



Research Report

“Left and right prefrontal routes to action comprehension”



Lucia Amoruso^{a,b,c,*}, Alessandra Finisguerra^d and Cosimo Urgesi^{a,d}

^a Laboratory of Cognitive Neuroscience, Department of Languages and Literatures, Communication, Education and Society, University of Udine, Udine, I-33100, Italy

^b Basque Center on Cognition, Brain and Language, San Sebastian, 20009, Spain

^c IKERBASQUE, Basque Foundation for Science, Bilbao, 48009, Spain

^d Scientific Institute, IRCCS E. Medea, Pasion di Prato, Udine, I-33037, Italy

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ABSTRACT

Successful action comprehension requires the integration of motor information and semantic cues about objects in context. Previous evidence suggests that while motor features are dorsally encoded in the fronto-parietal action observation network (AON); semantic features are ventrally processed in temporal structures. Importantly, these dorsal and ventral routes seem to be preferentially tuned to low (LSF) and high (HSF) spatial frequencies, respectively. Recently, we proposed a model of action comprehension where we hypothesized an additional route to action understanding whereby coarse LSF information about objects in context is projected to the dorsal AON via the prefrontal cortex (PFC), providing a prediction signal of the most likely intention afforded by them. Yet, this model awaits for experimental testing. To this end, we used a perturb-and-measure continuous theta burst stimulation (cTBS) approach, selectively disrupting neural activity in the left and right PFC and then evaluating the participant's ability to recognize filtered action stimuli containing only HSF or LSF. We find that stimulation over PFC triggered different spatial-frequency modulations depending on lateralization: left-cTBS and right-cTBS led to poorer performance on HSF and LSF action stimuli, respectively. Our findings suggest that left and right PFC exploit distinct spatial frequencies to support action comprehension, providing evidence for multiple routes to social perception in humans.

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* Corresponding author. Basque Center on Cognition, Brain and Language, Paseo Mikeletegi, 69, 20009 San Sebastian, Spain.

E-mail address: l.amoruso@bcbl.eu (L. Amoruso).

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1. Introduction

Action perception triggers the activation of the action observation network (AON), a set of fronto-parietal regions thought to underpin our ability to comprehend others' behaviors (Kilner, Friston, & Frith, 2007; Urgen & Saygin, 2020). To do so, this network exploits subtle kinematic information provided by perceived ongoing movements, but also contextual cues present in the scene where actions take place (Kilner, 2011).

Indeed, observers' motor activation and perceptual performance during action recognition are facilitated or hindered when movement kinematics unfolds in, respectively, congruent (e.g., reaching-to-grasp a mug full of coffee with a precision grip) or incongruent (e.g., reaching-to-grasp an empty mug with a precision grip) contexts (Amoruso & Finisguerra, 2019; Janssen, Steenbergen, & Carson, 2015; Riach, Holmes, Franklin, & Wright, 2018; Senot et al., 2011). Critically, it has been shown that the processing of actions embedded in incongruent contexts is altered by interferential stimulation of prefrontal cortex (PFC) activity (Amoruso, Finisguerra, & Urgesi, 2018; Balconi & Canavesio, 2014; Balconi & Vitaloni, 2014), suggesting that this region plays a key role in integrating motor and contextual cues during action processing. In particular, previous studies (Balconi & Canavesio, 2014; Balconi & Vitaloni, 2014) found that stimulation of left PFC with cathodal (inhibitory) transcranial direct current stimulation selectively hindered the ability to recognize semantically anomalous action sequences (i.e., brushing teeth with a comb), increasing error rates, reaction times and altering neurophysiological responses associated to semantic processing (e.g., N400). Similarly, transcranial magnetic stimulation (TMS) of left PFC, hampered the recognition of actions unfolding either in incongruent or congruent contexts, while leaving unaltered the prediction of actions unfolding in isolation (Amoruso et al., 2018). These results suggest that the PFC plays a key role in integrating semantic and motor knowledge during action representation and in detecting potential interference among these two sources of information (Amoruso et al., 2018; Balconi & Canavesio, 2014; Balconi & Vitaloni, 2014). Yet, the neural mechanism and the brain pathways supporting this process remain unclear (Urgen & Miller, 2015).

According to dual stream models on action comprehension (Kilner, 2011), the concrete motor aspects of an action (i.e., movement kinematics) are encoded through the classical AON. Contrarily, a ventral route linking posterior MTG and prefrontal structures would allow predicting most abstract aspects such as likely motor intentions based on the embedding context. Of note, this prediction will impact on the AON, laying the basis for estimating the kinematics of the expected action.

Recently, we proposed the existence of an alternative route (Amoruso, Finisguerra, & Urgesi, 2020) beyond the ventral pathway, involved in the generation of context-based expectations about likely motor intentions driving observed actions from coarse low spatial frequencies (LSF). Our proposal capitalizes on appealing models in the domain of object recognition (Bar, 2004, 2007; Bar et al., 2006; Fenske, Aminoff, Gronau, & Bar, 2006; Kveraga, Boshyan, & Bar, 2007), suggesting that regions in the PFC early exploit LSF information -carried via the dorsal magnocellular pathway- to generate top-down

predictions about object's identity. These LSF-based predictions would impact on the ventral pathway, facilitating recognition by narrowing the number of plausible object candidates. Given that multiple alternatives can be elicited, detailed information conveyed via high spatial frequencies (HSF) through parvocellular projections would be used to refine these predictions and solve the ambiguity.

In a similar vein, we propose an extended version of this model for action comprehension in which early LSF-based predictions are fed back not only to the ventral system, but also to the dorsal AON, generating early expectations about forthcoming kinematics based on affordances evoked by the objects (Amoruso et al., 2020). Further support to this hypothesis comes from monkey studies showing that neurons in the PFC (Simone, Rozzi, Bimbi, & Fogassi, 2015) as well as in premotor (Bruni, Giorgetti, Fogassi, & Bonini, 2017) and pre-supplementary motor areas (Livi et al., 2019) can encode "pragmatic" representations of objects in terms of the potential kinematics they afford before movement onset, highlighting the predictive nature of these mechanisms.

Thus, beyond current dual stream models suggesting that context-based expectations about others' intentions are primarily estimated through the ventral pathway, we propose the existence of an alternative dorsal-magnocellular route through which prior information can be injected to the AON. Here, we sought to experimentally test the involvement of these two routes (ventral and dorsal), using an off-line continuous theta burst stimulation (cTBS) protocol to perturb left and right PFC activity (vs. a control site) and measured changes in participants' performance during the observation of filtered action stimuli respectively containing HSF or LSF information. Briefly, cTBS constitutes a powerful tool to investigate causal relationships between neural activation and behavior (Bergmann & Hartwigsen, 2021) offering a unique opportunity to transiently disturb neural activity in regions of interest, and measure the consequent changes in participants' performance.

We reasoned that if the left or right PFC exploits information from the ventral pathway (i.e., fine-grained HSF representations of objects in context) to form expectations about others' actions as suggested by current dual stream models, then we should observe a cTBS-related effect for HSF stimuli. Moreover, if, as we propose in our model, the left or right PFC uses coarse LSF representations to form these expectations (Amoruso et al., 2020; Bar et al., 2006; Kveraga, Ghuman, & Bar, 2007; Trapp & Bar, 2015), then disruption of its activity should also affect participants' performance in processing LSF stimuli. This latter finding would support the use of LSF information and thus indicate that an additional (i.e., the magnocellular) route contributes to context-based action comprehension.

Interestingly, there is evidence (Peyrin, Baciú, Segebarth, & Marendaz, 2004; Peyrin, Chauvin, Chokron, & Marendaz, 2003; Peyrin et al., 2006) supporting the existence of left and right hemispheric preferences for processing, respectively, HSF and LSF information. While the original proposal of our model did not acknowledge any hemispheric differences in the instantiation of action comprehension routes, we took advantage on this evidence to also test for a potential distinct engagement of left and right PFC in processing context-embedded actions.

Finally, based on previous studies (Amoruso et al., 2018; Balconi & Canavesio, 2014; Balconi & Vitaloni, 2014) showing that interferential stimulation of PFC primarily disrupts the recognition of broadband displays of actions embedded in incongruent contexts, we expected that PFC cTBS would mainly affect filtered stimuli in incongruent contexts, where inconsistent hand posture and contextual information needs to be integrated.

2. Materials and methods

2.1. Participants

Following best practices, we report below how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, as well as detailed information about experimental manipulations and measures acquired in the present study.

A total of thirty-two students were recruited at the University of Udine and randomly allocated to left (left PFC stimulation; 10 females, mean age = 23.25 years-old, SD = 5.82) or right (right PFC stimulation; 11 females, mean age = 22.86 years-old, SD = 3.24) stimulation group, for an original sample of sixteen participants per group. Although no exclusion criteria based on behavioral performance was established prior to the study, one participant was excluded due to below-chance level accuracy (<50%) across all conditions (i.e., independently of the area being stimulated). In addition, another participant was eliminated due to technical problems during data acquisition. Thus, all final analyses were performed on two groups of fifteen participants each. All participants were right-handed according to the Standard Handedness Inventory (Oldfield, 1971) and had normal or corrected-to-normal visual acuity. None of the participants reported a history of neurological, psychiatric, or other major medical problems or any contraindications for TMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). They all gave their written informed consent prior to the experiment and received course credits for their contribution. The experimental procedures were approved by the local ethics committee (Comitato Etico Regionale Unico, Friuli Venezia Giulia, Italy) and were carried out in accordance with the revised Helsinki Declaration (World Medical Association General Assembly 2008). We determined the sample size for our mixed within- and between-subject $2 \times 3 \times 2 \times 2$ design (Area [vertex, PFC] \times Context [no-context, congruent context, incongruent context] \times Spatial Frequency [HSF, LSF] \times Group [left, right]) using the MorePower 6.0.4 toolbox (Campbell & Thompson, 2012). The expected effect size was set at .25 based on previous studies on contextual and spatial frequency modulations for observed actions (Amoruso et al., 2018, 2020), with α level at .05, and desired power ($1 - \beta$) at 90%. A between subject design for the left and right PFC stimulation (i.e., each participant being stimulated on either left or right PFC but not on both) was adopted to reduce for each participant the number of task/conditions exposure which are known to lead to reduced effects due to learning processes and/or neural habituation (e.g., repetition suppression).

No part of the study procedures or analyses was preregistered prior to the research being conducted.

2.2. Stimuli

We used snapshots with a resolution of $1,920 \times 1,080$ pixels taken with a Canon EOS 550D digital camera and edited them with the Adobe Photoshop 7 (Adobe Systems). Pictures depicted everyday-life actions performed by a woman model with her right hand reaching-to-grasp four different objects (i.e., a bottle, a cup, a glass, and a spray cleaner).

Depending on the hand preshaping (precision vs. power grips), each object could be grasped to perform either one of two possible actions. For instance, in the case of the object “bottle,” the two possible actions were 1) pour and 2) place, each of them performed with the correspondent hand posture: reaching-to-grasp and pour using a power grip and reaching-to-grasp and lift using a precision grip (Amoruso et al., 2018; Amoruso, Finisguerra, & Urgesi, 2016; Amoruso & Urgesi, 2016). Actions were shot in two different contextual settings: congruent and incongruent. In the former case, the action suggested by the context was compatible with the action suggested by the hand preshaping information (i.e., reaching to grasp an open bottle located near an empty glass, with a power grip directed towards the body of the bottle, as required to pour the water). Conversely, in the incongruent condition, the context was incompatible with the observed hand posture (i.e., reaching to grasp a corked bottle located near a glass full of water, with a power grip directed towards the body of the bottle, as required to pour the water). In addition, actions could be presented in isolation (i.e., hand image approaching a target object without background). In this latter case, images were the same as those presented with the context, except that the context was deleted. It is worth noting that actions embedded in incongruent contexts were not erroneous *per se*, but implausible given the intention predicted from the context. For instance, the hand preshaping for reaching and grasping a mug full of coffee from its rim using a whole-hand grip would not be suitable for drinking. Instead, a precision grip directed towards the mug’s handle would be more appropriate. That is, it would be strange, if not almost impossible, to drink from the mug when the hand grabs it from the rim as when moving it. For a complete description of objects, action labels, grip types, contexts, and their possible combinations, please see (Amoruso et al., 2020). Indeed, stimuli were validated in a series of previous studies (Amoruso et al., 2016; Amoruso & Urgesi, 2016), confirming the appropriate manipulation of action plausibility, with actions performed in incongruent contexts judged less plausible than those performed in congruent ones.

Following previous studies manipulating the spatial frequency content of images (Bar et al., 2006), we converted them to grayscale and applied a Gaussian blur filter with a 19 pixel kernel for low-pass filtering (resulting in images low-pass filtered at ≈ 6 cycles per image, LSF) and the high-pass filter application set to a radius of 3 pixels for the high-pass filtering (resulting in images filtered at ≈ 30 cycles per image, HSF). The mean contrast values were matched across images.

A final consideration regarding our experimental stimuli is the use of images of implied motion instead of videos. While

we acknowledge that the use of videos would have been a more ecological choice to capture kinematic aspects involved in action observation, here we opted for images implying motion given that they allow a better control of stimulus presentation, in terms of stimulus duration and amount of information given to participants. Importantly, in a previous study (Amoruso et al., 2020) using the same stimuli as here, we directly tested whether using pictures vs. videos differently affected behavioral performance and corticospinal excitability responses to congruent and incongruent contexts and found largely overlapping results. This reassured us that picture and video stimuli of motion trigger comparable effects during the observation of context-embedded actions. Detailed examples of the stimuli used in this study are provided in Fig. 1.

2.3. Experimental design and task

Each participant was enrolled in two sessions, where cTBS was administered either over the left or right PFC (according to stimulation group allocation) and over the vertex (active

control site for both groups). The two stimulation sessions took place within the same day, they were separated by 60 min (to minimize carryover effects of cTBS across sessions) and their order was counterbalanced. Fig. 2 shows the general design structure of the study.

Before starting the experiment, participants were familiarized with the action stimuli. More specifically, they were shown broadband grayscale videos of the different actions performed in either congruent or incongruent contexts. While participants watched the videos, we specifically signaled the most relevant motor and contextual cues and their potential relationship (e.g., precision grip for either grasping a mug full of coffee in the congruent condition or an empty mug in the incongruent one). This procedure was aimed at facilitating the recognition of grip and contextual cues (and their relation) while avoiding familiarization with the spatial frequency content of the stimuli.

In each session, participants initially underwent a *perturb* phase with cTBS (see below). Immediately after the perturb phase, participants underwent a *measure* phase, lasting about

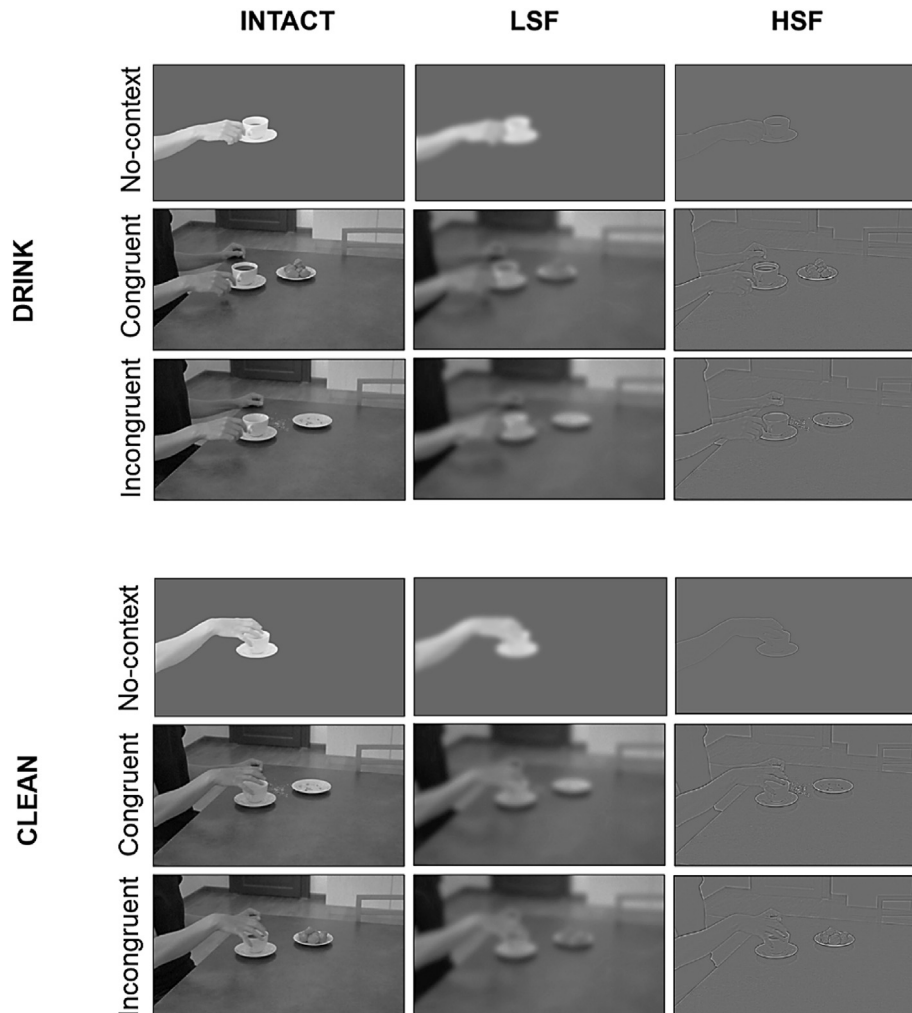


Fig. 1 – Examples of Stimuli. Visual stimuli depicted ongoing incomplete everyday actions. The actions could be presented in isolation (i.e., hand image approaching a target object) or embedded in either a congruent (i.e., grasping a cup to drink in a breakfast scenario with the cup filled with coffee and plate with biscuits) or an incongruent (i.e., grasping a cup to drink in a cleaning scenario with empty cup and biscuit crumbs) context. In addition, stimuli could be presented either in their intact form or only containing low- (LSF) or high-spatial frequency (HSF) information.

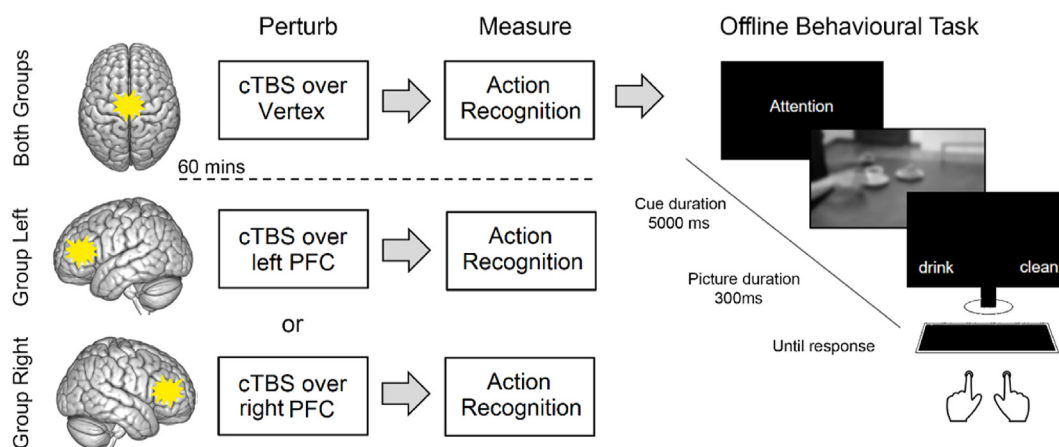


Fig. 2 – Study design. The experiment included two “perturb sessions” within each group. During these sessions, cTBS was administered over the left or right PFC (i.e., depending on the group) and over the vertex (active control site). The PFC and vertex sessions were separated by 60 m and their order was counterbalanced across participants. Immediately following the “perturb session”, participants performed an action prediction task in which performance was measured. During the “measure sessions”, participants watched snapshots depicting ongoing non-fully executed everyday actions performed in isolation or embedded in either congruent or incongruent contexts. Stimuli were filtered to contain only low- (LSF) or high-spatial frequency (HSF) information. Congruency was manipulated in terms of compatibility between grips (i.e., precision or power grips) and the intention suggested by the context (i.e., drink or clean). In a two-alternative forced choice task (2AFC), participants observed the snapshots and predicted what action was unfolding. Each trial began with a frame with the word “attention” on the screen for 5000 msec, followed by the picture, which lasted 300 msec. After picture offset, a frame with the verbal descriptors of two possible end-goals (e.g., ‘drink’, ‘clean’) was presented and remained on the screen until a response was recorded.

20 min. In this phase they performed a two-alternative forced-choice (2AFC) task, in which they observed, in random order, LSF and HSF images of actions presented in isolation or embedded in either a congruent or an incongruent context. Participants were instructed to observe the images and infer the overarching intention that caused them as fast and accurate as possible. To this end, they were requested to pay particular attention to both aspects of the scene: the agent’s hand preshaping and the contextual information in which the action was embedded.

Trials started with a visual warning cue (5000 msec), followed by the picture presented for 300 msec and, finally, by a frame with the verbal labels of the two possible intentions (e.g., “drink” and “clean”), one located on the left and the other on the right. The location of the two verbal labels was counterbalanced, ensuring that in half of the trials one of the labels was presented on the left side of the screen, and in the other half, it was presented on the right. This procedure enabled us to prevent participants from planning their response in advance on the basis of the verbal label spatial location. This frame remained on the screen until a response was recorded. Participants provided their responses by pressing with the index finger the keys “z” (for left choices) or “m” (for right choices) on a QWERTY keyboard. The response keys were covered with white stickers to facilitate localizing their position. Stimuli were presented using E-prime V2 software (Psychology Software Tools) on a 24-inch CRT monitor (resolution, 1,920 × 1,080 pixels; refresh frequency, 60 Hz), at the center of the screen on a neutral background (subtending- 15.96 × 11.97 of visual angle).

2.4. cTBS and neuronavigation

The cTBS protocol lasted 20 sec and consisted of trains of 3 bursts of TMS pulses delivered at 50 Hz every 200 msec (at 5 Hz), for a total of 300 pulses, over the target area (Vertex, lPFC or rPFC) (Oberman, Edwards, Eldaief, & Pascual-Leone, 2011). This protocol is known to reduce the excitability and alter the functions related to the target area for at least 20 m (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). After cTBS, it took no more than 5 m to start the “measure session”, which allowed us to capture the effect of the stimulation when it reached its maximum (Huang et al., 2005). Stimulation was administered with a 70 mm Double Air Film Coil connected to a Magstim Rapid2 stimulator (The Magstim Company, Carmarthen, Wales, UK). The stimulation intensity during cTBS was set at a fixed intensity of 40% of maximum stimulator output (MSO), in keeping with a previous study (Amoruso et al., 2018) showing that using this fixed intensity was effective in modulating motor and behavioural responses during action observation, while being below the resting motor threshold (rMT), and thus within the safety limits, for all participants (Wassermann, 1998).

To ensure that the stimulation intensity was below the rMT in all participants and to control for a dose-dependent effect of cTBS in relation to the individual rMT, we measured the rMT according to state-of-the-art procedures (Rossini et al., 1994) before the first experimental session. Motor evoked potentials (MEPs) were recorded from the First Dorsal Interosseous (FDI) muscle in participants’ right hand using surface Ag/AgCl

electrodes placed in a belly-tendon montage. The electromyographic signal was amplified, filtered (band-pass 5 Hz to 20 kHz) and recorded with Biopac MP-36 system (BIOPAC Systems, Inc., Goleta, CA) at a sampling rate of 50 kHz. The rMT, defined as the lowest intensity able to evoke MEPs in 5 out of 10 consecutive pulses with an amplitude of at least 50 μ V (Rossini et al., 1994), was determined by holding the stimulation coil over the optimal scalp position (OSP). The OSP was found by moving the coil in steps of 1 cm over the left M1, tangentially to the skull, with the handle pointing backward and approximately 45° lateral from the midline, perpendicular to the line of the central sulcus (Di Lazzaro et al., 1998), until the largest MEPs were found. The rMT ranged from 40% to 56% ($M = 46.19\%$, $SD = 5\%$) of the maximum stimulator output and did not differ between groups ($t = -.77$, $p = .44$).

Coil position for cTBS stimulation was identified on each participant's scalp with the SofTactic Navigator system (EMS, Italy). Skull landmarks (nasion, inion, and preauricular points) and 65 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra Optical Tracking System (NDI, Canada). Coordinates in Talairach space were automatically estimated by the SofTactic Navigator from an MRI-constructed stereotaxic template. In the case of the left PFC position ($x = -52$, $y = 32$, and $z = 20$), coordinates were estimated from the results of previous studies investigating the role of top-down prefrontal signals in action observation (Amoruso et al., 2018; Ubaldi, Barchiesi, & Cattaneo, 2015). For the right hemisphere, the homologue coordinates were targeted. As an active control site (i.e., to test for non-specific effects of stimulation), the vertex ($x = 0$, $y = -44$, $z = 69$) was targeted with the induced current running from posterior to anterior along the inter-hemispheric fissure as in two previous studies from our group (Amoruso et al., 2018; Cazzato, Mele, & Urgesi, 2014). No adverse effects during cTBS were reported or noticed in any participant.

2.5. Data analysis

In keeping with previous studies (Amoruso et al., 2016, 2020; Amoruso & Urgesi, 2016), accuracy in action recognition was coded based on hand grip identification (precision vs. power grips), and not based on the motor intention suggested by the context in which grips were observed. Thus, when participants observed a hand approaching a mug toward its handle with a precision grip, “drink” (and not “clean”) was the correct response irrespective of being observed in either a breakfast (i.e., congruent) or a cleaning (i.e., incongruent) scenario. The proportion of correct responses (Accuracy, %) and reaction times (RTs) were calculated for each participant and condition. Chance level was 50%. The individual accuracy and RT values for all conditions in the design were subjected to an omnibus repeated-measures ANOVA (RM-ANOVA) with Area (Vertex, PFC), Context (No-context, Congruent, Incongruent), and Spatial Frequency (HSF, LSF) as within-subject variables and Group (Left, Right) as a between-subject factor. In order to test for a dose-dependent effect of cTBS in relation to participant's individual rMT, we subtracted task performance (i.e., accuracy and RTs) under vertex and PFC conditions and correlated this index of behavioural change with participant's individual rMT. Overall, we expected to find a negative

correlation indicating that, for individuals with low rMT (i.e., <40%), stimulation over PFC was stronger and thus more effective in inducing the requested effect.

3. Results

3.1. Perturbing activity in the PFC impacts processing of spatial frequencies during perception of human actions in context

Mean accuracy values and RTs for action prediction in each condition, session, and group are reported in Table 1. \pm indicates standard error of the mean (SEM).

The RM-ANOVA performed on the accuracy yielded a main effect of Context ($F_{2, 56} = 13.78$, $p < .0001$, $\eta_p^2 = .33$), indicating that, regardless of the group and stimulation session, participants were worse at predicting unfolding actions when these were observed in incongruent than in either isolation or congruent contexts (both $ps < .0001$). Performance in isolation and congruent contexts did not differ ($p = .10$). A main effect of Spatial Frequency ($F_{1, 28} = 7.06$, $p = .01$, $\eta_p^2 = .20$) was also found, with overall better performance for LSF than HSF stimuli ($p = .01$). Finally, and more importantly, the 4-way Group \times Area \times $\eta_p^2 \times$ Spatial Frequency interaction ($F_{2, 56} = 6.71$, $p = .002$, $\eta_p^2 = .19$) was significant. Duncan post-hoc comparisons for this interaction ($MSE = 345.27$, $df = 37.7$) indicated that cTBS over the left and right PFC led to different spatial-frequency-tuned changes in performance. Specifically, while the group stimulated over the left PFC showed a selective reduction in performance on HSF stimuli compared to vertex ($p = .001$), the group stimulated over the right PFC exhibited a similar reduction but for LSF stimuli ($p = .006$). In both cases, these PFC vs. vertex differences were only observed for the incongruent condition, with no modulations when actions were observed in isolation or in congruent contexts (all $ps > .17$; see Fig. 3).

Of note, no main effect of Group ($F_{1, 28} = .08$, $p = .77$, $\eta_p^2 = .002$) or interactions between Group and Context ($F_{2, 56} = .24$, $p = .78$, $\eta_p^2 = .008$) or Group and Spatial Frequency ($F_{1, 28} = 3.33$, $p = .078$, $\eta_p^2 = .1$) were observed, suggesting that the effects yielded by our stimulation paradigm were indeed related to cTBS modulations and not to potential differences at baseline between the two groups of participants.

Importantly, using the Robust Correlation Toolbox (Pernet, Wilcox, & Rousselet, 2012) implemented in MatlabR 2012B, we tested for potential associations between performance change (i.e., accuracy and RTs in vertex minus accuracy and RTs in PFC, respectively) in the incongruent condition and participant's individual rMT. We used percentage-bend correlations (Wilcox, 1994), which are known to provide better estimates of the true relationship between two variables. This analysis yielded significant negative associations for HSF (Bend $r = -.77$, $p = .0006$) in the group left; and for LSF (Bend $r = -.58$, $p = .02$) in the group right. See Fig. 4.

These findings suggest that, while participants with lower rMT were more permeable to cTBS stimulation, those with higher rMT (>40%) were affected to a lesser degree, pointing to

Table 1 – Participants' performance in action recognition. Mean accuracy values and RTs for action prediction in each condition, session, and group. \pm indicates standard error of the mean (SEM).

Accuracy (%)		Vertex			PFC		
		No-context	Congruent	Incongruent	No-context	Congruent	Incongruent
Group Left	HSF	90.3 \pm 2.32	86.33 \pm 3.08	84.17 \pm 4.67	88.65 \pm 2.66	85.29 \pm 3.08	72.18 \pm 5.12
	LSF	85.83 \pm 4.78	86.13 \pm 3.79	83.31 \pm 4.0	87.08 \pm 3.08	85.81 \pm 3.82	83.57 \pm 3.53
Group Right	HSF	90.65 \pm 2.41	86.76 \pm 3.5	75.95 \pm 4.18	86.42 \pm 2.66	81.59 \pm 3.44	80.33 \pm 3.62
	LSF	93.25 \pm 1.78	89.77 \pm 2.34	88.25 \pm 2.15	89.63 \pm 2.54	88.99 \pm 2.02	77.72 \pm 3.26
Reaction Times							
Group Left	HSF	917.99 \pm 48.19	1073.1 \pm 69.8	1052.04 \pm 79.27	946.29 \pm 58.07	1003.8 \pm 65.11	1082.69 \pm 81.8
	LSF	997.16 \pm 84.13	1035.81 \pm 68.31	1031.3 \pm 70.09	980.45 \pm 67.04	1028.46 \pm 76.85	1044.36 \pm 81.78
Group Right	HSF	1078.3 \pm 88.78	1210.2 \pm 107.5	1211.87 \pm 118.6	1024.64 \pm 74.99	1109.36 \pm 56.86	1134 \pm 68.55
	LSF	1077.43 \pm 86.97	1148.8 \pm 101.4	1174.7 \pm 93.22	1055.53 \pm 72.51	1097.56 \pm 76.11	1091.38 \pm 64.33

the dose-dependency of the effects in our fixed intensity approach and documenting a relation between rMT and the effects of cTBS on non-motor areas.

For RTs, the RM-ANOVA yielded a main effect of Context ($F_{2, 56} = 21.09, p < .0001, \eta_p^2 = .43$), showing that participants were overall faster when actions were presented in isolation (i.e., without context) as compared to embedded in either congruent ($p = .0001$) or incongruent contexts ($p = .00006$), which in turn did not differ ($p = .35$). The interaction between Context and Spatial Frequency also reached significance ($F_{2, 56} = 3.37, p = .041, \eta_p^2 = .10$). Post-hoc analyses on this interaction indicated that actions without context were processed faster than context-embedded actions for both HSF (all $ps < .0001$) and LSF stimuli (all $ps < .01$); while congruent and incongruent conditions did not differ in either spatial frequency condition (all $ps > .3$). Planned comparisons, however,

showed that the effect of context (i.e., actions without context faster than overall context-embedded actions) was stronger for HSF than LSF ($p = .02, F = 5.93$). No significant main effects or interactions involving the factors Area and Group were observed (all $ps > .10$), confirming that the main cTBS results were not caused by a trade-off in which individuals achieved faster RTs by sacrificing accuracy. No correlations were found between the index of cTBS effects (i.e., RTs in vertex condition minus RTs in PFC) and rMT (all $r < .23$, all $ps > .4$).

4. Discussion

In the present study, we used a cTBS approach to perturb PFC activity and test a recently proposed model about action comprehension (Amoruso et al., 2020). This model states that

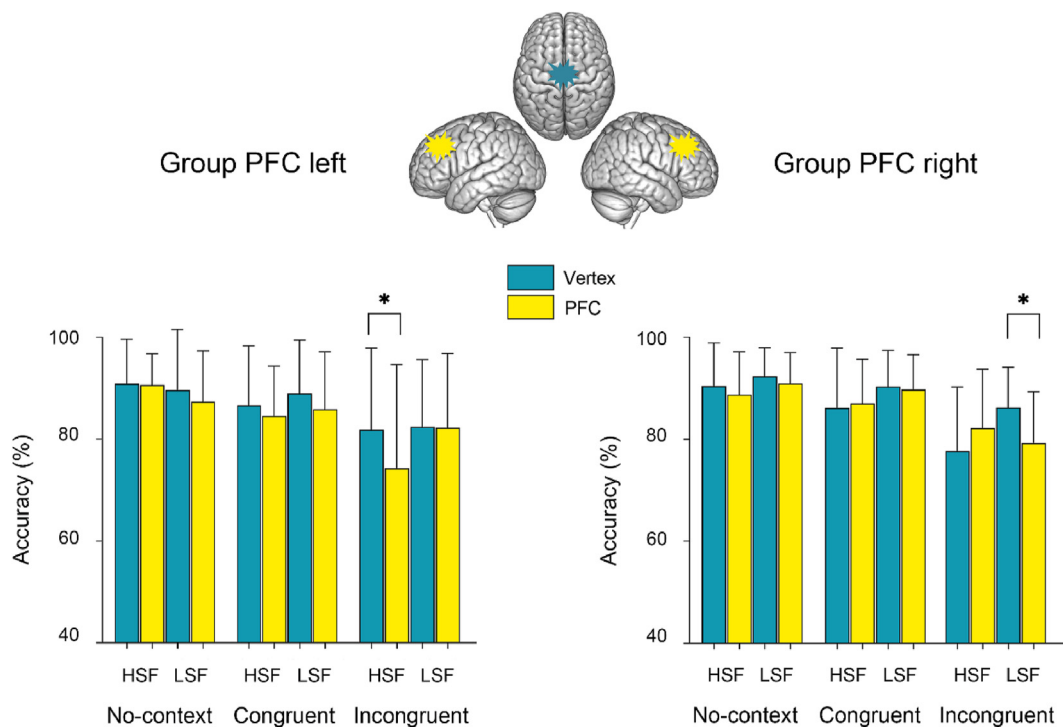


Fig. 3 – Behavioral Results. Participants' performance in predicting the course of the observed actions in the different groups (left vs. right) and stimulation site (PFC in yellow vs. vertex in blue). Actions could be observed in isolation or embedded in either congruent or incongruent contexts. Action stimuli could be filtered to contain only high-spatial frequency (HSF) or low-spatial frequency (LSF) information. Asterisks indicate significant comparisons ($p < .05$). Error bars represent SEM.

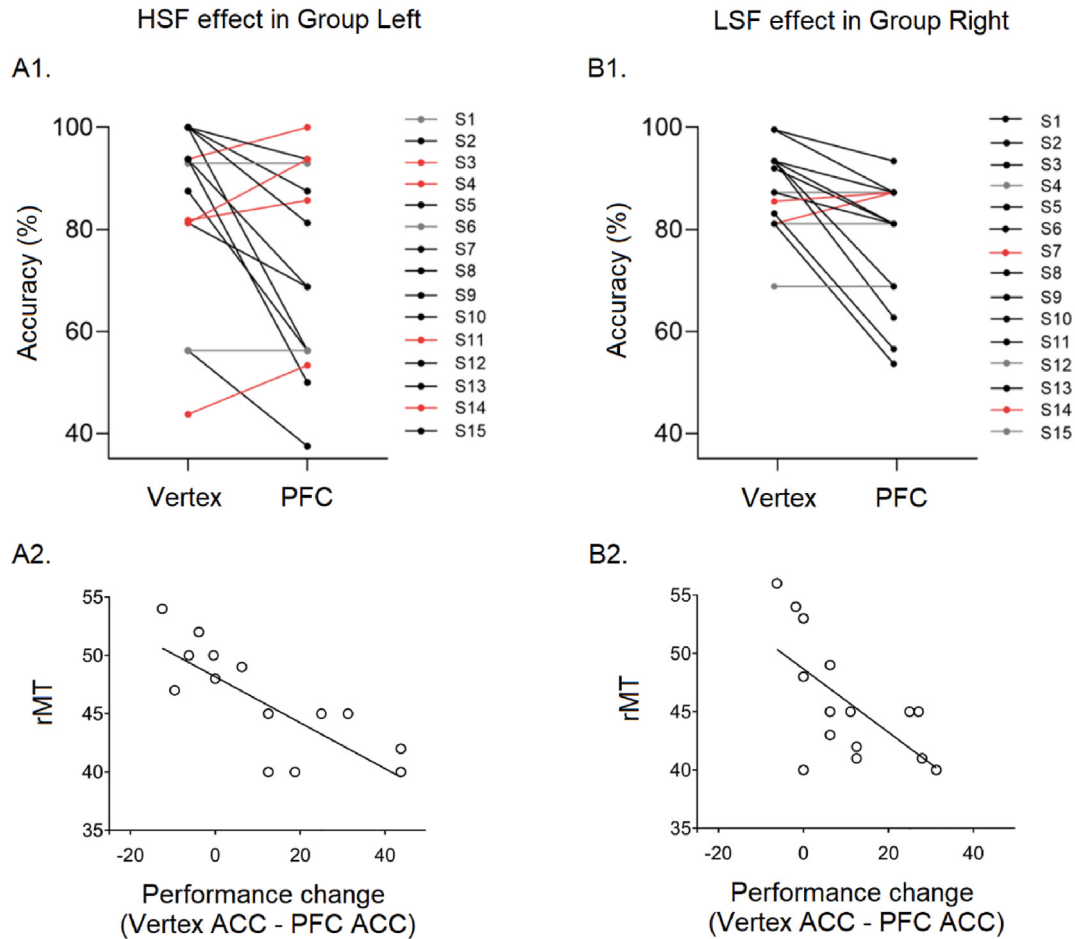


Fig. 4 – Dose-dependent effects of cTBS in relation to individual resting motor threshold (rMT). Individual performance for the processing of HSF (A1) and LSF action stimuli (B1) in the incongruent condition during vertex and PFC stimulation sessions in the different groups. Subjects depicted in black show the direction of the mean effect (i.e., decreased performance after cTBS-PFC); subjects in grey show no modulation (i.e., equal performance during vertex and cTBS-PFC) and subjects in red show the opposite pattern (i.e., increased performance after cTBS-PFC). Correlation between the indexes of behavioural change (i.e., vertex accuracy minus PFC accuracy) and participant's individual rMT for left (A2) and right (B2) groups in the incongruent condition.

the generation of context-based expectations about other's intentions are mediated not only via contributions from the ventral pathway (as indicated by current dual stream action models), but also via the magnocellular-dorsal route. The bedrock idea of this model is that coarse LSF-based information about objects in context is fed into the AON through a PFC-magnocellular neural shortcut, providing a prediction signal of the most likely intention afforded by them. Furthermore, capitalizing on evidence (Peyrin et al., 2003, 2004, 2006) supporting the existence of left and right hemispheric preference in processing HSF and LSF stimuli, respectively; we also tested for a potential difference in the hemispheric contributions to the aforementioned model. To this end, we perturbed left and right PFC activity (as well as an active control region) and measured changes in participant's performance during the recognition of filtered action stimuli containing only HSF or LSF information. Overall, we found that cTBS over PFC led to different spatial-frequency-tuned

changes depending on stimulation lateralization. Specifically, as compared to vertex, the stimulation over the left PFC led to a selective drop in accuracy for HSF, while stimulation over the right PFC selectively reduced performance for LSF action stimuli. In particular, these modulations were only observed for the incongruent context condition.

4.1. Beyond a two-pathway model of action comprehension

Dual stream models of action comprehension (Kilner, 2011) suggest that, while the AON is responsible for encoding the concrete motor aspects of perceived actions (i.e., movement kinematics), more abstract levels such as the intentional state guiding those actions is predicted via a ventral gradient linking the MTG with frontal regions (e.g., BA47). Evidence from a recent cTBS study (Amoruso et al., 2018) targeting two critical nodes of this ventral gradient (i.e., MTG and PFC) during the

comprehension of context-embedded actions provided partial support for this model. Indeed, both areas (as compared to vertex) altered the pattern of contextual modulation of motor and behavioral responses. However, only the PFC stimulation completely abolished contextual effects at the behavioral and neurophysiological levels. This is in keeping with our current results, suggesting a key role for the PFC in generating context-based predictions about others' intentions. Conversely, when hampering neural activity of MTG, participants' ability to use contextual information was still preserved. This latter finding (Amoruso et al., 2018) thus pointed to the existence of other route beyond the ventral pathway involved in context-based prediction. This alternative route could still process a context-based prediction signal that reached the AON and helped participants to accurately recognize observed actions even after interference on MTG activity.

Here, we show that the magnocellular-dorsal pathway could be one such route. While we found reduced performance for HSF stimuli following left PFC stimulation, confirming that the ventral object recognition pathway provides critical information for comprehending others' actions, we also observed that perturbing right PFC activity triggered a drop in participants' performance on recognizing LSF stimuli. This suggests that this brain area exploits coarse information during the processing of naturalistic actions. Thus, our findings support the need for an updated view of action processing, one that accounts for other—magnocellular—sources of prior information, beyond those provided by the ventral pathway (Urgen & Miller, 2015).

Our proposal aligns well with neurophysiological evidence from direct cell recordings in monkey studies (Battaglia-Mayer & Caminiti, 2019; Lu, Preston, & Strick, 1994), showing that the PFC is connected not only ventrally with inferior-temporal areas but also dorsally with core nodes of the AON including the premotor and the parietal cortex (Borra, Gerbella, Rozzi, & Luppino, 2011; Bruni et al., 2018), supporting the existence of a further anatomical route for processing actions in context. Interestingly, it has been recently shown that monkey PFC integrates contextual information during action processing (Bruni, Giorgetti, Bonini, & Fogassi, 2015; Simone, Bimbi, Roda, Fogassi, & Rozzi, 2017; Simone et al., 2015) and that neurons in monkey premotor (Bruni et al., 2017) and pre-supplementary motor areas (Livi et al., 2019) can encode semantic representations of objects and transform them into motor parameters of the actions they afford. Critically, activity in these object-related neurons can be triggered prior to action onset (thus, before any movement is perceived), suggesting that this information is used for planning own actions and for predicting those of others. Overall, evidence from primate studies points to the existence of an alternative dorsal route involving the exploitation of semantic object-based representations and their transformation into grip representations about likely motor affordances. This provides substantial support for our extended model of action comprehension. Nevertheless, an important consideration when comparing our findings with those obtained from direct cell recordings in non-primate studies is the limited spatial resolution of cTBS protocols (i.e., ranging from .5 to 1.5 cm depending on the stimulated tissue) as well as the rapid decline of magnetic fields which do

not reach depths greater than ~2–3 cm below the skull (Garcia-Sanz et al., 2022; Sandrini, Umiltà, & Rusconi, 2011). This precludes establishing causal relationships between more specific, confined areas in the PFC and the effects observed in our study.

An aspect that needs further consideration regards the temporal responses acquired in the present study. During the vertex session (i.e., control condition), RTs showed that the less the perceptual load (i.e., the less the information present in the observed scene) the faster participant's responses. Importantly, faster recognition of actions in isolation vs. context-embedded ones was stronger for HSF stimuli, suggesting that context processing was further facilitated for HSF stimuli. No congruency effect was, however, observed possibly indicating that visual complexity was comparable across congruent and incongruent contexts. Finally, RTs were not affected by stimulation, ensuring that cTBS results were not caused by a trade-off in which individuals sacrificed decision accuracy at the expenses of faster RTs. Nevertheless, it is worth noting that getting effects on both accuracy and RTs after disruptive stimulation is challenging, with this type of protocols typically affecting one or the other behavioral outcome. For instance, in a similar study applying inhibitory stimulation over the PFC during congruent vs. incongruent action recognition, RTs were affected (i.e., increased RTs for incongruent actions), while accuracy remained unaltered after stimulation (Balconi & Canavesio, 2014).

Conversely, in the present study, accuracy values were significantly affected by cTBS stimulation. Of note, both stimulation groups (i.e., left and right) showed a drop in accuracy after PFC stimulation in the incongruent condition. This condition is of interest since is the one allowing to dissociate the motor (i.e., hand shape) and the contextual aspects (i.e., ensemble of objects and their associations) of the observed stimuli. Furthermore, this condition actually provides misleading contextual information, and hence allows to directly measure error signals (i.e., when predictions are violated) (Urgen & Miller, 2015). A plausible explanation for the selective worst performance observed after PFC stimulation is that this area gets more strongly engaged under situations of representational conflict, using prediction errors (i.e., mismatches between predictions and sensory evidence) for updating disconfirmed predictive models. Indeed, there is evidence showing that neural activity in the human PFC encodes both prediction and error signals (Dürschmid et al., 2019; Phillips et al., 2016), suggesting its potential role in using mismatches for updating internal predictive models (Chao, Takaura, Wang, Fujii, & Dehaene, 2018). Thus, the observed effects might reflect that cTBS hampered PFC ability to detect these expectation violations and/or fail to update disconfirmed predictive models on the basis of error signals, leading to the maintenance of the dysfunctional context-based prediction. Accordingly, in our previous study (Amoruso et al., 2018) we found that left PFC cTBS altered behavioral and neurophysiological responses to actions displayed in intact (i.e., nonfiltered) images only at later stages of stimulus processing, when context expectations could be compared with upcoming movement information to update predictions.

Further support comes from patients with PFC damage showing deficits in contextual predictability (Barcelo & Knight, 2007; Fogelson, Shah, Scabini, & Knight, 2009) and, in particular, while processing incongruent trials in tasks involving semantic conflict (Szczepanski & Knight, 2014). This interpretation aligns well with previous action observation studies showing a selective decrease in performance for the processing of incongruent actions after inhibitory PFC stimulation (Balconi & Canavesio, 2014; Balconi & Vitaloni, 2014).

4.2. Distinct hemispheric contributions to action comprehension

Our results also point to differential contributions by the left and right hemispheres to action processing based, respectively, on HSF and LSF information. Hemispheric asymmetry in visual information processing and, in particular, the hypothesis (Sergent, 1982) of hemispheric preferences for spatial frequency detection (i.e., left for HSF and right for LSF) is still widely debated given contradictory findings. Nonetheless, some consensus has been reached about the existence of this asymmetry at least in cognitively demanding tasks that involve stimulus recognition (Grabowska & Nowicka, 1996; Kauffmann, Ramanoel, & Peyrin, 2014). This is in keeping with the findings obtained in our experimental design, in which participants had to recognize context-embedded actions under conditions of varying difficulty. In fact, lateralization effects were observed in the most demanding, namely the incongruent, condition. We acknowledge that our findings could be tapping on a more domain-general process (i.e., spatial-frequency preferences for processing complex visual stimulus). Indeed, similar hemispheric asymmetries have been found in other cognitive demanding tasks using different type of stimuli such as scenes (Kauffmann et al., 2014), letters (Han et al., 2002) and faces (Keenan, Whitman, & Pepe, 1989). Yet, what we show here is that this general mechanism also affects action comprehension, an aspect that has not been shown in the literature before.

The differential sensitivity of the left and right hemispheres for HSF and LSF information, respectively, in the context of our present study could also reflect the exploitation of different sources of information retrieved from different memory systems. Indeed, it has been shown that while the left PFC is engaged in object-based semantic memory retrieval, the right PFC is mostly involved in episodic memory retrieval, namely accessing memories linking facts to the context in which they were learned (Habib, Nyberg, & Tulving, 2003; Lepage, Ghaffar, Nyberg, & Tulving, 2000). Thus, semantic information about objects, in the former case, and information about personal past experience with contextual associations, in the latter one, could (additionally) explain the observed lateralization effects (Fenske et al., 2006). Furthermore, it has been shown that patients with ideomotor apraxia following left frontal damage show deficits in retrieving functional knowledge about objects from semantic memory to perform everyday actions (Dawson, Buxbaum, & Duff, 2010). Thus, the reduced performance for HSF action stimuli after cTBS over the left hemisphere could be explained by difficulties in retrieving object-related semantic knowledge,

which is primarily conveyed via HSF-based local features about objects present in the scene.

On the other hand, patients with right lesions seem to be mostly impaired in keeping track of multi-step actions (Hartmann, Goldenberg, Daumüller, & Hermsdorfer, 2005). In other words, the attentional resources required to maintain a global representation of a given action (i.e., sequence of steps required to achieve a motor goal) is reduced. Thus, it could be that cTBS over the right hemisphere impacted on this global representation, known to be conveyed by LSF information, leading to a narrower attentional focus on local action steps.

While these explanations remain speculative, future studies dissociating object-based and context-based mechanisms (Fenske et al., 2006) and testing pertinent patient populations could provide new insights into how these memory and attentional mechanisms are intertwined with action understanding.

4.3. Conclusions

In summary, we found that cTBS over PFC led to distinct spatial-frequency-tuned changes depending on stimulation lateralization. Specifically, as compared to vertex, stimulation over left PFC led to a selective drop in performance for HSF, while stimulation over the right PFC selectively reduced performance for LSF action stimuli. These findings shed new light on the existence of different prefrontal routes for the estimation of others' motor intentions, challenging current action models, which mainly focus on the ventral object recognition pathway. Specifically, our results suggest that these models should be updated to account for the contribution of an alternative route, namely, the magnocellular-dorsal pathway. Furthermore, they demonstrate that left and right PFC are differentially engaged depending on the spatial frequency of stimuli, providing a broader account for how naturalistic complex actions are processed by the human brain.

Author contributions

Lucia Amoruso: Conceptualization, Methodology, Investigation, Formal analysis, Writing- Original draft preparation, Writing- Reviewing and Editing. **Alessandra Finisguerra:** Methodology, Writing- Reviewing and Editing. **Cosimo Urgesi:** Conceptualization, Methodology, Writing - Reviewing and Editing.

Data/code availability statement

All the data that support the findings of this study are available at <https://osf.io/f5rmd/>.

Open practices section

The study in this article earned Open Data and Open Material badges for transparent practices. The data and materials for this study are available at: <https://osf.io/f5rmd/>

Declaration of competing interest

The authors declare no competing financial interests.

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