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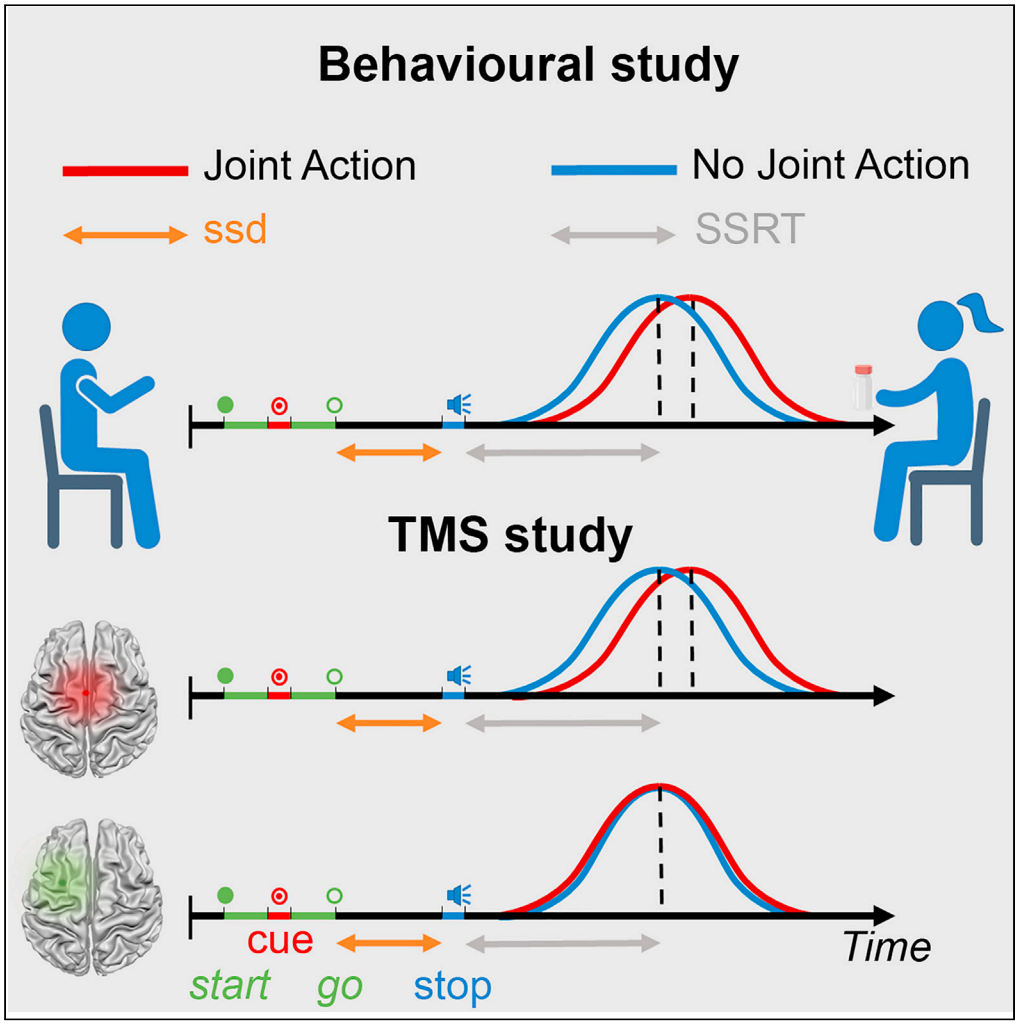

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Highlights

Interaction requires mutual adaptation and a shared cognitive task representation

Sensorimotor representations must be negotiated between partners to achieve the goal

Motor suppression mechanisms might be essential in Joint Action coordination

Dorsal premotor cortex (PMd) plays a key role in guiding Joint Action coordination

Cardellicchio et al., iScience *24*, 103330
November 19, 2021
https://doi.org/10.1016/j.isci.2021.103330

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The role of dorsal premotor cortex in joint action stopping

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SUMMARY

Human sensorimotor interaction requires mutual behavioral adaptation as well as shared cognitive task representations (Joint Action, JA). Yet, an under-investigated aspect of JA is the neurobehavioral mechanisms employed to stop actions if the context calls for it. Sparse evidence points to the possible contribution of the left dorsal premotor cortex (lPMd) in sculpting movements according to the socio-interactive context. To clarify this issue, we ran two experiments integrating a classical stop signal paradigm with an ecological JA task. The first behavioral study shows longer Stop performance in the JA condition. In the second, we use transcranial magnetic stimulation to inhibit the lPMd or a control site (vertex). Results show that lPMd modulates the JA stopping performance. Action stopping is an important component of JA coordination, and here we provide evidence that lPMd is a key node of a brain network recruited for online mutual co-adaptation in social contexts.

INTRODUCTION

In everyday life people flexibly coordinate their actions toward shared goals. These interactions, also defined Joint Actions (JAs; Sebanz et al., 2006), are based on mutual behavioral adaptations and on a shared cognitive representation of a given task (Gallotti et al., 2017; Konvalinka et al., 2010). JA is often introduced within discrete response inhibition tasks such as the Simon (Simon, 1969) or of the Eriksen flanker task (Eriksen and Eriksen, 1974). In their social version, relevant spatial cues are presented to a co-actor, and, although irrelevant for the participant, they can still interfere with their performance (Atmaca et al., 2011; Sebanz et al., 2003). These studies demonstrate overlapping of task representations in JA tasks (Sebanz et al., 2005, 2006). In other experimental scenarios, JA is based on continuous and mutual behavioral adaptations to smoothly negotiate actions in both time and space (Pezzulo et al., 2019). In these cases, participants modify and emphasize their action in order to make their intention clearer and movements more informative. Indeed, action readability is often an integral part of JA optimization (Pezzulo et al., 2013). In this context, successful JA is based upon the progressive build-up of inferences about others' actions to guide the neural control of movement toward optimal spatiotemporal behavioral coordination. However, optimal JA coordination may also call for a complete halt and, indeed, self-action stopping may result in a suitable behavior. Despite the clear relevance of action inhibition in JA tasks, very little research has been carried out in this direction.

From a neurophysiological point of view, corticospinal inhibition is modulated during the integration of conflicting motor activations triggered by the observation of others' actions and motor activations required for self-action control (Cardellicchio et al., 2020b). These results are in line with the idea that corticospinal inhibitory mechanisms are central in sculpting the motor output (Griffin and Strick, 2020) and might also be critical in the optimization of JA (Cardellicchio et al., 2020a).

During a JA one's own and others' actions may overlap in time and/or require the execution of complementary movements, potentially giving rise to behavioral interference effects (Cracco et al., 2018); all of this must be resolved to steer the appropriate course of (Joint) action. The premotor cortex, via its tight functional link with the primary motor cortex (O'Shea et al., 2007; Vesia et al., 2018), could play a key role in resolving competition between action representations, acting as a "comparator system" (Fornia et al., 2020; Haggard, 2005; Wolpert et al., 1995). In fact, single neuron activity in the monkey left dorsal premotor (lPMd) cortex integrates representations of self and others' actions, enabling successful coordination between individuals (Ferrari-Toniolo et al., 2019). Furthermore, previous studies in the macaque (Giarrocco

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https://doi.org/10.1016/j.isci.2021.103330

et al., 2020; Mirabella et al., 2011) and human (Parmigiani and Cattaneo, 2018) have shown that PMd, but not other frontal areas connected to PMd (i.e., supplementary motor area [SMA] and pre-SMA; see also Friehs et al., 2021; Scangos and Stuphorn, 2010), plays a distinctive role in processing inhibitory signals during visuomotor inhibitory behavior. However, whether PMd regulates JA in general and JA stopping in particular has not been explored in humans yet.

In the present study we aim at investigating the role played by the PMd in guiding JA, with a particular emphasis on behavioral inhibition in humans. To explore this issue, we have performed two experiments integrating a classical Stop Signal Task (SST) and a JA task. The SST is a reaction time task in which participants perform a speeded choice reaction and, occasionally, withhold their ongoing response when a stop signal appears (Lappin and Eriksen, 1966; for a review see Verbruggen and Logan, 2009). Although the relationship between cortical inhibition and SST has been established (Borgomaneri et al., 2020), far less is known about these processes during JA stopping. Performance in the SST with a partner making the task alone beside the participant is slowed down (Cavallo et al., 2014), suggesting that a selective suppression mechanism might be recruited in social contexts.

The JA task is designed to promote dynamic sensorimotor coordination between partners (Cardellicchio et al., 2020a). Participants reach and open a bottle using the right hand. The bottle is held by a co-actor (the JA condition) or by a mechanical holder (no-JA condition). Co-adaptation is demonstrated by the co-actor increasing grip force to stabilize the bottle well before haptic interaction. Trial-by-trial modulation of grip force amplitude explain corticospinal inhibition strength in the other participant, thus suggesting that online mutual adjustments are used to negotiate JA performance (Cardellicchio et al., 2020a). Here, as in SSTs, participants had to withhold their actions if an acoustic tone was presented during the reaching phase (stop signal). In the first behavioral study, we show longer Stop Signal Reaction Times (SSRTs) in the JA condition. This result strengthens current evidences that a socio-interactive context slows down action stopping (Cavallo et al., 2014), also when mutual co-adaptation was required. In the second experiment, we investigated the role of the lPMd in JA stopping. We applied a continuous theta burst stimulation (cTBS) protocol to interfere with the lPMd activity or a control site (vertex). We show that interference on lPMd cancels the SSRT difference between the JA and the no-JA tasks. Bayesian statistics further confirm that the PMd plays a key role in JA stopping.

RESULTS

The current SST required the participant to reach for and then open one of the two bottles placed in front of him/her by unscrewing its cap (similar to Cardellicchio et al., 2020a). One bottle was held by a co-actor (Joint Action, JA), the other by a mechanical holder (vice clamp, no-JA). Before each trial, a LED on the table cued which of the two bottles they were supposed to reach and open. In GO trials, they were required to perform the action and return to the initial position. In 33% of trials, an acoustic STOP signal asked to withhold the reaching action and return to the initial position. The time required for successful movement inhibition (i.e., stop-signal reaction time; SSRT; Figures 1A and 1B; see STAR Methods) gives a measure of behavioral inhibition performance. The first study characterized behavioral performance in our JA stopping task, whereas the second TMS study aimed at investigating the involvement of PMd in withholding a JA.

Reaction Time (RT) performance in Go trials show no significant difference between JA (567.2 $\pm$ 116.01 ms) and no-JA (566,25 $\pm$ 119,33 ms) conditions ($t(19) = -0.24$; $p = 0.81$). The percentage of correct inhibitions on STOP trials (%CIST) does not differ between conditions (no-JA 51.6% $\pm$ 0.8%; JA: 51.8% $\pm$ 0.6%) ($t(19) = 0.51$; $p = 0.61$). No difference for %CIST demonstrates the efficacy of the SSD staircasing algorithm (see STAR Methods). Paired t test on SSRTs reveals a significant difference between the two conditions. Participants are slower in JA (187.1 $\pm$ 26.8 ms) than in no-JA (177.85 $\pm$ 30.39 ms) ($t = (19) -2.38$; $p = 0.02$ Cohen's $\delta = 0.53$) conditions (Figure 2A).

In the second TMS study, cTBS (see STAR Methods) was used to interfere with the activity of the left PMd or the vertex, as a control site. To this aim we run a 2 × 2 within-subjects repeated measures ANOVA, with factor TMS site (two levels: PMd, control site) and Action (two levels: JA, no-JA), with %CIST, RTs, and SSRTs as dependent variables. We find no significant main effect on %CIST (all conditions: 51% $\pm$ 3; TMS site: $F(1,14) = 0.85$; $p = 0.37$; Action: $F(1,14) = 1.84$; $p = 0.19$) or interaction ($F(1,14) = 0.22$; $p = 0.64$), confirming the robustness of the staircase procedure. The 2 × 2 ANOVA on RTs shows only a main effect of Action (JA: 605.5 $\pm$ 90.3 ms; no-JA: 594.6 $\pm$ 87.77 ms; $F(1,14) = 11.11$; $p = 0.005$) but no significant effect of TMS

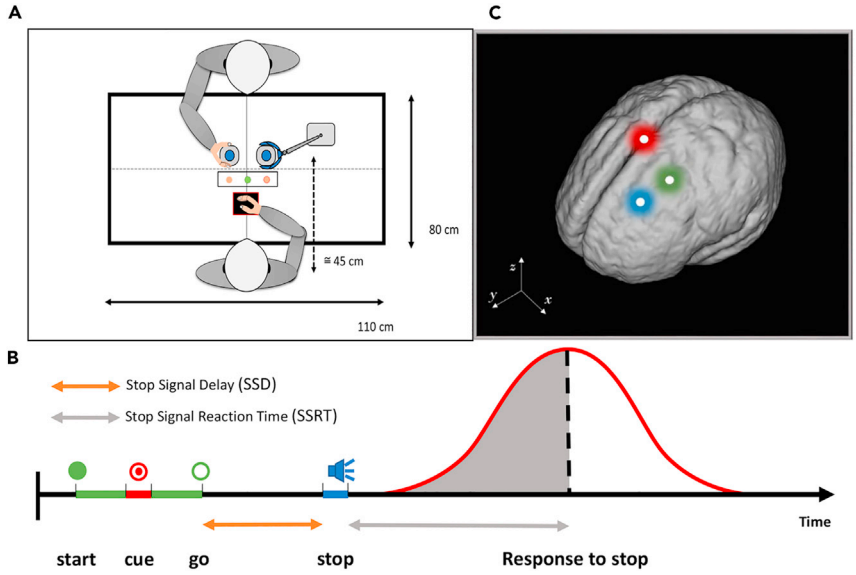

Figure 1. Experimental design

(A) The experimental setup. The button box, the three LEDs, and the two plastic bottles were positioned on the table in front of participants. One of the bottles was held by a co-actor (Joint Action, JA), the other was held by a mechanical holder (vice clamp, no-JA). Three LEDs were placed close to the bottles. The red LEDs indicated the bottle to reach. The GO signal consisted in the green LED being turned off. In 33% of trials the STOP signal was presented, and it was given by an acoustic signal.

(B) The experimental timeline. The red bell-shaped curve stands for the distribution of responses. The Stop Signal Delay (SSD) between GO and STOP signals was initially set at 500 ms but continuously adapted with a staircase procedure, guaranteeing a 50% of successful stopping. Only if the SSD is long enough, stopping will be unsuccessful.

(C) The position of the two TMS sites (PMd in blue, vertex in red) and hand M1 (in green) in a single participant.

site ($F(1,14) = 0.81$; $p = 0.38$) or interaction ($F(1,14) = 1.15$; $p = 0.30$). Subsequent Bayesian analyses, however, report that evidence of a difference in RTs across conditions is weak (Keysers et al., 2020), thus substantially confirming results of the first behavioral study (see Table S1).

The 2 × 2 ANOVA on SSRTs shows no main effect of TMS site ($F(1,14) = 0.97$; $p = 0.33$; PMd: 184 ± 33 ms; control site: 190 ± 42.2 ms) but a significant main effect of Action (JA/no-JA: $F(1,14) = 6.33$; $p = 0.02$; JA: 191.3 ± 37.9 ms; no-JA: 183.7 ± 37.6 ms). The interaction between TMS site and Action ($F(1,14) = 14.03$; $p = 0.002$) is also significant. Post hoc analyses with Bonferroni correction show that SSRTs in the control TMS site replicate results obtained in the first behavioral experiment. Specifically, participants were slower in withholding movements during JA ($p = 0.03$) (Figure 2B). Conversely, no significant difference is present between JA and no-JA when TMS was released on PMd ($p = 1.0$) (Figure 2B). SSRTs in the no-JA condition do not differ between PMd (mean: 186.13 ± 32.59 ms; $p = 1.0$) and control TMS sites (mean: 181.26 ± 43.14 ms). In the JA condition, SSRTs after PMd stimulation (182.73 ± 34.47 ms) are significantly faster than in the control TMS session (199.86 ± 40.53 ms; $p = 0.006$; Figure 2B). Basically, the interference on PMd seems to mostly impact the JA condition by canceling the slowing down of SSRTs.

The Bayesian repeated measure ANOVA (Tables 1 and 2) reveals moderate evidence for the presence of an interaction between TMS site and Action ($BF_{incl} = 3.83$). Thus, we use post hoc Bayesian t tests to obtain Bayesian confidence intervals (CIs) for specific contrasts of interest (Table 3). Although in the control TMS session we find extremely strong evidence for an increase of SSRTs during JA ($BF_{+0} = 296.23$ with median posterior $\delta = 1.14$; 95% CI = [0.474, 1.861] see Figure 3A), in the PMd session we find moderate evidence for the absence of a JA modulation ($BF_{+0} = 0.166$; $BF_{0+} = 6.01$ with median posterior $\delta = 0.112$; 95% CI = [0.005, 0.432]; see Figure 3B and 3C). The evidence for the alternative hypothesis is relatively stable across a wide range of prior distributions, indicating that the analysis is relatively robust (see Figure S1 in supplementary materials). All together, these results suggest that the PMd plays a causal role in producing the JA-related slowing down of SSRTs. For more information, see transparent methods in supplemental information.

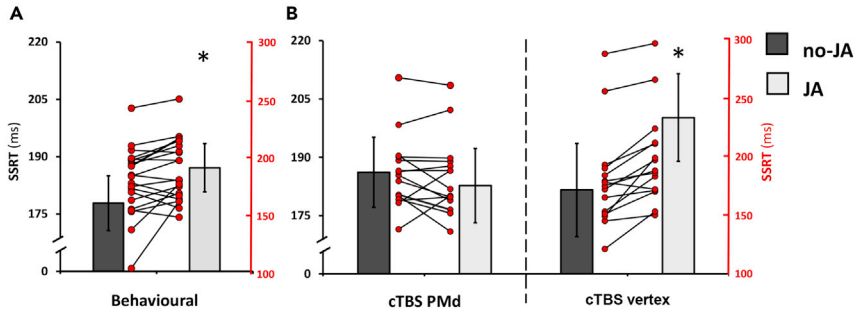

Figure 2. Results with t test analyses

The histogram on the left (A) shows the results of the first behavioral experiment. Paired t test on SSRT revealed a significant difference between the two conditions: participants were slower in JA than in no-JA conditions.

The two histograms on the right (B) show the results of the TMS study. In the control site (vertex) session results of the behavioral study were replicated: SSRTs in JA condition were longer than in no-JA. No significant difference was instead present between JA and no-JA when rTMS was released on PMd.

The asterisks in the graph represent significant differences, $p < 0.05$. The histograms represent the mean, whereas the bars represent +/− SEM (standard error of mean). The black axes are related to the SSRTs averaged values, whereas the red axes are related to individual performance data.

DISCUSSION

In an environment full of potential goals, how does the brain determine which one to pursue? Behavior often requires suppressing inappropriate movement tendencies (Bestmann and Duque, 2015; Duque et al., 2017; Luna et al., 2015; Mirabella et al., 2011), and without efficient inhibitory control, behavior may turn maladaptive (Bartholdy et al., 2016; Milad and Rauch, 2012). As far as the neural mechanisms controlling action suppression, the ability to adjust, stop, and reorganize an online motor plan might even be more relevant when coordinating with someone else. In fact, during JA, goal attainment no longer depends on how appropriate one's own action is, rather it is defined in relation to other's action properties. Therefore, suppression mechanisms might actually be at the basis of successful behavioral co-adaptation during JA. The current study aimed at investigating the cortical origin of such motor suppression during an online and relatively ecological JA stopping task. Indeed, our task replicates a relatively common occurrence happening at the dinner table when, for instance, we are passing an object to someone but an unpredictable event (e.g., our cat jumps on the table) calls for a replanning or a complete stop.

Our first behavioral experiment shows slower stopping performance (i.e., longer SSRTs) during JA. According to previous reports, during JA, self and other's action co-representation are thought to reverberate into an increased cost for stopping (Cavallo et al., 2014). A potential explanation for this phenomenon is that a processing bottleneck exists in JA motor representations and in JA cascading processes. Parallelization is a key property of the motor preparation cascade. In fact, multiple competing motor plans are normally prepared in parallel before the selection of just one of them (Cisek and Kalaska, 2005; Cui and Andersen, 2007; Dekleva et al., 2016; Mirabella, 2014; Seeds et al., 2014; but see also Dekleva et al., 2018; Hampel et al., 2017). The cost of parallelizing multiple processes at once would result in an increased processing time, when compared with a serial scheme (Cardellicchio et al., 2021; Marti et al., 2015; Pashler, 1994). In our task, action stopping must proceed in parallel with respect to representing both self and other's actions, therefore delaying processing of the rare stop-signal events. A recent study showed that interference with the activity of PMd could limit the competition between parallel motor programs leading to a reduction of RT (Cattaneo and Parmigiani, 2021).

The key novelty is that interference to the left PMd canceled the JA-induced slowing down of SSRTs that was observed in the first behavioral study and confirmed in the control TMS session. This would also be in line with recent evidence about the role of PMd in action cascading. In fact, PMd activity encodes the distribution of possible actions scaling for their degree of uncertainty. With decreasing uncertainty, activity in PMd narrows and converges on the optimal decision. In fact, the PMd represents and retains a distribution of potential motor plans that are not explicitly presented but arise as possibilities during uncertain conditions (Dekleva et al., 2016; Mysore and Kothari, 2020). Over time, the neural activities representing the chosen plan are enhanced while the other competing ones are gradually suppressed via specific inhibitory mechanisms (Cisek and Kalaska, 2005; Thura and Cisek, 2014). In this regards, neuronal activity in PMd

Table 1. Bayesian ANOVA

Models	P(M)	P(M|data)	BF_M	BF_{10}	Error %
TMS site + action + TMS site ✻ action	0.200	0.367	2.320	1.000	
Null model (incl. subject)	0.200	0.235	1.231	0.641	1.728
Action	0.200	0.180	0.878	0.490	1.914
TMS site	0.200	0.122	0.554	0.332	2.018
TMS site + action	0.200	0.096	0.424	0.261	2.200

The first column "Models" lists the models under consideration: the "Null model" that contains only the grand mean, the "Action" model that contains the effect of JA, the "TMS site" model that contains the effect of TMS stimulation, the "Action + TMS site" model that contains both main effects, and finally the "Action + TMS site + Action × TMS site" model that includes both main effects and the interaction. The "BF_{10}" column shows the Bayes factor for each model against the best model. The first entry is always 1 because the best model is compared against itself. The right-most column "% error" indicates the size of the error in the integration routine, relative to the Bayes factor and similar to a coefficient of variation. Column "P(M)" indicates the equal assignment of prior model probability across the five models. Column "P(M |data)" indicates the updated probabilities after having observed the data. Column "BF_M" indicates the degree to which the data have changed the prior model odds. The two main effects and their interaction model have received support from the data in the sense that the data have increased its model probability.

reflects the accumulation and change in information that is pertinent to the transition from decision processes to the planning and organization of forthcoming movements (Kaufman et al., 2015). Thus, pre-movement activity in PMd (Cisek and Kalaska, 2004) signals the momentary decision state about the transformation from a task-relevant to motor-compatible representations (Kaufman et al., 2014, 2015, 2016; ter Wal et al., 2020; Thura et al., 2012).

In JA, uncertainty is inherently larger and dynamically changing over the course of the interaction. In fact, our brain does not only have to select the most appropriate action but also has to continuously update it, given partner's movements. Basically, the brain has to extract relevant information from others' action, yet suppressing their automatic imitation (Cracco et al., 2018), while concurrently routing appropriate adjustments to downstream structures. All of this has to happen in an iterative manner and as quickly as possible. Given that both self and other's actions show overlapping activity in PMd (Tkach et al., 2007), this area might be essential in allowing the necessary self-other functional segregation to produce effective and coordinated JA, although still paying a relatively small cost in terms of execution speed. This would be in line with the general role assigned to PMd in guiding a selective mechanism to control a particular response while suppressing interfering ones (Aron and Verbruggen, 2008). Our data suggest that in JA the PMd segregates observed (other) and self-motor outputs via a selective inhibition mechanism that helps sculpting movements in function of the (interactive) context. Activity in PMd specifies the selected movement (Cavina-Pratesi et al., 2006; Terao et al., 2007), by generating inhibitory signals to M1 or its downstream structures (Kroeger et al., 2010; Tzvi et al., 2020) and may also have a key role in JA negotiation.

Finally, it is important to consider that selection of the appropriate action, notwithstanding all the interferences, and its delivery to downstream structures may be achieved via multiple paths. In this regards, the PMd modulates spinal circuits via direct projections (Bizzi et al., 2000; Dum and Strick, 1991) targeting

Table 2. Analysis of effects

Effects	P(incl)	P(incl|data)	BF_{incl}
TMS site	0.400	0.218	0.524
Action	0.400	0.276	0.773
TMS site ✻ action	0.200	0.367	3.826

This table shows the analysis of effects, averaging across models containing a specific factor. "P(incl)" is the prior inclusion probability for a specific factor. After the data are observed we can similarly consider the sum of the posterior model probabilities for the models that include each factor (column "P(incl|data)"). The change from prior to posterior inclusion odds is given in the column "BF_{incl}." Averaged across all candidate models, the data strongly support inclusion of both main factors and their interaction.

Table 3. Bayesian paired samples t test

Measure 1	*Measure 2*	BF_{+0}	Error %
Control (JA)	Control (no-JA)	296.232	$\sim 5.052 \times 10^{-6}$
PMd (JA)	PMd (no-JA)	0.166	~0.001
Control (JA)	PMd (JA)	6.658	$\sim 9.158 \times 10^{-4}$

This table reports the Bayes factor for a series of paired sample t test. Lower values of "Error %" indicate greater numerical stability of the result. For all tests, the alternative hypothesis specifies that Measure 1 is greater than Measure 2. (e.g., control site (JA) is greater than control site (no-JA)).

spinal interneurons (Dum, 2005; Galea and Darian-Smith, 1994) or via sub-cortical structures (Duque et al., 2012), originating indirect descending pathways (primarily the reticulospinal tract) that are partly involved in the control of distal hand muscles (Cohen et al., 2010; Riddle et al., 2009). These projections, as well as indirect descending pathways originating in post-central areas, basal ganglia, motor thalamus, brainstem, and cerebellum, would provide the essential spinal inhibitory motor control (Ebbesen and Brecht, 2017) that could help regulating JA performance by preventing premature movements or by stopping those that are no longer adaptive (Bizzi et al., 2000; Dum and Strick, 1991; Kroeger et al., 2010).

In conclusion, the dynamic and mutual behavioral adjustments that constitute the hallmark of JA may be based on the engagement of refined behavioral inhibition mechanisms, of which stopping is an extreme case scenario. Action stopping paradigms offer indeed a quite robust experimental and theoretical platform to investigate these mechanisms within a controlled but yet ecological and interactive scenario. Despite that, further investigation should analyze premotor areas contribution during a more naturalistic JA task, for example, while the two partners are moving together. With this study we suggest that, in order to advance a mechanistic understanding of JA coordination, one key missing component is the exploration of the physiological underpinnings of selective and time-resolved motor inhibition during socially relevant interactive behaviors. In this regard, our results significantly extend current knowledge about the role of PMd in interindividual action coordination, by suggesting a specific role in JA stopping.

Limitations of the study

In this study we investigated the cortical origin of behavioral inhibition and motor suppression during a JA stopping task. We designed an ecological JA task that simulates a real daily interaction, but more realistic

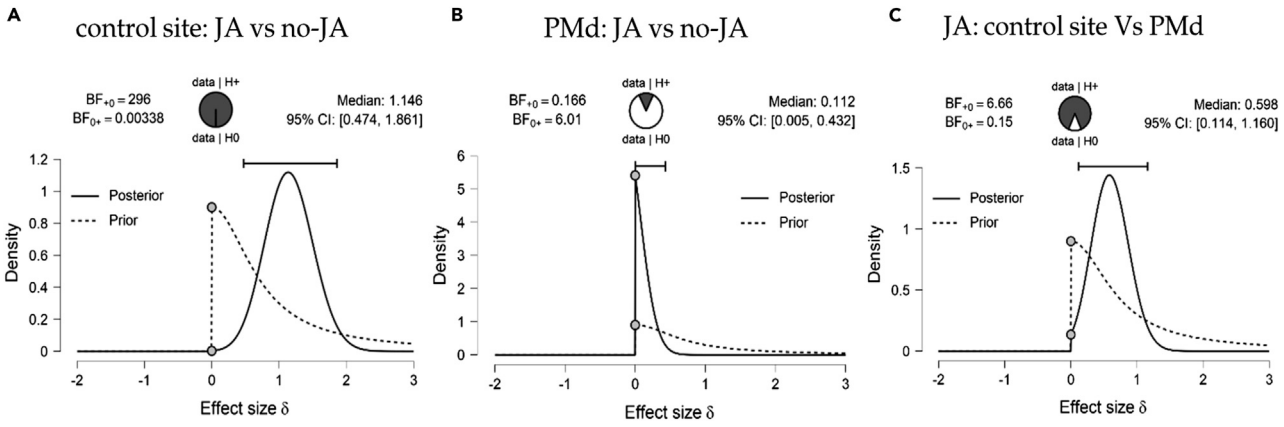

Figure 3. Bayesian analyses

Bayesian two-sample t test for the parameter δ. The probability wheel on top visualizes the evidence that the data provide for the two rival hypotheses. The two gray dots indicate the prior and posterior density at the test value (Dickey and Lientz, 1970; Wagenmakers et al., 2010). The median and the 95% central credible interval of the posterior distribution are shown in the top right corner.

(A) shows the one-sided procedure for hypothesis testing JA versus no-JA in control site. The resulting BF_{+0} is 296, indicating strong evidence in favor of H+: the data are approximately 296 times more likely under H+ than under H_0.

(B) shows the one-sided procedure for testing JA versus no-JA after rTMS in PMd. The resulting BF_{0+} is 6.01 showing moderate evidence for the absence of JA modulation.

(C) shows the procedure for testing JA differences after rTMS in control site versus PMd. The resulting BF_{+0} is 6.66 indicating moderate evidence for H_+.

scenarios should be verified. Furthermore, although we used Bayesian analyses to verify the role of PMd in our task, there are other neural pathways potentially contributing to similar inhibitory control functions (Hannah and Aron, 2021). In fact, future studies will have to investigate the differential contribution played by other premotor or supplemental motor areas.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2021.103330.

ACKNOWLEDGMENTS

This work has been supported by Ministero della Salute, Ricerca Finalizzata 2016 - Giovani Ricercatori (GR-2016-02361008); Ministero della Salute, Ricerca Finalizzata 2018 - Giovani Ricercatori (GR-2018-12366027) to A.D., and by the European Union H2020 - EnTimeMent (FETPROACT-824160). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

P.C. and A.D. had the idea and designed the experiments. P.C. and E.D. prepared the experimental setup and collected the data. P.C. and E.D. analyzed the data. All authors participated in interpretation of data and helped draft the manuscript. A.D. supervised the project. All authors gave final approval for publication.

DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Received: March 23, 2021
Revised: July 8, 2021
Accepted: October 20, 2021
Published: November 19, 2021

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Raw data	This paper	https://doi.org/10.17632/sy2tfm58yh.1 https://bit.ly/3liY0nn
Software and algorithms		
Psychtoolbox (version 3.0.14)	Psychophysics Toolbox	http://psychtoolbox.org/ RRID: SCR_002881
Jasp version 0.11.1	Jasp	https://jasp-stats.org/ RRID:SCR_015823
Signal software	Cambridge Electronic Design Limited	http://ced.co.uk/products/sigovin RRID:SCR_017081
MATLAB R2018a	MathWorks	https://www.mathworks.com/ RRID:SCR_001622
Statistica	Statsoft	http://www.statsoft.com/Products/STATISTICA/Product-Index RRID:SCR_014213
SofTaxic	E.M.S.	http://www.emsmedical.net
Other		
Figure-of-eight TMS coil (7 cm diameter)	Magstim	https://www.magstim.com
Figure-of-eight TMS coil (5 cm diameter)	Magstim	https://www.magstim.com
Magstim 200^2 stimulator	Magstim	https://www.magstim.com
Magstim Rapid^2 stimulator	Magstim	https://www.magstim.com
Magstim super rapid stimulator	Magstim	https://www.magstim.com
CED power1401	Cambridge Electronic Design Limited	http://ced.co.uk/ RRID:SCR_017282
Wireless EMG system	Cometa	https://www.cometasystems.com/
Polaris vicra optical tracker	Northern Digital	https://www.ndigital.com/

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Pasquale Cardellicchio (pasquale.cardellicchio@iit.it).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Original data have been deposited at Mendeley Data and are publicly available as of the date of publication. The accession numbers or URL for the datasets are listed in the key resources table.

This paper does not report original code.

Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Participants

A total of 35 healthy naive volunteers took part in two studies (15 males and 20 females; mean and standard deviation (SD) of age: 25.34, SD: ± 3.8). 20 subjects participated in the behavioral study and 15 participated in the repetitive Transcranial Magnetic Stimulation (rTMS) study. All subjects were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Participants were informed about the experimental procedure and gave their written consent according to the last update of the Helsinki Declaration. None of the participants reported neurological, psychiatric, or other contraindications to TMS (Rossi et al., 2009). The experiment was approved by the ethical committee "Comitato Etico Unico della Provincia di Ferrara" (approval N. 170592), and participants were compensated for their participation with 12,50 €.

METHOD DETAILS

Behavioral study

Procedure. The current Stop-Signal Task requires the participant to perform an interactive goal-directed action. The task requires the participant to reach for and then open a bottle by unscrewing its cap (similar to Cardellicchio et al., 2020a). Participants were seated in a comfortable chair with their forearm pronated and the right-hand resting on a button-box (Cedrus RB-840 response Box) on a table in front of them (length = 110 cm; width = 80 cm). Two Plastic bottles, distant 5 cm each other, were positioned on the table at a distance of 45 cm (about 2/3 of the participant's arm length) from the participants' chest along his/her midline. The bottles height were 25 cm and caps diameter were 5 cm. A capacitive sensor measured when participants touched the bottle caps. Meanwhile, a bottle was held by a co-actor (Joint Action, JA), the other was held by a mechanical holder (vice clamp, no-JA). The position of bottles (JA/no-JA) were counterbalanced across the participants. Three LEDs (two red, one green) spaced 5 cm from each other, were placed close to the two bottles (See Figure 1A).

Participants were instructed to fixate the green LED and were prompted to start reaching for the bottle when the LED went out (GO signal). The red LEDs indicated which of the two bottles they had to reach and open. The green LED remained on for 1800 ms; after 1000 ms one of the two red LEDs was turned on (for 300 ms) indicating the target bottle (JA or no-JA). As soon as the go signal was released (green LED switched off), in GO trials, participants were required to quickly reach the bottle and open its screw cap and return to the initial position. The Reaction time (RT) of the reaching phase was calculated as the movement elapsed from the starting of the action (the release of button-box) to the bottle cap touch. In 33% of trials, during the reaching phase, an acoustic signal acted as an STOP signal; participants were asked to withhold the reaching action and return to the initial position. The Stop Signal Delay (SSD) between GO and STOP signals (Figure 1A) was initially set at 500 ms but continuously adapted with a staircase procedure (Hilt and Cardellicchio, 2018; Osman et al., 1990). After each trial, the SSD was adjusted in 50 ms steps, as a function of the subject success or failure in stopping (decreasing this delay makes the task easier, and vice-versa). STOP trials were considered as failed when participants touched the cap. In these trials the SSD was decreased by 50 ms. This staircase procedure was independent for each of the two conditions.

Subjects were asked to perform the whole experiment paying attention to the possible STOP signal, but without slowing down their action (Verbruggen et al., 2019). Each trial terminated when the participants returned to the initial position. The time required for successful movement inhibition (i.e., stop-signal reaction time; SSRT; Figure 1B) provides a measure of inhibition performance. A total of 312 trials for each subject were run, equally divided into four blocks of 78 trials (26 JA GO trial, 26 no-JA GO trial; 13 JA Stop trials, 13 no-JA Stop trials), to let the subjects rest and avoid fatigue. Trials were randomized in every block. The total experiment contained 208 GO trials, 104 STOP trials (52 for each condition; JA, no-JA). Trials with a reaction time larger than 1.5 s were considered null (<1% of trials). Before the experimental session, participants familiarized with the task with an initial training phase (≅ 20 trials, with 5 stop signal). After each block, a feedback about their performance (movement time and percentage failed stoping) was provided to the participants. The experiment required a session of ~20 min per participant. The stimuli presentation was controlled via custom MATLAB (The MathWorks Inc., Natick, MA, USA) scripts using the Psychtoolbox 3 (Brainard, 1997).

TMS study

Procedure. The experimental procedure of this second study was the same as the behavioral one. Before the experimental session, participants underwent an initial training phase (≅20 trials, with 5 stop signal).

After familiarization, we moved to the TMS mapping procedure and motor threshold assessment (see cTBS and EMG section). The TMS was delivered, in two different sessions, to two scalp sites: the first corresponding to the left PMd and the second to the vertex (position of electrode Cz, according to the international 10–20 system) as a control site. Each session was carried out with at least 2 days apart and in a counterbalanced order across participants. Each session lasted ~ 40 min.

Continuous theta burst stimulation (cTBS) and electromyography (EMG). We used a cTBS protocol to produce a lasting suppression of regional excitability in the stimulated cortex (Huang et al., 2005). The cTBS protocol consists in the repeated administration of short high-frequency bursts. Each burst consists of three pulses given at an interstimulus interval (ISI) of 20 ms (corresponding to a rate of 50 Hz). These high-frequency triple-pulse bursts are repeated every 200 ms. The 600 pulses cTBS protocol lasts 40 s. Pulse intensity was defined on an individual basis at 80% of the Active Motor Threshold (aMT; Huang et al., 2005; Koch et al., 2008; Mochizuki et al., 2005; Nyffeler et al., 2008; Palmer et al., 2016). The mean (±SEM) aMT across participants was 51.3 ± 5.2% maximum stimulator output. We measured the aMT for the right Opponens Pollicis (OP) muscle. AMT was defined as the lowest TMS intensity that evoked a motor evoked potential (>100 μV) when participants maintained a slight contraction of the right OP (~10% of the maximum voluntary contraction) in at least 5 of 10 consecutive trials (Rossini et al., 1994). The aMT was estimated with a hand-held figure-of-eight coil (50 mm external diameter at each wing; Magstim Co., Ltd.) connected to a Magstim biphasic stimulator (Super Rapid; Magstim, Whitland, UK). This type of coil allows a more focal stimulation than the classical 70 mm coil. The same coil was used in the cTBS protocol delivered through the same biphasic stimulator.

The EMG signal was recorded through a wireless EMG system (Zerowire EMG, Aurion, Italy) with pairs of Ag/AgCl surface adhesive electrodes (5 mm in diameter) placed with a tendon-belly montage. EMG data were digitized (2 kHz) and acquired by a CED power3A 1401 board to be visualized on a monitor's PC (Signal 3.09 software; Cambridge Electronic Design, Cambridge, UK). The OP Optimal Scalp Position (OSP) was found by moving the coil in 0.5 cm steps around the left primary motor cortex hand area and using a slightly suprathreshold stimulus. The TMS coil was held tangentially to the scalp with the handle pointing backward and laterally to form a 45° angle with the midline.

The PMd stimulation site was defined in relation to the motor hot spot, and precisely 2.5 cm anterior and 1 cm medial, as recommended in previous reports (Fink et al., 1997; Mochizuki et al., 2004; Ortu et al., 2009; Picard and Strick, 2001; Stephan et al., 2016). During the cTBS on PMd the coil was oriented at a 45° angle to the midline with the handle pointing backwards inducing a posterior-anterior current flow (Cincotta et al., 2004; Giovannelli et al., 2012; Rizzo et al., 2004; Siebner et al., 2003; Ward et al., 2010). In the first 7 subjects, the PMd location was also estimated by a neuronavigational system (SofTaxic, E.M.S., Bologna, Italy) using digitized skull landmarks (nasion, inion, and 2 preauricular points) and about 23 scalp points provided by a Polaris Vicra optical tracker (Northern Digital, Canada). The selected site was marked on the bathing cap and then the neuronavigation system was used to extract the brain surface coordinates. In these subjects, scalp PMd localization matched the Talairach coordinates of left PMd (−25 ± 10, −1 ± 11, 62 ± 8). For the control cTBS site, the coil handle, pointing backward, was oriented parallel to the longitudinal fissure (cTBS stimulation sites in Figure 1C).

The control site was the vertex (Cz in the 10-20 system) that is unlikely to affect other potentially task-relevant brain areas (i.e., Supplementary Motor Area; SMA). In fact, the stimulation of SMA requires the coil to be placed 4 cm anterior to the Cz position and higher stimulations to reach deeper within the longitudinal fissure.

After cTBS (in both sites), participants rested for 5 min without moving their hands or feet (Gentner et al., 2008; Huang et al., 2005; van Nuenen et al., 2012). Based upon previous findings (Di Lazzaro et al., 2005; Huang et al., 2005) the time window of reduced excitability following cTBS was expected to last between 20 and 30 min. During the cTBS stimulation, the EMG activity was monitored to exclude residual direct stimulation of the adjacent M1. The absence of any spread of the current toward the motor cortex was confirmed by the lack of any motor evoked responses.

QUANTIFICATION AND STATISTICAL ANALYSIS

Behavioral analysis

Performance on GO trials was examined via a two-tailed t test on mean RTs. The behavioral performance of the SST was quantified as the stop-signal reaction time (SSRT (Congdon et al., 2012; Logan and Cowan,

1984). The SSRTs were computed for each condition using the integration method (Logan and Cowan, 1984; Verbruggen and Logan, 2009), known as being more reliable than the alternative mean method (Verbruggen et al., 2013). First, we ranked the RT to reach the bottle in GO trials and selected the Nth RT (representative RT), where N was calculated by multiplying the number of GO trials by the probability of mistakes in STOP trials. We then estimated SSRT by subtracting the average SSD from the representative RT. Accuracy, expressed as percent of correct inhibitions (%CIST) in the SST for each conditions, ranged between 0.4 and 0.6 (Hilt and Cardellicchio, 2018; Verbruggen et al., 2008) and is only used to evaluate efficacy of the staircase procedure. No subjects had SSD staircases that continued to increase or decrease over the whole experiment. To assess the efficacy of the SSD staircasing algorithm across blocks, the accuracy in the SST was quantified block by block. These values were then tested against 0.5 using a Wilcoxon signed rank test, showing that all subjects fulfilled the criteria and were thus all were included in the analyses. Normality was evaluated via the Kolmogorov–Smirnov test. Two-tailed t test followed by Bonferroni corrections were performed to evaluate differences (alpha level $p < 0.05$) between the two conditions (JA vs. no-JA). Statistical analyses were conducted using STATISTICA 9 (StatSoft, Inc.).

TMS analysis

To investigate the involvement of PMd in our JA-stopping task we run a 2 × 2 within-subjects repeated measures ANOVAs, with factor TMS site (two levels: PMd, control site) and Action (two levels: JA, no-JA), with %CIST, RTs and SSRTs as dependent variables. Partial eta-squared was used as a measure of effect size and, in case of a significant interaction, we run Bonferroni post-hoc comparisons. All frequentist statistics were run with STATISTICA 9 (StatSoft, Inc.).

We also used Bayesian analyses to further discriminate between "absence of evidence" and "evidence of absence" that was not possible with classic frequentist statistics. Indeed, a non-significant p value (i.e., usually, $p > 0.05$) may either indicate that the manipulation had no true effect or that the sample size was unable to detect a true non-zero effect of the manipulation. In Bayesian words, inferences update probabilities to hypotheses in light of observed data. The probabilities could be prior assigned before knowing the new information, or posterior, updated with the new information. Thus, every acquisition of new data or an absence of data allows to revise the hypothesis. Absent data could be explained in two different ways: absent event will never occur, or the event is possible but has not yet been observed. The evidence - the relative predictive performance of null hypothesis (H0) versus the alternative hypothesis (H1) - is known as the Bayes factor (BF). The magnitude of the BF should be considered as a continuous quantity of evidence. This continuous nature of the BF measure can be interpreted as 1) providing enough evidence to accept the alternative hypothesis; 2) providing enough evidence to accept the null hypothesis ("evidence of absence"); or 3) stating the inconclusiveness of the evidence toward either hypothesis ("absence of evidence").

This analysis was conducted using JASP v0.11.1 (JASP Team, 2019) with default priors. Effects are reported as the Bayes factor for the inclusion of a particular effect, calculated as the ratio between the likelihood of the data given the model vs. the next simpler model without that effect. Moreover, we used a Bayesian approach to test differences across SSRTs in JA and no-JA conditions. Specifically, we used Bayesian Paired Samples t Test (see also; Jeffreys, 1961; Rouder et al., 2009) as implemented in JASP using the default effect size priors (Cauchy scale 0.707). Results are reported using the one-tailed Bayes factor BF_{+0} that represents p (data| H+: JA > no-JA)/p (data| H0: JA = no-JA). One-tailed testing is typically a fairer balance between the ability to provide evidence for H0 and H1 (e.g., Jeffreys, 1961; Keysers et al., 2020; van Doorn et al., 2020; Wetzels et al., 2009). For hypothesis testing, we compare the null hypothesis (i.e., no difference between JA and no-JA SSRTs) to a one-sided alternative hypothesis (i.e., slower SSRTs in JA compared to no-JA condition), in line with the directional nature of the original research question. The rival hypotheses are thus H0: $\delta = 0$ and H+: $\delta > 0$, where δ is the standardized effect size (i.e., the population version of Cohen's d), H0 denotes the null hypothesis, and H+ denotes the one-sided alternative hypothesis. Since we specified a one-sided alternative hypothesis, the prior distribution is truncated at zero, such that only positive effect size values are allowed. Effect size estimates are reported as median posterior Cohen's δ with 95% credibility interval.