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Moving without sensory feedback: online TMS over the dorsal premotor cortex impairs motor performance during ischemic nerve block

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Abstract

In forward models of motor control, predictions about the sensory consequences of movements ('corollary discharge') are derived from motor commands' copies and compared with actual feedback to refine motor control. Our study investigates the role of dorsal premotor cortex (PMd) in generating corollary discharge. We disrupted PMd and parietal hand's multisensory integration site (control area) with TMS during a motor task. The task was performed with normal sensory feedback and during upper-limb ischemic nerve block (INB), in a time-window where participants moved without somatosensations. Objective motor performance and subjective movement perception were tested. We found that INB overall worsens objective performance, but crucially, after PMd disruption, participants showed more errors, less synchronized movements, and increased subjective difficulty ratings. Contrarily, after parietal area interference, when sensory information is already missing due to INB, motor performance is not aggravated. The overall worsened performance after INB confirms the critical role of sensory feedback during movement execution. The increased error rate when INB is combined with PMd disruption suggests that the loss of actual (through INB) and predicted (through PMd disruption) somatosensory feedback degraded motor performance and perception. Altogether these results highlight the crucial role of PMd in generating corollary discharge.

Keywords: corollary discharge; somatosensory feedback; proprioception; internal model; voluntary movement.

Abbreviations: Transcranial Magnetic Stimulation, TMS; Ischemic nerve block, INB; dorsal premotor cortex, PMd; hand's multisensory integration area in parietal cortex, Parietal.

1. Introduction

Somatosensory and proprioceptive feedback is important sensory information involved in the performance of actions and provides information for the perceptual experience of one's own movements. While running in a park, the contact between the foot and the ground after each step is fundamental information that advises the runner about his movements. On the same line, an unexpected contact between the runner's knees and the ground, informs the athlete about a sudden fall on the path. Indeed, it seems clear that movement perception relies on sensory feedback. However, sensory feedback alone is not sufficient for the control and the perception of actions. It has been proposed that efferent signals, such as voluntary motor commands (McCloskey et al. 1983; Gandevia et al. 2006), and copies of motor commands know as efference copies (Holst and Mittelstaedt 1971), play a crucial role in predicting the sensory consequences of the movements (Kawato et al. 1987) likely as a corollary discharge (Sperry 1950; McCloskey 1981) that can influence sensory processes. In the present study, we ask i) to what extent the predictions about the sensory consequences of the movement are necessary to build an effective motor performance and movement perception, ii) which anatomical brain area is responsible for the generation of corollary discharge.

Examples of the fundamental role of sensory predictions in the construction of perception of movement arise from neuropsychological evidence from brain-damaged patients. Indeed, some pathological cases suggest that the perception of movement is possible even in the absence of somatosensory and proprioceptive feedback. In the pathological condition known as anosognosia for hemiplegia (Babinski 1914; Langer and Levine 2014), after a stroke, brain-damaged hemiplegic patients are firmly convinced to execute voluntary movements with their paralyzed limb (Babinski 1914; Vallar and Ronchi 2006; Langer and Levine 2014). An anatomo-clinical explanation of this behavior has been proposed in the light of the influential internal model for motor control and learning (Blakemore et al. 2002; Haggard 2005; Parr et al. 2021). An important component of the internal model idea is the comparison between the predicted and actual sensory consequence of a movement, which is used to update and refine ongoing and future actions. If discrepancies between sensory feedback and predictions are noted, an error signal is generated to alert the system about the incongruency. Furthermore, forward models can be inverted and used to infer other people's actions

(Amoruso et al. 2018). In the context of anosognosia for hemiplegia, it has been proposed a balance between spared brain areas implementing motor intentionality and damaged areas involved in the neural counterpart of the comparator system (Berti et al. 2005; Vocat et al. 2010; Garbarini et al. 2012, 2013; Gandola et al. 2014; Piedimonte et al. 2015; Moro et al. 2016; Pacella et al. 2019). Indeed, in these patients, brain lesions involving the comparator system are supposed to prevent them from detecting the mismatch between motor planning and (the lack of) somatosensory inputs coming from the paralyzed limb. Interestingly for the present study, these patients show to be able to perceive movements even in the absence of somatosensory feedback, basing their movement perception on their (spared) intention (Garbarini et al. 2012; Piedimonte et al. 2016). Another example of "spared" movement perception in absence of somatosensory feedback comes from amputated people (Ackerley and Kavounoudias 2015) with phantom movements (Ramachandran and Hirstein 1998; Raffin, Giraux, et al. 2012; Raffin, Mattout, et al. 2012; Garbarini et al. 2018; Bruno et al. 2019). These patients, after the amputation of a body part, not only continue to perceive the presence of their missing limb (i.e., phantom limb), but they claim they can voluntarily move it (for a review see Scaliti, Gruppioni, and Becchio 2020). Unlike patients with anosognosia for hemiplegia, which are not aware of their motor deficit and which have a brain damage, amputees know and visually perceive that the limb is missing. However, the movement experience persists, often accompanied by the distinct perception that the joints of the missing limb have moved (Anderson 2018). Altogether these studies in the pathological context, strongly highlight that the perception of movement is clearly not only based on somatosensory feedback, but also on the predictions about the sensory consequences of the movement, which seem to assume an essential contribution.

In the present study, we focused on the premotor cortex (PM) as the responsible for generating corollary discharge predicting the sensory consequences of the movement, as highlighted by previous literature (McCloskey 1981; Chronicle and Glover 2003; Ellaway et al. 2004; Cui et al. 2014; Murata et al. 2016), and more specifically we focused on the dorsal part of the PM (PMd) (Christensen et al. 2010; Sun et al. 2015). In particular, a transcranial magnetic stimulation (TMS) study (Christensen et al. 2010) found that 20 Hz 0.5 s trains of high-frequency stimulation of the PMd in absence of sensory feedback induces a sensation of movement, to the same extent as that for a movement illusion evoked by M1 stimulation.

Interestingly, induced movement sensation after the PMd stimulation was less affected by sensory and motor deprivation than comparable induced movement sensations after M1 stimulation. These results suggest that PMd may play a fundamental role in the prediction of somatosensory consequences, and therefore that a corollary discharge evoked by TMS over PMd is perceived as a movement.

Here, we investigated the specific role of the PMd in mediating the somatosensory and proprioceptive predictions on which, at least in part, the motor performance and the movement perception relies on. To this aim, we take advantage of TMS, but not as a mean to induce movements, but rather to interfere or disturb PMd activity during an online finger tapping sequence task paced by a metronome (see Experimental task). Then, to expressly isolate the predictive component of the movement from the motor performance itself, we employ ischemic nerve block (INB) procedure. During INB, afferent and efferent neural transmission can be abolished by inflating a tourniquet around the limb, thus producing a peripheral blockade. The loss of afferent somatosensory feedback (tactile and proprioception) and efferent motor output signaling happens at different time points. Typically, after 20-25 minutes after the tourniquet inflation, proprioceptive and tactile sensations are blocked via the large diameter 1a afferent fibers, and then with a small delay of 3-10 minutes, the block of the smaller diameter efferent motor fibers follows. The INB provides, therefore, a time window during which participants can perform voluntary movements (because of the intact efferences) without sensory feedback (due to the blocked afferences). For this reason, INB is a valid model to investigate the loss of feedback from large diameter sensory fibers. This procedure has been largely employed in different experimental paradigms aiming at investigating several aspects of motor control since it offers the exceptional possibility to investigate movements in absence of afferent information and the consequent rapid plasticity modulations in cortical and corticospinal pathways (Christensen et al. 2007; Maffei et al. 2012; Vallence et al. 2012; Bruttini et al. 2014; Kurabe et al. 2014). For this reason, in the present study, the motor task was performed either with normal sensory feedback or during INB, in the specific time-window during which participants can voluntarily perform movements (because of the intact efferences) in absence of somatosensory feedback (due to the afferences block). After each motor sequence, an *ad-hoc* questionnaire (see Experimental task) about their subjective movement perception and

the monitoring of their motor performance was administered. Single-pulse suprathreshold online TMS (see Methods), used to interfere with the PMd activity, was delivered alternatively both as a real and as a sham stimulation (see Experimental timeline). In addition, in a separate session, TMS was delivered over a control brain area, i.e., a parietal site (Parietal) 3 cm posterior to the primary motor cortex. This control site has been selected for its role in multisensory integration, being a brain area where all the sensory information converges (e.g., somatosensory feedbacks from the primary somatosensory cortex, visual feedback from the primary visual cortex, acoustic information from the primary auditory cortex, etc.), especially for stimuli concerning the hand (Kitada et al. 2006; Gentile et al. 2013; Konen and Haggard 2014; American Psychological Association 2017; Grivaz et al. 2017).

We anticipate that, concerning the *objective performance* (i.e., number of errors and movement synchronization during the motor task), the INB, when somatosensory and proprioceptive feedbacks are lacking due to the sensory blockade, would overall impair the performance (i.e., increased number of errors and less synchronized movements) regardless of the stimulation site (i.e., PMd and Parietal), but crucially significant differences between the PMd and the Parietal session are expected. In particular, when the INB prevents the afferent information during the motor task execution, the system may rely more on the predicted sensory consequences of movement generated by PMd. Thus, the lack of both sensory feedback (induced by the INB) and sensory predictions (induced by the TMS over PMd) could lead participants to worsen their motor performance, thus making more sequence errors and being less synchronized with the metronome during the motor task. On the opposite, we expect that the disruption of the Parietal (i.e., an area in which sensory feedback converges) in the condition in which sensory information is missing in any case due to the sensory blockade, could not interfere with the motor performance, since the predictive component of the movement is still present. Additionally, since the *subjective performance* is evaluated after each motor sequence (both during noINB and INB conditions) by employing the questionnaire about the movement performance and the monitoring perception, we expect significant differences between the PMd and Parietal interference, with lower ratings after the PMd rather than after the Parietal disruption.

2. Materials and methods

2.1 Participants

Ten volunteers (6 women, mean age = 26.1 years, SD = 4.2) participated in the study. All participants were right-handed, as determined by the Edinburgh Handedness Inventory (mean score = 18.2, SD = 1.6) (Oldfield 1971). Participants were naïve to the purpose of the experiment; none of them had a history or evidence of neurological and psychiatric illness and contraindication to TMS (Rossi et al. 2009; Bruno et al. 2018). All participants gave informed written consent before participation. The investigation (H-17027109) was approved by the local ethics committee of the Capital Region of Copenhagen and conforms to the Declaration of Helsinki.

2.2 Experimental timeline

Each participant underwent two experimental sessions, interleaved by at least one week between them. During each session, participants performed a motor monitoring task (see details in *Experimental task*). After a training session, the task could be accompanied by TMS and/or INB. Indeed, in each session, the experimental task was performed alone (i.e., baseline condition), with TMS (i.e., TMS without INB condition), and with both TMS and INB (i.e., TMS with INB). The two experimental sessions differed with respect to the stimulation site, since in one session the TMS was delivered over the PMd, and in the other session the TMS was delivered over the Parietal. In each TMS condition (i.e., TMS without INB, TMS with INB) of each experimental session (i.e., TMS over PMd, TMS over Parietal), the online TMS was administered both as a real and sham stimulation (see details in *TMS, EMG, and goniometers*). Half of the participants performed the PMd session first and then the Parietal session, the other half performed the Parietal session first, and then the PMd session.

2.3 Experimental task

Participants were seated on a chair in front of a table. The left arm of the subject was comfortably positioned on a carton box and the participant was requested to put his/her left hand in a latex glove, which contained a carton template of a left hand. Three buttons were placed at the end of the box, exactly under the participant's left hand fingers. In particular, these buttons were positioned under the index, middle, and ring fingers. The left hand carton template, placed in the glove, was used so that the participants could hold their hand relaxed, always with the three fingers leaning on the three buttons (Figure 1A). The experimental task consisted of a finger tapping sequence, i.e., participants were requested to press the buttons according to a motor sequence. Each participant was instructed that the index finger corresponded to 2, middle finger to 3, and ring finger to 4. A laptop positioned on the table in front of the participant showed a five numbers sequence and the participant had to reproduce with the fingers the sequence, by pressing the corresponding buttons and keeping the rhythm of a 2 Hz metronome (120 BPM). To monitor the objective motor performance accuracy, each button was connected to an analog-to-digital converter (Micro 1401, Cambridge Electronic Design) using a 9V battery as power supply. Each button press was registered as a square voltage wave recorded in the Signal software (Cambridge Electronic Design). The participant read the sequence, and then he/she alerted the experimenter he/she was ready to perform the motor sequence. At this point, the experimenter manually triggered the metronome: the sequence started with a "go signal" beep, which was followed 1 second later by the 2 Hz metronome which emitted 5 beeps, one for each number of the sequence. At the end of each sequence, the participants' monitoring during the motor performance was assessed with an *ad-hoc* questionnaire designed to investigate the subjectively perceived easiness, accuracy, timing, tactile, and movement sensation of the motor sequence they just made. This movement performance and monitoring perception questionnaire was composed of the following five questions: "How easy did you find the task?" (i.e., easiness question); "How accurate do you believe you did the instructed movements?" (i.e., accuracy question); "How synchronous was your movement with respect to the metronome rhythm?" (i.e., synchronicity question); "How strongly did you feel the tactile sensation between the fingers during movements?" (i.e., sensory question); "How intense was the sensation of movement you perceived?" (i.e., movement question) (Figure 1B). For each item, participants gave a

subjective rating on a Likert Scale from 1 (i.e., lowest rating) to 9 (i.e., highest ratings), by pressing with their right hand (i.e., the one not involved in the task) on the keyboard. Importantly, the left arm was always covered with a panel during the task, such that participants could not rely on visual information about their motor performance (Figure 1A).

Before starting the experiment, in each experimental session, 30 motor sequences were performed as training, so that participants could familiarize themselves with the motor task. Then, to familiarize themselves with the questionnaire about movement performance and monitoring perception, 4 motor sequences followed by the questionnaire were executed as training. After the training phase (i.e., 34 sequences in total), participants underwent 20 trials of motor monitoring task (i.e., baseline). Then, they performed 20 trials of the motor monitoring task in the TMS without INB condition, and then 20 trials of the motor monitoring task in the TMS with INB condition were completed. In each TMS condition (i.e., TMS without INB, TMS with INB) of each experimental session (i.e., TMS over PMd, TMS over Parietal), the online TMS was administered at the beginning of each beep of the 2 Hz metronome. The TMS was real in half of the trials (i.e., 10 trials in the TMS without INB condition, 10 trials in the TMS with INB condition) and sham in the other half (i.e., 10 trials in the TMS without INB condition, 10 trials in the TMS with INB condition) (Figure 1B). Real and sham TMS were always alternated so that after every sequence with a real TMS, a sham stimulation followed. The continuous electromyographic (EMG) activity and goniometers recordings (see details in *TMS, EMG, and goniometers*) started with the first "go signal". The trigger of sounds and single-pulse TMS, as well as the EMG and goniometers recording, was managed by Signal 4.00 software (Cambridge Electronic Design, Cambridge, UK) (Figure 1C).

2.4 Peripheral sensorimotor blockade

The afferent neural transmission was abolished by inflating a tourniquet placed around the arm to produce a peripheral INB. The tourniquet was inflated to ~250 mmHg. While the participant gradually lost sensation in the forearm and hand, the sensation of light touch and passive movement of the fingers was tested using gentle skin strokes while the subject's eyes were closed. When the subjects had lost sensation, which in this specific experiment

happened between 16:15 min and 22:15 min after initiation of ischemia, the subjects were asked to perform 20 trials of the motor sequence and monitoring task with real and sham TMS applied. Participants controlled when to start each trial and, in total, the 20 trials lasted about 5 min.

2.5 Transcranial magnetic stimulation, electromyography, and goniometers recording

Online TMS was performed using two figure-of-eight coils connected to two different Magstim Rapid^2 stimulators (Magstim, Whitland, Dyfed, Wales, UK) so that one stimulator was employed for the real TMS and the other for the sham. For the real TMS trials, the coil was placed through BrainSight, a system for frameless stereotaxis (Rogue Research Inc., Montreal, Canada), over the right primary motor cortex (M1). The initial placement was based on the neuroanatomy of a normalized brain aiming for the hand knob on the precentral gyrus. With this as starting point, the individual optimal point for eliciting motor evoked potentials was found. The coil was placed tangentially to the scalp with the handle pointing posterolaterally 45 degrees from the midline. This orientation is optimal for trans-synaptic activation of the corticospinal pathway (Brasil-Neto et al. 1992; Mills et al. 1992). The resting motor threshold (rMT) was defined as the lowest stimulator output intensity capable of inducing EMG responses with a magnitude greater than 50 μV of the peak-to-peak motor evoked potentials (MEPs) amplitude in the left extensor digitorum communis muscle for a minimum of five of the ten trials (Rossini et al. 1994; Groppa et al. 2012) and it was measured at the beginning of each experimental session, following the international standards (Rossi et al. 2009). After having individuated the rMT, the coil was positioned with the use of the neuro-navigation system over PMd defined as 2 cm anterior to the M1 hotspot or Parietal defined as 3 cm posterior to the M1individual hotspot, according to the experimental session. The accuracy and stability of coil placement were ensured using BrainSight and a normalized brain. During the experiment, the stimulus intensity was kept at 110% of the rMT during data collection. rMTs were found to be between 41% and 71% of maximal stimulator output across the participants. On average, the difference in rMT between sessions 1 and 2 was 2.4%-points of maximal stimulator output. In sham trials, the second figure-of-eight coil was

placed on the left hemisphere, in an analogous position to that of the coil for the real TMS, and tilted away from the scalp by 90° of angle. Hence, the sham coil plane was not tangential to the skull, in turn reducing its effectiveness due to power dissipation in the air by that part of the coil that loses contact with the scalp. With this strategy, the stimulator discharges still give an audible clicking sound along with peripheral sensations associated with TMS, but maintaining contact and sound, thereby giving the impression to the naïve subjects of being stimulated (e.g., Bolognini and Ro 2010; Fossataro et al. 2018).

MEPs were recorded from the left extensor digitorum communis. EMG activity from the extensor digitorum communis was recorded by pairs of Ag–AgCl surface pre-gelled electrodes (Ambu, Ballerup, Denmark) following standard skin preparation. The electrodes were connected to the electromyograph, and the EMG signals were amplified with custom EMG amplifiers developed and manufactured at Department of Neuroscience of the University of Copenhagen and recorded using Signal 4.00 software (Cambridge Electronic Design, Cambridge, UK). Besides, during the task, to control individual finger movements, two goniometers connected to the polygraph system were attached respectively to middle and ring fingers to control and monitor the angle's movement during the button press (see Figure 2 for examples of single trials recording in one participant during noINB and INB conditions).

--- Figure 1 about here ---

--- Figure 2 about here ---

2.6 Data analysis

We calculated the objective performance during the motor task (i.e., the number of the committed errors and synchronicity to the metronome), by analyzing the button pressure. When the information about the button pressure was uncertain, like during the INB, when movements were possible, but in absence of afferences, EMG and goniometers activity was checked to control for possible movements. We considered errors as both wrong pressure/finger movements (i.e., the participant had to press one button with one finger, but

he/she pressed another one with another finger) and omissions (i.e., the participant had to press a button, but he/she did not press anything). To control for objective synchronicity to the metronome, a root mean square (RMS) value (expressed in ms) was computed for each trial as the square root of the squared difference between the beginning of each of the 5 beeps of the metronome and the beginning of the each of the button press/finger movements. If no movement was detected, a default difference of 500 ms was used for a specific movement. If no movements had been made during the entire trial, the RMS was set to 2500ms. Furthermore, concerning the subjective performance, we analyzed the individual subjective ratings to the five items of the questionnaire about movement performance and monitoring perception. Therefore, separately for the objective measures (i.e., errors and synchronization) and for subjective measures (i.e., each question of the movement performance and monitoring perception questionnaire: easiness – Q1, accuracy – Q2, synchronicity – Q3, sensory – Q4, movement – Q5), we ran separate Linear Mixed Models (LMM) in R (version 4.0.0, https://www.r-project.org/), using the lme4 package (Bates et al. 2015). We included errors, synchronization, Q1, Q2, Q3, Q4, and Q5 ratings as the dependent variables and we parameterized the model into the combined variable Site (baseline PMd, PMd, baseline Parietal, Parietal), Stimulation (noTMS, TMS, sham) and Feedback (noINB, INB), resulting in the following conditions: baselinePMd.noTMS.noINB, PMd.TMS.noINB, PMd.sham.noINB, PMd.TMS.INB, PMd.sham.INB, baselineParietal.noTMS.noINB, Parietal.TMS.noINB, Parietal.sham.noINB, Parietal.TMS.INB, Parietal.sham.INB. Since we were interested in specific tests within the Site.Stimulation.Feedback parameterization, we ran, between conditions, simultaneous tests for general linear hypotheses with multiple comparisons of means by employing Tukey contrasts (Bonferroni corrected). We focused only on comparisons between conditions in which one factor is different. Participants' age and gender were added as fixed effects, while subject, trial, and condition order as random effects. Regarding the subjective ratings, each subjective measure was tested including the objective measures (error and synchronization) as fixed effects covariates.

3. Results

3.1 Objective measures

As regards to the objective measures (i.e., errors and synchronization), significant differences between conditions were found (Figure 3, upper panel).

3.1.1 Errors

To investigate possible effects induced by the TMS *per se* in modulating the motor performance accuracy when somatosensory feedback was preserved (i.e., noINB), separately for each area (i.e., PMd and Parietal), we compared the baseline conditions with the conditions in which the TMS was delivered (both during real and sham TMS). No significant differences were found, neither in the PMd (p always > 0.79) nor in the Parietal session (p always = 1.00), suggesting that the TMS alone does not modulate the motor performance (Figure 3A). Interestingly, when comparing conditions with preserved somatosensory feedback (i.e., noINB) with conditions without somatosensory feedback (i.e., INB), participants performed significantly more errors, both in the PMd (PMd.TMS.INB *vs* PMd.TMS.noINB: beta=4.14, z=31.294, p<0.0000001; PMd.sham.INB *vs* PMd.sham.noINB: beta=4.15, z=31.160, p<0.0000001) and in the Parietal session (Parietal.TMS.INB *vs* Parietal.TMS.noINB: beta=3.84, z=29.026, p<0.0000001; Parietal.sham.INB *vs* Parietal.sham.noINB: beta=3.99, z=30.160, p<0.0000001), suggesting that, overall, INB reduces performance regardless of Site.Stimulation. Crucially, when comparing PMd and Parietal during the INB condition, significantly more errors were performed in the PMd than in the Parietal session (Parietal.TMS.INB *vs* PMd.TMS.INB: beta=-0.46, z=-3.447, p=0.0076; Parietal.sham.INB *vs* PMd.sham.INB: beta=-0.45, z=-3.402, p=0.0101), suggesting that in absence of somatosensory feedback, TMS (and sham) over PMd significantly reduces the objective performance, by inducing participants to make more errors. It is important to note that no significant difference was found in the INB condition between the (real) TMS and the sham within the same stimulation site (i.e., PMd and Parietal), suggesting a carryover effect induced by the real TMS in the sham stimulation.

3.1.2 Synchronization

As for the errors, to investigate possible effects induced by the TMS *per se* in modulating the synchronicity of the motor performance when somatosensory feedback was preserved (i.e., noINB), separately for each area (i.e., PMd and Parietal), we compared the baseline conditions with the conditions in which the TMS was delivered (both during real and sham TMS). No significant differences were found, neither in the PMd (p always = 1.00) nor in the Parietal session (p always = 1.00), suggesting that the TMS alone does not modulate the motor performance (Figure 3B). However, as for the errors, when comparing conditions with preserved somatosensory feedback (i.e., noINB) with conditions without somatosensory feedback (i.e., INB), participants were less synchronized with the metronome, both in the PMd (PMd.TMS.INB *vs* PMd.TMS.noINB: beta=1526.05, z=17.387, p<0.0000001; PMd.sham.INB *vs* PMd.sham.noINB: beta=1693.00, z=20.399, p<0.0000001) and in the P session (Parietal.TMS.INB *vs* Parietal.TMS.noINB: beta=1372.892, z=16.542, p<0.0000001; Parietal.sham.INB *vs* Parietal.sham.noINB: beta=1374.464, z=16.561, p<0.0000001), suggesting that, overall, the absence of somatosensory feedback induced by the INB reduces performance regardless of Site.Stimulation. Interestingly, when comparing PMd and P during the INB condition, participants were more asynchronous to the metronome in the PMd than in the P session, with significant differences between the sham sessions, and a tendency towards significance in the (real) TMS (Parietal.TMS.INB *vs* PMd.TMS.INB: beta=-219.187, z=-2.641, p=0.12; Parietal.sham.INB *vs* PMd.sham.INB: beta=-318.080, z=-3.833, p=0.001), suggesting that in absence of somatosensory feedback, the TMS (including the real and the sham) over PMd significantly reduce the objective performance, by inducing participants to be less synchronized to the metronome when performing their movements. Again, the lack of difference in the INB condition between the (real) TMS and the sham within the stimulation site (i.e., PMd and Parietal), suggests a carryover effect induced by the real TMS in the sham stimulation.

--- Figure 3 about here ---

3.2 Subjective measures

Significant differences between conditions were also found relative to the subjective measures (i.e., each question of the movement performance and monitoring perception questionnaire) statistical models, in which objective measures (i.e., errors and synchronization) were used as covariates (Figure 3, bottom panel).

3.2.1 Q1 – easiness

Significant differences were found regarding the easiness' rating (Figure 3C). When comparing conditions with preserved somatosensory feedback (i.e., noINB) in combination or not with TMS, we found that only after the PMd interference participants rated the task as more difficult (baselinePMd.noTMS.noINB vs PMd.TMS.noINB: beta=0.51, zeta=3.200, p=0.02), suggesting a PMd involvement of in rating the sensation of difficulty during the motor task. When comparing conditions with preserved somatosensory feedback (i.e., noINB) with conditions without somatosensory feedback (i.e., INB), participants rated the motor task as more difficult during the sensory blockade, both in the PMd (PMd.TMS.INB vs PMd.TMS.noINB: beta=-2.64, z=-10.373, p<0.0000001; PMd.sham.INB vs PMd.sham.noINB: beta=-3.24, z=-12.722, p<0.0000001) and in the Parietal session (Parietal.TMS.INB vs Parietal.TMS.noINB: beta=-2.05, z=-8.342, p<0.0000001; Parietal.sham.INB vs Parietal.sham.noINB: beta=-2.62, z=-10.460, p<0.0000001), suggesting that, overall, INB lowered the subjective feeling of easiness regardless of Site.Stimulation. Crucially, when comparing PMd and P during the INB condition, participants rated the motor task as more difficult in the PMd session (regardless of the real TMS or sham, Parietal.TMS.INB *vs* PMd.TMS.INB: beta=0.94, z=5.152, p=0.00000387; Parietal.sham.INB *vs* PMd.sham.INB: beta=0.81, z=4.454, p=0.00012), suggesting that in absence of somatosensory feedback, TMS (and sham) over PMd significantly lowered the subjective feeling of easiness. As for the previously reported results, it is important to note that no significant difference was found in the INB condition between the (real) TMS and the sham within the same stimulation site (i.e., PMd and Parietal), suggesting a carryover effect induced by the real TMS in the sham stimulation.

3.2.2 Q2 – accuracy

When analyzing the accuracy, no effect of Site.Stimulation.Feedback, when errors and synchronization were included as covariates, was found, suggesting that participants had good monitoring of their motor performance not only after the TMS over PMd and Parietal, but surprisingly also in absence of sensory feedback (i.e., during the INB) (Figure 3D).

3.2.3 Q3 – synchronization

Regarding the subjective sensation of synchronization, significant differences were found (Figure 3E). In particular, when comparing conditions with preserved somatosensory feedback (i.e., noINB) with conditions without somatosensory feedback (i.e., INB), participants had a lower sensation of synchronization with the metronome only in the PMd session (PMd.TMS.INB *vs* PMd.TMS.noINB: beta=-0.69, z=-2.848, p=0.06; PMd.sham.INB *vs* PMd.sham.noINB: beta=-0.81, z=-3.346, p=0.01), suggesting that INB combined with the PMd interference reduces the sensation of synchronization. As for the previously reported results, no significant difference was found in the INB condition between the (real) TMS and the sham within the same stimulation site (i.e., PMd), suggesting a carryover effect induced by the real TMS in the sham stimulation.

3.2.4 Q4 – tactile sensation

Concerning the tactile sensation experienced during the motor task significant differences were found (Figure 3F). In particular, when comparing conditions with preserved somatosensory feedback (i.e., noINB) with conditions without somatosensory feedback (i.e., INB), participants experienced a reduced tactile sensation, both in the PMd (PMd.TMS.INB *vs* PMd.TMS.noINB: beta=-4.52, z=-19.777, p<0.0000001; PMd.sham.INB *vs* PMd.sham.noINB: beta=-4.62, z=-20.143, p<0.0000001) and in the Parietal session (Parietal.TMS.INB *vs* Parietal.TMS.noINB: beta=-4.77, z=-21.611, p<0.0000001; Parietal.sham.INB *vs* Parietal.sham.noINB: beta=-4.91, z=-21.797, p<0.0000001), suggesting that, overall, INB reduces tactile sensation regardless of Site.Stimulation. Again, no significant difference was found in the INB condition between the (real) TMS and the sham within the same stimulation site (i.e., PMd and Parietal), suggesting a carryover effect induced by the real TMS in the sham stimulation.

3.2.5 Q5 – movement sensation

As regards the movement sensation experienced during the motor tasks, significant differences were found (Figure 3G). In particular, when comparing conditions with preserved somatosensory feedback (i.e., noINB) with conditions without somatosensory feedback (i.e., INB), participants experienced a reduced movement sensation, both in the PMd (PMd.TMS.INB *vs* PMd.TMS.noINB: beta=-4.38, z=-14.518, p<0.0000001; PMd.sham.INB *vs* PMd.sham.noINB: beta=-4.18, z=-13.825, p<0.0000001) and in the P session (P.TMS.INB *vs* P.TMS.noINB: beta=-4.11, z=-14.124, p<0.0000001; P.sham.INB *vs* P.sham.noINB: beta=-4.41, z=-14.829, p<0.0000001), suggesting that, overall, INB reduces movement sensation regardless of Site.Stimulation. As for the previous results, the lack of difference between real TMS and sham within the same stimulation site (i.e., PMd and Parietal) suggests a carryover effect induced by the real TMS in the sham stimulation.

3.3 Ischemic nerve block information

On average across the two rounds, participants lost sensation after 19:13 min, range 16:15 min to 22:15 min after the tourniquet was inflated. The difference for the individual participant in time to lose sensation between the two rounds was on average 16 s ranging from -1:30 min to +2:20 min.

4. Discussion

In the present study, we investigated the role of the PMd in mediating the somatosensory and proprioceptive predictions on which, at least in part, the movement performance is built. Suprathreshold online single-pulse TMS was used to interfere with the PMd and, in a separate session, with the hand's multisensory hotspot in the parietal cortex (Parietal), as a control area (Kitada et al. 2006; Gentile et al. 2013; Guterstam et al. 2013; Konen and Haggard 2014; Grivaz et al. 2017) during a finger tapping sequence motor task, timed by a metronome. To isolate the predictive component of the movement from the sensory consequences coming from the movement itself, the motor task was performed either with normal sensory feedback or during an upper-limb INB, in the specific time-window during which participants can

voluntarily perform movements (because of the intact efferences) in the absence of somatosensory and proprioceptive feedback (due to the afferences block). The objective performance (i.e., errors in the motor sequence and synchronization with the metronome), and the subjective motor performance and monitoring perception were tested. We found that the TMS *per se* (i.e., noINB condition) over the two cortical sites (i.e., PMd and Parietal) did not interfere with the motor performance, suggesting no differential role between the two areas in our motor task when somatosensory and proprioceptive information are normally available. Interestingly, the INB, as compared to the noINB condition, overall worsen the objective performance, and made participants lower their ratings about the movement perception and the monitoring performance, regardless of the stimulation site (i.e., PMd and Parietal). Crucially, participants performed significantly more errors and significantly less synchronized movements during the INB only after the PMd interference (as compared to the Parietal interference). Besides, only after the PMd disruption, participants subjectively rated the task as more complex. These results might suggest that PMd plays a crucial role in generating the predictions of a movement.

To have a correct motor performance, somatosensory feedbacks are fundamental (see as for example the role of proprioceptive inputs in the prevention of hemispheric unbalance during limb immobilization, Avanzino et al., 2014). Consequently, in our study, the lack of somatosensory and proprioceptive afferences induced by the INB led to an overall worsen motor performance, as suggested by the increased number of errors in the motor sequences and less synchronized movements, regardless of the TMS disruption site (i.e., PMd and Parietal). Crucially, our results suggest that sensory feedbacks alone are necessary, but not sufficient, for appropriate motor performance. Indeed, we found that only after the PMd disruption, during the INB condition in which sensory feedback was absent, participants worsen their objective motor performance. Why does the motor performance become impaired after the PMd and not after the Parietal interference? Our interpretation is that the PMd computes the predictions of the sensory consequences of the movement, and, therefore, the lack of both sensory information (due to the INB) and the sensory predictions (due to PMd disruption) caused greater impairment in the motor performance. Differently, the interference of the parietal area chosen as a control site for its multisensory integration function (especially for the hand), did not show, as expected, any effect during the sensory

blockade. Indeed, when somatosensory and proprioceptive feedback was absent during the INB, no converging information could be sent to the parietal cortex, and since it was not properly fed, it did not play a crucial role in our motor task. The role of the PMd in generating corollary discharge based on a forward model, which contains the predictions about the consequences of the movement, has been previously suggested. In the absence of sensory feedback, an excitatory TMS over PMd can generate the sensation of movement (Christensen et al. 2010). An fMRI study (Blankenburg et al. 2006) on the cutaneous rabbit illusion (Asai and Kanayama 2012), in which repeated rapid stimulation at the wrist and then near the elbow create the illusion of continuous touches along the arm, showed that not only the illusory touches activated the somatosensory cortex, but also the contralateral PMd, suggesting a premotor involvement in predicting the sensory perception of the touch. In the same vein, it has been shown that even by maintaining normal somatosensory afference, the PM (and/or the supplementary motor cortex) predicts brain activity in primary somatosensory regions activity during active and passive touch of soft materials, suggesting that signals in primary somatosensory regions can reflect input from motor cortices (Cui et al. 2014). In addition, in the monkey brain, it has been shown that actual movements are represented in the M1, whereas the visualized, presumably perceived movements are represented in PMd (Schwartz et al. 2004). The results of our study are in line with the above-mentioned literature. In our motor task, the absence of somatosensory feedback due to the INB would lead participants to assign more importance to the corollary discharge, generated by PMd. Interfering with the online single-pulse TMS on PMd implied that both somatosensory and proprioceptive feedback and corollary discharge were disrupted, and this may have led to worsening the objective motor performance of our participants. Also, only after the PMd disruption, the subjective ratings about the easiness of the task were significantly lower, suggesting that participants evaluate the task as more difficult, even considering their objective performance. In other words, participants overestimate the task's difficulty, suggesting, again, an incorrect perception of their own movements.

Alternatively, our differential findings between PMd and Parietal can be explained in light of the role of PMd in motor planning (Pearce and Moran 2012; Dekleva et al. 2018; Pilacinski and Lindner 2019). Accordingly, the more significant impairment in motor performance after TMS over PMd in the INB condition could be ascribed to PMd motor planning function: it

is reasonable that the TMS interference over a motor planning area could lead to a worsen objective movement. However, the lack of difference in motor performance between the PMd interference condition in the noINB condition (when the TMS was delivered but sensory feedback was available, i.e., PMd.TMS.noINB) and its baseline, may suggest that the planning component of PMd does not play a fundamental role, at least in our task. Furthermore, the lack of difference in motor performance between PMd and Parietal in the noINB condition seems to be in line with this interpretation. However, we cannot exclude that the PMd motor planning function could have been more relevant with the task's increasing difficulty, already shown by previous literature (Harrington et al. 2000; Ceballos et al. 2002; Davare et al. 2006), as during the INB condition. Therefore, it is not possible to rule out that PMd planning function has influenced the situation in which, as during the sensory block (i.e., INB condition), the movement was more difficult. A third alternative explanation of our results could be that PMd plays a role as the inverse model computing the signals needed to make the desired movement (Blakemore et al. 2000). However, if PMd plays that role, we would expect to observe differences in motor performance in the noINB condition, but this is not the case.

It is important to note that the neuronavigation system ensures that only the control and target areas were stimulated, and as consequence, were disturbed during the motor task. This clarification is necessary since the scientific literature suggests different functions of these cortical sites according to specific portions and coordinates. For example, the ventral portion of PM (PMv) has been largely investigated also for the comparator system-related role both in healthy individuals (Bolognini, Zigiotto, Carneiro, & Vallar, 2016; Fornia et al., 2020; Garbarini et al., 2019; Bruno et al., 2017) and in the pathological population (Berti et al. 2005). Indeed, these previous findings promote the role of PMv as a shared neural substrate for both motor execution and motor awareness of voluntary actions, highlighting, with different techniques, the role of the PMv in motor monitoring, and especially in motor awareness. On the other side, other parietal sites have been investigated during voluntary movements for their role in motor intention and programming. For example, it has been shown that the direct electrical stimulation of the dorsoposterior parietal cortex, a site different from the hand's multisensory parietal area employed in our study, prevents

movement initiation and instantly inhibits ongoing volitional upper-limb motor responses (Desmurget et al. 2018).

Our study is not free from limitations. The main limitation of our study is that we did not find significant differences between the real and the sham stimulation, both in the PMd and in Parietal sessions, and both in the noINB and INB conditions, suggesting a carryover effect induced by the TMS. The short time window in which the INB disrupts afferences while the efferences are still present led us to opt for an online TMS protocol, able to interfere with the cortical activity during the task, by creating a momentaneous "virtual lesion", such as the one used the classic work of Amassian (Amassian et al. 1989; Ritterband-Rosenbaum et al. 2014). More recently, there have been attempts to explain TMS effects on behavior more mechanistically, in terms of inducing noise. The idea is that TMS indiscriminately activates neurons in a targeted region and, in this manner, it adds noise to neural processing (Silvanto and Cattaneo 2017). This noise reduces the signal-to-noise ratio of the cognitive task under investigation and thus impairs performance (Miniussi et al. 2013). Probably, in our task, the necessary short time between the real and the sham stimulation, due to the time constraints of the INB, made sure that the induced noise over the target area during the real stimulation did not run out its effect. This would have, in turn, caused that even during the sham stimulation, the induced noise over the target area impacted the task. A possibility to overcome this carryover effect problem would have been to add one more identical session, where only the sham would have been delivered, to have three sessions in total (i.e., one with the TMS over PMd, one with the TMS over Parietal, and one with sham stimulation). However, we did not opt for this solution to not repeat the task and the INB three different times in the same participants.

In conclusion, our results suggest that the lack of both sensory feedback (induced by the INB) and sensory predictions (induced by the interference of the TMS over PMd) leaded participants to worsen their objective and subjective motor performance. Contrarily, the disruption of the Parietal, when sensory information is missing as during INB, does not interfere with the motor performance since the predictive component of the movement is still present. Altogether, these results highlight the crucial role of PMd in generating the prediction of the sensory consequences of the movement.

Conflict of interest

None

Data availability statement

Data are available upon request.

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References

Ackerley R, Kavounoudias A. 2015. The role of tactile afference in shaping motor behaviour and implications for prosthetic innovation. Neuropsychologia. 79:192–205.

Amassian VE, Cracco RQ, Maccabee PJ. 1989. A sense of movement elicited in paralyzed distal arm by focal magnetic coil stimulation of human motor cortex, Brain Research.

American Psychological Association. 2017. Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD). Washington, DC APA, Guidel Dev Panel Treat Posttraumatic Stress Disord Adults. 139.

Amoruso L, Finisguerra A, Urgesi C. 2018. Contextualizing action observation in the predictive brain: Causal contributions of prefrontal and middle temporal areas. Neuroimage. 177:68–78.

Anderson ML. 2018. What phantom limbs are. Conscious Cogn. 64:216–226.

Asai T, Kanayama N. 2012. "Cutaneous rabbit" hops toward a light: Unimodal and cross-modal causality on the skin. Front Psychol. 3:1–12.

Avanzino L, Pelosin E, Abbruzzese G, Bassolino M, Pozzo T, Bove M. 2014. Shaping motor cortex plasticity through proprioception. Cereb Cortex. 24:2807–2814.

Babinski JFF. 1914. Contribution à l'Étude des Troubles Mentaux dans l'Hémiplégie Organique Cérébrale (Anosognosie). Rev Neurol (Paris). 27:845–848.

Bates D, Mächler M, Bolker BM, Walker SC. 2015. Fitting linear mixed-effects models using lme4. J Stat Softw. 67.

Berti A, Bottini G, Gandola M, Pia L, Smania N, Stracciari A, Castiglioni I, Vallar G, Paulesu E. 2005. Neuroscience: Shared cortical anatomy for motor awareness and motor control. Science (80-). 309:488–491.

Blakemore SJ, Wolpert D, Frith C. 2000. Why can't you tickle yourself? Neuroreport. 11:R11–R16.

Blakemore SJ, Wolpert DM, Frith CD. 2002. Abnormalities in the awareness of action. Trends Cogn Sci. 6:237–242.

Blankenburg F, Ruff CC, Deichmann R, Rees G, Driver J. 2006. The cutaneous rabbit illusion affects human primary sensory cortex somatotopically. PLoS Biol. 4:0459–0466.

Bolgnini N, Ro T. 2010. Transcranial magnetic stimulation: Disrupting neural activity to alter and assess brain function. J Neurosci. 30:9647–9650.

Bolognini N, Zigiotto L, Carneiro MIS, Vallar G. 2016. "How did I make It?": Uncertainty about own motor performance after inhibition of the premotor cortex. J Cogn Neurosci. 28:1052–1061.

Brasil-Neto JP, Cohen LG, Panizza M, Nilsson J, Roth BJ, Hallett M. 1992. Optimal focal transcranial magnetic activation of the human motor cortex: Effects of coil orientation, shape of the induced current pulse, and stimulus intensity. J Clin Neurophysiol. 9:132–136.

Bruno V, Fossataro C, Garbarini F. 2018. Report of seizure induced by 10 Hz rTMS over M1. Brain Stimul. 11:454–455.

Bruno V, Ronga I, Fossataro C, Capozzi F, Garbarini F. 2019. Suppressing movements with phantom limbs and existing limbs evokes comparable electrophysiological inhibitory responses. Cortex. 117:64–76.

Bruttini C, Esposti R, Bolzoni F, Cavallari P. 2014. Ischemic block of the forearm abolishes finger movements but not their associated anticipatory postural adjustments. Exp Brain Res. 232:1739–1750.

Ceballos O, Haslinger B, Erhard P, Weilke F, Schwaiger M, Conrad B, Bartenstein P, Gra H, Boecker H. 2002. The role of lateral premotor–cerebellar–parietal circuits in motor sequence control: a parametric

fMRI study ´. Cogn Brain Res. 13:159–168.

Christensen MS, Lundbye-Jensen J, Geertsen SS, Petersen TH, Paulson OB, Nielsen JB. 2007. Premotor cortex modulates somatosensory cortex during voluntary movements without proprioceptive feedback. Nat Neurosci. 10:417–419.

Christensen MS, Lundbye-Jensen J, Grey MJ, Vejlby AD, Belhage B, Nielsen JB. 2010. Illusory sensation of movement induced by repetitive transcranial magnetic stimulation. PLoS One. 5:e13301.

Chronicle EP, Glover J. 2003. A ticklish question: Does magnetic stimulation of the primary motor cortex give rise to an "efference copy"? Cortex. 39:105–110.

Cui F, Arnstein D, Thomas RM, Maurits NM, Keysers C, Gazzola V. 2014. Functional magnetic resonance imaging connectivity analyses reveal efference-copy to primary somatosensory area, BA2. PLoS One. 9:1–12.

Davare M, Andres M, Cosnard G, Thonnard JL, Olivier E. 2006. Dissociating the role of ventral and dorsal premotor cortex in precision grasping. J Neurosci. 26:2260–2268.

Dekleva BM, Kording KP, Miller LE. 2018. Single reach plans in dorsal premotor cortex during a two-target task. Nat Commun. 9.

Desmurget M, Richard N, Beuriat PA, Szathmari A, Mottolese C, Duhamel JR, Sirigu A. 2018. Selective Inhibition of Volitional Hand Movements after Stimulation of the Dorsoposterior Parietal Cortex in Humans. Curr Biol. 28:3303-3309.e3.

Ellaway PH, Prochazka A, Chan M, Gauthier MJ. 2004. The sense of movement elicited by transcranial magnetic stimulation in humans is due to sensory feedback. J Physiol. 556:651–660.

Fornia L, Puglisi G, Leonetti A, Bello L, Berti A, Cerri G, Garbarini F. 2020. Direct electrical stimulation of the premotor cortex shuts down awareness of voluntary actions. Nat Commun. 11:705.

Fossataro C, Bruno V, Giurgola S, Bolognini N, Garbarini F. 2018. Losing my hand. Body ownership attenuation after virtual lesion of the primary motor cortex. Eur J Neurosci. 48:2272–2287.

Gandevia SC, Smith JL, Crawford M, Proske U, Taylor JL. 2006. Motor commands contribute to human position sense. J Physiol. 571:703–710.

Gandola M, Bottini G, Zapparoli L, Invernizzi P, Verardi M, Sterzi R, Santilli I, Sberna M, Paulesu E. 2014. The physiology of motor delusions in anosognosia for hemiplegia: Implications for current models of motor awareness. Conscious Cogn. 24:98–112.

Garbarini F, Bisio A, Biggio M, Pia L, Bove M. 2018. Motor sequence learning and intermanual transfer with a phantom limb. Cortex. 101:181–191.

Garbarini F, Cecchetti L, Bruno V, Mastropasqua A, Fossataro C, Massazza G, Sacco K, Valentini MC, Ricciardi E, Berti A. 2019. To move or not to move? Functional role of ventral premotor cortex in motor monitoring during limb immobilization. Cereb Cortex. 29:273–282.

Garbarini F, Piedimonte A, Dotta M, Pia L, Berti A. 2013. Dissociations and similarities in motor intention and motor awareness: The case of anosognosia for hemiplegia and motor neglect. J Neurol Neurosurg Psychiatry. 84:416–419.

Garbarini F, Rabuffetti M, Piedimonte A, Pia L, Ferrarin M, Frassinetti F, Gindri P, Cantagallo A, Driver J, Berti A. 2012. "Moving" a paralysed hand: Bimanual coupling effect in patients with anosognosia for hemiplegia. Brain. 135:1486–1497.

Gentile G, Guterstam A, Brozzoli C, Henrik Ehrsson H. 2013. Disintegration of multisensory signals from the real hand reduces default limb self-attribution: An fMRI study. J Neurosci. 33:13350–13366.

Grivaz P, Blanke O, Serino A. 2017. Common and distinct brain regions processing multisensory bodily signals for peripersonal space and body ownership. Neuroimage. 147:602–618.

Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, Kaelin-Lang A, Mima T, Rossi S, Thickbroom GW, Rossini PM, Ziemann U, Valls-Solé J, Siebner HR. 2012. A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee. Clin Neurophysiol. 123:858–882.

Haggard P. 2005. Conscious intention and motor cognition. Trends Cogn Sci. 9:290–295.

Harrington DL, Rao SM, Haaland KY, Bobholz JA, Mayer AR, Binder JR, Cox RW. 2000. Specialized neural systems underlying representations of sequential movements. J Cogn Neurosci. 12:56–77.

Holst E, Mittelstaedt H. 1971. The principle of reafference: Interactions between the central nervous system and the peripheral organs, PC Dodwell (Ed. and Trans.), Perceptual processing: Stimulus equivalence and pattern recognition.

Kawato M, Furukawa K, Suzuki R. 1987. A hierarchical neural-network model for control and learning of voluntary movement. Biol Cybern. 57:169–185.

Kitada R, Kito T, Saito DN, Kochiyama T, Matsumura M, Sadato N, Lederman SJ. 2006. Multisensory activation of the intraparietal area when classifying grating orientation: A functional magnetic resonance imaging study. J Neurosci. 26:7491–7501.

Konen CS, Haggard P. 2014. Multisensory parietal cortex contributes to visual enhancement of touch in humans: A single-pulse TMS study. Cereb Cortex. 24:501–507.

Kurabe S, Itoh K, Matsuzawa H, Nakada T, Fujii Y. 2014. Expansion of sensorimotor cortical activation for unilateral hand motion during contralateral hand deafferentation. Neuroreport. 25:435–439.

Langer KG, Levine DN. 2014. Babinski, J. (1914). Contribution to the study of the mental disorders in hemiplegia of organic cerebral origin (anosognosia). Translated by K.G. Langer & D.N. levine. Translated from the original Contribution à l'Étude des troubles mentaux dans l'hémiplé. Cortex. 61:5–8.

Maffei A, Bucher D, Fontanini A. 2012. Homeostatic plasticity in the nervous system. Neural Plast. 2012:1115–1123.

McCloskey DI. 1981. Corollary Discharges: Motor Commands and Perception. Bethesda,. ed, Comprehensive Physiology.

McCloskey DI, Colebatch JG, Potter EK, Burke D. 1983. Judgements about onset of rapid voluntary movements in man. J Neurophysiol. 49:851–863.

Mills KR, Boniface SJ, Schubert M. 1992. Magnetic brain stimulation with a double coil: the importance of coil orientation. Electroencephalogr Clin Neurophysiol Evoked Potentials. 85:17–21.

Miniussi C, Harris JA, Ruzzoli M. 2013. Modelling non-invasive brain stimulation in cognitive neuroscience. Neurosci Biobehav Rev.

Moro V, Pernigo S, Tsakiris M, Avesani R, Edelstyn NMJ, Jenkinson PM, Fotopoulou A. 2016. Motor versus body awareness: Voxel-based lesion analysis in anosognosia for hemiplegia and somatoparaphrenia following right hemisphere stroke. Cortex. 83:62–77.

Murata A, Wen W, Asama H. 2016. The body and objects represented in the ventral stream of the parieto-premotor network. Neurosci Res.

Oldfield RC. 1971. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia. 9:97–113.

Pacella V, Foulon C, Jenkinson PM, Scandola M, Bertagnoli S, Avesani R, Fotopoulou A, Moro V, Thiebaut De Schotten M. 2019. Anosognosia for Hemiplegia as a tripartite disconnection syndrome. bioRxiv.

Parr T, Limanowski J, Rawji V, Friston K. 2021. The computational neurology of movement under active inference. Brain. 144:1799–1818.

Pearce TM, Moran DW. 2012. Strategy-dependent encoding of planned arm movements in the dorsal premotor cortex. Science (80-). 337:984–988.

Piedimonte A, Garbarini F, Pia L, Mezzanato T, Berti A. 2016. From intention to perception: The case of anosognosia for hemiplegia. Neuropsychologia. 87:43–53.

Piedimonte A, Garbarini F, Rabuffetti M, Pia L, Montesano A, Ferrarin M, Berti A. 2015. Invisible grasps: Grip interference in anosognosia for hemiplegia. Neuropsychology. 29:776–781.

Pilacinski A, Lindner A. 2019. Distinct contributions of human posterior parietal and dorsal premotor cortex to reach trajectory planning. Sci Rep. 9.

Raffin E, Giraux P, Reilly KT. 2012. The moving phantom: Motor execution or motor imagery? Cortex. 48:746–757.

Raffin E, Mattout J, Reilly KT, Giraux P. 2012. Disentangling motor execution from motor imagery with the phantom limb. Brain. 135:582–595.

Ramachandran VS, Hirstein W. 1998. The perception of phantom limbs. The D. O. Hebb lecture. Brain. 121:1603–1630.

Ritterband-Rosenbaum A, Karabanov AN, Christensen MS, Nielsen JB. 2014. 10 Hz rTMS over right parietal cortex alters sense of agency during self-controlled movements. Front Hum Neurosci. 8:471.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Avanzini G, Bestmann S, Berardelli A, Brewer C, Canli T, Cantello R, Chen R, Classen J, Demitrack M, Di Lazzaro V, Epstein CM, George MS, Fregni F, Ilmoniemi R, Jalinous R, Karp B, Lefaucheur JP, Lisanby S, Meunier S, Miniussi C, Miranda P, Padberg F, Paulus W, Peterchev A, Porteri C, Provost M, Quartarone A, Rotenberg A, Rothwell J, Ruohonen J, Siebner H, Thut G, Valls-Solè J, Walsh V, Ugawa Y, Zangen A, Ziemann U. 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 120:2008–2039.

Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijević MR, Hallett M, Katayama Y, Lücking CH, Maertens de Noordhout AL, Marsden CD, Murray NMF, Rothwell JC, Swash M, Tomberg C. 1994. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol. 91:79–92.

Scaliti E, Gruppioni E, Becchio C. 2020. And Yet It Moves: What We Currently Know about Phantom Arm Movements. Neuroscientist. 26:328–342.

Schwartz AB, Moran DW, Reina GA. 2004. Differential Representation of Perception and Action in the Frontal Cortex. Science (80-). 303:380–383.

Silvanto J, Cattaneo Z. 2017. Common framework for “virtual lesion” and state-dependent TMS: The facilitatory/suppressive range model of online TMS effects on behavior. Brain Cogn. 119:32–38.

Sperry RW. 1950. Neural basis of the spontaneous optokinetic response produced by visual inversion. J Comp Physiol Psychol. 43:482–489.

Sun H, Blakely TM, Darvas F, Wander JD, Johnson LA, Su DK, Miller KJ, Fetz EE, Ojemann JG. 2015. Sequential activation of premotor, primary somatosensory and primary motor areas in humans during cued finger movements. Clin Neurophysiol. 126:2150–2161.

Vallar G, Ronchi R. 2006. Anosognosia for motor and sensory deficits after unilateral brain damage: A review. Restor Neurol Neurosci. 24:247–257.

Vallence AM, Hammond GR, Reilly KT. 2012. Increase in flexor but not extensor corticospinal motor outputs following ischemic nerve block. J Neurophysiol. 107:3417–3427.

Vocat R, Staub F, Stroppini T, Vuilleumier P. 2010. Anosognosia for hemiplegia: A clinical-anatomical prospective study. Brain. 133:3578–3597.

Figure captions:

Figure 1 A. Experimental setting. The participant was seated on a chair, in front of a table. The left arm, occluded from the participant's view with a panel, underwent the INB, through an inflated tourniquet. On the participant's right side, a laptop presented the sequences of the finger-tapping task and the right hand was used to answer to the motor performance and monitoring perception questionnaire with the laptop's keyboard. In the NoINB and INB conditions, the coil for the real TMS was positioned over the right PMd or right Parietal, according to the session. The coil for the sham TMS was positioned over the left PMd or left Parietal, according to the session. **B. Experimental task.** The task consisted of a left-hand finger tapping sequence (index finger=2, middle finger=3, ring finger=4), timed by a metronome. Objective (accuracy and synchronization) and subjective motor performance (ad hoc questionnaire) were tested. In each TMS condition (i.e., TMS.noINB; TMS.INB) of each session (i.e., PMd; P), the online TMS was administered both as a real and sham stimulation. **C. Experimental timeline.** Each participant underwent two experimental sessions, interleaved by at least one week between them. The two experimental sessions differed for the stimulation site since in one session, the TMS was delivered over the PMd, and in the other session, the TMS was delivered over the Parietal. Half of the participants performed the PMd session first and then the Parietal session, the other half *vice versa*.

Figure 2. Single trials recording in one participant during noINB condition (**A**. TMS trial, **B**. sham trial) and INB condition (**C**. TMS trial, **D**. sham trial). From the top, the first three rows of each panel indicate the button presses (index, middle, and ring fingers), the fourth row represents the EMG activity of the extensor digitorum communis, and the last two rows represent the goniometers' signals (Gonio1 was applied over the middle finger; Gonio was applied over the ring finger).

Figure 3. Results of objective (A, B) and subjective (C, D, E, F, G) measures. A. Mean values of the number of errors during the finger-tapping sequence motor task. **B.** Mean values of the RMS value (expressed in ms) of the objective synchronicity to the metronome, computed for each trial as the square root of the squared difference between the beginning of each of the 5 beeps of the metronome and the beginning of the each of the button press/finger movement. Error bars represent standard error of the mean. **C, D, E, F, G.** Mean values of the ratings for each question of the motor performance and monitoring perception questionnaire. °p=marginally significant; *$p < 0.05$; **$p \leq 0.01$; ***$p < 0.001$. Error bars represent the standard error of the mean. Each dot represents the mean of each subject's value in each condition.

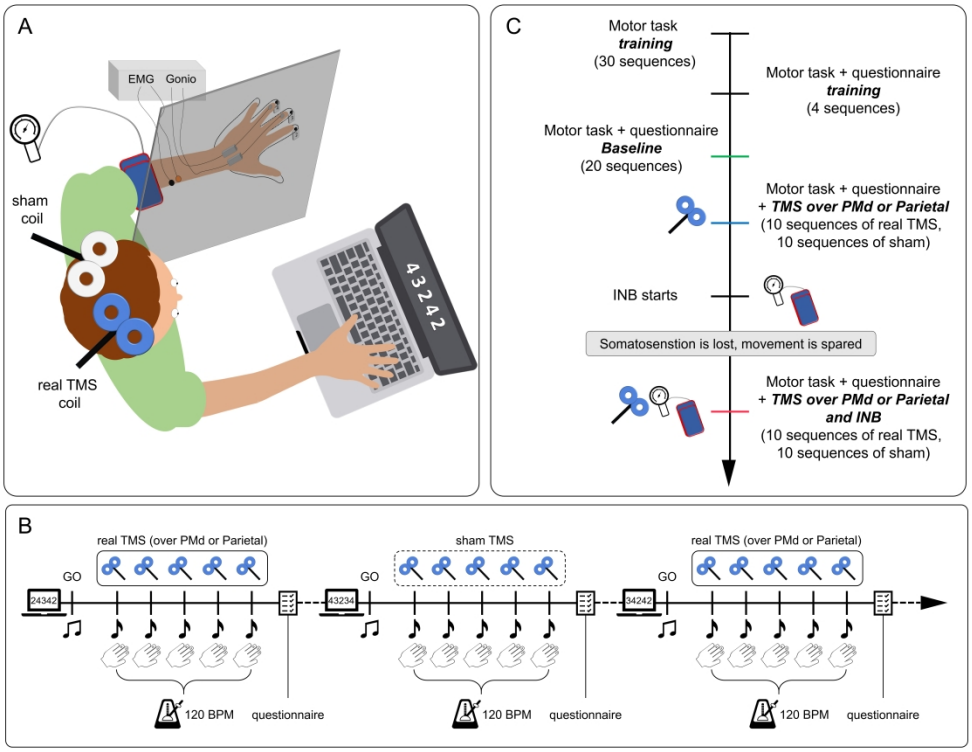

Figure 1 A. Experimental setting. The participant was seated on a chair, in front of a table. The left arm, occluded from the participant's view with a panel, underwent the INB, through an inflated tourniquet. On the participant's right side, a laptop presented the sequences of the finger-tapping task and the right hand was used to answer to the motor performance and monitoring perception questionnaire with the laptop's keyboard. In the NoINB and INB conditions, the coil for the real TMS was positioned over the right PMd or right Parietal, according to the session. The coil for the sham TMS was positioned over the left PMd or left Parietal, according to the session. B. Experimental task. The task consisted of a left-hand finger tapping sequence (index finger=2, middle finger=3, ring finger=4), timed by a metronome. Objective (accuracy and synchronization) and subjective motor performance (ad hoc questionnaire) were tested. In each TMS condition (i.e., TMS.noINB; TMS.INB) of each session (i.e., PMd; P), the online TMS was administered both as a real and sham stimulation. C. Experimental timeline. Each participant underwent two experimental sessions, interleaved by at least one week between them. The two experimental sessions differed for the stimulation site since in one session, the TMS was delivered over the PMd, and in the other session, the TMS was delivered over the Parietal. Half of the participants performed the PMd session first and then the Parietal session, the other half vice versa.

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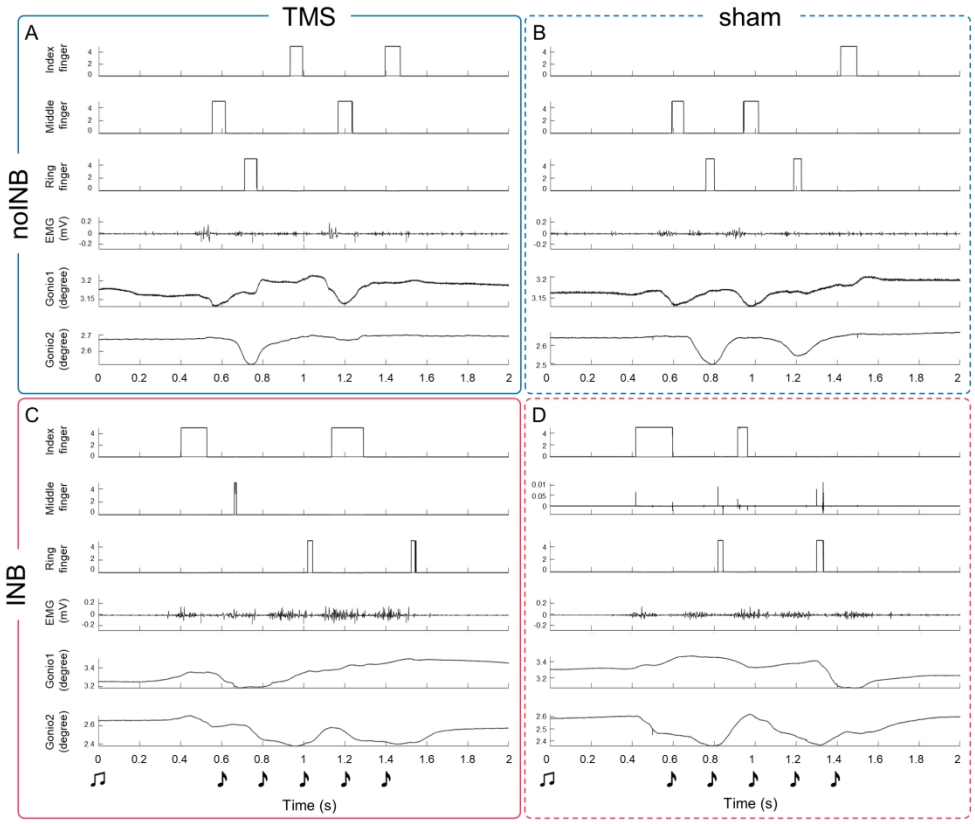

Figure 2. Single trials recording in one participant during noINB condition (A. TMS trial, B. sham trial) and INB condition (C. TMS trial, D. sham trial). From the top, the first three rows of each panel indicate the button presses (index, middle, and ring fingers), the fourth row represents the EMG activity of the extensor digitorum communis, and the last two rows represent the goniometers' signals (Gonio1 was applied over the middle finger; Gonio was applied over the ring finger).

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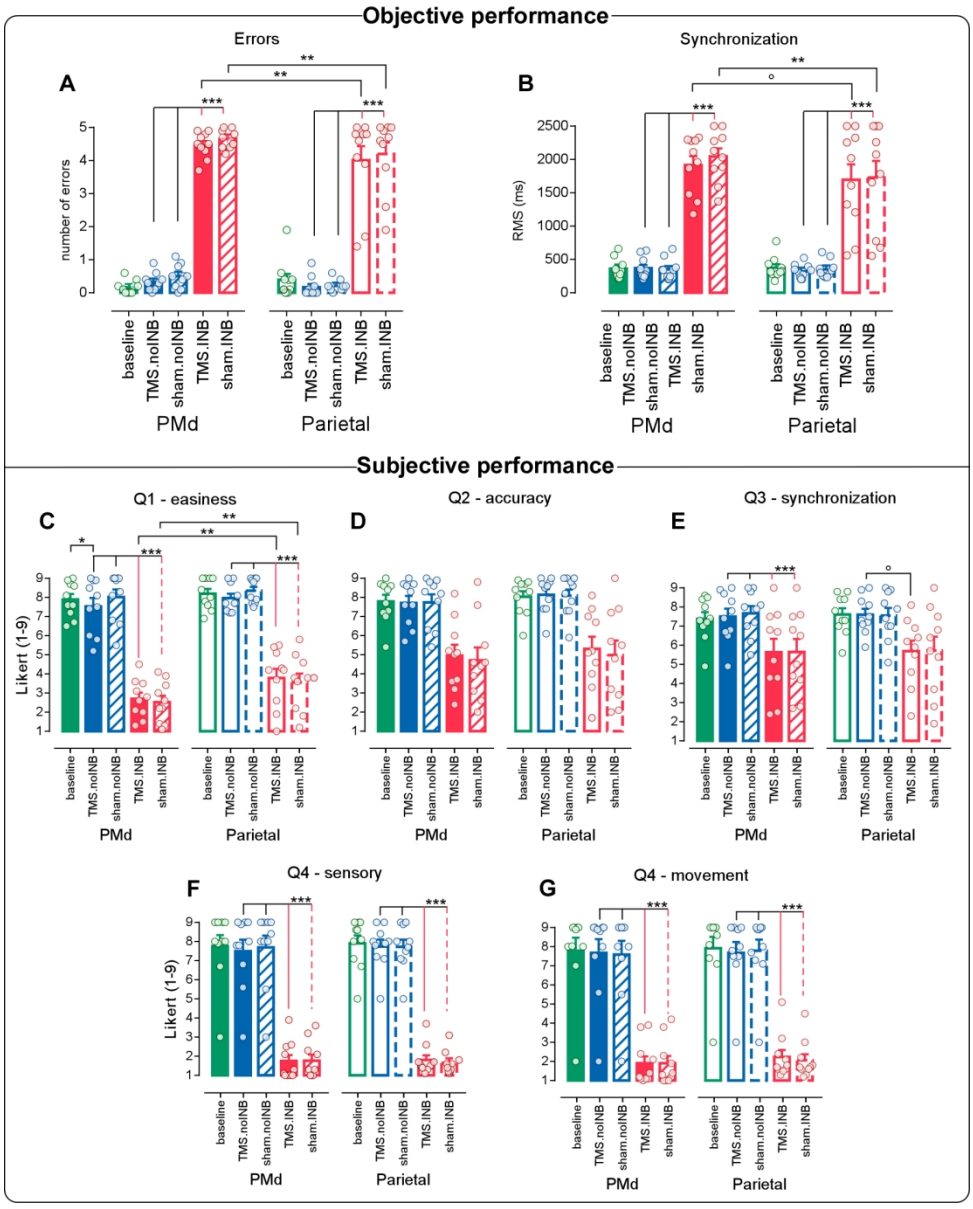

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