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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

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3 31 (Amoruso et al. 2018). In the context of anosognosia for hemiplegia, it has been proposed a
4 32 balance between spared brain areas implementing motor intentionality and damaged areas
5 33 involved in the neural counterpart of the comparator system (Berti et al. 2005; Vocat et al.
6 34 2010; Garbarini et al. 2012, 2013; Gandola et al. 2014; Piedimonte et al. 2015; Moro et al.
7 35 2016; Pacella et al. 2019). Indeed, in these patients, brain lesions involving the comparator
8 36 system are supposed to prevent them from detecting the mismatch between motor planning
9 37 and (the lack of) somatosensory inputs coming from the paralyzed limb. Interestingly for the
10 38 present study, these patients show to be able to perceive movements even in the absence of
11 39 somatosensory feedback, basing their movement perception on their (spared) intention
12 40 (Garbarini et al. 2012; Piedimonte et al. 2016). Another example of “spared” movement
13 41 perception in absence of somatosensory feedback comes from amputated people (Ackerley
14 42 and Kavounoudias 2015) with phantom movements (Ramachandran and Hirstein 1998;
15 43 Raffin, Giraux, et al. 2012; Raffin, Mattout, et al. 2012; Garbarini et al. 2018; Bruno et al.
16 44 2019). These patients, after the amputation of a body part, not only continue to perceive the
17 45 presence of their missing limb (i.e., phantom limb), but they claim they can voluntarily move
18 46 it (for a review see Scality, Gruppioni, and Becchio 2020). Unlike patients with anosognosia
19 47 for hemiplegia, which are not aware of their motor deficit and which have a brain damage,
20 48 amputees know and visually perceive that the limb is missing. However, the movement
21 49 experience persists, often accompanied by the distinct perception that the joints of the
22 50 missing limb have moved (Anderson 2018). Altogether these studies in the pathological
23 51 context, strongly highlight that the perception of movement is clearly not only based on
24 52 somatosensory feedback, but also on the predictions about the sensory consequences of the
25 53 movement, which seem to assume an essential contribution.

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44 54 In the present study, we focused on the premotor cortex (PM) as the responsible for
45 55 generating corollary discharge predicting the sensory consequences of the movement, as
46 56 highlighted by previous literature (McCloskey 1981; Chronicle and Glover 2003; Ellaway et
47 57 al. 2004; Cui et al. 2014; Murata et al. 2016), and more specifically we focused on the dorsal
48 58 part of the PM (PMd) (Christensen et al. 2010; Sun et al. 2015). In particular, a transcranial
49 59 magnetic stimulation (TMS) study (Christensen et al. 2010) found that 20 Hz 0.5 s trains of
50 60 high-frequency stimulation of the PMd in absence of sensory feedback induces a sensation
51 61 of movement, to the same extent as that for a movement illusion evoked by M1 stimulation.

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3 62 Interestingly, induced movement sensation after the PMd stimulation was less affected by
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5 63 sensory and motor deprivation than comparable induced movement sensations after M1
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7 64 stimulation. These results suggest that PMd may play a fundamental role in the prediction of
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9 65 somatosensory consequences, and therefore that a corollary discharge evoked by TMS over
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11 66 PMd is perceived as a movement.

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13 67 Here, we investigated the specific role of the PMd in mediating the somatosensory and
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15 68 proprioceptive predictions on which, at least in part, the motor performance and the
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17 69 movement perception relies on. To this aim, we take advantage of TMS, but not as a mean
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19 70 to induce movements, but rather to interfere or disturb PMd activity during an online finger
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21 71 tapping sequence task paced by a metronome (see Experimental task). Then, to expressly
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23 72 isolate the predictive component of the movement from the motor performance itself, we
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25 73 employ ischemic nerve block (INB) procedure. During INB, afferent and efferent neural
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27 74 transmission can be abolished by inflating a tourniquet around the limb, thus producing a
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29 75 peripheral blockade. The loss of afferent somatosensory feedback (tactile and
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31 76 proprioception) and efferent motor output signaling happens at different time points.
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33 77 Typically, after 20-25 minutes after the tourniquet inflation, proprioceptive and tactile
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35 78 sensations are blocked via the large diameter Ia afferent fibers, and then with a small delay
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37 79 of 3-10 minutes, the block of the smaller diameter efferent motor fibers follows. The INB
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39 80 provides, therefore, a time window during which participants can perform voluntary
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41 81 movements (because of the intact efferences) without sensory feedback (due to the blocked
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43 82 afferences). For this reason, INB is a valid model to investigate the loss of feedback from
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45 83 large diameter sensory fibers. This procedure has been largely employed in different
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47 84 experimental paradigms aiming at investigating several aspects of motor control since it
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49 85 offers the exceptional possibility to investigate movements in absence of afferent information
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51 86 and the consequent rapid plasticity modulations in cortical and corticospinal pathways
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53 87 (Christensen et al. 2007; Maffei et al. 2012; Vallence et al. 2012; Bruttini et al. 2014; Kurabe
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55 88 et al. 2014). For this reason, in the present study, the motor task was performed either with
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57 89 normal sensory feedback or during INB, in the specific time-window during which
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59 90 participants can voluntarily perform movements (because of the intact efferences) in absence
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91 of somatosensory feedback (due to the afferences block). After each motor sequence, an *ad-*
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hoc questionnaire (see Experimental task) about their subjective movement perception and

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3 93 the monitoring of their motor performance was administered. Single-pulse suprathreshold
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5 94 online TMS (see Methods), used to interfere with the PMd activity, was delivered
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7 95 alternatively both as a real and as a sham stimulation (see Experimental timeline). In addition,
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9 96 in a separate session, TMS was delivered over a control brain area, i.e., a parietal site
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11 97 (Parietal) 3 cm posterior to the primary motor cortex. This control site has been selected for
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13 98 its role in multisensory integration, being a brain area where all the sensory information
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15 99 converges (e.g., somatosensory feedbacks from the primary somatosensory cortex, visual
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17 100 feedback from the primary visual cortex, acoustic information from the primary auditory
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19 101 cortex, etc.), especially for stimuli concerning the hand (Kitada et al. 2006; Gentile et al.
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21 102 2013; Konen and Haggard 2014; American Psychological Association 2017; Grivaz et al.
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23 103 2017).

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25 104 We anticipate that, concerning the *objective performance* (i.e., number of errors and
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27 105 movement synchronization during the motor task), the INB, when somatosensory and
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29 106 proprioceptive feedbacks are lacking due to the sensory blockade, would overall impair the
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31 107 performance (i.e., increased number of errors and less synchronized movements) regardless
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33 108 of the stimulation site (i.e., PMd and Parietal), but crucially significant differences between
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35 109 the PMd and the Parietal session are expected. In particular, when the INB prevents the
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37 110 afferent information during the motor task execution, the system may rely more on the
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39 111 predicted sensory consequences of movement generated by PMd. Thus, the lack of both
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41 112 sensory feedback (induced by the INB) and sensory predictions (induced by the TMS over
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43 113 PMd) could lead participants to worsen their motor performance, thus making more sequence
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45 114 errors and being less synchronized with the metronome during the motor task. On the
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47 115 opposite, we expect that the disruption of the Parietal (i.e., an area in which sensory feedback
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49 116 converges) in the condition in which sensory information is missing in any case due to the
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51 117 sensory blockade, could not interfere with the motor performance, since the predictive
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53 118 component of the movement is still present. Additionally, since the *subjective performance*
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55 119 is evaluated after each motor sequence (both during noINB and INB conditions) by
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57 120 employing the questionnaire about the movement performance and the monitoring
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59 121 perception, we expect significant differences between the PMd and Parietal interference, with
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122 lower ratings after the PMd rather than after the Parietal disruption.

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4 1235 124 **2. Materials and methods**6
7 125 **2.1 Participants**

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9 126 Ten volunteers (6 women, mean age = 26.1 years, SD = 4.2) participated in the study. All
10 127 participants were right-handed, as determined by the Edinburgh Handedness Inventory
11 128 (mean score = 18.2, SD = 1.6) (Oldfield 1971). Participants were naïve to the purpose of the
12 129 experiment; none of them had a history or evidence of neurological and psychiatric illness
13 130 and contraindication to TMS (Rossi et al. 2009; Bruno et al. 2018). All participants gave
14 131 informed written consent before participation. The investigation (H-17027109) was approved
15 132 by the local ethics committee of the Capital Region of Copenhagen and conforms to the
16 133 Declaration of Helsinki.

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26 135 **2.2 Experimental timeline**

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28 136 Each participant underwent two experimental sessions, interleaved by at least one week
29 137 between them. During each session, participants performed a motor monitoring task (see
30 138 details in *Experimental task*). After a training session, the task could be accompanied by TMS
31 139 and/or INB. Indeed, in each session, the experimental task was performed alone (i.e., baseline
32 140 condition), with TMS (i.e., TMS without INB condition), and with both TMS and INB (i.e.,
33 141 TMS with INB). The two experimental sessions differed with respect to the stimulation site,
34 142 since in one session the TMS was delivered over the PMd, and in the other session the TMS
35 143 was delivered over the Parietal. In each TMS condition (i.e., TMS without INB, TMS with
36 144 INB) of each experimental session (i.e., TMS over PMd, TMS over Parietal), the online TMS
37 145 was administered both as a real and sham stimulation (see details in *TMS, EMG, and*
38 146 *goniometers*). Half of the participants performed the PMd session first and then the Parietal
39 147 session, the other half performed the Parietal session first, and then the PMd session.

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149 **2.3 Experimental task**

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

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3 180 subjective rating on a Likert Scale from 1 (i.e., lowest rating) to 9 (i.e., highest ratings), by
4 181 pressing with their right hand (i.e., the one not involved in the task) on the keyboard.
5 182 Importantly, the left arm was always covered with a panel during the task, such that
6 183 participants could not rely on visual information about their motor performance (Figure 1A).
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11 184 Before starting the experiment, in each experimental session, 30 motor sequences were
12 185 performed as training, so that participants could familiarize themselves with the motor task.
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14 186 Then, to familiarize themselves with the questionnaire about movement performance and
15 187 monitoring perception, 4 motor sequences followed by the questionnaire were executed as
16 188 training. After the training phase (i.e., 34 sequences in total), participants underwent 20 trials
17 189 of motor monitoring task (i.e., baseline). Then, they performed 20 trials of the motor
18 190 monitoring task in the TMS without INB condition, and then 20 trials of the motor monitoring
19 191 task in the TMS with INB condition were completed. In each TMS condition (i.e., TMS
20 192 without INB, TMS with INB) of each experimental session (i.e., TMS over PMd, TMS over
21 193 Parietal), the online TMS was administered at the beginning of each beep of the 2 Hz
22 194 metronome. The TMS was real in half of the trials (i.e., 10 trials in the TMS without INB
23 195 condition, 10 trials in the TMS with INB condition) and sham in the other half (i.e., 10 trials
24 196 in the TMS without INB condition, 10 trials in the TMS with INB condition) (Figure 1B).
25 197 Real and sham TMS were always alternated so that after every sequence with a real TMS, a
26 198 sham stimulation followed. The continuous electromyographic (EMG) activity and
27 199 goniometers recordings (see details in *TMS, EMG, and goniometers*) started with the first
28 200 “go signal”. The trigger of sounds and single-pulse TMS, as well as the EMG and
29 201 goniometers recording, was managed by Signal 4.00 software (Cambridge Electronic Design,
30 202 Cambridge, UK) (Figure 1C).
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204 ***2.4 Peripheral sensorimotor blockade***

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

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3 210 happened between 16:15 min and 22:15 min after initiation of ischemia, the subjects were
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5 211 asked to perform 20 trials of the motor sequence and monitoring task with real and sham
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7 212 TMS applied. Participants controlled when to start each trial and, in total, the 20 trials lasted
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9 213 about 5 min.

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12 13 215 ***2.5 Transcranial magnetic stimulation, electromyography, and goniometers*** 14 15 216 ***recording***

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17 217 Online TMS was performed using two figure-of-eight coils connected to two different
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19 218 Magstim Rapid² stimulators (Magstim, Whitland, Dyfed, Wales, UK) so that one stimulator
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21 219 was employed for the real TMS and the other for the sham. For the real TMS trials, the coil
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23 220 was placed through BrainSight, a system for frameless stereotaxis (Rogue Research Inc.,
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25 221 Montreal, Canada), over the right primary motor cortex (M1). The initial placement was
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27 222 based on the neuroanatomy of a normalized brain aiming for the hand knob on the precentral
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29 223 gyrus. With this as starting point, the individual optimal point for eliciting motor evoked
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31 224 potentials was found. The coil was placed tangentially to the scalp with the handle pointing
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33 225 posterolaterally 45 degrees from the midline. This orientation is optimal for trans-synaptic
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35 226 activation of the corticospinal pathway (Brasil-Neto et al. 1992; Mills et al. 1992). The resting
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37 227 motor threshold (rMT) was defined as the lowest stimulator output intensity capable of
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39 228 inducing EMG responses with a magnitude greater than 50 μ V of the peak-to-peak motor
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41 229 evoked potentials (MEPs) amplitude in the left extensor digitorum communis muscle for a
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43 230 minimum of five of the ten trials (Rossini et al. 1994; Groppa et al. 2012) and it was measured
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45 231 at the beginning of each experimental session, following the international standards (Rossi
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47 232 et al. 2009). After having individuated the rMT, the coil was positioned with the use of the
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49 233 neuro-navigation system over PMd defined as 2 cm anterior to the M1 hotspot or Parietal
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51 234 defined as 3 cm posterior to the M1 individual hotspot, according to the experimental session.
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53 235 The accuracy and stability of coil placement were ensured using BrainSight and a normalized
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55 236 brain. During the experiment, the stimulus intensity was kept at 110% of the rMT during data
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57 237 collection. rMTs were found to be between 41% and 71% of maximal stimulator output
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59 238 across the participants. On average, the difference in rMT between sessions 1 and 2 was
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239 2.4%-points of maximal stimulator output. In sham trials, the second figure-of-eight coil was

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3 240 placed on the left hemisphere, in an analogous position to that of the coil for the real TMS,
4 241 and tilted away from the scalp by 90° of angle. Hence, the sham coil plane was not tangential
5 242 to the skull, in turn reducing its effectiveness due to power dissipation in the air by that part
6 243 of the coil that loses contact with the scalp. With this strategy, the stimulator discharges still
7 244 give an audible clicking sound along with peripheral sensations associated with TMS, but
8 245 maintaining contact and sound, thereby giving the impression to the naïve subjects of being
9 246 stimulated (e.g., Bolognini and Ro 2010; Fossataro et al. 2018).

16 247 MEPs were recorded from the left extensor digitorum communis. EMG activity from the
17 248 extensor digitorum communis was recorded by pairs of Ag–AgCl surface pre-gelled
18 249 electrodes (Ambu, Ballerup, Denmark) following standard skin preparation. The electrodes
19 250 were connected to the electromyograph, and the EMG signals were amplified with custom
20 251 EMG amplifiers developed and manufactured at Department of Neuroscience of the
21 252 University of Copenhagen and recorded using Signal 4.00 software (Cambridge Electronic
22 253 Design, Cambridge, UK). Besides, during the task, to control individual finger movements,
23 254 two goniometers connected to the polygraph system were attached respectively to middle
24 255 and ring fingers to control and monitor the angle's movement during the button press (see
25 256 Figure 2 for examples of single trials recording in one participant during noINB and INB
26 257 conditions).

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259 --- **Figure 1 about here** ---

260 --- **Figure 2 about here** ---

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262 ***2.6 Data analysis***

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

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3 269 he/she pressed another one with another finger) and omissions (i.e., the participant had to
4 270 press a button, but he/she did not press anything). To control for objective synchronicity to
5 271 the metronome, a root mean square (RMS) value (expressed in ms) was computed for each
6 272 trial as the square root of the squared difference between the beginning of each of the 5 beeps
7 273 of the metronome and the beginning of the each of the button press/finger movements. If no
8 274 movement was detected, a default difference of 500 ms was used for a specific movement. If
9 275 no movements had been made during the entire trial, the RMS was set to 2500ms.
10 276 Furthermore, concerning the subjective performance, we analyzed the individual subjective
11 277 ratings to the five items of the questionnaire about movement performance and monitoring
12 278 perception. Therefore, separately for the objective measures (i.e., errors and synchronization)
13 279 and for subjective measures (i.e., each question of the movement performance and
14 280 monitoring perception questionnaire: easiness – Q1, accuracy – Q2, synchronicity – Q3,
15 281 sensory – Q4, movement – Q5), we ran separate Linear Mixed Models (LMM) in R (version
16 282 4.0.0, <https://www.r-project.org/>), using the lme4 package (Bates et al. 2015). We included
17 283 errors, synchronization, Q1, Q2, Q3, Q4, and Q5 ratings as the dependent variables and we
18 284 parameterized the model into the combined variable Site (baseline PMd, PMd, baseline
19 285 Parietal, Parietal), Stimulation (noTMS, TMS, sham) and Feedback (noINB, INB), resulting
20 286 in the following conditions: baselinePMd.noTMS.noINB, PMd.TMS.noINB,
21 287 PMd.sham.noINB, PMd.TMS.INB, PMd.sham.INB, baselineParietal.noTMS.noINB,
22 288 Parietal.TMS.noINB, Parietal.sham.noINB, Parietal.TMS.INB, Parietal.sham.INB. Since we
23 289 were interested in specific tests within the Site.Stimulation.Feedback parameterization, we
24 290 ran, between conditions, simultaneous tests for general linear hypotheses with multiple
25 291 comparisons of means by employing Tukey contrasts (Bonferroni corrected). We focused
26 292 only on comparisons between conditions in which one factor is different. Participants' age
27 293 and gender were added as fixed effects, while subject, trial, and condition order as random
28 294 effects. Regarding the subjective ratings, each subjective measure was tested including the
29 295 objective measures (error and synchronization) as fixed effects covariates.

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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.

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--- Figure 3 about here ---

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354 **3.2 Subjective measures**

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

359 *3.2.1 Q1 – easiness*

360 Significant differences were found regarding the easiness' rating (Figure 3C). When
361 comparing conditions with preserved somatosensory feedback (i.e., noINB) in combination
362 or not with TMS, we found that only after the PMd interference participants rated the task as
363 more difficult (baselinePMd.noTMS.noINB vs PMd.TMS.noINB: $\beta=0.51$, $z=3.200$,
364 $p=0.02$), suggesting a PMd involvement of in rating the sensation of difficulty during the
365 motor task. When comparing conditions with preserved somatosensory feedback (i.e.,
366 noINB) with conditions without somatosensory feedback (i.e., INB), participants rated the
367 motor task as more difficult during the sensory blockade, both in the PMd (PMd.TMS.INB
368 vs PMd.TMS.noINB: $\beta=-2.64$, $z=-10.373$, $p<0.0000001$; PMd.sham.INB vs
369 PMd.sham.noINB: $\beta=-3.24$, $z=-12.722$, $p<0.0000001$) and in the Parietal session
370 (Parietal.TMS.INB vs Parietal.TMS.noINB: $\beta=-2.05$, $z=-8.342$, $p<0.0000001$;
371 Parietal.sham.INB vs Parietal.sham.noINB: $\beta=-2.62$, $z=-10.460$, $p<0.0000001$),
372 suggesting that, overall, INB lowered the subjective feeling of easiness regardless of
373 Site.Stimulation. Crucially, when comparing PMd and P during the INB condition,
374 participants rated the motor task as more difficult in the PMd session (regardless of the real
375 TMS or sham, Parietal.TMS.INB vs PMd.TMS.INB: $\beta=0.94$, $z=5.152$, $p=0.00000387$;
376 Parietal.sham.INB vs PMd.sham.INB: $\beta=0.81$, $z=4.454$, $p=0.00012$), suggesting that in
377 absence of somatosensory feedback, TMS (and sham) over PMd significantly lowered the
378 subjective feeling of easiness. As for the previously reported results, it is important to note
379 that no significant difference was found in the INB condition between the (real) TMS and
380 the sham within the same stimulation site (i.e., PMd and Parietal), suggesting a carryover
381 effect induced by the real TMS in the sham stimulation.

382 3.2.2 *Q2 – accuracy*

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

387 3.2.3 *Q3 – synchronization*

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

398 3.2.4 *Q4 – tactile sensation*

399 Concerning the tactile sensation experienced during the motor task significant differences
400 were found (Figure 3F). In particular, when comparing conditions with preserved
401 somatosensory feedback (i.e., noINB) with conditions without somatosensory feedback (i.e.,
402 INB), participants experienced a reduced tactile sensation, both in the PMd (PMd.TMS.INB
403 vs PMd.TMS.noINB: $\beta=-4.52$, $z=-19.777$, $p<0.0000001$; PMd.sham.INB vs
404 PMd.sham.noINB: $\beta=-4.62$, $z=-20.143$, $p<0.0000001$) and in the Parietal session
405 (Parietal.TMS.INB vs Parietal.TMS.noINB: $\beta=-4.77$, $z=-21.611$, $p<0.0000001$;
406 Parietal.sham.INB vs Parietal.sham.noINB: $\beta=-4.91$, $z=-21.797$, $p<0.0000001$),
407 suggesting that, overall, INB reduces tactile sensation regardless of Site.Stimulation. Again,
408 no significant difference was found in the INB condition between the (real) TMS and the
409 sham within the same stimulation site (i.e., PMd and Parietal), suggesting a carryover effect
410 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

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3 440 voluntarily perform movements (because of the intact efferences) in the absence of
4 441 somatosensory and proprioceptive feedback (due to the afferences block). The objective
5 442 performance (i.e., errors in the motor sequence and synchronization with the metronome),
6 443 and the subjective motor performance and monitoring perception were tested. We found that
7 444 the TMS *per se* (i.e., noINB condition) over the two cortical sites (i.e., PMd and Parietal) did
8 445 not interfere with the motor performance, suggesting no differential role between the two
9 446 areas in our motor task when somatosensory and proprioceptive information are normally
10 447 available. Interestingly, the INB, as compared to the noINB condition, overall worsen the
11 448 objective performance, and made participants lower their ratings about the movement
12 449 perception and the monitoring performance, regardless of the stimulation site (i.e., PMd and
13 450 Parietal). Crucially, participants performed significantly more errors and significantly less
14 451 synchronized movements during the INB only after the PMd interference (as compared to
15 452 the Parietal interference). Besides, only after the PMd disruption, participants subjectively
16 453 rated the task as more complex. These results might suggest that PMd plays a crucial role in
17 454 generating the predictions of a movement.

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20 455 To have a correct motor performance, somatosensory feedbacks are fundamental (see as for
21 456 example the role of proprioceptive inputs in the prevention of hemispheric unbalance during
22 457 limb immobilization, Avanzino et al., 2014). Consequently, in our study, the lack of
23 458 somatosensory and proprioceptive afferences induced by the INB led to an overall worsen
24 459 motor performance, as suggested by the increased number of errors in the motor sequences
25 460 and less synchronized movements, regardless of the TMS disruption site (i.e., PMd and
26 461 Parietal). Crucially, our results suggest that sensory feedbacks alone are necessary, but not
27 462 sufficient, for appropriate motor performance. Indeed, we found that only after the PMd
28 463 disruption, during the INB condition in which sensory feedback was absent, participants
29 464 worsen their objective motor performance. Why does the motor performance become
30 465 impaired after the PMd and not after the Parietal interference? Our interpretation is that the
31 466 PMd computes the predictions of the sensory consequences of the movement, and, therefore,
32 467 the lack of both sensory information (due to the INB) and the sensory predictions (due to
33 468 PMd disruption) caused greater impairment in the motor performance. Differently, the
34 469 interference of the parietal area chosen as a control site for its multisensory integration
35 470 function (especially for the hand), did not show, as expected, any effect during the sensory

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3 471 blockade. Indeed, when somatosensory and proprioceptive feedback was absent during the
4 472 INB, no converging information could be sent to the parietal cortex, and since it was not
5 473 properly fed, it did not play a crucial role in our motor task. The role of the PMd in generating
6 474 corollary discharge based on a forward model, which contains the predictions about the
7 475 consequences of the movement, has been previously suggested. In the absence of sensory
8 476 feedback, an excitatory TMS over PMd can generate the sensation of movement (Christensen
9 477 et al. 2010). An fMRI study (Blankenburg et al. 2006) on the cutaneous rabbit illusion (Asai
10 478 and Kanayama 2012), in which repeated rapid stimulation at the wrist and then near the elbow
11 479 create the illusion of continuous touches along the arm, showed that not only the illusory
12 480 touches activated the somatosensory cortex, but also the contralateral PMd, suggesting a
13 481 premotor involvement in predicting the sensory perception of the touch. In the same vein, it
14 482 has been shown that even by maintaining normal somatosensory afference, the PM (and/or
15 483 the supplementary motor cortex) predicts brain activity in primary somatosensory regions
16 484 activity during active and passive touch of soft materials, suggesting that signals in primary
17 485 somatosensory regions can reflect input from motor cortices (Cui et al. 2014). In addition, in
18 486 the monkey brain, it has been shown that actual movements are represented in the M1,
19 487 whereas the visualized, presumably perceived movements are represented in PMd (Schwartz
20 488 et al. 2004). The results of our study are in line with the above-mentioned literature. In our
21 489 motor task, the absence of somatosensory feedback due to the INB would lead participants
22 490 to assign more importance to the corollary discharge, generated by PMd. Interfering with the
23 491 online single-pulse TMS on PMd implied that both somatosensory and proprioceptive
24 492 feedback and corollary discharge were disrupted, and this may have led to worsening the
25 493 objective motor performance of our participants. Also, only after the PMd disruption, the
26 494 subjective ratings about the easiness of the task were significantly lower, suggesting that
27 495 participants evaluate the task as more difficult, even considering their objective performance.
28 496 In other words, participants overestimate the task's difficulty, suggesting, again, an incorrect
29 497 perception of their own movements.

30 498 Alternatively, our differential findings between PMd and Parietal can be explained in light
31 499 of the role of PMd in motor planning (Pearce and Moran 2012; Dekleva et al. 2018; Pilacinski
32 500 and Lindner 2019). Accordingly, the more significant impairment in motor performance after
33 501 TMS over PMd in the INB condition could be ascribed to PMd motor planning function: it

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3 502 is reasonable that the TMS interference over a motor planning area could lead to a worsen
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5 503 objective movement. However, the lack of difference in motor performance between the PMd
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7 504 interference condition in the noINB condition (when the TMS was delivered but sensory
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9 505 feedback was available, i.e., PMd.TMS.noINB) and its baseline, may suggest that the
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11 506 planning component of PMd does not play a fundamental role, at least in our task.
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13 507 Furthermore, the lack of difference in motor performance between PMd and Parietal in the
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15 508 noINB condition seems to be in line with this interpretation. However, we cannot exclude
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17 509 that the PMd motor planning function could have been more relevant with the task's
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19 510 increasing difficulty, already shown by previous literature (Harrington et al. 2000; Ceballos
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21 511 et al. 2002; Davare et al. 2006), as during the INB condition. Therefore, it is not possible to
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23 512 rule out that PMd planning function has influenced the situation in which, as during the
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25 513 sensory block (i.e., INB condition), the movement was more difficult. A third alternative
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27 514 explanation of our results could be that PMd plays a role as the inverse model computing the
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29 515 signals needed to make the desired movement (Blakemore et al. 2000). However, if PMd
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31 516 plays that role, we would expect to observe differences in motor performance in the noINB
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33 517 condition, but this is not the case.

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35 518 It is important to note that the neuronavigation system ensures that only the control and target
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37 519 areas were stimulated, and as consequence, were disturbed during the motor task. This
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39 520 clarification is necessary since the scientific literature suggests different functions of these
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41 521 cortical sites according to specific portions and coordinates. For example, the ventral portion
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43 522 of PM (PMv) has been largely investigated also for the comparator system-related role both
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45 523 in healthy individuals (Bolognini, Zigiotta, Carneiro, & Vallar, 2016; Forna et al., 2020;
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47 524 Garbarini et al., 2019; Bruno et al., 2017) and in the pathological population (Berti et al.
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49 525 2005). Indeed, these previous findings promote the role of PMv as a shared neural substrate
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51 526 for both motor execution and motor awareness of voluntary actions, highlighting, with
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53 527 different techniques, the role of the PMv in motor monitoring, and especially in motor
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55 528 awareness. On the other side, other parietal sites have been investigated during voluntary
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57 529 movements for their role in motor intention and programming. For example, it has been
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59 530 shown that the direct electrical stimulation of the dorsoposterior parietal cortex, a site
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61 531 different from the hand's multisensory parietal area employed in our study, prevents

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3 532 movement initiation and instantly inhibits ongoing volitional upper-limb motor responses
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5 533 (Desmurget et al. 2018).

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7 534 Our study is not free from limitations. The main limitation of our study is that we did not find
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9 535 significant differences between the real and the sham stimulation, both in the PMd and in
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11 536 Parietal sessions, and both in the noINB and INB conditions, suggesting a carryover effect
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13 537 induced by the TMS. The short time window in which the INB disrupts afferences while the
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15 538 afferences are still present led us to opt for an online TMS protocol, able to interfere with the
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17 539 cortical activity during the task, by creating a momentaneous “virtual lesion”, such as the one
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19 540 used the classic work of Amassian (Amassian et al. 1989; Ritterband-Rosenbaum et al. 2014).
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21 541 More recently, there have been attempts to explain TMS effects on behavior more
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23 542 mechanistically, in terms of inducing noise. The idea is that TMS indiscriminately activates
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25 543 neurons in a targeted region and, in this manner, it adds noise to neural processing (Silvanto
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27 544 and Cattaneo 2017). This noise reduces the signal-to-noise ratio of the cognitive task under
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29 545 investigation and thus impairs performance (Miniussi et al. 2013). Probably, in our task, the
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31 546 necessary short time between the real and the sham stimulation, due to the time constraints
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33 547 of the INB, made sure that the induced noise over the target area during the real stimulation
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35 548 did not run out its effect. This would have, in turn, caused that even during the sham
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37 549 stimulation, the induced noise over the target area impacted the task. A possibility to
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39 550 overcome this carryover effect problem would have been to add one more identical session,
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41 551 where only the sham would have been delivered, to have three sessions in total (i.e., one with
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43 552 the TMS over PMd, one with the TMS over Parietal, and one with sham stimulation).
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45 553 However, we did not opt for this solution to not repeat the task and the INB three different
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47 554 times in the same participants.

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49 555 In conclusion, our results suggest that the lack of both sensory feedback (induced by the INB)
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51 556 and sensory predictions (induced by the interference of the TMS over PMd) leded
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53 557 participants to worsen their objective and subjective motor performance. Contrarily, the
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55 558 disruption of the Parietal, when sensory information is missing as during INB, does not
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57 559 interfere with the motor performance since the predictive component of the movement is still
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59 560 present. Altogether, these results highlight the crucial role of PMd in generating the
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61 561 prediction of the sensory consequences of the movement.

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6 562 **Conflict of interest**

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8 None
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13 563 **Data availability statement**

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15 Data are available upon request.
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22 564 **Acknowledgment**

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For Peer Review

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3 **Figure captions:**
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5 **Figure 1 A. Experimental setting.** The participant was seated on a chair, in front of a table. The left
6 arm, occluded from the participant's view with a panel, underwent the INB, through an inflated
7 tourniquet. On the participant's right side, a laptop presented the sequences of the finger-tapping task
8 and the right hand was used to answer to the motor performance and monitoring perception
9 questionnaire with the laptop's keyboard. In the NoINB and INB conditions, the coil for the real TMS
10 was positioned over the right PMd or right Parietal, according to the session. The coil for the sham
11 TMS was positioned over the left PMd or left Parietal, according to the session. **B. Experimental**
12 **task.** The task consisted of a left-hand finger tapping sequence (index finger=2, middle finger=3, ring
13 finger=4), timed by a metronome. Objective (accuracy and synchronization) and subjective motor
14 performance (ad hoc questionnaire) were tested. In each TMS condition (i.e., TMS.noINB;
15 TMS.INB) of each session (i.e., PMd; P), the online TMS was administered both as a real and sham
16 stimulation. **C. Experimental timeline.** Each participant underwent two experimental sessions,
17 interleaved by at least one week between them. The two experimental sessions differed for the
18 stimulation site since in one session, the TMS was delivered over the PMd, and in the other session,
19 the TMS was delivered over the Parietal. Half of the participants performed the PMd session first and
20 then the Parietal session, the other half *vice versa*.
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33 **Figure 2.** Single trials recording in one participant during noINB condition (**A.** TMS trial, **B.** sham
34 trial) and INB condition (**C.** TMS trial, **D.** sham trial). From the top, the first three rows of each panel
35 indicate the button presses (index, middle, and ring fingers), the fourth row represents the EMG
36 activity of the extensor digitorum communis, and the last two rows represent the goniometers' signals
37 (Gonio1 was applied over the middle finger; Gonio was applied over the ring finger).
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43 **Figure 3. Results of objective (A, B) and subjective (C, D, E, F, G) measures.** **A.** Mean values of
44 the number of errors during the finger-tapping sequence motor task. **B.** Mean values of the RMS value
45 (expressed in ms) of the objective synchronicity to the metronome, computed for each trial as the
46 square root of the squared difference between the beginning of each of the 5 beeps of the metronome
47 and the beginning of the each of the button press/finger movement. Error bars represent standard error
48 of the mean. **C, D, E, F, G.** Mean values of the ratings for each question of the motor performance
49 and monitoring perception questionnaire. °p=marginally significant; *p < 0.05; **p ≤ 0.01; ***p <
50 0.001. Error bars represent the standard error of the mean. Each dot represents the mean of each
51 subject's value in each condition.
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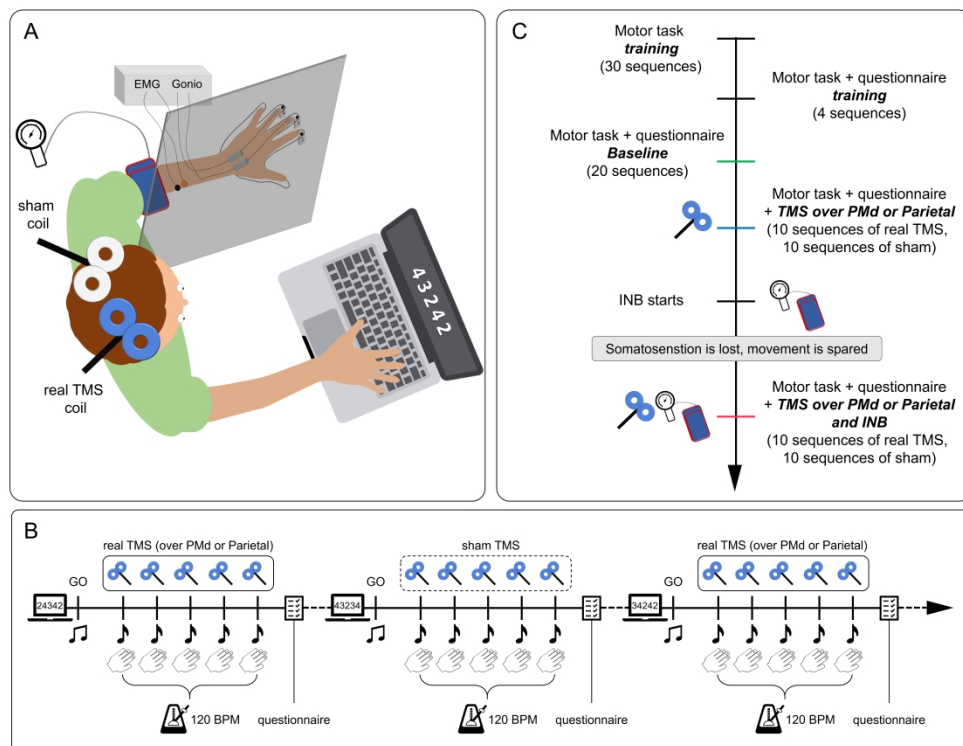


Figure 1 A. Experimental setting. The participant was seated on a chair, in front of a table. The left arm, occluded from the participant's view with a panel, underwent the INB, through an inflated tourniquet. On the participant's right side, a laptop presented the sequences of the finger-tapping task 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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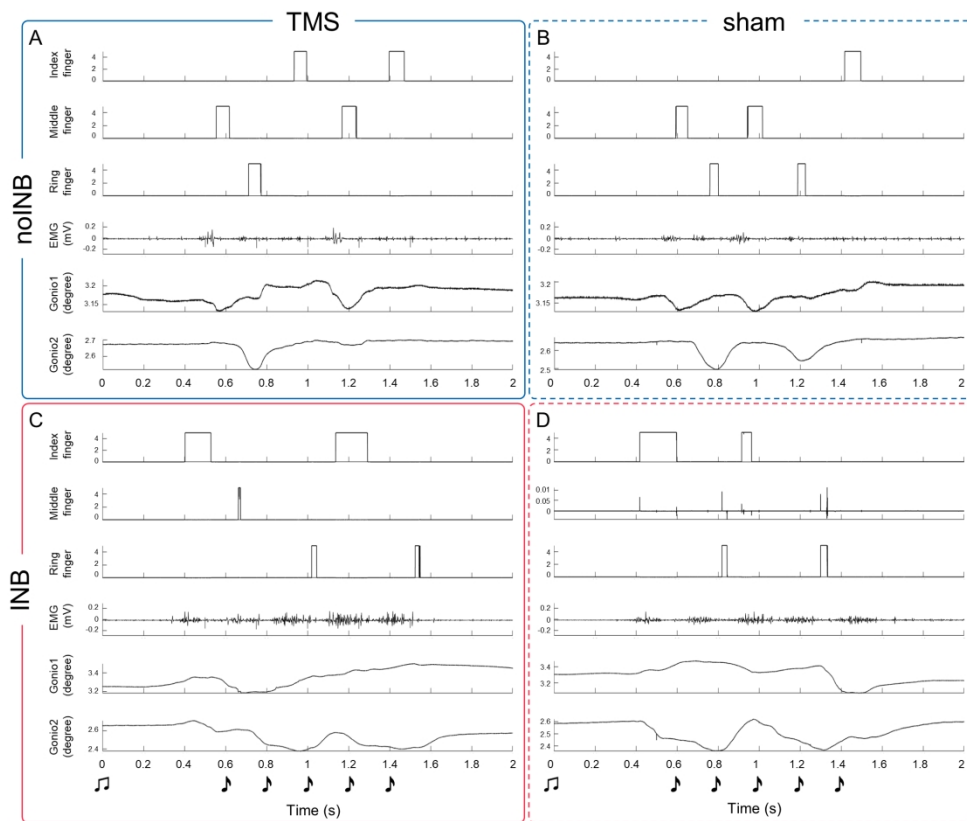


Figure 2. Single trials recording in one participant during noINB condition (A. TMS trial, B. sham trial) and INB condition (C. TMS trial, D. sham trial). From the top, the first three rows of each panel indicate the button presses (index, middle, and ring fingers), the fourth row represents the EMG activity of the extensor digitorum communis, and the last two rows represent the goniometers' signals (Gonio1 was applied over the middle finger; Gonio2 was applied over the ring finger).

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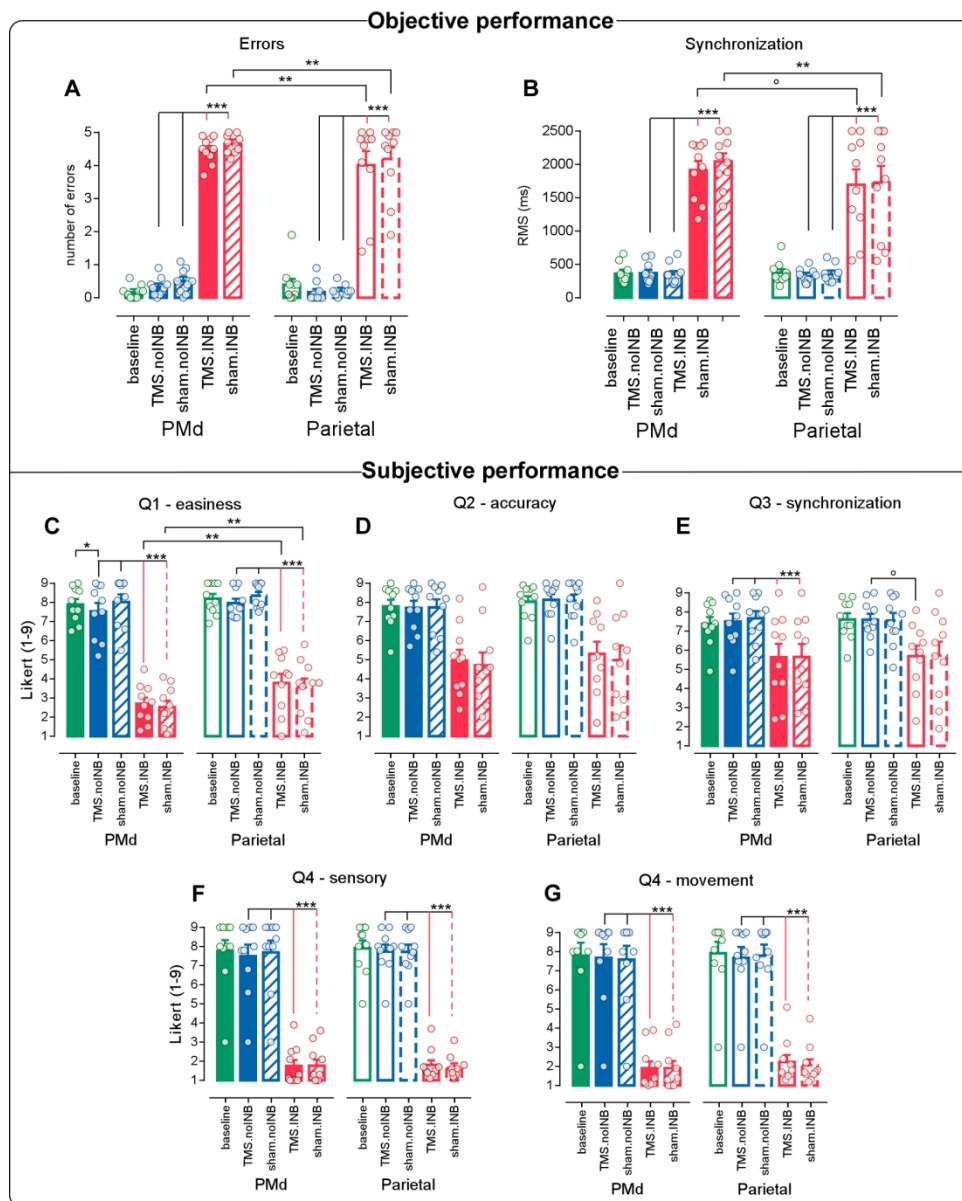


Figure 3. Results of objective (A, B) and subjective (C, D, E, F, G) measures. A. Mean values of the number of errors during the finger-tapping sequence motor task. B. Mean values of the RMS value (expressed in ms) of the objective synchronicity to the metronome, computed for each trial as the square root of the squared difference between the beginning of each of the 5 beeps of the metronome and the beginning of 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 ≤ 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.