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# Dissociating the causal role of left and right dorsal premotor cortices in planning and executing bimanual movements – A neuro-navigated rTMS study

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ABSTRACT

*Background:* The dorsal premotor cortex (PMd) is a key region in bimanual coordination. However, causal evidence linking PMd functionality during motor planning and execution to movement quality is lacking.
*Objective:* We investigated how left ($PMd_L$) and right PMd ($PMd_R$) are causally involved in planning and executing bimanual movements, using short-train repetitive transcranial magnetic stimulation (rTMS). Additionally, we explored to what extent the observed rTMS-induced modulation of performance could be explained by rTMS-induced modulation of PMd-M1 interhemispheric interactions (IHI).
*Methods:* Twenty healthy adults (mean age ± SD = 22.85 ± 3.73 years) participated in two sessions, in which either $PMd_L$ or $PMd_R$ was targeted with rTMS (10 Hz) in a pseudo-randomized design. PMd functionality was transiently modulated during the planning or execution of a complex bimanual task, whereby the participant was asked to track a moving dot by controlling two dials. The effect of rTMS on several performance measures was investigated. Concurrently, rTMS-induced modulation of PMd-M1 IHI was measured using a dual-coil paradigm, and associated with the rTMS-induced performance modulation.
*Results:* rTMS over $PMd_L$ during planning increased bilateral hand movement speed ($p = 0.03$), thereby improving movement accuracy ($p = 0.02$). In contrast, rTMS over $PMd_R$ during both planning and execution induced deterioration of movement stability ($p = 0.04$). rTMS-induced modulation of PMd-M1 IHI during planning did not predict rTMS-induced performance modulation.
*Conclusion:* The current findings support the growing evidence on $PMd_L$ dominance during motor planning, as $PMd_L$ was crucially involved in planning the speed of each hand, subserving bimanual co-ordination accuracy. Moreover, the current results suggest that $PMd_R$ fulfills a role in continuous adjustment processes of movement.


*Abbreviations:* base, baseline; BTT, bimanual tracking task; CS, conditioning stimulus; EMG, electro-myography; FDI, first dorsal interosseus; fMRI, functional magnetic resonance imaging; IHI, interhemispheric interaction; LS, left-hand speed; M1, primary motor cortex; $M1_L$, left M1; $M1_R$, right M1; MEP, motor-evoked potential; MI, movement instability; normLS, normalized LS; normRS, normalized RS; PMd, dorsal premotor cortex; $PMd_L$, left PMd; $PMd_R$, right PMd; prep, preparation; rMT, resting motor threshold; RS, right-hand speed; rTMS, repetitive TMS; STIM-SIDE, side of stimulation; TMS, transcranial magnetic stimulation; TE, tracking error; TS, test stimulus.

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## Introduction

Many daily life activities, such as texting or preparing food, require fine-tuned bimanual coordination. To date, neuroscientific research exploring the mechanisms of bimanual coordination mainly uses conventional brain imaging techniques [such as functional magnetic resonance imaging (fMRI) and electroencephalography] and single or paired pulse transcranial magnetic stimulation (TMS) protocols for assessing changes in cortical excitability, inhibition and interhemispheric interactions during bimanual tasks [1–7]. These studies have significantly contributed to our understanding of the neural correlates of planning and executing cyclical bimanual tasks in terms of location and timing of activation peaks [1–4], as well as dynamics in functional connectivity [5–7]. However, these approaches are limited in establishing causal associations between neurophysiological and behavioral processes. To infer causal associations from the previously identified correlations, neuromodulation techniques targeting respective neurophysiological processes are required, which evoke specific changes in respective behavior.

Next to the assessment of neurophysiology, specific applications of non-invasive brain stimulation offer unique opportunities to study the causal involvement of brain regions in motor functions [8–14]. For example, TMS can be used to create a transient "virtual lesion" when applied in a brief pulse train (i.e., short-train repetitive TMS, rTMS) while a motor task is being undertaken concurrently. Using such short-train rTMS protocols to interfere with neural activity in target regions, the causal contribution of those areas to motor coordination-related processing can be unveiled online [13,14]. Previous imaging studies have identified the supplementary motor and premotor cortices to be key regions of a distributed functional network, which show greater activity during tasks with high coordination needs, exceeding the sum of the single-effector demands [1,15–20]. Using short-train rTMS protocols, several studies have mapped the causal contribution of the supplementary motor area in bimanual coordination [21–24], whereas the causal role of the premotor cortex is less documented. It has been shown that disruption of the nondominant premotor cortex during a bimanual coordination task creates more transitions from anti-phase (i.e., parallel) to more intrinsic in-phase (i.e., mirror-symmetrical) coordination (see also [25]) than disruption of the dominant premotor cortex [26,27]. This suggests a role of the nondominant premotor cortex in preventing mirror-symmetric movements. Importantly, the premotor cortex is not only involved in movement execution, but also plays a pivotal role in motor planning [4,5,28,29]. More specifically, previous neuroimaging studies suggest that the dorsal part of the premotor cortex (PMd) is engaged in generating and updating motor plans for bimanual movements [4], particularly by integrating commands for both hands into a unified spatiotemporal structure [1,16,18–20,30]. Remarkably, how bilateral premotor cortices causally shape the spatiotemporal organization of complex bimanual movements during both motor planning and execution has not been studied previously and requires further investigation.

Although both left ($PMd_L$) and right PMd ($PMd_R$) are active during bimanual coordination [1,2,4], PMd function is likely lateralized [1,4,5,7,31,32]. For example, with respect to motor planning, $PMd_L$ is considered to be dominant, irrespective of which hand is moved [5,33–36]. During movement, particularly $PMd_R$ functionality is modulated by task complexity [1,7], with greater involvement in more complex conditions [20,30,37]. Some studies also report that the preparatory interhemispheric connectivity between PMd and the primary motor cortex (M1) predicts bimanual performance [5,32,38–40]. Modulating PMd with rTMS could complement and substantiate these findings by establishing causality.

The primary goal of the current study was to identify the causal role of PMd in bimanual coordination, using a pseudo-randomized within-subject design. We induced a transient modulation (i.e., inhibition [41,42]) of either $PMd_L$ or $PMd_R$ using short-train rTMS during both planning and execution of a bimanual coordination task, and observed its direct effect on performance [43]. We hypothesized a more pronounced detrimental effect of rTMS on performance (1) when $PMd_L$ was targeted as compared to $PMd_R$ during motor planning; and (2) when $PMd_R$ was targeted as compared to $PMd_L$ during execution, particularly in complex conditions. In a secondary analysis, we examined to what extent the assumed rTMS-induced performance effect(s) could be explained by rTMS-induced effects on interhemispheric PMd-M1 connectivity, using a dual-coil TMS paradigm.

## Material and methods

### Participants

Twenty young healthy adults (age range 18–33 years; mean ± SD = 22.85 ± 3.73; 11 females) participated in this experiment. All participants had (corrected-to-) normal vision. They did not report any history of neurological or psychiatric disorders, and had not played a musical instrument for the last three years. Scores on the Edinburgh Handedness Questionnaire [44] ranged from +53 to +100 (mean ± SD = 92.37 ± 12.79), indicating that participants were right-handed. They all met the safety criteria for MRI and TMS, based on standard screening questionnaires of UZ Leuven and TMS guidelines by Rossi et al. (2009) [45], respectively.

All participants provided written informed consent prior to participation and were financially compensated. The study was approved by the local Ethics Committee Research of UZ/KU Leuven (study number: 60448), according to the Declaration of Helsinki and its amendments (World-Medical-Association, 1964, 2008).

### Bimanual tracking task (BTT) and outcome measures

To measure bimanual coordination, a bimanual visuomotor tracking task (BTT) was used [46]. Here, a TMS compatible BTT setup was used for specifically targeting the first dorsal interosseus (FDI) muscles [5,38,43].

The goal of the BTT was to accurately track a white dot that moved over a straight blue line by controlling two rotatable dials with the index fingers (Fig. 1A–C), see Ref. [43] for a detailed description. Fig. 1C presents the timeline of a single BTT trial, which was characterized by a 2-sec preparatory (planning) period and a 5-sec (tracking) movement period. The three coordination modes, varying in relative inter-hand frequencies, are presented in Fig. 1B.

BTT outcome was assessed by two measures: Tracking Error (TE) and Movement Instability (MI) (Fig. 2) [43]. TE is the sum of the Euclidean distance between the participant's cursor and the dot plus the orthogonal distance between the participant's cursor and the target line, averaged over the course of the trajectory. TE is therefore a measure for general performance accuracy, indicating how well the participant complies with the required temporal organization of both hands. A low TE implies that the participant correctly produced the imposed coordination pattern at an adequate speed. In contrast, MI is the shortest distance between the participant's cursor and the participant's mean track, averaged over the course of the trajectory. MI is independent of the *imposed* pattern, but only indicates how stable the *performed* pattern is. In other words, a high MI indicates a variable relative inter-hand frequency over the course of a trial, reflecting adjustment processes.

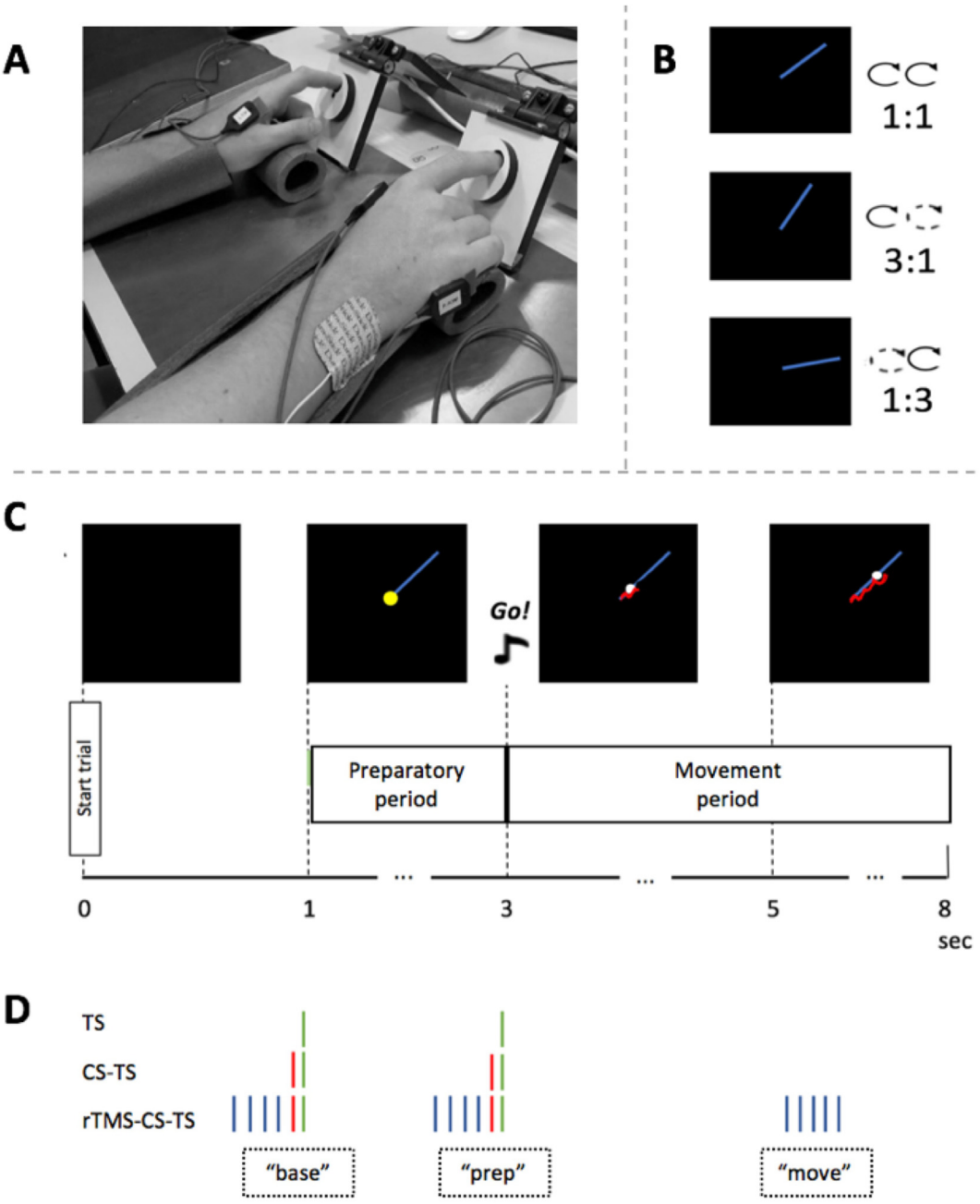


**Fig. 1.** (From Verstraelen et al., 2020, with permission) **(A)** Experimental setup. Arms were placed in palm rests for comfort. The index fingers controlled two rotatable dials. Left and right dial rotations were associated with cursor movement along the ordinate and abscissa, respectively. (**B**) The three different coordination modes. In each mode, the participant had to rotate the dials in clockwise direction. In the 1:1 mode, the relative frequency was the same for the left- and right-hand. In the 3:1 mode, the left index finger had to rotate the dial three times faster than the right index finger, while in the 1:3 mode, the opposite coordination was required. **(C)** Timeline of a trial. After 1s, the appearance of a straight blue line indicated the start of the preparatory period. Two seconds after the preparatory period onset, an imperative signal indicated the start of the movement period (5s). Concurrently, the white target dot started to move over the line at constant speed. The participant was instructed to track the dot as accurately as possible. Hands were covered and the participant received on-line feedback of his/her track by a red tail-like line **(D)** The three different TMS conditions (i.e., TS, CS-TS and rTMS–CS–TS). and their timing of delivery during a trial. For "base" the TS (green stripe) timing was at preparatory period onset. For "prep", the TS timing was 50 ms before movement period onset. The rTMS train (blue stripes) onset at "move" was 2s after movement period onset. A red stripe represents the CS. Abbreviations: TS, Test Stimulus; CS, Conditioning Stimulus; rTMS, repetitive TMS. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

In addition, performance of each hand was assessed by calculating the absolute speed of the left and right index finger movements (i.e., LS and RS, respectively), normalized to the target speed (i.e., *normLS = LS/target LS* and *normRS = RS/target RS*). Hence, values $> 1$ and $< 1$ indicated too fast and too slow movements, respectively.

These outcomes were processed offline using Matlab (2018a, The MathWorks Inc, USA).

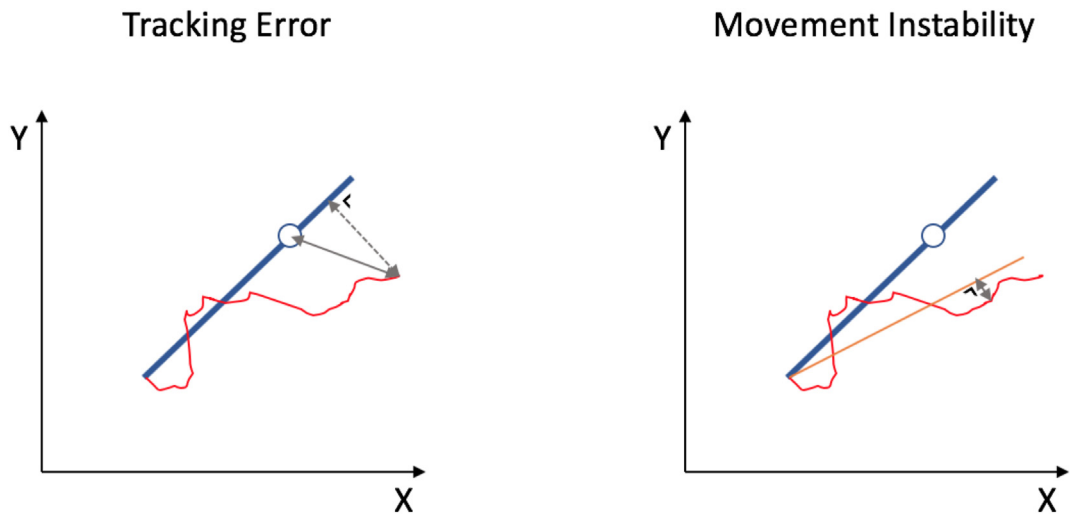


**Fig. 2.** (From Verstraelen et al., 2020, with permission) Bimanual outcome measures. Tracking Error is the sum of the Euclidean distance between the participant's cursor and the target dot plus the orthogonal distance between the participant's cursor and the blue target line, averaged over the course of the trajectory. Movement Instability is the shortest distance between the participant's cursor and the participant's mean track (orange line), averaged over the course of the trajectory. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

### *Transcranial magnetic stimulation (TMS) and electromyographic (EMG) recording*

#### *TMS conditions and outcome measures*

Three TMS conditions were applied either at baseline ("base") or during the preparatory ("prep") period (Fig. 1C–D) [43]. The first TMS condition was a test stimulus (TS) over M1, used to calculate the average peak-to-peak motor-evoked potential (MEP) amplitude of the contralateral FDI, within a time window of 10–80 ms following the TS. In the second condition, one conditioning stimulus (CS) over the contralateral PMd preceded the TS over M1 with an inter-stimulus interval of 8 ms [5,38,47–49], to assess the PMd-M1 interhemispheric interaction (IHI), whereby $IHI = MEP_{CS\text{-}TS}/MEP_{TS}$. In the third condition, four repetitive pulses over PMd preceded the CS-TS pulses. This resulted in a rTMS train of five (4 + 1) pulses over PMd applied at 10Hz [43]. Using this short rTMS train, ongoing activity in the underlying cortex is transiently inhibited for at least 500 ms [41,42]. This rTMS–CS–TS condition served to study the effect of PMd modulation on subsequent bimanual performance and on PMd-M1 IHI, expressed as $IHI_{LESION}$, whereby $IHI_{LESION} = MEP_{rTMS\text{-}CS\text{-}TS}/MEP_{TS}$.

A separate rTMS condition (five pulses, 10 Hz) was applied during the movement, 2s after the imperative Go-signal. This $rTMS_{move}$ condition aimed to assess whether PMd modulation changed ongoing bimanual performance.

#### *Neuronavigation and TMS settings*

Each TMS coil was continuously tracked with neuronavigation (Brainsight, Rogue Research Inc, Montreal, Quebec, Canada). PMd was localized on a 3D brain reconstruction (Brainsight, version 2.3.6), based on a structural T1-weighted image obtained from each participant (Philips Achieva 3 T MR scanner with a 32 channel receiver head coil, MPRAGE, TR/TE = 9.6 ms/4.6 ms, voxel size = 0.98 mm × 0.98 mm × 1.2 mm, field of view = 250 mm × 250 mm × 240 mm, 200 sagittal slices). This localization was immediately anterior to the precentral sulcus and adjacent to the dorsal bank of the superior frontal sulcus [5,38,42,50]. Mean Talairach coordinates are shown in Table 1.

For the CS and rTMS over PMd, a MCF-B70 static cooled 97 mm figure-8 coil (Magventure, A/S, Farum, Denmark) was held perpendicular to the mid-sagittal line to induce a current in latero-medial direction [51]. The intensity of the CS (biphasic, pulse width: 280 μs) was 110% of the individual resting motor threshold (rMT), as measured on the ipsilateral M1 [5,38,47–49]. The rMT is defined as the minimal stimulation intensity required to evoke MEPs with a peak-to-peak amplitude >50 μV in at least five out of ten consecutive trials [52]. For the TS (monophasic) applied over M1, a 70 mm figure-8 coil, connected to a Magstim 200 (Magstim Company, Whitland, UK), was used to target the motor hotspot of the contralateral FDI. The handle of the TS coil was oriented with an angle of 45° away from the mid-sagittal line to induce a current in postero-anterior direction and the intensity was individually set to evoke a MEP of ~1 mV peak-to-peak at rest. Mean rMT, CS and TS intensities are provided in Table 2.

#### *EMG recording*

Self-adhesive 2-slot Bagnoli surface electromyographic (EMG) sensors were placed on both FDIs and connected to a Bagnoli-16 EMG system (Delsys Inc, Boston, USA). The EMG signals were sampled at 2000 Hz. They were amplified (gain = 1000), band pass filtered (20–2000 Hz) and 50/60 Hz noise was eliminated

**Table 1**
Talairach Coordinates of left and right PMd (mean ± SD).

| | x | y | z |
|---|---|---|---|
| Left PMd | −31.59 ± 4.96 | −1.78 ± 4.71 | 56.57 ± 3.81 |
| Right PMd | 27.27 ± 3.33 | −0.01 ± 3.62 | 58.05 ± 3.71 |

**Table 2**
Resting motor threshold (rMT), Conditioning Stimulus (CS) and Test Stimulus (TS) intensities are presented for the left and right hemisphere, expressed as % of maximum stimulator output. Values are rounded off to the nearest %. Corticospinal Excitability (CSE) during rest (12 trials for each hemisphere) is expressed in mV (mean ± SD).

| | Left hemisphere | Right hemisphere |
|---|---|---|
| rMT (%) | 40 ± 7 | 39 ± 8 |
| CS intensity (%) | 44 ± 7 | 43 ± 9 |
| TS intensity (%) | 56 ± 10 | 55 ± 10 |
| CSE during rest (MEP amplitude, mV) | 0.95 ± 0.56 | 0.90 ± 0.40 |

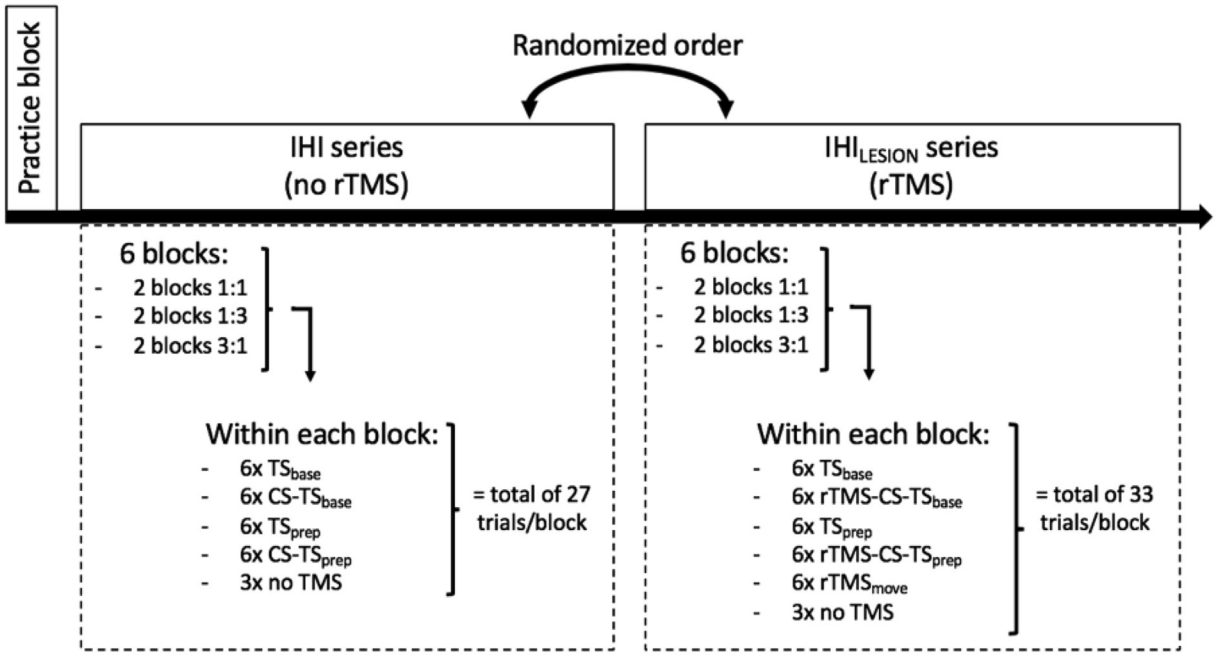


**Fig. 3.** (From Verstraelen et al., 2020, with permission) Schematic overview of the course of a session. Within a session, the rTMS and CS were applied on either the $PMd_L$ or $PMd_R$. After a practice block (i.e., 12 trials of each coordination mode; first session only), the participant had to perform two series of six blocks of trials, wherein he/she had to execute one of the three coordination modes (1:1, 1:3 and 3:1). The order of the blocks was randomized within each series, grouped per coordination mode. Each block contained two TMS conditions [TS and CS-TS in the IHI series, and TS and rTMS–CS–TS in the $IHI_{LESION}$ series], delivered either at "base" or "prep". In the $IHI_{LESION}$ series, an extra TMS condition was included during the movement period (i.e., $rTMS_{move}$). Each TMS condition was presented six times in each block. Additionally, three trials without TMS were included in each block.

(Humbug, Quest Scientific, North Vancouver, Canada). MEP signals were stored for offline analysis.

*Experimental protocol*

This study consisted of two sessions, separated by at least one week. In one session, rTMS and CS were applied on either the $PMd_L$ or $PMd_R$. The order of sessions was pseudo-randomized across participants.

A schematic illustration of this protocol is shown in Fig. 3 (for more details, see Ref. [43]).

The triggers for TMS, EMG, BTT and the auditory signal were controlled by Signal Software (version 6.0, Cambridge Electronic Design, UK).

*Statistical analyses*

All statistical analyses were performed using R-based packages [53] (see below for details) applied with the statistical software RStudio (version 1.3.959) [54].

*Effect of PMd modulation on subsequent BTT performance*

rTMS over PMd was applied either during motor planning or during motor execution (Fig. 4A–B). In both cases, performance data were analyzed within two subsequent limited time windows following the last pulse of the rTMS train [43]: the *early* time window (500 ms duration) and the *late* time window (1000 ms duration). The choice for calculating the performance effect of rTMS modulation in limited time windows rather than over the full 5-sec trial was based on two arguments. First, the physiological effect of short-train rTMS (10 Hz) lasts for ~500 ms [41,42], which implies that the highest chance for detecting an effect would be immediately after the rTMS train (i.e., at the stage of lowered local excitability). Second, previous work suggests that PMd-M1 IHI modulations during planning only predict subsequent BTT performance for the first 2 s of motor execution [5]. Supplementary correlational analyses support the validity of using limited time windows for performance calculation, as these indicated that performance calculated in the limited time windows was representative for performance over the full trial (Supplementary Figs. 1 and 2).

The effects of PMd modulation on BTT performance were analyzed using full factorial linear mixed models (nlme package, version 3.1–131) [55]. Normality and homoscedasticity of the residual data were checked via normal quantile and residual plots, respectively. In case of violated model assumptions, the outcome variable was transformed using the Box-Cox procedure [56], as implemented in the MASS package (version 7.3–47) [57]. For further analysis of the models, we used Tukey-corrected pairwise comparisons (emmeans package, version 1.3.0) [58], for contrasting the estimates of the factor of interest (TMS CONDITION). Cohen's d was provided as a measure of effect size with cutoffs $\geq$0.2 (small), $\geq$0.5 (medium), and $\geq$0.8 (large) [59]. The level of significance was $\alpha = 0.05$.

For the effect of **PMd modulation during the preparatory period**, TE, MI, normLS and normRS were compared between $rTMS\text{-}TS_{prep}$ trials (note that the CS is considered to be part of the rTMS train), $TS_{prep}$ trials to control for the effect of the TS on performance, and no-TMS trials, using a 3 [TMS CONDITION: no-TMS, TS, rTMS-TS] x 2 [STIM-SIDE: $PMd_L$, $PMd_R$] x 3 [COORDINATION MODE: 1:1, 1:3 and 3:1] x 2 [SESSION: session 1, session 2] full factorial linear mixed model, with TMS CONDITION, STIM-SIDE, COORDINATION MODE and SESSION as fixed effects and PARTICIPANT added as a random intercept, to account for repeated measures within a participant.

For the effect of **PMd modulation during the movement period**, we examined whether the natural course of performance within a trial changed by rTMS. We, therefore, quantified the course

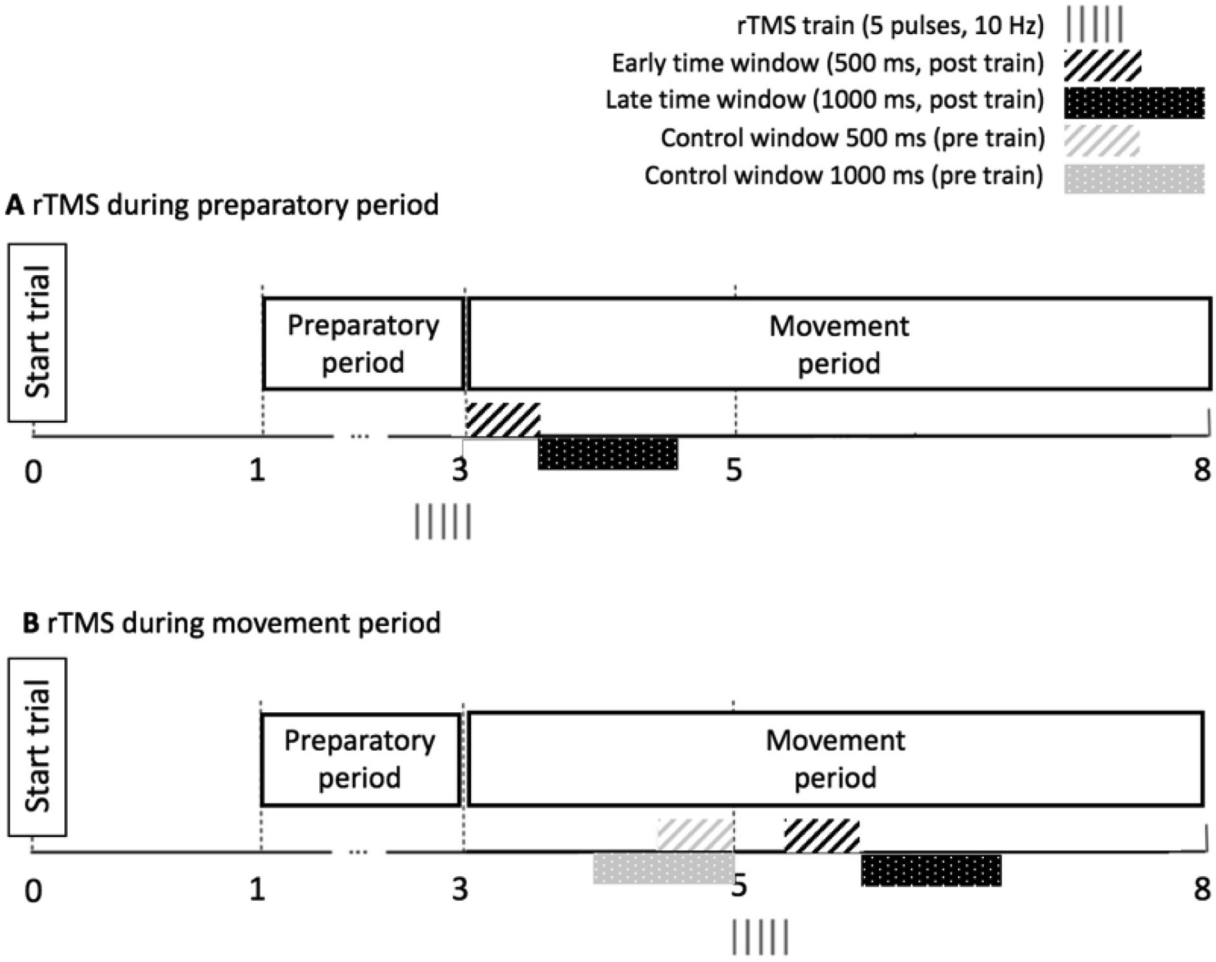


**Fig. 4.** (From Verstraelen et al., 2020, with permission) Early (shaded black rectangle) and late (full black rectangle) time windows, used for calculation of performance outcomes when rTMS was delivered in the preparatory period **(A)** or in the movement period **(B).** The vertical stripes represent the timing of the rTMS train. Note that for the movement period, we calculated performance ratios by dividing the performance after the pulse train (black rectangles) by the performance right before pulse train onset (grey rectangles).

of performance within a trial by computing the ratio $Performance_{post\text{-}train}/Performance_{pre\text{-}train}$ for both the early (500 ms) and late (1000 ms) time windows. The "pre-train" values were obtained by computing the four performance measures within a time window of equal size (i.e., 500 or 1000 ms, respectively) immediately before the pulse-train onset (Fig. 4B). TE, MI, normLS and normRS ratios were analyzed by a 2 [TMS CONDITION: $rTMS_{move,}$ no-TMS] x 2 [STIM-SIDE: $PMd_L$, $PMd_R$] x 3 [COORDINATION MODE: 1:1, 1:3 and 3:1] x 2 [SESSION: session 1, session 2] full factorial linear mixed model, with TMS CONDITION, STIM-SIDE, COORDINATION MODE and SESSION as fixed effects and PARTICIPANT as a random intercept.

Both analyses were run separately for the early and late time windows.

The analysis for pure BTT performance (i.e., *without* PMd modulation) is attached as Supplementary data.

*Relationship between rTMS-induced modulation of BTT performance and rTMS-induced modulation of PMd-M1 IHI during planning*

If rTMS during the preparatory period significantly affected performance (see Results), additional analyses were performed to investigate to what extent the observed rTMS-induced performance effect could be explained by rTMS-induced modulation of PMd-M1 IHI.

Simple linear regression analyses (stats package, version 3.4.1) [53] were performed. We defined an index for rTMS-induced modulation of performance ($Performance_{rTMS}$ index) as the dependent variable, and an index for rTMS-induced modulation of IHI change during motor planning ($PMd\text{-}M1_{rTMS}$ index) as the independent variable (see Appendix for the computation of these indices). The dependent and independent variables in the regression models were, respectively, (1) $TE_{rTMS}$ and $PMd_L\text{-}M1_{R,rTMS}$ indices; (2) $MI_{rTMS}$ and $PMd_R\text{-}M1_{L,rTMS}$ indices; (3) $normLS_{rTMS}$ and $PMd_L\text{-}M1_{R,rTMS}$ indices, and (4) $normRS_{rTMS}$ and $PMd_L\text{-}M1_{R,rTMS}$ indices. A Bonferroni correction was applied to correct for multiple testing (i.e., $\alpha = 0.05/4 = 0.0125$).

## Results

*The effect of PMd modulation on BTT performance*

*Preparatory period*

In the following, only the contrast of interest is discussed, which is the comparison of performance between the rTMS-$TS_{prep}$ trials and $TS_{prep}$ trials, controlling for a possible TS effect on performance. The remaining two contrasts (i.e., rTMS-$TS_{prep}$ versus no-TMS trials

and $TS_{prep}$ versus no TMS trials) are illustrated in Fig. 5(A-D) and Supplementary Figs. 4–11.

Both in the early and late time windows, $PMd_L$ modulation improved accuracy (decreased TE) in the 1:1 mode in session 2 ($t_{(296)}$=2.72, p = 0.02, d = 0.55 and $t_{(296)}$ = 3.35, p = 0.003, d = 0.75, respectively; Fig. 5A). In all other conditions, rTMS had no significant effect on TE (all p > 0.09).

Significantly less stability (higher MI) was observed when $PMd_R$ was modulated in session 1 in the 3:1 mode, in the early time window ($t_{(296)}$=-2.78, p = 0.02, d = 0.71; Fig. 5B). In all other conditions, rTMS had no effect on MI (all p > 0.30).

$PMd_L$ modulation increased (improved) both hand speeds in the early time window in session 2. Specifically, normLS improved in the 1:1 and 1:3 modes ($t_{(296)}$=-3.33, p = 0.003, d = 1.18 and $t_{(296)}$ = -2.60, p = 0.03, d = 0.69, respectively; Fig. 5C), and normRS improved in the 1:1 mode ($t_{(296)}$=-2.67, p = 0.02, d = 0.75; Fig. 5D). In all other conditions, PMd modulation had no significant effect on hand speed (all p > 0.08).

*Movement period*

The effect of rTMS on performance accuracy (TE ratio) and normLS ratio did not reach the a-priori level of significance in any condition (all p > 0.07).

In contrast, $PMd_R$ modulation decreased stability (higher MI ratio) in the early time window in the 1:3 and 3:1 modes in session 2 ($t_{(191)}$=-2.16, p = 0.03, d = 0.69 and $t_{(191)}$ = -2.09, p = 0.04, d = 0.72, respectively; Fig. 6A). In all other conditions, PMd modulation had no effect on MI ratio (all p > 0.13).

In the early time window, $PMd_R$ modulation affected normRS ratio in the 3:1 mode in session 2 ($t_{(191)}$=2.09, p = 0.04, d = 0.63). $PMd_L$ modulation also affected normRS ratio in the 3:1 mode in the late time window, but only in session 1 ($t_{(191)}$=-2.46, p = 0.01, d = 0.70; Fig. 6B). In all other conditions, normRS ratio was not affected by rTMS (all p > 0.14).

*Relationship between rTMS-induced modulation of BTT performance and rTMS-induced modulation of PMd-M1 IHI during planning*

The $PMd\text{-}M1_{rTMS}$ indices did not significantly predict the $Performance_{rTMS}$ indices (all p > 0.08). There was a weak positive correlation (Pearson's r = 0.24) between the $MI_{rTMS}$ index and the $PMd_R\text{-}M1_{L,rTMS}$ index, but this was not significant ($F_{(1,56)}$=3.23, p = 0.08). We refer to Table 3 for a summary of all simple regression analyses.

## Discussion

*The role of $PMd_L$ versus $PMd_R$ during motor planning*

Based on previous research, we hypothesized a dominant role of $PMd_L$, as compared to $PMd_R$, during motor planning [5,33–36]. The current results indeed suggest that during planning $PMd_L$, and not $PMd_R$, determines subsequent general performance accuracy (TE). However, in contrast to our initial hypothesis, $PMd_L$ modulation led to performance improvement rather than deterioration. It should be noted that whether a TMS burst impairs or improves a function, may depend on whether or not rhythmically synchronized brain activity in the target region is beneficial for the task [13]. The used short-train rTMS paradigm was initially assumed to be disruptive, which is based on multiple mechanisms such as an initial excitation of random neuronal elements decreasing the signal-to-noise ratio [60,61], and induced transient GABA-ergic inhibition [13,41,42,60,62,63]. If, however, the induced neuronal noise is synchronized with the ongoing relevant activity [64], it may augment the signal and improve its function [14]. In other words, the rTMS train of the current study may have caused neuronal entrainment in a frequency (10 Hz) that was beneficial for $PMd_L$ functionality during late preparation [13,65].

Given the timing of rTMS delivery (i.e., at the end of a 2-sec preparatory period), it is more likely that the rTMS-induced

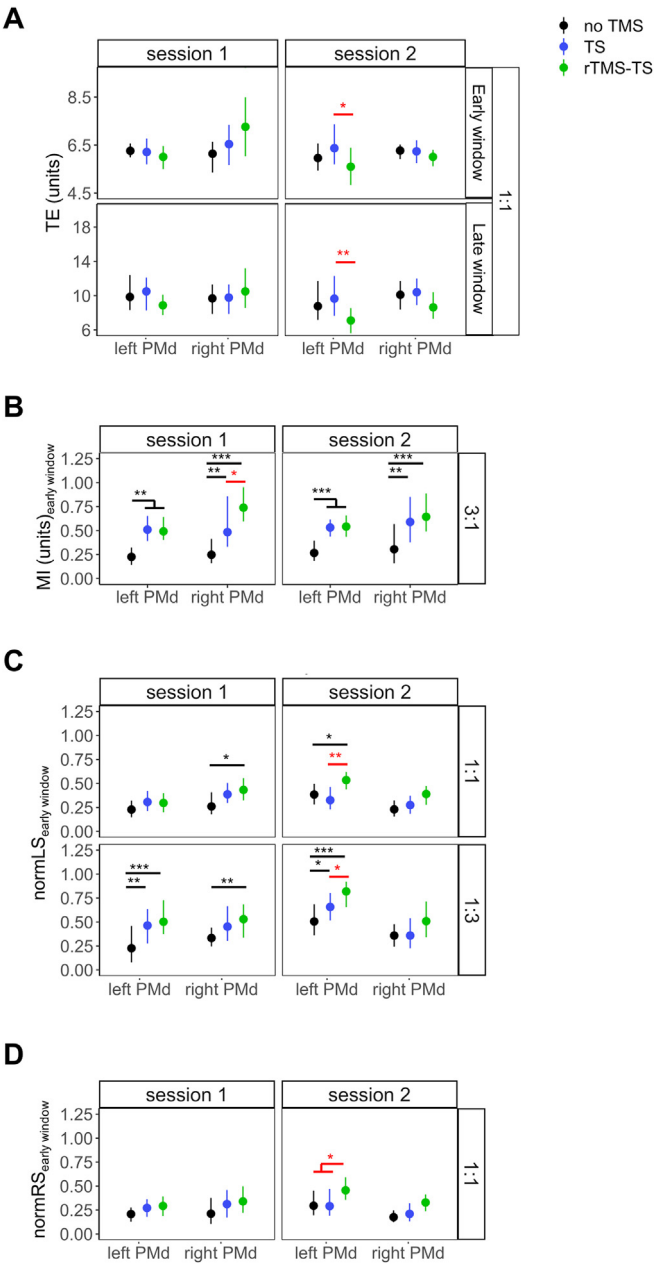


**Fig. 5.** Performance outcomes when PMd was modulated at "prep" (i.e., in the late preparatory period). Performance outcomes are presented by session for left PMd and right PMd modulation: **(A)** Tracking Error (TE) in the early and late time window for coordination mode 1:1; **(B)** Movement Instability (MI) in the early time window for coordination mode 3:1; **(C)** normalized left-hand speed (normLS) in the early time window for coordination modes 1:1 and 1:3; and **(D)** normalized right-hand speed (normRS) in the early time window for coordination mode 1:1. Red asterisks represent a significant difference between rTMS-TS and TS conditions, while black asterisks represent the remaining significant pairwise comparisons between TMS conditions. Error bars represent 95% CIs. "*", p < 0.05; "**", p < 0.01; "***", p < 0.001. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

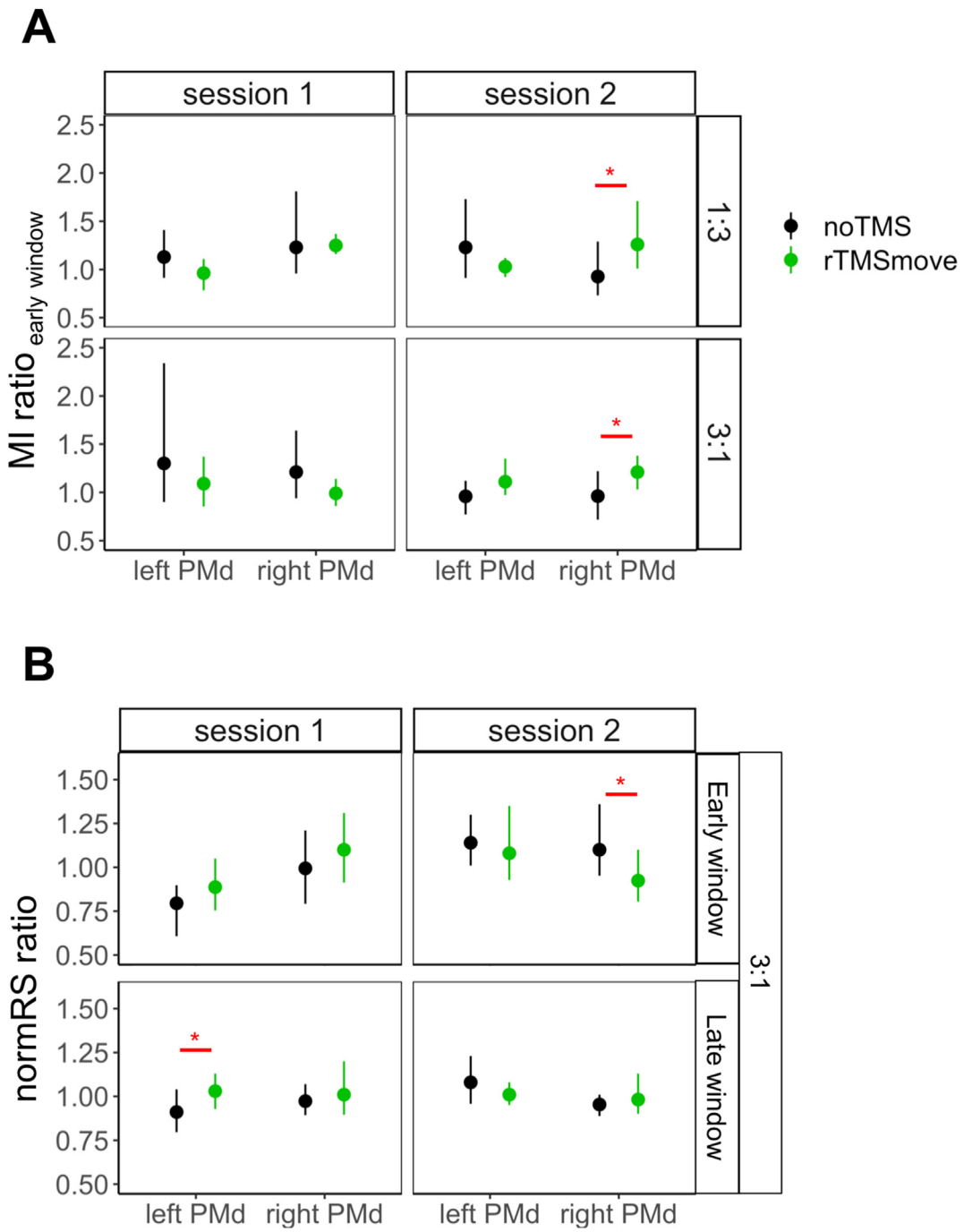


**Fig. 6.** Performance ratios (post-train/pre-train) when PMd was modulated at "move" (i.e., in the movement period). Results are presented by session for left PMd and right PMd modulation: **(A)** MI ratio in the early time window for coordination modes 1:3 and 3:1; **(B)** normRS ratio in the early and late time window for coordination mode 3:1. Error bars represent 95% CIs. Abbreviations: MI, Movement Instability; normRS, normalized Speed for Right index finger movement; "*", $p < 0.05$.

**Table 3**
Summary of the simple regression analyses.

| | Modulation side | Dependent variable | Independent variable | F-ratio$_{(DFs)}$ | Pearson's r | $R^2$ | p-value |
|---|---|---|---|---|---|---|---|
| (1) | Left | $TE_{rTMS}$ | $PMd_L$-$M1_{R,rTMS}$ | $F_{(1,55)} = 1.03$ | 0.14 | 0.02 | 0.32 |
| (2) | Right | $MI_{rTMS}$ | $PMd_R$-$M1_{L,rTMS}$ | $F_{(1,56)} = 3.23$ | 0.24 | 0.05 | 0.08 |
| (3) | Left | $normLS_{rTMS}$ | $PMd_L$-$M1_{R,rTMS}$ | $F_{(1,55)} = 0.41$ | −0.09 | 0.007 | 0.53 |
| (4) | Left | $normRS_{rTMS}$ | $PMd_L$-$M1_{R,rTMS}$ | $F_{(1,55)} = 0.03$ | 0.02 | 0.001 | 0.87 |

performance improvement would specifically be driven by effects on the network involved in motor planning [28], rather than by effects on primary visual processing (i.e., stimulus detection etc.), since the latter processes occur typically earlier (i.e., ~100 ms following the presentation of the visual cue) [66–68]. Interestingly, it has been suggested that low-frequency (alpha, 10 Hz) cortico-cortical interactions reflect top-down processing, subserving the selection and integration of relevant information in order to form a mental construct, such as a planned action [69,70]. Accordingly, PMd has a key role in retrieving and integrating information necessary for action planning [28]. Applied to our findings, an rTMS-induced augmentation of the alpha signal might have indeed facilitated motor planning and thus overall performance accuracy.

The performance accuracy enhancement after $PMd_L$ modulation might have resulted from rTMS-induced improvements in the speed of each hand separately (see Supplementary Fig. 12). In line with these findings, discharges of PMd cells have been shown to strongly predict the speed and accuracy of the required movement in unimanual reaching tasks [71,72], and rTMS over $PMd_L$, and not $PMd_R$, has been shown to increase velocity peaks in subsequent movement [73]. In preparing bimanual movements, previous studies indicated that $PMd_L$ gates motor output, depending on the imposed speed of each hand [5,38]. Taken together, the current findings suggest that $PMd_L$ prepares bimanual performance accuracy by encoding the required speed of each hand, in line with the assumption that PMd integrates motor commands into a single spatiotemporal structure (see also [1,18,19]).

In contrast with $PMd_L$, $PMd_R$ modulation specifically increased the variability of relative inter-hand frequency (MI). MI increases with increasing coordination complexity (Supplementary Fig. 3B), reflecting an augmented need for continuous adjustment of ongoing bimanual coordination to fit with the overall imposed spatiotemporal structure. Because modulating $PMd_R$ increased MI particularly in complex coordination modes, one could argue that $PMd_R$ plays a role in such adjustment processes. This view is consistent with fMRI findings of Beets et al. [4], who suggested that $PMd_R$ plays a role in bimanual movement adjustment in relation to an internal reference of correctness.

### *The role of $PMd_L$ versus $PMd_R$ during movement execution*

In line with the obtained results for planning, $PMd_R$ seems to be relevant for continuously adjusting bimanual coordination, particularly in non-isofrequent coordination modes (see also [20,30,37]), corroborating our hypothesis. $PMd_R$ activation is thought to suppress neural cross-talk, which is necessary to decouple hand movements, enabling the production of more complex coordination patterns [18,26,27,37]. In line with this evidence, the current results indicate that $PMd_R$ modulation increased instability for particularly complex coordination modes.

While the motor planning function of PMd appeared clearly lateralized, rTMS over both $PMd_L$ and $PMd_R$ during motor execution affected ongoing right-hand speed in the most complex (i.e., 3:1) mode. This seems counterintuitive, considering that $PMd_L$ is thought to control left- and right-hand movements [5,34,35], while $PMd_R$ is suggested to control exclusively the left hand [34,35]. As it is assumed that during bimanual movement the dominant hand leads the non-dominant hand [74,75], one would expect that $PMd_R$ adjusts particularly left-hand movement, such that it is associated with the leading right-hand. The current results, however, rather suggest that in the 3:1 mode, movement is corrected by bilateral PMd through adjusting right-hand speed. We hypothesize that this apparent shift towards increased $PMd_R$ involvement during complex coordination can be viewed as based on increased spatial attentional demands for both left and right hemifields, in which the right hemisphere plays a dominant role [75–77]. Here, rTMS over $PMd_L$ accelerated right-hand speed, while rTMS over $PMd_R$ slowed right-hand speed. These findings suggest that during complex bimanual movement, bilateral PMd contribute to the fine-tuning of the speed of the dominant hand in a complementary manner.

### *The role of rTMS-induced modulation of PMd-M1 IHI*

Although PMd-M1 modulation tended to explain the variance of MI modulation, this was not significant. Altogether, the current results indicate that only considering the rTMS-induced modulation of PMd-M1 IHI is not sufficient to explain the observed rTMS-induced effects on motor execution, even though some studies have shown a relation between PMd-M1 IHI and motor performance [5,38–40]. This suggests that short-train rTMS affects inter-regional connections of PMd with regions other than contralateral M1 as well (see also [43]). Conceptually, if all inter-regional connections that are relevant for bimanual coordination are affected by rTMS, these changes could all contribute to the observed net effect of rTMS on performance. These inter-regional connections may include PMd-SMA connectivity [78,79]; ipsilateral PMd-PMv [28] and PMd-M1 [28,79–81] connectivity; and direct connectivity between PMd and the spinal cord [79,82,83]. Accordingly, it has been shown that rTMS over PMd changes the BOLD signal in remotely connected brain regions [84]. Future studies are needed to investigate the exact contribution of each part of this network to the rTMS-induced performance effect.

### *Limitations*

Performance modulation by rTMS over PMd was practice-dependent. During planning, $PMd_L$ modulation affected performance in session 2, while $PMd_R$ modulation affected performance in session 1. In contrast, during movement, the opposite pattern of results was observed. However, the current protocol was not designed to study the effect of motor learning on PMd functionality. In general, bimanual task-related PMd activity is shown to be most prominent in the early bimanual learning stage [2,4,85]. However, Puttemans et al. (2005) indicated that the evolution of PMd function over time during bimanual learning is not linear [2], and the current data also suggest that the learning effect may be complex and hemisphere-dependent. Clearly, a future study protocol with more sessions is needed to unravel this complexity.

In the current protocol, the rTMS trials in the late preparatory phase were always combined with a TS over contralateral M1, for concurrently assessing PMd-M1 IHIs. Therefore, for examining the effect of rTMS on performance, we included both the $TS_{prep}$ and no-TMS trials to control for a possible TS effect on performance. As visualized in Fig. 5, the TS indeed affected performance in part of the cases, which might impede the isolation of a possible effect of PMd modulation. This might have led to false negative results, mainly for the MI outcome.

## Conclusion

The current findings suggest that $PMd_L$ is in charge of planning and controlling speed of each hand during bimanual coordination, while $PMd_R$ plays a dominant role in continuous adjustment of movement to fit with the overall spatiotemporal organization of movement, governed by $PMd_L$. Additionally, we were unable to explain the rTMS-induced performance effect by means of PMd-M1 IHI modulation during planning.

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## CRediT authorship contribution statement

**Stefanie Verstraelen:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft. **Kim van Dun:** Formal analysis, Writing - review & editing. **Siel Depestele:** Formal analysis, Writing - review & editing. **Sybren Van Hoornweder:** Writing - review & editing. **Asif Jamil:** Writing - review & editing. **Ensiyeh Ghasemian-Shirvan:** Investigation, Writing - review & editing. **Michael A. Nitsche:** Writing - review & editing. **Shanti Van Malderen:** Investigation, Writing - review & editing. **Stephan P. Swinnen:** Resources, Writing - review & editing, Funding acquisition. **Koen Cuypers:** Conceptualization, Methodology, Investigation, Writing - review & editing, Supervision, Funding acquisition. **Raf L.J. Meesen:** Conceptualization, Investigation, Resources, Writing - review & editing, Supervision, Funding acquisition.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.02.006.

## Appendix

Computation of rTMS-induced modulation indices.

1. Index for rTMS-induced modulation of performance (Performance$_{rTMS}$ index)

The Performance$_{rTMS}$ index is calculated by the ratio between the mean performance in rTMS-TS$_{prep}$ trials and the mean performance in TS$_{prep}$ trials:

$$Performance_{rTMS}\ index = Performance_{rTMS-TS_{prep}} \Big/ Performance_{TS_{prep}}$$

For computing the TE$_{rTMS}$ index, we considered TE during PMd$_L$ modulation in the initial 1500 ms of movement (i.e., early + late time window).

For computing the MI$_{rTMS}$ index, we considered MI during PMd$_R$ modulation in the early time window.

The normLS$_{rTMS}$ and normRS$_{rTMS}$ indices were computed during PMd$_L$ modulation in the early time window.

A.2. Index for rTMS-induced modulation of PMd-M1 IHI change during motor planning (PMd-M1$_{rTMS}$ index).[2]

Trials with TMS in which root mean square EMG in FDI exceeded 20 μV during the 40 ms preceding the TS were discarded from the analysis.

We first calculated mean IHI change over time in trials without and with short-train rTMS preceding the CS at "prep" by the ratios $IHI_{prep}/IHI_{base}$ and $IHI_{LESION,prep}/IHI_{base}$, respectively. Values > 1 indicate a less inhibition (or facilitation) of the PMd-M1 IHI during motor planning, whereas values < 1 indicate more inhibition. Next, the PMd-M1$_{rTMS}$ index was computed by the following ratio:

$$PMd-M1_{rTMS}\ index = \frac{IHI_{LESION,prep}/IHI_{base}}{IHI_{prep}/IHI_{base}} = IHI_{LESION,\ prep} \Big/ IHI_{prep}$$

Based on the results in section "The effect of PMd modulation on BTT performance – Preparatory period", we computed the PMd$_L$-M1$_{R,\ rTMS}$ index for the simple regression analyses of TE$_{rTMS}$, normLS$_{rTMS}$ and normRS$_{rTMS}$ indices; and the PMd$_R$-M1$_{L,\ rTMS}$ index for the analysis of the MI$_{rTMS}$ index.

[2] Data for pure CSE during motor preparation are illustrated in Supplementary Fig. 13.

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