvement of the left SMG in the processing of manipulation knowledge (Andres et al., 2013) and correctly positioning fingers on manipulable objects (Andres et al., 2017).

4.1.3. Pantomime-situation task (PS)

The novel aspect of our second pantomime task, in which participants had to judge whether a pantomime matched with the presented situation (PS task), was that the pantomime-related manipulable object was *not* shown in this task. Thus, in contrast to the PO task, analysis of the object's shape and additional physical features was *not* possible in the PS task. Remarkably, online TMS over the left SMG also interfered with this novel task, uncovering the SMG's causal role in processing of pantomimes *per se*, including recognising and comprehending a pantomime's meaning.

4.2. Underlying mechanisms in processing the different facets of object-use pantomime

As expected, when compared to a control stimulation over the vertex, TMS applied over the left SMG interfered with the performance in the PO task, while there was no interference with the semantic control (OS) task. Online TMS over the left SMG also interfered with the PS task, even though the pantomime-related object was not shown in the PS task, precluding any processing of physical object features. Moreover, the TMS interference effects on the PO and the PS task correlated, while the TMS effects on both pantomime tasks did not correlate with the TMS effects on the control task (OS task).

In summary, these findings provide evidence for a causal involvement of the left SMG in processing both investigated facets of pantomimes (by the PO and PS tasks) as revealed by significant interference effects of online TMS when applied over the left SMG. Please note that the advantages of online TMS and its deductions regarding interference and causality have been framed in detail in the introduction (1.4.).

However, according to previous studies (Andres et al., 2013; Andres et al., 2017; Pelgrims et al., 2011) and taking into consideration that we applied a TMS paradigm (5 pulses, 10 Hz, 400ms, onset 250ms after stimuli onset) that creates a so-called ‘virtual lesion’ (Pascual-Leone et al., 2000), we had expected an RT increase instead of the observed RT shortening. Nevertheless, the causal role of the left SMG during the PO and PS tasks is unravelled by interference in either way (see introduction 1.4.). Importantly, an artefact or unspecific TMS-induced effect is ruled out as the control task (OS task) was unaffected by online TMS. We will discuss the manifold factors that might have driven performance improvement during processing the pantomime tasks i) by task-related considerations and ii) by TMS-related aspects.

4.2.1. Processing the different facets of object-use pantomime from a cognitive view

A TMS effect on task performance is the sum of its network effects, including changes in connectivity between the region stimulated by TMS and adjacent and remote regions. Accordingly, with Dynamic Causal Modeling (DCM, (Friston et al., 2003)) assessing effective connectivity, recent studies have revealed diverse bidirectional couplings between different brain regions within the left hemisphere’s praxis network, including interactions between dorsal stream and ventral stream areas (Kleineberg et al., 2018; Malfatti & Turella, 2021). Our current PO task resembles the “manipulation task” (matching of hand configurations to manipulable objects) applied in a previous fMRI-DCM study (Kleineberg et al., 2018). During this manipulation task, effective connectivity was weakened from the SMG to the intraparietal sulcus (IPS) and angular gyrus (AG) of the left hemisphere. Thus, one hypothesis to reconcile the finding of TMS-evoked improvements in response times may be that interfering with SMG resulted in a disinhibition of the IPS and the AG, two critical regions for object-related action processing. In a similar vein, TMS over the left SMG could have disinhibited left AG and IPS during the current PO task, in which objects had to be matched to pantomimes that also included hand configurations. Such disinhibition would allow for faster processing in the PO task by enhancing the couplings within the dorsal processing stream and between the dorsal and ventral stream. Thereby, online TMS interference applied over the left SMG could have led to faster task performance, as observed in the current study.

As comprehending the pantomime was inevitable to solve the PS task, we assume that the left IFG is beneficial in solving this task. The left IFG is known to be involved in pantomime processing (Goldenberg et al., 2007), especially in the communicative aspects of pantomimes (Finkel et al., 2018; Goldenberg, 2017). Notably, during the already mentioned manipulation task (Kleineberg et al., 2018), left IFG exerted a negative effective connectivity on left SMG. If TMS inhibits the left SMG, the IFG's negative influence on SMG activity is no longer required. This may free neural processing capacities in the left IFG, which then can support the processing of the pantomime's meaning as required in the PS task, again leading to a faster performance in this pantomime task. However, as the PS task is novel, any assumptions about the effective connectivity patterns underlying this task and the potential effects of TMS on these connectivity patterns remain conjectural. Interestingly, we found a significant correlation of the online TMS interference effects on both pantomime tasks. Although such a finding would be compatible with the left SMG being involved in both pantomime aspects to a similar degree, such a conclusion cannot be drawn from a correlation analysis. Other data like network parameters extracted from fMRI analyses, e.g., by using dynamic causal modelling, are needed to infer causality.

Regarding cognitive processing, pantomiming the use of objects loaded to a similar extent on two different components of a principal component analysis of apraxic deficits in 91 LH stroke patients (Schmidt et al., 2022). In the first component, together with the imitation of arm/hand gestures, processing spatial relationships between body parts and the pretended objects (pantomiming) or other body parts (imitation) was presumed as a shared underlying process, which was especially important in our PS task. Correct processing of spatial relations to body parts is inevitable to identify/understand the meaning of the pantomime, e.g., pantomiming drinking out of a glass becomes unrecognizable when the same gesture is misplaced in relation to the body. For the other component (shared with the imitation of finger configurations and actual object use), processing of structural features of the body parts or objects was assumed as common underlying factor. This was precisely demanded in the PO task, i.e., matching a pantomime to an object, by correctly extracting the structural object features to match these with the hand/finger configurations of the pantomime.

Notably, these two components underlying pantomiming the use of objects were associated with the left AG and left IPS (Schmidt et al., 2022). As argued above, the current online TMS may have led to disinhibition of these two regions. This disinhibition would allow left AG and IPS to better support the cognitive processes associated with components 1 (processing of spatial relationships) and 2 (processing of structural features) and thus improve performance in the current PS and PO tasks.

4.2.2. Processing the different facets of object-use pantomime from a methodological view

Besides the aspects discussed above, TMS-related issues can account for an interference effect resulting in improved or deteriorated task performance. Stimulation timing relative to task performance is one significant factor (Davare et al., 2007; Foltys et al., 2001; Jahanshahi & Rothwell, 2000; Walsh & Cowey, 2000). Using a 10Hz online rTMS-protocol in a step-tracking task, Davare and colleagues could show a time-dependent effect of online TMS for the motor system. When interference with ipsilateral M1 by online TMS occurred about 100ms before a muscle became active, it led to earlier muscle recruitment. Instead, when online TMS occurred later and closer to contraction, it delayed muscle recruitment (Davare et al., 2007). Similarly, investigating motor cortex excitability during word comprehension, using symbolic gestures (congruent/incongruent with the following word) as primes, de Marco and colleagues found increased motor evoked potentials by TMS for meaningful words compared to meaningless words, but only for the earlier processing phase (100 and 250ms from target onset), and not for later (500ms after target onset) processing (De Marco et al., 2018).

At 250ms after stimuli onset, we applied online TMS later than in previous studies (Andres et al., 2013; Andres et al., 2017; Pelgrims et al., 2011), who found a RT reduction for SMG stimulation compared to vertex. Thus, the current online TMS affected pantomime processing at a different, i.e., later stage, at which the stimulation could well lead to an improved task performance rather than the stimulation at earlier processing stages.

Regarding stimulation frequency, Jung and colleagues investigating semantic processing with TMS over the anterior temporal lobe found a reduced performance by low-frequency stimulation (1Hz) and improved performance by high-frequency (20 Hz) stimulation (Jung & Lambon Ralph, 2021).

Another factor influencing the response to brain stimulation is the instantaneous brain state and network configuration at stimulation (Silvanto et al., 2008; Zrenner et al., 2018). These aspects may explain why an ‘inhibitory stimulation’ protocol (i.e., application of continuous theta-burst stimulation over M1) produced an inhibitory effect as assessed by MEP amplitudes only in 32% of cases and even evoked a facilitatory effect in 58% (Hamada et al., 2013).

These findings question a simple relationship between a given TMS protocol and its ‘facilitatory’ or ‘inhibitory’ effects (for a recent review, see (Goldsworthy et al., 2021)).

Noteworthy, the TMS interference, revealed here for the pantomime tasks, cannot be accounted for by unspecific or prevailing TMS-induced effects on cognitive performance as the OS task (control task) remained unaffected. Therefore, our results demonstrate a specific and differential causal role of the left SMG in processing the different investigated facets of object-use pantomimes.

Taken together, this pattern of online TMS interference strongly suggests that the role of the SMG in pantomiming extends over and above mere processing of object features (as assessed in the PO task), but instead also includes the identification, recognition, and comprehension of pantomimes (prerequisite to solve the PS task).

4.3. Results in the context of the 'gesture engram' and 'technical reasoning' theories

While our results can neither prove nor falsify the 'manipulation-based/ gesture engram' hypothesis (Buxbaum, 2001, 2017; Buxbaum & Kalenine, 2010) or 'technical reasoning' hypothesis (Lesourd et al., 2017; Osiurak & Badets, 2016), our findings strongly suggest that the role of the left parietal cortex in pantomiming the use of objects goes beyond the mere linking relationship between pantomimed gestures and objects, but also entails the identification and recognition of the pantomime itself and its conveyed meaning. The current finding that online TMS over the left SMG influenced the novel PS task despite the absence of the corresponding object can hardly be reconciled with the technical reasoning theory, which postulates that object-use relies on the online processing of object properties by a mental simulation of the action based on mechanical knowledge and technical reasoning over the object/tool. In contrast, the current observation that both pantomime tasks were affected by online TMS over the left SMG speaks to the gesture-engram theory postulating that manipulation knowledge is retrieved by the left parietal cortex through gesture engrams. It is conceivable that solving the PS task also probably draws upon recalling semantic action-knowledge regarding the object-use pantomime, thus retrieving prior experienced/learned gesture engrams. As outlined above, retrieval of such manipulation knowledge indeed does not depend on the parietal lobe only. Rather, the left SMG can be considered a crucial hub in the network featuring various interactions with other brain regions, thereby interacting with other processing streams (Garcea & Buxbaum, 2019; Garcea et al., 2016; Kristensen et al., 2016).

4.4. Task-related considerations

Of note, the observed TMS effects on the PO and PS tasks were confined to changes in RT since no differential TMS effect was found for the accuracy rates. This finding is not uncommon in healthy participants and previously reported for the performance of comparable cognitive tasks during online TMS in healthy participants (Andres et al., 2013; Andres et al., 2017; Pelgrims et al., 2011).

The mean RTs in the two pantomime tasks (PO, PS) were longer than in the object-situation (OS) task probing semantic knowledge. Similar RT differences were found when tasks assessing action knowledge were compared to tasks assessing semantic knowledge (Garcea & Mahon, 2012; Kleineberg et al., 2018). Additionally, the current study employed a control stimulation condition (TMS over vertex) for each task to assess the differential TMS effect between the two stimulation conditions (left SMG versus vertex) in a given task. These *within*-task comparisons are not confounded by differences in the mean RTs *between* the tasks.

4.5. Limitations

Regarding the methodology, the magnetic field induced by TMS causes inevitable sensory side effects that include auditory (clicking sound, caused by current flow in the TMS coil) and somatosensory experiences (skin and peripheral nerve stimulation) that may impact behavioral performance and alertness, making a sham/control condition crucial (for further details on side effects, blinding issues, and different TMS sham conditions, see (Davis et al., 2013; Duecker & Sack, 2015). Like many previous online TMS studies on (motor-)cognitive behavior, we chose an active stimulation over the vertex as control/sham condition (Andres et al., 2013; Andres et al., 2017; Kuhnke et al., 2020; Pelgrims et al., 2011; Potok et al., 2019; Zhao et al., 2021), even though left SMG and vertex stimulation lead to different sensory effects. Notably, in our experiment, the participants were naïve to the stimulation sites and *not* informed that one site served for control. Taken together, as no sham condition can fully control for the TMS-induced side effects, it is essential to consider other methodical aspects (Duecker & Sack, 2015). Therefore, in addition to the control stimulation, we controlled for unspecific or general TMS-induced effects by including a control task (OS task), which revealed no differential effect between stimulation conditions ruling out that merely sensory differences led to the observed differential effects in the PS and PO tasks.

It must be considered that despite prior practice with 60 stimuli (not used in the main experiment), a strong learning effect was observed, which led to discarding the first two blocks and four participants by our predefined criteria (see methods section 2.6. - also for possible explanations of the learning effect). This elimination of data is a limitation of the current study as it led to a reduced statistical power but was mandatory for unambiguously detecting the effects of the applied online TMS, which requires stable task performance. Despite this reduction in statistical power, we found a significant interaction effect of task by stimulation in the ANCOVA.

Our experiment can only provide evidence for left SMG involvement in processing the investigated pantomime tasks. We are blind to the underlying network effects and the putative causal involvement of other regions in these tasks (also see 4.2.1.). Further studies are warranted to shed light on the causal role of different regions of interest, for instance, the inferior frontal gyrus, especially for the novel PS task. Such questions could be addressed by future TMS studies and patient lesion studies.

5. Conclusion

During online TMS of the left SMG, we found significant interference with two pantomime tasks compared to a control stimulation (vertex), resulting in new insights into the parietal cortex's role in processing of object-use pantomime. The current results confirm the findings of previous studies showing an involvement of the left SMG in matching pantomimes to the corresponding object (as in the current pantomime-object task, PO). Importantly, the current study extends previous knowledge by adopting a novel pantomime-situation task (PS), in which participants had to match a pantomime to the corresponding situation without the object being shown. The TMS interference with the PS task, when applied over the left SMG, strongly suggests that the parietal cortex's role in the pantomime of object-use goes beyond mere processing of object features and its link to manipulation, but comprises the identification, recognition, and comprehension of the pantomime. These findings support the manipulation-based hypothesis rather than the technical reasoning hypothesis, as the assumption of gesture engrams stored in the parietal cortex is compatible with the interference of SMG stimulation with both pantomime tasks.

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References

Achilles, E. I. S., Ballweg, C. S., Niessen, E., Kusch, M., Ant, J. M., Fink, G. R., & Weiss, P. H. (2019). Neural correlates of differential finger gesture imitation deficits in left hemisphere stroke. *Neuroimage Clin*, *23*, 101915. https://doi.org/10.1016/j.nicl.2019.101915

Allen, M., Poggiali, D., Whitaker, K., Marshall, T. R., & Kievit, R. A. (2019). Raincloud plots: a multi-platform tool for robust data visualization. *Wellcome Open Res*, *4*, 63. https://doi.org/10.12688/wellcomeopenres.15191.1

Andres, M., Pelgrims, B., & Olivier, E. (2013). Distinct contribution of the parietal and temporal cortex to hand configuration and contextual judgements about tools. *Cortex*, *49*(8), 2097-2105. https://doi.org/10.1016/j.cortex.2012.11.013

Andres, M., Pelgrims, B., Olivier, E., & Vannuscorps, G. (2017). The left supramarginal gyrus contributes to finger positioning for object use: A neuronavigated TMS study. *Eur J Neurosci*. https://doi.org/10.1111/ejn.13763

Awiszus, F. (2003). TMS and threshold hunting. *Suppl Clin Neurophysiol*, *56*, 13-23. https://doi.org/10.1016/s1567-424x(09)70205-3

Bach, P., Nicholson, T., & Hudson, M. (2014). The affordance-matching hypothesis: how objects guide action understanding and prediction. *Front Hum Neurosci*, *8*, 254. https://doi.org/10.3389/fnhum.2014.00254

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, *57*(1), 289-300. http://www.jstor.org/stable/2346101

Binkofski, F., & Buxbaum, L. J. (2013). Two action systems in the human brain. *Brain Lang*, *127*(2), 222-229. https://doi.org/10.1016/j.bandl.2012.07.007

Buxbaum, L. J. (2001). Ideomotor apraxia: a call to action. *Neurocase*, *7*(6), 445-458. https://doi.org/10.1093/neucas/7.6.445

Buxbaum, L. J. (2017). Learning, remembering, and predicting how to use tools: Distributed neurocognitive mechanisms: Comment on Osiurak and Badets (2016). *Psychol Rev*, *124*(3), 346-360. https://doi.org/10.1037/rev0000051

Buxbaum, L. J., & Kalenine, S. (2010). Action knowledge, visuomotor activation, and embodiment in the two action systems. *Ann N Y Acad Sci*, *1191*, 201-218. https://doi.org/10.1111/j.1749-6632.2010.05447.x

Canessa, N., Borgo, F., Cappa, S. F., Perani, D., Falini, A., Buccino, G., . . . Shallice, T. (2008). The different neural correlates of action and functional knowledge in semantic memory: an FMRI study. *Cereb Cortex*, *18*(4), 740-751. https://doi.org/10.1093/cercor/bhm110

Davare, M., Duque, J., Vandermeeren, Y., Thonnard, J. L., & Olivier, E. (2007). Role of the ipsilateral primary motor cortex in controlling the timing of hand muscle recruitment. *Cereb Cortex*, *17*(2), 353-362. https://doi.org/10.1093/cercor/bhj152

Davis, N. J., Gold, E., Pascual-Leone, A., & Bracewell, R. M. (2013). Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications. *Eur J Neurosci*, *38*(7), 2973-2977. https://doi.org/10.1111/ejn.12307

De Marco, D., De Stefani, E., Bernini, D., & Gentilucci, M. (2018). The effect of motor context on semantic processing: A TMS study. *Neuropsychologia*, *114*, 243-250. https://doi.org/10.1016/j.neuropsychologia.2018.05.003

Dovern, A., Fink, G. R., & Weiss, P. H. (2012). Diagnosis and treatment of upper limb apraxia. *J Neurol*, *259*(7), 1269-1283. https://doi.org/10.1007/s00415-011-6336-y

Dressing, A., Nitschke, K., Kümmerer, D., Bormann, T., Beume, L., Schmidt, C. S. M., . . . Martin, M. (2018). Distinct Contributions of Dorsal and Ventral Streams to Imitation of Tool-Use and Communicative Gestures. *Cereb Cortex*, *28*(2), 474-492. https://doi.org/10.1093/cercor/bhw383

Duecker, F., & Sack, A. T. (2015). Rethinking the role of sham TMS. *Front Psychol*, *6*, 210. https://doi.org/10.3389/fpsyg.2015.00210

Evans, C., Edwards, M. G., Taylor, L. J., & Ietswaart, M. (2016). Perceptual decisions regarding object manipulation are selectively impaired in apraxia or when tDCS is applied over the left IPL. *Neuropsychologia*, *86*, 153-166. https://doi.org/10.1016/j.neuropsychologia.2016.04.020

Finkel, L., Hogrefe, K., Frey, S. H., Goldenberg, G., & Randerath, J. (2018). It takes two to pantomime: Communication meets motor cognition. *Neuroimage Clin*, *19*, 1008-1017. https://doi.org/10.1016/j.nicl.2018.06.019

Foltys, H., Sparing, R., Boroojerdi, B., Krings, T., Meister, I. G., Mottaghy, F. M., & Töpper, R. (2001). Motor control in simple bimanual movements: a transcranial magnetic stimulation and reaction time study. *Clin Neurophysiol*, *112*(2), 265-274. https://doi.org/10.1016/s1388-2457(00)00539-3

Friston, K. J., Harrison, L., & Penny, W. (2003). Dynamic causal modelling. *Neuroimage*, *19*(4), 1273-1302.

Garcea, F. E., & Buxbaum, L. J. (2019). Gesturing tool use and tool transport actions modulates inferior parietal functional connectivity with the dorsal and ventral object processing pathways. *Hum Brain Mapp*. https://doi.org/10.1002/hbm.24565

Garcea, F. E., Kristensen, S., Almeida, J., & Mahon, B. Z. (2016). Resilience to the contralateral visual field bias as a window into object representations. *Cortex*, *81*, 14-23. https://doi.org/10.1016/j.cortex.2016.04.006

Garcea, F. E., & Mahon, B. Z. (2012). What is in a tool concept? Dissociating manipulation knowledge from function knowledge. *Mem Cognit*, *40*(8), 1303-1313. https://doi.org/10.3758/s13421-012-0236-y

Gerloff, C., Cohen, L. G., Floeter, M. K., Chen, R., Corwell, B., & Hallett, M. (1998). Inhibitory influence of the ipsilateral motor cortex on responses to stimulation of the human cortex and pyramidal tract. *J Physiol*, *510 (Pt 1)*, 249-259.

Gerloff, C., Corwell, B., Chen, R., Hallett, M., & Cohen, L. G. (1998). The role of the human motor cortex in the control of complex and simple finger movement sequences. *Brain*, *121 (Pt 9)*, 1695-1709. https://doi.org/10.1093/brain/121.9.1695

Goldenberg, G. (2001). Imitation and matching of hand and finger postures. *Neuroimage*, *14*(1 Pt 2), S132-136. https://doi.org/10.1006/nimg.2001.0820

Goldenberg, G. (2017). Facets of Pantomime. *J Int Neuropsychol Soc*, *23*(2), 121-127. https://doi.org/10.1017/S1355617716000989

Goldenberg, G., & Hagmann, S. (1998). Tool use and mechanical problem solving in apraxia. *Neuropsychologia*, *36*(7), 581-589.

Goldenberg, G., Hermsdörfer, J., Glindemann, R., Rorden, C., & Karnath, H. O. (2007). Pantomime of tool use depends on integrity of left inferior frontal cortex. *Cereb Cortex*, *17*(12), 2769-2776. https://doi.org/10.1093/cercor/bhm004

Goldsworthy, M. R., Hordacre, B., Rothwell, J. C., & Ridding, M. C. (2021). Effects of rTMS on the brain: is there value in variability? *Cortex*, *139*, 43-59. https://doi.org/10.1016/j.cortex.2021.02.024

Hamada, M., Murase, N., Hasan, A., Balaratnam, M., & Rothwell, J. C. (2013). The role of interneuron networks in driving human motor cortical plasticity. *Cereb Cortex*, *23*(7), 1593-1605. https://doi.org/10.1093/cercor/bhs147

Hoeren, M., Kummerer, D., Bormann, T., Beume, L., Ludwig, V. M., Vry, M. S., . . . Weiller, C. (2014). Neural bases of imitation and pantomime in acute stroke patients: distinct streams for praxis. *Brain*, *137*(Pt 10), 2796-2810. https://doi.org/10.1093/brain/awu203

Ishibashi, R., Lambon Ralph, M. A., Saito, S., & Pobric, G. (2011). Different roles of lateral anterior temporal lobe and inferior parietal lobule in coding function and manipulation tool knowledge: evidence from an rTMS study. *Neuropsychologia*, *49*(5), 1128-1135. https://doi.org/10.1016/j.neuropsychologia.2011.01.004

Jahanshahi, M., & Rothwell, J. (2000). Transcranial magnetic stimulation studies of cognition: an emerging field. *Exp Brain Res*, *131*(1), 1-9. https://doi.org/10.1007/s002219900224

Jarry, C., Osiurak, F., Delafuys, D., Chauviré, V., Etcharry-Bouyx, F., & Le Gall, D. (2013). Apraxia of tool use: more evidence for the technical reasoning hypothesis. *Cortex*, *49*(9), 2322-2333. https://doi.org/10.1016/j.cortex.2013.02.011

Jung, J., & Lambon Ralph, M. A. (2021). Enhancing vs. inhibiting semantic performance with transcranial magnetic stimulation over the anterior temporal lobe: Frequency- and task-specific effects. *Neuroimage*, *234*, 117959. https://doi.org/10.1016/j.neuroimage.2021.117959

Kalenine, S., & Buxbaum, L. J. (2016). Thematic knowledge, artifact concepts, and the left posterior temporal lobe: Where action and object semantics converge. *Cortex*, *82*, 164-178. https://doi.org/10.1016/j.cortex.2016.06.008

Kalenine, S., Buxbaum, L. J., & Coslett, H. B. (2010). Critical brain regions for action recognition: lesion symptom mapping in left hemisphere stroke. *Brain*, *133*(11), 3269-3280. https://doi.org/10.1093/brain/awq210

Kleineberg, N. N., Dovern, A., Binder, E., Grefkes, C., Eickhoff, S. B., Fink, G. R., & Weiss, P. H. (2018). Action and semantic tool knowledge - Effective connectivity in the underlying neural networks. *Hum Brain Mapp*. https://doi.org/10.1002/hbm.24188

Kristensen, S., Garcea, F. E., Mahon, B. Z., & Almeida, J. (2016). Temporal Frequency Tuning Reveals Interactions between the Dorsal and Ventral Visual Streams. *J Cogn Neurosci*, *28*(9), 1295-1302. https://doi.org/10.1162/jocn_a_00969

Kuhnke, P., Beaupain, M. C., Cheung, V. K. M., Weise, K., Kiefer, M., & Hartwigsen, G. (2020). Left posterior inferior parietal cortex causally supports the retrieval of action knowledge. *Neuroimage*, *219*, 117041. https://doi.org/10.1016/j.neuroimage.2020.117041

Lesourd, M., Baumard, J., Jarry, C., Etcharry-Bouyx, F., Belliard, S., Moreaud, O., . . . Osiurak, F. (2017). Rethinking the Cognitive Mechanisms Underlying Pantomime of Tool Use: Evidence from Alzheimer's Disease and Semantic Dementia. *J Int Neuropsychol Soc*, *23*(2), 128-138. https://doi.org/10.1017/s1355617716000618

Li, L. M., Uehara, K., & Hanakawa, T. (2015). The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Front Cell Neurosci*, *9*, 181. https://doi.org/10.3389/fncel.2015.00181

Malfatti, G., & Turella, L. (2021). Neural encoding and functional interactions underlying pantomimed movements. *Brain Struct Funct*, *226*(7), 2321-2337. https://doi.org/10.1007/s00429-021-02332-6

Niessen, E., Fink, G. R., & Weiss, P. H. (2014). Apraxia, pantomime and the parietal cortex. *Neuroimage Clin*, *5*, 42-52. https://doi.org/10.1016/j.nicl.2014.05.017

Osiurak, F., & Badets, A. (2016). Tool use and affordance: Manipulation-based versus reasoning-based approaches. *Psychol Rev*, *123*(5), 534-568. https://doi.org/10.1037/rev0000027

Pascual-Leone, A., Gates, J. R., & Dhuna, A. (1991). Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology*, *41*(5), 697-702. https://doi.org/10.1212/wnl.41.5.697

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience--virtual lesion, chronometry, and functional connectivity. *Curr Opin Neurobiol*, *10*(2), 232-237.

Pelgrims, B., Olivier, E., & Andres, M. (2011). Dissociation between manipulation and conceptual knowledge of object use in the supramarginalis gyrus. *Hum Brain Mapp*, *32*(11), 1802-1810. https://doi.org/10.1002/hbm.21149

Potok, W., Maskiewicz, A., Kroliczak, G., & Marangon, M. (2019). The temporal involvement of the left supramarginal gyrus in planning functional grasps: A neuronavigated TMS study. *Cortex*, *111*, 16-34. https://doi.org/10.1016/j.cortex.2018.10.010

Rizzolatti, G., & Matelli, M. (2003). Two different streams form the dorsal visual system: anatomy and functions. *Exp Brain Res*, *153*(2), 146-157. https://doi.org/10.1007/s00221-003-1588-0

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*, *120*(12), 2008-2039. https://doi.org/10.1016/j.clinph.2009.08.016

Rossini, P. M., Burke, D., Chen, R., Cohen, L. G., Daskalakis, Z., Di Iorio, R., . . . Ziemann, U. (2015). Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol*, *126*(6), 1071-1107. https://doi.org/10.1016/j.clinph.2015.02.001

Schluter, N. D., Rushworth, M. F., Passingham, R. E., & Mills, K. R. (1998). Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. *Brain*, *121 (Pt 5)*, 785-799. https://doi.org/10.1093/brain/121.5.785

Schmidt, C. C., Achilles, E. I. S., Fink, G. R., & Weiss, P. H. (2022). Distinct cognitive components and their neural substrates underlying praxis and language deficits following left hemisphere stroke. *Cortex*, *146*, 200-215. https://doi.org/10.1016/j.cortex.2021.11.004

Silvanto, J., Muggleton, N., & Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends Cogn Sci*, *12*(12), 447-454. https://doi.org/10.1016/j.tics.2008.09.004

Sperber, C., Wiesen, D., Goldenberg, G., & Karnath, H. O. (2019). A network underlying human higher-order motor control: Insights from machine learning-based lesion-behaviour mapping in apraxia of pantomime. *Cortex*, *121*, 308-321. https://doi.org/10.1016/j.cortex.2019.08.023

Tarhan, L. Y., Watson, C. E., & Buxbaum, L. J. (2015). Shared and Distinct Neuroanatomic Regions Critical for Tool-related Action Production and Recognition: Evidence from 131 Left-hemisphere Stroke Patients. *J Cogn Neurosci*, *27*(12), 2491-2511. https://doi.org/10.1162/jocn_a_00876

Tscherpel, C., Hensel, L., Lemberg, K., Vollmer, M., Volz, L. J., Fink, G. R., & Grefkes, C. (2020). The differential roles of contralesional frontoparietal areas in cortical reorganization after stroke. *Brain Stimul*, *13*(3), 614-624. https://doi.org/10.1016/j.brs.2020.01.016

Tunik, E., Lo, O. Y., & Adamovich, S. V. (2008). Transcranial magnetic stimulation to the frontal operculum and supramarginal gyrus disrupts planning of outcome-based hand-object interactions. *J Neurosci*, *28*(53), 14422-14427. https://doi.org/10.1523/jneurosci.4734-08.2008

Vingerhoets, G. (2014). Contribution of the posterior parietal cortex in reaching, grasping, and using objects and tools. *Front Psychol*, *5*, 151. https://doi.org/10.3389/fpsyg.2014.00151

Vingerhoets, G., Nys, J., Honore, P., Vandekerckhove, E., & Vandemaele, P. (2013). Human left ventral premotor cortex mediates matching of hand posture to object use. *PLoS One*, *8*(7), e70480. https://doi.org/10.1371/journal.pone.0070480

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nat Rev Neurosci*, *1*(1), 73-79. https://doi.org/10.1038/35036239

Watson, C. E., & Buxbaum, L. J. (2015). A distributed network critical for selecting among tool-directed actions. *Cortex*, *65*, 65-82. https://doi.org/10.1016/j.cortex.2015.01.007

Weiss, P. H., Ubben, S. D., Kaesberg, S., Kalbe, E., Kessler, J., Liebig, T., & Fink, G. R. (2016). Where language meets meaningful action: a combined behavior and lesion analysis of aphasia and apraxia. *Brain Struct Funct*, *221*(1), 563-576. https://doi.org/10.1007/s00429-014-0925-3

Wheaton, L. A., & Hallett, M. (2007). Ideomotor apraxia: a review. *J Neurol Sci*, *260*(1-2), 1-10. https://doi.org/10.1016/j.jns.2007.04.014

Zhao, W., Li, Y., & Du, Y. (2021). TMS Reveals Dynamic Interaction between Inferior Frontal Gyrus and Posterior Middle Temporal Gyrus in Gesture-Speech Semantic Integration. *J Neurosci*, *41*(50), 10356-10364. https://doi.org/10.1523/jneurosci.1355-21.2021

Zrenner, C., Desideri, D., Belardinelli, P., & Ziemann, U. (2018). Real-time EEG-defined excitability states determine efficacy of TMS-induced plasticity in human motor cortex. *Brain Stimul*, *11*(2), 374-389. https://doi.org/10.1016/j.brs.2017.11.016

Figure legends

Figure 1. Stimuli of the experimental tasks. Participants had to judge whether the picture in the upper half portrayed a match or a mismatch in regard to the picture below and indicate their response by pressing a green (match) or red button (mismatch) with their left index finger.

Figure 2. Experimental design and procedure.

2a. Illustration of the stimulation coordinate over the left supramarginal gyrus (SMG), here in the normalized brain in MNI space in MRIcron. The lower right picture shows the placement and orientation of the coil over the left SMG.

2b. Content of an exemplary experimental block. The experiment consisted of 8 blocks: 4 SMG (verum), 4 vertex (control) stimulation. Each block included 16 trials of each of the three tasks (8 matches, 8 mismatches).

L SMG, left supramarginal gyrus; PS, pantomime-situation; OS, object-situation; PO, pantomime-object; rTMS, repetitive transcranial magnetic stimulation

2c. Course of the experiment. 250ms after each stimuli presentation, rTMS trains of 5 pulses, 10 Hz were applied over 400ms. Participants indicated their response by pressing the green or red button, which terminated the stimuli presentation. The interstimulus interval (ISI) was jittered between 5 and 6 seconds.

Figure 3. Response times in the experimental tasks by TMS stimulation.

Raincloud plots (Allen et al., 2019) illustrating the TMS effects on a group level, error bars indicate 95% confidence intervals. Significant differences in response times between vertex (control) and left SMG (verum) stimulation were found for the Pantomime-Object (blue) and the Pantomime-Situation task (red), no significant difference for the Object-Situation task (yellow, control task).

SMG L, left supramarginal gyrus; p_{FDR}, p-value corrected for multiple comparisons by false-discovery rate; *, significant differential effect; n.s., non-significant

Authorship statement

Nina N. Kleineberg: Conceptualization, Methodology, Creation and piloting of stimuli, Data acquisition, Analysis, Interpretation of results, Visualization, Writing - original draft

Caroline Tscherpel: Methodology, Software, Data acquisition, Analysis, Interpretation of results, Writing - review & editing

Gereon R. Fink: Project administration, Writing - review & editing

Christian Grefkes: Supervision, Methodology, Resources, Writing - review & editing

Peter H. Weiss: Conceptualization, Supervision, Interpretation of results, Writing - review & editing

Table 1. Group results for accuracy rate and response time

	Left SMG	Vertex	
Mean Accuracy Rate (%) ± SD			**p-value (uncorr.)**
PO task	98 ± 2.8	97 ± 2.9	0.44
PS task	96 ± 3.6	96 ± 4.2	0.97
OS task	98 ± 2.4	98 ± 3.1	0.42
Mean Response times (ms) ± SD			**p-value (FDR)**
PO task	931 ± 169	954 ± 187	0.03*
PS task	997 ± 213	1033 ± 227	0.04*
OS task	917 ± 168	929 ± 165	0.33

SMG, supramarginal gyrus; PO, pantomime-object; PS, pantomime-situation; OS, object-situation; SD, standard deviation; FDR, corrected for multiple comparisons by false-discovery rate; *, statistically significant.

Table 2. Correlations of TMS interference between tasks

	PO task	PS task	OS task
PO task		0.42* (p=0.04)	-0.34 (p=0.87)
PS task	0.42* (p=0.04)		0.24 (p=0.25)
OS task	-0.34 (p=0.87)	0.24 (p=0.25)	

PO, pantomime-object; PS, pantomime-situation; OS, object-situation; *, statistically significant.

The differences of response times between control and verum conditions of each task correlated. Spearman's rank correlation coefficients are shown. The PO and PS task are statistically significantly positively correlated. No significant correlations between the PO or PS with the OS task were revealed.

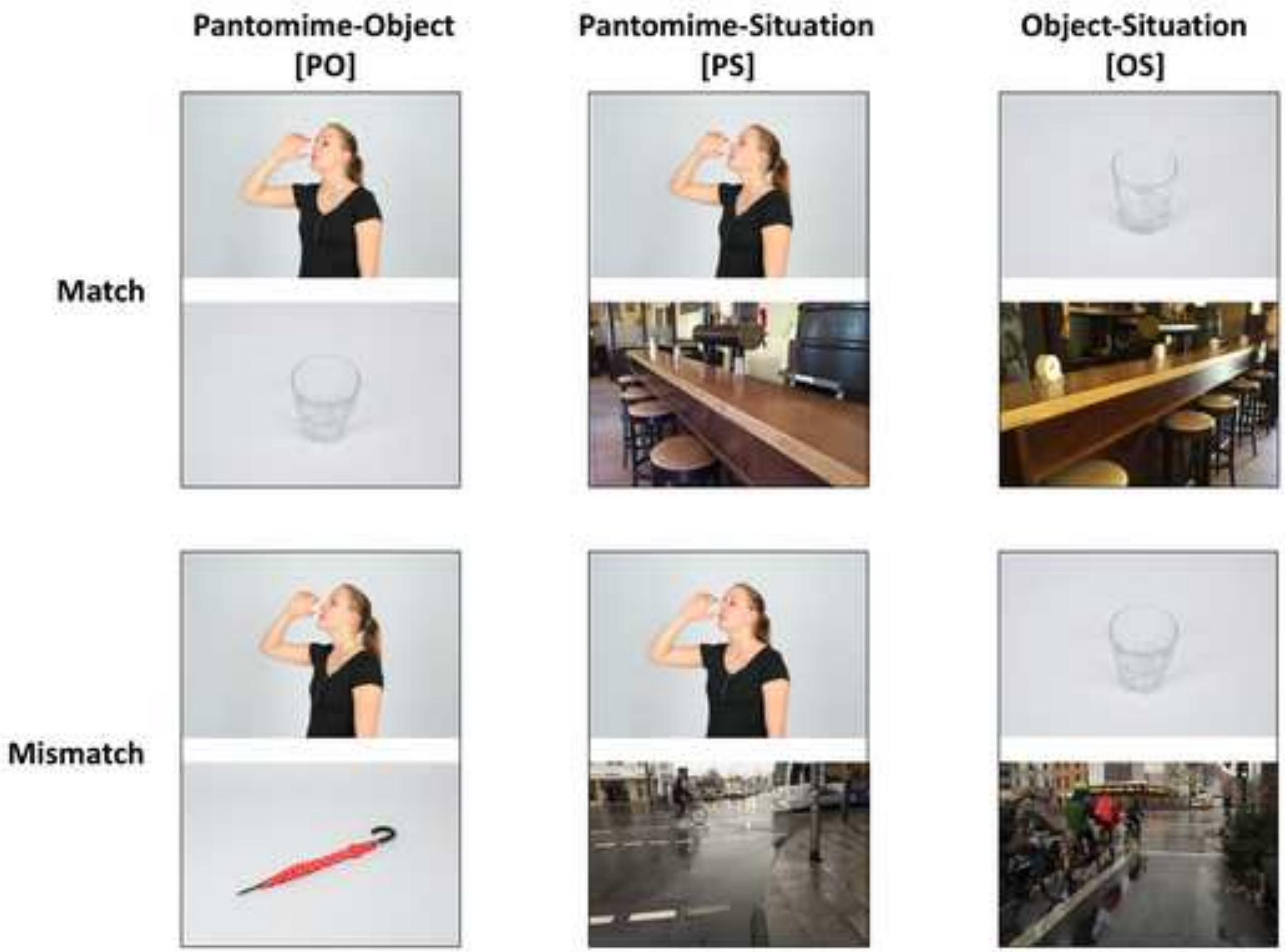
Pantomime-Object
[PO]
Pantomime-Situation
[PS]
Object-Situation
[OS]
Match
Mismatch

Figure 1

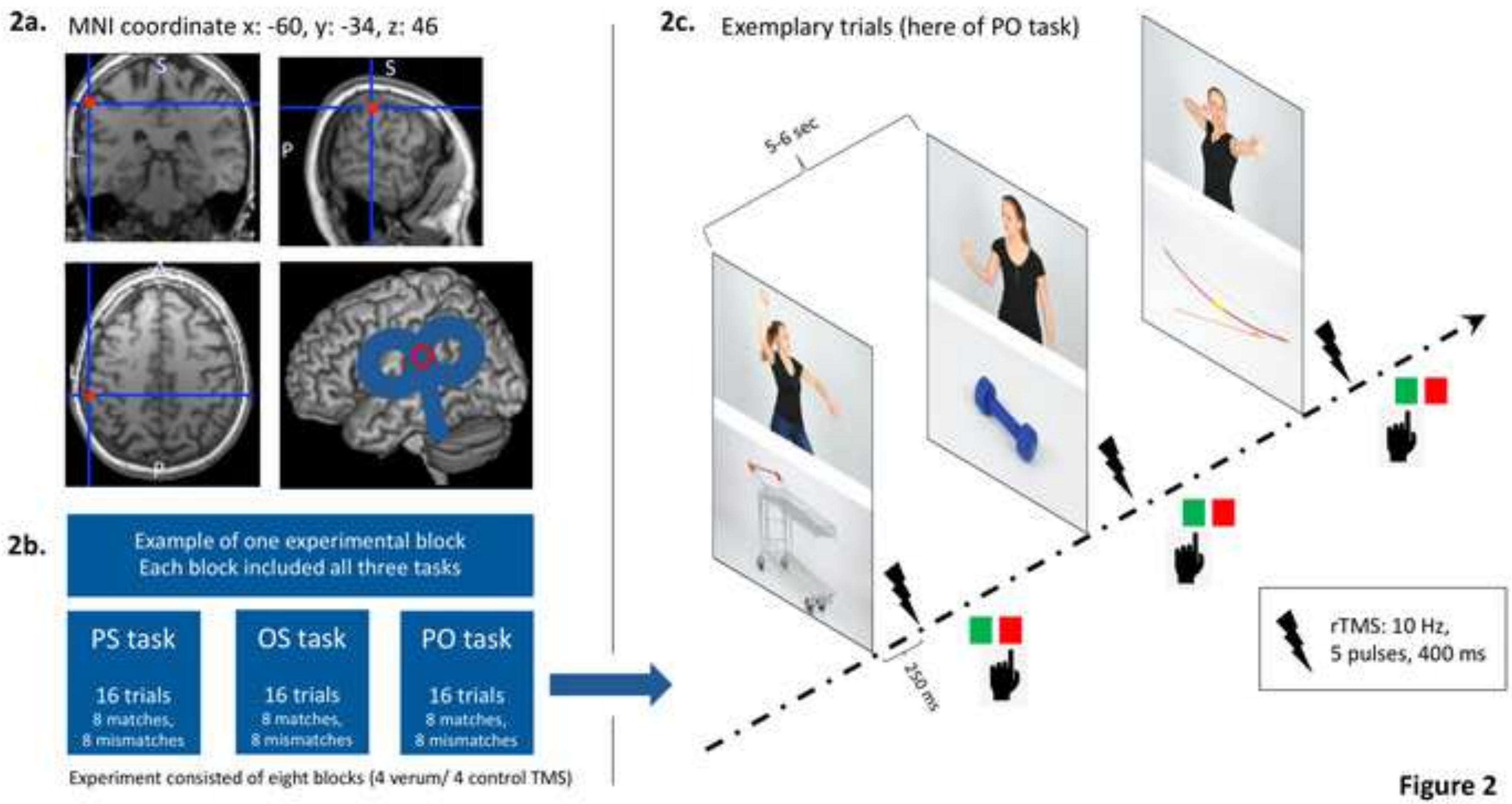
2a.
MNI coordinate x: -60, y: -34, z: 46
S
S
P
P
2b.
Example of one experimental block
Each block included all three tasks
PS task
16 trials
8 matches,
8 mismatches
OS task
16 trials
8 matches,
8 mismatches
PO task
16 trials
8 matches,
8 mismatches
Experiment consisted of eight blocks (4 verum/ 4 control TMS)
2c.
Exemplary trials (here of PO task)
5-6 sec
250 ms
rTMS: 10 Hz,
5 pulses, 400 ms

Figure 2

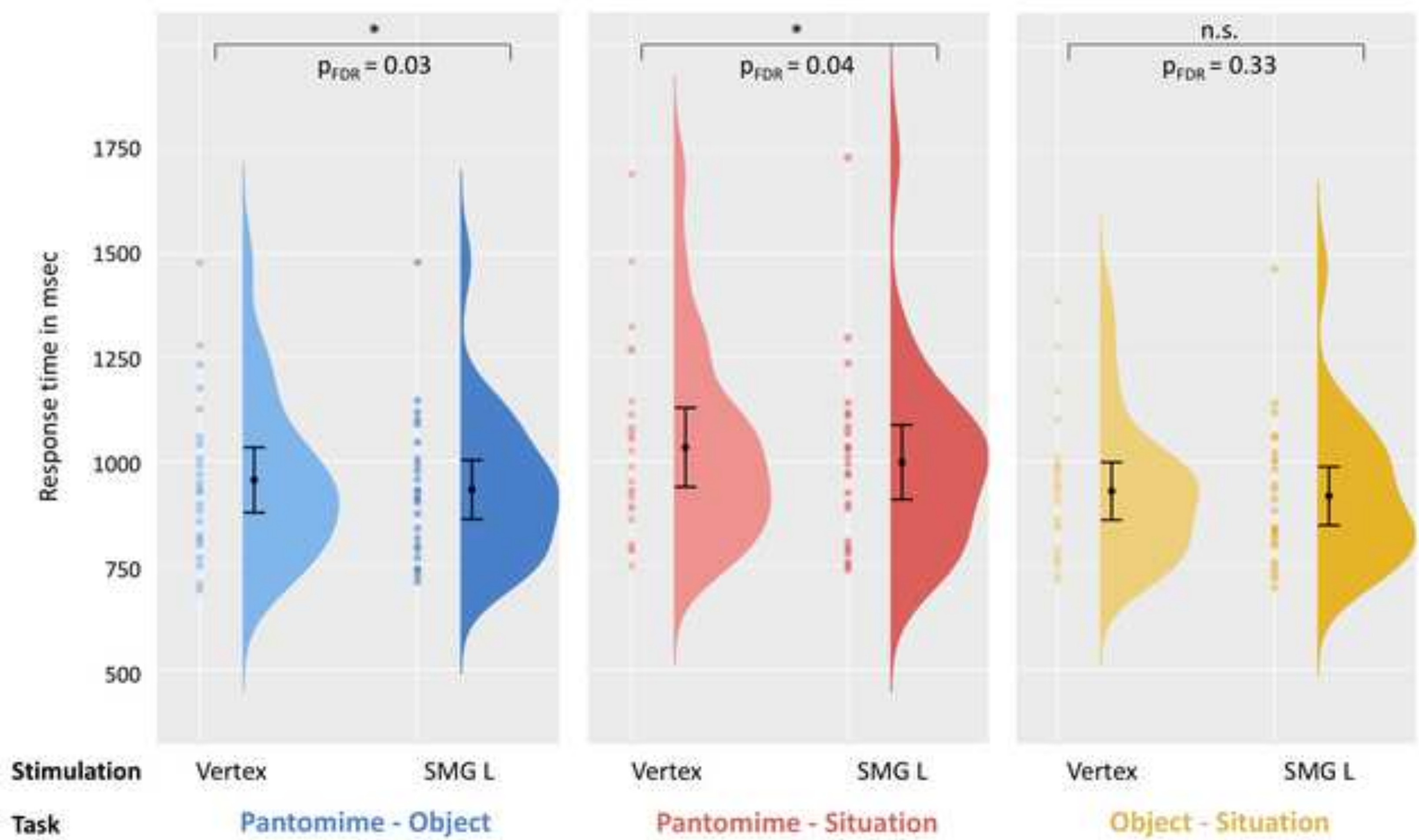
*
$p_{FDR} = 0.03$
*
$p_{FDR} = 0.04$
n.s.
$p_{FDR} = 0.33$
Response time in msec
1750
1500
1250
1000
750
500
Stimulation
Vertex
SMG L
Vertex
SMG L
Vertex
SMG L
Task
Pantomime - Object
Pantomime - Situation
Object - Situation

Figure 3

Highlights:

- TMS over the left supramarginal gyrus (SMG) interferes with pantomime of tool use
- Studies suggest a direct link between an object and the respective pantomime
- A novel task assessed the recognition and comprehension of object-use pantomimes' meaning
- Online TMS over left SMG revealed that SMG supports both facets of pantomime