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SENSORIMOTOR NETWORK IN SOCIAL COGNITION

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ABSTRACT

Our motor and somatosensory cortices originally evolved to control our movement through the environment. In the past decade, one of the most exciting developments in cognitive neuroscience is the discovery that the same sensorimotor brain regions that are used to control our body are involved in the perception of others' actions, sensations and emotions. Human beings are equipped with a mechanism mapping perceptual representations of actions, sensations, and emotions onto sensorimotor representations, thus, perception of others might be inherently grounded in the same brain regions involved in first-hand subjective experiences. While the notion that observing, or imagining actions, emotions, and sensations in others triggers vicarious activations in the sensorimotor network is widely accepted, evidence about the specific role of these activations in social cognition is meagre and still largely based on correlational data. The experiments included in the present thesis aim at exploring the functional role of the sensorimotor network in understanding others' internal emotional and cognitive states. We used neuromodulation tools to interfere with brain activity in regions involved in moving and sensing the body while participants were asked to understand others' emotions or intentions. In experiment 1 to 7 we focused on the ability to accurately understand amusement from observed smiles, while in experiment 8 to 10 we explored the ability to rate the pain felt by another individual when her/his experience is described only through text. Our results show that interference with activity within somatosensory and motor cortices impairs participants' ability to understand others' emotions. Combining complex naturalistic tasks to neuromodulation tools, the present thesis sheds novel light on the behavioural relevance of vicarious activations in the sensorimotor network, by establishing a strong and direct causal link between sensorimotor brain networks and others' understanding that was only suggested in the past.

GENERAL INTRODUCTION

I. SENSORIMOTOR EXPERIENCE SHARING / VICARIOUS ACTIVATIONS

Social cognition encompasses all the cognitive processes underlying interactions with conspecifics. These include perceiving, interpreting, and generating responses to the behaviours others are exhibiting. Our motor and somatosensory cortices originally evolved to allow our interactions with the environment and with others in the environment, after all, our bodies are the tool we use to interact with others and react to them. In the past decade, one of the most exciting developments in cognitive neuroscience is the discovery that the same sensorimotor brain regions that are used to control our own actions and experience our own sensations and emotions are involved in the perception of others' actions, sensations and emotions (Bastiaansen et al., 2009; Keysers et al., 2010; Rizzolatti et al., 2014; Rizzolatti and Sinigaglia, 2016). The link between perception and the body is not new to psychology, but since the discovery of mirror neurons in the macaque brain social cognitive neuroscience shifted from cognitivist approaches to embodied approaches (Gallese, 1998)

Seminal studies in monkeys showed that neurons in the premotor and parietal cortices respond both during action production and to the observation of an action with a similar goal (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 1996; Fogassi et al., 2005).

After the discovery of mirror neurons in monkeys, several studies suggested the existence of vicarious activations in the human inferior frontal gyrus / premotor cortex (IFG / vPMc), coupling action perception and action production (Fadiga et al., 1995; Hari et al., 1998; Buccino et al., 2001, 2004; Gazzola et al., 2006; Avenanti et al., 2007; Mukamel et al., 2010). The IFG is consistently active both during the execution and the observation of actions, and is considered a key region of the mirroring network involved in simulating observed actions within one's own motor system (Caspers et al.,

2010; Gallese and Sinigaglia, 2011; Avenanti et al., 2013b). These vicarious activations, though, are not limited to the premotor cortex, but can be observed in several brain regions involved in action production like the primary somatosensory cortex (SI). Recent work in humans suggests that the SI responds to action observation (Gazzola and Keysers, 2009; Caspers et al., 2010; Jacquet and Avenanti, 2015) and to the observation of touch (Keysers et al., 2004, 2010; Blakemore et al., 2005; Bufalari et al., 2007).

This suggests that mirror-like mechanisms in the sensorimotor network might be deeply involved social interaction: a mechanism mapping visual representations of the observed actions onto corresponding sensorimotor representations providing meaning to others' motor acts by a common coding for both first and third person perspectives (Rizzolatti and Craighero, 2004; Wilson and Knoblich, 2005; Kilner et al., 2007; Schütz-Bosbach and Prinz, 2007b; Gazzola and Keysers, 2009; Friston et al., 2011; Press et al., 2011; Schippers and Keysers, 2011; Avenanti et al., 2013b; Pezzulo et al., 2013). Keysers 2010, valchev 2016 These observation of shared activations have motivated sensorimotor simulationist models, which suggest that perception of others' behavior is grounded in the same network that is involved in moving and sensing the body (Goldman and Sripada 2005; Gallese 2007; Keysers et al. 2010; Niedenthal et al. 2010; Wood et al. 2016). Therefore, the mirror system might provide a basis not just for understanding actions and somatic sensations, but also for all domains of social cognition (Gallese et al., 2004), including processing of others' emotions. Evidence shows that the same system linking first-hand and third-hand experiences has been observed for emotions, suggesting that internal simulation might occur also for others' emotional experiences (Keysers and Gazzola, 2006; Niedenthal, 2007; Bastiaansen et al., 2009).

Interestingly, several studies show that those sectors of the inferior frontal gyrus (IFG) that are involved in controlling facial movements and those sectors of the somatosensory cortex (SI) that are involved in processing sensations from the body, are involved in processing others' emotional behavior whether it is perceived or imagined (Adolphs et al., 2000; Wicker et al., 2003; Winston et

al., 2003; Carr et al., 2003; Leslie et al., 2004; Avenanti et al., 2005; Hennenlotter et al., 2005; Warren et al., 2006; Dapretto et al., 2006; Gazzola et al., 2006; Lamm et al., 2007b; van der Gaag et al., 2007; Cheng et al., 2007; Valeriani et al., 2008; Gallese, 2008; Keysers et al., 2010; Bolognini et al., 2011, 2013b, 2014; Tamietto et al., 2015).

In sum, human beings are capable of understanding internal states in others by looking or imagining others' behaviour. In this view, internal simulation in the sensorimotor network can be used to interpret the internal mental state that caused an action. Previous studies indicate that others' internal emotional states are represented in the mind of the observer and that sensorimotor regions are involved in processing others' emotion and social cognition in general (Pobric and Hamilton, 2006; Avenanti et al., 2007; D'Agata et al., 2011; de Gelder et al., 2012; Tidoni et al., 2013; Bolognini et al., 2014; Costa et al., 2014; Urgesi et al., 2014; Jacquet and Avenanti, 2015; Tamietto et al., 2015; Valchev et al., 2016). Embodied simulation of others' action and sensations might constitute the basis of a form of mind-reading that is not propositional and is based on the body and mirror-like mechanisms in the human brain are its neural substrate.

II. PERSPECTIVE TAKING / THE MENTALIZING NETWORK

A different approach to social cognition focuses on explicit attribution of mental states to others. Scholars following this theory-theory approach claim that when we are asked to explicit infer others' intentions, beliefs, thoughts, we don't rely on simulation, but instead we build a propositional representation of the internal state we assume others have (Mitchell et al., 2002; Saxe, 2005; Shamay-Tsoory et al., 2005). Therefore, they propose a system providing a different route to understanding others that it is not through sharing, but through the creation of explicit cognitive knowledge about what others are feeling. This approach to social cognition was also fuelled by critiques to the

simulative approach to social cognition, mainly focused on the problem of self/other distinction in a pure simulative framework and on the lacking of behavioural evidence in favour of a central role of mirror mechanisms in understanding others (Jacob and Jeannerod, 2005; Saxe, 2005; Southgate and de C. Hamilton, 2008; Hickok, 2009, 2013; Heyes, 2010; Baird et al., 2011). Scholars focusing on the neural substrate of cognitive processes involved in reasoning about others' mental states isolated a subset of brain regions that is consistently involved in thinking about others' minds: the mentalizing network. This network includes dorsomedial and ventromedial prefrontal (dm/vmPFC) cortices, posterior cingulate cortex/precuneus (PCC/PC), temporoparietal parietal junction (TPJ), the posterior superior temporal sulcus (pSTS), and the anterior temporal cortex (aTC) (Amodio and Frith, 2006; Frith and Frith, 2006; Saxe, 2006; Mitchell, 2009; Mar, 2011; Schurz et al., 2014; Kanske et al., 2015) and is active when participants are asked to make explicit judgments regarding the internal states of others, such as their beliefs (Saxe and Kanwisher, 2003; Bzdok et al., 2012), preferences (Mitchell et al., 2006) or emotional state (Budell et al., 2010; Ochsner et al., 2004). The temporo-parietal junction is a key structure within the mentalizing network whose activity has been reliably associated with tasks in which individuals are asked to infer another person's mental state (Saxe and Kanwisher, 2003; Decety and Lamm, 2007; Van Overwalle, 2009) and in tasks requiring to explain actions in terms of mental states (Grèzes et al., 2004; Brass et al., 2007; de Lange et al., 2008; Spunt et al., 2010).

III. CONTRIBUTION OF SENSORIMOTOR SIMULATION AND MENTALIZING NETWORKS IN COMPLEX SOCIAL TASKS

Beyond pure simulationist or theorist approaches to social cognition, it seems that both the sensorimotor and the mentalizing network participate in understanding others (Olsson and Ochsner, 2008; Bastiaansen et al., 2009; Shamay-Tsoory et al., 2009; Zaki et al., 2012). However, several critical issues remain unexplored. Among these, the main one pertains the actual functional contribution of sensorimotor simulation and mentalizing network in understanding others' internal states and the interactions (or lack thereof) between the two networks in social cognition.

The two systems are anatomically independent and several studies show that they might even be functionally independent (van Overwalle and Baetens, 2009)(Keysers and Gazzola, 2007; Olsson and Ochsner, 2008). During emotion perception, the two systems appear to process distinct categories of social information, with the mirror system engaged by nonverbal, motor features and the mentalizing system engaged by either contextualizing verbal information (cf. Waytz and Mitchell, 2011; Zaki et al., 2010) or the explicit evaluation of another's emotional state (Budell et al., 2010). However, recent imaging studies suggest that the two systems might be concurrent active in complex social tasks especially when observers are explicitly induced to make judgments regarding the target's internal state (Brass et al., 2007; Zaki et al., 2009b; Lombardo et al., 2010; Schippers et al., 2010; Spunt et al., 2011; Schippers and Keysers, 2011; Spunt and Lieberman, 2013, 2012a, 2012b; Harvey et al., 2013; Sperduti et al., 2014; Kanske et al., 2015; McGettigan et al., 2015).

Although, these studies suggest the possibility that the two systems may work in synergy to enable fine-grained emotion understanding, no study to date has explicitly tested this possibility, as most of the evidence about the involvement of the sensorimotor network and the mentalizing network in high-level inferences about another's internal state comes from neuroimaging studies. Correlational approaches to social cognition, despite being fundamental in exploring the neural substrate of

cognitive function, cannot inform about the functional role of the two networks in understanding others' internal cognitive and emotional states.

How does the brain understand the emotional states of other brains?

Simulation and mentalizing, despite their differences represent two routes for the same goal: understanding others' internal states. It is thus plausible (and even supported by indirect evidence) that both processes and corresponding brain networks might be involved in every social interaction.

The aim of the present thesis is to provide causal evidence of the role of vicarious activations within the sensorimotor cortices and of the mentalizing network in social cognition. To this aim, in a series of experiments, we used neuromodulation techniques to independently alter activity of key regions within the two networks to assess their functional contribution in understanding others' emotional and cognitive states. Moving beyond simple tasks designed to explore specific aspects of social cognition, we employed specifically designed naturalistic tasks, with the aim to grasp the complexity of everyday social interactions.

From Experiment 1 to 7 we focused on the emotional facial expression of amusement. The smile is a prominent facial expression in social life, however, it is also the most ambiguous expression we encounter. We designed two novel tasks to track participants' accuracy in judging others' internal emotional states (Empathic Accuracy, EA) and used repetitive TMS to interfere with key regions of the sensorimotor simulation and the mentalizing network. This way, we explored if these networks are critical for fine-grained judgments about amusement from observed smiles.

In Experiment 8, 9 and 10 we focused on the involvement of the somatosensory cortex in moral judgment and in explicit judgments of another's emotional experience described through text. We know from previous studies that healthy moral judgments in adulthood strongly rely on our theory about others' intentions, however, observing or imagining a person causing pain to another leads to vicarious activation in brain regions involved in our first-hand painful experiences. Here we used

tDCS to inhibit the sensorimotor simulation or the mentalizing network while participants were asked to read written narratives describing harmful situations involving two individuals and judge different aspects of these.

Finally, in Appendix A and B we explored the role of premotor and primary motor cortices in predicting others' actions. We devised a novel action prediction task where participants observed the initial phases of right-hand reaching-to-grasp actions and had to predict their outcome (i.e., the goal/object to be grasped). We found that suppression by cathodal (inhibitory) tDCS of the left IFC, selectively impaired performance on the action prediction task. Remarkably, anodal (excitatory) tDCS of the left IFC brought about a selective improvement in the action prediction task. These findings indicate that the left IFC is necessary for predicting the outcomes of observed human right-hand actions. Crucially, this study shows for the first time that down- and up-regulating excitability within the motor system can hinder and enhance AP abilities, respectively. In Appendix B, we explored the role of the primary motor cortex in predicting others' actions. Although correlational studies suggest that the motor cortex (M1) might be involved in this process, it is unclear whether M1 is also causally essential for making predictions about observed actions. To test the functional relevance of M1 to action prediction we used offline monopolar transcranial direct current stimulation (tDCS) in healthy participants. We found that 2mA cathodal tDCS selectively impaired performance on the action prediction task. The effect was specific to polarity (it was not present after anodal currents) and intensity (it was not present after 1mA tDCS). These findings establish specific tDCS parameters for effective M1 stimulation in action prediction and highlight the functional relevance of M1 to making accurate predictions about the outcome of human actions.

Altogether, results found in Appendix A and B, support predictive coding theories of action perception and have implications for enhancement of action prediction abilities.

Chapter 1

Sensorimotor network crucial for inferring amusement from smiles

Introduction

Understanding whether a smiling individual is experiencing authentic amusement is a common challenge in everyday social interactions. A smile is, without any doubt, the most easily recognizable facial expression, and yet the most nuanced one. Indeed, a smile can be flexibly used to communicate a wide range of feelings (Ekman, 2001; Shiota et al., 2003; Niedenthal et al., 2010). Critically, in many social contexts, it can be used deceptively by showing that amusement is felt when it is not. People are typically accurate in classifying smiling faces as emotionally positive expressions, but commit many more errors when they are asked to evaluate the emotional feeling behind a smile (Niedenthal et al., 2010). Accurate recognition of the emotion felt by another person (a social target) is often referred to as empathic accuracy (EA), and is commonly operationalized as the correspondence between the feelings reported by the social target and the feelings that perceivers infer from the social target's behavior (Ickes and Stinson 1990; Levenson and Ruef 1992; Ickes 1997; Zaki et al. 2008, 2009). EA requires accurate perception of the social target's behavior and explicit inferences of the underlying feelings based on available information (e.g. facial expressions, prior knowledge or contextual information). It is believed that perceptual and cognitive processes underlying EA could provide a key mechanism for empathy, i.e., the ability to share the feelings of others, grounded affective brain regions engaged during first-hand emotion experiences (de

Vignemont and Singer 2006; Singer and Lamm 2009; Batson 2011; Decety et al. 2012; Lamm and Majdandžić 2015; Rütgen et al. 2015a, 2015b; Zaki et al. 2016).

Inferring amusement from another person's smile requires the perceiver to visually process and integrate multiple morphological and dynamic features of the observed facial expression (Ekman, 2001; Ambadar et al., 2009; Krumhuber and Manstead, 2009; McLellan et al., 2010). However, for accurate recognition of the underlying emotional feeling, further non-visual brain mechanisms are likely involved (Zaki et al., 2009b, 2012). Previous studies suggest that at least two related but distinct sets of brain regions may be involved in EA: i) sensorimotor "mirroring" regions which support perception and understanding of others' behavior, possibly through an embodied simulation of the observed actions; and ii) "mentalizing" regions which support the ability to explicitly consider others' mental states and their sources, and to draw explicit inferences about them (Preston and de Waal 2002; Gallese et al. 2004; Amodio and Frith 2006; Frith and Frith 2006; Saxe 2006; Mitchell 2009; Gallese and Sinigaglia 2011; Decety et al. 2012; Zaki et al. 2012; Zaki 2014).

However, it is still debated whether and when these sensorimotor and cognitive networks provide routes to understanding others, or merely reflect such understanding (Gallese et al. 2011; Uithol et al. 2011; Avenanti et al. 2013b; Lamm and Majdandžić 2015). This is because knowledge of these networks is mostly based on indirect correlational imaging evidence, and the need for novel methods and causal approaches is increasingly recognized by social neuroscientists (Decety 2011; Hétu et al. 2012; Avenanti et al. 2013b; Rütgen et al. 2015a, 2015b; Zaki et al. 2016; Lamm et al. 2016). In particular, to date no studies have specifically tested the critical role of sensorimotor and mentalizing networks in the empathic ability to infer authentic amusement from the smiles of others. Establishing this role is the goal of the present study.

Indirect correlational evidence has suggested that sensorimotor networks may support EA. For example, watching emotional motor behavior such an emotional facial expression vicariously activates those sectors of the inferior frontal gyrus (IFG) that are involved in controlling facial

movements and those sectors of the somatosensory cortex (SI) that are involved in processing sensations from the face (Carr et al., 2003; Leslie et al., 2004; Dapretto et al., 2006; Keysers et al., 2010; Tamietto et al., 2015). These observation of shared activations have motivated sensorimotor simulationist models, which suggest that perception of others' facial expressions is (at least partially) grounded in the same network that is involved in performing and sensing facial movements (Goldman and Sripada 2005; Gallese 2007; Keysers et al. 2010; Niedenthal et al. 2010; Wood et al. 2016). Yet, it should be noted that studies exploring vicarious activations during perception of emotional facial expressions have traditionally used passive viewing tasks without asking participants to make explicit inferences about the targets' emotional feelings (for a review see Zaki et al. 2012).

On the other hand, studies focusing on the mentalizing network have commonly asked participants to make explicit judgments about another's internal state using verbal material (i.e., scripts) or highly stylized nonverbal social cues, including vignettes, static displays of facial expressions or even more isolated cues such as target eye gaze (Amodio and Frith, 2006; Frith and Frith, 2006; Saxe, 2006; Mitchell, 2009). These studies highlighted a midline and lateral temporo-parietal network supporting mental state attribution, which includes the medial prefrontal cortex (mPFC) and the temporo-parietal junction (TPJ) (Amodio and Frith, 2006; Frith and Frith, 2006; Saxe, 2006; Mitchell, 2009). However, none of these studies presented participants with dynamic expressions of natural behaviors.

Recently, more naturalistic neuroscientific paradigms combining dynamic social cues and explicit inferential tasks (Redcay et al., 2010; Wolf et al., 2010; Spunt and Lieberman, 2013) have revealed co-activation and functional coupling of sensorimotor and mentalizing networks during complex social tasks (Wheatley et al., 2007; Zaki et al., 2009b; Lombardo et al., 2010; Schippers et al., 2010; Raz et al., 2014), including EA tasks. Notably, studies have shown that neural activity in both networks predicts EA performance in tasks requiring observation of others' expressive behavior and inferences of the underlying emotional feelings (Zaki et al., 2009b; Harvey et al., 2013). Activity in both sensorimotor and mentalizing networks also predicts EA performance in simpler tasks, for

example, when evaluating emotion authenticity from sounds of laughter (McGettigan et al., 2015). In this case, there was no contextual information about the possible source of the emotion, so the explicit inference about the emotion had to be based only on social cues. While these studies have underscored the integrated nature of empathic processing during naturalistic social inference and the potential contributions of the sensorimotor and mentalizing networks to accurate empathic inferences, no study has thus far addressed the key question of whether these networks play causal roles in EA. Indeed, it should be noted that the above-mentioned conclusions about the involvement of sensorimotor and mentalizing networks in EA were mostly based on imaging methods. These methods can only provide indirect correlational data, and cannot establish direct causal links between brain structures and cognitive functions.

Here, we administered repetitive transcranial magnetic stimulation (rTMS) to perturb key regions within the sensorimotor network (i.e., the face representation in IFG and SI) and the mentalizing network (i.e., mPFC and TPJ), and provide direct evidence for their functional relevance to EA. To this aim, we designed a novel EA task combining dynamic displays of smiles with the explicit empathic inferences of whether the social target is feeling authentic amusement or not. We used signal detection theory to test whether interference with key nodes of the two networks would disrupt participants' sensitivity to the authenticity of amused expressions.

Materials and Methods

Participants

A total of 180 healthy subjects took part in the study. Sixty-four subjects participated in one of the four TMS experiments. In each TMS experiment, we targeted a different brain area: right IFG (**Experiment 1:** 16 participants, 8 females, mean age ± SD: 23.6 y ± 1.9), right SI (**Experiment 2:**

16 participants, 8 females, 22.3 ± 2.3), mPFC (**Experiment 3:** 16 participants, 9 females, 22.5 y ± 0.5) or right TPJ (**Experiment 4:** 16 participants, 10 females, 23.6 y ± 1.5). Sixteen subjects (8 females; 25.4 y ± 2.2) participated in a peripheral stimulation experiment, and 100 subjects (**Experiment 5:** 50 females) were tested in one of five pilot studies, whose aim was to validate the two behavioral tasks. All subjects were right-handed, had normal or corrected-to-normal visual acuity in both eyes, and were naïve to the purposes of the experiment. None of the participants had neurological, psychiatric, or other medical problems or any contraindication to TMS (Rossi et al., 2009; Rossini et al., 2015). Participants provided written informed consent. The procedures were approved by the ethics committee at the Psychology Department of Bologna University and were in accordance with the ethical standards of the 1964 Declaration of Helsinki. No discomfort or adverse effects of TMS were reported by participants or noticed by the experimenter.

Stimulus creation and selection

Stimuli consisted of 32 dynamic movies (lasting 2 seconds, 60 frames) presented centrally on a 19-inch monitor (resolution: 1024 x 768; refresh rate: 60 Hz) subtending 27 x 21° of visual angle. Movies depicted 8 individuals ("social targets"; including 4 females and 4 males, aged 24.5 y ± 2.1) who were filmed individually while smiling. Movies were edited using Adobe Premiere Pro C6 software in order to correct lighting, contrast and color, and remove the audio tracks.

During stimulus creation, social targets sat against a white background, and lighting equipment was used to avoid the formation of shadows. The social targets were instructed to gaze directly towards the camera and try not to move their bodies. Ten social targets (5 females) were initially filmed while making smiling expressions associated with authentic positive feelings of amusement or posed expressions associated with an emotionally neutral state. Authentic and fake expressions of amusement were recorded in two separate sessions that were performed under emotionally congruent contexts to provide realistic stimuli.

In the “authentic” session, the social targets used a laptop with loud speakers to select audio clips that elicited strong feelings of amusement and spontaneous smiles (Instruction: “Please watch the camera and smile only if you feel like doing so”). Auditory stimuli were chosen based on social targets’ preferences and were retrieved from the internet (e.g., http://www.youtube.com). In the “fake” session, social targets were not presented with auditory stimuli, and were instead instructed to produce a voluntary smile (Instruction: “Please watch the camera, think about something neutral and produce a smile that you think could be interpreted as an authentic expression of amusement by an observer”). They were allowed to watch the pre-recorded authentic smiles in order to achieve more convincing posed facial expressions.

Notably, after each smiling expression, social targets were instructed to provide subjective evaluations of the amusement they felt while smiling using a 9-step Likert scale (0 = neutral state; 9 = maximal amusement). Moreover, they were asked to evaluate their subjective confidence in their amusement judgments using a categorical response (I am 100% sure of my judgment / I am not 100% sure of my judgment) (cf. Ickes and Stinson 1990; Levenson and Ruef 1992). These subjective reports allowed us to select only smiling expressions that were associated with the highest subjective ratings of amusement (authentically amused smiles) or without any emotional feeling (falsely amused smiles) and with strong subjective confidence in the ratings. For each social target, only smiles associated with the highest ratings of felt amusement (mean values across social targets: M = 6.3, SD = 1.4) and full amusement judgment confidence (i.e., “I am 100% sure of my judgment”) were considered authentic expressions of amusement. False expressions of amusement were smiles with subjective amusement ratings equal to zero and full amusement judgment confidence. This initial selection brought about a sample of 30 authentic and 30 fake expressions of amusement for each social target (600 movies).

Smile dynamics

Each movie showed a transition from a neutral/moderately positive facial expression to an apparent expression of amusement: in the initial phase (lasting 500 ms, 15 frames) the social target's face was still, and in the subsequent phase (lasting 1500 ms, 45 frames) showed the smiling expression. The last frames of each video clip contained the apex of the smile. Although smile offset can also be informative of amusement authenticity, the smile offset was excluded from the video clips in order to cover their entire duration (2 s) with a short rTMS train.

We analyzed facial markers of authentically and falsely amused smiles (Ekman, 2001; Shiota et al., 2003; Ambadar et al., 2009; Krumhuber and Manstead, 2009; McLellan et al., 2010; Niedenthal et al., 2010). To analyze the key muscles involved in smiling, two independent raters blind to the experimental conditions evaluated the activation of the orbicularis oculi (i.e., the muscle that makes crow's feet at the outer corner of the eye; AU6 according to the Ekman's Facial Action Coding System; Ekman et al. 2002), and the zygomaticus major (i.e., the muscle that extends the mouth and acts as a lip corner puller; AU12), in the 16 authentically and 16 falsely amused smiles using a 3-point scale (scored 0, 0.5, 1). Rater's judgments were highly correlated ($r > .7$) and were thus averaged. Using movement analysis software (Kinovea 0.8.15), we also tracked changes in mouth extension (distance in pixels between the two lip corners) over time, and checked the size of the maximal enlargement (increase in lip corner distance relative to the initial frame), when it occurred in time, and the peak velocity of the movement. Table 1 shows activation ratings, motion parameters and statistical comparisons between the 16 authentically and 16 falsely amused smile movies.

Table 1. *Mean values ± SD of activation ratings and motion parameters computed for authentically and falsely amused smiles.*

	AU6 activation rating (0-1)	**AU12 activation rating (0-1)**	**Maximal mouth enlargement (change in pixel)**	**Time of maximal mouth enlargement (ms)**	**Mouth enlargement peak velocity (pixel/ms)**
Authentic amusement	0.72 ± .21	0.92 ± 0.14	24.19 ± 4.48	1510 ± 318	0.018 ± 0.006
False amusement	0.58 ± .22	0.82 ± 0.15	21.06 ± 6.50	1515 ± 295	0.015 ± 0.005
Statistical comparison	$t_{30} = 1.79$, $P = 0.08$	$t_{30} = 1.82$, $P = 0.08$	$t_{30} = 1.58$, $P = 0.12$	$t_{30} = 0.07$, $P = 0.94$	$t_{30} = 1.53$, $P = 0.14$

Mean AU6 and AU12 activation ratings, maximal mouth enlargement and peak velocity tended to be greater for authentically amused smiles relative to falsely amused smiles, although none of the analyses reached statistical significance. Also, maximal mouth enlargement occurred non-significantly earlier for authentically than for falsely amused smiles (Table 1). In a further analysis, we z-transformed these dependent variables and submitted them to a Measure (AU6 activation, AU12 activation, maximal mouth enlargement, time of maximal mouth enlargement, mouth enlargement peak velocity) x Expression type (authentic vs. falsely amused) ANOVA that showed a main effect of Expression type ($F_{1,30} = 5.63$, $P = 0.02$), with greater values for authentically than for falsely amused smiles. Taken together, these analyses suggest that, while none of the facial markers alone could have been used to robustly discriminate between the two types of facial expressions, observers could have used a combination of the different markers to infer amusement authenticity (for similar conclusions see Abe et al. 2002; Niedenthal et al. 2010).

Experimental tasks

In the Empathic accuracy (EA) task (Fig. 1A), participants were presented with authentic and falsely amused smile movies and asked to monitor the social target's expression to explicitly infer what she/he truly felt (i.e., authentic amusement, no amusement). To rule out that any change in EA task performance could have been due to nonspecific effects of rTMS, we also assessed participants'

performance on a difficulty-matched non-social (NS) control task (Fig. 1B) using the same set of stimuli used in the EA task. Similarly to the EA task, the NS task required participants to constantly monitor the social target's face, particularly the eye and mouth regions (which are critical for discriminating between real and fake expressions of amusement; Ekman 2001; Shiota et al. 2003; Ambadar et al. 2009; Krumhuber and Manstead 2009; McLellan et al. 2010; Niedenthal et al. 2010). However, in contrast to the EA task, the NS task required participants to judge spatial features of the observed expressions (i.e., whether a white bar presented for 350 ms at the end of each clip was located below or above the social target's eye or mouth corners), rather than empathically understanding whether these expressions were associated with authentic amusement or not (Fig. 1B, D).

Using custom software (programmed in C#), we extracted the X and Y coordinates of each social target's outer canthus and labial commissure (over both the left and right sides of the face) from the very last frame of each video-clip. The estimated positions were then shifted vertically on the Y axis in order to locate the white bars above and below the mouth or the eye. To ensure subjects explored the whole face for the duration of the video, the white bar appeared after the end of the video clip, and observers were instructed to pay attention to the social target's facial movements and track the position of the outer canthus and labial commissure throughout the entire movie. The white bar remained onscreen for 350 ms and was followed by the instruction: "Mouth: above or below" or "Eye: above or below". The position of the white bar was equally distributed above and below our landmarks (eyes and mouth).

Stimuli and task validation

Videos were selected based on the results of five pilot studies carried out with a total of 100 subjects who did not participate in any of the subsequent rTMS or electrical stimulation experiments.

Five sequential pilot experiments (**Pilot 1**, **Pilot 2**, **Pilot 3**, **Pilot 4** and **Pilot 5**) were conducted to select the video clips for the main interferential experiments. Only stimuli associated with ~75%

accuracy in both the EA and the NS tasks were included in the final pool. In each pilot experiment, 20 participants (10 females) were tested.

-Pilot 1: In the first pilot experiment, participants watched the whole set of 600 clips (30 authentic/30 fake expressions x 10 social targets) and performed the EA task. Each clip was presented only once. Based on participants' EA performance, 30 clips were selected for each social target so that each clip was associated with a percentage of correct responses ranging between 65% and 85% across participants. One social target (a female) was excluded from the final sample because of an insufficient number of videos meeting the accuracy criterion.

-Pilot 2: Participants performed the EA task on a set of 270 clips (15 authentic/15 fake expressions x 9 social targets) that were selected in PE1. Each clip was presented twice. Based on PE2, 8 clips for each social target were selected (accuracy range 65-85%) and another social target was excluded.

-Pilot 3: Participants performed both the EA and the NS tasks on a set of 64 clips (4 authentic/4 fake expressions x 8 social targets). In the EA task, each of the 64 clips was presented only once. In the NS task, each movie was repeated 4 times for a total of 256 trials. For each movie, a facial landmark (left/right outer canthus, left/right labial commissure) and a position of the bar (above or below the landmark) were selected. Then, for each of the 4 movie repetitions, we manipulated the Y coordinates of the white bar by gradually spacing it from the selected landmark by 4-5 pixels. In this way, we manipulated the difficulty of the spatial judgment across the 4 movie repetitions and could select the position of the white bar that was closest to the 75% accuracy criterion in the NS task (8 smiles x 8 social targets x 4 positions).

-Pilot 4: Participants performed both the EA and the NS tasks on the same set of movies used in PE3. For the NS task, we rearranged the position of the white bar and tested 3 positions for each movie (192 trials) on the basis of the PE3 data; the position of the white bar that came the closest to yielding 75% accuracy in PE3 was selected as the median bar in PE4, and two additional bars, one above and

one below, were added. Based on participants' performance in PE4, we selected the final set of stimuli that included 4 smiles (2 authentic/2 fake expressions) x 8 social targets (4 female).

-**Pilot 5**: In the last pilot experiment, the final set of 32 stimuli was tested again for both the EA and NS tasks to ensure the tasks were matched for difficulty. Results confirmed that the percentage of correct responses ranged between 65% and 85% for all the stimuli in both tasks. Moreover, a paired *t*-test comparing the percentages of correct responses in the two tasks confirmed the successful matching (t_{19} = 0.38, P = 0.71).

These pilot studies allowed us to select a subset of 32 movies from 8 social targets, and ensured that performance on the two experimental tasks was similar for each stimulus used in the main experiments (~75% accuracy).

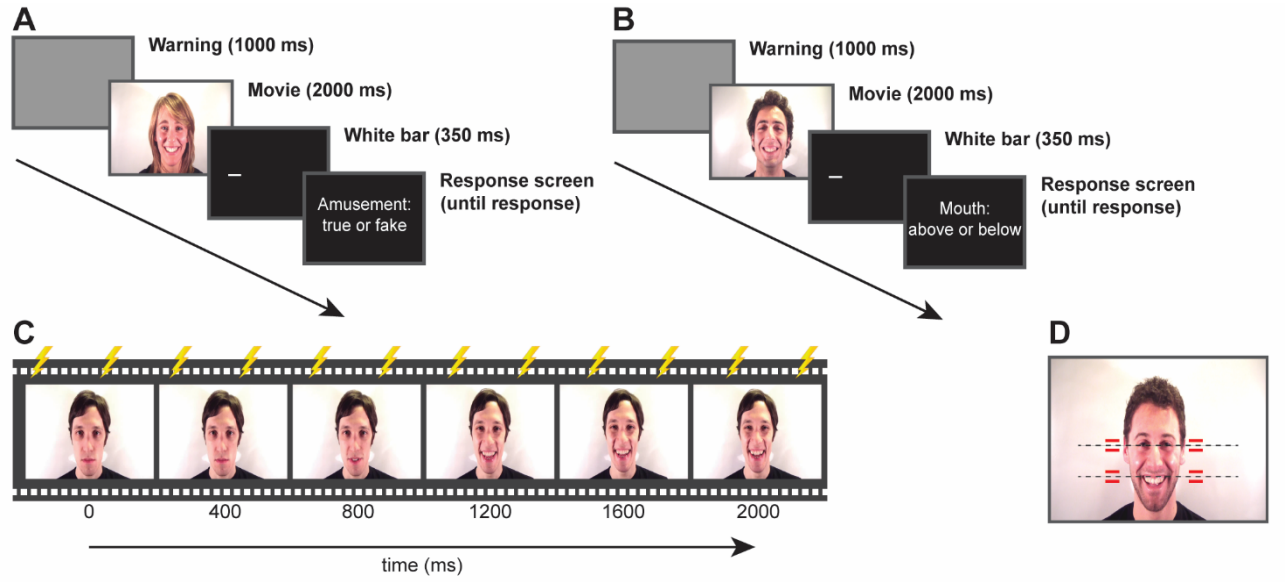

Figure 1. *Schematic representation of the experimental paradigm. (A) In the EA task, participants were asked to judge whether the smiling social target was feeling authentic or false amusement. (B) In the NS task, participants had to judge whether the white bar appeared above or below the social target's mouth/eye (above the mouth in the example). (C) In both tasks, a continuous 6 Hz train of 12 pulses of rTMS or electrical stimulation was applied at onset of the movies. (D) Exemplar representation showing (in red) the possible locations of appearance of the white bar relative to the social target's mouth and eye.*

Procedure

Custom software (written in C#) was used to control the video clip sequence and trigger TMS or electrical stimulation. For the rTMS experiments, participants were initially tested in electrophysiological and neuronavigation sessions in which rTMS intensity and coil position over the scalp were determined, respectively (see below). Then, participants were presented with task instructions and an example of the trial structure. Each subject performed the EA and NS tasks in two separate sessions presented in a counterbalanced order. For each task, two blocks of 16 active rTMS trials and two blocks of 16 sham rTMS trials were performed in an ABBA/BAAB counterbalanced order (i.e., active-sham-sham-active or sham-active-active-sham). After each block, a break of ~1 minute was allowed. A break of ~5 minutes was allowed between the two sessions.

For both tasks, each trial started with a grey screen (1000 ms) followed by the video clip (2000 ms). After the clip, a white bar (24 x 1 pixels subtending 0.72 x 0.03° of visual angle) appeared on a black screen (350 ms), followed by a response screen (presented until response). Participants provided their response by pressing one of two keys on the keyboard. They were asked to answer as accurately as possible, using the index and middle fingers of the right hand (ipsilateral to the target stimulation site). After the keypress, the response screen was replaced by a black screen (inter-trial interval: 7000-9000 ms).

On each trial, a time-locked single train of subthreshold 6Hz rTMS (12 pulses) was administered using a figure-of-eight coil (diameter: 70 mm) connected to a Magstim Rapid2 stimulator (Magstim, Whitland, Dyfed, U.K.). The coil was placed over a target brain region that differed by participant group (IFG, SI, mPFC or TPJ). The rTMS train lasted 2 seconds. It was administered at the onset of the movie and thus covered its entire duration (Fig. 1C). The stimulation intensity corresponded to 90% of the resting motor threshold (see below). During active rTMS blocks, the intersection of the coil was placed tangentially to the scalp directly above the scalp location of the target region. Sham rTMS blocks were performed by tilting the coil at 90° over the same target region, to provide some

scalp sensations and TMS sounds similar to active stimulation but without inducing a current in the brain.

Since online rTMS may cause slight activations of facial muscles, and altering facial mimicry can impair visual recognition of positive expressions (Oberman et al., 2007; Wood et al., 2016), we performed a peripheral site control experiment (PS). In the PS experiment, we directly stimulated participants' face using electric pulses. Specifically, we stimulated the right masseter muscle by applying a time-locked single train of 6Hz electrical square wave pulses (pulse duration: 0.2 ms), thus mimicking the stimulation frequency used in the rTMS experiments. Ag-AgCl surface electrodes connected to a DS7A Digitimer Constant Current Stimulator (Digitimer, Hertfordshire, UK) were placed between the condyle and the coronoid process of the mandible, immediately below the zygomatic process. Electrode position and stimulation intensity were individually adjusted to evoke facial contractions that were visually similar to those evoked by active rTMS (mean intensity = 0.41 mA, SD = 0.06). For each task, two blocks of 16 active stimulation trials and two blocks of non stimulation (control) trials were performed in an ABBA/BAAB counterbalanced order.

At the end of the experimental session, participants in the TMS or PS experiments were asked to provide subjective ratings of the unpleasant sensations caused by the magnetic or electrical stimulation, using a 5-point Likert scale ranging from 1 ('not unpleasant at all') to 5 ('extremely unpleasant').

Electrophysiological and neuronavigation sessions

To set rTMS intensity, the resting motor threshold (rMT) was estimated for all participants in a preliminary phase of the experiment using standard procedures (Rossi et al., 2009). Motor-evoked potentials (MEPs) induced by stimulation of the right motor cortex were recorded from the left first dorsal interosseous (FDI) by means of a Biopac MP-35. EMG signals were band-pass filtered (30-

500 Hz) and digitized (sampling rate: 5 kHz). Pairs of Ag-AgCl surface electrodes were placed in a belly-tendon montage with a ground electrode on the wrist. The intersection of the coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle away from the midline. The rMT was defined as the minimal intensity of stimulator output that produces MEPs with an amplitude of at least 50 μV in the FDI with 50% probability (Rossini et al., 2015).

Each brain area was individually targeted using image-guided neuronavigation. The coil position was identified on each participant's scalp using the SofTaxic Navigator System (Electro Medical Systems, Bologna, Italy). Skull landmarks (nasion, inion and 2 preauricular points) and ~80 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra digitizer (Northern Digital), as in our previous research (Avenanti et al. 2007, 2012, 2013a; Tidoni et al. 2013; Jacquet and Avenanti 2015). An individual estimated magnetic resonance image (MRI) was obtained for each subject through a 3D warping procedure that fits a high-resolution MRI template with the participant's scalp model and craniometric points. This procedure has been proven to ensure a global localization accuracy of roughly 5 mm, a level of precision closer to that obtained using individual MRIs than can be achieved using other localization methods (Carducci and Brusco, 2012).

Stimulation sites were identified on the basis of previous fMRI studies using the SofTaxic Navigator (IFG, SI and TPJ), or established anatomical methods (mPFC). For IFG, SI and TPJ, Talairach coordinates of target regions and corresponding scalp projections were automatically estimated by the SofTaxic Navigator from the MRI-constructed stereotaxic template. When necessary, coordinates in Talairach space were obtained by converting MNI coordinates reported in previous studies using GingerALE 2.3.1. To target sensorimotor regions, we selected Talairach coordinates corresponding to the cortical face representations in premotor and somatosensory sites. The IFG scalp site was localized based on the following coordinates: x = 47, y = 8, z = 28, which were identified on the basis of previous fMRI meta-analyses exploring activations associated with the execution and/or observation of facial movements and emotional expressions (Molenberghs et al., 2009; Caspers et al.,

2010; Grosbras et al., 2012). The S1 site was identified based on the following coordinates: x = 56, y = -16, z = 40, corresponding to the face representation in the post-central gyrus (Huang and Sereno, 2007; Dresel et al., 2008; Kopietz et al., 2009; Holle et al., 2013).

Key nodes of the mentalizing network were identified as follows: the mPFC site was identified at one-third of the distance between the nasion and the inion on the midline between the left and the right preauricular points, as in previous TMS studies (Harmer et al., 2001; Mattavelli et al., 2011, 2013). The right TPJ site was localized based on the following coordinates: x = 51, y = -54, z = 21, which were identified on the basis of neuroimaging studies exploring areas related to theory of mind and mentalizing (van Overwalle and Baetens, 2009; Mar, 2011; Bzdok et al., 2012).

Locations of scalp regions identified by neuronavigation (IFG, SI, TPJ) or anatomical methods (mPFC) were marked with a pen on each participant's head and used to place the rTMS coil. Then, individual Talairach coordinates corresponding to the projection of the targeted scalp sites on the surface of the MRI-constructed stereotaxic template were automatically estimated through the neuronavigation system. These estimated coordinates indicate the most superficial cortical site where rTMS effects are expected to be maximal. Group mean coordinates are illustrated in Figure 2.

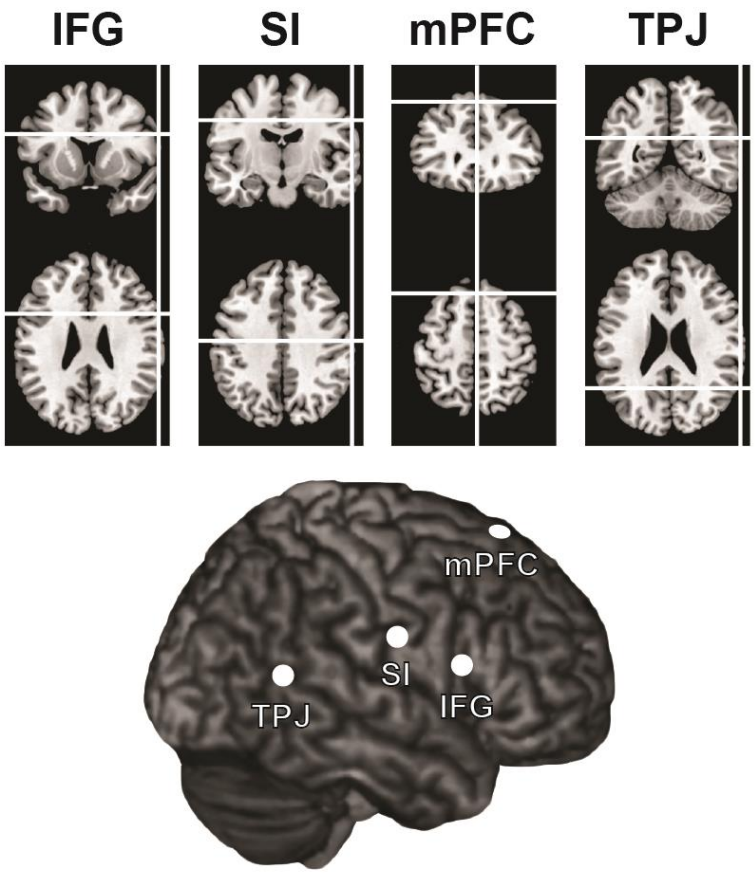

Figure 2. *Schematic representation of the brain stimulation sites reconstructed on a standard template using MRIcron (MRIcron/NPM/dcm2nii). Talairach coordinates corresponding to the projection of the IFG, SI, mPFC and TPJ scalp sites on the brain surface were individually estimated through the neuronavigation system. Group mean brain surface coordinates ± SD for the IFG site were: x = 56.1 ± 1.1; y = 7.4 ± 1.2; z = 29.6 ± 2.3. Coordinates for the SI were: x = 57.8 ± 0.8; y = -17.0 ± 0.9; z = 39.2 ± 1.0. Coordinates for the mPFC were: x = 0.0 ± 0.7; y = 22.0 ± 4.8; z = 56.6 ± 4.3. Coordinates for the TPJ were: x = 58.0 ± 0.8; y = -54.8 ± 1.8; z = 22.1 ± 1.5. Talairach coordinates were then converted to the MNI space (using GingerALE 2.3.1) for visualization with the MRIcron software.*

Data Analysis:

Behavioral data were processed offline. Accuracy on each task (EA, NS) was converted into measures of sensitivity (d') and response bias (β) in accordance with signal detection theory (Macmillan and

Creelman, 1991) for each stimulation type (active, control) and stimulation site (SI, IFG, TPJ, mPFC, PS). For the EA task, two types of responses were scored as correct: a "fake" response to a false expression of amusement (hit) and a "true" response to an authentic expression of amusement (correct rejection). Two types of responses were scored as incorrect: a "fake" response to an authentic expression (false alarm) and a "true" response to a fake expression (miss). For the NS task, responses were coded as follows: "above" to a white bar above the mouth or the eye (hit), "below" to a white bar below the mouth or the eye (correct rejection), "above" to a white bar below the mouth or eye (false alarm) and "below" to a white bar above the mouth or eye (miss). Mixed factors ANOVAs were performed on d' and β with stimulation type (active, sham) as a within-subjects factor and stimulation site (IFG, SI, mPFC, TPJ, PS) as a between-subjects factor. Post-hoc analysis was performed using the Newman-Keuls test to correct for multiple comparisons. *Partial eta*^{2} was computed as a measure of effect size for the main effects and interactions, whereas repeated measures *Cohen's d* was computed for post-hoc comparisons. To test the robustness of the ANOVA results, we additionally performed Wilcoxon matched-pairs tests to confirm the significance of critical comparisons (i.e., sham vs. active stimulation) across stimulation sites.

Results

rTMS over IFG and SI interferes with EA task sensitivity, not response bias

The stimulation type x stimulation site ANOVA conducted on measures of EA task sensitivity (d') revealed significant main effects of stimulation site ($F_{4,75}$ = 3.02, P = 0.02, *Partial eta*^{2} = 0.14) and stimulation type ($F_{1,75}$ = 11.79, P = 0.001, *Partial eta*^{2} = 0.14; Fig. 3A). Importantly, these two main effects were qualified by a significant two-way stimulation site x stimulation type interaction ($F_{4,75}$ = 4.82, P = 0.001, *Partial eta*^{2} = 0.20). Post-hoc analysis showed that the interaction was accounted for by the strong reduction in task sensitivity found in the IFG and SI groups during active rTMS (mean d' value ± SD.: IFG = 1.20 ± 0.10; SI = 1.07 ± 0.09) compared to sham rTMS (IFG = 1.81 ± 0.13; SI

= 1.58 ± 0.14; all *Cohen's d* > 0.94, all $P < 0.002$). No change in sensitivity due to active stimulation was found when stimulating mPFC (sham rTMS: 1.87 ± 0.81; active rTMS: 1.80 ± 0.65; $P = 0.96$), TPJ (sham rTMS: 1.66 ± 0.18; active rTMS: 1.65 ± 0.11; $P = 0.96$), or peripheral site (no stimulation: 1.84 ± 0.18; active stimulation: 1.94 ± 0.14; $P = 0.80$).

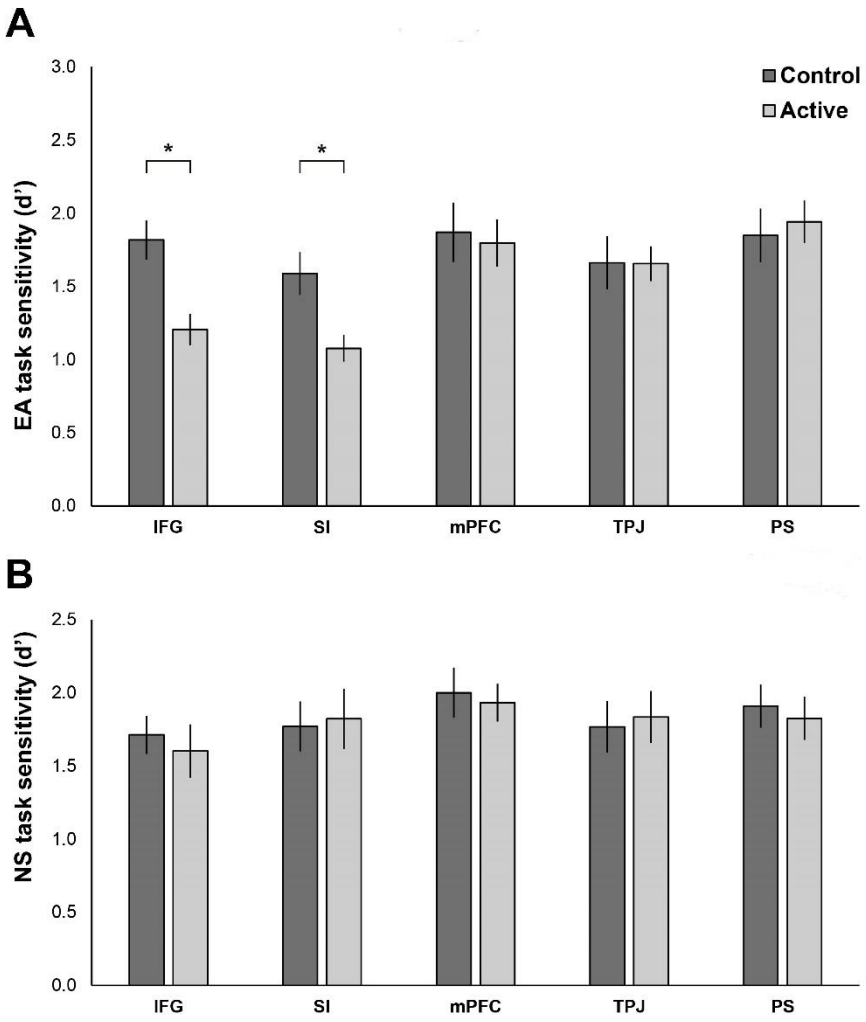

Figure 3. (A) *Mean sensitivity (d') in the EA task. Dark-gray and light-gray columns represent control and active stimulation, respectively. Active stimulation of IFG and SI, but not of mPFC, TPJ or PS, reduced sensitivity in the EA task. No change in sensitivity due to active stimulation was observed in the NS task.* ***(B)*** *Mean sensitivity (d') in the NS task. Dark-gray and light-gray columns represent control and active stimulation, respectively. No change in sensitivity due to active stimulation was observed. Asterisks indicate significant post-hoc comparisons (P < 0.05). Error bars denote s.e.m.*

The stimulation type x stimulation site ANOVA performed on the β index (Table 2) showed no significant no main effects or interactions (all $F < 2.14$, $P > 0.1$), indicating that neither magnetic stimulation of the cortex nor electrical stimulation of the face muscles affected response bias in the EA task.

Table 2. *Mean β index ± SD computed for the EA task and the NS task in the control (sham rTMS or no electrical stimulation) and active interference conditions (active rTMS or active electrical stimulation).*

	IFG		**SI**		**mPFC**		**TPJ**		**PS**	
	Control	**Active**	**Control**	**Active**	**Control**	**Active**	**Control**	**Active**	**Control**	**Active**
EA task	2.2 ± 3.1	1.5 ± 0.5	1.2 ± 1.2	0.9 ± 0.3	1.3 ± 0.6	1.2 ± 0.7	1.2 ± 0.6	1.1 ± 0.6	1.5 ± 1.0	1.3 ± 0.9
NS task	1.7 ± 1.8	1.6 ± 1.4	1.7 ± 1.4	1.9 ± 1.4	1.9 ± 1.6	1.8 ± 1.8	1.6 ± 1.3	1.4 ± 1.1	2.5 ± 1.8	1.6 ± 1.2

The stimulation type x stimulation site ANOVA performed on d' for the NS task (Fig. 3B) showed no significant main effects or interactions (all $F < 0.61$, $P > 0.66$). A further ANOVA performed on the β index (Table 2) showed no main effects or interactions (all $F < 1.51$, $P > 0.22$).

Thus, performance on the NS task was not affected by interference with sensorimotor regions, the mentalizing network, or peripheral facial muscles. This suggests that rTMS over sensorimotor regions did not simply impair visual processing of facial stimuli but specifically worsened the ability to accurately infer mental states based on such processing.

Changes in task sensitivity are selective

In a further analysis, we directly compared performance on the two tasks. A task (EA, NS) x stimulation type x stimulation site mixed factors ANOVA on d' showed significant main effects of

stimulation type ($F_{1,75}$ = 5.69, P = 0.02, *Partial eta2* = 0.07) and stimulation site ($F_{4,75}$ = 2.65, P = 0.04, *Partial eta2* = 0.12), a significant two-way task x stimulation type interaction ($F_{1,75}$ = 4.83, P = 0.03, *Partial eta2* = 0.06) and, critically, a significant three-way task x stimulation type x stimulation site interaction ($F_{3,75}$ = 2.69, P = 0.04, *Partial eta2* = 0.13). This interaction was driven by greater active rTMS interference with EA task performance relative to NS task performance in the IFG and SI groups, compared to the mPFC, TPJ and PS groups {[(sham-active)EA - (sham-active)NS]$_{IFG,SI}$ > [(sham-active)EA - (sham-active)NS]$_{mPFC,TPJ,PS}$; two sample *t*-test, P = 0.002}. The significance of the triple interaction provided the statistical grounds for carrying out separate stimulation type x stimulation site ANOVAs for the two tasks (see previous paragraph).

To directly test the interferential effect of rTMS over different brain regions, a stimulation site x task mixed factors ANOVA was conducted on the difference in performance (*d'*) between the sham and active rTMS conditions for each group of participants (Fig. 4). The ANOVA showed no significant main effect of stimulation site ($F_{4,75}$ = 2.01, P = 0.10), a significant main effect of task ($F_{1,75}$ = 4.83, P = 0.03, *Partial eta*^{2} = 0.06) and, most importantly, a significant stimulation site x task interaction ($F_{4,75}$ = 2.69, P = 0.04, *Partial eta*^{2} = 0.13). Greater interference with EA task performance was obtained with IFG (0.61 ± 0.45) and SI stimulation (0.51 ± 0.57) than with mPFC (0.07 ± 0.69), TPJ (0.01 ± 0.51) and PS (-0.09 ± 0.63) stimulation (all *Cohen's d* > 0.69, all P < 0.042) which in turn did not differ from one another (all P > 0.63). Statistically comparable interferential effects were found for EA task performance when stimulating IFG and SI (P = 0.64). These interferential effects were greater for the EA task than for the NS task when stimulating the same regions (all *Cohen's d* > 0.74, P < 0.013). No significant effects were found for the NS task (all P > 0.49).

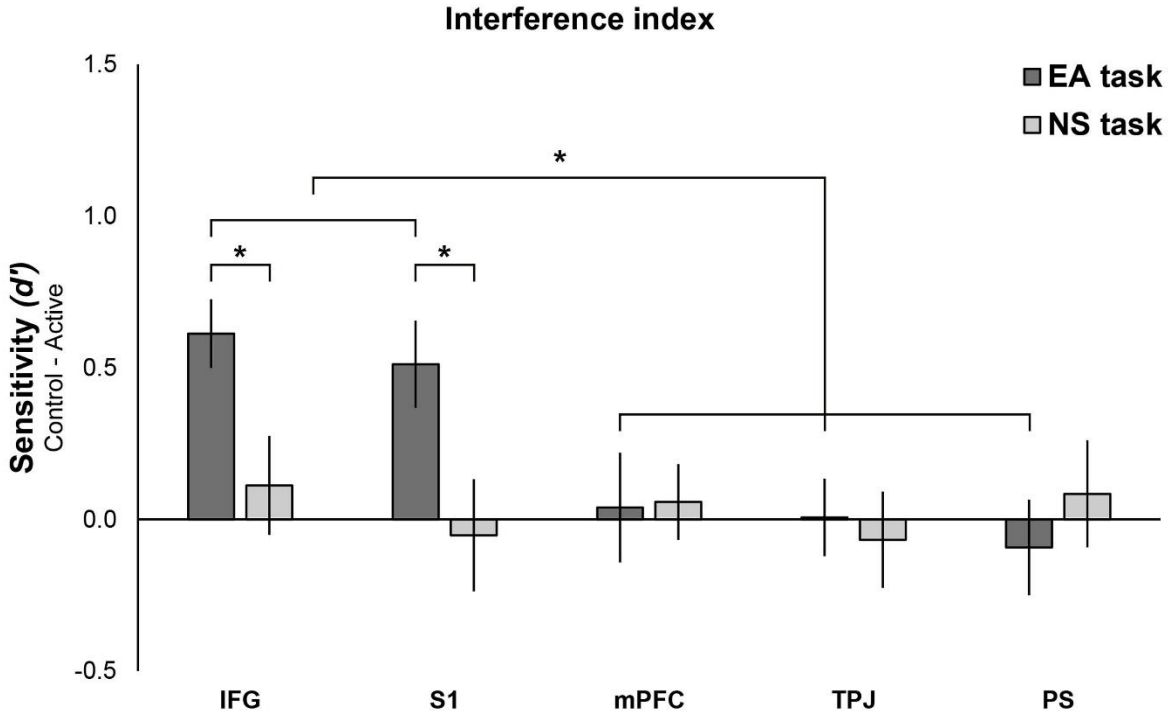

Figure 4. *Interferential effect of active relative to control stimulation on sensitivity (d') in the EA (dark-gray) and NS (light-gray) tasks. Positive values indicate greater interference with task performance. Greater EA interference was obtained with IFG and SI stimulation relative to mPFC, TPJ and PS stimulation. No similar effects were found for the NS task. Asterisks indicate significant post-hoc comparisons (P < 0.05). Error bars denote s.e.m.*

To ensure that any interferential effects of rTMS were not due to speed-accuracy trade-offs, we also analyzed response times (RTs) in the two tasks (Table 3). The task x stimulation type x stimulation site ANOVA performed on RTs revealed no main effects or interactions (all $F < 1.42$, $P > 0.23$), ruling out any speed-accuracy trade-offs.

Table 3. *Mean RTs ± SD computed for the EA task and the NS task in the control (sham rTMS or no electrical stimulation) and active interference conditions (active rTMS or active electrical stimulation).*

	IFG		SI		mPFC		TPJ		PS	
	Control	**Active**	**Control**	**Active**	**Control**	**Active**	**Control**	**Active**	**Control**	**Active**
EA task	665 ± 281	689 ± 240	659 ± 200	633 ± 191	730 ± 243	712 ± 227	756 ± 349	721 ± 295	689 ± 213	689 ± 246
NS task	727 ± 322	675 ± 256	670 ± 230	651 ± 233	699 ± 247	735 ± 255	712 ± 348	705 ± 356	668 ± 235	682 ± 179

Ruling out nonspecific effects

Finally, we performed a series of control analysis to test the influence of nonspecific effects. We checked whether the unpleasantness of the stimulation could explain our results. A one-way ANOVA on unpleasantness ratings showed no significant effect of stimulation site ($F_{4,75}$ = 2.06, P = 0.1; see Table 4). Adding these ratings as covariates in the preceding analyses (d', β, RTs) did not change the pattern of statistical results reported above and revealed no main effects of or interactions with the covariate.

Table 4. *Mean subjective ratings ± SD of the unpleasantness felt during active brain stimulation (active rTMS over IFG, S1, mPFC and TPJ) or peripheral stimulation (electrical stimulation of the PS).*

IFG	SI	mPFC	TPJ	PS
3.0 ± 1.3	2.3 ± 0.9	2.1 ± 0.5	2.4 ± 1.2	2.6 ± 0.8

In a series of analyses restricted to the four rTMS groups (IFG, SI, mPFC, TPJ), we checked the influence of rTMS intensity. Values of rMT (mean ± SD) were not statistically different across the four rTMS groups although there was a non-significant trend (IFG group: 55 ± 4%; S1 group: 59 ± 6%; mPFC group: 48 ± 4%; TPJ group: 57 ± 8%; $F_{3,60}$ = 2.53, P = 0.07). To rule out that rTMS intensity affected our results, we first repeated all the previously reported mixed factors ANOVAs on d', β and RTs, focusing only on the four rTMS groups, and fully replicated the pattern of statistical results reported above for the rTMS groups. Then, we entered stimulation intensity as a covariate

(alone or in combination with unpleasantness ratings) in the same analyses and found no influence of such covariate(s).

Non-parametric control analyses of task performance

The main analyses indicated that EA task sensitivity (d') was strongly affected by rTMS over IFG and SI, as shown by the large effect sizes of the critical comparisons (active vs. control stimulation). Although d' values were normally distributed (Shapiro Wilk tests: all $P > .18$), to further show the robustness of our findings, we additionally performed non-parametric analyses on the critical comparisons.

Wilcoxon matched-pairs tests performed on d' values in the EA task confirmed the significance of the critical comparisons for the IFG and SI groups (all $P < 0.0097$), whereas the same comparisons were not significant for the mPFC, TPJ or PS groups (all $P > 0.53$). No significant comparisons were found for the NS task across groups (all $P > 0.36$).

Additionally, confirming the results of the parametric analyses, Wilcoxon matched-pairs test performed on the β index (Table 2) and RTs (Table 3) showed no significant difference between active and control stimulations across tasks and groups (all $P > 0.36$).

Discussion

Sensorimotor and mentalizing networks have often been conceptualized as supporting mutually exclusive mechanisms for social perception and empathy. However, recent theoretical (Keysers and Gazzola, 2007; Uddin et al., 2007; Zaki et al., 2012; Lamm and Majdandžić, 2015) and empirical (Wheatley et al., 2007; Zaki et al., 2009b; Lombardo et al., 2010; Redcay et al., 2010; Schippers et al., 2010; Wolf et al., 2010; Lamm et al., 2011; Spunt and Lieberman, 2013; Raz et al., 2014) work

suggests that both networks are recruited during complex social tasks and could provide routes to understanding others. Therefore, a central aim of neuroscience is to clarify the circumstances in which these networks are critical for social cognition (Mitchell 2009; Zaki et al. 2012; Avenanti et al. 2013b).

This is particularly relevant for the development of mechanistic models of EA (i.e., the ability to accurately recognize and understand what another individual is experiencing; Ickes and Stinson 1990; Levenson and Ruef 1992; Ickes 1997; Zaki et al. 2008, 2009), but also for empathy in general, as sensorimotor and cognitive processes underlying EA are supposed to provide a key mechanism for evoking affective sharing processes underlying the empathic response (Preston and de Waal 2002; Singer and Lamm 2009; Batson 2011; Decety et al. 2012; Bird and Viding 2014; Zaki 2014). Previous empathy research has established a close link between vicarious experience of the emotions felt by others and neural activity in affective brain regions like the anterior insula and the anterior midcingulate cortex (Wicker et al. 2003; Singer et al. 2004; Jabbi and Keysers 2008; Fan et al. 2011; Lamm et al. 2011; see in particular Corradi-Dell'Acqua et al. 2011; Rütgen et al. 2015a, 2015b; Zaki et al. 2016 for recent advancements supporting a simulative account of affective sharing).

Yet, multiple mechanisms are likely involved in EA, possibly depending on task demands and the information available to make inferences about what other people are feeling.

In the present study, we provide causal evidence that sensorimotor networks, more so than mentalizing networks, play a crucial role in evaluating the authenticity of observed smiles. We designed a new EA task adapted from previous psychological and neuroscientific research (Ickes and Stinson, 1990; Levenson and Ruef, 1992; Ekman, 2001; Shiota et al., 2003; Zaki et al., 2008; Ambadar et al., 2009; Krumhuber and Manstead, 2009; McLellan et al., 2010; Tidoni et al., 2013) and used rTMS to test whether sensorimotor (IFG and SI) and mentalizing areas (mPFC and TPJ) are necessary for drawing explicit inferences about the amusement supposedly felt by smiling social targets.

We observed that active rTMS administered over the observers' face representation in IFG and SI, but not over mPFC or TPJ, disrupted EA. Thus, the reduction in EA performance was not due to nonspecific effects of rTMS, but to the interference with fronto-parietal regions involved in controlling and sensing facial movements. A further control experiment also assured that the reduction in EA was not due to the peripheral interference with facial muscles indirectly caused by rTMS. Indeed, direct electrical stimulation of facial muscles (PS stimulation) did not affect EA. Thus, the reduction in EA performance was due to cortical sensorimotor interference. Our signal detection approach demonstrated that the EA disruption consisted of a pure reduction in participants' sensitivity to the authenticity of amused expressions, rather than a change in participants' response bias. Further analyses ruled out that the decrease in sensitivity was caused by a trade-off in which participants achieved faster RTs by sacrificing accuracy. Moreover, differences in stimulation unpleasantness or rTMS intensity could not explain the results.

Remarkably, no change in performance due to sensorimotor (or mentalizing network) interference was found in a difficulty-matched NS task requiring participants to monitor the social target's expression but not to explicitly infer amusement authenticity. Thus, the reduction in EA performance did not simply reflect impaired low-level processing of the social target's facial movements (i.e., the emotion expression), but, rather, a disruption of explicit inferences about the covert mental state underlying those movements (i.e., the social target's emotional feeling). These findings highlight, for the first time, the functional relevance of IFG and SI to accurate recognition of the authenticity of amused expressions, and thus suggest a grounding of EA in sensorimotor networks.

From neural correlates to neural bases of EA

Mounting evidence suggests that both sensorimotor and mentalizing networks are engaged during EA tasks (Zaki et al., 2009b; Harvey et al., 2013), although none of these studies have used causal methods to establish the neural bases for discrimination between authentic and false emotional

expressions. Zaki and colleagues (2009; see also Harvey et al. 2013) recently found that both sensorimotor and mentalizing networks show increased activity during accurate relative to inaccurate explicit inferences about social targets' emotional states. In their EA task, participants watched individuals discussing emotional autobiographical events and had to infer the underlying emotional feelings (Zaki et al., 2009b; Harvey et al., 2013). In the auditory domain, McGettigan and colleagues (2015) investigated brain activity associated with the ability to discriminate between authentic and fake laughter (McGettigan et al., 2015). As already mentioned in the introduction, in that study, inferences about laughter authenticity had to be based on social cues only, as participants had no prior knowledge or contextual information about the laughter. Under these conditions, McGettigan and colleagues (2015) found that neural activity in both networks predicted accurate emotion recognition. However, those correlational data could not answer the key question of whether sensorimotor and mentalizing networks are also essential for EA.

Here, by using a novel EA task and active stimulation of cortical sites, compared to control stimulations, we were able to provide the first direct causal evidence that the motor and somatosensory face representations in IFG and SI are functionally relevant to empathic inference of amusement authenticity from smiles, whereas frontal and parieto-temporal regions involved in mental state reasoning, i.e., the rTPJ and mPFC, do not appear to play similarly critical roles. These findings indicate that EA performance is (at least partially) grounded in the self: inferring amusement authenticity from smiling facial expressions requires one's own sensorimotor networks for making and sensing facial movements.

Sensorimotor grounding of EA

A growing body of evidence suggests that sensorimotor regions play key roles in emotion processing and social cognition (Pobric and Hamilton, 2006; Avenanti et al., 2007; D'Agata et al., 2011; de Gelder et al., 2012; Tidoni et al., 2013; Bolognini et al., 2014; Costa et al., 2014; Urgesi et al., 2014; Jacquet and Avenanti, 2015; Tamietto et al., 2015; Valchev et al., 2016). It is well established that

IFG and SI show overlapping activations when participants make emotional expressions and when they see the same expressions or hear associated nonverbal vocalizations (Carr et al., 2003; Winston et al., 2003; Leslie et al., 2004; Dapretto et al., 2006; Warren et al., 2006; Keysers et al., 2010). IFG and SI are also active both during the execution and the observation of actions, and are considered to be part of a mirroring network involved in simulating observed actions within one's own sensorimotor system (Caspers et al. 2010; Keysers et al. 2010; Gallese and Sinigaglia 2011; Avenanti et al. 2013b; Valchev et al. 2016). Also, previous studies have shown that more empathic people show stronger activation in the IFG and SI (and interconnected sensorimotor regions) than less empathic people when they are watching the actions or the emotions of others (Gazzola et al., 2006; Schulte-Rüther et al., 2007; Pfeifer et al., 2008; Avenanti et al., 2009). However, a major issue hampering the development of a neuroscientific model of EA has been the lack of established connections between these neuroimaging findings and key behavioral indices of EA (but see (Zaki et al., 2009b; Harvey et al., 2013; McGettigan et al., 2015). Our study significantly expands upon previous evidence by demonstrating that those sectors of IFG and SI showing vicarious activations are not only correlated with stable empathic dispositions for sharing emotions, but also critical for EA performance. These findings establish a strong and direct causal link between sensorimotor brain networks and emotion understanding that was only suggested in the past (e.g. Carr et al. 2003; Avenanti et al. 2005).

What is the specific role of sensorimotor networks in understanding others' emotions?

Theoretical models propose that one mechanism for inferring the unobservable emotional feelings of others is to simulate their observed facial movements within one's own sensorimotor system (Adolphs et al. 2000; Adolphs 2002; Gallese et al. 2004; Goldman and Sripada 2005; Gallese 2007; Keysers et al. 2010; Niedenthal et al. 2010; Gallese and Sinigaglia 2011; Avenanti et al. 2013b; Wood et al. 2016). According to these models, sensory representations of observed facial expressions in high-order visual regions (e.g., the superior temporal sulcus, STS) would be coupled with sensorimotor representations of the same expressions in the IFG and SI. This sensorimotor embodiment would help

observers to intuitively grasp what the other person is experiencing. Some theorists also maintain that sensorimotor simulation would support access to stored knowledge, grounded in the distributed emotion system (including the anterior insula and cingulate cortex), about the emotional states associated with the facial expression (Goldman and Sripada, 2005; Niedenthal et al., 2010; Wood et al., 2016). Thus, when observing facial expressions in others, activity in sensorimotor networks may partially or fully reactivate related concepts and affective states and thus contribute not only to accurate cognitive inferences about the underlying emotional feeling (i.e., EA) but also its sharing – as theorized by current neuroscientific models of empathy.

Remarkably, these theoretical models imply that sensorimotor regions are not only essential for perceptual processing of overt movements (i.e., the social target's facial expression), but also for accurate inference of the covert mental state underlying those movements (i.e., the social target's emotional feeling).

However, to date these hypotheses have received only partial empirical support from studies using causal methods. Those studies have established that both stable brain lesions and transient rTMS interference with inferior frontal and somatosensory regions reduce performance on tasks requiring participants to process mouth actions (Pazzaglia et al., 2008a; Michael et al., 2014) and emotional facial expressions (Adolphs et al. 2000; Pitcher et al. 2008; see also Keysers et al. 2010; Avenanti et al. 2013b). However, they used static pictures of actions or facial expressions and did not clarify to what extent IFG and SI: i) are necessary for perceptual processing of the dynamic facial movements which constitute the observed emotional expressions; or ii) play a role in higher-level explicit inferences about the emotional feelings underlying those facial movements (possibly via access to stored knowledge in affective brain regions). Our study provides evidence supporting the latter hypothesis. Indeed, one important feature of our findings is that rTMS over IFG and SI selectively disrupted performance on the EA task but not on the NS task. Similarly, to the EA task, the NS task required participants to monitor and track facial movements. Thus, we suggest that rTMS over

sensorimotor regions did not simply interfere with visual processing of facial movements. Rather, rTMS disrupted sensorimotor processing necessary for making sense of those movements and inferring the underlying emotional feelings.

Altering facial feedback does not affect EA

Our study appears to support an *as-if* loop hypothesis (Damasio, 1994; Adolphs et al., 2000; Atkinson, 2007; Wood et al., 2016) more than the classical facial feedback hypothesis (for excellent reviews see Goldman and Sripada 2005; Niedenthal et al. 2010), as we obtained behavioral impairments while interfering with cortical sensorimotor networks for moving and sensing the face (rTMS over IFG and SI), but not while interfering with peripheral facial muscles (PS stimulation). However, our findings do not necessarily speak against the facial feedback hypothesis or conflict with the evidence that altering facial feedback impairs recognition of emotional expressions. Effective manipulations of facial feedback typically require participants to constantly bite a pen (Oberman et al., 2007), to wear mouthguards (Rychlowska et al., 2014), or to prevent mimicry over time, either intentionally (Davis et al., 2009) or as consequence of botulinum toxin-induced denervation of target muscles (Neal and Chartrand, 2011). On the other hand, manipulations like chewing gum that only transiently alter facial mimicry (and somatosensory facial feedback) are not effective at altering emotion recognition (Oberman et al., 2007). It should be noted that our PS stimulation was not designed to constantly alter facial feedback during observation of smiles, but rather to mimic the potential peripheral consequences of rTMS, i.e., the transient contractions of facial muscles. Thus, while our data do not conflict with the facial feedback hypothesis, they can firmly rule out that rTMS-induced facial contractions *per se* are the key factor driving our EA impairments.

It could be further considered that effective facial feedback manipulations reported in the literature are sensorimotor rather than purely somatosensory in nature, as they also entail altered facial motor commands. However, many of these manipulations also plausibly alter several brain processes (e.g.,

they may reduce attention or increase cognitive load) in addition to affecting sensorimotor brain regions controlling and sensing facial movements. Therefore, our study extends prior behavioral research by showing that selective targeting of cortical face representations in IFG and SI disrupts EA performance. Indeed, based on our findings, it could be suggested that sensorimotor regions like the IFG and SI may mediate the behavioral effects that are known to be induced by altering facial feedback.

Final remarks

Two final issues require attention for drawing appropriate conclusions from our findings. First, although we show site-specific effects of rTMS, it is unlikely these effects are site-limited. The effect of IFG or SI stimulation might be at least partially due to the spread of TMS-induced excitation along interconnected regions (Siebner et al. 2009; Avenanti et al. 2013b; Valchev et al. 2015, 2016) that may have contributed to the observed impairment in EA. The IFG and SI are strongly interconnected with other parietal regions of the sensorimotor mirroring network, but also anterior insular and frontal opercular regions involved in affective sharing mechanisms of empathy (Wicker et al., 2003; Gallese et al., 2004; Jabbi and Keysers, 2008; Lamm et al., 2011). Therefore, in keeping with simulationist models (Goldman and Sripada, 2005; Niedenthal et al., 2010; Wood et al., 2016), it is possible that interconnected affective regions – possibly involved in emotional rather than sensorimotor simulation – may contribute to explicit inferences about the authenticity of amused expressions.

Second, while it is widely assumed that seeing emotional facial expressions triggers sensorimotor simulation in the observer's IFG and SI face representation —and, indeed, we may have interfered with simulation processes necessary for EA— caution is needed when using such reverse inferences logic because IFG and SI functioning may include additional processes (Avenanti et al. 2013b; Borgomaneri et al. 2015; Press and Cook 2015; Zaki et al. 2016). For example, studies have suggested that cortical motor areas (near to or interconnected with the sector of the IFG we have stimulated)

may be involved in interval timing or orienting processes (Eimer et al., 2005; Schubotz, 2007; Coull et al., 2008; Borgomaneri et al., 2015; Press and Cook, 2015), which in turn could contribute to processing the temporal dynamics of facial expressions and thus to EA task performance. Although these domain-general motor system processes themselves have been interpreted within the simulation framework (Schubotz, 2007), the possibility that our rTMS effects were partially due to interference with non-simulative processes should not be excluded. This does not undervalue our findings that the IFG and SI are crucial for EA, as it is theoretically plausible that domain-general processes could contribute to domain-specific social cognitive functions (Michael and D'Ausilio, 2015). Yet, our study allows us to conclude that, under our experimental conditions, EA performance is grounded in sensorimotor networks that are primarily involved in controlling face movements and sensing feelings from the face.

Mentalizing network and EA

Experiments 1 to 5 provide insights into the neural bases of EA under conditions in which explicit inferences about another's emotional feelings can be drawn only on the basis of social cues. Similarly to McGettigan and colleagues (2015), our dynamic social cues were not embedded in a context that could provide information about *why* the actors were smiling. On this point, previous imaging studies have suggested that the purpose of understanding others might trigger activity in the mentalizing network, despite the lack of a context. For example, watching deceptive actions (Grèzes et al., 2004) and discriminating between authentic and false emotional vocal expressions (Drolet et al., 2012) activate a mentalizing network encompassing the mPFC and TPJ regions, and this network was found to predict accurate emotion recognition as in the study of McGettigan and colleagues (2015). It could thus be suggested that the mental attitude to infer another's mental state – even if based on social cues only – might be sufficient to trigger neural activity in the mentalizing network, even when the social cues are not contextually embedded. The kind of mind-reading performed in the simulation network is almost automatic and is not explicit or propositional. Moreover, previous studies suggest that activity in the simulation network precedes activity in the mentalizing network during social cognition. In this framework, the lack of behavioural effects when TMS was applied on mentalizing regions might be due to our dichotomic EA task (authentic/false amusement). Therefore, in Experiment 6 and 7 we modified our dichotomic EA task to make it more deliberate and explicit, asking participants to rate the amusement felt by the social target on a Likert scale from 1 to 9.

Experiment 6 and 7 thus have three main aims: i) Exploring the lack of causal effects with interference over the mentalizing network in Experiment 3 and 4, ii) Exploring the boundaries of the functional role of the sensorimotor network in more fine-grained judgments about the internal emotional state of another individual and iii) Exploring the contribution of high- and low-level visual regions to Empathic Accuracy.

Chapter 2

Visual, motor and cognitive routes to accurate understanding of amusement from smiles

Introduction

Among all the faces we encounter during social interactions, the smiling face is both one of the most common and yet one of the most ambiguous ones (Niedenthal et al., 2010). Smiles are readouts of felt amusement and are essential for the creation and maintenance of social bonds (Cashdan 2004; Fridlund 1991; 2002). Thus, being able to accurately understand the amusement behind a smile is a key challenge in social life. The ability to accurately understand the internal emotional state felt by another individual (a social target) is often referred to as Empathic Accuracy (EA) (Ickes and Stinson, 1990; Levenson and Ruef, 1992; Ickes, 1997; Zaki et al., 2008, 2009a). The chain of processes ultimately leading to accurate understanding (EA) of the amusement behind an observed smile starts with the visual processing of morphological and dynamic features of the social target's expression (Ambadar et al., 2009; Vuilleumier and Huang, 2009; Pourtois et al., 2013). This processing is supported by high-order visual regions such as the superior temporal sulcus (STS) which encodes socially relevant cues and biological motion (Allison et al., 2000; Grossman and Blake, 2002; Nummenmaa and Calder, 2009) (Narumoto et al., 2001; Fusar-Poli et al., 2009; Peelen et al., 2010; Skerry and Saxe, 2014). Further sensorimotor and cognitive processes might support EA (Paracampo et al. 2016; Wood et al. 2016), including; 1) sensorimotor simulation, i.e., a process by which a viewer

partially reproduces the social target's facial expression in their own sensorimotor system; and 2) "mentalizing" processes allowing the viewer to explicitly consider others' mental states and their sources, and to draw explicit inferences about them (Haxby et al., 2000; Preston and de Waal, 2002; Gallese et al., 2004; Amodio and Frith, 2006; Frith and Frith, 2006; Saxe, 2006; Mitchell, 2009; Atkinson and Adolphs, 2011; Gallese and Sinigaglia, 2011; Zaki et al., 2012; Decety and Svetlova, 2012).

Involvement of sensorimotor simulation in EA has been supported by the evidence that people often mimic the observed facial expressions and such facial mimicry appears to contribute to EA (Wood et al., 2016). It is held that when people simulate a perceived facial expression, they partially reactivate the corresponding emotional state in themselves, which provides a basis for inferring the underlying emotion of the observed social target. Neural evidence supporting sensorimotor simulation comes from functional studies showing that watching emotional facial expressions vicariously activates the inferior frontal gyrus (IFG), a region involved in controlling facial movements (Carr et al., 2003; Leslie et al., 2004; Dapretto et al., 2006) and interfering with the face representation in the IFG hindered the ability to accurately recognize whether a smiling individual was feeling authentic amusement or not (Paracampo et al. 2016), suggested a grounding of emotion understanding in sensorimotor regions involved in performing the same expression (Goldman and Sripada, 2005; Gallese, 2007a; Niedenthal et al., 2010; Wood et al., 2016).

In addition to perception and sensorimotor simulation, EA implies the creation of cognitive propositional representation of others' minds for explicit judgments about the internal emotional state. Studies exploring mental state attributions highlighted a specific subset of regions including the medial prefrontal cortex (mPFC) and the temporo-parietal junction (TPJ) (Amodio and Frith, 2006; Frith and Frith, 2006; Mitchell, 2009).

Extant studies have often tested visual, motor and mentalizing involvement in social cognition through separate tasks (Zaki et al., 2012). Visual regions like the STS are usually tested using tasks

focusing on specific features of facial expressions like eye gaze or head movements (Nummenmaa and Calder, 2009). Vicarious motor involvement during observation is often assessed by simple emotion discrimination tasks or tasks requiring passive view of others' actions or somatic states (). Studies exploring mentalizing processes typically used verbal materials, abstract visual cues or stylized cues like static facial expressions or in which internal emotional states are implied in pictures or verbal descriptions (Frith and Frith, 2006; Saxe, 2006; Mitchell, 2009).

Recently, more naturalistic neuroscientific paradigms combining dynamic social cues and explicit inferential tasks have revealed a coactivation and functional coupling of sensorimotor and mentalizing networks during complex social tasks (Wheatley et al., 2007; Zaki et al., 2009b; Lombardo et al., 2010; Schippers et al., 2010; Harvey et al., 2013; Spunt and Lieberman, 2013; Raz et al., 2014).

While until recently most of the studies addressing EA did not take into account participants' behaviour, a recent neuroimaging study (Zaki et al., 2009b) provided correlational evidence about the involvement of these neural networks in EA. In specific, in a task requiring observation of others' expressive behaviour and explicit inferences about the underlying emotions, they showed that EA performance can be predicted (among the others) by activity within visual system for emotional faces, the motor system and the mentalizing system.

While these studies hinted at an interplay between visual, motor and mentalizing regions in emotion recognition, no study has tested their functional role in EA and whether these neural systems are crucial for accurate understanding of others' emotional states remains unclear.

In the present study, we used repetitive transcranial magnetic stimulation (rTMS) to perturb regions within the visual system for emotional face perception (i.e., the primary visual cortex – V1 and STS), the premotor simulation network (i.e., IFG) and the mentalizing network (i.e., TPJ) to explore their causal involvement in accurate understanding of others' amusement through smiles.

In two experiments, we applied rTMS while participants performed a novel EA task adapted from previous psychological and neuroscientific research (Ickes and Stinson, 1990; Levenson and Ruef, 1992; Zaki et al., 2008; Paracampo et al., 2016). The EA task required participants to watch dynamic smiles (see Paracampo 2016) to rate the quantity of amusement felt by the observed social target.

In Experiment 6, we perturbed activity within V1 and the right STS. In Experiment 7 we applied rTMS over the right IFG and the right TPJ.

Materials and Methods

Participants

A total of 56 healthy participants took part in the study. Thirty-two subjects participated in one of the 2 TMS experiments. In each TMS experiment, we targeted two different brain regions: V1 and right STS for Experiment 6 (xx participants, x females, mean age ± SD:), right IFG and right TPJ for Experiment 7 (xx participants, x females, mean age ± SD:). Moreover, 24 subjects were tested in a pilot study (Pilot6), conducted to select the stimuli for the TMS experiments. All subjects were right handed, had normal or corrected-to-normal visual acuity in both eyes, and were naive to the purposes of the experiment. None of the participants had neurological, psychiatric, or other medical problems or any contraindication to TMS (Rossi et al. 2009; Rossini et al. 2015). Participants provided written informed consent. The procedures were approved by the ethics committee at the Psychology Department of Bologna University and were in accordance with the ethical standards of the 1964 Declaration of Helsinki. No discomfort or adverse effects of TMS were reported by participants or noticed by the experimenter.

Task and Stimuli

Stimuli consisted of 90 dynamic movies (lasting 2 s, 60 frames) presented centrally on a 24-inch monitor (resolution: 1024 × 768; refresh rate: 60 Hz) subtending 27 × 21° of visual angle. Movies

depicted 6 individuals ("social targets"; including 3 females and 3 males, aged 24.5 ± 2.1 years) who were filmed individually while smiling (Paracampo et al. 2016) (see Chapter 1 for stimuli creation). During stimuli creation, non-professional actors were filmed while making smiling expressions associated with authentic positive feelings of amusement. After each smiling expression, they were asked to provide subjective evaluations of the amusement felt while smiling using a 10-step Likert scale (0 = neutral state; 9 = maximal amusement). Moreover, they were asked to evaluate their subjective confidence in their amusement judgments using a categorical response (I am 100% sure of my judgment/I am not 100% sure of my judgment) (Ickes and Stinson, 1990; Levenson and Ruef, 1992). Stimuli for which actors reported ratings of 0 (no amusement) were excluded from the present study. Participants in the rTMS experiments were asked to watch all the smile videos and were asked to rate how much amusement they believed actors had felt after each movie on a 9-step Likert scale (1 = low/mild amusement; 9 = maximal amusement). Participants' ratings and actors' ratings were then correlated to provide a measure of Empathic Accuracy (EA) (Zaki et al., 2008, 2009a). Videos for the final experiments were selected based on the result of a pilot study conducted on 24 subjects who did not participate in the subsequent rTMS experiments. The pilot study allowed us to select 90 movies from 6 actors which were associated with moderately accurate EA ratings (mean r = 0.50).

Procedure

Experiments were programmed using a custom software (Matlab 7.13) to control video clip sequence and trigger TMS stimulation. Participants were initially tested in an electrophysiological and a neuronavigation session in which intensity and coil position for rTMS were determined (see below). Then, they were presented with task instructions and they performed a training on a subset of stimuli not included in the main session.

In the rTMS experiments three conditions were included (two active conditions and one sham condition). Each subject performed 3 blocks of 30 EA trials for each rTMS condition, for a total of 270 trials. Blocks were presented in a counterbalanced order. Each trial started with a gray screen

(1000ms) followed by the video clip (2000ms). After the clip, a response screen appeared and it was presented until participant's response (Figure 5A). Participants provided their response by pressing one of 9 keys on the keyboard. They were asked to answer as accurately as possible using their right hand. After keypress, the response screen was replaced by a black screen (intertrial interval: 5000-6000 ms). On each trial, a time-locked single train of 6 Hz rTMS (12 pulses) was administered using a figure-of-eight coil (diameter: 70 mm) connected to a Magstim Rapid2 stimulator (Magstim).

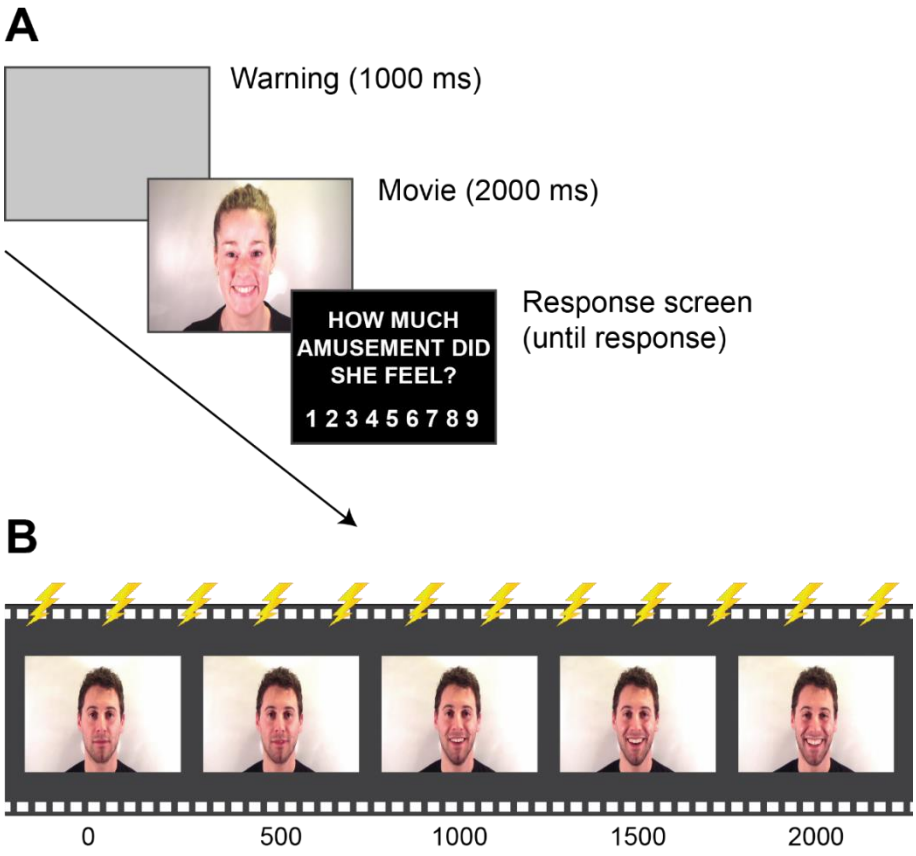

Figure 5. *Trial example for the EA task (A). Participants were asked to rate the quantity of amusement felt by the actor on a Likert-scale from 1 to 9. A continuous 6 Hz train of 12 pulses of rTMS was applied at onset of the movies (B).*

In each TMS experiment, the coil was placed over two target brain regions (V1 and STS in Experiment 6; IFG and TPJ in Experiment 7). The rTMS train was administered at the onset of each movie and covered its entire duration (Fig. 5B). The stimulation intensity corresponded to 90% of the resting motor threshold (rMT) (see below). During active rTMS blocks, the intersection of the coil

was placed tangentially to the scalp and directly above the scalp location of the target region. Sham rTMS blocks were performed by tilting the coil at 90° over the same target region, to provide some scalp sensations and TMS sounds similar to active stimulation but without inducing a current in the brain.

At the end of the session, participants were asked to evaluate the discomfort caused by the TMS, on a 5-point Likert scale with 1 indicating "not unpleasant at all" and 5 corresponding to "extremely unpleasant".

Electrophysiological and Neuronavigation Sessions

To set rTMS intensity, the rMT was estimated for all participants in a preliminary phase of the experiment using standard procedures (Rossi et al. 2009). Motor-evoked potentials (MEPs) induced by stimulation of the right motor cortex were recorded from the left first dorsal interosseous (FDI) by means of a Biopac MP-35. Electromyography (EMG) signals were band-pass filtered (30–500 Hz) and digitized (sampling rate: 5 kHz). Pairs of Ag-AgCl surface electrodes were placed in a belly-tendon montage with a ground electrode on the wrist. The intersection of the coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle away from the midline. The rMT was defined as the minimal intensity of stimulator output that produces MEPs with an amplitude of at least 50 μV in the FDI with 50% probability (Rossini et al. 2015).

Each brain area was individually targeted using image guided neuronavigation. The coil position was identified on each participant's scalp using the SofTaxic Navigator System (Electro Medical Systems). Skull landmarks (nasion, inion and 2 preauricular points) and ~80 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra digitizer (Northern Digital), as in our previous research (Avenanti et al. 2007, 2012, 2013a; Tidoni et al. 2013; Jacquet and Avenanti 2015; Paracampo 2016; Avenanti 2017). An individual estimated magnetic resonance image (MRI) was obtained for each subject through a 3D warping procedure that fits a high-resolution MRI template with the participant's scalp model and craniometric points. This procedure has been

proven to ensure a global localization accuracy of roughly 5 mm, a level of precision closer to that obtained using individual MRIs than can be achieved using other localization methods (Carducci and Brusco 2012). Stimulation sites were identified on the basis of previous fMRI studies, using the SofTaxic Navigator (STS, IFG, TPJ) or established anatomical methods (VI). For STS, IFG and TPJ, Talairach coordinates of target regions and corresponding scalp projections, were automatically estimated by the SofTaxic Navigator from the MRI-constructed stereotaxic template. When necessary, coordinates in Talairach space were obtained by converting MNI coordinates reported in previous studies using GingerALE 2.3.1. To target sensorimotor regions, we selected Talairach coordinates corresponding to the cortical face representations in premotor and somatosensory sites.

The VI site was identified at two centimetres above the inion, as in previous TMS studies (Silvanto et al., 2005; Koivisto et al., 2010; Romei et al., 2016a).

The right STS site was localized based on the following coordinates: x = 48 , y = -49 , z = 4 , which were identified on the basis of a meta-analysis including 100 neuroimaging studies exploring brain regions involved in emotional face processing (Sabatinelli et al., 2011).

The right IFG scalp site was localized based on the following coordinates: x = 47, y = 8, z = 28, which were identified on the basis of previous fMRI meta-analyses exploring activations associated with the execution and/or observation of facial movements and emotional expressions (Molenberghs et al. 2009; Caspers et al. 2010; Grosbras et al. 2012).

The right TPJ site was localized based on the following coordinates: x = 51, y = −54, z = 21, which were identified on the basis of neuroimaging studies exploring areas related to theory of mind and mentalizing (van Overwalle and Baetens 2009; Mar 2011; Bzdok et al. 2012).

Locations of scalp regions identified by neuronavigation (STS, IFG, TPJ) or anatomical methods (VI) were marked with a pen on each participant's head and used to place the rTMS coil. Then, individual Talairach coordinates corresponding to the projection of the targeted scalp sites on the surface of the

MRI-constructed stereotaxic template were automatically estimated through the neuronavigation system. These estimated coordinates indicate the most superficial cortical site where rTMS effects are expected to be maximal. Brain surface coordinates were converted to MNI space (using GingerALE 2.3.1) for visualization with the MRIcron software (MRIcron/NPM/dcm2nii). Fig. 6 illustrates the estimated group mean MNI surface coordinates.

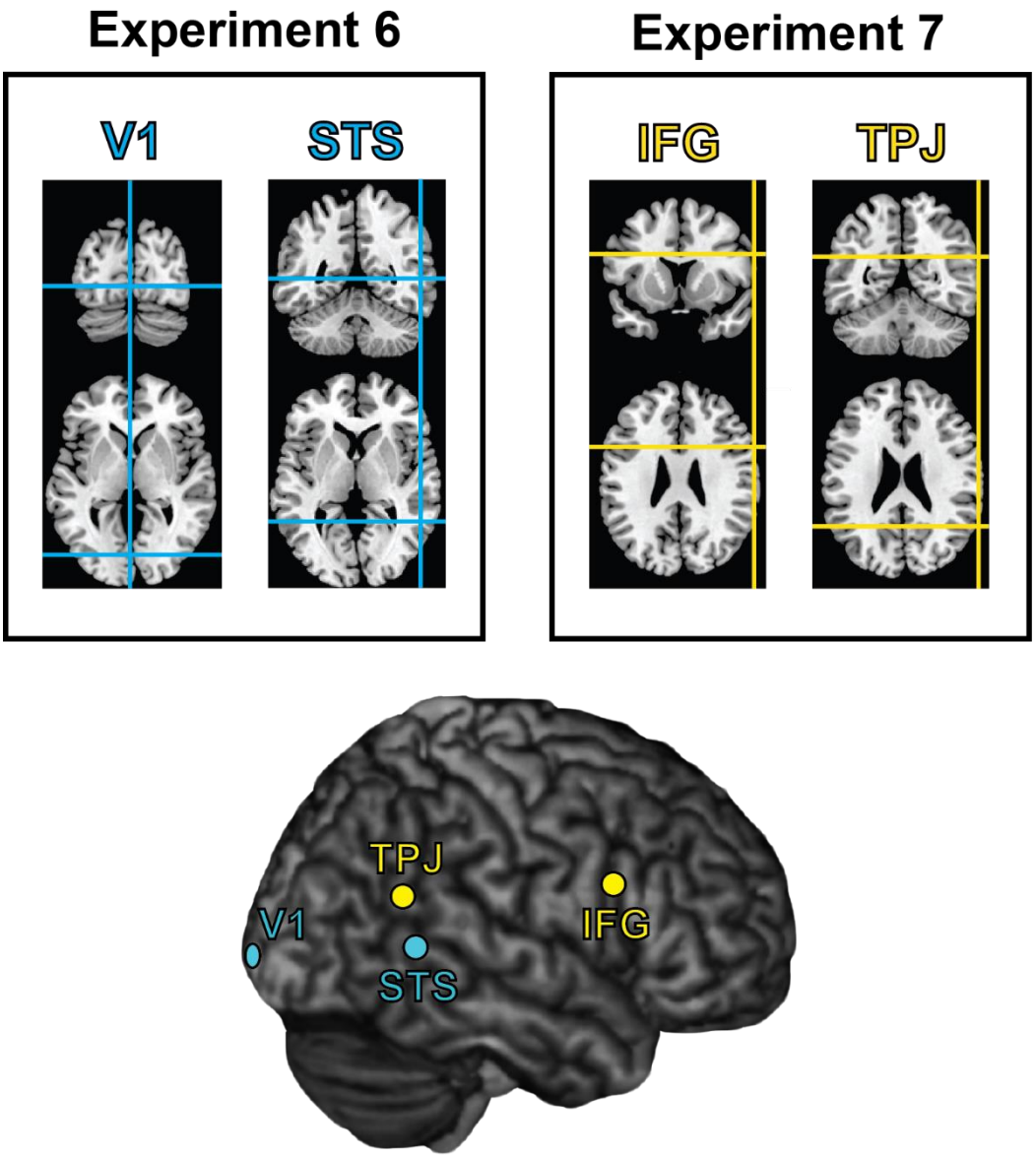

Figure 6. *Schematic representation of the brain stimulation sites reconstructed on a standard template using MRIcron (MRIcron/NPM/dcm2nii). Talairach coordinates corresponding to the projection of the V1, STS, IFG, and TPJ scalp sites*

on the brain surface were individually estimated through the neuronavigation system. Group mean brain surface coordinates ± SD for the V1 site were: x = 1.6 ± 4.0; y = -75.6 ± 16.8; z = -4.7 ± 14.9. Coordinates for the STS were: x = 60.5 ± 5.1; y = -52.2 ± 1.9; z = 3.8 ± 1.2. Coordinates for the IFG were: x = 58.8 ± 1.9; y = 13.1 ± 0.7; z = 25.8 ± 0.7. Coordinates for the TPJ were: x = 61.0 ± 0.9; y = -53.8 ± 0.8; z = 24.0 ± 0.9. Talairach coordinates were then converted to the MNI space (using GingerALE 2.3.1) for visualization with the MRIcron software.

Data Analysis

Behavioral data were processed offline. Empathic Accuracy (EA) was calculated as the correlation between participants' ratings and actors' ratings for each Condition (V1 and STS for Experiment 6; IFG and TPJ for Experiment 7).

A direct comparison was performed for EA in the SHAM condition between Experiment 6 and 7 to make sure that the two experiments had the same EA at baseline

After this, for each experiment a one-way ANOVA was performed on EA ratings with Condition (3 levels: V1, STS, SHAM for Experiment 6 and IFG, TPJ, SHAM for Experiment 7) as within-subjects factor. Post hoc analysis was performed using Newman-Keuls test to correct for multiple comparisons. Partial eta^2 was computed as a measure of effect size for the main effects and interactions, whereas repeated measures Cohen's *d* was computed for post hoc comparisons.

Results

To make sure that our two groups had the same EA at baseline, a t-test was conducted on participants' scores in the SHAM condition for both experiments. Our t-test showed that these scores were comparable ($t_{(30)} = 1.36$, $P = 0.18$), thus, no difference existed at baseline between our experimental groups (Figure 7).

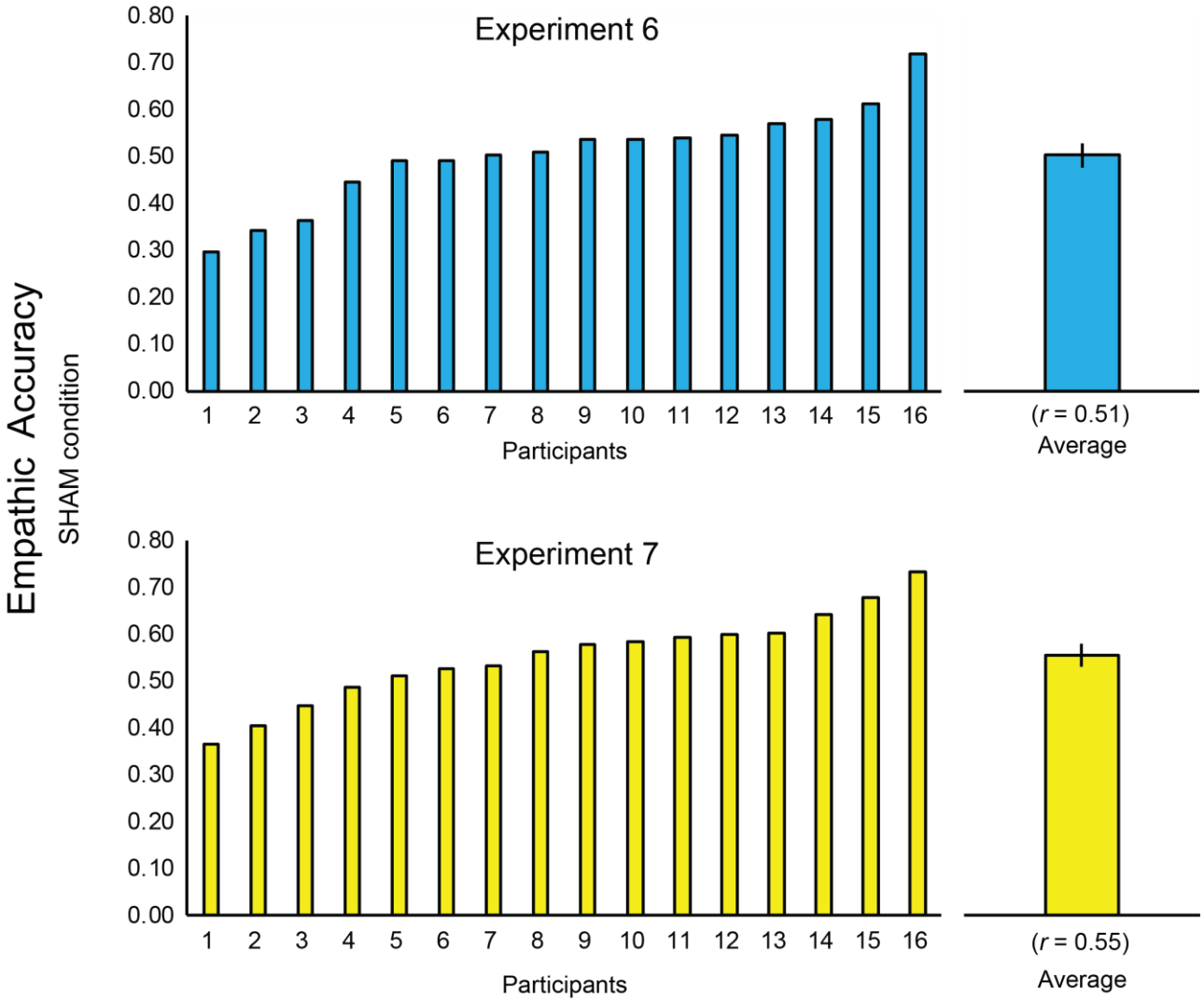

Figure 7. *Baseline EA for participants and Average EA for Experiment 6 (above) and 7 (below).*

The ANOVA conducted on EA ratings for Experiment 6 revealed a significant effect of Condition ($F_{2,30}$ = 6.67, P = 0.004, *Partial eta*^{2} =). Post hoc analysis showed that the STS condition caused this effect. In specific, in the STS condition (0.44 ± 0.12) participants had a significant reduction in EA when compared to the SHAM condition (0.51 ± 0.11; P = 0.004) and to the V1 condition (0.49 ± 0.12; P = 0.01). No difference was found when comparing the V1 and the SHAM conditions (P = 0.42).

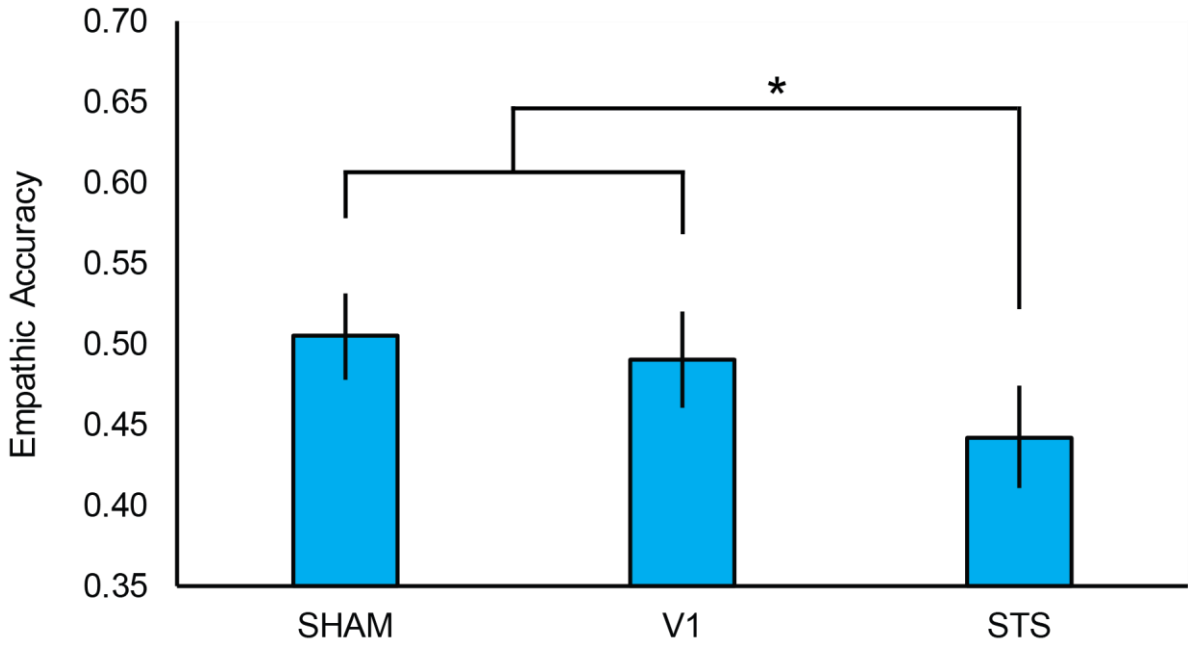

Figure 8. *EA scores for the three experimental conditions. Active stimulation over STS reduced EA compared to both V1 stimulation and SHAM condition. Asterisks indicate significant post-hoc comparisons (P < 0.05). Error bars denote s.e.m.*

The ANOVA conducted on EA for Experiment 7 revealed a significant effect of Condition ($F_{2,30}$ = 5.70, P = 0.008). Interestingly, post hoc analysis showed that both in the IFG (mean EA ± SD: 0.50 ± 0.09) and TPJ (0.48 ± 0.13) condition participants had a reduction in EA when compared to the SHAM condition (0.55 ± 0.10; ALL P < 0.03). Moreover, the two active conditions did not show any significant difference (P = 0.28)

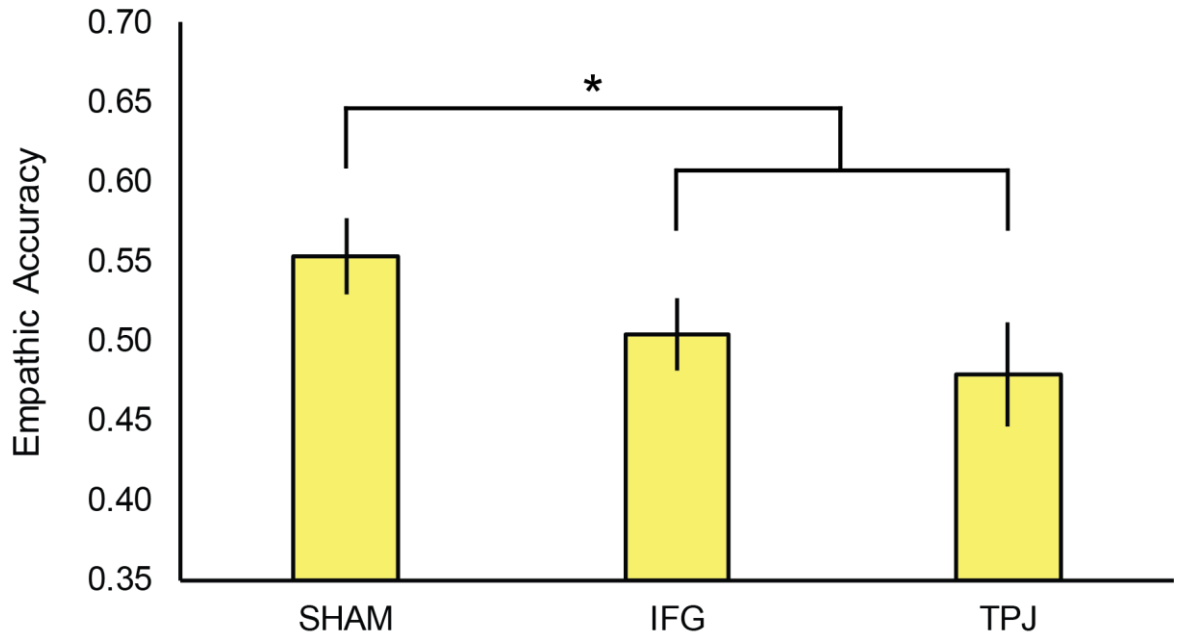

Figure 9. *EA scores for the three experimental conditions. Active stimulation over IFG and TPJ reduced EA compared to SHAM condition. Asterisks indicate significant post-hoc comparisons (P < 0.05). Error bars denote s.e.m.*

To ensure that any interferential effects of rTMS were not due to speed-accuracy trade-offs, we also analyzed response times (RTs) in the two experiments (Table 5). The ANOVA performed on RTs revealed no main effect of Condition both for Experiment 6 ($F_{(2,30)} = 1.82$, $P = 0.18$) and for Experiment 7 ($F_{(2,30)} = 2.73$, $P = 0.08$), ruling out any speed-accuracy trade-offs.

Table 5. *Mean RTs ± SD and Raw Amusement Ratings for the EA task in the sham rTMS and active interference conditions (V1-STS and IFG-TPJ).*

	Experiment 6			Experiment 7		
	SHAM	**V1**	**STS**	**SHAM**	**IFG**	**TPJ**
RTs	1.23 ± 0.31	1.22 ± 0.34	1.30 ± 0.43	1.42 ± 0.46	1.57 ± 0.64	1.54 ± 0.49
Amusement	5.03 ± 0.94	5.12 ± 0.95	5.11 ± 0.98	5.14 ± 0.82	5.19 ± 0.86	5.09 ± 0.74

Finally, we performed an ANOVA on participants' raw amusement ratings for each condition (Table 5), to make sure that our rTMS-related effects were not due to a generic lowering of participants' ratings. The ANOVA performed on Amusement Ratings revealed no main effect of Condition both for Experiment 6 ($F_{(2,30)} = 1.70$, $P = 0.20$) and for Experiment 7 ($F_{(2,30)} = 2.04$, $P = 0.15$).

Discussion

The process ultimately leading to accurate understanding the emotional state behind a facial expression (EA) is complex and is composed by multiple stages. Visual, motor and cognitive mechanisms are all involved in social perception. Recent theoretical (Keysers and Gazzola, 2007; Uddin et al., 2007; Zaki et al., 2012; Lamm and Majdandžić, 2015) and empirical (Wheatley et al., 2007; Zaki et al., 2009b; Lombardo et al., 2010; Redcay et al., 2010; Schippers et al., 2010; Wolf et al., 2010; Lamm et al., 2011; Spunt and Lieberman, 2013; Raz et al., 2014) work suggests that during complex social tasks, these mechanisms might all be involved. However, the link between activity in brain regions supporting these mechanisms and participants' behavior is often not explored because of the characteristics of the techniques or the paradigms used. In the present study, we provide causal evidence for the role of visual, motor and mentalizing processes in accurate ratings of amusement through observed smiles. In two separate experiments we used rTMS to test whether visual (V1 and STS), premotor (IFG) and mentalizing (TPJ) regions are functionally involved in accurate judgments about the amusement felt by a smiling individual (Zaki et al., 2008, 2009a; Paracampo et al., 2016). Our results show that the STS, IFG and TPJ are all crucial for understanding amusement in smiles.

Visual representation: The contribution of the Superior Temporal Sulcus to Empathic Accuracy

The face conveys crucial information during social interactions. Among the brain regions involved in face processing , the STS is a key region in directing attention towards dynamic features of faces (Puce et al., 1998; Allison et al., 2000; Hoffman and Haxby, 2000; Nummenmaa and Calder, 2009). The STS has a role in the perception of biological motion in general (Grossman et al., 2000; Grossman and Blake, 2002; Keysers and Perrett, 2004; Peelen et al., 2006) responding to the observation of bodies implying motion (Peigneux et al., 2000; Jellema and Perrett, 2003; de Gelder et al., 2015) and is believed to be one of the main sources of visual information for the Action Observation Network (AON), a subset of frontoparietal regions coupling action production and action observation (Nishitani and Hari, 2000; Nishitani et al., 2004; Rizzolatti et al., 2014). Interestingly this region is specifically tuned to emotionally salient visual cues. Previous evidence shows that the activity within the STS is preferentially associated with perception of emotional facial expressions (Fusar-Poli et al., 2009; Sabatinelli et al., 2011) even when this perception is passive (Dricu and Frühholz, 2016) with a preference for dynamic expressions over static ones (Pitcher et al., 2011).

Our study sheds novel light on our knowledge about the functional role of the STS in accurate understanding of emotion in facial expressions by showing that transiently disrupting activity in this region impairs accuracy in judging amusement from a smile. This evidence expands upon previous behavioural evidence, showing that stable and virtual lesions of the STS impair biological motion perception (Grossman et al., 2005; Saygin, 2007; Candidi et al., 2011) and interference with STS activity impairs simple facial expression recognition tasks (Pitcher, 2014), reduces responses to dynamic faces (Pitcher et al., 2014) and is able to produce changes in eye-gaze perception (Saitovitch et al., 2016) Models of face perception (Haxby et al., 2000; Calder and Young, 2005) suggest that the STS might have functional connections with the amygdala during observation of emotional facial

expressions and that this would (at least in part) explain its selectivity to emotion. Interestingly, a recent interferential study coupling TMS and fMRI showed that disruption of activity within the STS produces functional changes in the amygdala in response to faces (Pitcher et al., 2017).

Moreover, even if the face representation in the STS is visual, we know both from imaging and neuromodulation studies that the STS is functionally connected to parietofrontal regions – like the IFG - responsible of coupling visual and motor representation of actions during observation and involved in action understanding (Schippers and Keysers, 2011; Avenanti et al., 2013a). On this point, a recent study using MEG (Sato et al., 2015) showed that, during observation of dynamic facial expressions connections between the IFG and the STS (both forward and backward) are activated.

In this framework, the STS with its connections to regions in the limbic system and frontal regions within the action simulation network, is a perfect candidate to be the first stage of the face processing ultimately leading to accurate understanding of the emotion expressed by a facial expression. Our experimental design is not suited for exploration of the information flow during emotional facial expression, however, here we show that the STS is not only involved in eye-gaze perception or simple emotion discrimination as shown in previous studies, but plays a crucial role in accurate emotion understanding. Thus, STS might represent the first step in processing salient features of the smile that are afterwards used for simulative and mentalizing processes to work with.

Simulation and Mentalizing in Empathic Accuracy

The observation of actions in others, including facial expressions, activates subset of frontoparietal regions that are involved in performing the same action, in particular the IFG (Carr et al., 2003; Winston et al., 2003; Leslie et al., 2004; Dapretto et al., 2006; Montgomery and Haxby, 2008; Caspers et al., 2010; Rizzolatti et al., 2014; Rizzolatti and Sinigaglia, 2016). These data show that the IFG is a key region within the mirroring network, involved in internal simulation of the observed action (Gallese 2011, Ave 2013). Interestingly for the present study, vicarious activations during visual

perception of emotional facial expressions are not limited to the IFG, but encompass limbic structures involved in first-hand emotional experiences (Carr et al., 2003; Wicker et al., 2003; Morrison et al., 2004; Singer et al., 2004; Corradi-Dell'Acqua et al., 2011).

Evidence is now consistent in showing that the IFG is involved in emotion recognition and social cognition in general (Pobric and Hamilton, 2006; Avenanti et al., 2007; de Gelder et al., 2012; Tidoni et al., 2013; Costa et al., 2014; Urgesi et al., 2014; Jacquet and Avenanti, 2015; Tamietto et al., 2015; Paracampo et al., 2016). These data have motivated an embodied approach to social cognition posing that this correspondence of experienced and observed affective, sensory, and motor responses allows perceivers to vicariously experience what it is like to be the target of their perception. This common coding between self and other states, in turn, is thought to aid perceivers in understanding targets emotions or intentions (Gallese et al., 2004; Goldman and Sripada, 2005; Niedenthal et al., 2010; Wood et al., 2016). During social interaction, the overt behaviour and covert emotional state are continuously associated. In a simulationist framework, the continuous association between the two could allow an observer to simulate the underlying emotion (amusement) embodying the observable motor behaviour (the smile) (Gallese, 2007a; Niedenthal et al., 2010). This view is consistent with data showing that more empathic people show stronger activations in the IFG when observing actions and emotions in others (Avenanti et al., 2009; Gallese and Sinigaglia, 2011; Bufalari and Ionta, 2013).

However, we cannot always understand others using our internal states as a basis. A different line of research has focused on the hypothesis that understanding others is based on explicit inferential processes (Mitchell et al., 2002; Saxe, 2005; Shamay-Tsoory et al., 2005). Focusing on the neural bases of mental state attributions, scholars have isolated a network of brain regions recruited during explicit inferences about the intentions, beliefs, and feelings of others (Amodio and Frith, 2006; Frith and Frith, 2006; Mitchell, 2009; Bzdok et al., 2012; Schurz et al., 2014). The temporo-parietal junction is a key structure within this so-called mentalizing network. Activity within the TPJ has been reliably associated with tasks in which individuals are asked to infer another person's mental

state (Saxe and Kanwisher, 2003; Decety and Lamm, 2007; Van Overwalle, 2009). Moreover it has been linked to observation of deceptive actions (Grèzes et al., 2004), discrimination of authenticity in vocal expressions (Drolet et al., 2012) and in tasks requiring to explain actions in terms of mental states (Grèzes et al., 2004; Brass et al., 2007; de Lange et al., 2008; Spunt et al., 2010). Therefore, the mentalizing system provides a different route to understanding others that it is not through sharing, but through the creation of propositional cognitive knowledge about what others are feeling, inherently based on self-other distinction.

The present study significantly expands previous evidence about the role of these networks in social cognition. Here, we manipulated simulative and mentalizing processes independently in the same healthy participants and tested their causal involvement in EA. Our results, show that both the IFG and the TPJ are causally involved in accurate ratings of amusement from smiles. Beyond purist approaches to social cognition we propose that motor simulation and mentalizing might represent two processes with the same goal. Both participate in understanding others (Olsson and Ochsner, 2008; Bastiaansen et al., 2009; Shamay-Tsoory et al., 2009; Zaki et al., 2012). However, their actual contribution and (possible) interactions in social cognition are still unclear. The two systems are anatomically independent and several studies showed that they might even be functionally independent (van Overwalle and Baetens, 2009). However, recent imaging studies show that the two systems might be concurrent active in complex social tasks (Schippers et al., 2010; Schippers and Keysers, 2011; Spunt et al., 2011; Spunt and Lieberman, 2012a, 2013; Sperduti et al., 2014; Kanske et al., 2015) and might even show functional connectivity during social interactions (Lombardo et al., 2010). Interestingly, recent correlational studies using EA tasks (Zaki et al., 2009b; Harvey et al., 2013) showed that activity within premotor and mentalizing regions correlated with accuracy in making explicit inferences about the emotional states of individuals discussing emotional autobiographical events. In the auditory domain, a recent study showed that when judging laughter authenticity activity in both networks predicted participants' accuracy, even if participants where not

provided with contextual information of prior knowledge about the person laughing (McGettigan et al., 2015). These studies suggested a link between neuroimaging data and behavioural indices of EA. However, they could only provide correlational evidence about the involvement of motor and mentalizing regions in EA. Here, we show that the IFG and the TPJ are not only active, but are causally involved in accurate understanding of others' internal emotional state, as active interference with activity in both regions impaired our participants' performance in the EA task.

As in the previous experiments (1 to 5), in experiments 6 and 7, participants were asked to make inferences about another's emotional state (amusement) based exclusively on the facial expression (smile). Our facial expressions were not embedded in contexts that might provide a framework to interpret the covert emotional state. Despite this, in experiment 7 we found that interference with the mentalizing network was able to impair participants' accuracy in the EA task. As stated in the previous chapter, imaging studies suggest that activity within the mentalizing network can be observed despite the lack of contextual information to drive interpretations about others' internal states (Grèzes et al., 2004; Drolet et al., 2012). However, using our dichotomic EA task we were not able to find any detrimental effect for interference over the mentalizing network (experiment 3 and 4)

One possible interpretation of this result is that the shift from a dichotomic EA task to a Likert-based EA task was associated with a shift in the mechanisms used to perform the task. The simulation network is responsible for a non-explicit, preverbal form of mind-reading, on the other hand the mentalizing network is preferentially involved in creating propositional knowledge about others' internal states. In this framework, at the behavioral level, the Likert-based EA task, being more cognitive and explicit, might trigger the mentalizing network more than the dichotomic one. Moreover, the sensorimotor network, even when more fine-grained judgments about the internal emotional state are involved, proved to be crucial in interpreting amusement from smiles.

Conclusions

The present study sheds novel light on the involvement of visual, motor and cognitive regions in EA. Previous evidence suggested that visual processing, motor simulation and mental state attributions are all needed for fruitful and complete interactions in social environment. However, extant studies could not establish their functional role in complex social tasks. Here, by using rTMS we showed that visual analysis of emotionally salient cues performed in the STS, the internal simulation of the observed facial expression performed in the IFG and cognitive mental inferences performed in the TPJ are all crucial in accurate understanding of amusement from observed smiles. Our study cannot highlight the specific interactions between the explored regions during judgments of the internal emotional state of an individual. Further studies are necessary to gain deeper knowledge of the complex interplay of visual processing, motor simulation and mental state attributions in accurate understanding of emotion through facial expressions. One possible development might involve the use of a cortico-cortical paired associative stimulation (ccPAS) protocol (Buch et al., 2011; Romei et al., 2016a, 2016b) to enhance connection between these regions to observe possible effects on behaviour. On a different point, we know from previous evidence that simulation and mentalizing can be modulated by different elements, such as context, prior knowledge, emotional state or gender (Singer et al., 2006; Lamm et al., 2007b; Hein and Singer, 2008; Hein et al., 2010; Christov-Moore et al., 2014; Proverbio, 2017). Another possible development of the present study would be to modulate one of these elements to test if, at the behavioural level, they can lead to prioritize one system over the other. Finally, future studies could manipulate task features to provide double dissociations within the same set of experiments, and/or use contextually-embedded social cues to test the generalizability of the present findings to “real-life” scenarios involving multiple sources of information.

Flexible use of the sensorimotor and mentalizing network in social cognition

Rather than being tied to specific experimental stimuli, the sensorimotor and the mentalizing network seem to be triggered by the specific mechanism used to interpret others' behaviour (whether it is internal simulation or cognitive propositional inferences). In the next chapter, we aim at exploring whether modulations of activity within the sensorimotor and mentalizing network can affect participants' behaviour when they are asked to rate others' internal states when information is conveyed using text. Following our view of the involvement of these networks in social cognition, the mechanism used by participants to perform the task will be central for the flexible use of the two networks.

Chapter 3

The moral and empathic brain: distinct neural representations of agent's intention and victim's suffering in judging harmful actions – a transcranial direct current stimulation study

Introduction

Unfortunately, we often read about episodes in which pain was caused by an individual to another. For a moral evaluation of the situation we have, among the others two main sources of information: the beliefs of the person performing the action, and the outcome of the action on the victim. These two elements are particularly important if we want to judge whether an action is morally right or wrong. Multiple mechanisms, however, may interact and compete during moral cognition (i.e., outcome processing versus mental state processing) (Greene, 2001; Greene et al., 2004; Young et al., 2007; Cushman, 2008; Cushman et al., 2010; Buon et al., 2016). Despite existing agreement on the role of multiple processes in moral judgment, it is widely believed that mature moral judgment largely depends on intentions (see (Barrett et al., 2016).

Therefore, cognitive neuroscience research on the neural substrate of moral judgment largely focused on the role of neural mechanisms supporting mental state reasoning and belief attribution for third party moral judgments (for reviews, see (Young and Tsoi, 2013).

Prior neuroimaging studies have found that mental state (e.g., beliefs, intentions) attribution for moral judgment is supported by a subset of brain regions mainly referred to as the Mentalizing Network (Frith and Frith, 2003; Saxe and Kanwisher, 2003; Bzdok et al., 2012; Schurz et al., 2014). The Mentalizing network, including sub-regions of medial prefrontal cortex, precuneus, and right and left temporoparietal junction (TPJ), has previously been associated with mental state reasoning (Saxe and Kanwisher, 2003; Frith and Frith, 2006; Jackson et al., 2006b; Lamm et al., 2007a; Hein and Singer, 2008; Mitchell, 2009; Bzdok et al., 2012). Among these regions, the pattern of activation observed in the right TPJ (rTPJ) is particularly interesting and seems to be linked to the ability to take others' perspective, self-other distinction and cognitive representations of others' intentions (Young et al., 2007, 2010).

Going back to the example at the beginning, while reading we are likely to rapidly respond to the victim's suffering. The aversive outcome on the victim (i.e., pain) is processed by a different network of brain regions. Several studies show that observing or imagining pain in others activates several brain regions that are active during first-hand experience of pain associated with the affective-motivational aspects of experienced pain, like the Anterior Insula and the Cingulate Cortex (Morrison et al., 2004, 2007; Singer et al., 2004; Botvinick et al., 2005; Jackson et al., 2005, 2006b; Morrison and Downing, 2007; Corradi-Dell'Acqua et al., 2011).

Interestingly, several studies show that brain regions involved in processing the sensory dimension of experienced pain, like the primary somatosensory cortex (SI) are also activated by the observation and imagination of pain felt by other individuals (Osaka et al., 2004; Avenanti et al., 2005, 2006, Jackson et al., 2005, 2006b; Bufalari et al., 2007; Gu and Han, 2007; Lamm et al., 2007b; Perry et al., 2010) see (Keysers et al., 2010) for a review).

In this vein, moral judgment might be the product of both intent- and outcome- based processes. Further evidence supporting this dual view comes from developmental studies or research on clinical

populations. Studies on the evolution of moral cognition across the life span show that young children tend to prioritize outcomes over intentions (Cushman 2013, Zelazo 1996, Yuill-Perner 1988) becoming more sensitive to the information about the intentions across age and that their moral judgments change accordingly (Baird and Astington, 2004; Saxe et al., 2004). This process probably reflects the maturation of structures associated with mental state attributions like the TPJ allowing to take into consideration others' minds for our judgments about their actions ToM as the recruitment of TPJ increases with increasing age (Young and Saxe, 2009; Güroğlu et al., 2011; Killen et al., 2011; Koster-Hale et al., 2013).

Clinical studies are another way of exploring mechanisms leading to moral judgments in adulthood. In particular individuals with psychopathy, showing reduced reaction to aversive outcome in others, tend to consider accidental harm as more morally permissible than controls (Young et al., 2012). Another clinical population that might help in understanding this issue are individuals with autism spectrum disorder (ASD). Individual with ASD usually have impairments in mental state attributions and studies show that they consider accidental harm as less morally permissible than controls (Buon et al., 2013). These findings suggest that forgiving an agent for causing an accidental harm requires strong mental state representations.

Finally, correlational evidence show that healthy adults observing visual stimuli depicting a person causing pain to another show activity within brain regions involved in first-hand experience of pain, like the somatosensory cortex and in regions within the mentalizing network like the TPJ (Decety et al., 2008; Akitsuki and Decety, 2009) and that in children this integration of somatosensory and mentalizing activation gradually changes with age (Decety et al., 2011).

In sum, indirect evidence points towards both outcome-based and intention-based processes to be present in adults' moral judgments and both developmental and clinical studies seem to support this view (Greene et al., 2004; Greene, 2009; Reniers et al., 2012). However, the specific functional role of these processes, and their possible interactions, has never been tested in healthy adults. Brain

stimulation techniques represent promising tools, allowing to directly modulate cortical excitability to infer causal relationship between activity within a target brain region and a specific cognitive function (Romei et al., 2016b). Among these techniques, tDCS is a valuable method of non-invasive cortical stimulation that allows researchers to induce polarity-dependent excitability changes in the underlying stimulated area. Using weak offline cathodal or anodal DC currents, tDCS can induce cortical inhibition or excitation, respectively, and alter neural functioning for several minutes after the end of the stimulation (Nitsche, 2003; Antal et al., 2004; Horvath et al., 2015). Thus far, studies employing brain stimulation techniques mainly focused on modulation of the temporoparietal junction to explore the role of mental state attributions in moral judgments (Young et al., 2010; Sellaro et al., 2015; Ye et al., 2015).

Here we used tDCS to test the role of the right temporoparietal junction (r-TPJ) and the right primary somatosensory cortex (r-SI) in evaluations of verbal description of painful interactions between two individuals. Participants were asked to read textual scenarios involving an active character harming or trying to harm a passive character (Young et al., 2010b, 2007; Young and Saxe, 2009b) in order to provide moral judgments for the action performed. Additionally, for each scenario, they were asked to provide explicit judgments concerning the mental state of the active character (belief/intention) or the outcome on the passive character. By independently modulating key regions involved in processing others' mental states and in reaction to others' outcomes we will shed novel light on the processes involved in implicit and explicit use of intent- and outcome-related information in evaluations of harmful situations.

Materials and Methods

Participants

A total of 48 healthy right-handed subjects (24 females; mean age ± SD: 23.64 years ± 2.85) participated in one of three tDCS experiments. In Experiment 8 (n = 16) tDCS was applied to the right primary somatosensory cortex (SI) (8 females; 23.80 ± 2.54), in Experiment 9 (n = 16) it was applied to the right temporo-parietal junction (TPJ) (8 females; 22.64 ± 3.03). Experiment 10 was used as our behavioural baseline and no tDCS was delivered (SHAM) (8 females; 24.38 ± 2.87). All subjects were right-handed according to a standard handedness inventory (Briggs and Nebes, 1975) had normal or corrected-to-normal visual acuity in both eyes, and were naïve as to the purposes of the experiment. Participants provided written informed consent and completed a tDCS safety screening form before taking part in the study (Nitsche, 2003; Poreisz et al., 2007; Brunoni et al., 2011; Fregni et al., 2014). Procedures were approved by the ethics committee at the Psychology Department of Bologna University and were in accordance with the ethical standards of the 1964 Declaration of Helsinki. No discomfort or adverse effect during or after tDCS were reported or noticed.

Stimuli and Task

Stimuli consisted of four variations of 48 textual scenarios for a total of 192 scenarios modified from a previously published set (Young et al., 2010). Situations described in each scenario always involved two characters: a protagonist and a passive character. Protagonists always performed an action that could cause a negative outcome (harm to the passive character) or a neutral outcome (no consequences for the passive character). Moreover, protagonists could act on a negative belief (that they will cause harm) or a neural belief.

Based on variations in outcomes and belief, four versions of each scenario were presented: Intentional Harm (**Int-Harm**: Negative Outcome/Negative Belief), Accidental Harm (**Acc-Harm**: Negative Outcome/Neutral Belief), Attempted Harm (**Att-Harm**: Neutral Outcome/Negative Belief) and Neutral (**Neutral**: Neutral Outcome/Neutral Belief).

Scenarios consisted of four segments presented in a cumulative fashion:

1- Background (8 sec): characters are introduced and information about the setting is given.

2- Foreshadow (8 sec): the outcome is anticipated to the reader.

3- Belief (8 sec): the protagonist's belief (neutral/negative) is stated.

4- Action + Outcome (8 sec): action performed by the protagonist and resulting outcome (neutral/negative)

BACKGROUND

Kristin (A) works at a rock-climbing shop. She is unpacking some equipment when a customer (B) walks in, looking for a safety cord.

FORESHADOW	
NEGATIVE	NEUTRAL
The safety cords from the new company are about to be recalled. They will not hold the customer (B) who is rock-climbing for longer than 20 min.	The safety cords from the new company are incredibly well made. They come with a lifetime guarantee and work very well for expert rock-climbers like the customer (B) is.
BELIEF	
NEGATIVE	NEUTRAL
Kristin (A) sees that the equipment is from a new company that a rock-climbing friend of hers finds really unreliable. So, she believes that their safety cords will not be safe for the customer (B).	Kristin (A) sees that the equipment is from a new company that a rock-climbing friend of hers finds really reliable. So, she believes that their safety cords are safe for the customer (B) to use
OUTCOME	
NEGATIVE	NEUTRAL
Kristin (A) sells the customer (B) one of the new safety cords. The safety cord snaps during the customer's next rock-climbing expedition. The customer falls 6 m fracturing his collarbone.	Kristin (A) sells the customer (B) one of the new safety cords. The safety cord serves the customer (B) well on his next rock-climbing expedition. The customer is very pleased

Figure 10. *Example of scenario. Each segment is presented both in the negative (left) and neutral (version). Based on the combination of these segments 4 versions of each scenarios existed. Each participant was presented with only one version of each scenario.*

Negative outcome for the passive character never resulted in her/his death but always involved emotional suffering and physical pain. Scenarios were divided in six categories based on the type of outcome for the passive character: **Limb Crushes**, **Fractures**, **Nausea**, **Wounds**, **Burns** and **Skin Conditions**. After each scenario participants performed a modified version of the Empathy for Pain task (EPT) (Decety et al., 2011; Baez et al., 2012, 2013, 2014; Couto et al., 2013). They were asked to perform six judgments about the active and passive characters' internal states in random order:

Moral Judgment (moral correctness of the active character's action), **Punishment** attributed to the active character's action, **Intention to Harm** attributed to the active character. **Physical Pain** and **Emotional Suffering** attributed to the passive character**, Displeasure** felt for the outcome. Three control judgments were added to control for participants' understanding of scenarios: **Intention to Act** attributed to the active character, **Positive Valence**, **Negative Valence.**

Participants were asked to answer using a Likert scale from 1 to 7 on a computer keyboard. Four orders of presentation were created, each one containing only one version of each scenario and an equal number of scenarios for each version. This way, across subjects every scenario occurred in each of the four conditions, but individual subjects saw each scenario only once. These orders were then divided in two lists (List1 and List2), each one containing 24 scenarios (Fig. 10).

Brain Stimulation

tDCS is a non-invasive technique able to induce and modulate neuroplasticity in humans through the application of weak electrical currents to specific brain regions (Nitsche et al., 2008; Nitsche and Paulus, 2011; Paulus, 2011; Ruffini et al., 2013). In tDCS current flows from a negatively charged electrode (cathode) to a positively charged one (anode), the polarity and position of electrodes determines the physiological (Antal et al., 2004; Nitsche and Paulus, 2011) and behavioural (Jacobson et al., 2012) effects observed (see (Horvath et al., 2015) for a review.

tDCS was administered using a battery-driven electrical stimulator (neuroConn DC-Stimulator Plus) connected to a pair of rubber electrodes. In Experiment 1 (SI) the active electrode (Cathode – 5 X 5 cm) was placed 2 cm posterior to C4 (Bolognini et al., 2013a; Sehm et al., 2013; Sugawara et al., 2014). In Experiment 2 (TPJ), active electrode was placed at the following coordinates: x=51, y=-54, z= 21 (van Overwalle and Baetens, 2009; Mar, 2011; Bzdok et al., 2012). The reference electrode (Anode – 5 X 7 cm) was placed over the left deltoid to avoid any effect due to a combination of the modulations of both the active and the reference electrode (Cogiamanian et al., 2007; Priori et al., 2008; Bolognini et al., 2010; Brunoni et al., 2011). Before stimulation, electrodes were inserted in perforated sponges covered with conductive gel and soaked in saline solution. A current of 2mA was applied for 15 minutes (fade in/fade out: 40 seconds, current density: 0.06 mA/cm^2 for the active electrode, 0.04 mA/cm^2 for the reference). In the SHAM group (Experiment 3) a current of 2mA was applied for 30 seconds (fade in/fade out: 20 seconds), this produced the same initial itching sensation as in actual stimulation. At the end of the tDCS modulation, participants were asked to provide subjective unpleasantness ratings of the sensations caused by the stimulation using a 5-point Likert scale from 1 to 5.

Scenarios			Orders			
List1	List2	Outcome	A	B	C	D
Latex	Peanuts	Skin Conditions	Int-Harm	Att-Harm	Neutral	Acc-Harm
Jellyfish	Sesame		Att-Harm	Neutral	Acc-Harm	Int-Harm
Mexican Food	Pond		Neutral	Acc-Harm	Int-Harm	Att-Harm
Vitamin	Porridge		Acc-Harm	Int-Harm	Att-Harm	Neutral
Cable	Safety Cord	Fractures	Int-Harm	Att-Harm	Neutral	Acc-Harm
Pool	Belt		Att-Harm	Neutral	Acc-Harm	Int-Harm
Teenager	Run		Neutral	Acc-Harm	Int-Harm	Att-Harm
Parachute	Chairlift		Acc-Harm	Int-Harm	Att-Harm	Neutral
Mushrooms	Sushi	Nausea	Int-Harm	Att-Harm	Neutral	Acc-Harm
Mayo	Meatloaf		Att-Harm	Neutral	Acc-Harm	Int-Harm
Ham	Spinach		Neutral	Acc-Harm	Int-Harm	Att-Harm
Veterinarian	Coffee		Acc-Harm	Int-Harm	Att-Harm	Neutral
Holyday	Rabies	Wounds	Int-Harm	Att-Harm	Neutral	Acc-Harm
Isle	Zoo		Att-Harm	Neutral	Acc-Harm	Int-Harm
Hunt	River		Neutral	Acc-Harm	Int-Harm	Att-Harm
Ball	Bike		Acc-Harm	Int-Harm	Att-Harm	Neutral
Fraternity	Laptop	Burns	Int-Harm	Att-Harm	Neutral	Acc-Harm
Hair Straightener	Inflatable		Att-Harm	Neutral	Acc-Harm	Int-Harm
Bonfire	Bar		Neutral	Acc-Harm	Int-Harm	Att-Harm
Hair Dryer	Pizza		Acc-Harm	Int-Harm	Att-Harm	Neutral
Beach	Wet Floor	Limb Crushes	Int-Harm	Att-Harm	Neutral	Acc-Harm
House	Shed		Att-Harm	Neutral	Acc-Harm	Int-Harm
Lab	Tram		Neutral	Acc-Harm	Int-Harm	Att-Harm
Bookshelf	Bridge		Acc-Harm	Int-Harm	Att-Harm	Neutral

Structure (SI, TPJ, SHAM)			
Participant	Order	Pre-Session	Post-Session
1	A	List1	List2
2	B	List1	List2
3	C	List1	List2
4	D	List1	List2
5	A	List1	List2
6	B	List1	List2
7	C	List1	List2
8	D	List1	List2
9	A	List2	List1
10	B	List2	List1
11	C	List2	List1
12	D	List2	List1
13	A	List2	List1
14	B	List2	List1
15	C	List2	List1
16	D	List2	List1

Figure 11. *Experimental design. From left to right: Lists for Scenarios (1, 2), Outcome categories (Skin Conditions, Fractures, Nausea, Wounds, Burns, Limb Crushes), Orders of presentation (A, B,C,D), Structure for each participant in the three experiments*

Procedure

Experiments were programmed using custom software (developed in MATLAB 7.12) controlling each scenario's cumulative presentation and the global random order of scenarios in each session. Participants were randomly assigned to one of the three groups (SHAM, SI, TPJ). Each target region was individually targeted using image-guided neuronavigation. Before starting the experimental sessions, the position for the active electrode was localized on each participant's scalp using the SofTaxic Navigator System (Electro Medical Systems, Bologna, Italy). Skull landmarks (nasion, inion and 2 preauricular points) and ~80 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra digitizer (Northern Digital), as in our previous research (Avenanti et al., 2007; Tidoni et al., 2013; Jacquet and Avenanti, 2015; Paracampo et al., 2016). An

individual estimated magnetic resonance image (MRI) was obtained for each subject through a 3D warping procedure that fits a high-resolution MRI template with the participant's scalp model and craniometric points. This procedure has been proven to ensure a global localization accuracy of roughly 5 mm, a level of precision closer to that obtained using individual MRIs than can be achieved using other localization methods (Carducci and Brusco, 2012). After neuronavigation, position for the active electrode was marked on each subject's scalp. Participants were then introduced to the experimental procedures and underwent a Training in which they performed a block of 4 scenarios not included in the final sample (Intentional Harm, Accidental Harm, Attempted Harm and Neutral) to familiarize with the task. After Training, participants were tested in two identical sessions: Pre-Session and Post-Session. In each one, they performed the task on 24 scenarios (either List1 or 2 in counterbalanced order between participants) (Fig. 10). Between the two sessions, participants underwent 15 minutes of tDCS

Data analysis

A mixed-model ANOVA was performed on participants' ratings for each question, with Version (Intentional, Accidental, Attempted, Neutral) and Session (Pre, Post) as within-subjects factors, and Group (SHAM, SI, TPJ) as between-subjects factor. Post-hoc analysis was performed using the Newman-Keuls test to correct for multiple comparisons.

Results

A preliminary was conducted for every judgment, comparing the three tDCS experiments. This analysis revealed a main effect of Version for every judgment in the present study (Fig.12). This suggests that participants could distinguish between the different versions of the scenarios we proposed.

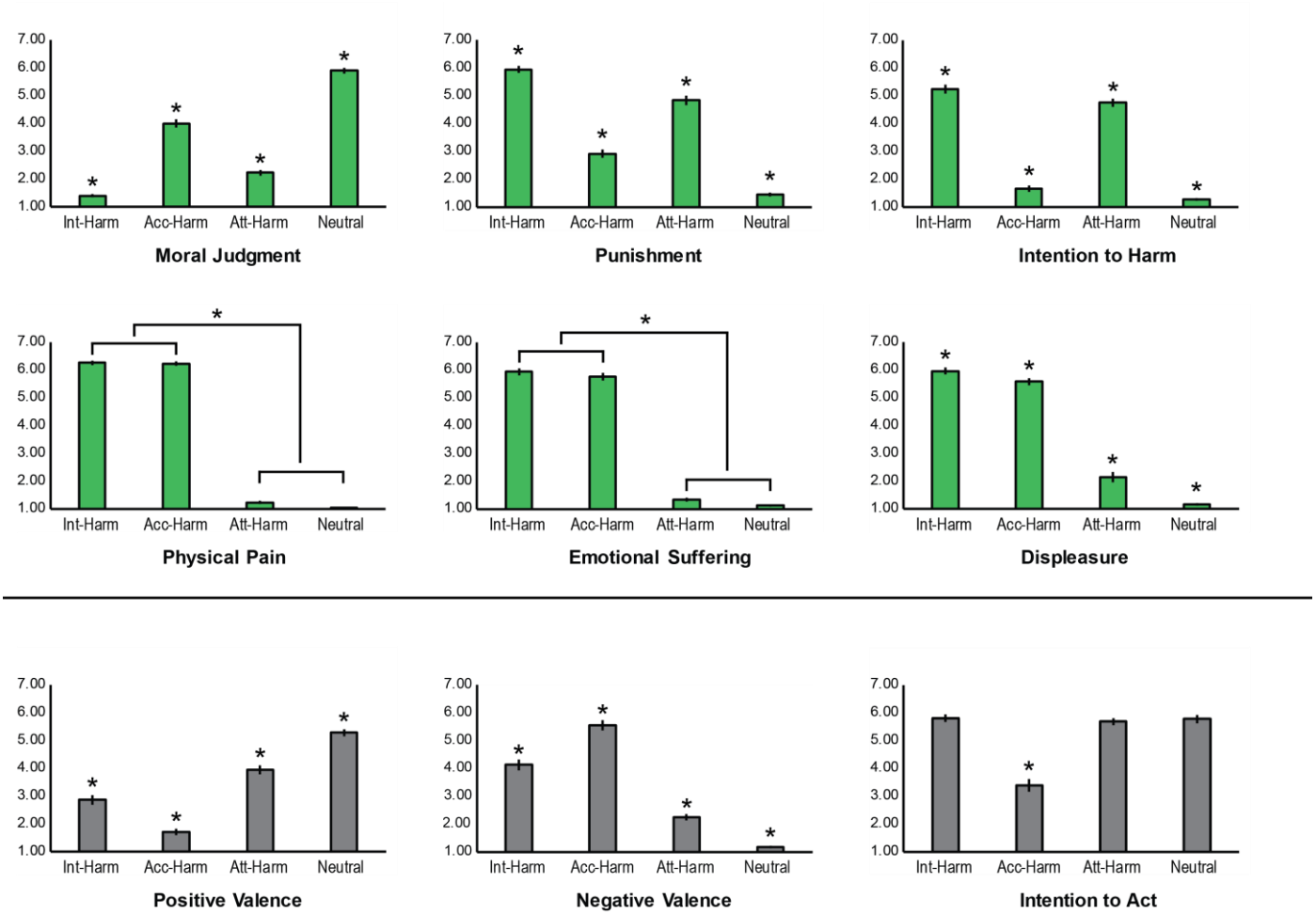

Figure. 12. *Participants' ratings for each judgment (independent from Session and Group). Asterisks indicate significant post-hoc comparisons (P < 0.05). Error bars denote s.e.m.*

Moral Judgment

Analysis on moral judgments revealed a significant main effect of Session ($F_{(1,45)} = 4.45$; $p = 0.04$), showing that participants expressed more permissive judgments in the Post-Session compared to the Pre-Session

The main effect of Version (), explored using post hoc analysis, revealed that all the versions proposed were associated with significantly different moral judgments (ALL $P < 0.001$): Intentional Harm was judged as the least permissive scenario (mean rating ± SD: 1.41 ± 0.39) whereas the Neutral scenario was the most permissive one (5.90 ± 0.69). Judgments for Accidental (4.00 ± 1.08) and Attempted Harm (2.24 ± 0.70) scenarios reported values in between the other two, suggesting that both intention and outcome modulated participants' responses.

Interestingly, a significant three-way interaction, Session X Version X Group ($F_{(6,135)} = 6.22$; $p < 0.001$). Post-hoc analysis showed that participants, in judgments of Accidental Harm scenarios, only in the TPJ group, were less morally permissible in the Post-Session (mean rating value ± SD.: 3.70 ± 1.01) compared to Pre-Session (4.19 ± 1.06; $p = 0.04$). Moreover, they were more morally permissible in judgments about Attempted Harm scenarios in the Post-Session (2.63 ± 0.69) compared to Pre-Session (1.79 ± 0.55; $p < 0.001$). For Intentional Harm and Neutral scenarios no significant difference in moral judgments were observed in any group (all $p > 0.30$).

For Accidental Harm scenarios, an opposite effect was found for the SHAM group, in which participants provided more morally permissible judgments in the Post-Session (4.33 ± 1.05) compared to the Pre-Session (3.85 ± 1.15; $p = 0.05$). (the same effect approached significance in the SI group: Tendency to be more morally permissible in Post-Session (4.20 ± 1.35) compared to Pre-Session (3.74 ± 1.50; $p = 0.07$).)

Table 6. *Mean ratings ± SD for Moral Judgment*

		Moral Judgment							
		Int-Harm		Acc-Harm		Att-Harm		Neutral	
		mean	SD	mean	SD	mean	SD	mean	SD
SHAM	Pre	1.45	0.60	3.85	1.15	2.23	0.74	5.88	0.71
	Post	1.19	0.25	4.33	1.05	2.21	0.83	6.20	0.55
SI	Pre	1.27	0.30	3.74	1.50	2.31	1.09	5.69	0.94
	Post	1.44	0.47	4.20	1.35	2.25	0.95	5.99	0.84
TPJ	Pre	1.61	0.58	4.19	1.06	1.79	0.55	5.92	0.84
	Post	1.48	0.45	3.70	1.01	2.63	0.69	5.76	0.70

Figure 13. *Mean ratings ± SD for Moral Judgment. Asterisks indicate significant post-hoc comparisons (P < 0.05). Error bars denote s.e.m.*

Punishment

Explicit judgments on punishment for the active character's action did not show any effect associated with session or group. However, a main effect of Version emerged ($F_{(3,135)} = 303.790$; $p < 0.001$). Post hoc analysis showed that (independently from session or experiment) participants attributed different levels of punishment to every version proposed in the current design. This suggests that they

took into account both intention and outcome to express their judgments about the punishment for the action of the active character.

Table 7. *Mean ratings ± SD for Punishment*

		Punishment							
		Int-Harm		Acc-Harm		Att-Harm		Neutral	
		mean	SD	mean	SD	mean	SD	mean	SD
SHAM	Pre	6.06	0.74	2.78	0.81	5.06	0.87	1.55	0.52
	Post	6.20	0.62	2.60	0.90	5.13	0.84	1.32	0.36
SI	Pre	6.13	0.82	3.30	1.30	4.80	1.58	1.73	0.69
	Post	5.90	1.14	3.26	1.27	4.59	1.70	1.42	0.54
TPJ	Pre	5.60	1.00	2.68	0.91	4.74	1.23	1.44	0.45
	Post	5.80	0.85	2.85	1.28	4.68	1.28	1.23	0.30

Intention to Harm

Explicit judgments of active character's intention to harm revealed a main effect of Version ($F_{(3,135)} = 327.896$; $p < 0.001$), explained by significantly different judgments for all the different versions in the current design. As for **Moral Judgment** and **Punishment**, post hoc analysis revealed that this judgment was influenced both by information about intention and outcome in scenarios.

Table 8. *Mean ratings ± SD for Intention to Harm*

		Intention to Harm							
		Int-Harm		Acc-Harm		Att-Harm		Neutral	
		mean	SD	mean	SD	mean	SD	mean	SD
SHAM	Pre	5.27	1.11	1.63	0.68	4.96	0.99	1.43	0.56
	Post	5.61	1.02	1.57	0.65	4.95	0.99	1.16	0.22
SI	Pre	5.04	1.42	1.88	1.14	4.69	1.36	1.45	0.51
	Post	4.99	1.60	1.57	0.76	4.40	1.37	1.17	0.31
TPJ	Pre	5.17	1.06	1.63	0.84	4.82	1.13	1.27	0.41
	Post	5.33	1.09	1.66	0.94	4.70	1.02	1.17	0.29

Physical Pain:

Analysis on the explicit judgment about the victim's physical outcome showed a main effect of Session ($F_{(1,45)} = 5.196$; $p = 0.03$), indicating that participants reported victims to have felt less pain in the Post-Session, compared to the Pre-Session. Post hoc analysis on the main effect for Version revealed a significant difference between scenarios with negative outcome (Intentional Harm: 6.26 ± 0.56; Accidental Harm: 6.23 ± 0.51) for the passive character and scenarios with neutral outcome (Attempted Harm: 1.24 ± 0.42; Neutral: 1.06 ± 0.17).

Moreover, we observed a significant two-way interaction Session X Group ($F_{(2,45)} = 9.020$; $p < 0.001$). Post-hoc analysis showed that participants reported the passive character to have felt less physical pain in the SI group, comparing Post-Session (3.52 ± 0.40) to Pre-Session (3.80 ± 0.47; $p < 0.001$). No other comparison reached statistical significance (ALL $p > 0.18$).

Interestingly, also a three-way Session X Version X Group ($F_{(6,135)} = 2.99$; $p = 0.009$) interaction was discovered. Further exploration with post-hoc analysis showed that, this analgesic-like effect in the SI group was specific for Intentional and Accidental Harm scenarios. In these scenarios participants attributed less pain to the victim in Post-Session (5.81 ± 0.86, 5.90 ± 0.76) compared to Pre-Session (6.27 ± 0.73, 6.41 ± 0.53; all $p < 0.001$).

Table 9. *Mean ratings ± SD for Physical Pain*

		Physical Pain							
		Int-Harm		Acc-Harm		Att-Harm		Neutral	
		mean	SD	mean	SD	mean	SD	mean	SD
SHAM	Pre	6.35	0.43	6.39	0.47	1.14	0.38	1.11	0.28
	Post	6.46	0.35	6.31	0.46	1.28	0.43	1.01	0.04
SI	Pre	6.27	0.73	6.41	0.53	1.41	0.86	1.13	0.42
	Post	5.81	0.86	5.90	0.76	1.33	0.46	1.03	0.09
TPJ	Pre	6.35	0.45	6.11	0.45	1.14	0.34	1.04	0.17
	Post	6.32	0.57	6.29	0.51	1.14	0.34	1.02	0.08

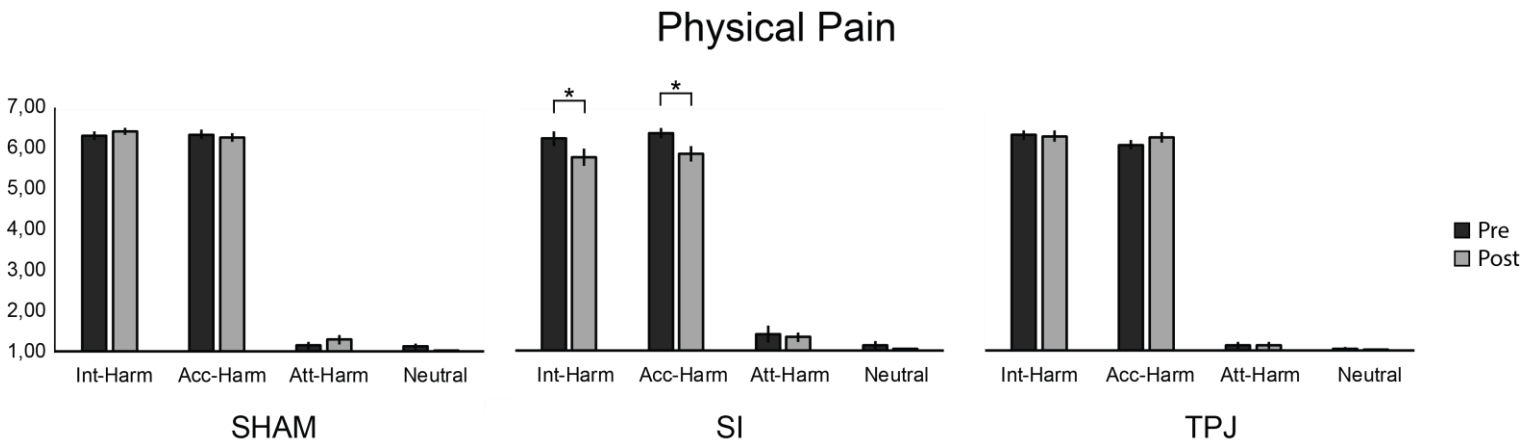

Figure 14. *Mean ratings ± SD for Physical Pain. Asterisks indicate significant post-hoc comparisons (P < 0.05). Error bars denote s.e.m.*

Emotional Suffering:

Analysis of judgment of emotional suffering for the passive character showed a significant two-way interaction Session X Group ($F_{(2,45)} = 0.99$; $p = 0.005$). Post-hoc analysis showed that, in the SI group, participants reported that the passive character had felt less emotional suffering in the Post-Session (3.30 ± 0.57) compared to the Pre-Session (3.57 ± 0.77; $p = 0.002$), all other $p > 0.16$.

Post hoc analysis on the main effect for Version revealed a significant difference between scenarios with negative outcome (Intentional Harm: 5.94 ± 0.86; Accidental Harm: 5.77 ± 0.93) for the passive character and scenarios with neutral outcome (Attempted Harm: 1.34 ± 0.52; Neutral: 1.13 ± 0.24).

Table 10. *Mean ratings ± SD for Emotional Suffering*

		Emotional Suffering							
		Int-Harm		Acc-Harm		Att-Harm		Neutral	
		mean	SD	mean	SD	mean	SD	mean	SD
SHAM	Pre	5.96	± 0.83	5.83	± 0.91	1.19	± 0.55	1.20	± 0.48
	Post	6.07	± 0.76	5.89	± 0.72	1.42	± 0.59	1.04	± 0.17
SI	Pre	5.82	± 1.19	5.65	± 1.40	1.54	± 0.97	1.26	± 0.45
	Post	5.32	± 1.09	5.28	± 1.15	1.47	± 0.68	1.13	± 0.29
TPJ	Pre	6.26	± 0.55	5.95	± 0.85	1.21	± 0.32	1.08	± 0.24
	Post	6.20	± 0.57	6.03	± 0.56	1.22	± 0.36	1.08	± 0.18

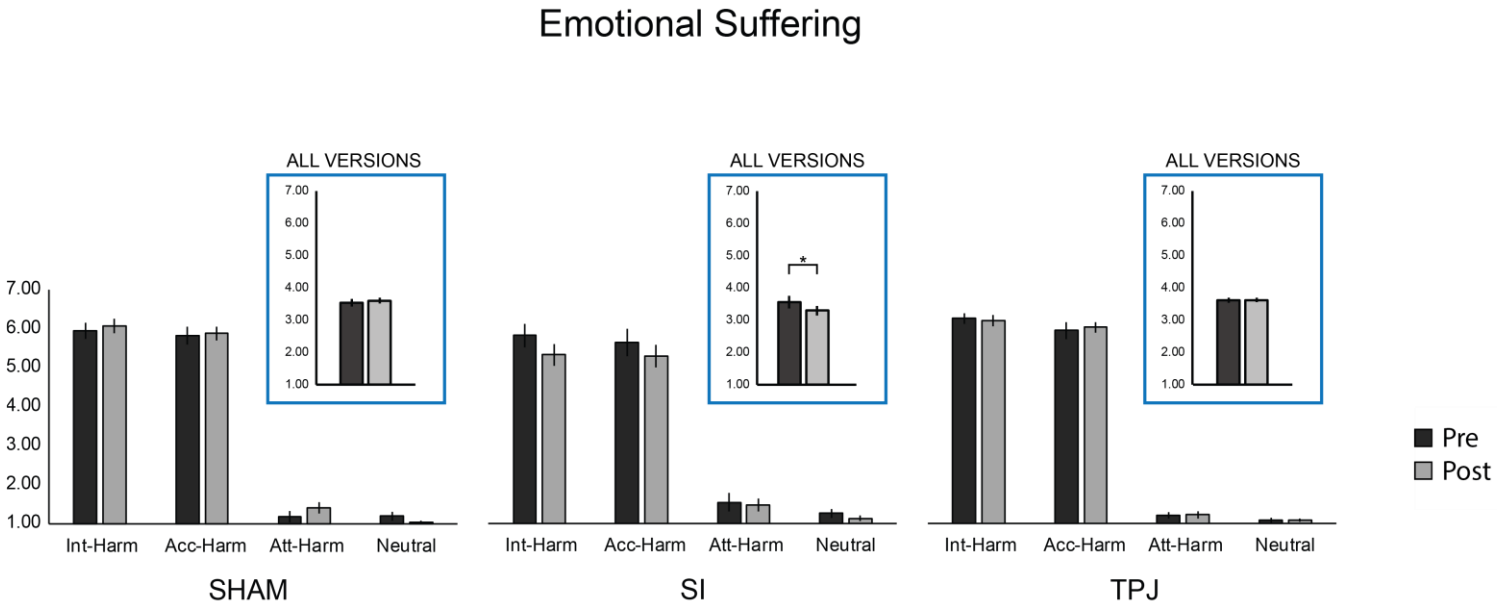

Figure 15. *Mean ratings ± SD for Emotional Suffering. Asterisks indicate significant post-hoc comparisons (P < 0.05). Error bars denote s.e.m.*

Displeasure:

Participants reported less displeasure in reading scenarios in the Post-Session compared to the Pre-Session ($F_{(1,45)} = 7.013$; $p = 0.01$). The main effect of Version discovered ($F_{(3,135)} = 498.568$; $p < 0.001$) was accounted for by different judgments for each version, with displeasure felt by participants decreasing from Intentional Harm (5.96 ± 0.87) to Accidental Harm (5.59 ± 0.89), Attempted Harm (2.15 ± 1.23) and finally Neutral (1.17 ± 0.32) scenarios.

Table 11. *Mean ratings ± SD for Displeasure*

		Displeasure							
		Int-Harm		Acc-Harm		Att-Harm		Neutral	
		mean	SD	mean	SD	mean	SD	mean	SD
SHAM	Pre	6.14	0.78	5.77	0.77	2.00	1.07	1.18	0.37
	Post	6.27	0.60	5.78	0.65	1.90	1.25	1.08	0.20
SI	Pre	5.99	1.18	5.52	1.20	2.72	1.55	1.38	0.67
	Post	5.72	1.34	5.51	1.33	1.91	1.09	1.23	0.45
TPJ	Pre	5.94	0.60	5.43	0.76	2.33	1.47	1.08	0.22
	Post	5.72	0.87	5.51	0.70	2.07	1.44	1.06	0.12

Positive and Negative Valence

Explicit judgments about valence active characters attributed to their own actions were divided in positive and negative valence. Analysis on positive valence revealed a main effect of Version ($F_{(3,135)} = 121.045$; $p < 0.001$), accounted for by a post hoc difference for all versions (ALL $p < 0.01$).

Analysis on negative valence revealed a main effect of Session ($F_{(1,45)} = 6.668$; $p = 0.01$), showing that participants attributed less negative valence to active character's actions in the Post-Session () compared to the Pre-Session (). Moreover, the main effect of Version discovered ($F_{(3,135)} = 199.105$;

$p < 0.001$), was again accounted for by a post hoc difference for all versions (ALL $p < 0.001$). Moreover, a significant two-way interaction Session X Version ($F_{(3,135)} = 3.678$; $p = 0.01$) was explained by less negative valence judgments for Intentional Harm in the Post-Session (3.20 ± 0.68) compared to the Pre-Session (3.35 ± 0.57).

Table 12. *Mean ratings ± SD for Positive Valence*

		Positive Valence							
		Int-Harm		Acc-Harm		Att-Harm		Neutral	
		mean	SD	mean	SD	mean	SD	mean	SD
SHAM	Pre	2.86	1.42	1.67	0.94	4.38	1.40	5.53	0.92
	Post	3.04	1.43	1.74	0.82	4.47	1.19	5.41	1.24
SI	Pre	2.67	1.19	1.69	0.75	3.76	1.18	5.15	1.07
	Post	3.18	1.19	1.63	0.65	3.81	1.18	5.16	0.95
TPJ	Pre	2.67	1.22	1.75	0.93	3.70	0.88	5.27	0.95
	Post	2.80	1.17	1.81	1.11	3.57	0.62	5.21	0.95

Table 13. *Mean ratings ± SD for Negative Valence*

		Negative Valence							
		Int-Harm		Acc-Harm		Att-Harm		Neutral	
		mean	SD	mean	SD	mean	SD	mean	SD
SHAM	Pre	4.42	1.55	5.98	1.28	2.15	0.79	1.22	0.49
	Post	3.95	1.72	5.64	1.26	2.07	0.74	1.09	0.24
SI	Pre	4.22	1.29	5.58	1.08	2.18	0.76	1.33	0.52
	Post	3.78	1.51	5.47	1.43	2.36	0.97	1.10	0.18
TPJ	Pre	4.38	1.40	5.31	1.21	2.16	1.18	1.24	0.48
	Post	4.02	1.45	5.31	1.41	2.51	1.17	1.08	0.12

Intention to Act:

The main effect of Version ($F_{(3,135)} = 134.77$; $p < 0.001$) for judgments about the active characters' intention to act was accounted for by the different intentionality attributed to Accidental Harm scenarios compared to all others (ALL $P < 0.001$). This showed that participants were able to understand the active characters' mental states, correctly attributing to her intention to act.

Table 14. *Mean ratings ± SD for Intention to Act*

		Intention to Act							
		Int-Harm		Acc-Harm		Att-Harm		Neutral	
		mean	SD	mean	SD	mean	SD	mean	SD
SHAM	Pre	5.73	± 0.91	2.99	± 1.53	5.63	± 0.79	5.83	± 0.51
	Post	6.05	± 0.60	3.39	± 1.66	5.55	± 0.92	6.06	± 0.85
SI	Pre	5.57	± 1.38	3.44	± 1.71	5.54	± 1.18	5.80	± 1.18
	Post	5.66	± 1.14	3.19	± 1.71	5.61	± 1.14	5.52	± 1.43
TPJ	Pre	5.96	± 0.73	3.58	± 1.82	5.99	± 0.73	5.84	± 1.07
	Post	5.86	± 0.75	3.74	± 1.72	5.78	± 0.71	5.58	± 1.43

Unpleasantness of the stimulation:

To control for a possible involvement of unpleasantness of the stimulation, a control analysis was conducted on subjective ratings provided by participants after tDCS. The ANOVA on Group (SHAM, SI, TPJ) did not show any significant difference that might explain the specific results found in the task ($F_{(2,45)} = 0.78$; $p = 0.47$).

Table 15. *Mean subjective ratings ± SD of the unpleasantness felt during neuromodulation (SHAM, tDCS over SI and TPJ)*

SHAM	SI	TPJ
1.1 ± 0.3	1.4 ± 0.2	1.3 ± 0.4

Discussion

Evidence from cognitive psychology and cognitive neuroscience suggests that morality is composed by multiple processes taking place in several brain regions (Moll et al., 2005; Young and Dungan, 2011; Fumagalli and Priori, 2012). Among these processes, two central aspects used in third party moral judgments about harmful actions are the attributions of intentions and beliefs to the person performing the action and the reactions to the outcome of the action on the victim (Young et al., 2007; Cushman, 2008; Greene, 2009; Reniers et al., 2012; Buon et al., 2016). In this view, morality is supported by distinct evaluative systems that can act in concert or in conflict, each resting upon specific cognitive processes, helping individuals decide what is right and what is wrong. However, most of the evidence available is correlational, and clear functional evidence of the contribution of these systems (and networks) in healthy adults' moral judgment is missing.

In the present study, we used cathodal tDCS to inhibit two key regions subserving mental state attributions or reaction to others' pain, namely the temporo-parietal junction (TPJ) and the primary somatosensory cortex (SI). We thus explored whether these regions are functionally involved in moral judgments about textual scenarios depicting harmful interactions between two individuals or in explicit judgments about the two characters' internal states. Scenarios were previously designed (Young et al., 2010) to explore the role of agents' beliefs (neutral vs negative) and actions' outcomes (neutral vs negative). Moreover, we specifically adapted them to include more subtle modulations of the outcome, to test participants' reactions to it. In specific, in the published version of our scenarios,

negative outcomes always implied death for the victim, whereas in our version negative outcomes implied physical pain and emotional suffering for the victim, but not death.

We found that cathodal tDCS over the TPJ altered participants' moral judgments. In specific, after modulation of TPJ, participants judged accidental harm situations as more morally forbidden and were more permissive in judging attempted harm situations. The effect we found on moral judgments after TPJ modulation was specific for situations in which intent- and outcome-based processes are conflicting (Accidental and Attempted Harm scenarios), this suggests that information about the victim's outcome is present at the behavioural level, contributing to moral judgments. Traditionally, these changes in moral judgments for accidental and attempted harm after modulation of the TPJ are interpreted as a proof of a reduction of the influence of beliefs in moral judgments after interference on a key node for mental state attribution (Young et al., 2010; Sellaro et al., 2015; Ye et al., 2015). To test this interpretation, in the present study we directly tested participants' judgments about the active characters' internal mental states. However, our results did not show any tDCS-related change in participants' ratings when they were explicitly asked to rate the active character's intention to harm the passive character, or when they were asked to attribute punishment to her/his actions. After inhibition of the SI, a brain region involved in processing others' pain, we did not observe any changes in participants' moral judgments. Interestingly, in the present study when the victim's outcome was explicitly explored, we found that after SI modulation participants reported significantly milder rating for both the physical pain and the emotional suffering felt by passive characters in scenarios.

From this complex set of results, we can conclude that:

1. Inhibition of the TPJ altered participants' moral judgments for scenarios in which intention and outcome are in conflict. However, it had no effect on participants' explicit judgments of the agent's internal mental states.
2. Inhibition of the SI altered participants' explicit judgments of the outcome on the passive character but had no effect on participants' moral judgments.

Rating others' pain in our somatosensory cortex

The primary somatosensory cortex is essential for our sense of touch and pain (Peyron et al., 2000; Bingel et al., 2004). Moreover, evidence shows that somatosensory cortices are also active during observation of action (Costantini et al., 2005; Avenanti et al., 2007; Dinstein et al., 2007; Gazzola and Keysers, 2009) touch (Keysers et al., 2004; Blakemore et al., 2005; Ebisch et al., 2008; Schaefer et al., 2009) and pain (Morrison et al., 2004; Avenanti et al., 2005, 2006, Jackson et al., 2005, 2006a; Bufalari et al., 2007; Lamm et al., 2007a; Morrison and Downing, 2007; Decety and Meyer, 2008; Akitsuki and Decety, 2009; Keysers et al., 2010) in others. Previous studies show that stronger SI activation are associated with visual stimuli suggesting more pain (Costantini et al., 2008) and correlate with the intensity participants attribute to the observed pain (Bufalari et al., 2007). Taken together these results suggest that activity in the primary somatosensory cortex might convey discriminative/quantitative information to the observed painful stimulus, following an intensity coding (Keysers et al., 2010). Moreover, activity in the SI has been observed when participants are directly asked to judge how painful a stimulus was (Lamm et al., 2009). In this framework, the somatosensory cortices might be a part of the simulation network, processing the perceived pain into a somatic representation that conveys information about how it would feel to experience the observed or imagined pain ourselves. This would provide useful information for judging the underlying emotional state (i.e., pain). Previous neuromodulation studies show that interference with somatosensory cortices impairs processing of observed actions (Valchev et al., 2016, 2017) emotional facial expressions (Paracampo et al., 2016) and touch (Bolognini et al., 2011).

Our results significantly expand our knowledge about the role of the somatosensory cortices in emotion processing and social cognition by showing that the SI has a role in rating others' pain, even when participants cannot directly observe the painful interaction and must extract information through verbal descriptions.

Text (e.g. in books, newspapers, websites, social networks) is one of the dominant modalities through which we interact and (try to) understand others. A single sentence can convey a vivid representation of another's internal emotional and cognitive state, in some cases much more effectively than any image. Previous studies show that reading descriptions of pain in others produces activity in brain regions involved in first-hand painful experiences (Osaka et al., 2004; Gu and Han, 2007; Richter et al., 2010; Bruneau et al., 2012, 2013). Following an embodied approach, several authors have proposed that sensorimotor neurons that are active during both production and perception have a role in language comprehension (Gallese, 2008; Pulvermüller and Fadiga, 2010; Glenberg and Gallese, 2012; Marino et al., 2012; Pulvermüller, 2013). Beyond correlational evidence, this study shows that activity within the somatosensory cortex is causally involved in creating a vivid representation of pain perceived through language. Despite this behavioural effect on explicit ratings for the victim's outcome, modulation of the SI did not produce any change in participants' moral judgments. This dissociation is consistent with a framework that puts mental state attribution in a dominant position for healthy adults' moral judgments and reaction to the victim's outcome as a secondary source of information (Cushman 2008, Decety 2012, Young-Tsoi 2013).

Behavioural changes after TPJ modulation

Inhibitory modulation of the TPJ altered our participants' moral judgments. Research on the neural mechanisms supporting moral judgments has focused on the mentalizing network (Young and Dungan, 2011; Young and Tsoi, 2013). The temporo-parietal junction is a key region within the mentalizing network (Saxe and Kanwisher, 2003; Bzdok et al., 2012) and previous correlational studies show that its activation correlates with participants' consideration for agent's intentions during moral judgments (Young et al., 2007; Young and Saxe, 2009; Koster-Hale et al., 2013). Moreover, previous interferential studies show that transient disruption of TPJ activity has a behavioural effect on participants' moral judgments (Young et al., 2010; Jeurissen et al., 2014; Sellaro et al., 2015; Ye et al., 2015).

In line with previous findings, our results show that, after TPJ inhibitory modulation, participants' moral judgments were more outcome-based and less intent-based. In specific, they were less morally permissible in judging scenarios in which the agent had no intention to cause harm but ended up causing harm anyway and were more morally permissible in judging scenarios in which the agent had the intention to cause harm but did not manage to do it. No differences were observed for intentional harm or neutral scenarios. However, when explicit judgments of characters' mental states were tested, TPJ modulation did not produce any behavioural change. Previous studies show that modulation of TPJ activity can impair performance in false belief tasks (Costa et al., 2008), change interpretation of others' behaviours (Giardina et al., 2011), interfere with self-other distinction (Santiesteban et al., 2012; Silani et al., 2013; Kelly et al., 2014) see (Hétu et al., 2012; Schuwerk et al., 2014). The lack of any change in participants' explicit judgments after TPJ modulation in our task might be due to the specific stimuli used. Indeed, in our scenarios, internal mental states are clearly described to participants and their interpretation doesn't pose any challenge. Neuromodulation techniques require calibrated tasks as their effect on behaviour might be subtle. A possible future development of the present task might consist of more subtle description of characters' internal mental states, to highlight the possible contribution of the mentalizing network (in specific the TPJ) to their interpretation.

Conclusion

Previous studies suggest that morality is supported by multiple processes, in particular judging an action as morally right or wrong implies both reacting to its outcome and to the intention of the agent performing the action. In the present study, we aimed at exploring the contribution of a key region for intention attribution (i.e., the temporo-parietal junction - TPJ) and a key region for reactions to others' emotions and sensations (i.e., the primary somatosensory cortex - SI) in moral judgment and explicit judgments about others' internal emotional and cognitive states, using tDCS to modulate their activity. Our results show that modulation of the TPJ had a behavioural effect on participants' moral judgment. This effect was specific for situations in which agent's intention and outcome are in

conflict, thus showing that the victim's outcome is taken into account when judging the morality of an action. Moreover, SI modulation produced changes in participants' explicit ratings of the physical pain and emotional suffering felt by the victim. However, modulation of the SI did not produce any change in moral judgments. This evidence shows that moral judgment largely depends on mental state attribution taking place in the temporo-parietal junction, information about the victim's outcome despite being present both at the neural and behavioural level, is secondary when participants are asked to judge whether an action is morally right or wrong. On the other hand, the somatosensory cortex is functionally involved in creating vivid representation of pain in others, even when the painful experience is conveyed through text and is not directly observable.

GENERAL DISCUSSION

The idea that our bodies participates in our understanding of the world is ancient. We use them as a tool to interact with others.

The discovery of mirror neurons in monkeys and mirror mechanisms in humans provided simulation theories with a biological substrate.

Regions involved in moving and sensing our bodies show overlapping activations when…

The activation of the same parieto-premotor regions active when performing a motor act during observation of the same action, has been thus interpreted as internal simulation of the perceiver action. A mechanism matching perceptual representation (visual or auditory) of the observed action with one's own motor representation is the perfect candidate to be the cornerstone of social cognition with the power to attribute intention to others' motor act in the same way as we plan our motor acts before performing them (Caspers et al. 2010; Keysers et al. 2010; Gallese and Sinigaglia 2011; Avenanti et al. 2013b; Valchev et al. 2016). A growing body of evidence suggests that the same mirror mechanisms in sensorimotor cortices are involved in processing others' sensations and emotions (Carr et al., 2003; Winston et al., 2003; Leslie et al., 2004; Dapretto et al., 2006; Warren et al., 2006; Keysers et al., 2010). Sensorimotor regions might, thus, be involved in processing others' emotion and in social cognition in general (Pobric and Hamilton, 2006; Avenanti et al., 2007; D'Agata et al., 2011; de Gelder et al., 2012; Tidoni et al., 2013; Bolognini et al., 2014; Costa et al., 2014; Urgesi et al., 2014; Jacquet and Avenanti, 2015; Tamietto et al., 2015; Valchev et al., 2016). In sum, human beings can understand internal states in others by looking or imagining others' behaviour. In this view, internal simulation in the sensorimotor network can be used to interpret the internal mental state that caused the behaviour. However, a major unsolved issue for a clear understanding of the role of these mirror mechanisms in social cognition has been the lack of established connections between

shared activations and behavior, in particular for high-level explicit inferences about others' internal emotional states.

The present thesis significantly expands upon previous evidence by demonstrating that those sectors of the sensorimotor cortex showing vicarious activations are critical for our ability to understand others' internal states from behavior. Our findings establish a strong and direct causal link between sensorimotor brain networks and emotion understanding that was only suggested in the past. From Experiment 1 to 7 we focused on the emotional facial expression of amusement. The smile is a prominent facial expression in social life, however, it is also the most ambiguous expression we encounter. We designed two novel tasks to track participants' accuracy in judging others' internal emotional states (Empathic Accuracy, EA) and used repetitive TMS to interfere with key regions of the sensorimotor simulation and the mentalizing network. This way, we explored if these networks are critical for fine-grained judgments about amusement from observed smiles. TMS over sensorimotor regions representing the face (i.e., in the inferior frontal gyrus, IFG, and ventral primary somatosensory cortex, SI), disrupted the ability to infer amusement authenticity from observed smiles. In Experiment 8, 9 and 10 we focused on the involvement of the somatosensory cortex in moral judgment and in explicit judgments of another's emotional experience described through text. We know from previous studies that healthy moral judgments in adulthood strongly rely on our theory about others' intentions, however, observing or imagining a person causing pain to another leads to rapid vicarious activation in brain regions involved in our first-hand painful experiences. Here we used tDCS to inhibit the sensorimotor simulation or the mentalizing network while participants were asked to read written narratives describing harmful situations involving two individuals and judge different aspects of these. Theoretical models propose that one mechanism for inferring the unobservable emotional feelings of others is to simulate their observed or imagined behavior within one's own sensorimotor system (Adolphs et al. 2000; Adolphs 2002; Gallese et al. 2004; Goldman and Sripada 2005; Gallese 2007; Keysers et al. 2010; Niedenthal et al. 2010; Gallese and Sinigaglia

2011; Avenanti et al. 2013b; Wood et al. 2016). According to these models, sensory representations of observed behavior in high-order visual regions (e.g., the superior temporal sulcus, STS) would be coupled with sensorimotor representations of the same expressions. This sensorimotor embodiment would help observers to intuitively grasp what the other person is experiencing. Covert emotional states (e.g., happiness) are continuously associated with overt motor behaviours (e.g., smiling). Given this, observers can simulate the covert emotional state of another by embodying their overt motor state (Carr et al., 2003; Gallese, 2007b; Jabbi et al., 2007; Bastiaansen et al., 2009; Niedenthal et al., 2010). Thus, sensorimotor simulation could support access to stored knowledge, grounded in the brain regions involved in first-hand emotional experiences (including the anterior insula and cingulate cortex), about the emotional states associated with the behavior (Goldman and Sripada, 2005; Niedenthal, 2007; Bastiaansen et al., 2009; Niedenthal et al., 2010; Wood et al., 2016). Thus, when observing or imagining behaviors with emotional content in others, activity in sensorimotor networks may partially or fully reactivate related concepts and affective states and thus contribute to accurate cognitive inferences about the underlying emotional feeling.

However, to date the idea that sensorimotor regions are essential for accurate inference of the covert mental state underlying performed actions (i.e., the social target's emotional feeling) has received only partial empirical support from studies using causal methods. Previous studies used simplified stimuli for the most part (e.g., static pictures of actions or facial expressions) and did not clarify to what extent sensorimotor cortices play a role in higher-level explicit inferences about the emotional feelings underlying those facial movements (possibly via access to stored knowledge in affective brain regions) (Adolphs et al. 2000; Pitcher et al. 2008; see also Keysers et al. 2010; Avenanti et al. 2013b) (Pazzaglia et al., 2008a; Michael et al., 2014).

The present thesis provides evidence supporting this hypothesis. Indeed, one important feature of our findings is that active interference with the sensorimotor network using neuromodulation tools (TMS and tDCS) disrupted participants' performance in tasks requiring to perform fine-grained explicit

inferences. Thus, we suggest that rTMS and tDCS disrupted sensorimotor processing necessary for making sense of those behaviors and inferring the underlying emotions.

These shared activations reflect one form of mind-reading, involving attributions of mental states (goals, intentions, emotions, sensations) that have a bodily format (that are grounded in the self). However, we cannot always understand others using our internal states as a basis to understand others. A different line of research has focused on the hypothesis that understanding others is based on explicit inferential processes (Mitchell et al., 2002; Saxe, 2005; Shamay-Tsoory et al., 2005). Focusing on the neural bases of mental state attributions, scholars have isolated a network of brain regions recruited during explicit inferences about the intentions, beliefs, and feelings of others: the mentalizing network (Amodio and Frith, 2006; Frith and Frith, 2006; Mitchell, 2009; Bzdok et al., 2012; Schurz et al., 2014). The mentalizing system provides a different route to understanding others that it is not through sharing, but through the creation of propositional cognitive knowledge about what others are feeling, inherently based on self-other distinction. As we are considering complex social tasks, the present thesis would not be complete without considering the role of the mentalizing network alongside the sensorimotor simulation network

The present thesis provides significant evidence on the role of the two networks in social cognition. Neuromodulation of the mentalizing network produced different behavioural outcomes depending on the specific task participants were asked to perform. In experiment 3 and 4, interference with the mentalizing network did not produce behavioural effects on our dichotomic EA task, however, in experiment 7, interference with this network affected participants' performance in a modified version of the same EA task. Finally, in experiment 9, tDCS modulation of the mentalizing network altered subjects' moral judgments. Beyond purist approaches to social cognition we propose that motor simulation and mentalizing might represent two processes with the same goal. Both participate in understanding others (Olsson and Ochsner, 2008; Bastiaansen et al., 2009; Shamay-Tsoory et al., 2009; Zaki et al., 2012). Recent imaging studies show that the two systems might be concurrent active

in complex social tasks (Zaki et al., 2009b; Schippers et al., 2010; Schippers and Keysers, 2011; Spunt et al., 2011; Spunt and Lieberman, 2012a, 2013; Harvey et al., 2013; Sperduti et al., 2014; Kanske et al., 2015) and might even show functional connectivity during social interactions (Lombardo et al., 2010). Our results suggest that the role of the simulation and the mentalizing networks is not tied to specific stimuli used to convey information about internal states in others. Instead, it seems to be flexibly influenced by the specific process that people use to understand the situation they encounter during social cognition.

Finally, our sensorimotor cortices are not only crucial to retrodict the internal emotional state from behaviors, but influential theories suggest that humans predict others' upcoming actions by using their own motor system as an internal forward model. However, functional evidence that the motor system is causally essential for predicting others' actions is meager. In Appendix A, using transcranial direct current stimulation (tDCS) we tested the role of the inferior frontal cortex (IFC), in action prediction (AP). We devised a novel AP task where participants observed the initial phases of right-hand reaching-to-grasp actions and had to predict their outcome (i.e., the goal/object to be grasped). We found that suppression by cathodal (inhibitory) tDCS of the left IFC, but not the left superior temporal sulcus (STS) or the right IFC, selectively impaired performance on the AP task, but not on a difficulty-matched control task (Non-human Prediction, NP task). Remarkably, anodal (excitatory) tDCS of the left IFC brought about a selective improvement in the AP-task. These findings indicate that the left IFC is necessary for predicting the outcomes of observed human right-hand actions. Crucially, our study shows for the first time that down- and up-regulating excitability within the motor system can hinder and enhance AP abilities, respectively. These findings support predictive coding theories of action perception and have implications for enhancement of action prediction abilities.

In Appendix B, we explored the role of the primary motor cortex in predicting others' actions. Although correlational studies suggest that the motor cortex (M1) might be involved in this process,

it is unclear whether M1 is also causally essential for making predictions about observed actions. To test the functional relevance of M1 to action prediction we used offline monopolar transcranial direct current stimulation (tDCS) in healthy participants. In four different tDCS experiments, we administered 15 minutes of anodal or cathodal currents at 1 or 2 mA over the left M1 before participants performed the AP and NP task. In each experiment, participants received sham and active tDCS on two separate sessions. We found that 2mA cathodal tDCS selectively impaired performance on the AP task, but not on the NP task. The effect was specific to polarity (it was not present after anodal currents) and intensity (it was not present after 1mA tDCS). These findings establish specific tDCS parameters for effective M1 stimulation in action prediction and highlight the functional relevance of M1 to making accurate predictions about the outcome of human actions.

From reaching the things we want to grasp, to reaching the minds we want to grasp, brain regions that primarily evolved to allow movement are crucial to accurately understand what others are feeling or to predict what they are about to do.

APPENDIX A

Boosting and decreasing action prediction abilities through excitatory and inhibitory tDCS of inferior frontal cortex

INTRODUCTION

The ability to predict the outcomes of observed actions is vital for social life, given its importance for both cooperative (e.g., joint actions) and competitive interactions (e.g., sport). Yet, the neural bases of this ability are poorly understood. There is widespread evidence that seeing the actions of others activates an action observation network (AON) that includes higher-order visual regions involved in encoding biological motion (i.e., the superior temporal sulcus, STS) and parieto-frontal regions involved in controlling and sensing body actions (Keysers and Perrett, 2004; Gazzola and Keysers, 2009; Perrett et al., 2009; Caspers et al., 2010; Rizzolatti et al., 2014; Urgesi et al., 2014). In particular, the inferior frontal cortex (IFC), which includes the ventral premotor cortex and the posterior part of the inferior frontal gyrus, represents a key node of the AON involved in coupling action perception with execution. In the monkey IFC, a class of multimodal neurons – called mirror neurons – is directly involved in such coupling, which may be important for making sense of others' actions (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 2014).

Studies suggest that the motor node of the AON builds up an anticipatory representation of observed actions (Kilner et al. 2004; Urgesi et al. 2006, 2010; Sebanz et al. 2006; Aglioti et al. 2008; Abreu et al. 2012; Avenanti et al. 2013a; Avenanti, Candidi, et al. 2013; Wurm et al. 2014; Balser et

al. 2014; Ondobaka et al. 2014; Makris and Urgesi 2015; Sacheli, Christensen, et al. 2015). This proposal echoes influential theoretical models positing that the motor system is designed to act as an anticipation device, and that one's own motor system can be used as an internal forward model when perceiving the actions of others (Prinz, 1997; Blakemore and Decety, 2001; Wolpert et al., 2003; Grush, 2004; Wilson and Knoblich, 2005; Kilner et al., 2007; Schütz-Bosbach and Prinz, 2007; Friston et al., 2011). In this vein, predicting the outcomes of observed actions would critically rely on motor areas of the AON like the IFC. However, whether the IFC or other nodes of the AON are causally essential for predicting others' actions remains speculative, and establishing whether the IFC is critical for action prediction is the goal of the present study.

Human and monkey correlational studies indicate that: i) activity in motor regions can occur prior to the observation of a predictable grasping movement (Umiltà et al., 2001; Kilner et al., 2004; Fogassi et al., 2005; Maranesi et al., 2014); and ii) there is a clear anticipatory bias in simulating the upcoming phases of observed reaching-grasping actions (Gangitano et al. 2004; Borroni et al. 2005; Urgesi et al. 2010; Avenanti et al. 2013b). These anticipatory motor activations appear to rely on the AON, as they are disrupted if the IFC is suppressed by low-frequency repetitive transcranial magnetic stimulation (TMS) (Avenanti et al. 2013a). Moreover, the IFC and other motor nodes of the AON are recruited during tasks requiring participants to predict the outcomes of observed actions (Abreu et al., 2012; Amoruso et al., 2014; Balser et al., 2014; Ondobaka et al., 2014; Wurm et al., 2014). An anticipatory bias in processing observed actions has also been shown in STS neurons (Perrett et al., 2009).

It is worth noting here that the notion of anticipatory bias is supported almost exclusively by indirect correlational evidence that leaves unsolved the fundamental question of whether motor and visual nodes of the AON are causally essential for behavior and, in particular, for the ability to make predictions about others' actions. Only two interferential studies on the anticipatory bias have been conducted thus far in humans. The first showed that, while low-frequency TMS suppression of the

IFC disrupted anticipatory motor activations during observation of implied actions (see above), suppression of the STS had an opposite, enhancing effect on anticipatory motor activations, suggesting that motor simulation plays a compensatory role when visual input is degraded (Avenanti et al. 2013a). The second study showed that online repetitive TMS interference of the STS disrupted the ability of both novices and soccer players with great visual expertise (i.e., goalkeepers) to predict the direction of a ball after perceiving the initial phases of penalty kicks. In contrast, TMS interference with the dorsal premotor cortex impaired performance only in soccer players, whether outfield players or goalkeepers (Makris and Urgesi, 2015). Although the lack of a control task for assessing nonspecific, distracting effects of online TMS makes any conclusion tentative, this study is in keeping with the idea that visual and motor nodes of the AON may play different roles in action prediction. Yet, the causal roles of the STS and the IFC in the ability to predict the outcomes of observed actions have not been established. Crucially, whether action prediction abilities can be enhanced by exogenous boosting of cortical excitability in the AON is a critical and entirely unexplored question.

Another fundamental, but thus far unresolved, theoretical issue is whether the IFC is critical for predicting event dynamics in general, or whether its involvement is specific to predicting human actions (Schubotz and von Cramon, 2004; Schubotz, 2007; Press and Cook, 2015). Imaging evidence indicates that the IFC is active when predicting sequences of events, suggesting domain-general involvement (Schubotz and von Cramon, 2004; Schubotz, 2007). However, only causal methods can establish the domain-general vs. domain-specific role of IFC in action prediction.

All these issues are dealt with in the present study, which used transcranial direct current stimulation (tDCS) to alter cortical excitability in the IFC and the STS before participants made predictions about human actions and non-human movements. tDCS is a valuable method of non-invasive cortical stimulation that allows researchers to induce polarity-dependent excitability changes in the underlying stimulated area. Using weak offline cathodal or anodal DC currents, tDCS can induce cortical inhibition or excitation, respectively, and alter neural functioning for several minutes

after the end of the stimulation (Nitsche, 2003; Antal et al., 2004; Horvath et al., 2015). In four tDCS experiments, we applied 15 minutes of tDCS just before participants performed two novel tasks requiring them to predict the future end-states/outcomes of human actions (Action Prediction, AP) or non-human movements (Non-human Prediction, NP) based on the initial phases of the movements. The tasks were calibrated and matched for difficulty in three behavioral studies that allowed us to select sets of AP and NP stimuli in which the outcome could be correctly predicted with ~75% accuracy. With this accuracy criterion, we prevented ceiling and floor effects, thus providing the optimal behavioral conditions for revealing any potential detrimental or beneficial effects of tDCS.

In the tDCS experiments, task performance was assessed after active tDCS or a control sham tDCS condition that provided a baseline for behavioral performance. In Experiment 1 and Experiment 2 we applied cathodal tDCS (c-tDCS) to suppress neural functioning in the left IFC and the left STS, respectively. We tested whether these regions are specifically tuned to (and critical for) the prediction of human actions, or involved in event prediction in general. To test hemispheric specificity, in Experiment 3 we applied active and sham c-tDCS over the right IFC. Moreover, to test stimulation-polarity specificity, in Experiment 4 we applied anodal tDCS (a-tDCS) over the left IFC with the goal of increasing its excitability and thus enhancing its functioning.

MATERIALS AND METHODS

Participants

A total of 142 healthy volunteers took part in the study. Fifty-two participants were tested in one of four tDCS experiments, and 90 participants were tested in one of three pilot studies. Thirteen different participants were assigned to each tDCS experiment (Experiment 1: 6 females, mean age ± S.D. 23.4 ± 3.8 years, range 19-32; Experiment 2: 6 females, mean age 23.2 ± 1.5 years, range 21-

31; Experiment 3: 6 females, mean age 24.3 ± 2.6 years, range 21-26; Experiment 4: 6 females, mean age 23.6 ± 3.6 years, range 19-30).

Sample size was determined though a power analysis conducted using G*Power 3 (Faul et al., 2007), with power (1 – β) set at 0.80 and α = .05, two-tailed. We expected a large effect size based on three recent transcranial stimulation experiments from our laboratory (exp2 and exp3 in Tidoni et al. 2013; Paracampo et al. 2016). In these studies, we targeted the left IFC to test its role in action perception, and used similar design and task requirements (i.e., participants had to discriminate between two observed actions and their performance was compared during active and sham stimulation), indices of task performance (d'), and task validation procedures (all stimuli were selected to be recognized with 75% accuracy) as in the present study (see below). We conducted two power analyses, one using the mean effect size across the three experiments (Cohen's d = 0.94), and the other using the effect size obtained by pooling data across the experiments (Cohen's d = 0.89). These analyses yielded required sample sizes of 11 and 12 participants, respectively. We thus decided to have 13 participants in each group.

All participants were right-handed and had normal or corrected-to-normal vision. Participants were screened for any general contraindications to non-invasive brain stimulation (Brunori et al. 2011) using the questionnaire developed by Rossi and colleagues (2009, 2011) for TMS. No participant was on medication at the time of the experiment or reported a history of neurological or psychiatric disorders. Participants provided written informed consent. Experimental procedures were approved by the ethics committee at the Psychology Department of Bologna University, and were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki. All participants were naïve to the purposes of the study. Information about the experimental hypothesis was provided only after the experimental tests were completed. No discomfort or adverse effects during tDCS were reported or noticed.

General Design

In four tDCS experiments, we tested the roles of the IFC and the STS in predicting the outcomes of observed movements. In Experiments 1, 2 and 3 we applied c-tDCS over the left IFC, the left STS and the right IFC, respectively. In Experiment 4, we applied a-tDCS over the left IFC. In each experiment, participants were tested in two separate sessions that were carried out immediately after 15 min of active (cathodal or anodal) or sham tDCS over the target region. The order of the sessions was counterbalanced across participants, and the two sessions were separated by 7 ± 3 days.

Tasks and stimuli

In the Action Prediction (AP) task, participants observed 120 video-clips (640 x 480 pixels, 30 fps) depicting actors who were individually filmed while reaching and grasping an object. All stimuli subtended a 22.3° x 33.4° visual angle from the participant's viewing position. Videos started by showing two objects (left side of the screen) located in front of a still right hand (right side of the screen; see Figure 1A). The two objects were placed at a distance of ~45 cm from the actors' hand. One object was located to the left and the other to the right of the actor's hand (~15-20 cm from one another). After a variable delay (1000-2200 ms), the hand started to reach for and grasp one of the two objects. The final phases of the action were occluded and the video interrupted. In these clips, only 30-70% of the entire movement duration was shown, followed by a random-dot mask (150 ms duration) that interrupted the video. Then a response screen showing the two objects appeared and lasted until the response (Figure 1B). The objects placed to the left and to the right of the actor were displayed on the left and right sides of the screen, respectively. Participants had to guess which of the two objects was going to be grasped by the actor's hand, and provided their answers using two

computer keys. The left and right keys were used to select the left and right target objects, respectively.

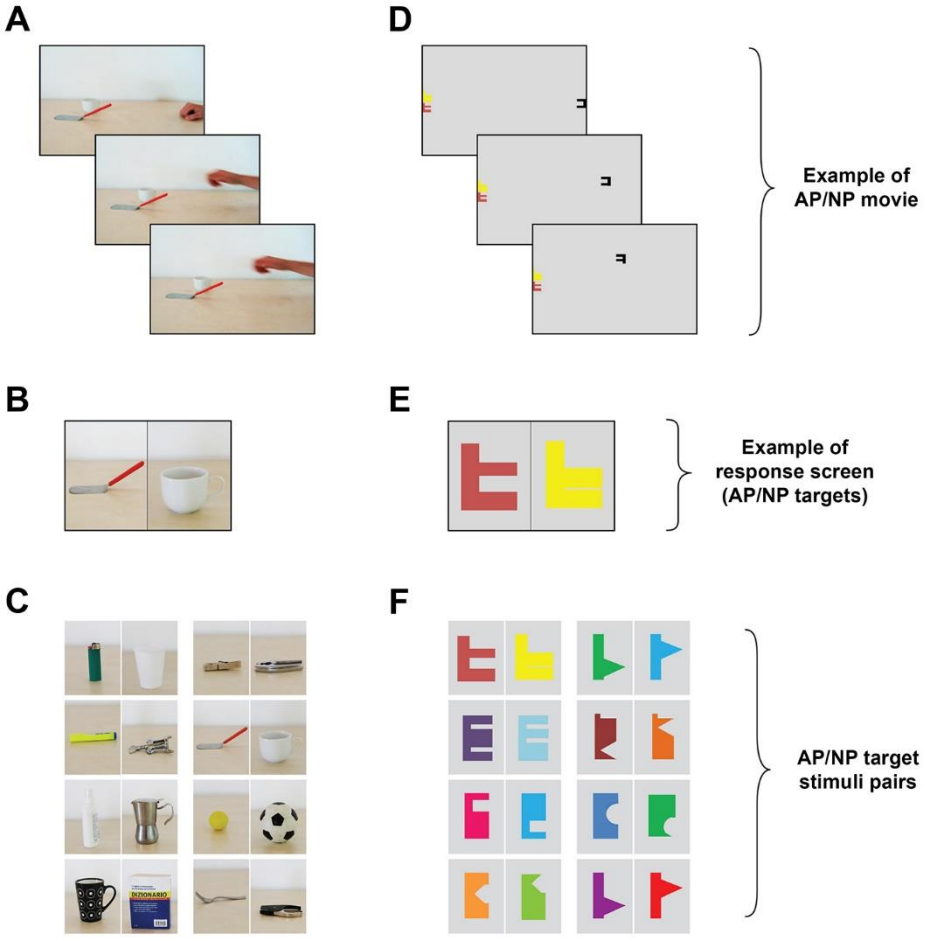

Figure 1. Trial example and stimuli. Example of Action Prediction (AP) task movie **(A)** and response screen **(B).** Target stimulus pairs in the AP task **(C)**. Example of Non-human Prediction (NP) task movie **(D)** and response screen **(E).** Target stimulus pairs in the NP task **(F)**. On each trial, a video-clip showed the initial movement of a hand (in the AP task) or a geometrical form (in the NP task) reaching and adapting to one of two targets. Participants were then presented with the two targets and had to guess which was selected by the hand/form.

Video-clips in the AP task included 8 non-professional actors (4 females; mean age ± S.D.; 23.6 y ± 1.06) reaching and grasping 8 different pairs of objects (i.e., lighter vs. glass; highlighter vs. corkscrew; deodorant spray vs. coffeepot; mug vs. book; clothespin vs. nutcracker; scoop vs. cup; little ball vs. soccer ball; fork vs. stapler; Figure 1C). The two objects in each pair were located near to each other in space, thus implying slightly different reaching trajectories of the grasping hand. The two objects in each pair also presented different affordances, thus implying different grips (i.e., from power grips performed with the whole hand to precision grips performed with the index finger and the thumb). The hand-object interaction was not visible in any of the videos. Thus, the AP task required participants to process kinematic cues (i.e., hand trajectory and finger pre-shaping before grasping) signaling the upcoming grasping of one the two objects.

In the NP control task, participants observed 120 video-clips showing an articulated geometrical form approaching one of two targets (Figure 1D). Participants had to guess which target was going to be approached by the geometrical form by pressing one of two keys during the presentation of the response screen (Figure 1E). The NP videos (640 x 480 pixel, 30 fps) were animations created with Adobe Flash Professional software to grossly match temporal and spatial features of the AP stimuli. Similarly to the AP task, the NP stimuli showed incomplete movements (30-70% of the total duration) of a geometrical form which moved from the right side of the screen in order to reach and fit with one of two different geometrical targets placed on the opposite side. The trajectories of the moving forms were designed to roughly match the hand movements in the AP task.

As in the AP task, the two targets were located in different spatial positions and had different geometrical properties. Analogous to pre-shaping of the fingers in the AP task, the configuration of the moving geometrical form changed over time during the reaching phase in order to optimally fit with one of the two targets. Yet, the NP movement was clearly non-biological. For the NP video clips, we created eight different pairs of geometrical targets (Figure 1F) and eight moving geometrical forms, and random-dot images were used for masking.

Pilot studies and task validation

The final sets of 120 AP videos and 120 NP videos used in the main experiment were selected from an initial sample of ~1400 AP and ~1200 NP videos using a two-step procedure. Initially, we selected 180 stimuli for each task based on the performance of two groups of participants. We presented the initial sample of AP stimuli to 30 participants (15 female, mean age: 24.5 y ± 2.4) and the sample of NP stimuli to 30 other participants (15 female, mean age: 24.2 y ± 2.6). In these two pilot studies, stimuli included movies showing 30-80% of the entire movement. We selected stimuli that were recognized with ~75% accuracy (range: 65-85%) in these two groups of participants. This resulted in about 350 stimuli per task, from which 180 stimuli per task were chosen (90 stimuli for the upper object/target and 90 stimuli for the lower object/target, with comparable representations of the different actors/forms). To assure that the two tasks were matched for difficulty, in a third pilot study, 30 additional participants (15 female, mean age: 23.9 y ± 2.9) were presented with the 180 AP and 180 NP stimuli selected in the first step. Each video was presented twice (720 trials in total).

The final set of stimuli included 120 AP stimuli and 120 NP stimuli whose outcome could be correctly predicted with ~75% accuracy (range: 65-85%). In both tasks, the hand/form reached both objects/targets with 50% probability. The percentage of the total movement shown in the two tasks was matched (AP: mean 45% of total movement, range 30-70%; NP: mean 45% of total movement,

range 30-70%; $p > 0.99$). With this procedure we created two difficulty-matched tasks with an optimal accuracy level for avoiding floor and ceiling effects. Importantly, half of stimuli in the AP task (N=60) showed only 30-40% of the total movement, with the hand remaining far from the target objects (not crossing the midline of the screen) and displaying only the initial phase of hand pre-shaping (well before the maximal grip aperture). In a control analysis, we used this subsample of AP stimuli to assure that tDCS acted on the ability to predict the outcomes of observed actions based on the processing of very early kinematic cues.

Transcranial direct current stimulation (tDCS) and neuronavigation

tDCS was delivered using a battery-driven Eldith constant direct current stimulator (neuroConn GmbH, Ilmenau, Germany). A pair of surface sponge electrodes was soaked in a standard saline solution (NaCl 0.9%) and held in place with elastic rubber bands. In Experiments 1-3 the cathodal electrode (25 cm^2) was applied over the target region (left IFC, left STS, or left IFC). In Experiment 4 the anodal electrode (25 cm^2) was applied over the left IFC. In all four experiments, the reference electrode (35 cm^2) was applied over the contralateral deltoid muscle (Priori et al., 2008; Bolognini et al., 2010). It is thought that extracephalic electrode montages allow more focal stimulation, and avoid the confounding effect of the reference electrode (Cogiamanian et al., 2007; Brunoni et al., 2011).

tDCS has been shown to elicit polarity-dependent excitability changes in the cortical area under the stimulation electrodes. Studies of the motor cortex showed that anodal tDCS increases motor excitability while cathodal tDCS decreases it (Nitsche and Paulus 2001; Nitsche 2003; Antal et al. 2004; Nitsche et al. 2008 see Horvath et al. 2015 for a recent quantitative meta-analysis), although many factors may contribute to the efficacy of the stimulation, including intensity, electrode size and disposition and duration of stimulation (Cogiamanian et al., 2007; Nitsche et al., 2008;

Moliadze et al., 2010; Brunoni et al., 2011). Importantly, similar polarity-dependent effects can be reliably observed at the behavioral level, at least when testing perceptual/attentional cognitive functions (Jacobson et al., 2012), with anodal and cathodal tDCS being involved in the enhancement and inhibition of such functions, respectively.

Active tDCS was delivered with a constant current of 2 mA (current density ~0.08 mA/cm^2), complying with current safety guidelines (Nitsche, 2003; Poreisz et al., 2007). Stimulation lasted for 15 min, plus 20 s of ramp-up and ramp-down at the beginning and end of stimulation. Impedance was constantly monitored and kept below 8 kOhm. This protocol is known to affect cortical excitability for more than 30 minutes after the end of stimulation (Nitsche and Paulus, 2001; Nitsche et al., 2008), thus covering the entire duration of the testing phase. For sham tDCS the electrodes were placed on the same locations, but the current was turned on for only 30 seconds at the beginning of the session, and then turned off in a ramp-shaped fashion (fade in/out: 20 sec), so that participants experienced the sensations initially associated with the onset of stimulation (mild local tingling), without inducing any effective modulation of cortical excitability. This procedure ensures successful blinding of participants (Gandiga et al., 2006; Ambrus et al., 2012). Although, the intensity used in our study (2 mA) may be less effective in ensuring blinding (O'Connell et al., 2012); but see (Loo et al., 2010, 2012), we used relatively small cephalic electrodes to reduce scalp sensations and make active and sham stimulation feel comparable (Turi et al., 2014; Fertonani et al., 2015; Tang et al., 2016).

Electrode positions were identified on each participant's scalp with the SoftTaxic Navigator system (Electro Medical Systems, Bologna, Italy), as in previous research (Avenanti et al., 2007, 2012; Bertini et al., 2010; Serino et al., 2011; Tidoni et al., 2013; Jacquet and Avenanti, 2015; Sacheli et al., 2015a). Skull landmarks (nasion, inion and two preauricular points) and ~80 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra digitizer (Northern Digital Inc, Ontario, Canada). An individual estimated magnetic resonance image (MRI) was obtained for each participant through a 3D warping procedure fitting a high-resolution MRI template

with the participant's scalp model and craniometric points. This procedure has been proven to ensure a global localization accuracy of roughly 5 mm, a level of precision closer to that obtained using individual MRIs than can be achieved using other localization methods (Carducci and Brusco, 2012). Talairach coordinates of target regions and corresponding scalp projections were automatically estimated by the SofTaxic Navigator from the MRI-constructed stereotaxic template. Figure 2 shows the stimulated sites. In Experiments 1, 3 and 4, the IFC was targeted over the pars opercularis of the inferior frontal gyrus at the border with the anterior-ventral aspect of the precentral gyrus i.e., the ventral premotor cortex (coordinates: x = ± 54, y = 10, z = 24, corresponding to Brodmann's area 6/44) (Mayka et al. 2006; Avenanti et al. 2007, 2012; Gazzola et al. 2007; van Overwalle and Baetens 2009; Caspers et al. 2010; Avenanti et al. 2013a). In Experiment 2, the STS was targeted in its posterior aspect (x = –52, y = –53, z = 9, corresponding to Brodmann's area 21; (van Overwalle and Baetens 2009; Caspers et al. 2010; Avenanti et al. 2013a). Talairach coordinates corresponding to the projections of the IFC and STS target sites on the brain surface were automatically estimated through the neuronavigation system. In Experiment 1, mean left IFC surface coordinates ± S.D. were: x = -53.6 ± 1.5; y = 10.0 ± 0.6; z = 24.0 ± 0.5. In Experiment 2, left STS coordinates were: x = -55.1 ± 1.9; y = -53.6 ± 0.8; z = 9.3 ± 1.0. In Experiment 3, right IFC coordinates were: x = 55.3 ± 1.7; y = 10 ± 0.6; z = 24.5 ± 0.8. In Experiment 4, left IFC coordinates were: x = -54.0 ± 1.5; y = 10.1 ± 0.7; z = 24.2 ± 0.4 (Figure 2A).

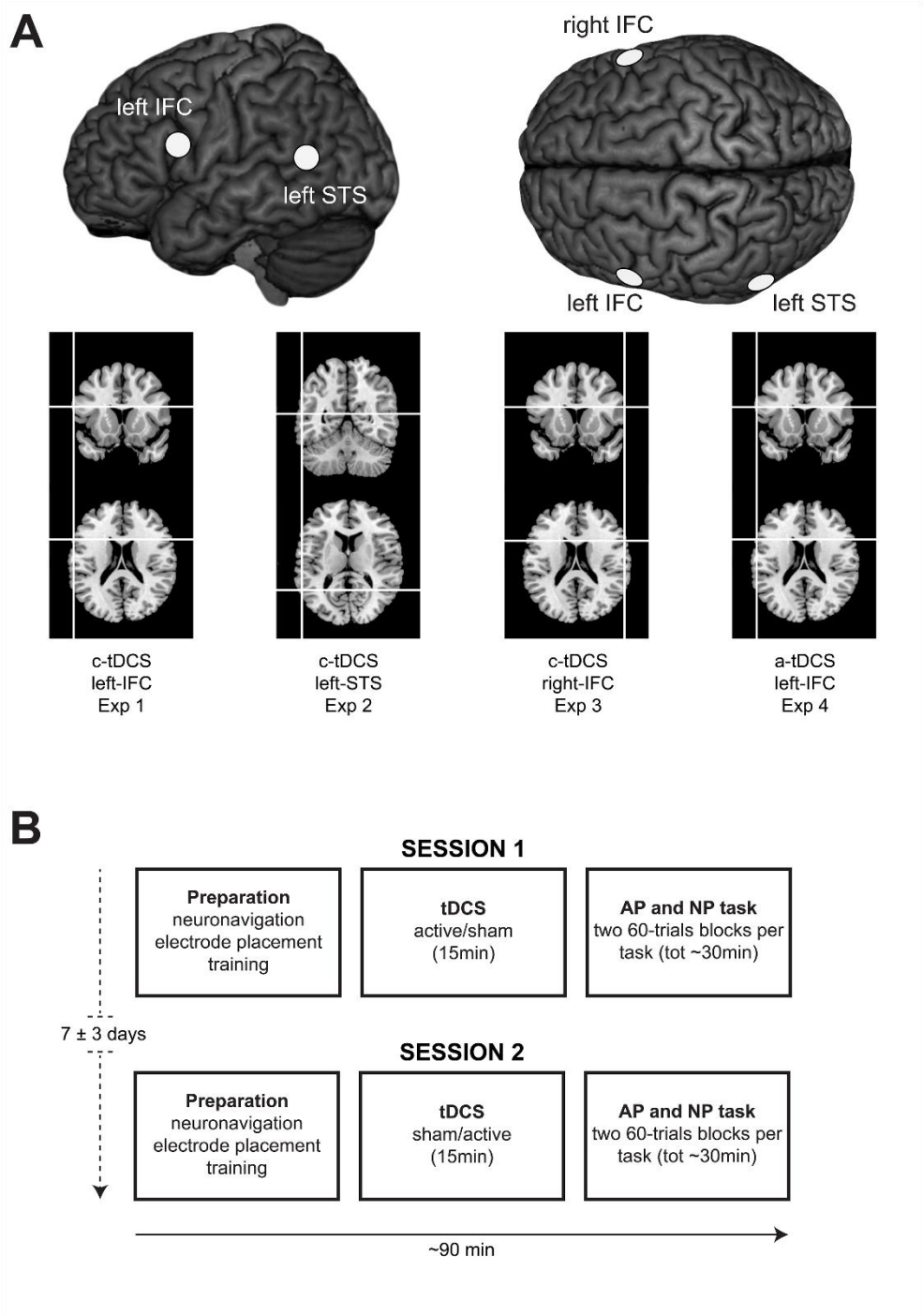

Figure 2. Brain stimulation sites and experimental design. **(A)** Brain areas targeted in Experiments 1-4. Stimulation sites are reconstructed on a standard template using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). **(B)** Schematic representation of the experimental design. Participants took part in two sessions in which performance in the two tasks was tested immediately after 15 minutes of sham/active tDCS over a target brain region.

Procedure

The experiments were programmed using Matlab software to control the video-clip sequence and acquire behavioral responses. Participants sat in front of a computer screen located ~50 cm from their head in a dimly illuminated room. After neuronavigation and tDCS electrode setup, participants received task instructions and performed two training blocks (one for each task, 30 trials each) in order to familiarize them with the tasks. They were asked to respond as quickly and accurately as possible by pressing one of two response buttons with the hand ipsilateral to the tDCS scalp site (the left hand in Experiments 1, 2 and 3, and the right hand in Experiment 4). Training trials were not included in the experimental blocks, but were similarly difficult (~75% accuracy). If a participant's accuracy was < 60% in one of the tasks, the corresponding instructions and training block were repeated.

After training, participants received a 15-min session of active or sham-tDCS over the target site (left IFC, left STS or left IFC) and then performed four blocks of 60 trials (2 blocks for each task). Block order and the order of trials within each block were randomized. A one-minute break was allowed between blocks. All participants completed the four blocks within 35 minutes after tDCS (mean ± S.D. across experiments: 30 min ± 2), well within the temporal window of cortical modulation induced by active tDCS (Figure 2B). Indeed, tDCS with a current density and duration comparable to those used in our study can alter neural activity for approximately 1 hour (Nitsche and Paulus, 2001; Nitsche, 2003; Antal et al., 2004; Ardolino et al., 2005; Kuo et al., 2013; Horvath et al., 2015).

To test whether sham or active tDCS induced different scalp sensations, at the end of each session we asked participants to evaluate the discomfort caused by the stimulation using a 5-point Likert scale with 1 indicating "not unpleasant at all" and 5 indicating "extremely unpleasant".

Data Analysis

Behavioral data were processed offline. For each task (AP, NP), tDCS condition (sham, active) and Experiment (1-4), we calculated measures of sensitivity (*d'*) and response bias (*β)* in accordance with signal detection theory (Macmillan and Creelman, 1991; Stanislaw and Todorov, 1999). For both tasks, the target objects/forms located in the left/bottom and right/upper parts of the scene were considered targets 1 and 2, respectively. Two types of responses were scored as correct: a "target 1" response to target 1 (hit), and a "target 2" response to target 2 (correct rejection). Two responses were scored as incorrect: a "target 2" response to target 1 (miss), and "target 1" response to target 2 (false alarm). A three-way mixed analysis of variance (ANOVA) was performed on *d'* and *β* with Task (2 levels: AP and NP) and Stimulation (2 levels: sham tDCS and active tDCS) as within-subjects factors and Experiment (4 levels: Exp 1, Exp 2, Exp 3 and Exp 4) as the between-subjects factor.

Response times (RTs) were extracted for each trial associated with a correct answer. RTs longer than 2 s were removed from the analysis (less than 1%). For each task and tDCS condition, we computed the median RTs as this measure is less sensitive to outlier values than the mean. RTs were analyzed with a Task x Stimulation x Experiment ANOVA.

The tDCS discomfort ratings collected at the end of each session were analyzed with a two-way mixed ANOVA with Stimulation as a within-subjects factor and Experiment as a between-subjects factor.

In all the ANOVAs, post-hoc comparisons were performed using Newman-Keuls tests to correct for multiple comparisons. *Partial* η^2 was computed as a measure of effect size for the main effects and interactions, whereas repeated measures *Cohen's d* was computed for post-hoc comparisons. The normal distribution assumption was checked for each dependent variable using Shapiro-Wilk tests. In all the ANOVAs, we checked for participants with outlier values deviating >3

S.D. from the group mean. When outliers were detected, we assured that the results of the ANOVA were not due to such participants by replicating the ANOVA effects after removal of these participants. When violations of normality were detected, we also computed Wilcoxon matched pair tests to confirm critical comparisons using non-parametric analyses. Statistical analyses were carried out using STATISTICA 8.0 software (StatSoft, Inc.).

RESULTS

Task sensitivity (*d'*)

The Experiment x Task x Stimulation ANOVA conducted on *d'* values revealed a significant three-way interaction ($F_{3,48} = 3.83$ $p = .02$, *Partial* $\eta^2 = .19$) indicating that sensitivity in the two tasks was differentially modulated by active tDCS across the four experiments. No other effects were detected in the analysis (all $F < 2.11$, all $p > .11$). To identify the source of the triple interaction, two separate Experiment x Stimulation ANOVAs were performed, one for each task.

The Experiment x Stimulation ANOVA conducted on *d'* values from the AP task (Figure 3) showed a significant two-way interaction ($F_{3,48} = 7.95$, $p < .001$, *Partial* $\eta^2 = .33$) but no main effects (all $F < .93$, all $p > .34$). Post-hoc analysis showed that, relative to sham c-tDCS (mean *d'* ± S.D.: 1.64 ± .42), active c-tDCS of the left IFC in Experiment 1 robustly reduced AP sensitivity (1.31 ± .59; $p = .04$, *Cohen's d* = .85). No similar effects were found in Experiments 2 and 3, suggesting that suppression of the left STS and the right IFC did not change AP sensitivity (all $p > .42$). In contrast, relative to sham a-tDCS (1.47 ± .72), active a-tDCS of the left IFC in Experiment 4 strongly increased AP sensitivity (1.85 ± .69; $p = .006$, *Cohen's d* = 1.07).

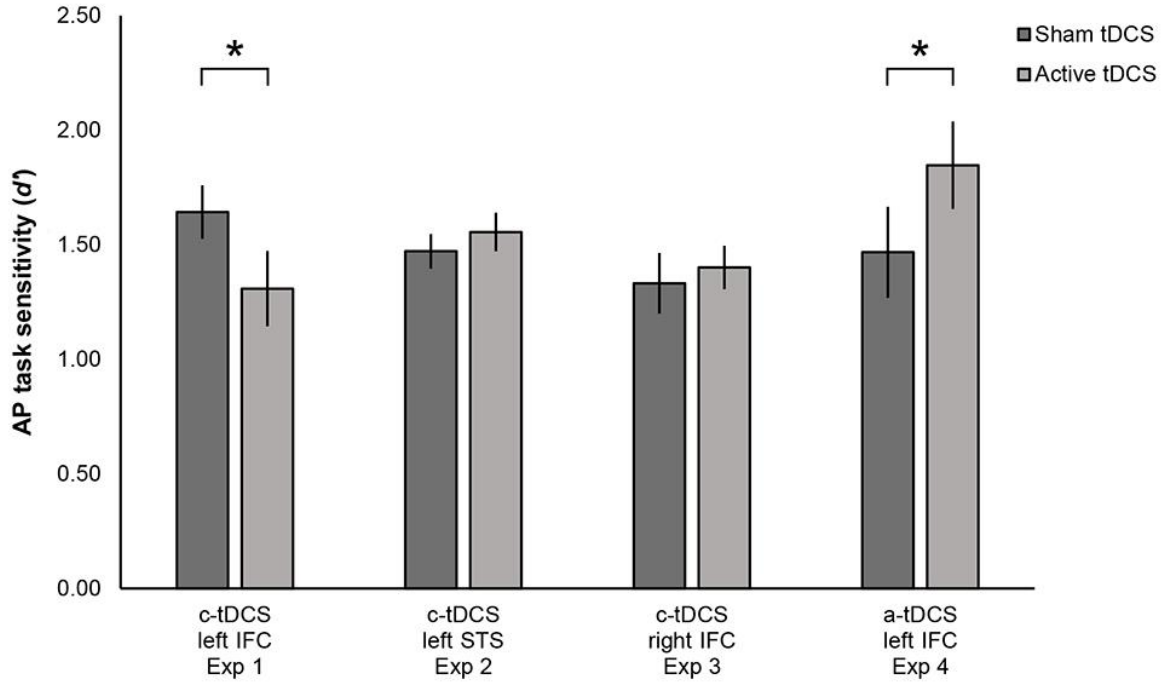

Figure 3. AP task sensitivity in Experiments 1-4. Dark grey and light grey columns indicate *d'* values in the sham and active tDCS conditions, respectively. Suppression (Exp 1) and excitation (Exp 4) of the left IFC disrupted and boosted task sensitivity, respectively. No change in AP task sensitivity was found after suppression of the left STS (Exp 2) or the left IFC (Exp 3). Asterisks indicate significant post-hoc comparisons ($p < .05$). Error bars denote s.e.m.

We directly compared the influence of different types of tDCS on AP task sensitivity by computing an index of change in *d'* (active tDCS – sham tDCS) in each of the four experiments (Figure 4A). Mean index values in Experiment 1 were negative (mean difference index ± S.D.: -.33 ± .39), indicating task interference after active c-tDCS over left IFC (see Figure 4B for individual index difference values). They were also lower than the difference indexes in Experiments 2, 3 and 4 (all difference indexes > .07 ± .44; all $p < .009$, all *Cohen's d* > .97). Mean index values in Experiment 4 were positive (.38 ± .36), indicating task enhancement after active a-tDCS over left IFC (see Figure 4C for individual values). They were also greater than the difference indexes in Experiments 1 and 2 (all difference indexes < .08 ± .30, all $p < .05$, all *Cohen's d* > .78). Indexes were comparable in

Experiments 3 and 4 (p = .92). Thus, the reduction (Experiment 1) and increase (Experiment 4) in *d'* values induced by active tDCS were large, as indicated by the effect sizes, and corresponded to changes of -20% and +26% relative to sham tDCS.

In sum, the analysis of the differential indexes further demonstrates the selectivity and robustness of the bidirectional influence of left IFC tDCS on the ability to predict others' actions.

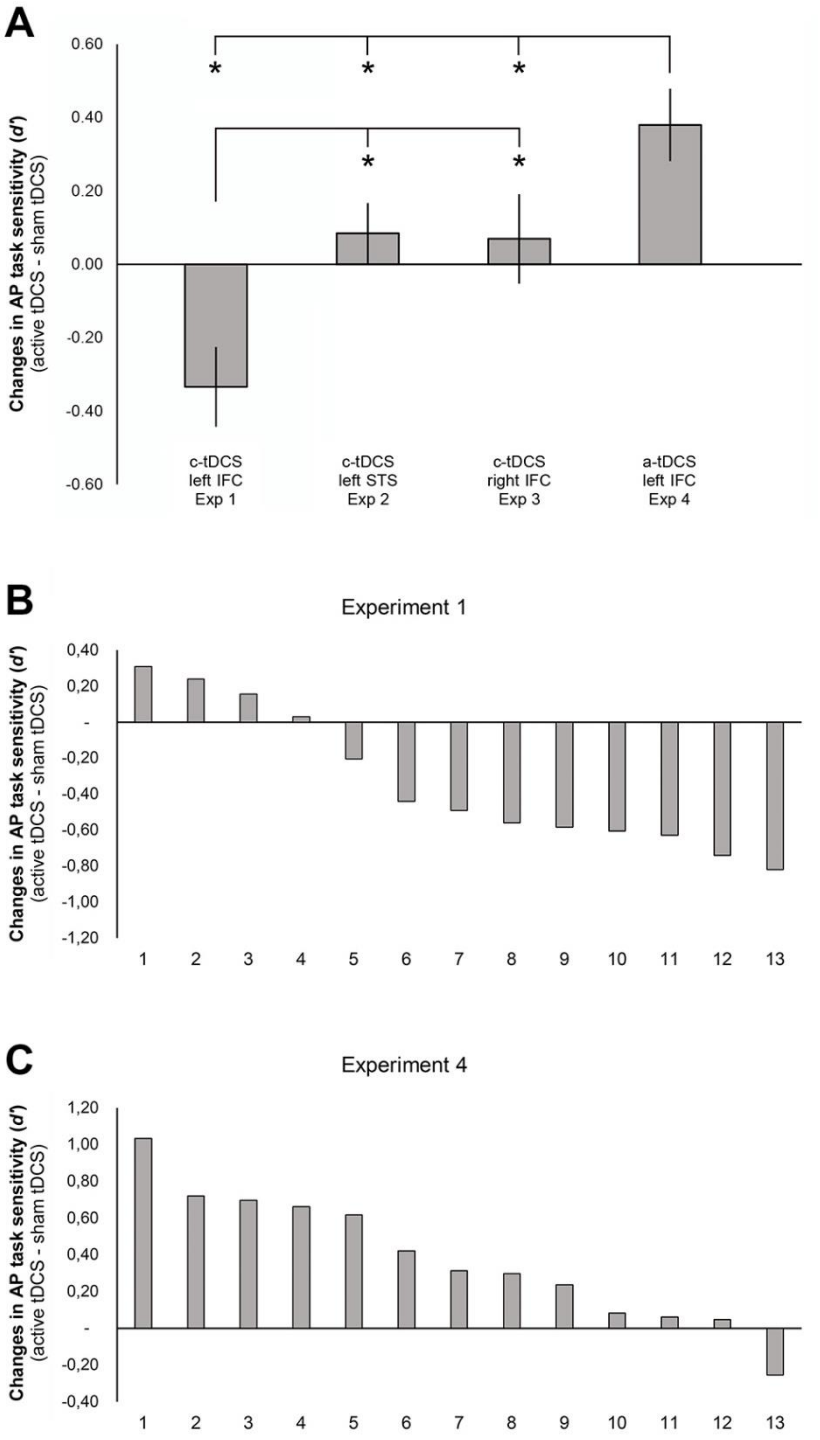

Figure 4. Changes in AP task sensitivity (active – sham tDCS). **(A)** Mean changes in Experiments 1-4. When applied over the left IFC, active c-tDCS (Experiment 1) and a-tDCS (Experiment 4) brought about a reduction and an increase in AP task sensitivity, respectively. Asterisks indicate significant post-hoc comparisons ($p < .05$). Error bars denote s.e.m. **(B)** Changes in the AP task sensitivity of individual participants in Experiment 1. **(C)** Changes in the AP task sensitivity of individual participants in Experiment 4.

To ensure that the modulatory effects of tDCS found in Experiments 1 and 4 influenced the ability to predict the outcomes of observed actions based on the processing of early kinematic cues, we conducted an additional control analysis. For these two critical experiments, we computed a measure of AP task sensitivity (d') on a subsample of 60 AP videos (i.e., half of the total number of videos in the AP task) that showed only the initial 30-40% of the entire movement (i.e., displaying the initial phase of hand pre-shaping, well before the maximal grip aperture). Planned t-tests showed that relative to sham c-tDCS (1.60 ± .46), active c-tDCS of the left IFC in Experiment 1 reduced AP sensitivity (1.20 ± .60; p = .01, Cohen's d = .85), whereas, relative to sham a-tDCS (1.46 ± .72), active a-tDCS of the left IFC in Experiment 4 increased AP sensitivity (1.92 ± .65; p = .004, Cohen's d = .98). These values corresponded to a d' change of -25% in Experiment 1 and +31% in Experiment 4, suggesting reliable tDCS modulation of performance with this subsample of AP stimuli.

The Experiment x Stimulation ANOVA conducted on the *d'* index for the NP task (Figure 5) revealed no main effects or interactions (all $F < 0.64$, all $p > .59$), thus indicating that active tDCS specifically affected AP but not NP task sensitivity.

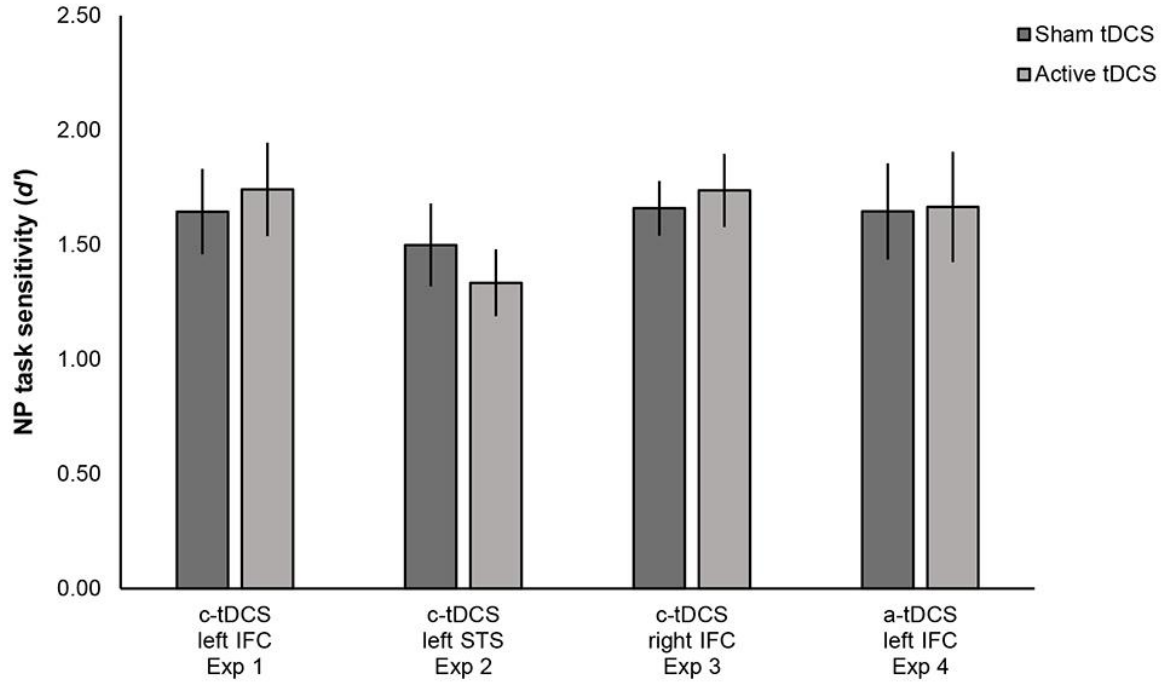

Figure 5. NP task Sensitivity in Experiments 1-4. Dark grey and light grey columns indicate *d'* values in the sham and active tDCS conditions, respectively. No effects on NP task sensitivity were found. Error bars denote s.e.m.

Note that the tDCS effects on AP task sensitivity and the lack thereof on the NP task sensitivity were not due to outlier participants, as no participant had *d'* values (or a *d'* difference index) deviating 3 S.D. or more from the group mean. We also checked whether our findings were due to tDCS acting mostly on some outlier trials by performing an item analysis. Thus, for each trial, we computed a difference in accuracy (% of correct answer) between the sham and active tDCS session across participants. This was done for each task and experiment separately. In both tasks, no trial deviated 3 S.D. or more from the mean group difference. In sum, although there was variability in the magnitude of c-tDCS (Figure 4B) and a-tDCS effects (Figure 4C) across participants, the results at the group level were strong, as shown by large effect sizes, and not driven by outlier participants or outlier trials.

Response bias (β)

The Experiment x Task x Stimulation ANOVA conducted on the β index showed no significant main effects or interactions (all $F < 2.35$, all $p > .08$; Table 1). However, there were violations of normality in the distribution of β values (Shapiro-Wilk tests: $p < .05$). These were mostly due to one participant with β values deviating 3.15 S.D. from the group mean in one condition (active a-tDCS in the NP task) of Experiment 4. Removing this participant partially normalized the distribution of β values, but kept the results of the ANOVA non significant (all $F < 3.11$, all $p > .08$). Additionally, we used Wilcoxon matched pair tests on the entire sample to confirm that, relative to sham tDCS, active tDCS did not change response bias in the AP task (all $p > .15$) or the NP task (all $p > .31$) across experiments. In sum, manipulations of AON cortical excitability through active tDCS only affected task sensitivity, and did not change response bias.

Table 1. Mean ± S.D. Response bias (β) index.

	Exp 1 **c-tDCS left IFC**		**Exp 2** **c-tDCS left STS**		**Exp 3** **c-tDCS right IFC**		**Exp 4** **a-tDCS left IFC**	
	sham	**active**	**sham**	**active**	**sham**	**active**	**sham**	**active**
AP task	.97 ± .51	.94 ± .54	1.55 ± .70	1.30 ± .54	1.06 ± .48	1.04 ± .43	.87 ± .28	.75 ± .45
NP task	.94 ± .48	.99 ± .65	.97 ± .91	.75 ± .45	1.11 ± .84	.90 ± .60	.90 ± .52	1.39 ± 1.91

Response times (RTs)

The Experiment x Task x Stimulation ANOVA conducted on RTs showed a significant Experiment x Stimulation interaction ($F_{3,48} = 2.99$ $p = .04$, *Partial* $\eta^2 = .16$), but no other main effects or interactions (all $F < 1.72$, all $p > .20$; see Table 2). The two-way interaction was accounted for by

faster RTs in the active tDCS session (RTs ± S.D.: 376 ms ± 130) than in the sham tDCS session of Experiment 2 (470 ms ± 178; p = .014; *Cohen's d* = .71), indicating that c-tDCS over the left STS made participants respond faster in both the AP and NP tasks. No significant effects of active vs. sham tDCS were found in the other experiments (all p > .24). It should be noted that the RT data in Experiment 3 (right IFC) slightly violated the normality assumption (Shapiro-Wilk test p < .05), possibly due to one participant with RTs deviating 3.03 S.D. from the group mean in one condition. Removing this participant corrected the violation of normality in that experiment (Shapiro-Wilk test, all p > .21), but did not change the Experiment x Stimulation interaction ($F_{3,47}$ = 2.93 p = .04, *Partial* η^2 = .16). In addition, the critical post-hoc comparison between sham and active tDCS in Experiment 2 remained significant (p = .016), whereas the same comparisons were not significant in the other experiments (all p > .25), a pattern of results that was further replicated using Wilcoxon matched pair tests on the entire sample of participants (p = .05 and all p > .27, respectively).

Table 2. Mean ± S.D. RTs

	Exp 1 **c-tDCS left IFC**		**Exp 2** **c-tDCS left STS**		**Exp 3** **c-tDCS right IFC**		**Exp 4** **a-tDCS left IFC**	
	sham	**active**	**sham**	**active**	**sham**	**active**	**sham**	**active**
AP task	462 ± 142	508 ± 222	470 ± 178	376 ± 130	433 ± 115	431 ± 139	452 ± 112	432 ± 103
NP task	440 ± 138	475 ± 151	460 ± 165	378 ± 174	445 ± 117	427 ± 126	457 ± 128	433 ± 130

We also calculated an index of the RT difference in each experiment by subtracting the RT in the sham tDCS session from the RT in the active tDCS session. The RT difference found in Experiment 2 (mean RTs ± S.D.: -88 ms ± 124) was more negative than the RT difference found in Experiment 1 (+40 ms ± 120; p =.008; *Cohen's d* = 1.05) and non-significantly more negative than the RT differences in Experiments 3 (-10 ms ± 80; p =.09; *Cohen's d* = .77) and 4 (-22 ms ± 109; p = .13; *Cohen's d* = .56).

Discomfort ratings

At the end of each session, we asked participants to rate the discomfort they felt during tDCS using a 5-point Likert scale. Discomfort ratings were very low, in keeping with the small size of the electrodes (Turi et al., 2014; Fertonani et al., 2015; Tang et al., 2016). Ratings were comparable across tDCS sessions and experiments, as suggested by the lack of any main effects or interactions in the Experiment x Stimulation ANOVA (all $F < 2.14$, all $p > 0.11$; Table 3).

Exp 1 **c-tDCS left IFC**		**Exp 2** **c-tDCS left STS**		**Exp 3** **c-tDCS right IFC**		**Exp 4** **a-tDCS left IFC**	
sham	**active**	**sham**	**active**	**sham**	**active**	**sham**	**active**
1.54 ± .66	1.62 ± .62	1.15 ± .38	1.77 ± .83	1.54 ± .66	1.46 ± .52	1.62 ± .65	1.77 ± .73

Table 3. Mean ± S.D. ratings of subjective tDCS unpleasantness.

Discussion

In four different experiments, we used tDCS to induce polarity-dependent excitability changes (inhibitory for c-tDCS and excitatory for a-tDCS) (Nitsche and Paulus, 2001; Antal et al., 2004; Ardolino et al., 2005; Nitsche et al., 2008; Kuo et al., 2013; Horvath et al., 2015) over two main nodes of the AON, namely, IFC and STS. We thus explored whether these regions play a causative role in action prediction, and whether any such role can be boosted or suppressed by exogenous manipulation of their functionality. In Experiment 1, we found that c-tDCS over the left IFC impaired AP task sensitivity (d'), compared to sham tDCS. No change in NP sensitivity was found. These results

indicate that suppression of the left IFC selectively disrupted the ability to choose between possible goals/outcomes of a reaching-to-grasp action (i.e., which object was going to be grasped) that could be predicted based on kinematic cues (reaching direction and finger pre-shaping) shown in the initial phases of the observed action. No similar impairments in AP task sensitivity were observed in Experiments 2 and 3, which targeted the left STS and right IFC, respectively. Remarkably, in Experiment 4, an opposite behavioral effect – i.e., enhanced sensitivity in the AP task – was obtained by a-tDCS excitation of the left IFC. No changes in the β index were found, indicating that tDCS-induced suppression and excitation of the IFC resulted in selective disruption and enhancement of AP task sensitivity, respectively. No significant changes in RTs were found in Experiments 1 or 4, thus ruling out that the observed effects were due to a speed-accuracy trade off. Finally, we found that disruption and enhancement of AP task sensitivity in Experiments 1 and 4 was detected even when testing performance with only those AP videos showing very early action kinematic cues (30-40% of the total movement).

From this complex set of results we can draw five main conclusions: i) the IFC is a crucial node of the AON involved in predicting the outcomes of observed hand actions based on early kinematic cues; ii) down- and up-regulation of left IFC excitability can hinder and boost action prediction abilities, respectively; iii) the critical involvement of the IFC in making predictions is specific for human actions, and does not extend to prediction of non-human movements; iv) prediction of right hand actions relies on the left, not the right, IFC; v) motor (left IFC) more than visual (left STS) regions appear to be critical for action prediction.

Functional relevance of motor vs. visual nodes of the AON for action prediction

We provide the first causal evidence that the IFC is involved not only in planning the execution of an upcoming action, but also in making predictions about the outcomes of observed actions. By optimally calibrating task difficulty through a series of behavioral pilot studies, we

demonstrate that down-regulation (Experiment 1) and up-regulation (Experiment 4) of cortical excitability in the left IFC reduce and boost the ability to predict others' actions, respectively. These novel findings provide strong support to theoretical models emphasizing that the IFC is a key node in the anticipatory neural network for the predictive coding of one's own and others actions (Prinz 1997; Blakemore and Decety 2001; Wolpert et al. 2003; Grush 2004; Wilson and Knoblich 2005; Kilner et al. 2007; Brown et al. 2011; Avenanti et al. 2013a; Urgesi et al. 2014) and provide the first direct demonstration of the essential role of the IFC in making explicit predictions about others' actions.

Our findings complement previous causal evidence showing that brain lesions and non-invasive stimulation of the IFC can affect the ability: i) to match/discriminate different actions/body postures (Urgesi et al., 2007; Pazzaglia et al., 2008a; Cattaneo et al., 2010; Tidoni et al., 2013; Michael et al., 2014; Jacquet and Avenanti, 2015; Paracampo et al., 2016); ii) to judge whether an observed action has been correctly performed (Pazzaglia et al., 2008b; Nelissen et al., 2010); iii) to estimate the weight of a box seen being lifted (Pobric and Hamilton, 2006); and iv) to perform/control the imitation of an observed action (Heiser et al., 2003; Catmur et al., 2009; Hogeveen et al., 2015). However, none of these previous studies tested whether the IFC (or the STS) is also critical for action prediction. Thus, our study goes beyond previous evidence by showing that the IFC is not only functionally relevant to recognition or imitation of others' actions, but also plays an essential causal role in action prediction.

Together with the recent study of Hogeveen et al. (2015) that addressed the neural bases of imitation control, our study is the first to show that off-line tDCS can affect the functioning of the AON. Hogeveen and colleagues (2015) found that a-tDCS over the right IFC (i.e., with anodal and cathodal electrodes over the FC6 and Cz scalp positions of the 10-20 system, respectively) improved performance in an imitation inhibition task and increased spontaneous imitation in a social interaction task. In contrast, a-tDCS did not change performance in a non-imitative inhibition task, suggesting

that increasing excitability in the IFC selectively improves the control of imitation. Our study expands previous evidence by showing that: i) c-tDCS and a-tDCS over the IFC can exert opposite behavioral influences; ii) tDCS can modulate not only motor (control of imitation) but also visual (action prediction) functions of the AON; iii) stimulation of motor and visual nodes of the AON lead to a combination of anatomical and polarity specific effects, suggesting a division of labor within different AON regions during action prediction. It would be also worth considering that the use of relatively small active electrodes applied with an image-guided monocephalic montage might allow us to draw stronger neuroanatomical inferences about the causal role of the AON in behavior.

Although prior evidence suggested STS involvement in anticipatory action mechanisms (Perrett et al., 2009; Abreu et al., 2012; Makris and Urgesi, 2015), we found no change in AP sensitivity after c-tDCS over this region (see Experiment 2). This suggests that the role of STS in action prediction is less crucial than that of the IFC. On the one hand, our AP task required participants to predict the goal of an action, and the IFC, more so than STS, may be critical for goal processing (di Pellegrino et al. 1992; Gallese et al. 1996; Cattaneo et al. 2010; Rizzolatti et al. 2014; Jacquet and Avenanti, 2015). On the other hand, our findings may appear to contradict brain stimulation and neuropsychological evidence that both the IFC and the STS may be critical for action perception (Saygin 2007; Pazzaglia, Smania, et al. 2008; Kalénine et al. 2010; van Kemenade et al. 2012; Avenanti et al. 2013a; Tidoni et al. 2013; Urgesi et al. 2014; Jacquet and Avenanti 2015).

Our AP task clearly differs from previous action perception tasks, as it requires participants to extrapolate, from limited visual cues, the outcome of an observed action (i.e., its goal/the object to be grasped) that is blocked from view. According to predictive coding theories (Kilner et al., 2007; Friston et al., 2011), action perception requires constant feedforward and feedback interactions between visual (STS) and frontal (IFC) regions, with the latter being involved in generating predictions about observed actions, and the former being involved in comparing predicted actions with incoming sensory input, so as to adjust the initial prediction. However, such a continuous

comparison in the STS may not be fully instantiated in our AP task because video interruption limited sensory inflow. This distinctive feature of the AP task could explain why task sensitivity (i.e., the *d'* index) was more affected by exogenous manipulations of the IFC than the STS – at variance with previous studies that tested action perception in full vision and found comparable sensitivity of action perception to both STS and IFC manipulations (Saygin 2007; Pazzaglia, Smania, et al. 2008; Kalénine et al. 2010; van Kemenade et al. 2012; Avenanti et al. 2013a; Tidoni et al. 2013; Urgesi et al. 2014).

Interestingly, active c-tDCS in Experiment 2 reduced RTs relative to the sham c-tDCS condition. This hints at a beneficial effect of c-tDCS over the STS, in keeping with studies showing that decreasing cortical excitability in visual regions evokes compensatory mechanisms that can improve task performance (Antal et al., 2004; Pirulli et al., 2014). The RT reduction was observed in both tasks, indicating nonspecific improvements. It is likely that this RT effect was not due to a local tDCS effect on the STS, a region that typically shows selectivity for biological movements (Press, 2011; Lingnau and Downing, 2015), but involved a spreading of the tDCS effect to nearby interconnected middle temporal regions (e.g., hMT+/V5) that represent dynamic information independently from the biological or non-biological nature of the stimulus (Antal et al., 2004; Lingnau and Downing, 2015). Indeed, the location of the reference electrode may have induced a spread of cathodal current in a ventral direction from the STS to hMT+, and this region may have contributed to the observed effects. The nonspecific RT changes found in Experiment 2 stand in contrast with the task-specific accuracy changes found in Experiments 1 and 4, further suggesting distinct roles of visual and motor AON nodes in action prediction (see also Avenanti et al. 2013a). Taken together, previous studies and our present data allow us to draw two preliminary conclusions. First, during classical action perception tasks where the entire action is visible, both the STS and the IFC are functionally relevant to task performance (Avenanti et al. 2013a; Rizzolatti et al. 2014; Urgesi et al. 2014). In contrast, the IFC, but not the STS, plays an essential role in making accurate predictions about an action's outcome when, as in our AP task, limited information is provided.

Second, brain stimulation over the STS may facilitate prediction of both human and non-human movements because of nonspecific effects, possibly involving visual motion-sensitive regions.

Human action selectivity in the IFC

The modulatory effects found in Experiments 1 and 4 were specific for the prediction of human actions, as c-tDCS and a-tDCS over the left IFC did not alter performance in the NP task, which was designed as a difficulty-matched control to assess prediction of non-human motion. This selectivity is in line with the notion that the AON responds more to the observation of human movement than non-human movement (Press, 2011). This tuning refers both to body form and kinematic profile. For example, reduced activation in the AON was found when participants saw humans moving with a non-human kinematics (Dayan et al., 2007; Casile et al., 2010). Moreover, interference with the IFC impairs perception (Candidi et al., 2008) and motor resonance with possible, but not biomechanically impossible, human body movements (Avenanti et al., 2007). Relevant to the present study, seeing human actions activates the anterior node of the AON more than seeing non-human movements – including movements of geometrical stimuli (Kessler et al., 2006; Engel et al., 2008), inanimate objects (Costantini et al., 2005; Oberman et al., 2005), humanoid robots (Tai et al., 2004; Chaminade et al., 2010) and virtual hands (Perani et al., 2001), even when all movements are matched for kinematic profile. While all the above studies indicate greater IFC sensitivity for human actions than for non-human movements, they cannot distinguish whether the IFC is only necessary for predicting human actions. Indeed, the same sector of the IFC that is involved in action perception is also recruited during predictions of abstract event sequences (Schubotz and von Cramon, 2004). These studies suggest that the predictive properties of the IFC are not limited to human actions, but extend to event prediction in general, and thus reflect domain-general processes (Schubotz, 2007; Press and Cook, 2015).

Our study provides novel insight into this issue by showing that altering cortical excitability in the left IFC affects the ability to predict the outcomes of human actions, but not the outcomes of non-human movements. Importantly, during the NP task participants were required to predict movements of an articulated geometrical form with a spatial trajectory resembling that of the reaching hand in the AP task. Moreover, the form changed its geometrical configuration during the approaching phase in order to fit one of the two target objects, a process analogous to the finger pre-shaping in the AP clips. Yet, only the hand appeared to be and moved as a biological entity. Although it can be safely assumed that moving hands in the AP task were more familiar than geometrical forms in the NP task (Press and Cook, 2015), it is worth noting that the two tasks were matched in difficulty based on a series of pilot studies with a large sample of participants. Thus, the fact that tDCS failed to induce changes in NP task sensitivity cannot be due to ceiling or floor effects (see (Pobric and Hamilton, 2006; Tidoni et al., 2013). Our data provide causal evidence that the frontal node of the AON is tuned to human actions, and suggest that motor activations during non-human event prediction may reflect an outflow of neural activity into the motor system that is not essential for making an accurate prediction.

The AP task required participants to predict the goal of the action (i.e., which object would be grasped) on the basis of kinematic cues (reaching direction, finger pre-shaping) observed in the initial phase. Thus, our study does not clarify whether the IFC could rely on a prediction of the future trajectory of the movement (i.e., where the hand will end up) to identify a goal that is blocked from view. To shed light on this point, future studies could investigate whether IFC modulation affects the ability to predict the end-state of intransitive actions. Also, it remains unclear whether IFC modulation could affect processing of reaching direction, finger pre-shaping or both. Dorsal and ventral sectors of the premotor cortex play critical roles in motor control for reaching movements and grasping movements, respectively (Davare et al., 2006; Hoshi and Tanji, 2007). Thus, future studies could

orthogonally manipulate these two action components to test whether the left IFC and dorsal premotor cortices maintain similar divisions of labor during AP.

In principle, tDCS may have also affected visuo-spatial processing of targets i.e., processing of their location or their geometrical properties, which would suggest specific grips. However, target objects were shown in full view for the entire duration of every clip (i.e. 1500-3000 ms) and it is unlikely that tDCS of premotor regions would have affected perceptual processing of non-visually degraded material (Avenanti et al. 2013a; Uithol et al. 2015). Moreover, spatial processing of targets was also required in the NP task, because the two targets were placed in distinct spatial locations and suggested different end-state configurations of the moving form. This suggests that tDCS mainly modulated prediction of (human) action-related information rather than visual processing of targets.

A lateralization of action prediction in the IFC?

Another issue we addressed in our study deals with the differential roles of the left IFC and the right IFC in action prediction. We found that only left IFC manipulation (in Experiments 1 and 4) but not right IFC manipulation (in Experiment 3) affected task performance. These data may suggest a left hemisphere lateralization in action prediction. However, it should be noted that only right hand actions were shown in the AP task, and our sample was limited to right-handers. Although AON activity is bilaterally distributed (van Overwalle and Baetens, 2009; Grosbras et al., 2012), studies have shown a gradient of lateralization which depends on the laterality of the body part involved in the observed action, as well as the observers' hand preference. In particular, during observation of right hand actions, AON activation of right-handers tends to be stronger (Aziz-Zadeh et al., 2002; van Schie et al., 2004; Shmuelof and Zohary, 2005; Gazzola and Keysers, 2009; Cabinio et al., 2010; Caspers et al., 2010) and can be detected earlier (Ortigue et al., 2010) in the left, relative to the right, hemisphere. Such (partial) lateralization may account for the observed effects. Further

studies will test whether suppression of activity in the left or the right IFC alters the ability to predict left hand actions both in right- and left-handers.

Because our AP task was optimized to show early kinematic cues of grasping (e.g., the pre-shaping of the right index finger and thumb), the AP stimuli depicted the mesial aspect of the actors' right arm, and the forward reaching movement of the actor went from the right to the left side of the screen, resulting in leftward visual motion for the viewer. Studies have suggested an asymmetry in the motor control of leftward vs. rightward movements with fronto-parietal regions in the right hemisphere controlling leftward movements (Fujii et al., 1998; Mattingley et al., 1998; Neggers et al., 2007). Our results may appear in contrast with this asymmetry, as we found that stimulation of the left IFC but not the right IFC modulated performance in the AP task. However, the aforementioned asymmetry pertains to the direction of performed actions, whereas the leftward motion in our AP movies is only due to the viewer's perspective, while the actors actually moved their hand in a forward direction. However, future studies might use different actions and test additional movement directions to fully address the issue of IFC laterality in action prediction.

Although only the left IFC (but not the left STS or the right IFC) seems to be critical for our AP task, it is worth noting that tDCS can modulate the excitability of distant interconnected regions (Boros et al., 2008; Nitsche et al., 2008; Avenanti et al., 2012). Thus, it is entirely possible that other interconnected frontal (e.g., dorsal premotor cortex; see Stadler et al. 2012; Makris and Urgesi 2015) or parietal (e.g., inferior parietal or somatosensory; Caspers et al. 2010; Valchev et al. 2015, 2016) regions of the AON may have contributed to the observed effects. For example, Stadler and colleagues (2012) have implicated the dorsal premotor cortex in the ability to detect timing incongruities between predicted and observed actions.

Conclusions

Predictive coding theories posit that the brain is a machine evolved to reduce any discrepancy between what is expected and what actually happens (i.e., prediction error) when acting and interacting with others. In keeping with these theories, our current findings emphasize the active role of the frontal node of the AON in the predictive coding of others' actions. Our findings fit with recent evidence supporting predictive coding in frontal regions when processing action language (García and Ibáñez, 2016), action intentionality (Hesse et al., 2016) and others' decisions (Ibañez et al., 2016; Melloni et al., 2016). Importantly, our experimental design allowed us to demonstrate that changes in the excitability of a specific region within the AON bring about impairment or enhancement of the ability to predict the outcomes of human actions, depending on the polarity of stimulation. This result indicates that tDCS represents an important tool not only for disrupting human performance, but also for improving it.

It should be considered that we found a performance enhancement in healthy neurotypical participants. Atypical or patient populations may present different baseline levels of cortical excitability, and additional factors might interact with the efficacy and direction of stimulation effects (Krause and Cohen Kadosh, 2014). Nevertheless, our study may have therapeutic value (e.g., in people with defective social prediction abilities, such as those with autism spectrum disorders or with impaired action perception due to a lesion affecting the AON), and implications for neuroenhancement (e.g., in healthy people who need to improve their prediction skills for professional reasons, like elite athletes of competitive and cooperative sports). Therefore, future studies should carefully assess clinical and applied potentialities of AON stimulation with tDCS.

APPENDIX B

Primary motor cortex crucial for action prediction: a tDCS study

INTRODUCTION

Seeing the actions of others activates an action observation network (AON), encompassing high-order visual regions encoding biological motion i.e. the superior temporal sulcus (STS) (Jellema and Perrett, 2003; Keysers and Perrett, 2004; Perrett et al., 2009) and parieto-frontal regions involved in controlling and sensing body actions (Gazzola and Keysers, 2009; Grafton, 2009; van Overwalle and Baetens, 2009; Caspers et al., 2010; Rizzolatti et al., 2014; Urgesi et al., 2014; Valchev et al., 2016). Premotor and parietal regions have been classically considered key nodes of the AON, as they implement a mirror mechanism coupling action perception with execution (di Pellegrino et al., 1992; Gallese et al., 1996; Fogassi et al., 2005; Rizzolatti and Sinigaglia, 2010; Bonini, 2016). Moreover, causal evidence indicates that transient stimulation or stable lesion of premotor or parietal region affect action recognition in humans (Pobric and Hamilton, 2006; Urgesi et al., 2007, 2014; Moro et al., 2008; Fazio et al., 2009; Cattaneo, 2010; Cattaneo et al., 2010; Avenanti and Urgesi, 2011; Avenanti et al., 2013b; Tidoni et al., 2013; Michael et al., 2014; Jacquet and Avenanti, 2015). Mounting evidence suggest that also the primary motor cortex (M1) might implement a mirror mechanism (Tkach et al., 2007; Dushanova and Donoghue, 2010; Vigneswaran et al., 2013). However, M1 is not classically considered as a key node of the AON (Keysers and Gazzola, 2009; Caspers et al., 2010) and whether M1 is causally essential for perceiving the actions of others remains unclear as previous studies using causal methods have provided mixed results (Avenanti et al., 2007; Cattaneo, 2010; Borgomaneri et al., 2015; Palmer et al., 2016; Valchev et al., 2016).

A key function of the AON is to process observed action in order to make predictions about their outcome. Theoretical models suggest that the motor system is designed to act as an anticipation device that humans use to generate internal forward models when perceiving the action of others (Prinz, 1997, 2006; Blakemore and Decety, 2001; Wolpert et al., 2003; Grush, 2004; Wilson and Knoblich, 2005; Kilner et al., 2007; Schütz-Bosbach and Prinz, 2007; Friston et al., 2011). There is substantial correlational evidence indicating that the motor nodes of the AON form an anticipatory representation of observed actions and M1 activity reflects such anticipatory encoding (Kilner et al., 2004; Sebanz et al., 2006; Urgesi et al., 2006, 2010; Abreu et al., 2012; Avenanti et al., 2013a, 2013b; Balser et al., 2014; Maranesi et al., 2014). Recently, brain stimulation studies have provided causal evidence that targeting frontal premotor regions of the AON affects action prediction abilities (Stadler et al., 2012; Makris and Urgesi, 2015; Avenanti et al., 2017).

Stadler and colleagues (Stadler et al., 2012) administered online rTMS over the dorsal premotor cortex (dPMc) during a task requiring to detect timing incongruities between predicted and observed everyday actions. On their side, Makris and Urgesi (Makris and Urgesi, 2015) administered online rTMS over the same brain region on soccer players during a task requiring to predict the outcome of a penalty kick. Both studies found that active dPMc stimulation reduced task performance relative to control rTMS conditions. More recently, Avenanti and colleagues (Avenanti et al., 2017) used transcranial Direct Current Stimulation (tDCS) to test the functional relevance of the AON to action prediction. Weak offline cathodal (c-tDCS) or anodal (a-tDCS) currents were used to alter AON functioning for several minutes after the end of the stimulation (Nitsche and Paulus, 2000; Nitsche, 2003; Antal et al., 2004; Kincses et al., 2004; Horvath et al., 2015). It was found that tDCS over the left inferior frontal cortex (IFC, in a position at the border between the ventral premotor cortex and the pars opercularis of the inferior frontal gyrus) affected performance in an Action Prediction (AP) task, requiring to observe the initial phases of a reaching-to-grasping action and to predict its outcome (i.e., which of two objects would be grasped) that was blocked from view. In

particular, c-tDCS and a-tDCS, which are expected to decrease and increase cortical excitability, respectively (Nitsche et al., 2008; Nitsche and Paulus, 2011), hindered and boosted AP task performance, respectively. No behavioral effects were observed when tDCS was administered over other visual or motor regions of the AON or when participants were tested in a difficulty-matched control task requiring to predict the outcome of a non-human movement (Non-human Prediction, NP). These findings provided strong evidence that classical frontal nodes of the AON – in particular the IFC – are critical for making predictions about human actions.

However, these previous studies have left unanswered the critical question of whether M1 is also causally essential for making predictions about others' actions and answering this question is the main goal of the present study. In four experiments (N=48), we targeted M1 using tDCS that, relative to rTMS, provides a better sham control and avoids any potential distracting effect of stimulation over frontal regions. As in Avenanti and colleagues (Avenanti et al., 2017), we administered offline tDCS using a monopolar montage (extracephalic reference) for 15 min before task performance. In that previous study, both anodal and cathodal currents affected AP task performance, however, stimulation occurred only at 2 mA intensities. Thus, it remained to be established whether the polarity-dependent influence on AP task performance is a unique attribute of IFC modulation and whether lower tDCS intensities (i.e., 1 mA) can be effective when targeting M1. This is particularly relevant as tDCS aftereffects can vary as a function of polarity and current intensity, but changes are not linear (Nitsche et al., 2008; Jefferson et al., 2009; Nitsche and Paulus, 2011; Bastani and Jaberzadeh, 2013; Batsikadze et al., 2013).

To address these issues, in four experiments we administered tDCS using different polarities (c-tDCS and a-tDCS) and intensities (1 mA and 2 mA) following a 2x2 between subject design. Also, in each experiment, we implemented a 2x2 within subject-design as we assessed participants' ability to make predictions about the future outcome of human actions or non-human motion (i.e., using the AP and NP tasks from Avenanti and colleagues, (Avenanti et al., 2017) and, in different

counterbalanced sessions, task performance was assessed after active tDCS or a control sham tDCS condition, which provided a baseline for behavioral performance.

MATERIALS AND METHODS

Subjects

Forty-eight healthy volunteers took part to the study. Twelve participants were assigned to Experiment 1 testing c-tDCS at 2mA intensity (6 females, mean age ± SD: 25.1 ± 3.34 years, range 21-30) and constituting the 'c-tDCS$_{2mA}$' group; 12 were assigned to Experiment 2 testing a-tDCS at 2mA intensity (7 females, mean age 25.6 ± 3.12 years, range 21-30) and constituting the 'a-tDCS$_{2mA}$' group; 12 were assigned to Experiment 3 testing c-tDCS at 1mA intensity (7 females, mean age 22.9 ± 1.7 years, range 20-25) and constituting the c-tDCS$_{1mA}$ group; and, 12 to Experiment 4 testing a-tDCS at 1mA intensity (6 females, mean age 22.3 ± 1.7 years, range 20-25) and constituting the a-tDCS$_{1mA}$ group. All subjects were right-handed according to a standard handedness inventory (Briggs and Nebes, 1975) and had normal or corrected-to-normal vision. None had a history of neurological, psychiatric illness, or any contraindication to brain stimulation (Rossi et al., 2009, 2011) or was on medication at the time of the experiments. Participants provided written informed consent, and the procedures were approved by the local ethics committee and were in accordance with the ethical standards of the 1964 Declaration of Helsinki. No discomfort or adverse effects during tDCS were reported or noticed.

Sample size was determined though a power analysis conducted using G*Power 3 (Faul et al., 2007), with power (1 – β) set at 0.80 and α = .05, two-tailed. We expected a large effect size based on our previous study showing strong modulation of action prediction task performance due to active a-tDCS and c-tDCS over the IFC (mean *Cohen's d* = 0.96) (Avenanti et al. 2017). The analysis

yielded required sample sizes of 11 participants. We thus decided to have 12 participants in each group.

Tasks and stimuli

In the Action Prediction (AP) task, participants observed 100 video-clips (640 x 480 pixels, 30 fps) depicting the initial phase of a reaching-grasping action. All stimuli subtended a 22.3° x 33.4° visual angle from the participant's viewing position. Videos started showing two objects (left side of the screen) placed in front of still right hand (right side of the screen; Figure 1). After a variable delay (1000-2200 ms), the hand started to reach and grasp one of the two objects. The final phases of the action were prevented by sight and subjects had to guess which object was going to be grasped by the hand. In different clips, only 30-70% of the entire movement duration was shown, followed by a random-dot mask (150 duration) interrupting the video. Then a response screen showing the two objects lasted until response. Participants provided their answer using two computer keys.

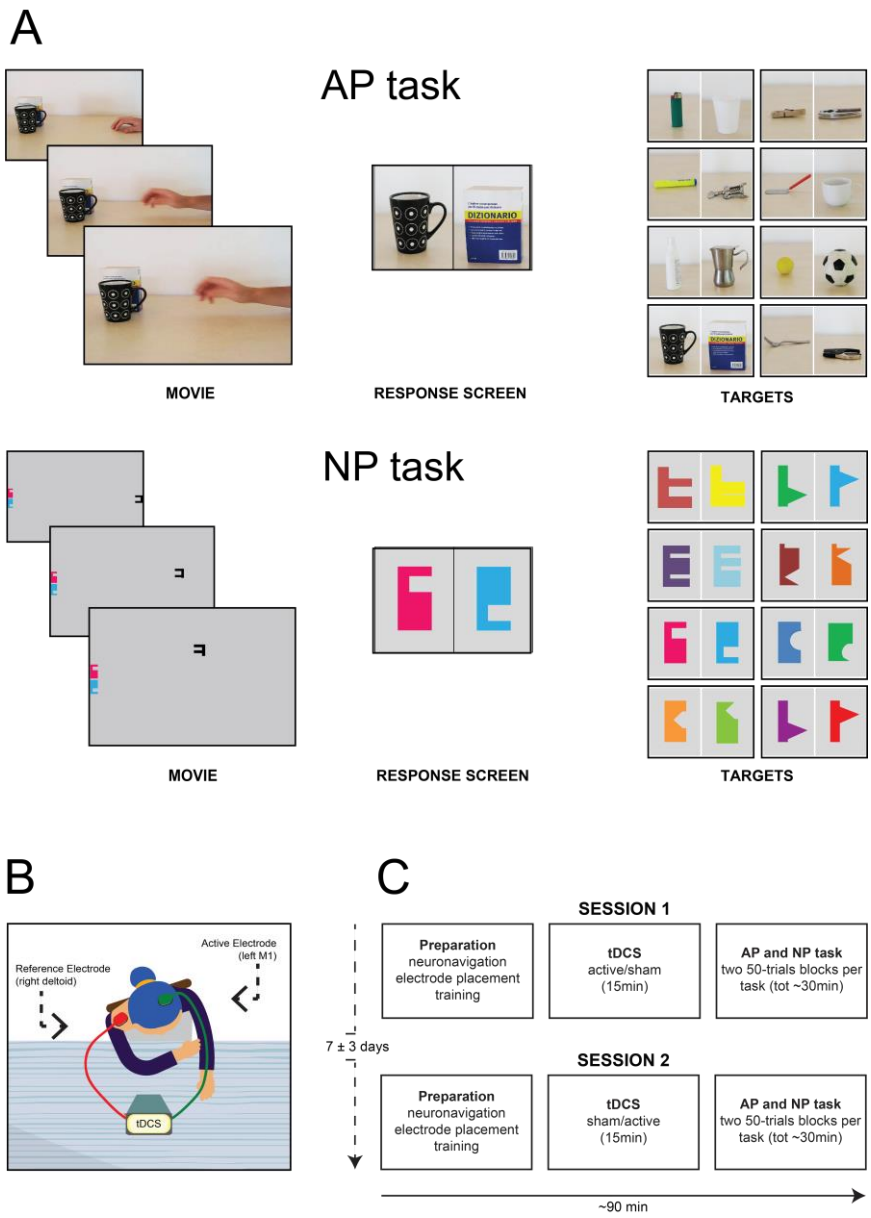

Figure 1 (A) Trial example and stimuli. Example of movie, response screen and targets in the Action Prediction (AP) task (above) and the Non-human Prediction (NP) task (below). On each trial, a short movie showed the initial movement of a hand (AP) or a geometrical form (NP) reaching and adapting to one of two targets. Participants were then presented with the two targets and had to guess which was selected by the hand/form. **(B)** tDCS montage showing the position of the active and reference electrode. **(C)** Schematic representation of the experimental design. Participants took part in 2 sessions in which performance in the 2 tasks was tested immediately after 15 min of sham/active tDCS over a target brain region.

Video-clips in the AP task included 8 non-professional actors (4 females) reaching and grasping 8 different couples of objects (i.e., lighter vs. glass; highlighter vs. corkscrew; deodorant spray vs. coffeepot; mug vs. book; clothespin vs. nutcracker; scoop vs. cup; little ball vs. soccer ball; fork vs. stapler). The two objects of each couple were located in two positions closed in space and presented different affordances, thus implying slightly different hand trajectories and grips (i.e. from power group performed with the whole hand to precision grips performed with the index finger and the thumb). In different trials, only a percentage of the entire movement was shown (from 30% to 70%). In none of the videos, the hand-object interaction was visible. Thus, AP task required to process contextual (objects' location and affordance) and kinematic cues (i.e. hand trajectory and finger pre-shaping) during the initial reaching component of the action.

In the NP control task, subjects observed 100 similarly interrupted video-clips showing a non-biological geometrical shape approaching one of two targets. Participants had to guess which target was going to be approached by the geometrical shape. The NP videos (640 X 480 pixel, 30 fps) were animations created with Adobe Flash Professional software to match temporal and spatial features of AP stimuli. Similarly, to the AP task, NP stimuli showed incomplete movement (30-70%) of a geometrical form which moved from the right side of the screen in order to reach and fit with one of two different geometrical targets placed on the opposite side. The path trajectory of the moving shapes was designed to roughly match hands' movement in the AP task. As in the AP task, the two targets were located in two different spatial positions and presented different geometrical properties. In analogy with the pre-shaping of the fingers (AP task), during the reaching phase, the configuration of the moving geometrical form changed over time in order to optimally fit with one of the two targets. Also for the NP video clips, we created eight different couples of geometrical targets and eight moving geometrical forms and random-dot image were used as masking.

The two tasks were adapted from Avenanti et al. (Avenanti et al., 2017) and were designed to have the same difficulty (~75% accuracy, i.e., they were doable but not trivial) based on a series of pilot studies. In both tasks, the hand/form reached both objects/targets with 50% probability. The percentage of the hand/shape total movement shown in the two tasks was matched (AP: mean 45% of total movement, range 30-70%; NP: mean 45% of total movement, range 30-70%; $p > 0.99$).

Transcranial direct current stimulation (tDCS) and Neuronavigation

tDCS was delivered using a battery-driven Eldith constant direct current stimulator (neuroConn GmbH, Ilmenau, Germany). A pair of surface sponge electrodes were soaked with a standard saline solution (NaCl 0.9%) and maintained in place by elastic rubber bands. To target M1, in all the Experiments the active electrode (5×5 cm^2) was placed over the C3 electrode of the 10-20 system and the reference electrode (5×7 cm^2) over the contralateral deltoid muscle (Priori et al., 2008; Bolognini et al., 2010). It is held that extra cephalic electrode montages allow more focal stimulation and avoid the confounding effect from the reference electrode (Cogiamanian et al., 2007; see Brunoni et al., 2011 for a review).

Active tDCS was delivered with a constant current of 2 mA (Experiment 1 and 2) or 1mA (Experiment 3 and 4) intensity (current density: ~0.08 mA/cm^2 for Experiment 1 and 2, ~0.04mA/cm^2 for Experiment 3 and 4) complying with current safety data (Poreisz et al., 2007; Nitsche et al., 2008). Stimulation lasted for 15 min not including 20 s of ramp up and ramp down at the beginning and end of stimulation. Impedance was constantly monitored and kept below 5 kOhm.

For the sham stimulation, the electrodes were placed on the same locations and the current was turned on for only 30 seconds at the beginning of the sham session and then was turned off in a ramp-shaped fashion (fade in/out: 20 sec), so that participants experienced the sensations initially associated with the onset of stimulation (mild local tingling), without inducing any effective

modulation of cortical excitability. This procedure ensures successful blinding of participants (Gandiga et al., 2006; Ambrus et al., 2012). Although, the 2 mA intensity used in Experiment 1 and 2 may be less effective in ensuring blinding (O'Connell et al., 2012; but see Loo et al., 2010, 2012), we used relatively small cephalic electrodes to reduce scalp sensations and make active and sham stimulation feel comparable (Turi et al., 2014; Fertonani et al., 2015; Tang et al., 2016).

After C3 localization over the scalp, Talairach coordinates corresponding to the target region were automatically estimated by the SofTaxic Navigator from an MRI-constructed stereotaxic template (Electro Medical Systems, Bologna, Italy) (Avenanti et al., 2007, 2012, 2013a; Bertini et al., 2010; Serino et al., 2011; Tidoni et al., 2013; Jacquet and Avenanti, 2015; Sacheli et al., 2015a). Skull landmarks (nasion, inion and two preauricular points) and ~100 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra digitizer (Northern Digital Inc, Ontario, Canada). An individual estimated magnetic resonance image (MRI) was obtained for each subject through a 3D warping procedure fitting a high-resolution MRI template with the participant's scalp model and craniometric points. Talairach coordinates corresponding to the projection of the targeted scalp sites on the brain surface were automatically estimated through the neuronavigation system (Fig. 1). An Experiment (4 levels: c-tDCS$_{2mA}$, a-tDCS$_{2mA}$, c-tDCS$_{1mA}$ and a-tDCS$_{1mA}$) x Coordinates (3 levels: x, y, z) ANOVA assured that coordinates were similar across Experiments (all $p > .34$).

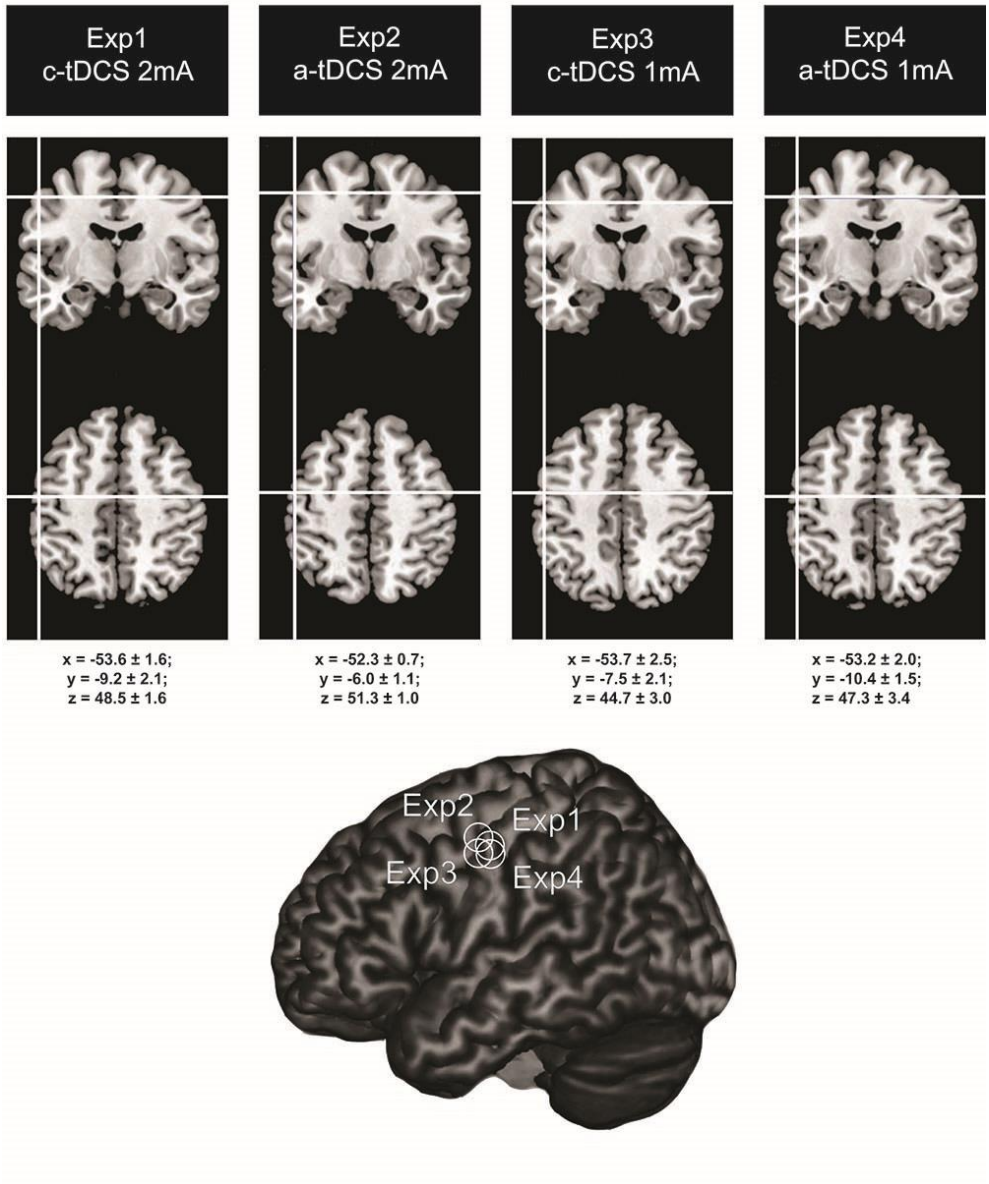

Figure 2. *M1 stimulation site for Exp1-4 reconstructed on a standard template using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Mean surface coordinates in Talairach space ± SEM were:* ***x = -53.2 ± 0.9; y = -8.3 ± 1.0; z = 48.0 ± 1.2.***

Procedure

Participants sat in front of a computer screen located ~50 cm from their head in a dimly illuminated room. After neuronavigation and tDCS electrodes montage, participants received instruction and performed two training blocks (one for each task, 30 trials each) in order to familiarize with the tasks. They were asked to respond as fast and accurately as possible by button press with the hand ipsilateral to the tDCS scalp site (left hand). If subject's accuracy was < 60% in one of the tasks, the corresponding instructions and training block were repeated.

After the training participants received a 15min session of active or sham-tDCS over the target site and then performed four blocks of 50 trials (2 blocks for each task). Block order and trials within each block were randomized. One minute break was allowed between different blocks. Subjects completed the four blocks within 30 minutes after tDCS, thus well within the temporal window of cortical modulation induced by active tDCS. Indeed, stimulations at current density and duration comparable to our study can alter neural activity for approximately 1 hour (Nitsche and Paulus, 2001; Nitsche, 2003; Antal et al., 2004; Ardolino et al., 2005; Kuo et al., 2013; Horvath et al., 2015).

To test whether sham or active tDCS induced different scalp sensations, after each session we asked participants to evaluate the discomfort caused by the stimulation using a 5-points Likert scale with 1 indicating "not unpleasant at all" and 5 "extremely unpleasant".

Data Analysis

Participants' accuracy (percentage of correct response) and median response times (RTs) were analyzed by means of a three-way mixed factors analysis of variance (ANOVA) with Task (2 levels: AP and NP) and Session (2 levels: sham tDCS and active tDCS) as within-subjects factors and Experiment (4 levels: c-tDCS$_{2mA}$, a-tDCS$_{2mA}$, c-tDCS$_{1mA}$ and a-tDCS$_{1mA}$) as the between-subjects factor. Subjective evaluation of discomfort caused by tDCS collected at the end of each session was analyzed with a two-way mixed ANOVA with Session (2 levels: sham tDCS and active tDCS) as

within-subjects factor and Experiment (4 levels: c-tDCS$_{2mA}$, a-tDCS$_{2mA}$, c-tDCS$_{1mA}$ and a-tDCS$_{1mA}$) as between-subjects factor. In all the ANOVAs, post hoc comparisons were performed using Tukey tests. Statistical analyses were carried out using STATISTICA 8.0 software (StatSoft, Inc.).

RESULTS

The Experiment x Task x Session ANOVA conducted on the accuracy index revealed a Task x Session interaction ($F_{1,44}$ = 6.88, p = .012, $P\eta^2$ = .14), and, most importantly, a three-way Experiment x Task x Session interaction ($F_{3,44}$ = 3.26 p = .03, $P\eta^2$ = .18; see Figure 3), indicating that tDCS differentially acted over accuracy in the two tasks and this was dependent on specific tDCS parameters being used in the different experiments. No other effects resulted significant in the ANOVA (all F < 1.21, all p > .31).

To identify the source of the three-way interaction, four separated Task x Session ANOVAs were performed, one for each Experiment. The Task x Session ANOVA conducted on accuracy in Experiment 1 (c-tDCS$_{2mA}$), showed a significant two-way interaction ($F_{1,11}$ = 24.19, p = .0005, $P\eta^2$ = .69), but no main effects (all F < 3.50, all p > .09). Post-hoc analysis (Tukey test) showed that accuracy in the AP task was strongly reduced in the active (mean ± SD = 76% ± 4) relative to the sham session (83% ± 2; p = .003, *Cohen's d* = 1.93), whereas no significant difference was found for the NP task between the active (80% ± 2) and sham sessions (83% ± 1; p = .17). Moreover, accuracy in the AP and NP tasks was comparable in the sham sessions (p = .51), but strongly differed in the active sessions (p = .001, *Cohen's d* = 1.12).

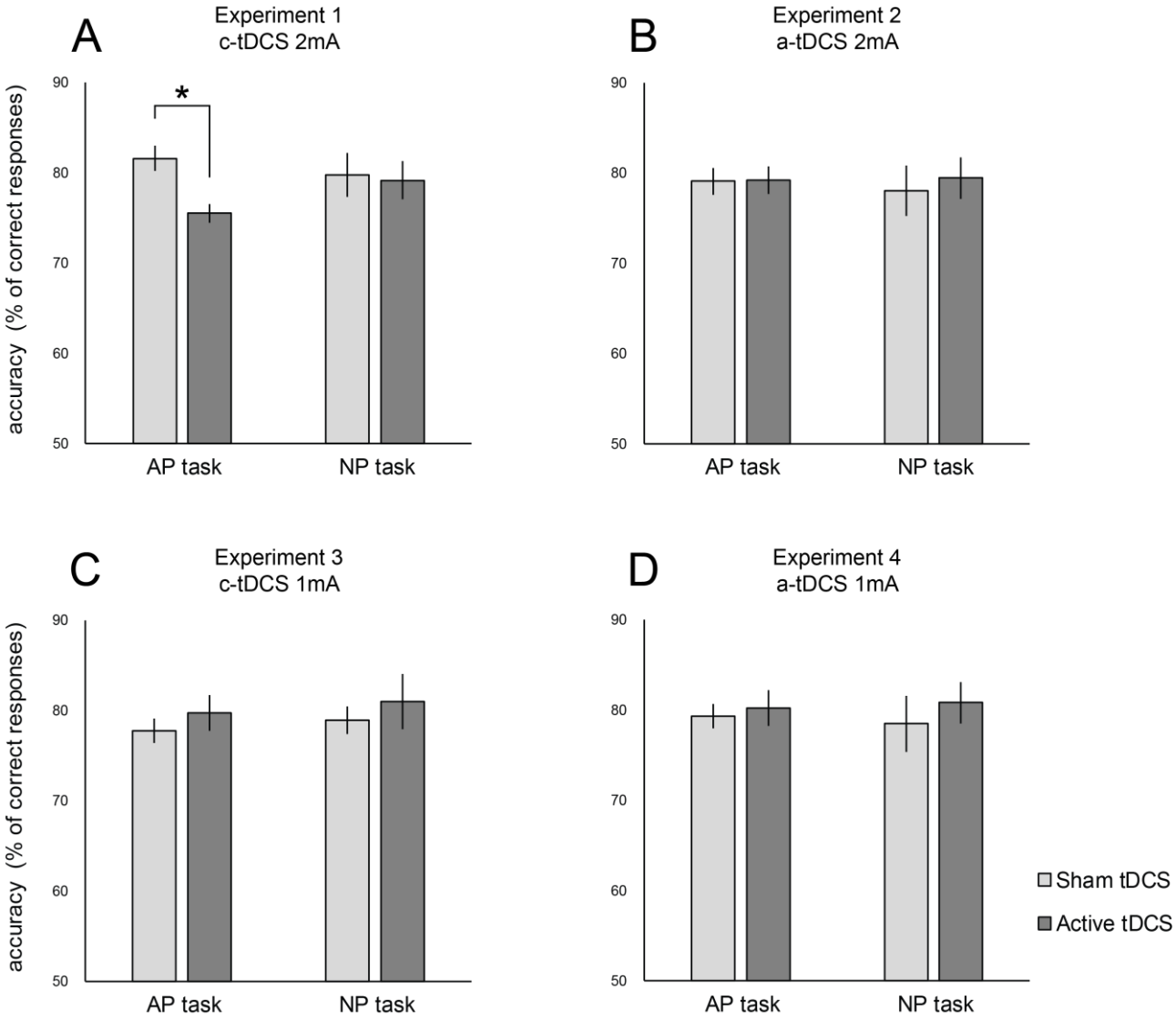

Figure 3. *Percentage of correct responses in Experiment 1 (A), Experiment 2 (B), Experiment 3 (C) and Experiment 4 (D). Grey and Light blue columns indicate Sham and Active tDCS conditions, respectively. Asterisks indicate significant post-hoc comparisons ($p < .05$). Error bars denote s.e.m.*

No main effects or interactions were found for ANOVAs conducted for the other experiments, i.e., a-tDCS$_{2mA}$ (all $F < 0.28$, all $p > .60$; Figure 3B), c-tDCS$_{1mA}$ (all $F < 1.21$, all $p > .29$; Figure 3C) or a-tDCS$_{1mA}$ (all $F < 1.42$, all $p > .26$; Figure 3D), suggesting that the selective drop in AP accuracy

found in Experiment 1 might be specific for both polarity (c-tDCS) and intensity (2mA) of the DC stimulation.

To directly compare the influence of different types of tDCS on AP task performance we computed an index of change in accuracy (active tDCS – sham tDCS) in each experiment. This index was negative in Experiment 1 (-6% ± 3) indicating AP task interference due to c-tDCS$_{2mA}$. The index values were lower in Experiment 1 than in Experiment 2-4 (range 0-2%; all $p < 0.05$; all *Cohen's d* > 1.35) which in turn did not differ from one another (all $p > 0.84$).

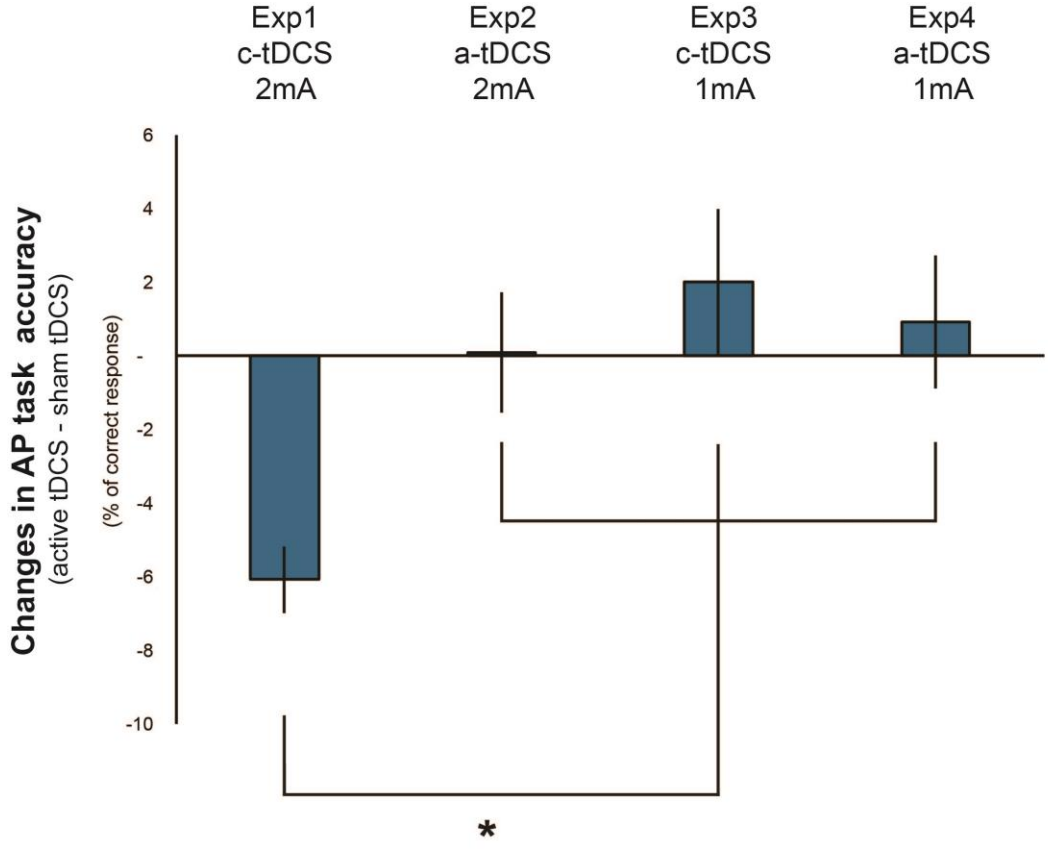

Figure 4. *Changes in AP task accuracy (active tDCS – sham tDCS) in Experiments 1-4. Active c-tDCS2mA (Experiment1) brought about a reduction in AP task accuracy relative to the other stimulation conditions in Experiment 2-4. Asterisks indicate significant post-hoc comparisons (p < .05). Error bars denote s.e.m.*

To assure that the effects found in the c-tDCS$_{2mA}$ group were not due to a speed accuracy trade off, a Session x Task ANOVA was computed on RTs (Table 1). No main effects or interactions were found (all F < 2.47, all p > .12).

Table 1. Mean ± SD RTs.

	Exp1		Exp2		Exp3		Exp4	
	c-tDCS $_{2mA}$		a-tDCS $_{2mA}$		c-tDCS $_{1mA}$		a-tDCS $_{1mA}$	
	Sham	Active	Sham	Active	Sham	Active	Sham	Active
AP task	447 ± 200	438 ± 209	406 ± 189	423 ± 194	485 ± 187	418 ± 92	334 ± 112	309 ± 129
NP task	457 ± 154	438 ± 190	437 ± 189	480 ± 185	533 ± 227	391 ± 125	384 ± 227	340 ± 108

Importantly, discomfort was very low, in keeping with the small size of the electrodes (Turi et al., 2014; Fertonani et al., 2015; Tang et al., 2016) and comparable across tDCS sessions and experiments as suggested by the lack of main effect or interaction in the Experiment x Stimulation ANOVA on stimulation unpleasantness ratings (all F < 2.31, all p > 0.09; Table 2).

Table 2. Mean ± SD Ratings of subjective unpleasantness.

Exp1		Exp2		Exp3		Exp4	
c-tDCS $_{2mA}$		a-tDCS $_{2mA}$		c-tDCS $_{1mA}$		a-tDCS $_{1mA}$	
Sham	Active	Sham	Active	Sham	Active	Sham	Active
1.75 ± 0.75	1.75 ± 0.75	1.33 ± 0.49	1.67 ± 0.78	1.25 ± 0.45	1.25 ± 0.45	1.25 ± 0.45	1.58 ± 0.67

DISCUSSION

In four different experiments, we used tDCS to exert polarity- and intensity-specific exogenous manipulation of the left M1 and test its role in action prediction. In Experiment 1, we found that c-tDCS$_{2mA}$ impaired accuracy in the AP task, compared to sham tDCS, whereas, accuracy in the NP task did not show any change. No changes were found in RTs, thus ruling out that detrimental effects of c-tDCS$_{2mA}$ were due to a speed-accuracy trade-off. No changes in performance were found in Experiment 2, 3 and 4 for either tasks, thus indicating that only the administration of cathodal currents at 2 mA were effective in modulating action prediction. These findings establish specific tDCS parameters for effective M1 stimulation and provide, to our knowledge, the first causal evidence of the critical role of M1 in action prediction.

Functional relevance of M1 to action prediction

Classically, the M1 has not been considered part of the AON as functional imaging studies have not consistently detected M1 activation during action observation (Gazzola and Keysers, 2009; Grafton, 2009; van Overwalle and Baetens, 2009; Caspers et al., 2010; Molenberghs et al., 2012) but see (Raos et al., 2007) and initial studies on monkey mirror neurons did not find any evidence of these neurons in M1 (di Pellegrino et al., 1992; Gallese et al., 1996) see also (Maranesi et al., 2012). Therefore, it was assumed that M1 had little role in action perception. However, more recently, three single-cell studies have reported modulation of neuronal activity in M1 during action observation (Tkach et al., 2007; Dushanova and Donoghue, 2010; Vigneswaran et al., 2013). Moreover, neurophysiological studies in humans have consistently reported 'motor resonance' effects in M1: similarly to action execution, action observation modulated the power of beta electro/magnetoencephalographic rhythms with source in M1 (Hari et al., 1998; Caetano et al., 2007; Koelewijn et al., 2008) and enhanced indices of M1 excitability collected in those muscles that would

be involved in performing the observed action, as shown by TMS-induced motor-evoked potentials (MEPs) (Fadiga et al., 1995; Strafella and Paus, 2000; Schütz-Bosbach et al., 2009; Alaerts et al., 2010; Borgomaneri et al., 2012; Naish et al., 2014; Valchev et al., 2015b). Taken together, these findings have led scholars to propose that M1 might be considered as an additional node of an extended AON (Kilner and Frith, 2007; Lepage et al., 2008; Pineda, 2008; Alaerts et al., 2009a, 2009b, 2012). Our study supports this proposal by providing causal evidence that, similarly to premotor stimulation, exogenous manipulation of M1 affects at least one key function of the AON, i.e., the ability to predict the actions of others.

Correlational evidence suggest that classical regions of the AON form an anticipatory representation of the action of others and M1 can reflect such anticipatory coding (Gangitano et al., 2004; Kilner et al., 2004; Urgesi et al., 2006, 2010; Avenanti et al., 2013a), possibly via top-down influence from premotor areas, such as the IFC (Nishitani and Hari, 2000; Nishitani et al., 2004; Avenanti et al., 2007, 2013a; Koch et al., 2010; Catmur et al., 2011; Enticott et al., 2012). For example, motor resonance in M1 (i.e., the muscle-specific increase of MEPs induced by action observation) was found to reflect the encoding of future phases of observed actions (Gangitano et al., 2004; Borroni et al., 2005; Urgesi et al., 2010) and inhibition of IFC by means of low-frequency repetitive TMS (rTMS) disrupted such anticipatory motor resonance in M1 (Avenanti et al., 2013a). However, while there is now causal evidence suggesting that IFC and other premotor areas might be critical for action prediction (Stadler et al., 2012; Makris and Urgesi, 2015; Avenanti et al., 2017), previous studies did not establish whether M1 activity is a mere epiphenomenon of the encoding of observed action in IFC (i.e., a simple downstream consequence of the strong reciprocal cortico-cortical connections between IFC and M1; see (Rizzolatti and Luppino, 2001; Shimazu et al., 2004; Dum and Strick, 2005; Prabhu et al., 2009; Fiori et al., 2016) or it played a causal role in action prediction. By using exogenous manipulation of M1 we could demonstrate that this region does not

only reflect an anticipatory representation of observed actions, but it plays a functionally relevant role in making predictions about the outcome of observed actions.

Biological tuning of M1 to human actions

The functional relevance of M1 appears specific for the prediction of human actions, as in Experiment 1, c-tDCS$_{2mA}$ did not alter performance in the NP task – which was designed as a difficulty-matched control to assess prediction of non-human motion. This selectivity is in line with the notion that motor regions of the AON respond more to the observation of human movement than non-human movement (Dayan et al., 2007; Casile et al., 2010; Press, 2011), including movements of geometrical stimuli (Kessler et al., 2006; Engel et al., 2008), inanimate objects (Costantini et al., 2005; Oberman et al., 2005), humanoid robots (Tai et al., 2004; Chaminade et al., 2010) and virtual hands (Perani et al., 2001), even when all movements are matched for kinematic profile. However, previous imaging evidence have also reported that the AON motor regions are active during predictions of abstract event sequences (Schubotz and von Cramon, 2004), raising the possible concern that anticipatory motor coding is not limited to human actions, but extends to event prediction in general, and thus can reflect domain-general processes (Schubotz, 2007; Press and Cook, 2015). Our study provides causal evidence that M1 is tuned to prediction of human actions and suggests that the motor activations, reported above, associated with non-human event prediction may reflect epiphenomenal activity that is not critical for making an accurate prediction.

Polarity- and intensity-specific modulations of task-relevant networks in M1

Using a factorial design manipulating the polarity and the intensity of tDCS we could demonstrate highly specific aftereffects of M1 perturbation. Not only c-tDCS$_{2mA}$ exerted a selective behavioral effect over AP task performance, while leaving unaffected NP task performance. Effects

of c-tDCS$_{2mA}$ on action prediction were also polarity- and intensity-specific. This indicates that task-relevant networks in M1 required for accurate AP task performance are more sensitive to c-tDCS$_{2mA}$ than other manipulations involving reduced current intensity and/or inverted polarity.

Polarity-specific effects suggest that c-tDCS$_{2mA}$ affected behavior through inhibitory interference with task-relevant networks, whereas excitatory manipulations of M1 were less effective in modulating such networks. This proposal finds support in the evidence that motor inhibition induced by several brain stimulation protocols affects alpha and beta band activity in sensorimotor regions (Chen et al., 2003; McAllister et al., 2013; Pellicciari et al., 2013; Baxter et al., 2016). For example, reduction of M1 excitability induced by continuous theta burst stimulation (cTBS) was associated with larger modulation of beta band activity in sensorimotor regions, relative to increase of M1 excitability (McAllister et al., 2013). In a similar vein, M1 inhibition induced by c-tDCS was associated with a larger alteration of alpha and beta oscillations than M1 facilitation induced by a-tDCS (Pellicciari et al., 2013; Baxter et al., 2016). Because modulation of alpha and beta oscillations reflects the activity of the sensorimotor nodes of the AON (Hari et al., 1998; Kilner et al., 2004; Caetano et al., 2007; Koelewijn et al., 2008; Sebastiani et al., 2014), the suggestion is made that M1 inhibition (c-tDCS) more than M1 excitation (a-tDCS) can alter motor resonance processes, including the anticipatory processing of observed actions that might underlie AP task performance (Gangitano et al., 2004; Kilner et al., 2004; Borroni et al., 2005; Urgesi et al., 2006, 2010; Avenanti et al., 2013a).

However, we did not assess the physiological effects of our stimulation protocol. It is widely held that a-tDCS increases motor excitability while c-tDCS decreases it (Nitsche and Paulus, 2001; Nitsche, 2003; Antal et al., 2004; Nitsche et al., 2008; Horvath et al., 2015), although many factors contribute to the polarity and efficacy of the stimulation, including intensity, electrode size and disposition and duration of stimulation (Cogiamanian et al., 2007; Nitsche et al., 2008; Batsikadze et al., 2013). This is relevant for interpreting not only polarity- but also intensity-specific effects as our study indicates that greater current intensities were necessary for c-tDCS to alter task-relevant motor

networks in M1. There is ample evidence of intensity-dependent tDCS aftereffects (Jefferson et al., 2009; Bastani and Jaberzadeh, 2013; Batsikadze et al., 2013) but see (Kidgell et al., 2013), however, such aftereffects are often not linear at higher intensities. For example, while c-tDCS$_{1mA}$ typically leads to reduction of M1 excitability (Nitsche et al., 2008; Nitsche and Paulus, 2011), a recent study of Batsikadze and colleagues reported that c-tDCS$_{2mA}$ performed for 20 minutes (with a 35 cm^2 cathodal electrode and a large supraorbital reference) increased M1 excitability, i.e., in a way that resembled the excitatory effects of a-tDCS (Batsikadze et al., 2013) see also (Jamil et al., 2016). Other studies indicate that the same stimulation produces M1 inhibition or no effect when the stimulation is administered for 10 minutes only (Kuo et al., 2013; Wiethoff et al., 2014) and clear inhibition when administered with a different montage (i.e., using the so called high-definition tDCS, with a small cathodal electrode surrounded by four small anodal electrodes; (Kuo et al., 2013). Several factors speak against the possibility that our c-tDCS$_{2mA}$ was excitatory. First, anodal currents – that are known to reliably induce M1 excitation (Cogiamanian et al., 2007; Nitsche et al., 2008; Moliadze et al., 2010; Brunoni et al., 2011; Kidgell et al., 2013) – did not affect AP task performance in Experiment 2 or 4. Second, as discussed above, oscillatory activity in the frequency bands that underlie motor resonance process in M1 (Hari et al., 1998; Kilner et al., 2004; Caetano et al., 2007; Koelewijn et al., 2008) is sensitive to inhibitory rather than excitatory manipulations (McAllister et al., 2013; Pellicciari et al., 2013; Baxter et al., 2016). Third, our stimulation protocol is quite different from that producing excitation with cathodal current at 2mA: relative to the study of Batsikadze and colleagues (Batsikadze et al., 2013), we used a smaller active electrode (25 cm^2) and thus a higher current density; however, this was counterbalanced by shorter stimulation duration (15 min) and an extracephalic montage that might have generically decreased the efficiency of the stimulation, possibly leading to a greater inhibitory modulation after c-tDCS$_{2mA}$ than after c-tDCS$_{1mA}$ (Cogiamanian et al., 2007; Nitsche et al., 2008; Moliadze et al., 2010; Brunoni et al., 2011). Notably, using the very same tDCS parameters, electrodes size and montage used here, Avenanti and colleagues (Avenanti et al., 2017) found that targeting the left IFC with a-tDCS$_{2mA}$ and c-tDCS$_{2mA}$

enhanced and hindered AP task performance, respectively. Thus, although further research is needed to clarify the physiological effects of such stimulation protocol, these behavioral findings are in agreement with the 'expected' physiological aftereffects of tDCS, with a-tDCS$_{2mA}$ and c-tDCS$_{2mA}$ leading to inhibition and excitation, respectively. Thus, we preliminary conclude that c-tDCS$_{2mA}$ likely exerted an inhibitory influence over task-relevant M1 networks involved in the anticipatory coding of observed actions.

Intensity-dependent recruitment of task-related networks for processing observed actions.

Our study provides insights into the heterogeneous results reported by previous brain stimulation studies addressing the role of M1 in action perception. These studies have used TMS to perturb M1 and test its role. By showing that task-relevant networks for action prediction require higher intensity to be altered by c-tDCS$_{2mA}$, our study suggests that previous inconsistencies might be related to the effectiveness of M1 stimulation.

Early studies targeted M1 at a near-threshold stimulation intensity (i.e., at 100% of the threshold for evoking MEPs or visible movements) found that offline low-frequency repetitive TMS (rTMS) did not affect neural response to observed actions (Avenanti et al., 2007) and online single-pulse TMS did not affect judgements about observed actions (Cattaneo, 2010). Conversely, online supra-threshold TMS disrupted effector recognition (Naish et al., 2016) and body posture recognition (Borgomaneri et al., 2015). Two recent studies used sub-threshold offline continuous theta burst stimulation (cTBS) (Palmer et al., 2016; Valchev et al., 2017) that avoids nonspecific, distracting effects of online supra-threshold TMS. Both studies reported variable behavioral responses following cTBS over M1, with no net changes in action perception. Remarkably, Palmer and colleagues (2016) also assessed M1 excitability and could demonstrate that cTBS induced highly variable physiological responses across participants, leading to suppression of M1 excitability in some and increase in other participants. Remarkably, only the subsample of participants showing reduction of M1 excitability

following cTBS showed hindered performance in the action perception task. In contrast, participants showing M1 facilitation did not show a significant change in performance (Palmer et al., 2016). This further provides convergent support to our proposal that effective M1 inhibition more than M1 excitation is able to alter task-relevant networks for processing observed actions.

Limitations

Our study has two potential limitations. First, in the four experiments we only stimulated M1 thus did not address the site-specificity of tDCS effects. However, using the very same procedure, Avenanti and colleagues (Avenanti et al., 2017) already demonstrated that AP task performance is disrupted by c-tDCS$_{2mA}$ over left IFC, but not by c-tDCS$_{2mA}$ over other visual (left STS) and motor (right IFC) nodes of the AON. Taken together present and previous findings indicate site-specificity of c-tDCS$_{2mA}$ and suggest that task-relevant networks for making prediction about the outcome of observed right hand actions are distributed across the M1 and IFC in the left hemisphere (contralateral to the observed hand). A second limitation is the focality of tDCS. To increase focality we used an extracephalic montage to avoid the confounding effect of a cephalic reference. Although the reduction in accuracy that we found with c-tDCS$_{2mA}$ over the left M1 (mean accuracy change ± s.e.m.: - 6.1% ± 0.9) was similar to that detected by Avenanti and colleagues (Avenanti et al., 2017) with c-tDCS$_{2mA}$ over the left IFC (-4.7% ± 1.6), different results were observed with a-tDCS$_{2mA}$: targeting left IFC increased performance in the previous study (+4.4% ± 1.5), whereas we found no effect when targeting left M1 (0.1% ± 1.6). Differential sensitivity of IFC and M1 to a-tDCS$_{2mA}$ further supports site-specificity of our manipulations. Lastly, although effects were site-specific, they were likely not site-limited. It is known that tDCS modulates the excitability of distant interconnected regions (Boros et al., 2008; Nitsche et al., 2008; Avenanti et al., 2012). Thus, it is entirely possible that other interconnected frontal (e.g., dorsal premotor cortex; see (Stadler et al., 2012; Makris and Urgesi,

2015) or parietal (e.g., inferior parietal or somatosensory; (Caspers et al., 2010; Valchev et al., 2015a, 2016) regions of the AON may have contributed to the observed effects.

Conclusions

All in all, our study demonstrates that monopolar offline c-tDCS$_{2mA}$ administered over the left M1 disrupts performance in a task requiring to make predictions about observed human actions, but not on a difficulty-matched task requiring to make predictions about non-human motion. No similar effects were found with 1mA current or when reversing the polarity of the stimulation, thus indicating that only c-tDCS$_{2mA}$ perturbed task-relevant motor networks necessary for making accurate predictions about others' actions. These findings provide causal evidence that M1 is functionally relevant to action prediction and highlight the tDCS parameters optimal to interfere with the anticipatory coding of observed action.

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