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Inhibition of left anterior intraparietal sulcus shows that mutual adjustment marks dyadic joint-actions in humans

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Abstract

Creating real-life dynamic contexts to study interactive behaviors is a fundamental challenge for the social neuroscience of interpersonal relations. Real synchronic interpersonal motor interactions involve online, inter-individual mutual adaptation (the ability to adapt one's movements to those of another in order to achieve a shared goal). In order to study the contribution of the left anterior Intra Parietal Sulcus (aIPS) (i.e. a region supporting motor functions) to mutual adaptation, here, we combined a behavioral grasping task where pairs of participants synchronized their actions when performing mutually adaptive imitative and complementary movements, with the inhibition of activity of aIPS via non-invasive brain stimulation. This approach allowed us to investigate whether aIPS supports online complementary and imitative interactions. Behavioral results showed that inhibition of aIPS selectively impairs pair performance during complementary compared to imitative interactions. Notably, this effect depended on pairs' mutual adaptation skills and was higher for pairs composed of participants who were less capable of adapting to each other. Thus, we provide the first causative evidence for a role of the left aIPS in supporting mutually adaptive interactions and show that the inhibition of the neural resources of one individual of a pair is compensated at the dyadic level.

Key words: joint-actions; brain stimulation; anterior intra-parietal sulcus; complementary inter-actions; closed-loop interactions; continuous theta burst stimulation

Introduction

Social neuroscience research is struggling to go beyond the study of cognition and brain activity in individuals who merely react to social contexts (i.e. 'open-loop' conditions). These isolated scenarios limit our understanding of how the bidirectional and continuous exchange of information between individuals in 'closed-loop' conditions affects their mutual coordination (Hasson *et al.*, 2012). Endorsing the idea that interacting individuals create a new, integrated, entity, 'second person' approaches (Schilbach *et al.*, 2013) propose that interpersonal encounters must be considered constitutive of human beings and their cognitive functions (De Jaegher, 2009). Indeed, when we interact with another person to achieve a shared goal (i.e. in joint actions, Sebanz *et al.*, 2006) our brains and bodies become a coupled unit through the continuous mutual adaptation of our

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own actions to those of our partner(s) (Konvalinka and Roepstorff, 2012), and we tend to align our cognitive representation of a given task to that of the partner (Konvalinka *et al.*, 2010; Gallotti *et al.*, 2017). This dynamical interactive process leads to interpersonal coupling at behavioral (Richardson *et al.*, 2007), physiological (Müller and Lindenberger, 2011: Mitkidis *et al.*, 2015) and neural levels (Konvalinka and Roepstorff, 2012; Babiloni and Astolfi, 2014; Novembre *et al.*, 2017).

Realistic joint actions often require partners to perform complementary movements which entails shifting from imitating the other (mirroring) to coupling our behavior and cognitive representations to those of the partner (Hasson and Frith, 2016). Neuroimaging studies indicate that neural activity within fronto-parietal networks is associated with both imitative and complementary motor interactions (Newman-Norlund *et al.*, 2007) possibly based on their role in sensory-motor transformations (Freund, 2001). Other regions within the fronto-parietal network have been targeted by studies using transcranial magnetic stimulation (TMS) to investigate their role during interpersonal coordination. These studies showed that interfering with the activity of the primary motor cortex (Novembre *et al.*, 2014) and dorsal premotor cortex (Hadley *et al.*, 2015) impairs coordination abilities in musical synchronous and turn-taking interactions, respectively.

However, complementary interactions seem to require additional neural resources, perhaps because of the need to integrate one's own actions with the different ones performed by a partner (Kokal *et al.*, 2009). Building on evidence from interactive human–human (Sacheli *et al.*, 2012, 2013) and human–avatar experimental set-ups (Sacheli *et al.*, 2015a), we have recently shown (Sacheli *et al.*, 2015b) that the inhibition of the left anterior intraparietal sulcus (aIPS), a region known to be active in coding the goals of both self-executed (Tunik *et al.*, 2005) and observed actions (Fogassi *et al.*, 2005; Hamilton and Grafton, 2006), impaired the performance of complementary but not imitative interactions during 'open-loop' (i.e. non mutually-adaptive) interactions.

However, while the role of motor regions in facilitating interpersonal synchronization has been investigated (Novembre *et al.*, 2017), to the best of our knowledge, information about the causal contribution of left aIPS (and the associated fronto-parietal network) to the ability to perform motor interactions in 'closed-loop' scenarios is currently lacking thus limiting our understanding of the role of the parietal cortex in controlling online interpersonal, complementary and imitative, interactions. In this study, we used non-invasive brain stimulation (continuous theta burst stimulation—cTBS) to inhibit the left aIPS activity in one member of a human dyad to investigate whether this area plays a causal role in supporting real-time complementary and imitative interactions. Pairs of participants performed a realistic joint-grasping task in which they were asked to perform reach-to-grasp movements implying either precision or power grips (see Materials and methods) (Figure 1). Participants were asked to mutually synchronize their movements and were required to reciprocally adapt online. Either opposite (complementary: one member of the dyad performing a precision grip and the other a power grip or vice versa) or same (imitative) synchronous actions were performed. Before performing the joint-grasping task, one member of each pair received real off-line cTBS of left aIPS (target site) or vertex (control site), while the other participant received sham stimulations of the same site. Grasping Asynchrony (see Materials and methods) was considered as the dependent variable indexing the success of interpersonal coordination. Behavioral results show that (1) our task was able to index pairs' ability to mutually adapt and compensate for individuals' aIPS inhibition; (2) inhibition of left aIPS selectively impairs synchrony performance during complementary compared to imitative interactions when the baseline ability of the pair members to adapt to each other is taken into account; (3) the less the two participants were able to adapt their movements' duration to each other at baseline, the more the pair's performance was impaired by the left aIPS stimulation. Thus, our results provide the first evidence for a causative role of left aIPS in human-human closed-loop interactions.

Materials and methods

Participants

Forty-four participants (22 same gender pairs) took part in the study (11 male and 11 female pairs, age 23.6 ± 2.44). Two pairs were not included in the analysis as they resulted to be outliers (see below, final sample of 20 pairs). All participants were right-handed as confirmed by the Standard Handedness Inventory (Briggs and Nebes, 1975), reported normal or corrected-to-normal vision and were naive as to the purpose of the experiment. Participants did not know each other before taking part in the task. The experimental protocol was approved by the ethics committee of the Fondazione Santa Lucia and was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki. None of the participants had neurological, psychiatric or other medical problems nor any contraindication for TMS (Rossini *et al.*, 2015). Participants gave their written informed consent to take part in the study, received a reimbursement for their participation and were debriefed as to the purpose of the study at the end of the experimental procedures. No discomfort or adverse effects to rTMS were reported in any of the participants.

Interactive task

Using an ecological but well-controlled joint-grasping task of our own development (Sacheli *et al.* 2012, 2013; Candidi *et al.*, 2015a; Curioni *et al.*, 2017), we asked pairs of participants to reach and grasp as synchronously as possible a bottle-shaped object placed in front of them. Participants were seated opposite each other and the set-up configuration was equivalent for both of them. Thus, each participant could reach and grasp his/her own bottle-shaped object. The go-signal was delivered to participants via headphones (a sound of 4 db and 787.5 Hz). Feedback signals concerning participants' performance were provided via two green/red LED lights placed on the table, one in front of each participant.

Given the shape of the objects, grasping the lower part required a whole-hand grasp (power grip), while grasping the upper part required a thumb-index finger precision grip. More specifically, participants did not know what part of the bottle to grasp and thus they needed to adapt to each other on a trial-by-trial basis, according to the instruction to perform opposite (complementary) or same (imitative) movements. We monitored the movements to ensure that partners did not implicitly agree on a consistent strategy throughout the task (e.g. one always grasping the upper part and the other the lower part). In the Imitative movements condition, both participants had to grasp the same portion of the object (both performing power or precision grips to the lower or upper part of the bottles, respectively). In the Complementary movements condition,

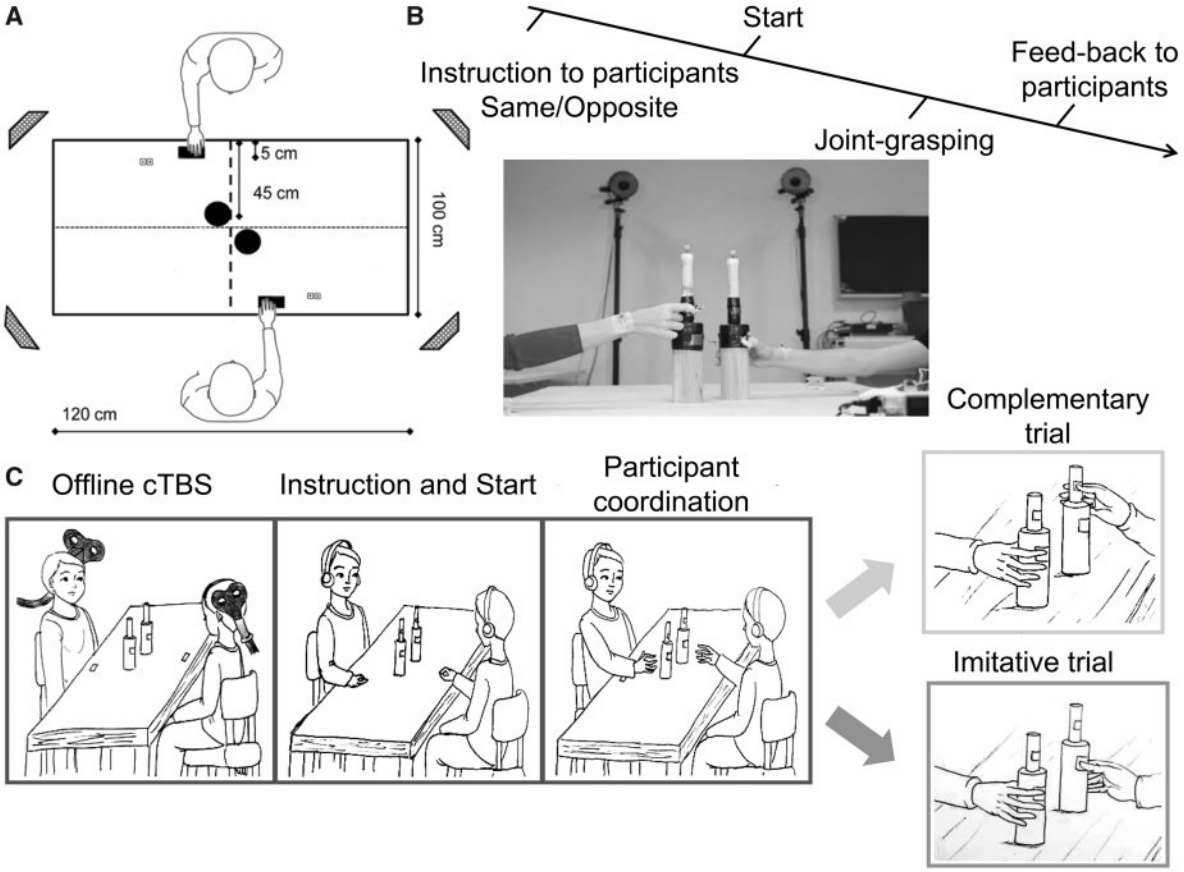

Fig. 1. Trial time-line and trials examples. (A) Image of the experimental set-up; (B) trial time-line; (C) experimental procedure.

conversely, participants had to perform opposite movements (one grasping the upper part via precision grip, the other grasping the lower part via power grip or vice versa) (Figure 1C).

In one of the experimental session, participants were instructed to grasp the object as synchronously as possible with their partner (Time-free session). In another experimental session (Time-cued session), the stimulated participant was still instructed to grasp the object as synchronously as possible with his/her partner, while the non-stimulated participant was instructed to synchronize his/her movements both with an auditory signal consisting in the last sound of sequence of three sounds delivered at constant time intervals and with her/his partner. Importantly, only the non-stimulated participant could hear the auditory sound. More specifically, the non-stimulated participant in the Time-cued block was told to synchronize with the third of three sounds he/she would hear, while also trying to be synchronous with his partner. We included the Time-cued block in order to have a condition in which the non-stimulated participant's ability to adjust to the stimulated one was temporally constrained. This procedure allowed us to test for whether such time limitation on mutual adjustment would highlight the effect of brain stimulation.

The trial timeline was as follows: participants heard the Imitative/Complementary auditory instruction and, upon receiving it, could release the start button and reach-to-grasp the bottle-shaped object. When participants started before hearing the instruction, the trial was classified as a false start and discarded from the analyses. At the end of each trial, participants received the feedback (by way of green or red LED lights) about their pair performance (win/loss trial) and, in the Time-cued condition, the non-stimulated participant received an auditory feedback about his/her synchronization with the sound (i.e. good/bad synchronization) (see also Figure 1B). A win trial meant that participants had followed their auditory instructions (i.e. correctly performed complementary/imitative movements) and achieved synchrony in grasping the object. The action was considered synchronous in the Time-free condition when the time-delay between the participants' index-thumb contact-times on their bottles fell within a given time-window that was narrowed or widened on a trial-by-trial basis according to a stair-case procedure. The same was true for the Time-cued condition, except for the fact that the time-delay determining the feedback was that between the non-stimulated participant contact-times and the moment in which the third sound was delivered to him. This procedure allowed us to tailor the time-window so as to tailor grasping asynchrony difficulty on the specific performance of each pair. In order to motivate individual commitment during the task, participants knew their final monetary reward would depend on the number of wins accumulated during the experimental sessions.

Movements were always performed with the right, dominant hand. The instruction to perform the opposite or same movement was delivered trial by trial via headphones.

In each session (after cTBS), participants performed two 64-trials Time-free/Time-cued sessions (in a counterbalanced order between participants). Thus, participants performed 32 complementary and imitative trials per condition after each stimulation session. Stimuli presentation and randomization were controlled by E-Prime2 software (Psychology Software Tools Inc., Pittsburgh, PA) (see Supplementary Material).

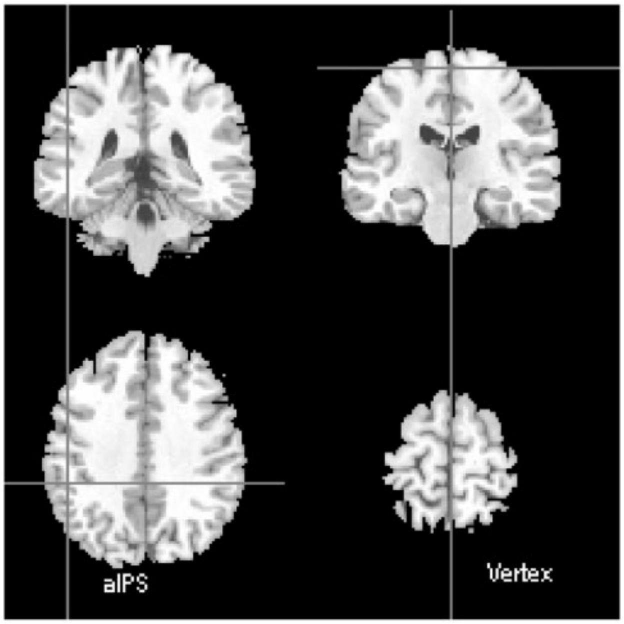

Fig. 2. Mean stimulation sites in Talairach coordinates: x = −47.15 ± 2.13, y = −33.85 ± 1.84 and z = 36.6 ± 0.5 for left aIPS and x = 1 ± 1.41, y = −16.7 ± 1.6 and z = 62.9 ± 2.65 for the Vertex.

Transcranial magnetic stimulation

The stimulation method was the same used in Sacheli *et al.* (2015b). cTBS was applied following Huang *et al.* (2005): three 50-Hz pulses were delivered in trains every 200 ms (i.e. at 5 Hz) for 20 s (300 pulses in total). cTBS was applied at 80% of the resting motor threshold, as this intensity has been used in different studies targeting the parietal cortex (Rosenthal *et al.*, 2009; Yazar *et al.*, 2017) (mean 46.45% ± 7.67% of the stimulator output). After the cTBS, participants rested for 5 min with their right arm relaxed on their side before starting the interactive task. The task never lasted more than 15 min so as to not exceed the inhibitory time-window.

While the rMT was only calculated for the stimulated participants (while the non-stimulated one was absent from the testing room), neuronavigation procedures were also performed on the non-stimulated ones. Stimulation sites were stereotactically identified on each participant's scalp with the SofTaxic Navigator system (EMS), (see Supplementary Material). TMS was delivered using a 70-mm figure-of-eight coil connected to a Magstim Super Rapid Transcranial Magnetic Stimulator (The Magstim Company). We used a continuous Theta-Burst stimulation paradigm (20 s) that has been shown to have an inhibitory effect over the stimulated site starting 5 min after stimulation and lasting up to 20 min (Huang *et al.*, 2005). SofTaxic Navigator system (EMS) was used to identify and store the sites that optimally targeted the left aIPS for each participant according to the coordinates reported by Hamilton and Grafton (2006) (MNI x = −52, y = −32, z = 44, converted in Talairach x = −47, y = −34, z = 37 according to Tunik *et al.*, 2007). The same procedure was adopted for the Vertex coordinates (Tal x = 0, y = −17, z = 63, Okamoto *et al.*, 2004). The resulting mean stimulation coordinates were x = −47.15 ± 2.13, y = −33.85 ± 1.84 and z = 36.6 ± 0.5 for left aIPS and x = 1 ± 1.41, y = −16.7 ± 1.6 and z = 62.9 ± 2.65 for the Vertex (Talairach coordinates, see Figure 2).

aIPS/Vertex stimulation was counterbalanced between participants. In both stimulation sessions, the non-stimulated participants received sham stimulation. During sham stimulation, a 3-cm-thick wooden rectangular-shaped object was placed on the target area between the coil and the participants' head. The 3-cm-thick wooden rectangular-shaped object was not visible to participants.

Experimental design and statistical analysis

We excluded from the analyses trials in which participants (1) missed the touch-sensitive copper-plates and thus no response was recorded, (2) released the start button before the go instruction or (3) did not respect their complementary/imitative instructions (on average, excluded trials = 9.49% ± 5.45% of total).

We considered the following as crucial individual (i.e. variable number 1–2–3) and pair (i.e. variable number 4) behavioral measures:

1. Accuracy, i.e. number of movements executed correctly (according to the instructions).
2. Reaction Times (RTs), i.e. time from the go-signal to the release of the start button.
3. Movement Times (MTs), i.e. time interval between participants releasing the start button and their index-thumb touching the bottle.
4. Grasping Asynchrony (GAsynchr), i.e. absolute value of time delay between the participants' index-thumb contact-times on the bottle-shaped object.

We calculated the individual/pair mean in each condition for each of these behavioral measures. The resultant values were entered in different within-subject or within-pair ANOVAs (see below).

Behavioral values that fell 2.5 s.d. above or below each individual mean for each experimental condition were excluded as outliers (on average, 2.6% ± 0.46% of total). At the group level, pairs with a mean above or below the group mean plus or minus 2.5 group s.d. were excluded from the analyses; two pairs were found to be outliers on grasping asynchrony according to this criterion. The ANOVAs for Grasping Asynchrony had stimulation SITE (aIPS/Vertex) × INTERACTION TYPE (Complementary/Imitative) × TIME (Time-free/time-cued) as within subjects factors (i.e. 2×2×2 within-subject design) (because this is a measure of pair performance and the factor MOVEMENT must be collapsed, as it cannot be coded in complementary interactions), while for all the other variables the ANOVAs had SITE (aIPS/Vertex) × INTERACTION TYPE (Complementary/Imitative) × TIME (Free, Cued) × MOVEMENT (Power/Precision grip) factors (i.e. 2×2×2×2 within-subject design). We used non-parametric tests, namely a Friedman ANOVA to analyze Accuracy. In order to test whether each pair's ability to mutually adapt and synchronize could modulate the effects of brain stimulation, we calculated an index of such ability at baseline (i.e. after vertex stimulation, Pairs' mutual compensation). This was done by correlating the Movement Times of each member of each pair in the 128 trials performed after the real stimulation of the vertex in the stimulated participant. We thus obtained correlation values for the 'closed-loop analyses'. These values were entered as a continuous predictor in a GLM on Grasping Asynchrony with SITE (aIPS/Vertex) × INTERACTION TYPE (Complementary/Imitative) × TIME (Time-free/Time-cued) as within subjects factors (i.e. 2×2×2 within-subject design). All tests of significance were based on an α level of 0.05. When appropriate, post-hoc tests were performed using the Newman–Keuls method. Statistical analyses were performed using Statistica 8 software (StatSoft). Data, code and materials are made available upon request.

Results

For all the individual measures see Supplementary Material.

Pair measures: mutual compensation counteracts aIPS inhibition

The ANOVA on Grasping Asynchrony (TIME (cued/free)×INTERACTION TYPE (complementary/imitative)×SITE (aIPS/Vertex) showed a significant main effect of TIME ($F(1, 19) = 5.72$, $P = 0.027$, $\eta p^2 = 0.23$), indicating that it was more difficult to coordinate with the partner in the Time-cued condition than the Time-free condition. The ANOVA also showed a significant main effect of INTERACTION TYPE ($F(1, 19) = 5.49$, $P = 0.03$, $\eta p^2 = 0.22$), indicating that it was more difficult to perform complementary movements than imitative ones. No other significant main effects or interactions were shown (all $Ps > 0.1$) (see Supplementary Table S1).

Accuracy was unaffected by the inhibition of left aIPS ($\chi^2 = 4.40$, $P = 0.73$).

Thus, when pair performance (synchrony) is analyzed without taking into account the pairs ability to adapt in the time domain, the inhibition of the left aIPS in one member of the pair did not result in an overall decrease of performance (synchrony) at the couple level, highlighting that the effect of the inhibition of left aIPS was compensated at dyadic level.

Closed-loop pair performance: aIPS impairs synchronization during complementary interactions

In order to study whether the inhibition of the left aIPS did influence the individual execution of complementary and imitative interactions and whether this effect impacted pairs' performance, we included in the same analysis performed above a continuous predictor indexing the ability of individuals to mutually adapt to each other (Pairs' Mutual Compensation). In details, to control for how Grasping Asynchrony was influenced by the participants' ability to mutually adapt to each other, we ran a GLM using the correlation between the Movement Times (i.e. time interval between participants releasing the start button and their index-thumb touching the bottle) of each pair at baseline (after stimulation of the vertex, see Material and methods) as continuous Predictor (i.e. Pairs' Mutual Compensation, more specifically, we used the R value of the correlation), and SITE (aIPS/vertex)×INTERACTION TYPE (complementary/imitative)×TIME (free/cued) as within subjects factors. This analysis showed a significant INTERACTION TYPE×SITE interaction ($F(1, 18) = 12.66$, $P = 0.002$, $\eta p^2 = 0.41$, Figure 3). Post-hoc tests showed that inhibition of left aIPS caused a selective decay of performance (i.e. Grasping Asynchrony was higher, indicating a larger time-delay between participants' grasp time on the bottle) during complementary interactions as compared to imitative ones ($P = 0.004$). On the contrary, complementary and imitative interactions achieved an equal level of joint synchrony after cTBS of the control site (vertex, $P = 0.26$). It is worth noting that the INTERACTION TYPE×SITE×TIME interaction did not reach statistical significance ($P = 0.85$), indicating that the Stimulation effect was significant across both the TIME conditions and suggesting that mutual adjustment was at play even during the Time Cued condition.

The ANOVA also showed a significant INTERACTION TYPE×SITE×Pairs' Mutual Compensation interaction ($F(1, 18) = 8.86$, $P = 0.008$, $\eta p^2 = 0.33$). No other main effect or interaction reached statistical significance (all $Ps > 0.14$) (Supplementary Table S1).

Because the Pairs' Mutual Compensation predictor interacted significantly with the factors SITE and INTERACTION TYPE, indicating that it significantly moderated the relationship between these two factors, we further investigated this effect with a correlational approach. We calculated an index of the effect of left aIPS stimulation on Grasping Asynchrony (i.e. the Stimulation Effect index) and correlated it with the Pairs' Mutual Compensation (correlation between participant pairs' performance) at baseline. The Stimulation Effect index was calculated by subtracting the difference between Grasping Asynchrony mean values in Complementary minus Imitative interactions after stimulation of the Vertex from the difference between Grasping Asynchrony mean values in Complementary minus Imitative interactions after stimulation of left aIPS:

$$[(\text{aIPS\_Asynchrony}\ (\text{Complementary} - \text{Imitative})) - (\text{Vertex\_Asynchrony}\ (\text{Complementary} - \text{Imitative}))].$$

This subtraction was performed for every pair. Positive Stimulation Effect index values thus indicated worse pair performance after left aIPS stimulation compared to vertex stimulation for complementary compared to imitative movements. The analysis showed a significant negative correlation, indicating that the lower the Pairs' Mutual Compensation (i.e. partners' ability to adapt to each other's movement times), the higher the Stimulation Effect ($r = -0.49$, $P = 0.028$; see Figure 4). This analysis thus indicates that the less the members of each pair were able to adjust their movement times to each other at baseline (i.e. after vertex stimulation), the more the inhibition of one member's left aIPS impaired their pair performance compared to vertex stimulation, reducing pair synchrony during complementary compared to imitative movements. This result suggests that the inhibition of the left aIPS was effective in impairing partners' synchronization during complementary interactions, but that this effect was masked by the ability of the pairs to mutually adapt. Importantly, this result demonstrates the inherently closed-loop nature of our task.

Finally, we ran a mixed ANOVA using the Pairs' Mutual Compensation to split the sample in participants with good and poor ability to mutually adjust (median split) and confirmed the above results (see Supplementary Material).

Discussion

Face to face joint-actions are characterized by the emergence of dynamic, online, mutual adaptation that allow for synchronization. Such adaptation is supported by the continuous integration of predictions as to what effects one's own and other actions will have. This type of integration process allows interactors to adjust their movements mutually on a moment-to-moment basis (Hasson and Frith, 2016) in order to achieve a shared goal which would not be achieved if individuals ignore the others' movements (Sacheli *et al.*, 2015c; Candidi *et al.*, 2015b; Hasson and Frith, 2016).

Realistic synchronous joint-actions in humans often imply individuals performing imitative and complementary movements,

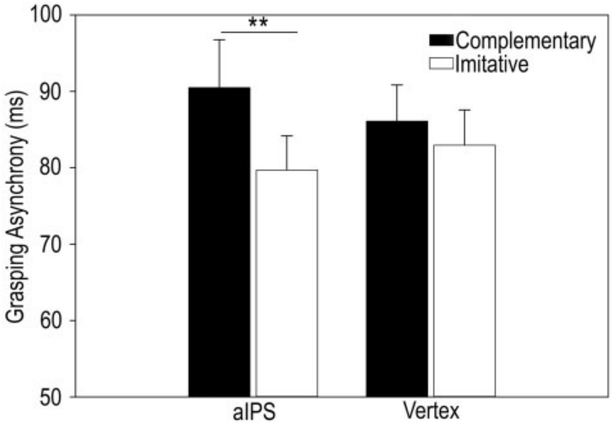

Fig. 3. Graph of grasping Asynchrony Results in the closed-loop pair analysis: significant INTERACTION TYPE×SITE interaction ($F(1, 18) = 12.66$, $P = 0.002$, $\eta p^2 = 0.41$). Post-hoc tests show that stimulation of left aIPS caused a selective decay of performance in complementary actions. Thus, joint-coordination was significantly lower after aIPS inhibition during complementary actions as compared to imitative actions ($P = 0.004$). On the contrary, an equal level of joint synchrony was achieved during complementary and imitative actions after cTBS of the control site (vertex, $P = 0.26$). Error bars show s.e.m.

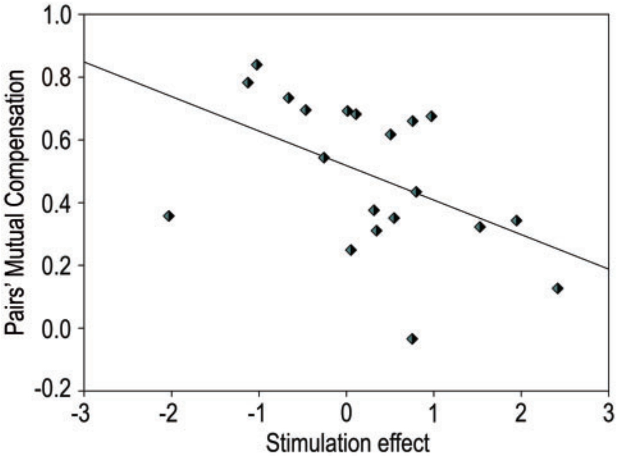

Fig. 4. Correlation between Stimulation Effect index and Pairs' Mutual Compensation. The analysis showed that the lower the Pairs' Mutual Compensation, the higher the Stimulation Effect ($r = -0.49$, $P = 0.028$).

two classes of actions that likely rely upon different neural and cognitive resources. At variance with imitative joint-actions, the complementary interactions requested by our experimental paradigm are specific test cases of the ability to integrate different executed and observed movements, as they require visuo-motor integration of non-overlapping movements of the pair members, rather than pure anticipatory action–perception–execution matching. Although performing complementary interactions in mutually adaptive contexts represents a crucial aspect of our social life, little is known about the causal role of specific brain regions in this behavior. Thus, one main point of novelty of our study is that transient inhibition of left aIPS induced by cTBS selectively impairs the ability to online coordinate with a partner when performing complementary motor responses with respect to imitative ones.

The fact that participants achieved an equal level of performance during complementary and imitative interactions after vertex stimulation is in line with previous studies showing that complementary interactions are not more difficult than imitative ones (Ocampo and Kritikos, 2010; Sacheli *et al.*, 2012, 2013). It is worth noting that, in this study, aIPS inhibition resulted in a relative impairment of complementary interaction compared to a facilitation of imitative ones. These results are in line with previous work (Sacheli *et al.*, 2015b) and a more recent study showing that aIPS inhibition has an opposite effect on complementary and imitative interactions, making the performance better during imitative and worse during complementary interactions (Sacheli *et al.*, 2018) and suggesting that impairing aIPS functioning makes motor interactions more similar to conditions in which participants perform actions at the same time, without needing to predict the partner's action in order to perform one's own (as in the imitation inhibition task, Brass *et al.*, 2000, in which performing incongruent actions is usually more difficult than performing congruent ones). This result also rules out that aIPS inhibition interfered with complementary interactions because they might be considered as more difficult.

Interestingly, the effect of aIPS inhibition was reflected in pair performance as an inverse function of the pairs' ability to mutually adjust: the less participants were able to mutually compensate, the more the stimulation impaired the pair performance.

aIPS as neural interface between action perception and action control during human-human interactions

The parietal lobe is strategically located between the occipital lobe (for vision of objects and movements) and the frontal lobe (for action programming and simulation). This location makes it an ideal region for visuo-motor transformations and integrations. Not surprisingly, the posterior parietal cortex has been shown to be a critical region for the planning and control of grasping actions (Milner and Goodale, 1995; Jeannerod, 1997). Recent work on the observation of actions in humans and monkeys indicates that the inferior frontal and inferior parietal cortices harbor a mirror system that responds to both the execution and observation of actions (Rizzolatti *et al.*, 2014). This experimental evidence inspired several speculative proposals on the role of the motor system in 'direct matching' of self and other motor representations (Iacoboni *et al.*, 1999), as well as in drawing predictive inferences about the intentions, goals and desires of other people (Gallese *et al.*, 2004). Brain stimulation (TMS) studies have shown that interfering with the activity of the left aIPS, a region within the left posterior parietal cortex, impairs individuals' ability to achieve an action goal. For example, inhibition of aIPS prevents people from correcting their reaching trajectory when the target of their grasping is moving (Desmurget *et al.*, 1999), and from adjusting their grasping actions online to a change in target orientation, regardless of the motor effectors employed (Tunik *et al.*, 2005). Intracortical stimulation/recording studies on monkeys and humans converge to indicate that the posterior parietal cortex codes for intention to move and motor goals (Batista and Andersen, 2001; Andersen and Buneo, 2002; Fogassi *et al.*, 2005; Desmurget *et al.*, 2009). Moreover, fMRI studies indicate left aIPS involvement, starting early in development (Southgate *et al.*, 2014), in the representation of the goal of observed actions (Hamilton and Grafton, 2006). The finding that aIPS encodes the goals of one's own actions as well as those of others is in line with the idea of a common representational system for the actions of self and other (Tunik *et al.*, 2007).

More importantly, we have recently demonstrated that inhibition of the left aIPS impairs individuals' performance during open-loop complementary but not imitative interactions, suggesting that this region may play a role in integrating predictions about one's own and others' complementary actions (Sacheli *et al.*, 2015b). However, in our previous human–avatar interaction study (Sacheli *et al.*, 2015b), participants had to adapt to a virtual partner who was not able to adjust its movements to those of the participants. Thus, another point of novelty of the present study is that left aIPS also plays a crucial role in realistic human–human interactions characterized by the essential feature of mutual adaptation. Indeed, when looking at the individual performance of the stimulated participants, the behavioral results showed that inhibition of left aIPS activity causes a slowing in movement times when coordinating with the partner in complementary movement conditions. Importantly, the selectivity of this effect indicates that off-line aIPS inhibition does not interfere with the general ability to perform grasping movements.

Mutual adaptation as a marker of the essential nature of closed-loop interactions

The inhibition of left aIPS did not produce any observable effect at the pair performance level. As it is the nature of joint-actions to induce the mutual adaptation of a partner to the other, we hypothesized that changes in the interfered participants' behavior may prompt the non-stimulated subjects to compensate for their partner's transient deficit. We thus used the correlation between partners' movement times at baseline (i.e. when no real stimulation is applied) in order to measure the participants' ability to compensate by slowing down or accelerating their movements according to the behavior of the partner. When combining this mutual adjustment index with the effect of the stimulation over the performance of each pair, the results demonstrate that the less participants were able to adjust their movements' duration to each other at baseline, the more the stimulation of one participant's left aIPS impaired the pair performance during complementary interactions compared to imitative ones. In line with the only other study applying off-line rTMS inhibition paradigms to interfere with joint-actions (Sacheli *et al.*, 2015b), we show that aIPS inhibition did not interfere with the movement kinematics of the stimulated participants.

It is worth noting that studies using cell recordings in monkeys indicate that also regions adjacent to the human aIPS might represent action's goal. Indeed, single neurons in the area PFG on the lateral convexity of the inferior parietal lobule are selective not only for the ongoing grasping action, but also for the subsequent movements to be performed, which could be considered as the overall goal of the movements chain (Fogassi *et al.*, 2005; Tunik *et al.*, 2007). We decided to specifically target aIPS because evidence of its activity coding for the goal of both executed and observed actions makes it the ideal candidate for supporting the integration of performed and observed actions during motor interactions. Although we specifically targeted the coordinates of aIPS (Hamilton and Grafton, 2006) in every participant and monitored the coil position online during the stimulation, it is important to consider that the offline cTBS protocol employed in the present study might have impaired the ability to integrate the performed and the observed action' goal also by interfering with the activity of other close parietal regions, like the human homologue of PFG.

The specific task used in this study required participants to predict the actions of their partner, while programming and executing their own actions, in order to achieve the shared goal of performing synchronous complementary and imitative interactions. Given the online nature of the task both participants performed their actions in parallel. Therefore, the processes of predicting-programming and executing the actions likely occurred in concert. For this reason, since aIPS inhibition interfered with the ability to perform complementary interactions in comparison to imitative ones, we suggest that an important function of this brain region is related to the ability to program and execute actions that require integration of predictions of non-overlapping movements of the pair members. Studies indicate that applying cTBS over a certain brain region reduces the functional connectivity of that brain region with the rest of the brain (Rahnev *et al.*, 2013; Valchev *et al.*, 2015). Therefore, it is worth emphasizing that our results might be interpreted as the effect of aIPS inhibition on the activity of the fronto-parietal network recruited during complementary joint actions (Newman-Norlund *et al.*, 2007). Indeed, the aIPS is anatomically (Schmahmann *et al.*, 2007) and functionally (Fogassi and Luppino, 2005; Davare *et al.*, 2011) connected to frontal regions, like the premotor cortex. Importantly, other (frontal) nodes of the fronto-parietal network, such as the primary motor cortex and dorsal premotor cortex, have been shown to play a causal role during interpersonal coordination (Novembre *et al.*, 2014; Hadley *et al.*, 2015). These studies showed that interfering with the activity of brain regions supporting internal motor representations by means of TMS impairs interpersonal coordination during synchronous and turn-taking musical interactions (Novembre *et al.*, 2014; Hadley *et al.*, 2015). Furthermore, another study (Novembre *et al.*, 2017) has shown that synchronizing beta activity (20 Hz) of the motor system of two individuals increases their ability to synchronize their finger tapping movements. Thus, aIPS might integrate information about individual action with motor predictions regarding the partner's action (from premotor areas) during motor planning (Tunik *et al.*, 2007). A main point of novelty of this study is that the impairment in motor coordination induced by cTBS in one member of an interacting dyad was compensated by the dyad's ability to mutually adapt. In a similar vein, a recent study showed that brain damaged patients with motor difficulties (apraxic patients) improve their motor behavior when interacting with a partner (i.e. patients synchronized better with a partner when acting as a dyad compared to when behaving in a low interactive condition) (Candidi *et al.*, 2017).

Previous brain activation studies during joint-action tasks involving pairs of participants showed higher activation of the left inferior parietal lobule in joint- *vs* solo actions (Egetemeir *et al.*, 2011), and in joint-actions compared to action observation and execution (Kokal *et al.*, 2009). A role of centro-parietal activity for interpersonal synchronization has also been supported by hyper-scanning approaches. Indeed, a dual EEG study reported that higher interpersonal synchronization during motor interactions (piano playing) was associated with alpha band suppression over centro-parietal regions, which was interpreted as a neurofunctional marker of 'self-other integration' (Novembre *et al.*, 2016). Moreover, by applying transcranial alternating electrical stimulation over the motor cortex of two individuals during the preparatory phase of finger-tapping task, Novembre *et al.* (2017) demonstrate that interpersonal synchrony was specifically enhanced by in-phase 20 Hz stimulation in the beta band (20 Hz). These studies (Novembre *et al.*, 2016, 2017) provide interesting evidence in support of the notion that interpersonal synchronization of movements is also reflected in interpersonal synchronization of brain oscillations. In conclusion, our findings expand those of previous brain stimulation studies on human–avatar interactions (Sacheli *et al.*, 2015b) by showing that left aIPS functioning is fundamental to effective motor synchronization during realistic human–human complementary compared to imitative interactions. Notably, we also show that the effect of the inhibition of left aIPS activity depends on the pair's ability of mutual adaptation thus indicating that this process is a crucial marker of human–human closed-loop interactions (Fuchs and De Jaegher, 2009).

Supplementary data

Supplementary data are available at *SCAN* online.

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