COGNITIVE NEUROSCIENCE

How the effects of actions become our own

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Every day, we do things that cause effects in the outside world with little doubt about who caused what. To some, this sense of agency derives from a post hoc reconstruction of a likely causal relationship between an event and our preceding movements; others propose that the sense of agency originates from prospective comparisons of motor programs and their effects. Using functional magnetic resonance imaging, we found that the sense of agency is associated with a brain network including the pre–supplementary motor area (SMA) and dorsal parietal cortex. Transcranial magnetic stimulation affected the sense of agency only when delivered over the pre-SMA and specifically when time-locked to action planning, rather than when the physical consequences of the actions appeared. These findings make a prospective theory of the sense of agency more likely.

INTRODUCTION

Although much of the functioning of our motor system occurs without awareness, we "know" when we are actors of our behavior. We also predict and are conscious of the consequences of our intended motor acts, with reference to our goals. The feeling of voluntarily controlling our own actions and, through them, the events in the outside world is the so-called "sense of agency" (*1*), a crucial component of action monitoring and self-awareness.

The sense of agency is experienced as a feeling of implicit interconnection between intentions to act and the ensuing environmental changes due to our actions. The sense of agency becomes a conscious experience when we pay attention to whether the external consequences of our actions match our plans or when the normal chain of events from action plans to their consequences is interrupted or perturbed (*1*).

According to a constructive or prospective hypothesis, the sense of agency arises from "predictive" and "comparative" processes (*2*). The former is based on an efference copy of the current motor program used to make predictions and expectations about the desired external consequences of an action. The latter compares these expectations with the actual external outcome of the movement. If the actual external feedback matches the prediction of the intended act, then the event is attributed to the self (*1*, *2*).

According to an alternative reconstructive hypothesis, the sense of agency is generated by a post hoc reconstruction of events and their likely causes (*3*). The sense of agency would arise from an inferential sense-making process drawn after the end of the movement to check whether the observed events are consistent and contingent with specific prior thoughts (*4*).

Under the constructive hypothesis, action awareness rests upon a constructive process, depending on consecutive analytical steps, taking advantage of efferent motor command signals. This model would be supported by the evidence that the magnitude of a sense of agency correlates with the activity of action planning–specific brain regions and that this correlation could be modulated by external manipulations. Conversely, the reconstructive model de-emphasizes the importance of predictive action monitoring at the stage of action planning. The sense of agency generation should arise outside the boundaries of the brain regions involved in action specification and control (*5*).

It remains to be established to what extent expectations and feedbacks should be tied in time for the emergence of a sense of agency (*6*). It is also not completely clear whether the sense of agency can be manipulated, e.g., by varying the timing of the feedback with regard to dominant expectations based on daily life experience or by modulation of the activity of the brain areas involved [see table S1 for a synopsis of previous functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and transcranial magnetic stimulation (TMS) studies on the sense of agency].

Here is where our investigation started. Instead of using explicit judgments that can be biased (*1*), we opted for implicit measures of the sense of agency. These are considered more reliable because they are based on judgments on physical events rather than on introspection.

In particular, we took advantage of the intentional binding phenomenon (*7*), an implicit measure of the sense of agency whereby the temporal interval between actions and consequences is perceived to be shorter than its real duration. While the phenomenon has been replicated several times [see for a review (*8*)], the validity of the action-effect binding as an implicit index of a sense of agency has been appreciated on the following grounds: (i) The measure is achieved via the comparison of active versus passive movements, the time compression (TC) between acts and consequences being systematically larger for active movements [i.e., shorter perceived temporal interval; see for example (*9*)]; (ii) patients with a perturbed sense of agency like schizophrenics with delusion of control have a perturbed intentional binding (*10*, *11*). At a mechanistic level, the action-effect binding has been explained as the result of the slowing down of an internal clock during the action-effect interval specifically for intentional acts (*12*). Accordingly, the anticipatory "imprecision" revealed by this measure is what permits us to tease apart the implicit appreciation of intentional from nonintentional acts. What counts here is that the temporal action/perception patterns of the intentional binding phenomenon may represent a measurable manifestation of a specific cognitive function whereby a coherent conscious experience of agency

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occurs, allowing one to distinguish the effects caused by one's own actions from those generated by others.

In our experiment, we devised a temporal judgment task based on visual feedback, in which participants received a visual cue and then either pressed a button (active condition) or had their finger pressed over the same button by an examiner (passive condition). Under both conditions, the consequence was the lighting up of a light bulb on a computer screen. Participants were asked to judge the perceived temporal interval between the action and its consequence. This paradigm allowed us to measure the intentional binding phenomenon (*7*) to investigate (i) the neurofunctional correlates of the sense of agency by means of fMRI and (ii) whether the sense of agency could be manipulated by modulating the activity of the brain areas involved using a repetitive TMS (rTMS) protocol.

The fMRI study allowed us to characterize the brain network involved in the genesis of the agency experience. Moreover, anatomical considerations on the nature of the areas that were involved in the agency experience eased the interpretations of the sense of agency in favor of a constructive or reconstructive mechanism. The rTMS study complemented our investigation by allowing us to make causal inferences on the relationship between local brain activities and their possible different roles in the genesis of the agency experience (i.e., the predictive and comparative processes of the sense of agency).

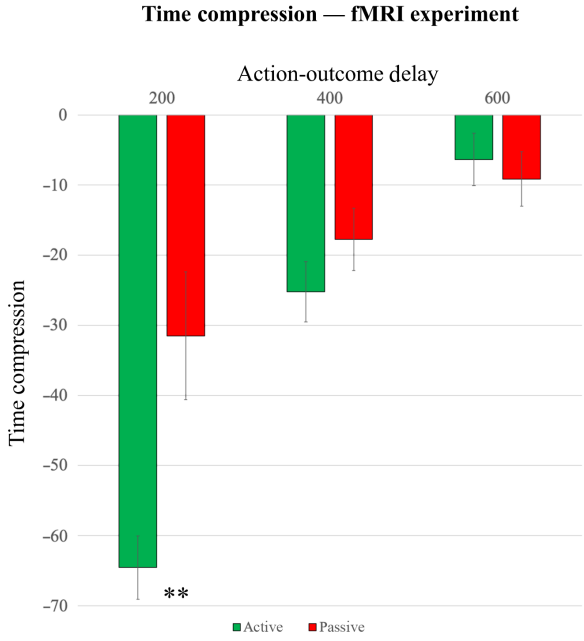

Fig. 1. Behavioral results (fMRI experiment) showing the intentional binding effect at 200-ms action-outcome delay. Time compression values for the active and passive conditions recorded at 200, 400, and 600 ms of action-outcome delay. Error bars = SE; asterisks indicate significant results at $P < 0.05$, Bonferroni corrected. TC is visualized as the percentage of the time delay of the outcome.

RESULTS—fMRI EXPERIMENT

Behavioral results

We found a significant effect of the factor Delay ($F_{2,48} = 4.45$, $P = 0.017$) and a significant Condition*Delay interaction ($F_{2,1297} = 6.8$, $P = 0.001$). The factor Condition was not significant ($F_{1,24} = 3.47$, $P = 0.075$). The Condition*Delay interaction was explored with planned post hoc comparisons. We observed that the perceived TC (namely, the difference between the real duration and the estimated duration of the action-outcome delay, our indirect measure of the sense of agency) was stronger in the active trials compared with the passive ones. However, this happened only when there was a temporal contingency between the movement and the lighting of the light bulb (post hoc test active condition versus passive condition at 200 ms of delay between the movement and its consequence: $t_{1297} = 3.34$, Bonferroni-corrected $P = 0.003$, Cohen's $d = 0.97$; post hoc test active condition versus passive condition at 400 ms of delay between the movement and its consequence: $t_{1297} = 1.67$, Bonferroni-corrected $P = 0.288$, Cohen's $d = 0.53$; and post hoc test active condition versus passive condition at 600 ms of delay between the movement and its consequence: $t_{1297} = -0.92$, Bonferroni-corrected $P > 0.9$, Cohen's $d = 0.25$). See Fig. 1.

fMRI results

Main effect of the factor condition

Active condition > passive condition. The comparison between the active trials and the passive ones showed activation of the motor and premotor network, including the bilateral middle cingulum, the pre–supplementary motor area (SMA) and the SMA, the left precentral gyrus, and the cerebellum bilaterally. See table S2 and fig. S1.

Passive condition > active condition. No region displayed a significant effect. As one would expect, given the presence of touches to the right hand under the passive condition, there was a sizeable trend in the left secondary somatosensory area (*x*: −44, *y*: −24, *z*: 18; *Z* score = 3.4).

Condition by delay interaction

No region displayed a significant effect.

Linear regression analyses between fMRI blood oxygenation level–dependent responses and behavioral data

Linear regression analysis for the differential TC values (active > passive trials) at 200-ms action-outcome delay. Of the action-related frontoparietal system, we found a significant correlation between the differential TC values of individual participants and the blood oxygenation level–dependent (BOLD) signal in the left pre-SMA, the inferior parietal lobule (Brodmann area 40), and the postcentral gyrus (Brodmann areas 3 and 2). We also found significant correlations in the insular cortex, in the precuneus and the cerebellum bilaterally, in the left superior temporal pole, in the left hippocampus, and in the right superior frontal gyrus (Brodmann areas 6 and 9). The more negative the TC (estimated time interval shorter than the real interval), the higher the BOLD response was in these areas for the active trials. See Table 1 and Fig. 2.

Linear regression analysis with the differential TC (active > passive trials) at 400- and 600-ms action-outcome delays. No region displayed a significant correlation with the differential TC values for these longer delays between action and the lighting up of the light bulb.

Interim discussion: fMRI experiment and rationale for the rTMS study

The fMRI experiment based on a temporal judgment task revealed the expected intentional binding phenomenon; however, this effect emerged only when there was a stringent temporal contiguity (200 ms,

Table 1. Linear regression analysis between fMRI data collected for trials with action-outcome of 200 ms, with TC data (at 200-ms action-outcome delay). MNI, Montreal Neurological Institute.

Brain regions (BA)	MNI coordinates											
	Left hemisphere						Right hemisphere					
	x	*y*	*z*	*Z* score	*P* value	Cluster size	*x*	*y*	*z*	*Z* score	*P* value	Cluster size
Linear regression analysis with TC for trials when the action-outcome delay was 200 ms.												
Superior front gyrus (6/9)	–	–	–	–	–	–	20	30	50	4.23*	0.00001	174
	–	–	–	–	–	–	10	40	46	3.9*	0.00005	
Pre-SMA (6)	**−16**	**12**	**64**	**4.00***	**0.00003**	**158**	**–**	**–**	**–**	**–**	**–**	**–**
	−10	16	62	3.78*	0.00008		–	–	–	–	–	–
	−6	18	62	3.46*	0.0003		–	–	–	–	–	–
Insula	−38	12	0	3.8*	0.00007	254	44	16	−6	4.32*	0.000008	243
	−46	8	0	3.29*	0.0005		–	–	–	–	–	–
	−42	6	−12	4.09*	0.00002		–	–	–	–	–	–
	−42	6	−4	3.78*	0.00008		–	–	–	–	–	–
Postcentral gyrus (3)	–	–	–	–	–	–	52	−26	48	3.55*	0.0002	331
Inferior parietal lobule (IPL) (40)/postcentral gyrus (2)	–	–	–	–	–	**–**	**36**	**−40**	**66**	**4.03***	**0.00003**	331
	–	–	–	–	–	–	40	−38	62	3.93*	0.00004	
	–	–	–	–	–	–	52	−30	50	3.59*	0.0002	
Precuneus (7)	−2	−60	52	3.44*	0.0003	204	10	−62	62	3.96*	0.00004	204
	–	–	–	–	–	–	0	−60	48	3.38*	0.0004	
	–	–	–	–	–	–	14	−68	60	3.47*	0.0003	
	–	–	–	–	–	–	0	−58	58	3.51*	0.0002	
Superior temporal pole (38)	−44	10	−18	4.33*	0.000008	254	–	–	–	–	–	–
Hippocampus (27)	−20	−30	0	4.35*	0.000007	679	–	–	–	–	–	–
	−20	−34	−2	3.70*	0.0001							
Parahippocampal gyrus (27)	−18	−34	−6	3.58*	0.0002	679	18	−36	−10	4.12*	0.00002	679
Cerebellum_4_5	−6	−42	−12	3.53*	0.0002	679	10	−44	−10	4.23*	0.00001	
	−14	−36	−10	3.97*	0.00004		8	−48	−2	3.6*	0.0002	

*$P < 0.05$, family-wise error rate (FWER)–corrected (cluster level). Bold indicates regions stimulated in the rTMS experiments.

rather than 400 or 600 ms) between actions and their outcomes. Hence, a sizeable intentional binding effect can be observed when actions are voluntary, and the delay between actions and outcomes is a tight one. This is in line with previous studies showing that sense of agency decreases along with the increase in delay (*13*, *14*), providing a validation of our approach. Notably, about 200 ms is the latency that can be measured in real life between the time when we press a light switch and the time that a conventional light bulb takes to be fully on [see (*15*)], suggesting that the implicit sense of agency is normally tuned to time intervals that represent our daily life experience for a given action and its usual effects.

The correlation between the fMRI BOLD activity and the individually measured intentional binding effect showed that the magnitude of the intentional binding effect was mirrored by meaningful brain activity. The linear regression analysis identified what we call the brain "agency network," a set of brain regions showing a BOLD response that was greater the stronger the intentional binding effect. The areas involved were, among others, a frontoparietal premotor network including the left pre-SMA and a region spanning over the dorsal right inferior parietal lobule and the postcentral gyrus. These correlations were significant only for the trials with a 200-ms action-outcome time window, while no significant correlation could be observed for other time windows (400 and 600 ms).

These results provide the first empirical evidence of the neural underpinning of the intentional binding phenomenon in a visual ecological scenario. Precisely, the involvement of premotor-parietal cortices, among a wider brain network, is what would be expected from the constructive hypothesis of the sense of agency, whereby the feeling of being actors of our actions and their physical consequences is part of the motor planning process (*16*, *17*).

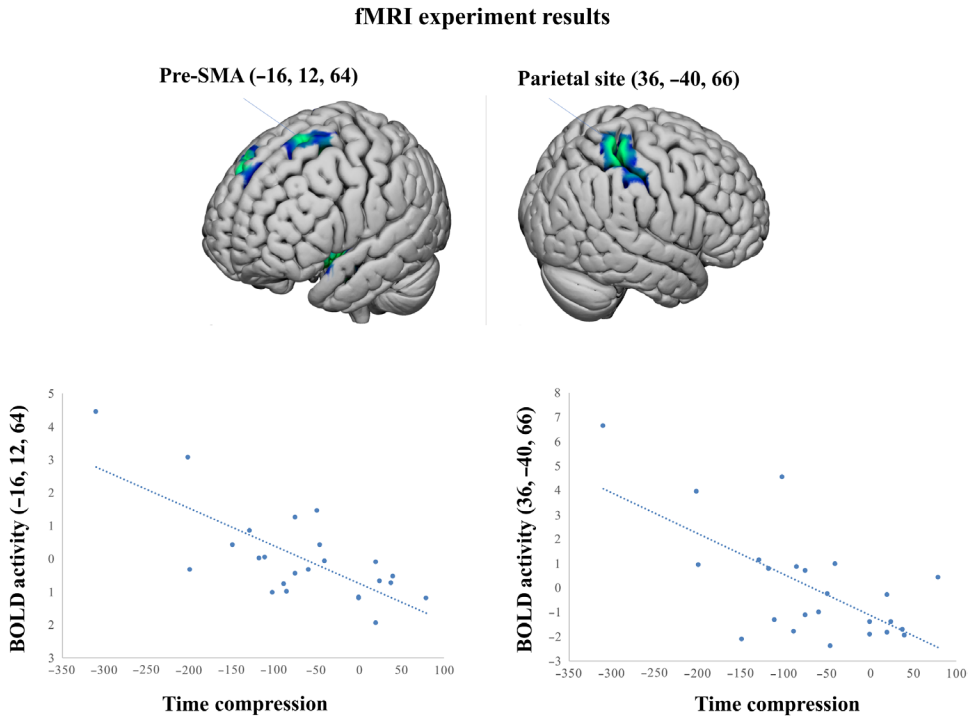

Fig. 2. fMRI results showing a significant association between the magnitude of the intentional binding effect and pre-SMA/parietal activity. Linear regression analysis between the BOLD activity recorded in the left pre-SMA and in the right parietal site and the differential time compression values (active trials − passive trials) when the action-outcome delay was 200 ms, and the intentional binding was observed (see also Table 1).

However, fMRI does not permit making causal inferences on the relationship between local brain activity and psychological effects. Moreover, it does not have the needed temporal resolution to make inferences on the relationship between local activities and their possible different role for the genesis of the agency experience under the constructive hypothesis (i.e., predictive and comparative processes).

To address these issues and explore whether the premotor-parietal responses identified by our fMRI analyses play a causal role in the sense of agency, we tested 40 additional healthy participants by means of high-frequency (10 Hz) rTMS. rTMS was delivered over the left pre-SMA and the right parietal sites identified with fMRI in two distinct time windows: when motor plans are being generated and when their consequences are being appreciated. We predicted that, according to the constructive hypothesis, the pre-SMA should be involved in the motor planning phase of the sense of agency, during the so-called predictive process of the sense of agency; we also predicted that the parietal cortex should contribute to the sense of agency when the motor plans and their effects are compared, during the so-called comparative process of the sense of agency.

These hypotheses stemmed from two lines of evidence. On the one hand, the pre-SMA is a key structure for the preparation and initiation of a voluntary action (*18*–*20*); hence, it should contribute to a premotoric generation of predictions of the consequences of actions. On the other hand, parietal structures are involved in the high-order processing of sensory and multisensory inputs and in the representation of the external space and the body (*21*); hence, they might be responsible for the processing of external feedbacks and for their comparison with the premotor signals.

RESULTS—rTMS EXPERIMENTS

rTMS experiment 1: rTMS delivered at the motor planning phase

These results are shown in Fig. 3 and described in detail below. Briefly, in all the experimental sessions at 200 ms of delay between the movement and the lighting of the light bulb, the perceived TC was stronger in the active trials compared with the passive ones. However, when the rTMS was applied over the pre-SMA at the time of action planning (at the appearance of the instruction cue), we also observed an intentional binding effect at 400 ms of delay.

In detail, we found a significant Condition*Delay interaction ($F_{2,4662}$ = 39.02, P < 0.0001), a significant Condition*Session interaction ($F_{3,4662}$ = 2.91, P = 0.03) and a significant Session*Delay interaction ($F_{6,4662}$ = 5.29, P < 0.0001). The triple Session*Condition*Delay interaction was significant as well ($F_{6,4662}$ = 2.18, P = 0.04). The main effects of the factors Session, Condition, and Delay were not significant (Session: $F_{3,57}$ = 0.24, P = 0.87; Condition: $F_{1,4662}$ = 0.01, P = 0.91; Delay: $F_{2,38}$ = 2.45, P = 0.10).

To explore the three-levels interaction, we ran planned post hoc comparisons that showed how, in all the experimental sessions, the perceived TC was stronger in the active trials compared with the passive ones when there was a temporal contingency of 200 ms between the movement and the lighting of the light bulb (post hoc test active condition versus passive condition at 200 ms of delay between the movement and its consequence for averaged baseline session: t_{4662} = 3.16, Bonferroni-corrected P = 0.004, Cohen's d = 1.48; for rTMS pre-SMA site session: t_{4662} = 3.33, Bonferroni-corrected P = 0.002, Cohen's d = 0.94; for rTMS parietal site session: t_{4662} = 2.42, Bonferroni-corrected P = 0.03, Cohen's d = 0.82; and for rTMS occipital control site session: t_{4662} = 2.74, Bonferroni-corrected P = 0.012, Cohen's d = 0.72).

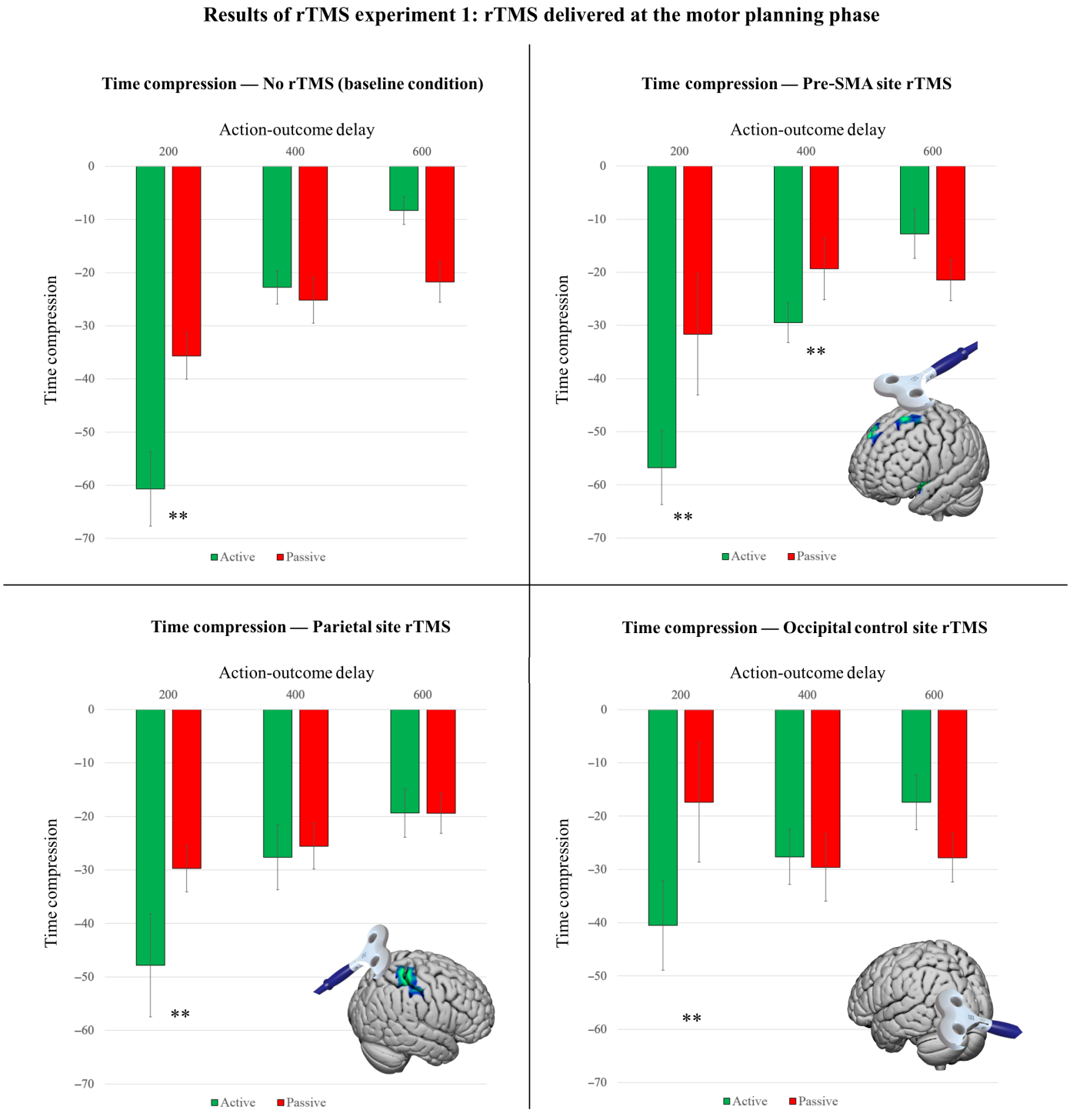

Fig. 3. Results of rTMS experiment 1, in which rTMS was applied during the action-planning phase. rTMS applied during the action planning. (**Top left**) Time compression values recorded before rTMS for active and passive trials: The intentional binding was present only when the action-outcome delay was 200 ms. (**Top right**) TC values recorded during rTMS over the pre-SMA: The intentional binding was present also when the action-outcome delay was 400 ms. (**Bottom left**) TC values recorded during rTMS over the parietal site: The intentional binding was present only when the action-outcome delay was 200 ms. (**Bottom right**) TC values recorded during rTMS over the occipital control site: The intentional binding was present only when the action-outcome delay was 200 ms. (Error bars = SE; asterisks indicate significant effects; $P < 0.05$, Bonferroni-corrected); TC is visualized as the percentage of the time delay of the outcome.

As anticipated, the critical finding was that rTMS over pre-SMA affects TC even when the action-outcome interval was 400 ms (post hoc test active condition versus passive condition at 400 ms of delay between the movement and its consequence for averaged baseline session: $t_{4662} = -1.05$, Bonferroni-corrected $P = 0.58$, Cohen's $d = 0.43$; for rTMS pre-SMA site session: $t_{4662} = 2.29$, Bonferroni-corrected $P = 0.04$, Cohen's d = 0.64; for rTMS parietal site session: $t_{4662} = 0.59$, Bonferroni-corrected $P > 0.9$, Cohen's $d = 0.16$; and for rTMS occipital control site session: $t_{4662} = -0.65$, Bonferroni-corrected $P > 0.9$, Cohen's $d = 0.17$). See Fig. 3.

rTMS experiment 2: rTMS delivered at the appearance of the lit light bulb

These results are shown in fig. S2 and described in detail below. Briefly, for all the experimental sessions, the perceived TC was stronger in the active trials compared with the passive ones, only for a delay of 200 ms between the movement and the lighting of the light bulb. Different from what we observed for rTMS delivered during the motor planning phase, there was no modulation of the aforementioned behavioral pattern when rTMS was delivered during a comparison phase.

In detail, we found a significant effect of the factor Condition ($F_{1,4662} = 5.63$, $P = 0.018$), a significant Condition*Delay interaction ($F_{2,4662} = 26.47$, $P < 0.0001$), a significant Condition*Session interaction ($F_{3,4662} = 2.66$, $P = 0.046$), and a significant Session*Delay interaction ($F_{6,4662} = 6.57$, $P < 0.0001$). The main effects of the factors Session and Delay were not significant (Session: $F_{3,57} = 0.06$, $P = 0.98$; Delay: $F_{2,38} = 1.04$, $P = 0.36$); the triple interaction Session*Condition*Delay was not significant as well ($F_{6,4662} = 1.16$, $P = 0.33$). To further explore the significant interactions of the model, we ran planned post hoc comparisons that showed how, in all the experimental sessions, the perceived TC was stronger in the active trials compared with the passive ones only when there was a temporal contingency of 200 ms between the movement and the lighting of the light bulb (post hoc test active condition versus passive condition at 200 ms of delay between the movement and its consequence for averaged baseline session: $t_{4662} = 2.66$, Bonferroni-corrected $P = 0.016$, Cohen's $d = 1.47$; for rTMS pre-SMA site session: $t_{4662} = 3.63$, Bonferroni-corrected $P = 0.0006$, Cohen's $d = 1.04$; for rTMS parietal site session: $t_{4662} = 3.29$, Bonferroni-corrected $P = 0.002$, Cohen's $d = 0.83$; and for rTMS occipital control site session: $t_{4662} = 3.29$, Bonferroni-corrected $P = 0.002$, Cohen's $d = 0.91$). See fig. S2.

Interim discussion: rTMS experiments

Online rTMS modulated the sense of agency, expanding the action-outcome time window of the intentional binding effect. However, this only occurred when the stimulation was applied over the pre-SMA, specifically during the motor planning phase. Under this condition, there was a sizeable intentional binding effect not only for the stringent 200-ms temporal contiguity between action and outcome but also when the outcomes followed the actions by 400 ms. Conversely, the rTMS applied during the appearance of the outcome (i.e., the lit light bulb) did not modulate the ongoing sense of agency, in any of the stimulated regions, including a control site in the occipital lobe.

DISCUSSION

Our findings show that the activity of brain regions involved in action at the stage of its planning is important for the manifestation of an implicit sense of agency, making the constructive hypothesis on the sense of agency more likely. By the same token, our findings allow us to reject a strictly post hoc reconstructive hypothesis, solely based on logical inferences about the circumstances that have led to a physical event to occur. We reach this conclusion because the magnitude of the intentional binding phenomenon strongly correlated, although not exclusively, with a frontoparietal and cerebellar network typically associated with motor planning and monitoring (*16*, *17*). Notably, not only the pre-SMA activity was strongly correlated with the magnitude of the intentional binding phenomenon but also interfering with its activity during the action planning phase with rTMS caused an extension of the temporal window of tolerance for the expected outcome of actions. This led our participants to implicitly consider as self-generated a delayed consequence that is normally treated as a non–self-induced one. Of relevance, the pre-SMA stimulation was effective only if delivered when motor plans were being formed and not if applied when physical consequences in the outside world were observed. This supports the view that the brain activity associated with generation of the motor plan is crucial for giving rise to the sense of agency. At a mechanistic level, we imply that rTMS over the pre-SMA made predictions about the time interval from action to their effects less precise. Effects at 600 ms are probably too remote to make the intentional binding effect expand in time that far. There is independent evidence of a general link of the pre-SMA and SMA with appreciation of time. In a recent 7-T fMRI study, it has been shown that the anterior portion of the SMA is a high-level station for temporal processing of small temporal intervals (including our crucial time window of 200 ms) (*22*). Moreover, the SMA is a distinctive node of an intentional action network operating when participants freely decide on the timing of their actions (*19*).

Our second finding is that neither the pre-SMA nor the parietal cortex can be considered, alone, the key—i.e., a sufficient and necessary—neural substrate for the comparative process of the sense of agency. rTMS did not affect the sense of agency during the comparative phase, since it did not produce any change, when compared with the baseline conditions, for any stimulation sites during this particular time window. This does not exclude the possibility that a simultaneous modulation of both the pre-SMA and the parietal site might cause an interference of the sense of agency when rTMS is delivered at the appearance of the sensory consequences of action. However, testing this hypothesis would require a TMS experiment with multiple synchronized coils.

Of course, our conceptualization of the sense of agency and the neurophysiological correlates described above does not exclude the possibility of an important contribution of bodily centered signals (motor commands while there are reaching target spinal cord structures and peripheral somatosensory signals) that inevitably arise when acting and differentiate active movements from passive ones. It is likely that some of these signals contribute to the making of a sense of agency. To assess their relative importance for the neurophysiological patterns described here, we will need further experiments, perhaps targeting patients with discrete lesions (e.g., in the dorsal fasciculi of the spinal cord to monitor the role of somatosensory feedbacks) that may permit us to infer the contribution of specific motor and somatosensory systems to the sense of agency.

While the present findings yield support to a constructive view of the implicit sense of agency, it is important to remember that a sense of agency can be experienced and tested also explicitly and within different and more diluted time windows. It is likely that

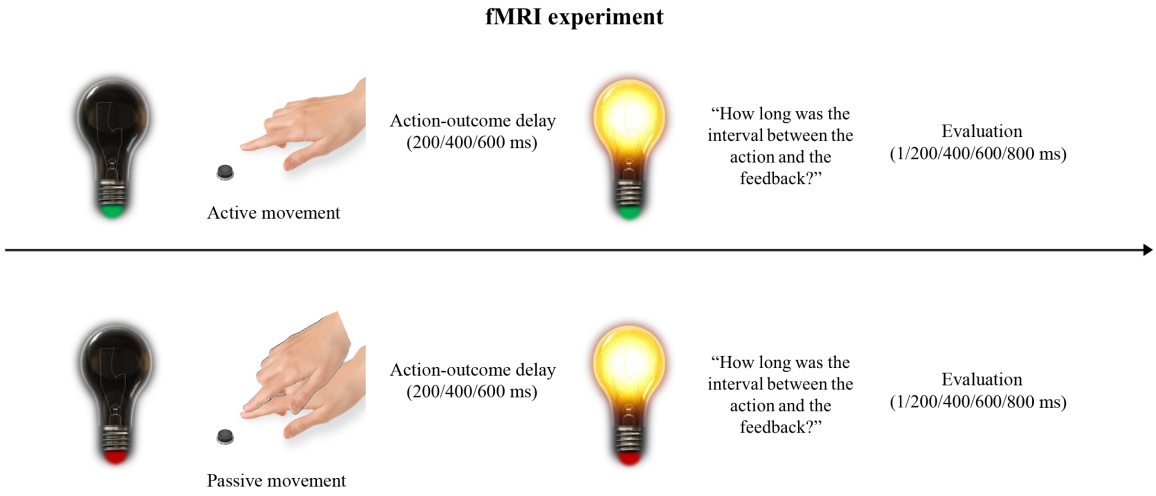

Fig. 4. Graphical illustration of an experimental trial of the fMRI experiment for active and passive conditions. During active trials, the picture of a turned-off light bulb with its base colored in green was shown. Participants were instructed to turn the light bulb on by pressing a button with their right index finger. After the button press, the light bulb went on with a variable delay of 200, 400, or 600 ms. Participants were then asked to rate the perceived temporal interval between their button press and the lighting of the light bulb.

the processes that lead us to take explicit responsibility of physical events that have occurred in the outside world may depend on additional processes. This may be particularly true when the actual motor plans that have generated an action are no longer available in terms of ongoing neural representations. In this case, we might need to reconstruct by memory or logic our role as causal actors of an event. The dissociation between implicit and explicit processing is constantly seen for psychological functions, like in measures of biases (*23*), and therefore the sense of agency represents no exception. Still, it is important to identify specific processes for different levels of the sense of agency: This may guide the interpretation of disorders in which a specific deficit of the sense of agency may play a role, as in the delusion of control in schizophrenia or in grandiose delusions. The former may depend on a malfunction of the implicit sense of agency that we described here at the neurophysiological level (*24*).

MATERIALS AND METHODS—fMRI EXPERIMENT

Participants

Twenty-five adult participants (mean age, 25.7 ± 3.8 years; mean education level, 15.6 ± 2.5 years; male/female ratio, 12:13) with no history of neurological or psychiatric illness participated in this study. One participant was removed from the fMRI analysis due to strong movement artifacts. The remaining 24 participants (mean age, 25.4 ± 3.5 years; mean education level, 15.5 ± 2.5 years; male/female ratio, 11:13) were all right-handed, as assessed by the Edinburgh handedness inventory (*25*). The study protocol was approved by the local Ethics Committee (IRCCS San Raffaele of Milan; Prot. SOA, 149/INT/2016), and written informed consent was obtained from all participants according to the Helsinki Declaration (1964). All participants took part in the study after the nature of the procedure had been fully explained. To exclude participants with cognitive deficits, a brief neuropsychological screening that included the Mini Mental State Examination (MMSE) (*26*), the Raven's Colored Progressive Matrices (Raven's Matrices) (*27*)), and the Frontal Assessment Battery (FAB) (*28*) was administered to each participant. None of the participants had pathological scores on any of the aforementioned tests. Moreover, participants were submitted to a training session composed of 10 trials when they were given feedback on their accuracy trial by trial.

Experimental task

fMRI scans were performed during the execution of a temporal judgment task (see Fig. 4). There were active and passive trials. During active trials, the picture of a turned-off light bulb with its base colored in green was shown. Participants were instructed to turn the light bulb on by pressing a button with their right index finger. After the button press, the light bulb went on with a variable delay of 200, 400, or 600 ms. Participants were then asked to rate the perceived temporal interval between their button press and the lighting of the light bulb. The judgment was reported by means of a visual analog scale to which they responded using a five-key response keypad placed under their left hand. They used their fingers starting from the pinkie, to the ring finger, and so on, to select one of five possible response options: 1, 200, 400, 600, and 800 ms. The lowest and the highest response options were included to make it possible for the participants to both underestimate and overestimate each temporal interval presented. In the passive trials, the base of the light bulb was colored in red. Under this condition, participants were instructed to stay still, while an experimenter pressed their right index finger to produce a passive movement. The passive movement turned the light bulb on. Participants were then asked to judge the action-outcome delay in the same way as for active trials.

We administered 60 trials, equally distributed between active and passive trials, with 10 trials for each of the three action-outcome delays. The interstimulus interval randomly varied between 1500 and 2500 ms.

Statistical analyses of the behavioral data

The behavioral data collected during the fMRI experiment were analyzed using the software SAS (Statistical Analysis System; version 9.4). In line with the description of the intentional binding phenomenon (*6*), the TC, namely, the difference between the estimated and the real duration of the action-outcome delay, was taken as an indirect

measure of the sense of agency: The greater the compression (i.e., more negative values), the higher the sense of agency.

This TC measure represented the dependent variable of the model, while the factors Condition (active/passive) and Delay (200/400/600 ms) were the independent variables. We tested this statistical model using linear mixed models, with random intercept. Significant interactions were explored by means of planned Bonferroni-corrected post hoc comparisons. Effect sizes were calculated by means of Cohen's *d* starting from estimated marginal means.

Before applying linear mixed models, we inspected our data distribution using the Cullen and Frey graph (*29*). This graph is also called the skewness-kurtosis graph, and it provides the best fit for an unknown distribution according to skewness level and kurtosis. The present data had a distribution similar to the normal distribution.

Last, we calculated the misclassification rates for each condition and each delay. To investigate whether these misclassifications were significantly more associated with active or passive trials across the different time delays, we calculated a chi-squared test on misclassification data. None of these tests was significant ($P = 0.32$; see table S3).

fMRI data acquisition and analysis

MRI scans were performed using a 1.5-T Siemens Avanto scanner, equipped with gradient-echo echo-planar imaging [flip angle, 90°; Echo Time (TE), 40 ms; Repetition Time (TR), 2000 ms; field of view (FOV), 250 mm; matrix, 64 by 64]. The overall number of the fMRI volumes collected varied from 269 to 292 volumes depending on the individual speed in generating the responses. The first 15 volumes of each sequence (corresponding to presentation of the instructions) were discarded from the analyses.

Preprocessing

After the image reconstruction, raw data visualization and conversion from DICOM to NIFTI format were performed with MRIcron (www.nitrc.org/projects/mricron) software. All subsequent data analyses were performed in MATLAB R2014a (MathWorks, Natick, MA, USA) using the software Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK). First, fMRI scans were realigned to the first image of the run to account for any movement during the experiment. Then, the structural T1 image was coregistered to the functional mean image to allow a more precise normalization; the unified segmentation and nonlinear warping approach of SPM12 was applied to normalize structural and functional images to the MNI (Montreal Neurological Institute) template to permit group analyses of the data (*30*, *31*); at this stage, the data matrix was interpolated to produce 2 mm by 2 mm by 2 mm voxels. The stereotactically normalized scans were smoothed using a Gaussian filter of 10 mm by 10 mm by 10 mm to improve the signal-to-noise ratio, making the data suited for cluster-level correction for multiple comparisons (*32*).

First-level fixed-effect analyses

The BOLD signal associated with each experimental condition was analyzed by a convolution with a canonical hemodynamic response function (*33*). Global differences in the fMRI signal were removed from all voxels with proportional scaling. High-pass filtering (128 s) was used to remove artifactual contributions to the fMRI signal, such as physiological noise from cardiac or respiratory cycles. A fixed-effect analysis was performed for each participant to characterize the BOLD response associated with the task before entering the relevant individual contrast images into a random-effect analysis.

At the first level, we characterized the brain activity between the appearance of the turned-off light bulb and the lighting of the light bulb. We included one regressor for each condition (active and passive trials) and each action-outcome delay (200/400/600 ms), for a total of six regressors. Moreover, brain activity occurring between the appearance of the evaluation scale and the judgment response was modeled separately for each delay and condition and added to the statistical model. Last, the parameters obtained from the realignment procedure were added as noninterest regressors to partial out the impact of motion artifacts on the estimates of the β parameters. For each participant and for each action-outcome delay, we generated a contrast image of the comparison active condition > passive condition (three contrast images per participant overall).

Second-level random-effect analysis

Each contrast image (active condition > passive condition for the three delays) was entered in different second-level analyses, conforming to a random-effect approach (*34*) to testing the following effects:

1) Main effect of the comparison active condition > passive conditions. This one-way analysis of variance (ANOVA) analysis identified the brain regions of greater BOLD response for the active conditions > passive conditions independently from the different action-outcome delays: We expected to observe the canonical motor network typical of voluntary finger movements (*35*).

2) Interaction effect between condition (active/passive) and the specific time delays (200/400/600 ms).

3) Linear regression analyses of the delay-specific contrast images with the delay-specific TC measure. These analyses allowed us to test the hypothesis that the activity of some brain regions covaried with the TC measure of the sense of agency in specific time windows. Note that, because the contrast images used in this analysis contained the differential effect between active and passive trials, a differential TC measure between active and passive trials was used as a regressor here.

All the results reported survive a correction for multiple comparisons: We used the nested taxonomy strategy recommended by Friston *et al.* (*36*), including regional effects meeting either a cluster-wise or voxel-wise family-wise error rate (FWER) correction. The voxel-wise threshold applied to the statistical maps before the cluster-wise correction was $P < 0.001$ uncorrected, as recommended by Flandin and Friston (*32*). For clusters significant at the $P < 0.05$ FWER-corrected level, we also report the other peaks at $P < 0.001$.

MATERIALS AND METHODS—rTMS EXPERIMENTS

Participants

For each rTMS experiment, we included 20 independent participants who, at the baseline task, showed a greater TC in the active condition than the passive one for trials with 200-ms delay between action and outcome. These were selected from an initial larger sample of 60 participants; participants who did not show the intentional binding phenomenon during the baseline session were not engaged in the other experimental sessions. The logic behind this screening was as follows: An external intervention to modulate a behavioral effect can only be implemented when the effect is present (*37*).

In each experiment, 20 participants were tested in a within-participants design (experiment 1: mean age, 22.2 ± 2.6 years; mean education level, 14 ± 2.1 years; male/female ratio, 5:15; experiment 2: mean age, 24 ± 4.9 years; mean education level, 14.7 ± 2.3 years; male/female ratio, 3:17). All participants were right-handed accordingly to the Edinburgh inventory (*21*), and none of them had

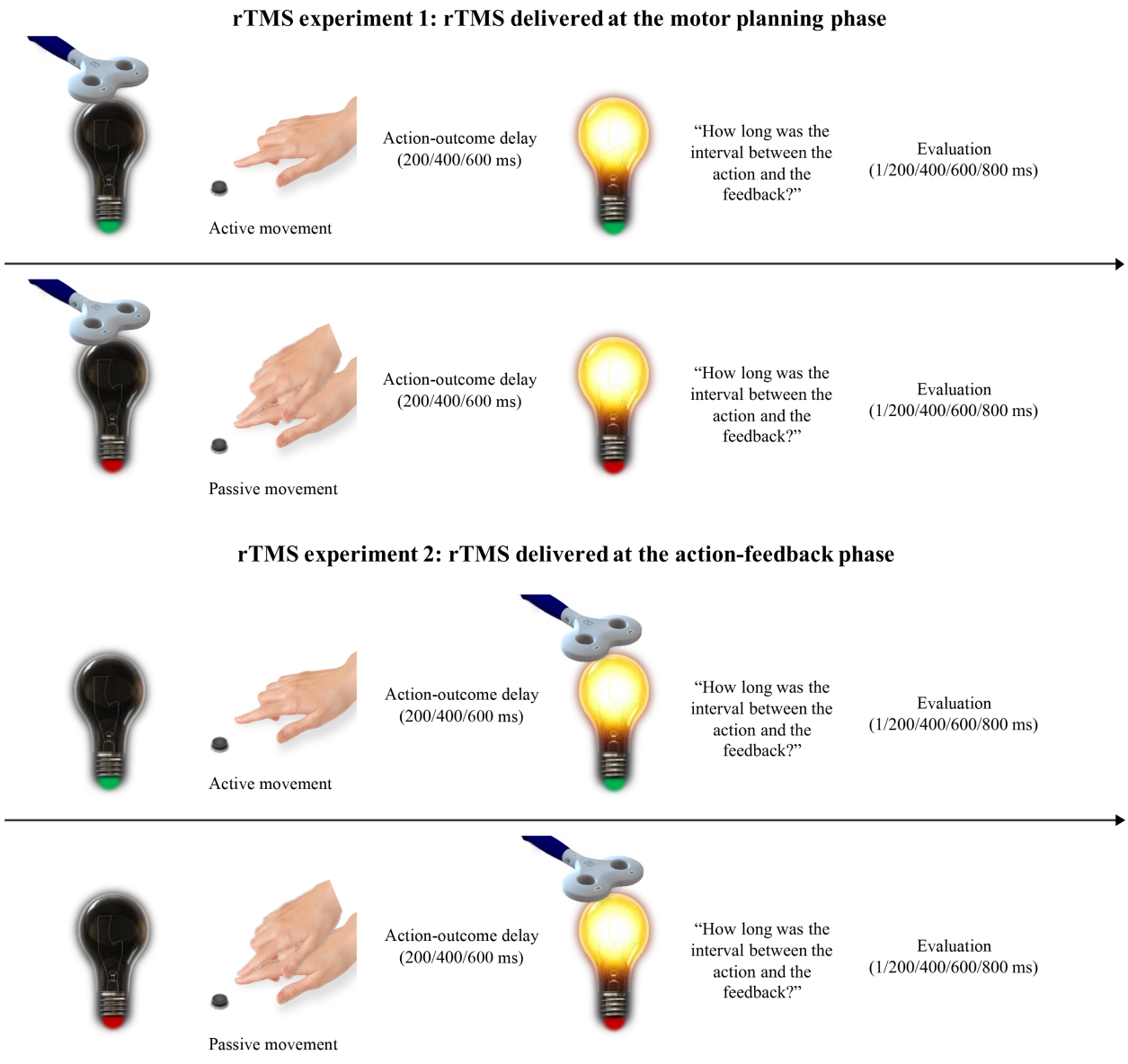

Fig. 5. Graphical illustration of an experimental trial of each rTMS experiment for active and passive conditions. In experiment 1, rTMS was applied during the action planning phase (at the appearance of a turned-off light bulb indicating an active or passive trial, depending on the green/red color of the base). In experiment 2, rTMS was applied at the appearance of the physical consequence of the button press (at the lighting of the light bulb). In the figure, the rTMS coils are placed according to the time points of rTMS delivery.

contraindications to TMS according to TMS safety guidelines (*33*, *34*). Before taking part in the study, they gave written informed consent. The protocol was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the local Ethics Committee (University of Milano-Bicocca; protocol number: 366).

Sample size calculation

To motivate the sample size of the TMS experiments, we used the data published by Moore *et al.* (*37*). In this work, the authors explored TMS-induced modulations of the sense of agency using the intentional binding phenomenon as dependent measure. The authors reported a greater intentional binding effect after the stimulation of the pre-SMA (mean post-TMS, 118 ± 22 ms) with respect to the stimulation of a control site (somatosensory leg area: mean post-TMS, 153 ± 24 ms). The effect size associated with this result was 1.07. Accordingly, a sample of 17 participants is needed to reliably detect, with a power greater than 0.9, an effect size of $\delta \geq 1.07$, assuming a two-sided criterion for detection that allows for a maximum type I error rate of $\alpha = 0.01$. On the basis of this analysis, we decided to include 20 participants for each experiment.

Experimental task

Participants performed the same temporal judgment task used in the fMRI experiment.

TMS protocol

TMS pulses were delivered by means of an Eximia TMS stimulator (Nexstim, Helsinki, Finland) using a biphasic figure-of-eight coil

(diameter, 70 mm). During the experimental task, a rapid train of five TMS pulses was delivered with a frequency of 10 Hz. In the first experiment (experiment 1), rTMS was delivered during the action planning phase, when the turned-off light bulb appeared. In the second experiment (experiment 2), rTMS was applied during the action feedback phase, at the lighting of the light bulb. See Fig. 5 for an illustration of the experimental structure.

rTMS was delivered over the pre-SMA and parietal site identified by the fMRI experiment. In principle, in a motoric perspective, it would have been interesting to deliver rTMS also on the cerebellar activation foci; however, these were too deep to realistically hope to achieve a selective modulation. The same considerations apply to other foci, such as the hippocampus and the insulae.

The coordinates of the stimulations, taken from the activation peaks found in the fMRI experiment, were *x*: 36, *y*: −40, *z*: 66 for the parietal site and *x*: −16, *y*: 12, *z*: 64 for the pre-SMA. Moreover, we identified an occipital control site (*x*: −14, *y*: −100, *z*: 7) taken from the previous fMRI literature (*38*).

In a preliminary session, we collected for each participant a standard volumetric T1 MRI (flip angle, 35°; TE, 5 ms; TR, 21 ms; FOV, 256 mm by 192 mm; matrix, 256 by 256; Inversion Time, 768 ms; for a total of 160 axial slices with 1-mm cubic voxels). To optimize the stimulation sites with reference to the fMRI data, the MNI coordinates of target areas were marked on the individual MRI using a stereotactic procedure: the native (T1-weighted) image normalized to the MNI space using SPM12. After the normalization, the images underwent a signal subtraction process in the target loci using the aforementioned coordinates with a 2-mm-radius sphere; the processed images were then back-transformed into the native individual space using the backward deformation parameters estimated during the normalization procedure. The coordinates of interest were then localized on the individual MRI using the stimulator's integrated navigated brain stimulation (NBS) system (Nexstim, Helsinki, Finland), which uses infrared-based frameless stereotaxy to map the participant's head and the position of the coil, within the reference space of the individual MRI. Furthermore, we used this system to continuously monitor the position and orientation of the coil during the experiments, assuring precision and reproducibility of the stimulation within and across participants.

Moreover, using a locally best-fitting spherical mode, which accounts for the head and brain shape of each participant and takes into consideration the distance from scalp and coil position, using the NBS system, we estimated on line the intensity (volts per meter) of the intracranial electric field induced by TMS at the stimulation hotspot. As the value for the rTMS intensity (corresponding to the percentage of the maximum stimulator output), we used the one that induces an electric field of at least 85 ≃ 90 V/m in the cortical target area (see table S4). See fig. S3 for a graphical illustration of each participant's estimate of the intracranial electric field induced by TMS at the stimulation hotspot.

TMS procedure

The experimental procedure was the same in both experiments 1 and 2.

The three stimulation sessions (pre-SMA, parietal site, and occipital control site) were administered on three different days. The order of the stimulation sessions was counterbalanced between participants and at least 24 hours passed between one session and the other.

Participants sat comfortably in a dark room, with the personal computer screen and the keyboard in front of them. Only in the first session, after given the informed consent, participants underwent the Edinburgh inventory (*25*), the TMS safety checklist questionnaire (*39*), the neuropsychological battery [MMSE (*26*), Raven's Matrices (*27*), and FAB (*28*)], and a training session composed by 10 trials, when participants were given a feedback on their accuracy trial by trial. Then, at the beginning of each session, participants performed the experimental task without rTMS (baseline condition). During the experimental task, an experimenter sat next to them thus to press their right hand index finger when the trial depicted was a passive one.

At the end of the baseline session, the resting motor threshold was determined, and the target area(s) were found using the described neuronavigation procedures. Then, participants performed the experimental task a second time, with rTMS delivered according to the stimulation site and timing (left pre-SMA, right parietal site, or left occipital control site). Crucially, the timing of the rTMS stimulations was digitally synchronized and triggered immediately after the appearance of the instruction cue (motor planning phase for the rTMS experiment 1) or when the lit light bulb appeared (physical consequences observation phase of the rTMS experiment 2).

Statistical analyses

We analyzed the rTMS behavioral performance using the SAS (v. 9.4) software. We used the same approach as for the behavioral data collected during the fMRI experiment: TC was taken as an indirect measure of the sense of agency (the greater the compression, the higher the implicit sense of agency); this was the dependent variable of the model, while the factors Session (averaged baseline/rTMS pre-SMA site/rTMS parietal site/rTMS occipital control site), Condition (active/passive), and Delay (200/400/600 ms) were the independent variables. The analyses were performed using linear mixed models with random intercept. Significant interactions were explored by means of planned Bonferroni-corrected post hoc comparisons. Effect sizes were calculated by means of Cohen's *d* starting from estimated marginal means.

Before applying linear mixed models, we inspected our data distribution using Cullen and Frey graphs (*29*). These graphs are also called the skewness-kurtosis graphs; they provide the best fit for an unknown distribution according to the skewness and kurtosis of the data distribution. The present data had a distribution best accounted by a normal distribution.

Moreover, we calculated the misclassification rates for each condition and each delay. To investigate whether these misclassifications were significantly more associated with active or passive trials across the different time delays, we calculated a chi-squared test on misclassification data. None of these tests was significant (smallest $P = 0.24$; see table S3).

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/6/27/eaay8301/DC1

View/request a protocol for this paper from *Bio-protocol*.

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