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**(XXV Cycle)**

# I know how you feel. The coding of others' somatosensory experience in the observer's somatosensory cortex.

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# Abstract

My doctoral thesis aims at exploring the role of the somatosensory cortices in the visual coding of others' tactile experiences. Several studies posit the existence in the human brain of a system which match the somatosensory and visual experience of touch (for a review see, Keysers et al., 2010);  in particular, the neural network involved in first-hand tactile stimulation is also responsible for understanding others' somatic sensations.

Firstly, by using online high-frequency repetitive transcranial magnetic stimulation (rTMS) I assessed whether the first (SI) and the second (SII) somatosensory cortices play a functional role in the visual processing of tactile events (Experiment 1). Healthy participants performed a discrimination task of visual stimuli depicting touch (a finger touching a hand) and a control task, with the visual discrimination of movements, not comprising a tactile component (the movement of a finger). rTMS over SI selectively impairs subject's ability to discriminate visual stimuli depicting a tactile event, suggesting that SI, a cortical area traditionally viewed as modality-specific, is implicated in the visual processing of touch. Instead, SII is not involved in the visual discrimination of touch.

Then, I assessed whether the visual processing of touch in SI is specific for the view of human to human contact, or it applies to the sight of 'any' touch (Experiments 2 and 3). Using the same rTMS paradigm, I show that in healthy subjects interfering with SI

activity specifically impairs the visual detection of the human touch, without affecting the visual perception of contact between objects, nor between human body-parts and objects.

Experiment 4 investigated whether SI is also involved in understanding others' sensations conveyed by tactile events, and whether this mechanism shows hemispheric specialization. Healthy subjects underwent a picture-based affective go/no-go task while receiving offline low-frequency rTMS to the right or left SI, or the right or left dorsolateral prefrontal cortex (DLPF); DLPF was chosen as active control site as it was shown to be involved in encoding the affective valance of emotional pictures (Bermpohl et al., 2005). Disruption of the right, but not left, SI activity by rTMS selectively reduces participants' performance, but only when the affective state is conveyed by touch; intriguingly, this interfering effect is associated with individual empathic ability to adopt others' subjective perspective. Then, the same task was given to a group of brain-damaged patients, to determine if specific brain lesions were associated with impaired recognition of the emotional valance of a visually presented somatic experience (Experiment 5). The main finding is that lesions affecting the right hemisphere are associated with a poorer performance in the affective go/no-go task, regardless of the visual tactile component.

Finally, I explored the neural underpinnings of mirror-touch synaesthesia (Experiment 6). When subjects with mirror-touch synaesthesia view a tactile stimulation on others they also feel the same somatic sensation on their own body, even in absence of a real touch (Blakemore et al., 2005). By using a facilitatory paired-pulse transcranial magnetic stimulation (ppTMS) protocol, I show that mirror-touch responses and synaesthesia-like sensations can be induced even in non-synaesthetes by increasing the excitability of SI, or by boosting its activity via ipsilateral posterior parietal cortex (PPC). Functionally connectivity between ipsilateral premotor cortex and SI is not involved in mirror-touch synaesthesia. Again, synaesthetic–like responses in non-synaesthetes are associated with different in emphatic abilities.

Overall, this series of studies demonstrates that: I) SI is causally involved in processing the sight of human-to-human contacts (Experiments 1-3); II) besides being involved in low-level visual processing of touch, SI of the right hemisphere participates in higher-level functions related to the encoding the affective valance of others' touch (Experiments 4,5); III) a right-hemisphere lesion may impair patient's ability of understanding others' somatosensation (Experiment 6); IV) the vicarious activation of SI by the sight of touch is associated to individual differences in affective and cognitive empathy (Experiments 4-6); V) synaesthesia-like mirror-touch sensations can be induced through the enhancement of SI activity, or by boosting its activity via PPC (Experiment 6).

# CHAPTER 1

## *1.1. Mirror Neuron System and the social cognition*

Animal studies have shown the existence of a particular class of visuo-motor neurons, which code for both execution and observation of action, the so-called mirror neurons (di Pellegrino et al., 1992): watching an action performed by other individuals activates the same areas involved in action planning and execution, namely frontal and parietal cortical areas, i.e., the mirror neuron system. Indeed, when monkey observe an action done by conspecific their motor cortex becomes active, in the absence of any overt motor activity. The importance of the discovery of mirror neurons is the fact that a neural mechanism allows a direct mapping of both the first-hand and assisted experiences. Several line of evidence demonstrated the existence of an analogous system in the human brain (e.g., Avenanti et al., 2007; Buccino et al., 2004; di Pellegrino et al., 1992; Fadiga et al., 1995, 2005; Gallese et al., 1996; Gazzola et al., 2007; Hari et al.,1998; Iacoboni et al., 2005; Rizzolatti et al., 1999, 2001; Rizzolatti and Craighero 2004; Rossi et al., 2002). For instance direct evidence for the existence of an action execution-observation matching system is provided by Trancranial Magnetic Stimulation experiments (TMS). Fadiga et al. (1995) recorded motor-evoked potentials (MEPs) from subjects' right hand and arm muscles induced by TMS of the left primary motor cortex (M1), while they were required to observe the experimenter grasping objects (transitive hand actions) or performing meaningless gestures (intransitive arm movements). The results showed that the observation of both transitive and intransitive actions increased the amplitude of MEPs. Similar conclusions were drawn in subsequent experiments (Maeda et al., 2002; Patuzzo et al., 2003). Hence, when we observe someone performing an action, besides the activation of various visual areas, there is a concurrent activation of the same motor circuits normally recruited during the execution of that action.

Thus it has been postulated that mirror neurons in human would not only allow understanding what others are doing, but also their intention and feelings. A fMRI study firstly confirmed this intuition, by showing that when individuals had to infer the intention of the agent from the context, there was a selective activation of the mirror premotor area (Iacoboni et al., 2005). Therefore mirror neurons in human are involved not only in action recognition, but also in understanding the actors' intentions.

On a broader level the discovery of mirror neuron system is a building block in social cognition research. The essential mechanism that allows us a direct understanding of others is not a declarative reasoning, but the simulation of the observed events through the mirror mechanism. There is fundamental difference between human interaction with inanimate world and conspecific: with the latter we share the same experiences and emotions, being endorsed with a similar body-brain system (Gallese et al., 2004). Mirror neurons network allows us to directly understand the meaning of others actions and intention by internally replicating (simulating) them without any explicit reflective mediation. The term *embodied simulation* (Gallese 2005, 2007) is adopted to describe our brain's peculiar ability to directly link the first-hand and observed experiences: others gestures and intentions are not needed to be cognitively decoded (it is not mandatory at least), because they 'penetrates' into the observers' motor knowledge, and they are automatically coded into the observer's brain, as he/she was having the same experience. In this perspective, it was proposed that the understanding of basic aspects of social cognition depends on the activation of neural structures normally involved in our own personally experience, leading to an automatic and implicit comprehension of others' behaviour. By means of this activation, a bridge is created between "me" and "others".

So far, I have briefly described the neural mechanism underlying action understanding. Does a similar mechanism mediate our understanding of somatic sensations and emotions of others? In the next chapters I will discuss evidence indicating that a similar mechanism is also involved in our capacity to understand and experience others' somatic feeling and emotional states, which is the topic of my doctoral thesis.

## *1.2 Neural underpinnings of the mirror–touch system*

Beyond the domain of action, other brain systems with mirror properties have been described, including systems that are involved in both the observation as well as the experience of emotions (Carr et al., 2003; Wicker et al., 2003), pain (Avenanti et al., 2005, Botvinick et al., 2005; Jackson et al., 2005; Morrison, et al., 2004; Singer et al., 2004; Valeriani et al., 2008), and touch (Blakemore et al., 2005; Keysers et al., 2010).

Here I will focus on the mirror mechanisms for touch, which represent the topic of the experiments done during my PhD.

A growing body of empirical evidence in humans supports the existence of a visuo-tactile mirror system, which matches observed touch with felt touch. Following the embodied simulation models (Gallese, 2005, 2007, see chap.1), it has been proposed that the observation of tactile experience in others activates the same brain regions normally devoted to the processing of tactile sensations from one's own body, namely the human somatosensory system; this mechanism may allow the understanding of others' somatic sensations.

Somatosensation involves the processing of tactile, proprioceptive and nociceptive information. The main cortical regions of the somatosensory system involved in this processing are the first (SI) and second (SII) somatosensory cortices, plus the insula and the rostral cingulate cortex. The latter however are thought to process the affective value of somatosensory stimuli (Kaas 2004). SI actually refers to four different sub-regions: BA3a and BA3b, roughly corresponding to the posterior bank of the central sulcus, BA1 to the crown of the postcentral gyrus and BA2 to the anterior bank of the postcentral gyrus. BA3a receives proprioceptive information from muscle spindle receptors through the ventroposterior superior nucleus (VPS) of the thalamus, and has close anatomical connections with the motor cortex. BA3b is primarily involved in tactile processing and receives inputs from neurons in the ventroposterior nucleus (VP) of the thalamus. BA3b also receives input from neurons in the VP and in the ventroposterior inferior nucleus (VPI) that are activated by nociceptive neurons in the brain stem and spinal cord. BA1 receives inputs from BA3b and thus is thought to be involved in later stages of somatosensory processing, together with BA2 which receives inputs from BA3a, BA3b and BA1 (for a review of the anatomical basis of the somatosensory system see Keysers et al., 2010). Neurons in BA2 are especially active during object manipulation and exploration. It also receives callosal connections from the contralateral BA2, and therefore this area is involved in processing both ipsi-and contra-lateral somatosensory stimuli. BA2 also has direct, reciprocal connections with regions of the fundus of the intraparietal sulcus, such as the ventral intraparietal area (VIP) and the inferior parietal lobule which combine visual, auditory and somatosensory information (Pons and Kaas 1986; Rozzi et al., 2006).

Animal and human studies have shown that the somatosensory cortices exhibit properties that are relevant for visual functions related to tactile events, and that may be also crucial to trigger vicarious, mirror, responses in somatosensory cortices. First, some SI neurons code for arbitrary visual–tactile associations. Animal studies have shown that SI neurons in monkeys may fire both in response to a tactile stimulus as well to a visual stimulus that may have previously been associated with the tactile stimulus (Zhou and Fuster 1997; 2000). Therefore, it is probable that mirror activation of SI for touch events may involve a local SI mechanism. Additionally, the caudal part of SI features multimodal receptive fields and direct connections with the posterior parietal cortex (PPC), which contains bimodal visuo-tactile neurons (Bremmer et al., 2001; Duhamel et al., 1998; Holmes and Spence 2004; Maravita et al., 2003; Nakashita et al., 2008; Rizzolatti 1997). In addition, SI also receives visual inputs from the more caudal parts of the PPC (Iwamura 1998). Therefore, the connectivity between these regions may indeed be associated with the mirror activation of SI by the view touch events.

In monkeys and humans, SII, which lies on the parietal operculum (OP), can be divided into two subregions: SII and PV (the parietal ventral area) (Disbrow et al., 2000; Eickhoff et al., 2007) SII and PV receive inputs from all four subareas of SI. These connections are reciprocal, allowing areas involved in early processing stages to be influenced by areas involved in later processing stages. Furthermore SII receives inputs also directly from the thalamus, which is responsible for tactile integration and is involved in higher-level somatosensory processing (Haggard 2006; Iwamura 1998). Therefore, SII has access to primary signal codes from the mechanoreceptors. Recent studies have also identified SII as a site of integration between somatosensory information and information from other sensory modalities, such as vision (Avikainen et al., 2002; Bremmer, et al., 2001; Carlsson et al., 2000).

Taken together, this evidence suggests that both the SI and SII cortices possess mechanisms that could be involved in some visual processing of tactile events. These areas, traditionally viewed as low level sensory-specific areas, indeed possess multisensory properties, processing both visual and tactile stimuli (Keysers et al., 2010). Next I will review the available data supporting the existence of mirror-touch mechanisms in the somatosensory cortical network.

### *1.3 Evidence for a mirror-touch system in human brain*

A seminal study by Keysers and co-workers (Keysers et al., 2004) first investigated the vicarious activation of somatosensory cortical network during the observation of touch. The authors used functional Magnetic Resonance Imaging (fMRI) to show that the SII (-PV), but not SI, was activated in response to a touch delivered to the subject's own body as well as to the visual presentation of the same tactile stimulation. Indeed, overlapping cortical areas in SII-PV were activated by both the experience of touch (i.e., touch on the legs) and the observation of someone else being touched on the same body part; noteworthy, this vicarious activation of SII-PV was induced when subjects observed both someone and something else getting touched by objects, suggesting that this area does not differentiate the recipient of the touch (animate or inanimate) (Keysers et al., 2004; Blakemore et al., 2005).

Following this pioneering experiment, other brain imaging studies have confirmed the existence of shared representation for the felt and observed touch in the somatosensory cortices (Blakemore et al., 2005; Ebisch et al., 2008; McCabe et al., 2008a; Pihko et al., 2010; Schaefer et al., 2009). For instance, Blakemore and colleagues (2005) investigated the neural system involved in the perception of touch in a synaesthete and in a group of non-synesthetic control subjects. Authors measured the neural activity to the observation of touch to a human face or neck compared with the observation of touch to equivalent regions of an object. Authors also compared the brain activity during the observation of a human face or neck being touched with the activation elicited by the direct tactile stimulation of the face or neck of the subjects themselves (Blakemore, et al., 2005). With this paradigm the authors showed that the view of touch induces a recruitment of areas of the mirror motor system, including the premotor cortex, superior temporal sulcus and parietal cortex. This pattern of activation was specific for the observation of touch to another human more than to an object. The synaesthete pattern of activation patterns differed in three ways from those of the non-synesthetic controls. First, activations in the somatosensory cortex were significantly higher as compared to control. Secondly, an area in left premotor cortex was activated in the synaesthete to a greater extent than in the non-synesthetic group. Finally bilateral anterior insula cortex activation was found only in the synaesthete while there was no evidence of such activation in the non-synesthetic group. In this study, the observation of another person being touched activates both SI and SII. In SI, these activations were somatotopically organized, following the so-called sensory homunculus magnification. As a result, observing a face being touched activates the corresponding area of SI which is active when the face receives a tactile stimulation, whereas observation of touch to the neck does not (Blakemore, et al., 2005). Moreover, there was a lateralization of SI responses by the sight of touch as typically occurs when the subject is touched on one side of the body: observation of touch delivered to one side of another person's body produces contralateral SI activation (Blakemore et al., 2005; Phiko et al., 2010; Schaefer et al., 2009; Wood et al., 2010). Using a different technique, Schaefer obtained similar result. Subjects were instructed to looked a video where a hand was touched in synchrony with a real touches delivered to their real hidden hand as compared with watching a video with asynchronous touches, where the hand in the video was stroked with a deley of 750 ms with respect to real stimulation. During synchronous stimulation, subjects reported to feel the tactile sensation on the video hand, thus indicating that in this condition the subjects regarded the video hand as their own touched hand. This feeling disappeared in the asynchronous condition (Schaefer et al., 2005).

The visual activation of the somatosensory cortical areas shows a peculiar chronometry, different to the temporal activation induced by tactile stimuli. A study used the magnetoencephalography technique (MEG) to analyse the temporal profile of SI activation. Authors found that watching someone else being touched activates SI within 300–600 ms, i.e. considerably later than the tactile activation (Phiko et al., 2010). A subsequent study using event-related potentials suggests that touch observation is associated with different temporal activation, with sensory-perceptual characteristic elaborated at earlier stage (100 and 250 ms) and a relatively late cognitive evaluation of touch (between 500 and 600 ms) (Streltsova and McCleery 2012).

Besides the somatotopic organization of the vicarious activation of the somatosensory cortices by touch observation, less clear is the existence of a hemispheric dominance of the mirror-touch system (Blakemore et al., 2005; Ebisch et al., 2008; Keysers et al., 2010). With respect to the motor mirror system, a major involvement of the left hemifield has been reported (Gallese and Craighero, 2004).

The mirror activation of SI can be modulated by several conditions: for instance activity in SI appears to be correlated with the degree of perceived intentionality of the observed touch (Ebisch, et al., 2008): authors examined whether the tactile mirror mechanism applies to the sight of any touch, irrespective of the intentionality of the observed touching agent. During fMRI scanning, participants viewed video clips depicting a touch that was intentional (i.e. a man gasping a seat, a caress between two people) or accidental (the branch of a palm touching either a seat or a human being), and occurring between animate or inanimate objects. Authors found a significant difference between the sight of an intentional touch compared to an accidental touch in left SI/BA2. This peculiar activation in SI might reflect a human tendency to "resonate" more with an intentional touching agent. Different activation of SI is also related to the observer point of view: increased posterior SI activity in response to observed touch versus no-touch occurs specifically when observing someone else being touch, as compared to condition were no touch were delivered or it was directed to viewer's own hand (Kuehn et al., 2013). Similar conclusions were drawn by Schaefer and colleague (Schaefer et al., 2009). In their study, participants observed video clips of a touched or non-touched hand either in an egocentric or in an allocentric perspective during fMRI. Results showed different activation of SI, depending on the perspective of the observed touch: the egocentric perspective showed activation in the anterior part of SI (BA3a, 3b). In contrast, the allocentric perspective involved significant activation of the posterior part of SI (BA2). Both these studies suggest that only the caudal part is strictly correlated with sharing tactile experience with others. These results are consistent with the findings reported by Ebisch et al. (2008), and further suggest that SI/BA2 may differentially respond to non egocentric body contact.

Summing up, the present studies underline a mirror activation of SI by the sight of touch, which is particularly relevant for interpersonal intentional somatic experiences, while the activation of SII is less specific, being recruited also during the vision of inanimate touch, regardless of the agent of touch.

A key question regards whether the vicarious activation of SI during touch observation is specifically related to the view of a tactile event per se, or whether it is more generally a consequence of mirror activation for action perception. Indeed, SI and SII are recruited during action observation, even if the observed action does not inherently implies a tactile stimulation (Avikainen et al., 2002; Gazzola and Keysers 2009; Gazzola et al., 2007a; Oouchida et al., 2004). Data support toward the former view: seeing a static hand being touched significantly increased activity in SI, thus providing a clear indication that observing an action is not the mandatory component for inducing a vicarious activation of SI activity (Kuehn et al., 2013; Schaefer et al., 2009).

Which is the function of the vicarious activity of SI and SII during the sight of touch? The activity of somatosensory cortices during touch observation may support, in line with the theory of embodied simulation (Gallese, 2005) the comprehension of another person’s tactile experience. That is, the existence of shared representations for viewing and experiencing touch may underpin our ability to understand others' somatic feelings. On a broader behavioural level, this system may be involved in anticipating the effect of tactile stimulation on our body from a feed-forward perspective, as well as in understanding the effects of tactile stimulation on other individuals as part of the broader neural circuitry for embodied simulation (Gallese 2005, 2007; Grafton 2009).

The vicarious somatosensory activity to observed touch has measurable behavioural effects. Perception of nearly-threshold tactile stimuli delivered to the observer's body can be enhanced by the observation of the same body part being touch (e.g., Cardini et al., 2011; Kennett et al., 2001; Serino et al., 2009). In particular, viewing someone being touched on the cheek can enhance detection of a tactile stimulus applied to our own cheek. This effect is known as visual remapping of touch (Serino et al., 2008).

Despite the growing body of evidence, to date the significance of somatosensory activity during the observation of touch remains unclear, as it is not known whether SI or SII (or both) can process visual information related to tactile events in a functionally relevant way. In the case of neuroimaging studies, only correlations between brain and behaviour are indicated. Nevertheless, it remains to be established whether these areas are *essential* for the visual processing of touch in the human brain.

## *1.4 The mirror-touch synaesthesia*

As described in Chapter 1.3, the visual of a tactile stimulation delivered to others body is able to activate the same neural network normally activated by first-hand somatic experience. Intriguingly, in a minority of persons with synaesthesia observing a tactile stimulation to another elicits conscious tactile experiences on their own bodies: this phenomenon is called '*mirror-touch synaesthesia*' (Blakemore et al., 2005).

Generally speaking, synesthesia is a condition in which stimulation in one modality also gives rise to a perceptual experience in a second modality (Rich and Mattingley 2002). Specifically, the property of a stimulus (*inducer*) results in conscious experiences of an additional attribute (*concurrent*). The most common form is the grapheme-colour synaesthesia, where words or letters elicit an experience of color when seen (Cohen Kadosh and Henik 2007).

Mirror-touch synaesthesia has been described more recently. It can occur seemingly developmentally (e.g., Blakemore et al., 2005; Banissy and Ward 2007; Maister et al., 2013) or be acquired, after brain injury (Halligan et al., 1996) or limb amputation (Fitzgibbon et al., 2010; Goller et al., 2013).

There are two main variants of mirror-touch synaesthesia: (i) the specular subtype, where observing touch to another person's left body induces synaesthetic touch on their right part, as they were looking in a mirror, with specular reference frame; (ii) the anatomical subtype, where subjects experiences synaesthetic touch on their left body when observing touch to another person's left body, with anatomical reference frame

(Banissy and Ward 2007). The specular type seems most common (Banissy et al., 2009). As previously discussed (see Chap 1.3), the neural correlates of mirror-touch synaesthesia were studied in a fMRI study (Blakemore et al., 2005). The most intriguingly finding was that in the subject with mirror-touch synaesthesia, the tactile mirror system, and specifically SI, was shown to be overactive, above the threshold for inducing a conscious tactile perception, such that observing touch results in a conscious somatic experience in the synaesthetes, but not in non-synesthetic controls.

Additionally, only in the synaesthete the anterior insula cortex was bilaterally activated, while there was no evidence of such activation in the non-synesthetic group; neuroimaging studies showed insular involvement when subjects were asked to imagine themselves performing actions, (Ruby and Decety 2001) look at pictures of their own face (Kircher et al., 2001) and identify their own memories (Fink et al., 1996), suggesting a specific insular role in attribution to the self. Hence it is possible that the anterior insula activity found in the synaesthete, along with overactivation of the mirror-touch system, explains why the synaesthete attributed to herself the observed touch.

Banissy and Ward (2007) have further demonstrated that mirror-touch synaesthesia is closed related to emphatic mechanisms. Mirror systems may be crucial for empathy because they enable the observer to simulate another's experience by activating the same brain areas that are active when the observer experiences the same emotion or state (Gallese 2007). In this perspective, an overactivation of the mirror-touch system, should not only determine synesthetic phenomena, but also enhanced empathy. To verify this hypothesis, the authors first developed a task for assessing the authenticity of mirror-touch synesthesia, and then look for associations between the behavioral performance at this task, and individual emphatic abilities. The tasks consisted in visual-tactile spatial congruity paradigm. Mirror-touch synaesthetes, and non-synaesthetes were asked to report where they were being touched (left or right cheek in one condition, right or left hand in the other) while, at the same time, observing a touch delivered to the same body part on another person. On congruent trials, the observed touch was delivered to the same location as the touch delivered to the participant. On incongruent trials, the observed touch was on a different location to where it was on the participant. The authors found that mirror-touch synaesthetes performed slower on incongruent trials compared to congruent trials, and made more errors overall than controls. These results provide the first objective behavioral evidence of the authenticity of mirror-touch synaesthesia as they indicate that mirror-touch synaesthetes have greater difficulty in discriminating between real and synaesthetic touch. Crucially, synaesthetes showed significantly higher scores in empathy quotient pertaining the emotional reactivity relative to controls. It has been suggested that the affective empathy may depend on shared interpersonal representations (Gallese 2009). This supports the hypothesis that tactile mirror system may modulate some aspects of empathy. Further evidence of the link between empathy and mirror-touch system will be given in next chapter.

Taken together, this evidence has led to the proposal that mirror-touch synaesthesia may reflect an extreme experience of an otherwise normal perception ranging from understanding others' somatic sensation to the actual experience of a similar sensation; when another person's touch sensation is consciously "shared", it becomes synaesthesia (Blackemore et al., 2005; Fitzgibbon et al., 2012; Keysers et al.,2010). This hypothesis of a hyper-activation of the mirror-touch system in synaesthesia is also supported by the fact that mirror-touch synaesthetes have enhanced tactile sensitivity (Banissy and Walsh 2009).

Moreover, synaesthetic-like behaviour can be also induced in non-synaesthetes through perceptual manipulation. Indeed, perception of sub-threshold stimulation to the face can be modulated by simultaneously observing the same tactile experience: subjects without synaesthesia show a benefit in tactile processing, namely detection of sub-threshold tactile stimuli on their own faces, by observing another person's face being touched (Serino et al., 2008). This effect is greater when observing one's own face being touched, as compared to the view of another's face being touched, while no advantage is induced by seeing an object being touched (Serino et al., 2008). Bolognini and colleagues tried to induce synaesthetic-like behaviour, by increasing the excitability of the putative tactile mirror system via transcranial direct current stimulation (tDCS). The authors found that non-synaesthetes became slower at localizing a site touched on their hands when they simultaneously viewed a touch to the opposite hand when SI was stimulated (Bolognini et al., 2013).

Summing up, current data demonstrate an interaction between perceived and observed touch, namely the mirror-touch system, which rely on a neural circuit including somatosensory cortices, parietal and premotor areas. It seems reasonable to propose that these mechanisms also underpin the visual effect on touch perception effects seen in mirror-touch synaesthesia. Nevertheless alternative hypothesis should be also considered. Some authors argued that mirror-touch synaesthesia may be the result of abnormal connectivity (Maurer et al., 1997). According to this view some synapses connecting one sensory cortical area with another may not be adequately pruned during early development. An alternative explanation consider synaesthesia the consequence of learned association (Heyes 2010): in this sense pairing the visual of somatic experience and the associated somatic experience would activate somatosensory mirror areas when seeing another being touched, considering the mirror system a product of Hebbian association. Following this learned association mechanism then mirror-sensory synaesthesia would be the result of a learned association through sensorimotor experience mediated by mirror systems. Further investigations are needed to clarify the mechanisms subtending mirror-touch synaesthesia.

## *I.5 Mirror neuron system: the neural basis of empathy?*

Somatosensory stimulation often brings along affective information: a pleasant caress may express kindness or love while a punch convey anger, or hate. In this view skin-to-skin contact provides a powerful non-verbal communication, crucial for social interactions. In fact, touch has an emotional as well as communicative meaning. According to the simulation theory of empathy (Gallese 2003), the automatic and subconscious simulation of others' somatic states produces an embodied representation in the observer, which can aid the understanding of the observed person's feelings (Decety and Sommerville 2003; Preston and de Waal 2002). Empathy is fundamental for human social interactions, since it allows the understanding of others' sensations and emotions through the sharing of sensory and affective states. Current neuroscientific research agrees that empathy comprises several components, supported by independent but interacting mechanisms, involving sensory-affective, cognitive, and emotional abilities (for a review see Bufalari and Ionta 2013). Empathy should be conceived as our natural proneness to firstly elaborate interpersonal experience in an implicit, pre-rational fashion, representing others' sensations within cortical areas that elaborate our own emotions. In other words, we do not simply assist to others emotions: rather we can directly understand them from the inside, as we were experiencing similar sensations.

Despite various definitions of empathy, there are three core aspects of this function which yielded broad agreement among researcher: (i) an affective response to others emotional state; (ii) a cognitive ability to assume others' perspective; (iii) emotion regulation (Decety and Jackson 2004).

The first aspect gathers the emotional aspects of empathy. Recently, it has been proposed that neural substrate activated when various emotions are directly experienced would also code for the affective response elicited when the same emotions are observed in others (Gallese 2003). In this view, others' sensations would be automatically and implicitly understood, through a mirror matching mechanism. This model is supported by several neuropsychological and neuroimaging evidences. An fMRI study demonstrated that observing various emotional facial expressions induced activity in areas normally involved when the same emotions are directly experienced by the observer, including the superior temporal sulcus, the anterior insula, the amygdala and premotor cortex (Carr et al., 2003). The neuropsychological literature also supports the view of shared mechanisms for one's own and others' emotions: for instance, bilateral amygdala resection prevents both the experience of fear as well as its recognition in others (Adolphs et al., 2005; Sprengelmeyer et al., 1998), while a patient with insular and putamen damage was shown to be unable to recognize disgust in others from multiple modalities (facial expression, non-verbal sounds, prosody), as well as to directly experience disgust (Calder et al., 2000). Finally, a study in a large sample of patients showed that a right-hemisphere brain damage, affecting SI and SII, insula and anterior supramarginal gyrus, impaired the recognition of other's emotional facial expressions (Adolphs et al., 2003).

The capability to assume others perspective requires one to mentally simulate others feelings, and therefore refers to a more cognitive aspect of empathy. fMRI evidence shows that when subjects are asked to adopt either their own perspective or the perspective of their mothers in response to situations involving social emotions, there is an activation of the same brain areas involved in self-generated emotions, including the temporal poles and the amygdala (Ruby and Decety 2004). Also, viewing somebody in a potentially painful situation activates areas typically involved in pain processing in a first-person perspective, including the parietal operculum, the anterior cingulate cortex and the anterior insula (Jackson et al. 2006).

Although there is a common neural basis underpinning first-hand and other’s sensations, we never get confuse between mine” and “others’ ” experience. Indeed we are able to adopt another person’s perspective, imagining how that person is affected by his or her situation, but without confusion between the feelings experienced by the self versus feelings experienced by the other person (de Vignemont and Singer 2006).

On a broader perspective, action imitation and understanding of others’ intentions also involve emphatic abilities (Gallese 2003). This link is supported by evidence in individuals with autism spectrum disease (ADS). ADS individuals show both an impairment of imitation and empathic abilities, leading to the proposal that the mirror neuron system can account for both these deficits (Williams et al., 2001). Indeed, different studies have enlightened an atypical activation of mirror neuron system regions during motor imitation in ASD group, as compared with neurologically healthy controls (Dapretto et al., 2006; Nishitani et al., 2004; Williams et al., 2006) even though motor imitation was not impaired in ASD subjects (for a review see Baird et al. 2011).

Given that the main topic of my PhD thesis is the mirror-touch system, I will focus my attention on the relation between empathy and mirror-touch activation. Adolphs et al. (2000) demonstrated that somatosensory cortices play a key role in the understanding of others' sensations: indeed, the damage of the right somatosensory cortices may impair the ability to encode emotional recognition of facial expressions. Based on this evidence, Adolphs has proposed that right somatosensory cortices may be a critical component in retrieving socially relevant information from faces (Adolphs et al., 2000). Mounting evidence supports this link between the role of mirror system for somatosenations and emotions in social cognition. This aspect is well described with respect to the processing of pain in others. Studies using MEG (Cheng et al., 2008) and somatosensory evoked potentials (SEPs) (Bufalari et al., 2007) have revealed that empathy for pain in others modulates SI and SII. Recent evidence showed empathy-related activation in contralateral SI when participants focused on the intensity of pain felt by the other person: Lamm and colleagues (2007) using fMRI found a strong activation of SI during pain observation which correlated with the 'empathic concern' subscale of the Interpersonal Reactivity Index (IRI) (Davis 1983), suggesting that somatosensory representations might be involved in identifying the precise body location where the painful stimulus is delivered, thus playing a more causal role in the emphatic coding of others somatic consequences. It worth noting that activity in SI was reliable only when the displayed painful event includes a somatosensory component. By using TMS, Avenanti and colleagues (Avenanti et al., 2009) showed that sensori-motor responses to the sight of others' pain were associated with individual differences in empathy, measured by the IRI. First, the authors recorded motor evoked potentials (MEPs) induced by single-pulse TMS to the primary motor cortex contingent upon the observation of needles penetrating a model of a human hand, a paradigm typically used to study motor cortex excitability during the perception of others' action (Fadiga et al., 1995). A reduction of corticospinal excitability was specific for the muscle that subjects observed being penetrated by the needle. This inhibition correlated with the observer's subjective rating of the sensory qualities of the pain attributed to the model. Moreover the somatomotor response to visual pain was higher in subject with high trait-cognitive empathy and lower in subjects with high state- and trait-personal distress. Other fMRI studies on empathy when witnessing pain also report correlations with affective subscore 'Empathic Concern' of the IRI. In particular, Empathic Concern has been related to insular activation while participants were aware of other people's pain (Singer et al., 2004, 2006)

Regarding non-painful somatic sensations, recently Schaefer and colleagues (Schaefer et al., 2012b) explored whether the association between the vicarious somatosensory activation and inter-individual differences in empathy. During fMRI, subjects were shown video clips where actors were gently stroked with a paintbrush to a hand.

Results showed that the vicarious somatosensory activation by seeing the hand being touched was associated with empathy subscale ‘Perspective Taking’ of the IRI, suggesting an involvement of the cognitive aspects of empathy in this mechanism. The results are in line with another study on empathy and the auditory mirror system (Gazzola et al., 2006), which showed a group of more empathic subjects compared with a group with lower empathy scores activated the auditory mirror system, including SI, more strongly. This relation was restricted to cognitive empathy, i.e., the subscale ‘Perspective Taking’ of the IRI.

Finally, as previously discussed (see Chap. 1.4), inter-inidividual differences in emphatic abilities are also linked to mirror-touch synaesthesia (i.e., affective empathy) (Banissy and Ward 2007; Goller et al., 2013), as well as to the induction, by the non-invasive stimulation of the somatosensory cortex, of mirror-touch synaesthesia-like responses in non-synaesthetes (Bolognini et al., 2013).

A further question arises: do personality traits influence the mirror activation for touch? To my knowledge, only one study has specifically addressed this issue, by evaluating whether personality traits influence the vicarious activation of somatosensory cortices during touch observation. In particular, Schaefer et al. (2013) showed that vicarious somatosensory activation when viewing the touched hand positively correlated with the personality trait ‘openness to experience’, suggesting that brain responses to seen touch interact with personality trait.

In conclusion, the available evidence indicates that mirror resonance mechanism may be crucially involved in empathy and, hence, in social cognition: indeed, more empathic people show stronger activation in SI than less empathic people when they perceive others' actions or sensations (Avenanti et al., 2009; Schaefer et al., 2012b), mirror-touch synaesthetes have heightened empathic ability (Banissy et al., 2009; Goeller et al., 2013), and lesions in the somatosensory cortices may impair social-emotion processing (Adolphs et al., 2000). With respect to the mirror-touch system, the current data suggest that the degree of vicarious activation in somatosensory brain regions may determine what it feels like to see other people being touched and, more generally, to what extend one might empathically share other people's somatosensations and emotions (Keysers et al., 2010).

# CHAPTER 2

# VISUAL PERCEPTION OF BODILY INTERACTIONS IN THE PRIMARY SOMATOSENSORY CORTEX

## *2.1 Experiment 1: Exploring the role of SI and SII in the visual processing of tactile events*

### Aim of the study

In the present study, I sought to address the causal role of SI and SII in the visual processing of touch. Indeed both SI an SII, beside the processing of tactile stimuli directly felt on our own body, seem to be also involved in coding visual events (see Chapter I, and Keysers et al., 2010; Fiorio and Haggard 2005; Macaluso 2006). However, the significance of somatosensory activity during the observation of touch remains debated. Indeed, it is still unclear whether SI, SII or both can process visual information related to tactile events in a functionally relevant way. Brain imaging studies, extensively used to address the crossmodal properties of somatosensory cortices, do not investigate causality in the brain–behaviour relationship, and therefore cannot clarifying whether somatosensory areas play a causal role in the visual processing of touch events. This issue can be explored by using the technique of Transcranial Magnetic Stimulation (TMS). TMS allows researchers to investigate causality in the brain-behaviour relationship, by temporarily interacting with the activity of neurons in brain areas that are underneath the magnetic field, which is administered by a coil positioned over the scalp (Bolognini and Ro 2010; Pascual-Leone et al., 2000; Miniussi et al., 2010;). In our study, high frequency repetitive TMS (rTMS) was applied over SI and SII during two tasks: a visual discrimination task involving tactile stimuli and a control visual discrimination task. The primary visual cortex (VI) was chosen as control area. We predicted that, if the somatosensory cortices selectively mediate visual functions in the tactile domain, rTMS over these areas may selectively interfere with the visual processing of tactile events.

## Materials and Method

### *Participants*

Ten healthy right-handed participated in the experiment (9 females and 1 male; mean age: 24 ± 3). All participants gave written informed consent. They were naïve to the experimental procedure and to the purpose of the study. Participants had no history of neurological, psychiatric, or other relevant medical problems, nor any contraindication to TMS (Rossi et al. 2009). The protocol was carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302: 1194) and was approved by the ethical committee at the University of Milano-Bicocca.

### *The Touch and No-Touch Tasks*

In both tasks, participants sat at a distance of 45 cm in front of a PC monitor (Samsung SyncMaster 1200NF). Subjects were shown video clips of the experimental conditions, which were displayed on a dark screen background with a luminance of 0.01 cd/m$^2$. All video clips depicted the index fingers of two hands, one in the left and one in the right side of the visual hemifield, each at 15 degrees of eccentricity from the central fixation point. During the video clips, only one index finger moved downward along the vertical dimension for 1 cm in the target trials, and for 0.50 cm in the catch trials. In the Touch task, a left hand on the left side and a right hand on the right side were presented below the fingers (see Figure 1-A). In this task, during the target trials, the video clip showed one of the (left or right) hand being touched by the index finger, whereas in the catch trials the finger simply approached the hand, without touching it. Instead, in the No-Touch task, no hands appeared below the index fingers, and thus the video clips showed only the left or right index finger moving downward to a different extent, making an identical motion to both the target trial and the catch trial of the Touch task. Therefore, in both experiments, the moving visual stimulus (i.e., the index finger) exhibited the same direction and amount of motion (duration 60 msec) across the observed actions. Noteworthy, the parameter determination for both tasks was guided by a series of preliminary behavioural experiments, in which we systematically change the size of the hand, the duration of the visual stimulus, the amount of the index finger's movement, and the direction of the movement, in order to opportunely increase the difficulty of the task and to obtain a mean performance accuracy of at least 90% in both tasks. Specifically, 10 different tasks were used, administered to a total of 28 subjects (mean age 25, ±1.5).

During the experimental session, subjects were required to look at a central fixation point. In the Touch task, subjects were asked to press the spacebar on the keyboard with their right index finger to report whether the visually presented moving finger had touched the hand below (target trial), regardless of the side on which the stimulus was presented, while refraining from pressing if the finger simply approached the hand without touching it (catch trial). During the No-Touch task, the participant's task was to discriminate the width of the finger's movement by pressing the response key (space bar) to report a greater shift of the finger (in the target trial this meant matching the extension of the movement of the touching finger of Touch task), and to refrain from responding to the smaller shift (in the catch trial this meant matching the extension of the movement of the catch trial from the Touch task).

For both tasks, 48 trials were presented: 12 target trials and 12 target-absent trials for each stimulus side (left vs. right hemifield). The inter-trial interval varied between 5 and 7 seconds, to prevent any TMS carry-over effects. The total duration of each task was about 10 minutes.

The sequence and timing of the video clips as well as the TMS pulses were under computer control (E-prime software, Psychology Software Tools, Inc., www.psychotoolbox.org).

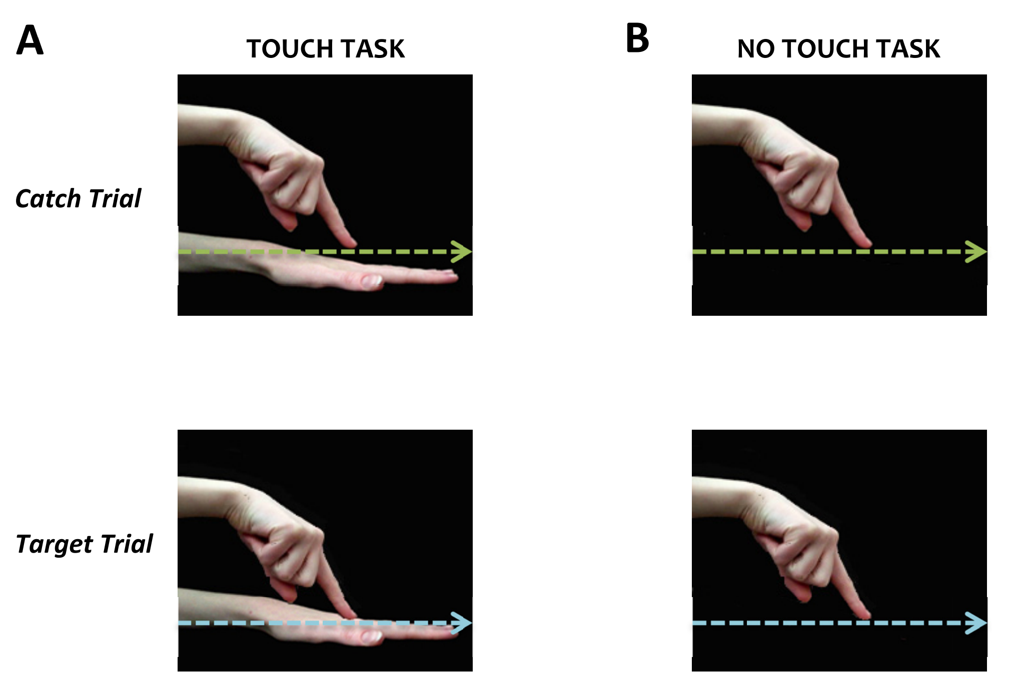

**Fig 1:** Stimuli used in the Touch Experiment **(A)** and in the No-Touch Experiment **(B).** The dashed lines represent the different movement amplitude in the target and catch trials. In both tasks the visual stimuli (video clips of the moving index finger) exhibited identical motion duration (60 ms) and amplitude across the observed actions

### *rTMS Protocol*

During the rTMS session, for both tasks, TMS pulses were delivered using a Super Rapid Transcranial Magnetic Stimulator (Magstim, Whitland, UK www.magstim.com) connected with a figure-of-eight coil (double 70 mm diameter), which allowed focal cortical stimulation (Wassermann et al., 2008).

Before the administering the task, the individual motor threshold (MT) at rest was determined for each participant by stimulating the hand area of the right motor cortex (M1). MT was defined as the minimum intensity that elicited detectable motor twitches in the digits of the resting left hand, i.e. a visible contraction during at least 3 out of 6 consecutive single TMS pulses. The mean MT was 55% ±10% of the maximal output of the stimulator.

For both tasks, the cortical areas targeted for stimulation were SI, SII and VI in the right hemisphere. The appropriate location for stimulating the SI hand area was identified for each subject as the site at which tactile extinction (i.e. failure to detect the contralateral stimulus when both hands are stimulated), or paraesthaesia, could be most readily obtained (see below). Before beginning the experimental task, the coil was moved approximately 2–4 cm posterior to the motor hotspot, until no detectable motor twitches occurred. In order to further confirm that this location was indeed within the SI hand area, the subject performed a tactile detection task while receiving single TMS pulses to SI (Bolognini and Maravita 2007; Fiorio and Haggard 2005). By moving the coil between trials, we were able to determine the optimal position and orientation of the coil at which the TMS most reliably interfered with the tactile detection task.

Custom-made electromagnetic solenoids (Heijo electronics, UK, www.heijo.com) attached to the participants' index fingers were used to deliver the tactile stimulations. Each subject was asked whether he or she felt a tactile stimulus on the left finger, right finger, or both fingers (10 trials for each stimulus location, plus 10 catch trials during which no tactile stimuli was presented). For each trial, a single TMS pulse, at 110% of MT intensity, was presented exactly 20 msec after the tactile stimulus, at which time we predicted it might disrupt tactile detection (Cohen et al., 1991; Harris et al., 2002). During TMS stimulation, almost every subject reported paraesthesia to the contralateral (left) hand. Seven subjects out of ten reported a deficit in detecting the contralateral-left tactile stimulus; the mean percentage of unfelt left stimuli during bilateral stimulation was 26%. These data provide independent confirmation that the scalp position chosen for the experiments was indeed over the somatosensory hand area.

The stimulation location corresponding to SII was localized 2.5 cm anterior and 6.5 cm superior to the periauricular point, in accord with previous TMS studies (Harris et al., 2002; Kanda et al., 2003). Finally, the stimulation location corresponding to VI was 2 cm dorsal and 0.6 cm lateral to the calcarine sulcus (Bolognini and Maravita 2007; Fernandez et al., 2002;).

Additionally, to check for mislocalisation, we also localized the targeted areas using the SofTaxic Evolution Navigator system (E.M.S., Bologna, Italy, www.emsmedical.net). With this system we further checked, for each subject, the Talairach coordinates of SI and SII (Talairach and Tournoux 1988), as reported in a previous fMRI study (Schaefer et al., 2005): right SI, X = 44, Y = -16, Z = 42; right SII, X = 66, Y = -12, Z = 22. The Talairach coordinates of the right VI were (on average) X = 19, Y = -97, Z = 1 (Talairach and Tournoux 1988).

After localizing each area over the scalp, the coil was positioned on the appropriate stimulation site during each experimental session and was held in place by a mechanical device.

During the rTMS sessions, rTMS was delivered as a train of three pulses at a frequency of 13 Hz (i.e., at 0-75-150 ms with respect to the onset of the visual stimulus). The stimulus intensity used during all the experiments was set at 110% of the individual MT. These parameters are consistent with safety recommendations for rTMS (Rossi et al., 2009) (see Figure 2). Participants tolerated the rTMS well and did not report any adverse effects.

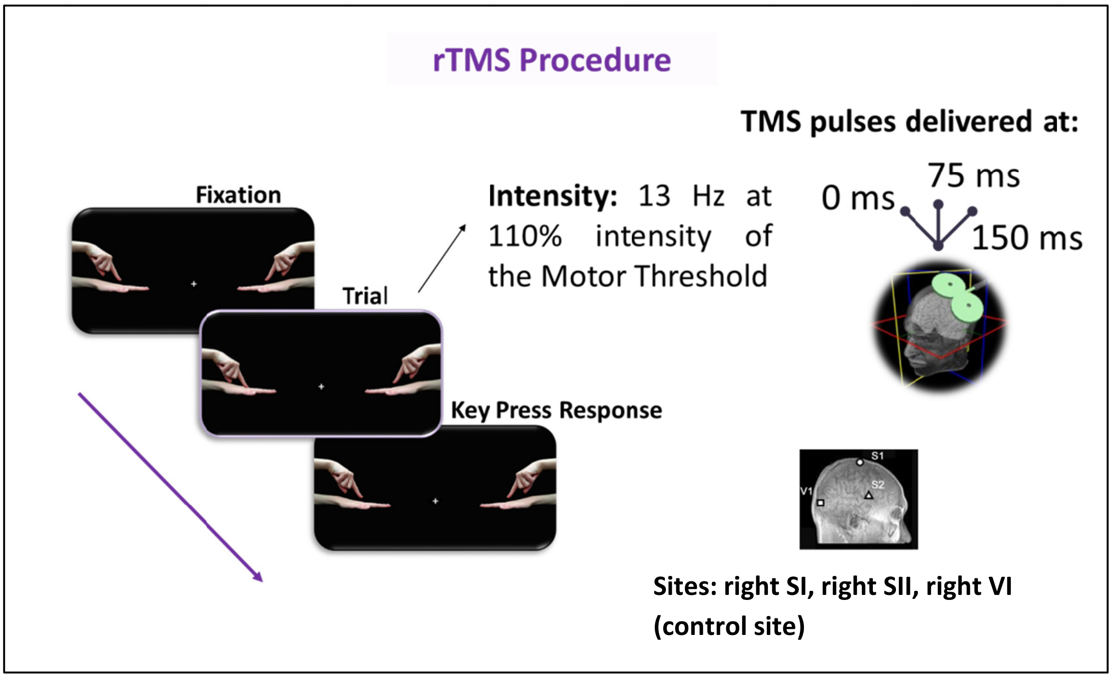

**Fig 2:** Sequence of events in the rTMS Session. Each trial started with the presentation of a central fixation cross. After at least 5 sec the video clip started. At its onset, rTMS (at 13 Hz) was delivered over one of the targeted areas (i.e. SI, SII, VI, in the right hemisphere). In the Touch Task, subjects were asked to indicate by pressing the response key whether the moving finger has touched the hand below (target trial), while refraining from pressing if the finger approached the hand, without touching it (catch trial). In the No-Touch task, subject were asked to discriminate the range of the finger's movement by pressing the response key to report the greater drop of the finger (target trial), and refrain from responding to the smaller drop (catch trial).

### *Experimental Procedure*

Throughout the experiment, subjects were comfortably seated in an armchair, in a quiet, dimly illuminated room. The experiment comprised ten sessions: a training session and four experimental sessions for each task. The training session preceded the experimental protocol and allowed participants to become familiar with the tasks. Verbal feedback was given concerning the subject's performance after each trial during the training phase only.

The experimental sessions consisted of a baseline session, during which no rTMS stimuli were delivered, followed by the three rTMS sessions (i.e., SI-rTMS, SII-rTMS and VI-rTMS).

The duration of every session was approximately 10 min, and consequently the entire procedure lasted about 2 hours per subject. Between the sessions, subjects were allowed to rest and enjoy light refreshments. The order of the two tasks in each experimental session, and that of the experimental sessions was counterbalanced across participants.

### *Statistical Analysis*

Statistical analysis was performed using Statistica for Windows, release 6.0 (StatSoft). A first analysis was conducted on the mean percentage of errors (i.e., target omissions in target trials plus false alarms in catch trials) through a repeated-measures Analysis of Variance (ANOVA) with Task (Touch vs. No-Touch), Session (Baseline, SI-rTMS, SII-rTMS, VI-rTMS), and Side (Left- vs. Right-sided stimuli, i.e., contralateral and ipsilateral to the TMS side) as within-subjects factors.

In addition, to separate genuine rTMS effects on perceptual sensitivity from changes in the response criterion, we then computed psychophysical indices derived from Signal Detection Theory (Green and Swets 1966). This is a particularly relevant issue in the present context, since rTMS delivered during the tasks might affect response accuracy by simply biasing the response criterion adopted by subjects. In this respect, the use of a rigorous psychophysical approach allows us to discern the stimulus-related (i.e., perceptual sensitivity, *d'*) and subject-related (i.e., response bias, *c*) rTMS influences on visual performance (Green and Swets 1966). Here changes in sensitivity (d' values) and in the response criterion (c values) were quantified for every experimental condition. Analyses of sensitivity and response bias were then performed via two (Task) by four (Session) by two (Side) ANOVAs. When appropriate, pairwise comparisons were done with the Newman-Keuls test.

Finally, we measured the effect size in the ANOVAs, by calculating the partial Eta Squared ($p\eta^2$), which measures the degree of association between an effect and the dependent variable, namely the proportion of the total variance that is attributable to a main factor or to an interaction (Cohen 1973).

## Results

The ANOVA results on error rate revealed a significant main effect only of the factor Session ($F_{3,27} = 3.86$, $p < 0.02$, $p\eta^2 = 0.30$), because errors increased when rTMS was delivered to SII (20%, $P < 0.03$) as compared to all the other experimental sessions: Baseline = 15%, SI-rTMS = 14%, VI-rTMS = 15% (see Fig. 3). No other significant effect was found.

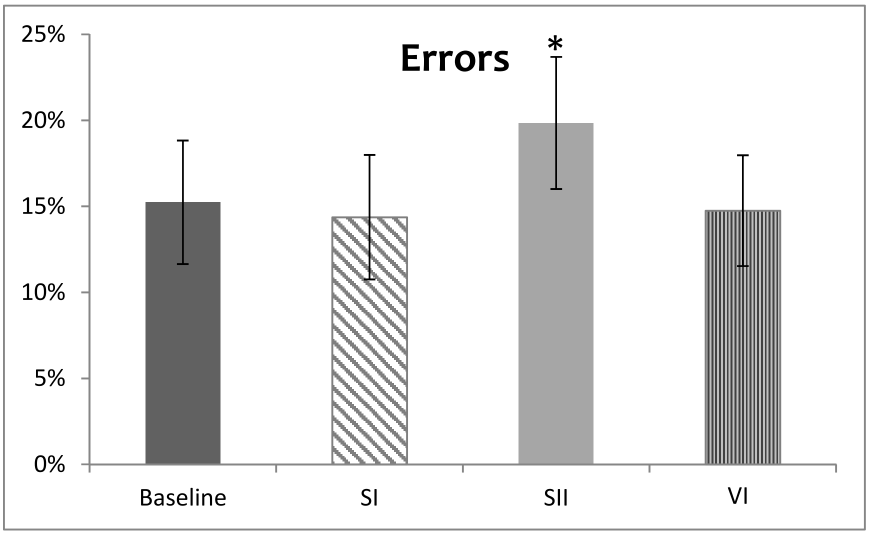

**Fig 3:** rTMS effects on behavior. Mean error rate in each experimental session. Asterisks indicate a significant rTMS effect. Error bars= standard error (S.E.)

The analysis of sensitivity (*d'*) showed a significant main effect of Session ($F_{3,27} = 3.48$, $p < 0.03$, $p\eta^2 = 0.28$), showing a significant difference only between the Baseline (3.08) and SII-rTMS (2.54, $p < 0.02$) (SI-rTMS = 2.78, $p = 0.2$; VI- rTMS = 2.79, $p = 0.09$ as compared to Baseline).

Of major interest was the significant interaction Task by Session by Side ($F_{3,27} = 4.15$, $p < 0.02$, $p\eta^2=0.32$) which highlighted the selectivity of the rTMS effect. To explore this interaction, we conducted separate 3-way ANOVAs for each stimulated area (i.e., SI, SII, VI), with Task (Touch vs. No-Touch), Session (Baseline vs. rTMS), and Side (Left- vs. Right-sided stimuli) as main factors. Only the ANOVA for SI-rTMS showed a significant Task X Session X Side interaction ($F_{1,9} = 4.88$, $p < 0.05$): as compared to the Baseline, there was a selective decrement of perceptual sensitivity in the Touch task by rTMS; crucially, this disruptive effect was specific for the processing of contralateral, left-sided visual stimuli depicting touches (2.23), as compared to left-sided touching stimuli in the Baseline (3.36, $p < 0.02$). Additionally, in the SI-rTMS session there was a significant difference between left-sided and right-sided stimuli in the Touch task ($p < 0.05$), and between left-sided t stimuli and left-sided no-touching stimuli (3.29, $p < 0.03$). Instead, sensitivity for left-sided and right-sided stimuli did not differ in the No-Touch task in the SI-rTMS session ($p = 0.07$), nor they differed from the same conditions of the baseline ($p = 0.07$) (see Fig. 4). For SII-rTMS there was only a main effect of Session ($F_{1,9} = 5.38$, $p < 0.05$), showing a significant difference between the performance in during SII-rTMS and in Baseline irrespective of side or task. For VI-rTMS, no effect reached significance ($p = 0.2$).

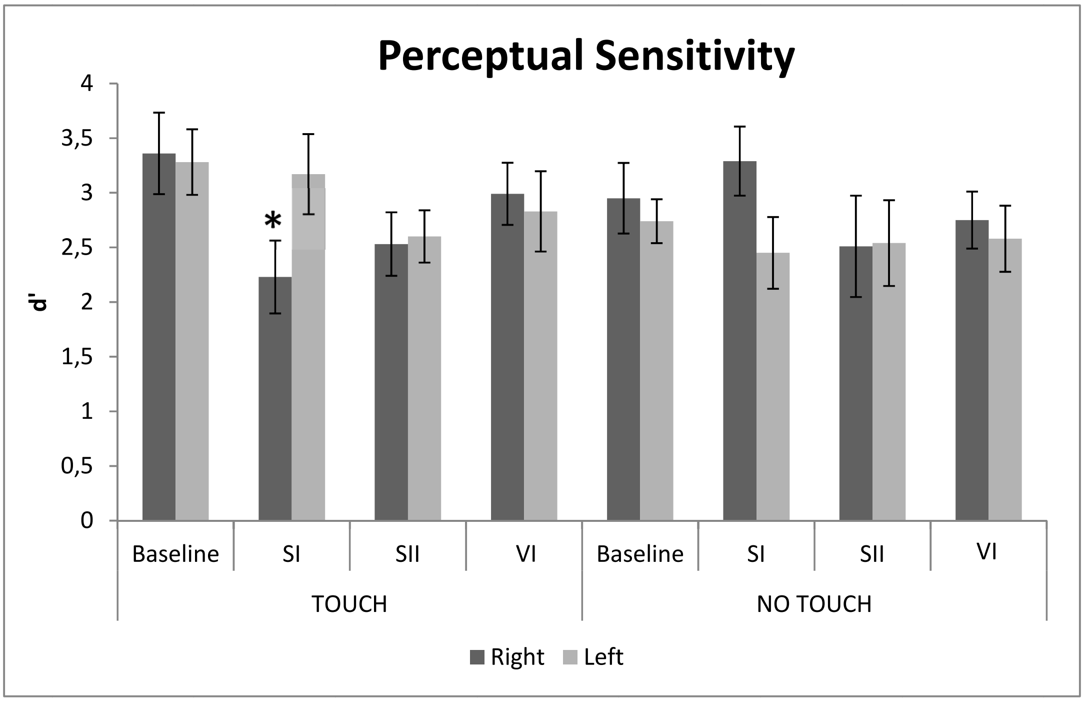

**Fig 4:** rTMS effects on behavior. Mean d′ values in each experimental condition. Asterisks indicate a significant rTMS effect. Error bars= S.E.

Finally, the analysis of the response criterion (*c*) showed a main effect of Task ($F_{1,9}$ = 12.22, p < 0.01, $p\eta^2$ = 0.58), with significantly lower c values for the Touch Task (0.25) as compared to the No-Touch task (0.60). This decrease in criterion value reflects a more liberal response criterion, with subjects more likely to report the target stimulus. A significant main effect of Session was also found ($F_{3,27}$ =4.30, p < 0.01, $p\eta^2$ = 0.32), again showing a significant decrease of the response criterion in the VI-rTMS session (0.23), as compared only to the Baseline (0.68, P < 0.01). A marginally significant difference was found between the Baseline and SII-rTMS (0.42, p = 0.056) and, to a lesser extent, with respect to SI-rTMS (0.38, p = 0.07). Other effects did not reach significance.

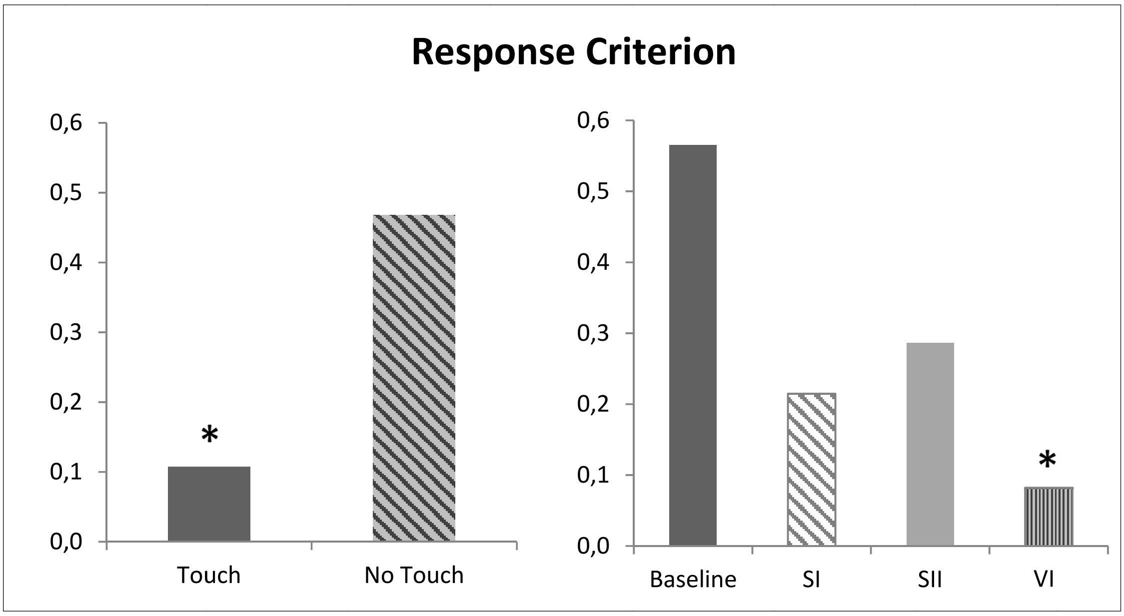

**Fig 5:** rTMS effects on behavior. Mean *c* values. Asterisks indicate a significant rTMS effect. Error bars= S.E.

## Discussion

The present study investigated the causal involvement of the human somatosensory cortices, namely SI and SII, in the visual processing of tactile events. A growing body of brain imaging evidence supports the existence of a somatosensory mirror neuron system in the human brain which matches observed and felt touch (Keysers et al., 2010). Here, I provide a direct evidence that SI and SII are activated as a result of visual input, namely during observation a human body being touched. The more critical and original result of this study is the selective impairment of visual processing of touch due to the disruption of SI activity. Indeed interfering with the activity of SI with rTMS selectively reduced visual perceptual sensitivity, as demonstrated by the decrease of d' values, for contralateral visual stimuli depicting a tactile stimulation. The interference of SI was selective for the task, given that lower performance were yielded only for events involving a tactile component (i.e., Touch Task), as well as for the side of the touching stimuli, as it affected only the perception of the contralateral (i.e., left-sided) touch stimuli. Moreover, the rTMS effect was evident only at the perceptual level, as no significant change in the response criterion or in the error rate was found in the SI-rTMS session.

Moreover, we found that rTMS over SII produced a non-specific impairment in detecting visual stimuli depicting hand movements. This effect occurred regardless of the experimental task (i.e., Touch and No-Touch) or the stimulated visual hemifield (i.e., ipsilateral or contralateral to the site of rTMS). Specifically, rTMS over SII significantly reduced the accuracy when subjects had to detect whether a left-sided or right-sided hand was touched by an approaching finger (Touch Task) and also when they were asked to discriminate the width of a finger's movement when touch was absent (No-Touch Task). This impairment of accuracy was accompanied by a significant decrement in perceptual sensitivity (i.e., lower d' values) and by a nearly significant response bias (i.e., lower c values). This last post-perceptual effect reflects a change in the response criterion adopted by subjects during SII-rTMS. Finally, the stimulation of VI affected a post-perceptual level of visual processing, biasing subjects' responses in every experimental condition, regardless of experimental task or stimulus side. Although occipital TMS typically induces a visual suppression in perceptual tasks (Amassian et al., 1989) here we did not observe any significant impairment of visual perception due to VI stimulation, although an overall decrement of perceptual sensitivity was highly consistent across all the VI-rTMS sessions. However, it is noteworthy that in both of our tasks the visual stimuli depicted a moving hand; in this regard, it should be noted that human actions with implied motion are preferentially processed by the visual motion area V5/MT, rather than by VI (Proverbio et al. 2009).

Regarding our pivotal finding, results indicate that SI, but not SII, is causally and specifically related to the processing of observed touch. Indeed, SI-rTMS selectively impaired the visual processing of contralateral stimuli depicting touch at the perceptual level. This effect was both task and spatially specific. This result is in line with most of the neuroimaging studies of the mirror-touch system, showing a preferential activation of SI when viewing a human touch, as compared to a no-touch condition (Kuehn et al., 2013; Schaefer et al., 2005, 2009), or to the view of an object being touched (e.g. Blakemore et al., 2005). Moreover the hemispheric lateralization in SI that occurred when being touched on one side is also present when observing touch events involving the same side (Blakemore et al., 2005; Schaefer et al., 2009); this is broadly consistent with our finding of a contralateral visual impairment for the sight of a hand being touched during unilateral SI-rTMS.

Evidence for a causal role of human SI in visuo-tactile processing related to the body was recently provided by Fiorio and Haggard (2005) with respect to a particular crossmodal phenomenon, known as the “Visual Enhancement of Touch” (VET). The VET consisted in the enhancement of tactile processing induced by viewing the body

(Kennett et al., 2001; Press et al., 2004; Taylor-Clarke et al., 2002). Fiorio and Haggard showed that the VET can be reduced through the use of TMS over SI, but not SII. This suggests that observing the body may act at an early stage in stimulus elaboration and perception, allowing for an anticipatory tuning of the SI neural circuits that underlie tactile processing (Fiorio and Haggard, 2005). The result of my experiment represent an advance, since I show that SI can process visually presented touches even when concurrent tactile stimulation is not present, suggesting the existence of some form of purely visual processing in SI. In this context, the present study provides novel evidence for a crossmodal role of SI in the visual perception of tactile events. Therefore SI traditionally considered a low-level unimodal area, actually displays multisensory properties (Macaluso 2006).

Beyond the evidence for a crossmodal activation of SI, brain imaging studies have also showed that SI might have mirror proprieties. As discussed in Chapter 1.1, action observation and execution increases neural activity in both motor and somatosensory areas (Rizzolatti and Craighero, 2004). Crucially, making the perceived action painful or more salient from a tactile or proprioceptive point of view causes an increase of the activity in SI (Betti et al., 2009; Bufalari et al., 2007; Costantini et al., 2005). More recently, a study (Avenanti et al., 2007) demonstrated that TMS over SI selectively reduced the typical corticospinal mapping of biomechanically impossible movements (Fadiga et al., 1995, 2005), which were associated with aversive somatic feelings, without impacting mirror responses to possible movements that did not evoke somatic feelings in the observer. Modulation of SI activity that is contingent upon observation of others' pain has also been described (Betti et al., 2009; Bufalari et al., 2007). Therefore, it seems that the mirror function of SI is that of preferentially encoding the somatic component of action simulation. Moreover, fMRI evidence (Ebisch et al., 2008; Schaefer et al., 2012b; 2013) also enlightened that SI activity increased in response to observing passive touch. In particular, this pattern of activation was localized in posterior parts of SI and was hampered when observing another person being touched. Self-related observed touch, in contrast, caused no significant activity changes within posterior SI. This data support the existence of a system for sharing tactile experiences with others, located in the caudal part of SI (Kuehn et al., 2013).

Regarding the contralateral effect of SI-rTMS during visual processing of touch events, there are two possible explanations for this side effect. The first rests on the assumption that visual stimuli presented in the left hemifield should be related to contralateral, right hemisphere processing; this hemifield effect should be independent of the type (left or right) of viewed hands. The alternative interpretation is related more to 'mirroring' theories, as our left hemifield stimuli depicted a left hand (egocentric perspective) being touched by a left index finger (allocentric perspective). In this view, the side-specific rTMS effect might suggest a 'resonance' with the experience of the person being touched. In this regard, previous evidence showed that each hemisphere is more strongly activated when viewing actions conducted by a model's contralateral hand than when viewing actions conducted by an ipsilateral hand

(Aziz-Zadeh et al. 2002), and mirror activations by the sight of touch are somatotopically organized, following the sensory homunculus magnification in SI (Blakemore et al., 2005; Schaefer, et al., 2009). Even in synaesthesic subjects there is often an anatomical mapping in which, for instance, the observed touch to a left cheek is felt on their left cheek and activates the right SI (Blakemore et al., 2005; Holle et al., 2011). Through this anatomical mapping, SI may convey a simulation of the precise body location at which the touch occurred, hence providing somatotopically specific representations of other people's somatosensations.

With respect to SII-rTMS effects, we found a significant perceptual impairment for detecting stimuli depicting a moving hand, regardless of the presence of a tactile component and the side (ipsilateral or contralateral) of the stimulus. Therefore, in contrast with SI, SII activity appears not to be specific for the visual perception of touches. This result is in broader agreement with fMRI reports, showing the recruitment of SII during action observations. As mentioned above, a simultaneous motor as well as somatosensory mapping of actions takes place in the parietal node of the mirror motor system (Avikainen et al., 2002; Costantini et al., 2005; Gazzola and Keysers, 2009). Most important for the present study, the somatic components of observed actions are encoded primarily in parietal areas, including SII, rather than in the frontal node of the mirror system (Avenanti et al., 2007; Avikainen et al., 2002; Gazzola and Keysers, 2009; Gazzola et al., 2007b; Grèzes et al., 2003; Hari et al., 1998). In both of our tasks (i.e., Touch and No-Touch), the video clips always depicted a moving hand. In this context, our SII effect would reflect an associative visuo-kinaesthetic function evoked by the perception of human hand movements in the video clips, instead of being specifically related to the sight of touch. Finally, bilateral activation of SII occurred during both the sight of touch as well as during action observation (Avikainen et al., 2002; Blakemore et al., 2005; Ebisch et al., 2008; Keysers et al., 2004), which is consistent with our observation of a bilateral impairment induced by SII-rTMS and with the existence of the bilateral receptive fields of SII cells (Iwamura 1998, 2000).

Summing up, this study provides novel evidence for a mirror system for touch observation, i.e. the mirror-touch system, while clarifying the functional significance of the cortical somatosensory activations that sub-serve the ability to process the sight of touch. The present study indicates that SI and SII are both part of a multimodal sensory-motor system with mirror properties, where somatic and visual properties of action converge. However, only SI, which seems to be involved in the visual processing of touch.

## *2.2 Experiments 2-3: The role of SI in discriminating biological vs. inanimate touch*

### Aim of the study

In the following experiments I have further investigated the functional involvement of SI in the visual processing of touch, in particular by exploring whether SI is involved in the visual processing of 'any' touch, or whether it exclusively pertains to the domain of human touch. In everyday life, the experience of touch is not entirely restricted to human interactions; rather, we frequently observe events that involve contact between the body and an object (e.g. hair-brushing) or between inanimate objects (e.g. an accident between cars). To date, brain imaging studies have provided controversial results regarding the involvement of SI in touch observation. There is evidence suggesting that the activation of a visuo-tactile mirroring mechanism might underpin an abstract notion of touch; in this view, biological as well as inanimate stimuli are both able to activate a shared neural circuitry for touch by vision (Ebisch et al., 2008). On the other hand, other studies suggest that somatosensory cortices are preferentially activated by the sight of social touch (i.e. tactile interactions between persons) and, more generally, when the target of the action is biological, rather than inanimate (Blakemore et al., 2005; Tai et al., 2004). In this context, the present study aims at clarifying the selectivity of the visual responses in SI to the sight of tactile events, investigated whether SI activation is restricted to the visual processing of human body-parts contact, or whether it can also play a role in processing contact between inanimate objects (Experiment 2), or between human body-parts and objects (Experiment 3).

### 2.2.1 Experiment 2: Human-to-Human Vs Object-to-Object touch

#### Materials and Method

*Participants*

12 healthy participants took part in the study (11 right-handed; 10 females; mean age: 23 ±4). All participants gave written informed consent. They were naïve to the experimental procedure and to the purpose of the study. None of the participants had neurological, psychiatric, or other relevant medical problems, nor any contraindication to TMS (Rossi et al. 2009). The protocol was carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302: 1194) and was approved by the ethical committee at the University of Milano-Bicocca.

*Tasks: Human-to-Human Touch and Object-to-Object Touch*

Two visual detection tasks were given to subjects. As in the previous experiment, during both tasks, subjects sat at a distance of 45 cm in front of a PC monitor (Samsung SyncMaster 1200NF), and they were shown video clips of the experimental conditions on a dark screen background (luminance= 0.01 cd/m$^2$). The first task, here named Human-to-Human Touch task, corresponded to the Touch task of the previous experiment, where video clips showed an left-sided or a right-sided index fingers touching the below hand (see above). Instead, in Object-to-Object Touch task, the video clip depicted two leaves, one in the left hemifield and one in the right hemifield, at 15° of eccentricity from the central fixation point. Two wooden sticks were presented below the leaves, one at each side (Fig.6b). The shape and size of the leaves and sticks broadly match with shape and size of the fingers and hands of the Human-to-Human Touch task. Now, during the video clips the target trials showed one leaf moving downward and making contact with the stick, while the catch trial showed the leaf approaching the stick by moving downward for 0.5 cm, without making any contact with it. In both tasks, the moving visual stimulus exhibited the same direction (vertical) and amount of motion across conditions (see above, 2.1 for details).

Subject were asked to look at the fixation point, and to press, with their right index finger, the spacebar on the keyboard to report whether the moving visual stimulus (finger or leaf) had touched the stimulus below (hand or stick, i.e., target trial), regardless of the side on which the stimulus was presented. Furthermore, subjects were instructed to refrain from responding if the moving stimulus simply approached, but did not touch, the stimulus below (catch trial).

In each task, 48 trials were presented: 12 target trials and 12 target-absent trials for each stimulus side (left vs. right). The inter-trial interval varied between 5 and 7 seconds, to prevent any TMS carry-over effects. The total duration of each task was about 10 minutes.

Sequence and timing of the video clips and the TMS pulses were under computer control (E-prime software, Psychology Software Tools Inc.).

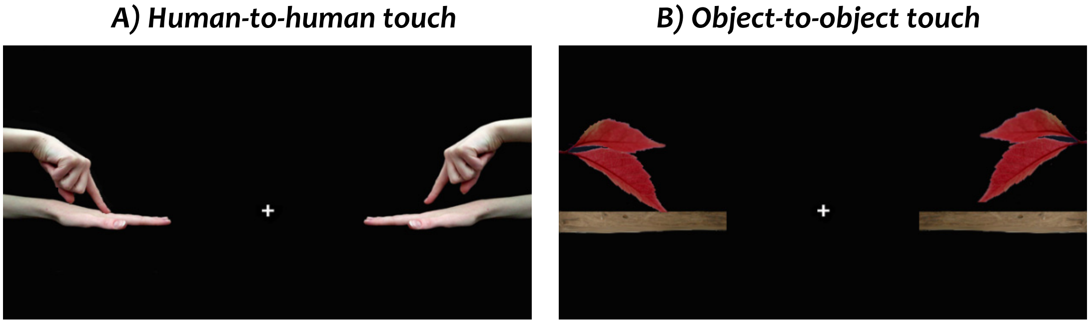

**Fig 6.** Stimuli used in the visual detection tasks; in each picture, the target trial depicting a left-sided touching stimulus is shown for example.

*TMS Protocol*

The TMS protocol is identical to Experiment 1. Given the previous results, showing that SI, but not, SII is selectively involved in visual processing of touch, in this experiment we only stimulated SI; VI was again our control area.

With respect to the functional localization of SI, almost every subject reported paraesthesia to the contralateral (left) hand during the stimulation of the SI area; 9 subjects out of 12 reported a deficit in detecting the contralateral-left tactile stimulus in bilateral trials (omissions: 13%).

*Experimental Procedure*

Throughout the experiment, subjects were comfortably seated in an armchair, in a quiet, dimly illuminated room. The experiment comprised four sessions for each of the two tasks: a training session, followed by three experimental sessions. The experimental sessions consisted of a baseline and two rTMS sessions (SI-rTMS, VI-rTMS). The order of the two tasks and that of the three experimental sessions for each task was counterbalanced across participants. The entire procedure lasted about 2 hours.

In this study, after the experiment, a questionnaire was administered to measure how participants interpreted the visual stimuli. The items were as follows:

1. “The tactile stimulation looked like to be very intense”
2. “The tactile stimulation looked like to be very unpleasant”
3. “The hand being touched could depict my hand”
4. “The touching finger could depict my finger”
5. “The touched hand and the touching finger belonged to different persons”

Items 1-2 were given for both Human-to-Human and Object-to-Object Touch tasks; items 3-4-5 were given only for the Human-to-Human Touch task. For every item, participants rated their agreement using a 5-point Likert scale, where +2 indicating “strongly agree”, -2 “strongly disagree”, and 0 “neither agree nor disagree,” although intermediate values (+/-1) could be used. Therefore, values above zero indicate agreement, whereas values below zero indicate disagreement.

*Statistical analysis*

Statistical analysis was performed using Statistica for Windows, release 6.0 (StatSoft). The mean percentage of errors (i.e., target omissions plus false alarms), perceptual sensitivity (d') and response criterion (c) were analysed via a repeated-measures

ANOVA with Task (Human-to-Human Touch vs. Object-to-Object Touch), Session (Baseline, SI-rTMS, VI-rTMS) and Side (Left-sided vs. Right-sided stimuli) as main factors. When appropriate, pairwise comparisons were calculated using the Newman-Keuls test.

Finally, for each task, the subjective ratings at each item of the questionnaire were analysed by comparing the mean score versus 0 using *t*-tests.

## Results

With respect to the errors, the ANOVA revealed a significant effect of Task ($F_{1,11} = 11.84$, $p < 0.01$, $p\eta^2 = 0.52$), as subjects overall committed more errors in the Object-to-Object Touch task (26%) than in the Human-to-Human Touch task (19%). Moreover, the significant Session by Side interaction ($F_{2,22} = 3.58$, $p < 0.05$, $p\eta^2 = 0.25$) showed a significant difference between left-sided (24% of errors) and right-sided (19% of errors, $p < 0.05$) stimuli only when rTMS was delivered on SI. Other effects did not reach significance: Session ($F_{2,22} = 2.37$, $p = 0.1$), Side ($F_{1,11} = 0.04$, $p = 0.8$), Task by Session ($F_{2,22} = 0.71$, $p = 0.5$), Task by Side ($F_{1,11} = 1.27$, $p = 0.3$), Task by Session by Side ($F_{2,22} = 2.52$ $p = 0.1$) (Fig. 7).

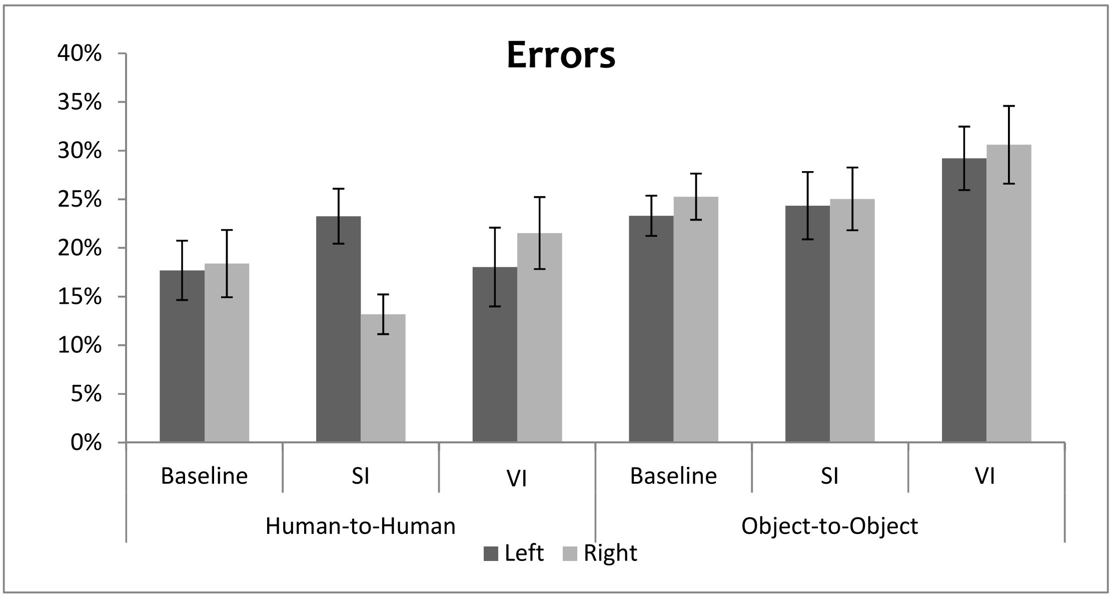

**Fig 7:** rTMS effects on behavior. Mean error rate in each experimental condition. Error bars= S.E.

Of major interest were the findings from the analysis of perceptual sensitivity (d') (Fig. 8). First, we found a significant Session by Side interaction ($F_{2,22} = 4.09$, $p < 0.03$, $p\eta^2 = 0.27$), showing a significant difference between left-sided (1.7) and right-sided (2.2, $p < 0.05$) stimuli only in the SI-rTMS session. Crucially, the significant Task by Session by Side interaction ($F_{2,22} = 4.62$, $p < 0.02$, $p\eta^2 = 0.42$) highlighted the selectivity of the rTMS interference. Other effects did not reach significance: Task ($F_{1,11} = 3.87$, $p = 0.08$), Session ($F_{2,22} = 0.35$, $p = 0.7$), Side ($F_{1,11} = 0.04$, $p = 0.8$), Task by Session ($F_{2,22} = 0.97$, $p = 0.4$), Task by Side ($F_{1,11} = 1.21$, $p = 0.7$).

To explore the Task by Session by Side interaction, we conducted separate two-ways ANOVAs for each task, with Session and Side as the main factors. The ANOVA for the Human-to-Human Touch task showed only a significant Session by Side interaction ($F_{2,22}$

= 7.21, $p < 0.01$, $p\eta^2 = 0.40$). Post-hoc comparisons showed a reduction of sensitivity for left-sided stimuli as compared with right- sided stimuli only in the SI-rTMS session ($p < 0.03$). Moreover, left- sided stimuli in the SI-rTMS session (1.55) were significantly different from left-sided stimuli in Baseline (2.38, $P < 0.05$) and in VI-rTMS (2.5, $p < 0.3$) sessions. Additionally, for the Human-to-Human Touch task, the one-way ANOVA with Session as main factor on the responses to contralateral, left- sided visual stimuli showed a significant effect ($F_{2,22} = 4.58$, $p < 0.02$, $p\eta^2 = 0.3$). Post-hoc comparisons showed a decrease of d' values during SI-rTMS (1.55), as compared to both the Baseline (2.38, $p < 0.02$) and the VI-rTMS session (2.5, $p < 0.03$). The same ANOVA model on the responses to ipsilateral, right- sided visual stimuli did not show a significant effect of Session (F2,22 = 1.49, P = 0.2, $p\eta^2 = 0.12$) (see Fig. 8).

The ANOVA for the Object-to-Object Touch task did not show any significant effect ($p > 0.3$).

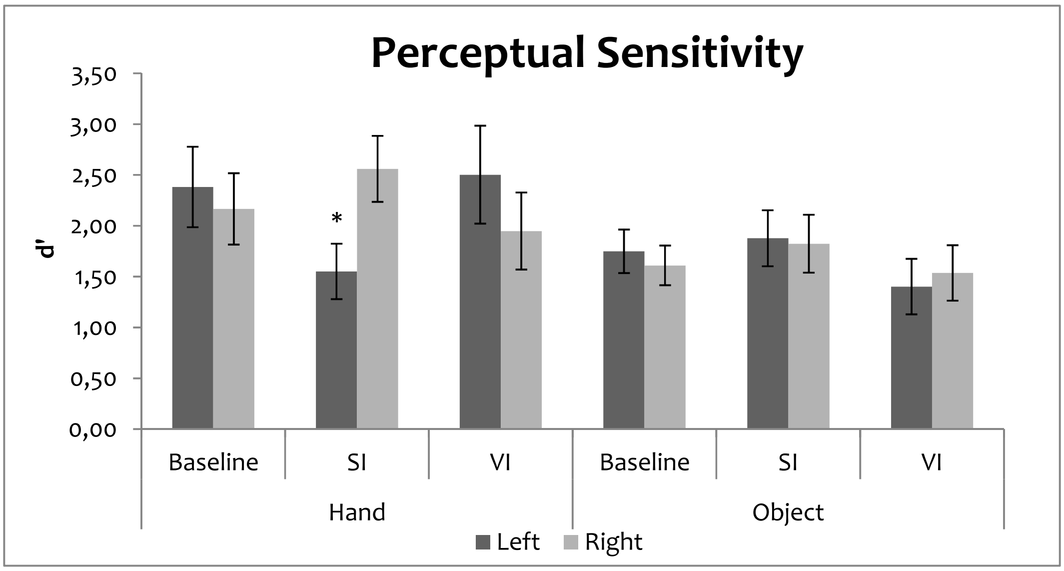

**Fig. 8.** rTMS effects on behavior. Mean d' values for the sensitivity in each experimental condition.

Analysis of response bias (c) did not show any significant effect: Task ($F_{1,11} = 1.94$, $p = 0.2$), Session ($F_{2,22} = 2.01$, $p = 0.2$), Side ($F_{1,11} = 0.01$, $p = 0.9$), Task by Session ($F_{2,22} = 1.15$, $p = 0.3$), Task by Side ($F_{1,11} = 1.62$, $P = 0.2$), Session by Side ($F_{2,22} = 0.12$, $p = 0.9$), Task by Session by Side ($F_{2,22} = 0.12$, $p = 0.8$) (see Fig. 9).

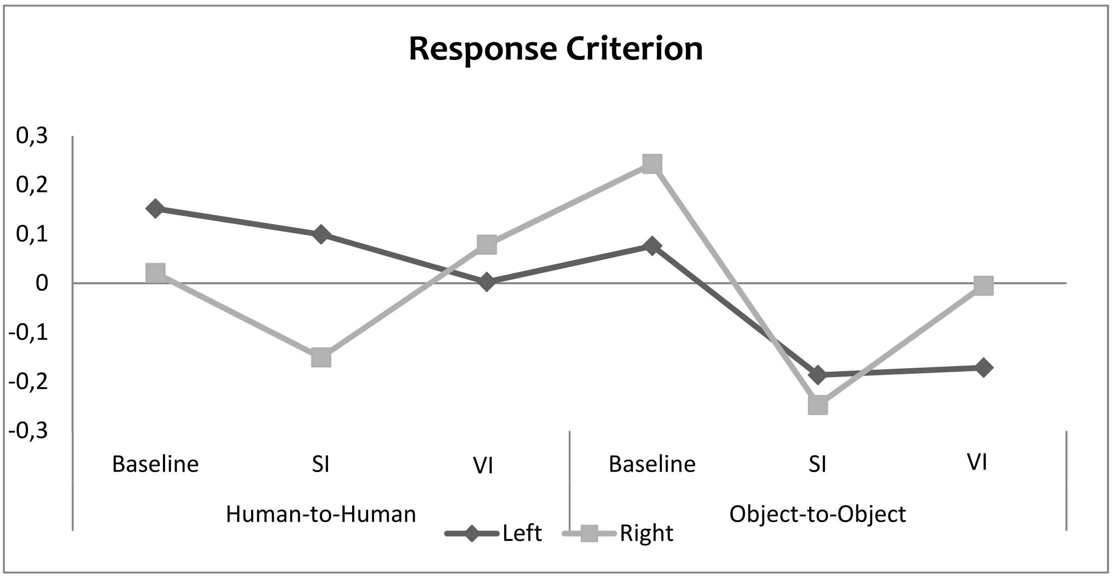

**Fig 9** rTMS effects on behavior. Mean c values for the response criterion. Error bars = S.E.

*Subjective Reports and Correlation analysis*

With respect to the subjective reports at the questionnaire assessing how the subjects judge the visual stimuli, the analysis shows that participants agreed that the Human-to-Human Touch seemed quite intense (0.64, $t_{11} = 2.32$, $p < 0.04$), but disagreed that it was unpleasant (-1.45, $t_{11} = -5.88$, $p < 0.01$). Additionally, they agreed that ‘The touched hand and the touching finger belonged to different persons’ (1.36, $t_{11} = 3.75$, $p < 0.01$), and consequently they disagreed that the touching index depicted their own finger (-0.58,

$t_{11} = -3.02$, $p < 0.01$); finally, they agreed that the hand being touched could represent their own hand (0.75, $t_{11} = 2.32$, $p < 0.04$). Subjects did not rate the Object-to-Object Touch as intense (-1.27, $t_{11} = -4.66$, $p < 0.01$) or unpleasant (-1.55, $t_{11} = -7.45$, $p < 0.01$).

To assess whether the SI-rTMS-induced interference was associated with the subjective reports, Pearson's correlation analyses were performed between the SI-rTMS effect, namely the difference between d' values for left-sided stimuli in the Baseline and in the SI-rTMS session (i.e. SI-rTMS minus Baseline, with negative values indicating a decrease of sensitivity during the stimulation of SI) and VAS ratings of intensity, pleasant and self-related touch. The SI-rTMS interference was significantly associated with VAS intensity ($r = -0.65$, $p < 0.02$) and with the report that the touched hand could represent the participant's own hand ($r = -0.77$, $p < 0.03$). No other significant correlation was found (VAS unpleasantness, $p = 0.2$; touching finger representing the participant's own finger, $p = 0.2$; hands belonging to different persons, $p = 0.6$).

### 2.2.2 Experiment 3: Human-to-Object and Object–to-Human Touch.

#### Matherials and method

*Participants*

12 participants (right-handed= 11; mean age= 25 ±3), selected using the same criteria of Experiment 2a.

*Task, procedure, and statistical analyses*

The tasks, the experimental setting and the statistical analysis were the same to those of Experiment 2, the only difference was related to the visual stimuli. In the Human-to-Object Touch task (Fig. 10.A) , the video clips depicted the right or the left index finger moving downward and touching the stick below, or simply approaching the stick, without touching it (target and catch trials, respectively). In the Object-to-Human Touch task (Fig 10.B), the video clips shows the left or the right stick moving downward and touching the hand below, or approaching without touching it (target and catch trials, respectively).

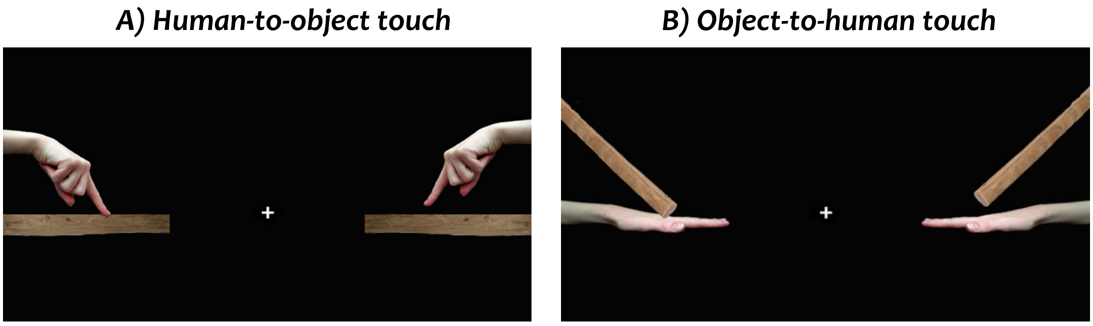

**Fig 10** Stimuli used in the visual detection tasks; in each picture, the target trial depicting a left-sided touching stimulus is shown for example.

The TMS procedure was identical to Experiment 2a, but now only SI cortex was stimulated. The mean individual MT at rest was 58% ± 7.8% of the maximal output of the stimulator. Analyses of errors, sensitivity and response bias were performed via a 2 (Task: Human-to-Object, Object-to-Human) by 2 (Session: Baseline, SI-rTMS) by 2 (Side: Left-, Right-sided stimuli) ANOVA.

The questionnaire for Experiment 2 comprised the following items:

1. “The tactile stimulation looked like to be very intense”
2. “The tactile stimulation looked like to be very unpleasant”
3. “The hand being touched could depict my hand”
4. “The touching finger could depict my finger”

Items 1-2 were given for both Human-to-Object and Object-to-Human Touch tasks; item 3 was given for the Object-to-human Touch task, while item 4 was given for the Human-to-object Touch task. For every item, participants rated their agreement using a 5-point scale (see above, Experiment 2).

**Results**

The analysis of the errors showed a significant effect of the Task ($F_{1,11}$= 7.88, $p < 0.02$, $p\eta^2 = 0.71$), showing that subjects made more errors in the Human-to-Object Touch task (19%), as compared to the Object-to-Human Touch task (15%). The main effect of Session ($F_{1,11}$= 6.76, $p < 0.02$, $p\eta^2 = 0.31$) showed that the errors were slightly higher in the Baseline (18%), as compared to the SI-rTMS session (16%). Other effects did not reach significance: Side ($F_{1,11}$= 0.06, $p = 0.8$), Task by Session ($F_{1,11}$= 0.03, $p = 0.9$), Task by Side ($F_{1,11}$= 0.95, $p = 0.5$), Session by Side ($F_{1,11}$= 0.26, $p = 0.6$), Task by Session by Side ($F_{1,11}$= 1.29, $p$= 0.3).

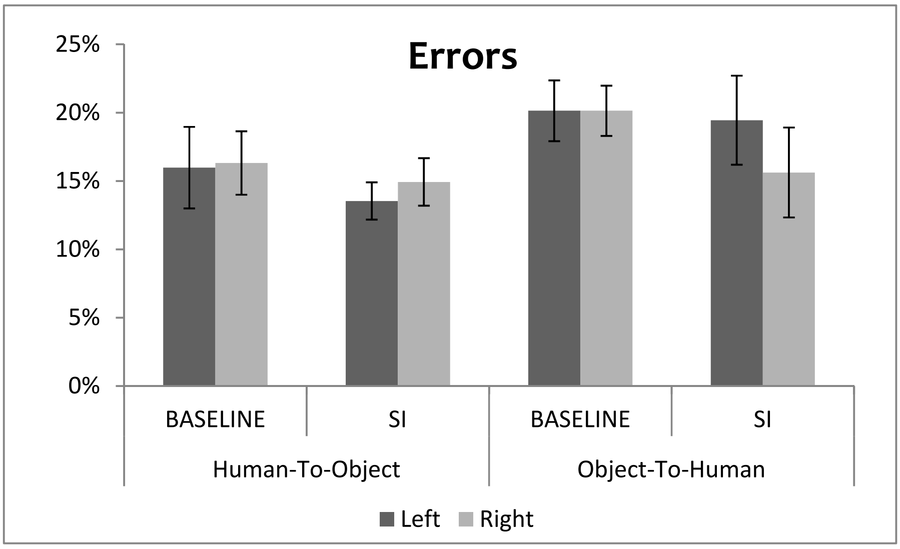

**Fig 12:** rTMS effects on behavior. Mean error rate in each experimental condition. Error bars= S.E.

Even the analysis of sensitivity did not show any significant main effect: Task ($F_{1,11}$= 2.67, p= 0.1), Session ($F_{1,11}$= 4.67, p= 0.07), Side ($F_{1,11}$= 0.01, p= 0.9), Task by Session ($F_{1,11}$= 0.58, p= 0.5), Task by Side ($F_{1,11}$= 1.33, p= 0.3), Session by Side ($F_{1,11}$= 1.71, p= 0.2), Task by Session by Side ($F_{1,11}$= 0.16, p= 0.7).

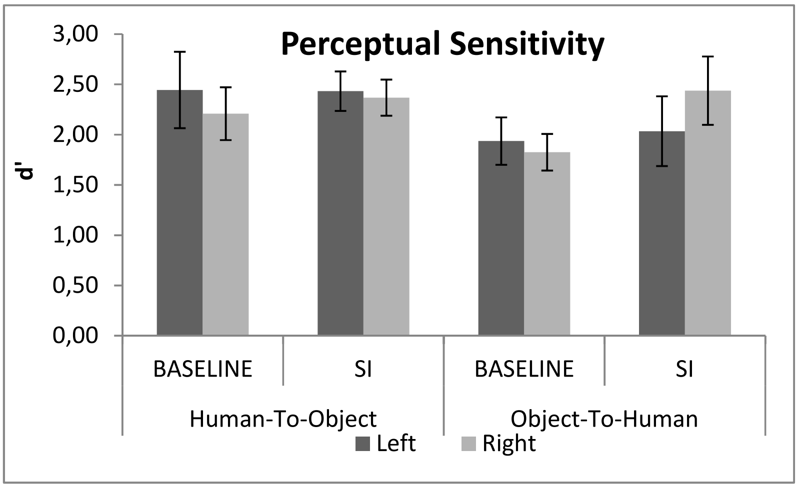

**Fig. 13** rTMS effects on behavior. Mean d' values for the sensitivity in each experimental condition. Error bars = S.E.

Similarly, the analysis of response bias did not show any significant main effect: Task ($F_{1,11}$= 1.94, p= 0.2), Session ($F_{1,11}$= 0.15, p= 0.7), Side ($F_{1,11}$= 0.56, p= 0.5), Task by Session ($F_{1,11}$= 3.07, p= 0.1), Task by Side ($F_{1,11}$= 0.77, p= 0.4), Session by Side ($F_{1,11}$= 0.93, p= 0.4), Task by Session by Side ($F_{1,11}$= 0.39, p= 0.5) (See Fig. 7).

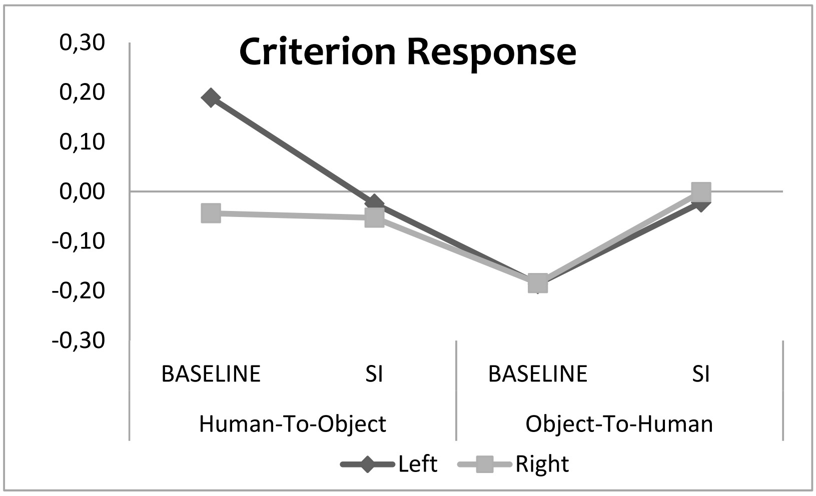

**Fig 14** rTMS effects on behavior. Mean values of response criterion. Asterisks indicate a significant rTMS effect. Error bars denote standard errors

To control for differences in the difficulty of the four tasks used in Experiments 2 and 3, the d' values of the baseline sessions were analysed via a three-way ANOVA with Experiment as between-subjects factor, and Task and Side as within-subjects factors. No significant effect emerged ($p > 0.09$), suggesting that the four tasks were equally sensitive.

*Subjective Reports*

Participants disagreed that the Human-to-Object Touch was unpleasant (-0.72, $t_{11}$= -2.18, $p < 0.05$), and that the touching index finger could depict their own finger (-1.18; $t_{11}$= -3.13, $p < 0.01$); their scores did not differ from 0 with respect to the intensity (-0.27; $t_{11}$= -0.55, $p = 0.5$).

The Object-to-Human Touch was not rated as intense (0.5, $t_{11}$= 2.17, $p = 0.07$), nor as unpleasant (-0,64, $t_{11}$ = -2.05, $p= 0.07$), but participants agreed that the touched hand could represent their own hand (0.72, $t_{11}$ = 2.66, $p< 0.02$).

## Discussion

The aim of the present study was to uncover the selectivity of SI in the visual processing of tactile events, with respect to the type of observed touching agent and the recipient of touch (in both cases, human vs. object). In particular, in Experiment 2 we compared the effect of rTMS interference of SI and VI on the ability to detect visual stimuli depicting a touch between body-parts (i.e. an index finger touching the back of a hand) and between objects (i.e. a leaf touching a wooden stick). rTMS delivered to SI selectively reduced visual perceptual sensitivity (i.e. decreased d’ values) for detecting contralateral visual events comprising a tactile component. Therefore the SI-rTMS interference is specific for the type of touch visually presented: interfering with SI activity reduces the ability to detect visual tactile stimuli, but only when a contact between body parts is shown. Moreover, we confirm the finding of Experiment 1, as SI-rTMS affected only the perception of the contralateral (left-sided) stimuli. SI disruption was evident only at the perceptual level (as assessed by d'), as no significant change in the response criterion or in the error rate emerged in the SI-rTMS session.

Notably, the SI-rTMS interference correlated with the intensity, but not with the unpleasantness, of the observed touch (i.e. the more intense the touch was rated, the greater was the visual impairment induced by SI stimulation), and with the report that the touched hand could represent the participant's own hand (i.e. more the touched hand was rated as depicting the participant's own hand, the greater was the SI interference). Moreover, subjects interpreted the touching and touched hands as belonging to different persons, hence representing an interpersonal (social) touch. These findings are in line with previous evidence suggesting the existence of specific relationships between the sensory qualities of the bodily touch, the embodiment of the observed sensations and the visual recruitment of somatosensory areas (e.g. Blakemore et al., 2005; Bufalari et al., 2007; Ebisch et al., 2008).

With respect to the effect of VI stimulation, the interference induced in this area did not affect visual processing of human bodily touch or object contact, in line with evidence from Experiment 1.

Experiment 3 further explored the role of SI in the visual processing of tactile interactions between body parts and objects. There was no SI-rTMS disruption of visual perception in the Human-to-Object Touch task or in the Object-to-Human Touch task. Hence, SI appears to be causally involved in the visual processing only of signals pertaining the domain of body parts contact. This suggests that the mirror activation of

SI requires that the recipient of the touch and the touching agent are both actually capable of feeling touch. This in turn informs us that the visuo-tactile mirroring mechanism of SI does not apply to the sight of ‘any’ touch, but rather is restricted to the sight of body-related experiences. In broad agreement with this, previous studies have shown a preferential activation of SI when viewing a human touch, as compared with the sight of a visual event not comprising a tactile component (Schaefer et al., 2005), or with the view of an object being touched by a human hand (Blakemore et al., 2005). Additionally, Ebisch et al. (2008) showed a significant difference in the mirror activation of SI by the sight of intentional touch by a human agent, as compared with accidental touch by an inanimate agent; SI activity was also associated to the degree of intentionality of the observed touch, as rated by the observers. However, the authors did not observe any difference in SI between animate (e.g., a hand touched the back of another hand) and inanimate (e.g., a hand touched a wooden chair) intentional touch, at odds with our findings. Other evidence support a selectivity of SI activation by the sight of human-to human touch, as provided by a study investigating the “Visual Remapping of Touch” (VRT), i.e. a phenomenon in which seeing a human face being touched enhances detection of tactile stimuli on the observer's own face (Serino et al., 2008). The VRT activates a network of fronto-parietal areas that includes the multimodal ventral premotor cortex (VPM) and the face area of SI/SII (Cardini et al., 2011). Beck and colleagues found no VRT when human subject watched monkey’s face, regardless of facial expression, suggesting that touch on a non-human face is not remapped onto the somatosensory system of the human observer (Beck et al., 2013).

On the other hand, equal overlapping activation for different tactile experiences, namely intentional and accidental touch between human body-parts and/or objects, emerged in the bilateral SII (Keysers et al., 2004). This evidence has led to the proposal that the mirror activity in SI might specifically reflect an automatic simulation of the proprioceptive aspects of the observed touch when intentionality is assumed by the observer; instead, in SII the activation by the sight of touch seems to underpin an abstract notion of touch (Ebisch et al., 2008). The selectivity of SI activity for touch observation is also in line with evidence in people with mirror-touch synaesthesia, the phenomenon by which watching touch to another person triggers consciously reported tactile experiences on their own body; such synaesthetic touch is not induced by the view of object being touched (see Chapter 1.4). Other psychophysical studies have shown that seeing a body-part, but not an object, can increase the accuracy with which one can localize a tactile stimulus on that body part. It has been proposed that viewing a body-part induces a top-down visual modulation of SI activity corresponding to the viewed body-part (Kennett et al., 2001).

Because the sense of touch has a close and interactive relationship with higher cognitive representations of the human body (Cardini et al., 2011; Serino and Haggard, 2010), the sight of body-parts touching each other's, at variance with the sight of object contact, may amplify the mirror recruitment of SI. We did not find any effect of rTMS interference over SI for the visual processing of human-to-object and/or object-to-human contacts. Different factors may explain this null result. First, there may be an 'intensity coding' explanation (Keysers et al., 2010) related to the touching inanimate stimulus we have used, namely a wooden stick; this kind of object may be not enough intense to trigger SI activity, as suggested by participants' reports at the questionnaire. Indeed, for objects touching the body, activations in SI appears stronger when the visual stimulus suggests intense pain, such as when a needle is shown penetrating a hand deeply, as opposed to pricking it, or if participants imagine that they are in a painful situation themselves (Bufalari et al., 2007; Keysers et al., 2010). The intensity of observed tactile stimulus can also modulate the intensity of the synaesthesic experience – touching the face with a knife tip or finger elicits a stronger synaesthetic sensation than using a feather (Holle et al., 2011). Second, SI is more active when viewing hands manipulating objects (Pierno et al., 2009); given the role of SI in haptic exploration, it has been proposed that SI might be particularly important for inferring the properties of objects from the way we see other people manipulate them (Keysers et al., 2010). In this view, in the present experiment the sight of an index finger merely touching a neutral object, without any goal-directed action, might be not sufficient to trigger a mirror engagement of SI. Finally, the sight of a touch between human body-parts may also amplify the somatosensory activation, as compared with a touch between a body-part and an object, because SI would respond to both the observed touching and touched hands. On a broader perspective, current evidence indicates that the somatosensory mirror system seems highly malleable, and susceptible to factors such as intensity of the stimuli, passive vs. active stimulation, intentionality, self-oriented experience, perspective-taking and attention (Fitzgibbon et al., 2012). Such modulatory factors may determine the visual recruitment of SI by touch observation.

In conclusion, Experiment 2 and 3 demonstrated that SI is causally involved in the visual perception of a human body-part being touched by a human a biological tactile experience. This suggests that the internal simulation of observed somatosensory events is primarily triggered by the view of a contact between human beings. In this perspective, SI may contribute to our capacity to understand the effect of human intentional tactile stimulations on another person, perhaps allowing us to more easily 'resonate' with the body-related experiences of both the touched person and the human agent.

# CHAPTER 3

# UNDERSTANDING OTHERS' FEELINGS: THE ROLE OF SI IN ENCODING THE AFFECTIVE VALENCE OF OTHERS' TOUCH

## *3.1 Experiment 4. Exploring the role of SI in the understanding of other's touch experience in healthy subjects*

### Aim of the study

The present experiments aim at exploring to what extent SI participates in processing the visual touch. Experiments 1-3 showed that SI is involved in low-level visual processing of touch, being recruited in the visual discrimination of bodily tactile stimulations. However, it has been proposed that the vicarious activation of SI by the sight of touch may be also directly implied in understanding others' somatosensations (Keysers et al., 2010). In this perspective, SI may be also involved in higher-level stages of visual processing. Indeed, the vicarious activation of the somatosensory system by the sight of touch can be seen in two, not mutually exclusive, ways. It might reflect the unspecific co-activation of somatosensory representations by parietal and premotor neurons that are involved in understanding action's consequences, by means of a feedback loop activating their associated somatosensory representations; alternatively, SI might play a more specific causal role in coding the sensory consequences of the observed action, thereby informing the observer about the resulting sensations in others (Lamm et al., 2007). So far, the functional role of SI in understanding others' sensations remains to be established. To address this issue, a series of rTMS studies in healthy subjects and a neuropsychological study in brain-damaged stroke adults were run to explore the causal involvement of SI, its possible hemispheric lateralization, and the role of emphatic abilities, in encoding the affective valence of emotional scenes depicting, or not, a tactile event.

## Materials and method

### *Participants*

Thirty-six healthy, naïve, volunteers participated in two experiments, namely eighteen of them were tested in Experiment 4a (2 males; 16 right-handed; age= 22.6± 3.5), and eighteen in Experiment 4b (3 males; 16 right-handed; age= 24.5± 3.8). Exclusion criteria included history of neurological and psychiatric disorders, and contraindications to rTMS (Rossi et al. 2009). The protocol was carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302: 1194) and was approved by the ethical committee at the University of Milano-Bicocca. Written informed consent was obtained from participants.

### *Affective go/no-go task (adapted from Bermpohl et al., 2005)*

Color photographs (18.4°X18.4°) were shown on a dark background (luminance=0.01cd/$m^2$). Stimuli belonged to two experimental conditions: the "Touch" condition, with emotionally-evocative pictures depicting a physical contact, namely a person being touched by another person or by an object (e.g., caress to the arm, a syringe into the arm); the "No-Touch" condition, with emotionally-evocative pictures depicting a scene not involving a physical contact (e.g., a person having fun, an injured person) (Fig. 1A). The task comprised 32 pictures: 8 positive and 8 negative pictures for both Touch and No-Touch conditions. Touch and No-Touch pictures were matched for: sex and number of characters, presence of facial or body emotions and meaningful social interactions. The reliable valance of these pictures was assessed through a preliminary experiment, where 22 healthy right-handed participants (3 males; age= 22.5±3) underwent the affective go/no go task, as described below, which comprised 44 pictures (11 for each positive/negative condition). After the task, participants rated each picture on three 100-mm Visual Analog Scales (VAS), namely:

1. "Which is the valence of the picture?" (left end-point= extremely negative/ right end-point= extremely positive);
2. "Which sensation is evoked by this picture?" (strong pain/great pleasure);
3. "How would you feel if you were in this situation?" (very bad/very well).

In this way, we selected the 32 pictures with the highest reliable valence ratings, namely: positive Touch, accuracy=93± 4%, VAS value 8.8± 0.5 mm; positive No-Touch, accuracy=91±4%, VAS 8.3±0.7 mm; negative Touch, accuracy=96±2%, VAS 0.9±0.8 mm; negative No-Touch, accuracy=92±4%, VAS 1.2±1 mm.

During the experimental task, the 32 pictures were presented twice, for a total of 64 trials (i.e., 16 positive and 16 negative trials for both Touch and No-Touch conditions), given in 4 blocks. Prior to each block, an instruction was given specifying either positive [P] or negative [N] pictures as targets. Instructions were presented in PNPN or NPNP order in every experimental session (see below), with half of participants starting with the P instruction. During the task, the target picture was presented for 300 ms, followed by a blank window lasting 900 ms (Fig. 1B). Participants were instructed to respond as fast as possible to the target by pressing the space bar, while refraining from responding to distracters. The task lasted about 10 min. Sequence/timing of the stimuli, and responses' recording were under computer control (E-prime software, Psychology Software Tools Inc.).

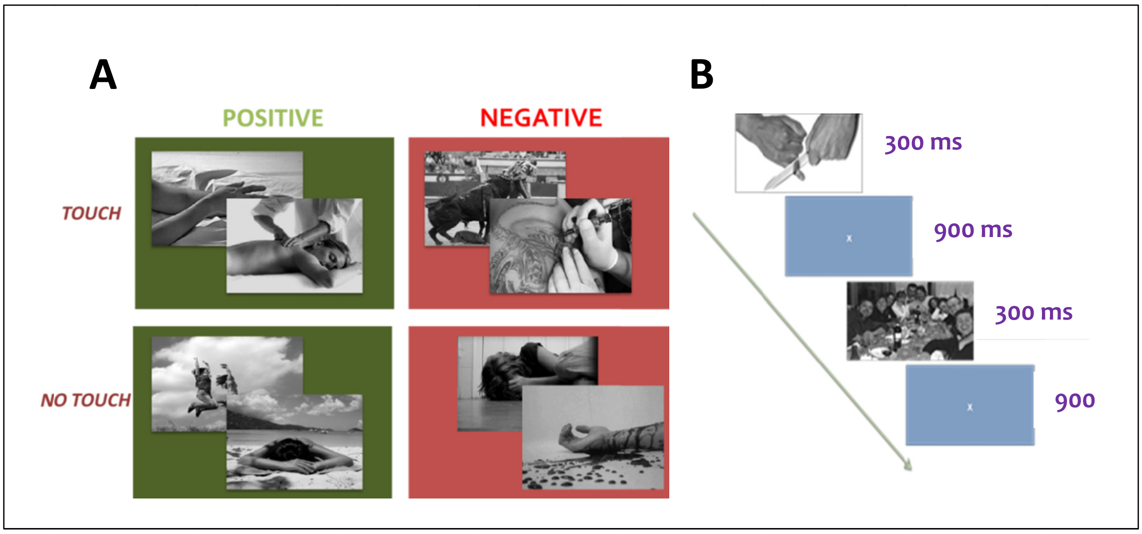

**Fig. 1** Conditions (A) and sequence of events (B) of the affective go/no-go

*TMS Protocol*

Low-frequency (1 Hz), off-line, rTMS was delivered using a Magstim Super Rapid magnetic stimulator (Magstim, Whitland-UK) and a figure-of-eight coil (Ø=70 mm) for focal cortical stimulation. rTMS was delivered for 10 minutes, with an intensity of 110% of the individual motor threshold at rest (rMT) (Rossi et al., 2009) (cfr. Chap. 2). rMT was determined by stimulating the hand area of the right (Experiment 4a) or left (Experiment 4b) primary motor cortex. The mean rMT was of 57± 6% of the maximal output of the stimulator in Experiment 4a, and of 55± 8% in Experiment 4b.

In Experiment 4a, we stimulated the right SI in light of the efficacy of this stimulation for disrupting the visual perception of touch as shown in Experiments 1-3 (cfr. Chap. 2) The left DLPFC was chosen as active control site, given the left lateralization of the prefrontal contribution to affective go/no-go performance (Bermpohl et al., 2005). In Experiment 4b, instead, the left SI and the right DLPF were stimulated, in order to further explore possible hemispheric asymmetries of SI functions (Bermpohl et al., 2005).

The appropriate location for stimulating the SI hand area was identified using the same functional procedure described in Experiment 1. During TMS, almost every subject reported paraesthesia in the contralateral hand; 29 participants also reported a deficit (omissions=14.7%) in detecting the contralateral touch.

The Talairach coordinates of the DLPFC (x=-/+32, y=24, z=42), as reported in a previous fMRI study (Herrington et al. 2005) were localized with the SofTaxic Navigator system (E.M.S., Bologna, Italy).

Throughout the rTMS sessions, the coil was fixed in position with the aid of an articulated mechanical arm.

### *Experimental procedure*

Participants were comfortably seated in an armchair, in a quiet, dimly illuminated room, at a distance of 45 cm in front of a PC monitor (Samsung SyncMaster 1200NF). Both experiments comprised 4 sessions. The training session allowed participants to familiarize with the task before the experiment (different pictures were presented, not included in the experimental task). There were three experimental sessions, counterbalanced across participants (ABC-BCA-CAB order) and separated by wash-out periods of at least 60 min: the baseline without rTMS; two Post-rTMS sessions, in which the task was given after the delivery of rTMS over SI or DLPFC. The entire procedure lasted about 2/3 hours. In the baseline, half of the participants responded with the left index finger, and half with the right one, as a pilot study showed no difference in performance due to the hand used for responding ($p > 0.1$); in the rTMS sessions, participants always responded with the hand ipsilateral to rTMS.

### *Interpersonal Reactivity Index*

In order to explore whether activity in SI is related to individual differences in empathy, after each experiment, participants completed the Interpersonal Reactivity Index (IRI) (Davis 1983) a 28-item self-report survey with four subscales: Perspective Taking (PT) and Fantasy (F), Empathic Concern (EC), Personal Distress (PD). Cognitive empathy includes PT and F, affective empathy EC and PD. While PD taps self-oriented aspects of interpersonal reactivity, higher scores on PT, F, and EC are associated with other-oriented interpersonal activity.

*Statistical analysis*

Mean error rates and reaction times (RTs) were analyzed via a repeated-measures ANOVA with Experiment (4a, 4b), as the between-subject factor, and Session (Baseline, SI-rTMS, DLPFC-rTMS), Condition (No-Touch, Touch), Valence (Negative, Positive), as the within-subjects factors. Post-hoc comparisons were performed with the Bonferroni Test. RTs above or below 2 standard deviations from the mean, as computed for each session, were discarded from the analysis; these data represented a minority of trials (<10%). The effect size in the ANOVAs was measured by calculating the partial Eta Squared ($p\eta^2$). Pearson's correlations were then performed to assess the possible association between the rTMS effect [namely, RTs difference between the Baseline and rTMS sessions for Touch and No-Touch conditions (Post-rTMS minus Baseline: positive/negative values= increased/decreased RTs by rTMS)], and the participants' scores on each IRI subscale, given the a priori hypothesis that some, but not all, aspects of the empathy may be linked to tactile mirror activations (Cheng et al. 2008; Gazzola et al. 2006; Schaefer et al. 2012b).

## Results

The ANOVA performed on errors showed that the Experiment by Session by Condition interaction was significant ($F_{2,68} = 3.76$, $p < 0.03$, $p\eta^2 = 0.2$). No other main effect and interaction was significant (all ps > 0.1). In the Post-SI-rTMS session, participants committed more errors in the Touch condition (8%), than in the No-Touch condition (4%, $p < 0.05$); no other difference between conditions and sessions was significant (all ps > 0.4) (Fig. 2 and 3).

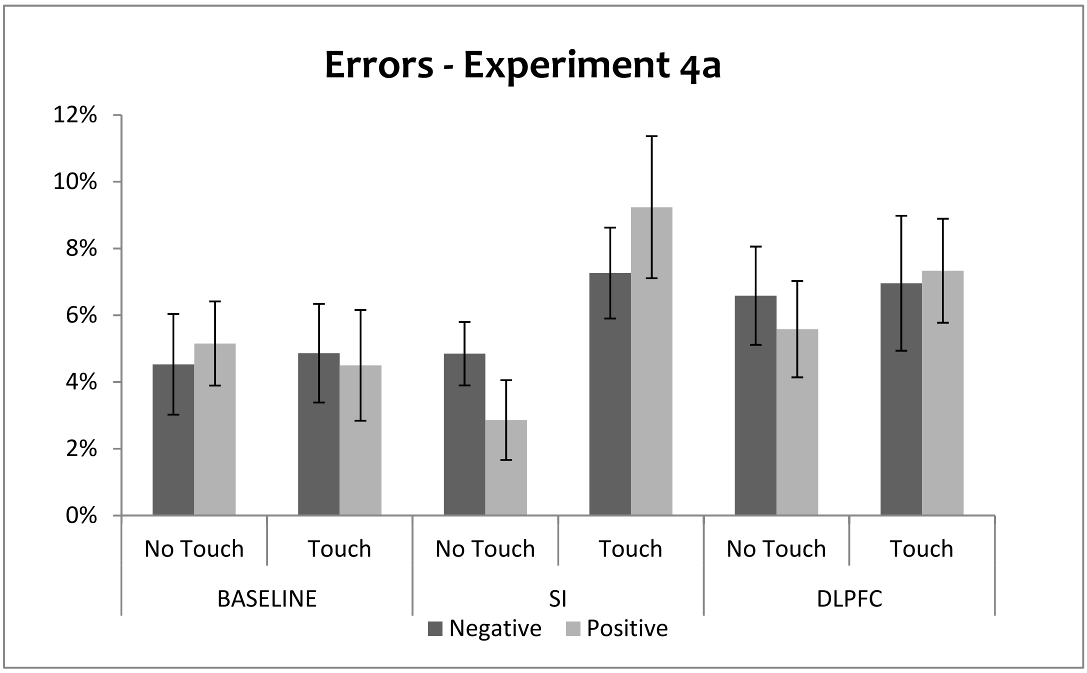

**Fig 2.** Error rate in Experiment 4a

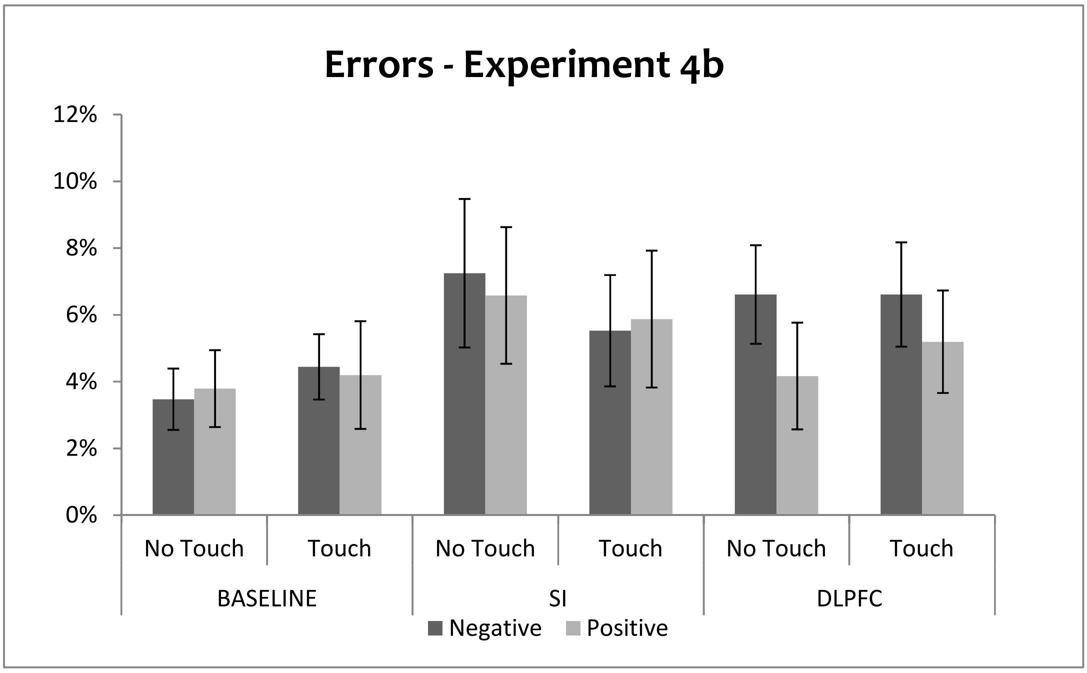

**Fig 3.** Error rate in Experiment 4b

For RTs the main effect of Session was significant ($F_{2,68}$= 7.15, p < 0.01, $p\eta^2$ = 0.2); the Experiment by Session ($F_{2,68}$= 7.75, p < 0.001, $p\eta^2$ = 0.2) and Session by Condition ($F_{2,68}$= 5.85, p < 0.01, $p\eta^2$= 0.2) interactions reached also significance. Crucially, the Experiment by Session by Condition interaction was significant ($F_{2,68}$ = 12.29, p < 0.0001, $p\eta^2$ = 0.4), highlighting the selectivity of the rTMS effect. No other main effect or interaction was significant (all ps > 0.1). Post-hoc comparisons showed that in Experiment 4a (i.e., rTMS delivered to right SI and to left DLPFC), in the No-Touch condition RTs increased after left DLPFC-rTMS (544.1 ms, p < 0.0001), as compared to both Baseline (510.3 ms) and right SI-rTMS (517.8 ms); in the Touch condition, RTs increased after rTMS to both the left DLPFC (540.2 ms) and the right SI (544.1 ms), compared to Baseline (511.2 ms, p < 0.0001), with no difference between the two rTMS sessions (p = 1) (Fig. 4). Touch and

No-touch conditions differed only after the stimulation for the right SI ($p < 0.0001$), but not in the Baseline ($p = 1$), nor after the stimulation of the left DLPFC ($p = 0.4$) (Fig. 4).

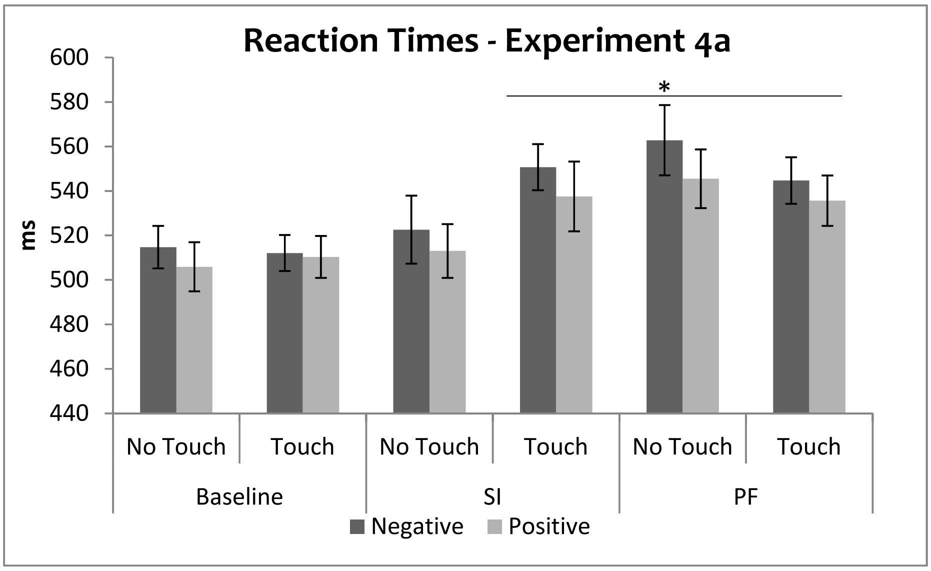

**Fig 4.** Reaction times in Experiment 4a

Instead, in Experiment 4b (i.e., rTMS delivered to left SI and to right DLPFC), there were no significant differences between conditions and sessions (all ps > 0.1) (Fig. 5).

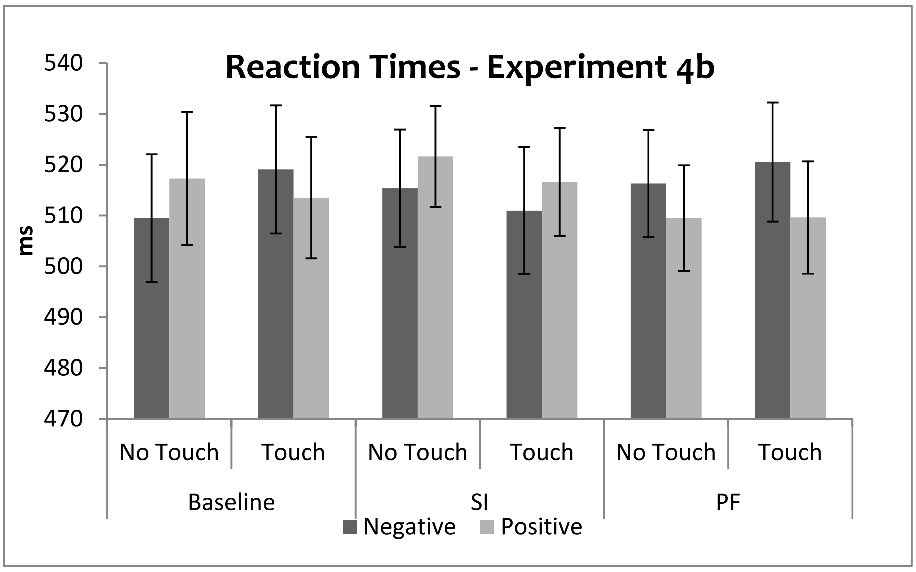

**Fig. 5.** Reaction times in Experiment 4b

A positive correlation was found between the right-SI-rTMS effect in the Touch condition and the participants' score on the PT subscale (r = 0.58, p < 0.01): the greater the individual PT score, the greater the disruptive effect of right SI-rTMS for Touch stimuli (Fig.6). No other significant correlations between the IRI subscales and the SI-rTMS and DLPFC-rTMS effects in the Touch and No-Touch conditions were found (all ps > 0.2).

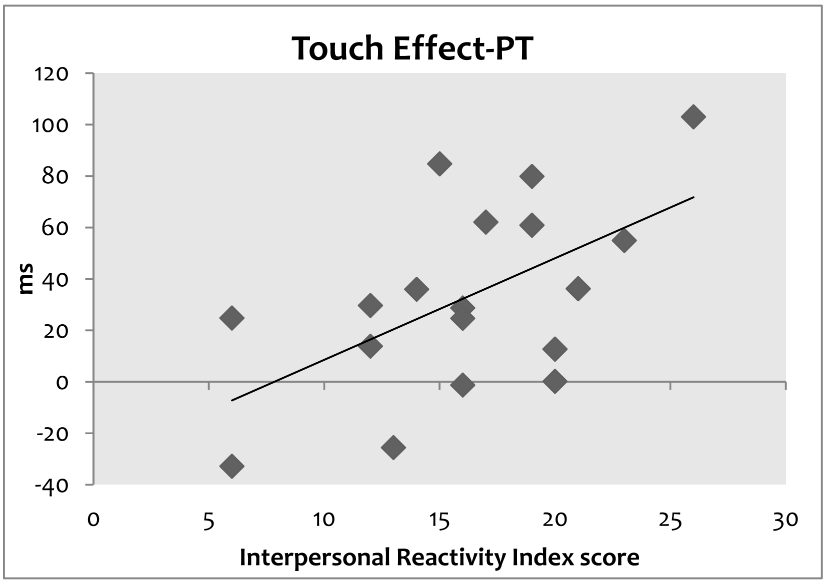

**Fig. 6** Correlation scatter plot for empathy subscale PT with the right-S1-rTMS effect

**Discussion**

The results from these experiments demonstrated that rTMS over SI disrupts affective go/no-go task performance, but only in response to pictures where the emotional state is conveyed by a tactile event; moreover, this effect is lateralized to the right SI. Additionally, there is an association between the interfering effect of right SI-rTMS and the empathy subscale PT, which assesses the ability to adopt the perspective of others (Davis 1983). Notably, the rTMS effect due to DLPCF disruption did not correlate with empathy, at variance with the SI effect. Finally, the activity of the left, but not the right, DLPFC is causally involved in affective go/no-go functions, as previously shown by Bermpohl and colleagues (2005). The recruitment of this area during the task is independent from the sight of touch. Overall, this evidence shows for the first time that SI is causally involved in encoding the valence of others' sensory states conveyed by a tactile event.

Therefore, this study represents a significant advance, as it further shows that SI not only participates in a 'low-level' visual detection of a tactile stimulation between body parts (Experiments 1-3),  rather SI is also essential to encode others' social or affective tactile experiences, independently from their positive or negative valence. This is an intriguing finding since SI has been considered a primary modality-specific area, involved in the processing of the lower-level sensory properties of touch (Penfield and Boldrey 1937). Here, SI was shown to be also sensitive to the affective features of the viewed touch, beyond the primary levels of visual processing. SI primarily discriminates sensory properties (i.e location, pressure, texture), whereas the insula, anterior cingulate cortex and the orbitofrontal cortex are mostly involved in the coding of the affective properties  of touch (Francis et al., 1999; McGlone et al., 2007; Morrison et al., 2011; Rolls et al., 2003). At odds with this construct, a fMRI study demonstrated that SI is modulated by the affective features of the seen touch. By decoupling the affective significance of a caress from its cutaneous sensory properties, Gazzola et al. (2012) demonstrated that SI can integrate visual and tactile information during the processing of interpersonal touch, and it is sensitive to the caressers' sex and to the perceived pleasantness of their sensual touch. Brain regions classically associated with affective processing of touch (insula, orbitofrontal and anterior cingulate cortices) are also activated by sensual caress, with only the orbitofrontal cortex being significantly modulated by visual sex (Gazzola et al., 2012). Ebisch et al. (2011) showed overlapping activation for the experience and observation of touch in SI and SII, while an opposite activation pattern emerged in the insula for the experience (positive modulation) and the observation (negative modulation) of touch. Summing up, recent evidences demonstrate that brain regions involved in emotion processing contribute to the generation of knowledge about another person's affective state and draw on SI for the construction of a shared representation of observed somatic feelings, via the process of simulation; this, in turn, would enable SI to participate in the affective encoding of the seen touch. The results of Experiments 4a-b support this proposal.

It is worth noting that it is the right, not the left, SI that can discriminate the valence of tactile events. This result is in line with neuropsychological and TMS evidence demonstrating that damage to right somatosensory-related cortices, including SI, impairs recognition of basic emotions, making intensity judgments from photographs, and emotional concept retrieval (Adolphs et al. 1997, 2000; Pitcher et al. 2008; Pourtois et al. 2004). Neuroimaging studies also show a right SI dominance for various social abilities. For instance: empathy and perspective taking in complex social situations activate right SI (Ruby and Decety, 2004); the simultaneous observation and execution of a finger movement activate somatosensory areas in the right hemisphere, a result interpreted as associated with the preservation of the sense of self (Iacoboni 1999); right SI activity due to tactile stimulation is affected by personality traits (Schaefer et al. 2012a). On a broader perspective, there is a dominance of the right hemisphere in social behavior and empathy (Brancucci et al., 2009; Decety and Sommerville, 2003; Hein and Singer, 2008;), such as understanding others' intention (Ortigue et al., 2009, 2010), agency attribution (Farrer and Frith, 2002; Lamm et al., 2007), and theory of mind (Happé et al., 1999; Gallagher et al., 2000; Saxe and Kanwisher, 2003). Finally, disorders of the sense of ownership of body parts are typically caused by right hemisphere lesions (Vallar and Ronchi, 2009).

The present study further shows that the right SI is also engaged in social touch, being recruited for encoding the affective valence of others' somatic feelings. This right hemispheric lateralization could be the bridge linking a shared somatic representation, triggered by the sight of touch, with higher-order metalizing processes involved in empathy. This view is supported by the significant correlation between the interfering effect of right SI-rTMS and the empathy subscale PT, which assesses the ability to adopt the perspective of others. This correlation indicates that with increasing PT, the more the subject are able to share the tactile consequences of seen touch, as also suggested by fMRI studies (Cheng et al., 2008; Gazzola et al., 2006; Schaefer et al., 2012b). Of note, the right SI also shows a high specificity for first-person perspective in emotional contexts (Ruby and Decety, 2004). Overall, cognitive empathy skills, such as PT, seem to rely on the use of internal models of shared sensations to understand another person's situation (Gallese 2007).

Finally, we confirm the causal role of the left DLPFC in affective go/no-go performance, regardless of the sight of touch. The novel outcome is that left DLPFC activity does not correlate with empathy. This finding may suggest that the left DLPFC is more linked to more general cognitive functions, possibly executive processes and on-line manipulation of emotional information (Bermpohl et al., 2005; Fuster 1989), rather than in empathic abilities. This, in turn, indicates that the neural basis of empathy may be dissociated from that implied in processing of affective information. Indeed, while the DLPFC is more relevant to executive aspects of cognition, orbitofrontal/ ventromedial frontal areas play a prominent role in empathy (Preston and de Waal, 2002; Rameson et al., 2012; Shamay-Tsoory et al., 2003; Salzman and Fusi, 2010). Nonetheless, the prefrontal cortex may allow empathy to take place in a top-down manner: the cognitive functions of the DLPFC may interact with the vicarious activity of SI when the encoding of others' feelings must be held in mind, and alternative interpretations considered.

In conclusion, the vicarious activity of the right SI does not merely reflect an unspecific co-activation of somatosensory representations by the sight of touch, being instead functionally relevant for encoding pleasant and aversive consequences of seen tactile events, a function associated with empathy. The mirror-touch mechanism supported by SI allows us to understand the affective consequence of touch faced by other people in social context, by internally simulating others' somatic experience.

## *3.2 Experiment 5: Understanding assisted somatic experience. Exploring the role of somatosensory perception in neurological patients.*

### Aim of the study

Experiment 5 aims at verifying whether acquired lesions to the somatosensory cortical system may impair the ability of understanding others' tactile sensations, and the hemispheric dominance of this impairment. As demonstrated in Experiement 4, SI is causally involved in understanding the affective consequence of an assisted somatic experience. We expected that patients with a lesion to the somatosensory cortices, besides showing tactile impairments, may also be impaired in coding the affective valance of others' touch.

### Materials and method

*Participants*

Eighteen patients (10 males and 8 females, mean age= 64 years, range= 35-75, all right-handed) with unilateral brain lesions with different etiology (hemorrhagic or ischemic stroke) participated in the study. Twelve patients had unilateral lesions to the right hemisphere (i.e., RBD), 6 patients presented unilateral lesions to the left hemisphere (i.e., LBD), as documented by CT and/or MRI. 17 out of 18 patients showed movement motor disorders of varying extent and severity; 8 patients showed right unilateral spatial neglect. Exclusion criteria to the study were: refusal to sign informed consent; bilateral encephalic ischemic and hemorrhagic or neoplastic lesions; severe unilateral spatial neglect (i.e., USN) (Letters cancellation, omissions cut-off: ≥5; Lines cancellation, cut-off omissions≥ 2; Line Bisection test, deviation cut-off: ≥ 21.1 %) (Fortis et al., 2010; Spinnler & Tognoni, 1987; Vallar et al., 1994) or severe aphasia comprehension (Token Test, accuracy cut-off: <26.5) (Spinnler & Tognoni, 1987); history of psychiatric disorders; mental or cognitive impairment so severe to prevent the understanding of instruction or to signing the informed consent.

All subjects gave their informed consent to participate in the experiment and were briefed on the procedures. They were also informed on the possibility to withdraw the experiment at any time.

A control group of 16 neurologically unimpaired right-handed patients were also tested, matched for age and education to the patients (8 males and 8 females, mean age=54 years, range=35-75).

| **Patient** | **Sex/Age** | **Education (year)** | **Length of Illness (months)** | **Ethiology/ Lesion Site** | **Neurological deficit** | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | **M** | **SS** | **V** | **N** |
| **V.M.** | 56 M | 17 | 1 | I/ FT Bg Ic In | + | | - | - |
| **M.A.** | 60 M | 13 | 3 | I/ T In | + | + | + | + |
| **S.D.** | 65 F | 13 | 5 | H/ TP Sub In | + | + | + | + |
| **B.M.** | 68 F | 8 | 1 | H/ P | + | - | - | + |
| **G.F.** | 76 F | 8 | 36 | H/ Fin | + | - | + | + |
| **C.S.** | 61 M | 13 | 12 | H/ Bg Ic Th In | + | + | + | - |
| **D.G.** | 71 M | 17 | 12 | I/ Bg In | + | + | - | - |
| **B.S.** | 60 M | 5 | 1 | I/ F In | + | + | + | + |
| **Z.G.** | 80 F | 13 | 1 | I/ P Cer Sub In | + | + | + | + |
| **D.G.F** | 75 M | 8 | 2 | H/ FTPO In | + | - | + | + |
| **C.G.** | 49 M | 18 | 1 | H/ Ic In | + | - | - | - |
| **T.D** | 61 F | 17 | 3 | I/ FTPO In | + | - | + | + |

**Tab. 1.** Demographic and clinical data of RBD patients.Etiology: I/H/N: ischemic/hemorrhagic/neoplastic lesion; Lesional Site: F: frontal, P: parietal, T: temporal, O: occipital, In: insula, Ic: internal capsule, Th: thalamus, Bg: basal ganglia, sub: subcortical,; Crb: cerebellum; neurological deficit: M/SS/V/N: motor/somatosensory/visual/neglect; +/- presence/absence of impairment.

| Patient | Sex/Age | Education (year) | Length of Illness (months) | Ethiology/ Site | Lesion | Neurological deficit | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | M | SS | V |
| B.E. | 44 F | 15 | 1 | H/ P In | | + | - | - |
| T.G. | 65 M | 8 | 18 | I/ FTP In | | + | - | - |
| L.M. | 70 F | 9 | 1 | H/ Bg Ic In | | + | - | - |
| G.A. | 69 M | 13 | 1 | I/ Sub | | + | - | - |
| L.L. | 78 F | 8 | 2 | I/ F Ic In | | - | - | - |
| P.G. | 46 M | 13 | 1 | H/ Bg Ic In | | + | - | - |

**Tab. 2.** Demographic and clinical data of the LBD patients. For legend see Tab. 1

*Neuropsychological assessment*

The assessment included the following tests

Sensory Deficit:

- Examination of the visual field by means of computerized campimetry; Examination of tactile sensitivity using the battery Rivermead Assessment of Somatosensory Performance (RASP) (Winward et al., 2000).
- Cognitive functions:
  - Left brain-damage, evaluation of: Ideational, Ideomotor, Constructional (AC) and Buccofacial Apraxia (Spinnler and Tognoni, 1987); language disorders:

Token test (De Renzi and Faglioni, 1978), Semantic and Phonemic fluency (Spinnler & Tognoni, 1987).

- Right brain-damage, evaluation of USN: Letters (Diller & Weinberg, 1977) and Bells (Gauthier et al., 1989) cancellation, lines bisection (Wilson et al., 1987), Clock-drawing test (Wilson et al., 1987).

The visual field examination was performed with a computerized campimetry. Visual sensitivity deficits were present in 8 (all RBD) out of 18 patients.

The Rivermead Assessment of Somatosensory Performance (RASP) (Winward et al., 2000) was used to evaluate somatosensory functions. RASP is a standardized battery for the analysis of somatosensory functions, particularly useful for the assessment of any tactile deficit due to neurological disorders such as stroke, multiple sclerosis or peripheral neuropathies. This test provides information about the tactile sensitivity of different body district (the cheeks, the back and the palm of the hands, the back and the soles of the feet.). It is also able to discriminate the presence of asymmetries in somatic sensitivity. The test assumes that the sensory modalities are not hierarchically organized, but they are relatively distinct. Although the battery uses original tools, all subtests derived from traditional clinical practice. The patients need to be blindfolded throughout the entire test, to avoid that visual sensitivity could supplies difficulties in somatosensory perception. RASP consists of 7 subtests, designed to assess whether the ability to discriminate different somatosensory stimulation, which resembles various everyday-life experiences of touch, are preserved, residual or pathological:

1. *Sharp/dull discrimination* assesses the ability to discriminate between a "soft" and a "sharp" stimulus (range scores: 0-30, impairment cut off: <22).
2. *Surface pressure touch* assesses the ability to perceive the presence of a tactile stimulation performed by a gentle touch that stimulates the various parts of the body (range scores: 0-30, impairment cut off: <29).
3. *Surface localization* required the patient to localize tactile stimulation, the subject must discriminate whether the stimulation was delivered on the right or left side or if a bilateral stimulation occurred (range scores: 0-30, left side impairment cut off: <29, right side impairment cut off: <28).
4. *Sensory extinction assesses* the inability to perceive a stimulus applied to the contralateral side to the lesion, when another stimulus is simultaneously presented on the ipsilesional side (range score: 6=normal, 4-5=mild extinction, 2-3= moderate extinction, 0-1=severe extinction).
5. *Two-point discrimination* asked to discriminate between two distant points of 3, 4 or 5 mm; this subtest in delivered only to the index fingertip of both hands (range score: pass-fail).
6. *Temperature Discrimination* evaluates the temperature sensitivity. Patient is required to discriminate between a "hot" and a "cold" stimulus (range score: 0-30, impairment cut off: <25).
7. *Proprioception movement discrimination (7a) and proprioception direction discrimination (7b)* require the patient to discriminate whether the evaluator has

moved or not one of his/her body-part and the perceived direction of the movement (score range: 0-30, 7a impairment cut off: <28).

In each test, patients are asked to give an oral answer immediately after the evaluator administered each stimulus. Two Neurometers are used to test sharp/dull discrimination, surface pressure touch, surface localization and sensory extinction. Neurometer is pen shaped instrument, having two distinct parts: a top half is for testing sharp/dull discrimination, and a lower half for measuring surface pressure touch, surface localization and sensory extinction.

Both the patients and the healthy controls underwent the RASP evaluation; no somatosensory deficit emerged in every control. Results from the assessment of the brain-damaged patients are reported in following tables.

|  |  | Cancellation |  | Line Bisection | Clock drawing Test |
|---|---|---|---|---|---|
|  |  | Letter | Bells |  |  |
| 1 | **V.M.** | 104 | 35 | 1.4% | 12 |
| 2 | **M.A.** | 103 | / | / | 10* |
| 3 | **S.D.** | 13* | 5* | 30.2%* | 10* |
| 4 | **B.M.** | 103 | 35 | 1.6% | 12 |
| 5 | **G.F.** | 6* | 33 | 55.4%* | 4* |
| 6 | **C.S.** | 100 | 33 | -2.6% | 12 |
| 7 | **D.G.** | 104 | 35 | 1.2% | 12 |
| 8 | **B.S.** | 86* | 29* | -2.4% | 12 |
| 9 | **Z.G.** | 5* | 3* | 46.4%* | 3* |
| 10 | **D.G.F** | 62* | 12* | 30.4%* | 3* |
| 11 | **C.G.** | 104 | 34 | -2.4% | 10 |
| 12 | **T.D.** | 21* | 8* | 72.4%* | 11 |

**Tab. 3.** Neuropsychological assessment for RBD patients; *: score below the cut off, /: test not administered

|  |  | Repetition |  |  |  |  |  | Naming |  |  |  |  |  | Comprehension |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  | Word |  | Non-Word |  | Phrase |  | Nouns |  | Verbs |  | Colour |  | Word |  | Phrase |  |
|  |  | **r.s.** | **a.s.** | **r.s.** | **a.s.** | **r.s.** | **a.s.** | **r.s.** | **a.s.** | **r.s.** | **a.s.** | **r.s.** | **a.s.** | **r.s.** | **a.s.** | **r.s.** | **a.s.** |
| **1** | **B.E.** | 9 | 8.8 | 3 | 2.5 | § | § | 9 | 9 | 7* | 6* | 5 | 5 | § | § | § | § |
| **2** | **T.G.** | 10 | 9.8 | 5 | 5 | 3 | 3 | 10 | 10 | 9 | 8.9 | 5 | 5 | 19 | 18.4 | 14 | 14 |
| **3** | **L.M.** | 8* | 7.8* | 5 | 5 | 1* | 1* | 7* | 7* | 4* | 3.5* | 5 | 5 | 20 | 19.4 | 10* | 10.1* |
| **4** | **G.A.** | 0* | 0* | 0* | 0* | 0* | 0* | 3* | 3* | 1* | 0.5* | 1* | 1* | 20 | 20 | 13 | 13.1 |
| **5** | **L.L.** | 9 | 8.8 | 1* | 1* | 3 | 3 | 10 | 10 | 9 | 9.5 | 5 | 5 | 19 | 19.9 | 14 | 14 |
| **6** | **P.G.** | 7* | 6.8* | 2* | 1.8* | 2* | 2* | 10 | 10 | 9 | 8.5 | 5 | 5 | 20 | 20 | 14 | 14 |

**Tab. 4** Neuropsychological assessment for LBD patients: r.s.: raw score a.s.: adjusted score *: score below the cut off, : test not administered §= test could not be executed

| | | Phonemic Fluency | | Semantic Fluency | | Token Test | |
|---|---|---|---|---|---|---|---|
| | | **r.s.** | **a.s.** | **r.s.** | **a.s.** | **r.s.** | **a.s.** |
| 1 | **B.E.** | 31 | 25 | 16* | 9* | 29.5 | 26.5 |
| 2 | **T.G.** | 25 | 29 | 11* | 15* | 31.5 | 31.25 |
| 3 | **L.M.** | 12* | 14* | 3* | 5* | 21.5* | 20.25* |
| 4 | **G.A.** | 6* | 8* | 2* | 2* | 26* | 25.75* |
| 5 | **L.L.** | 26 | 31 | 19 | 24 | 30 | 30.75 |
| 6 | **P.G.** | 41 | 39 | 35 | 32 | 33 | 31.75 |

**Tab.** 5. Neuropsychological assessment for LBD patients; r.s.: raw score a.s.: adjusted score, *: score below the cut off,

| | | **IA** | **IMA** | **CA** | | **BFA** |
|---|---|---|---|---|---|---|
| | | **r.s.** | **r.s.** | **r.s.** | **a.s.** | **r.s.** |
| 1 | **B.E.** | 120 | 63 | 13 | 11.2 | 19* |
| 2 | **T.G.** | 120 | 68 | 10 | 9.75 | 18* |
| 3 | **L.M.** | 115* | 48* | 11 | 10.2 | 18* |
| 4 | **G.A.** | 120 | 56 | 12 | 11.2 | 6* |
| 5 | **L.L.** | 120 | 53 | 14 | 14 | 24 |
| 6 | **P.G.** | / | 64 | 13 | 11.75 | 24 |

**Tab. 6.** Neuropsychological assessment for LBD patients; IA: Ideational Apraxia, IMA: Ideomotor Apraxia, CA: Constructional Apraxia, BFA Buccofacial Apraxia, r.s.: raw score a.s.: adjusted score, *: score below the cut off, /: test not available

| SUBTEST: | | 1 | | 2 | | 3 | | 4 | 5 | | 6 | | 7a | | 7b | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SIDE: | | R | L | R | L | R | L | B | R | L | R | L | R | L | R | L |
| 1 | **B.E.** | 27 | 27 | 30 | 30 | 30 | 30 | 12 | P | P | 29 | 30 | 30 | 30 | 23* | 30 |
| 2 | **T.G.** | 27 | 28 | 30 | 30 | 30 | 30 | 12 | P | P | 30 | 30 | 30 | 30 | 30 | 30 |
| 3 | **L.M.** | 28 | 22 | 30 | 30 | 30 | 30 | 12 | P | P | 29 | 30 | 30 | 30 | 30 | 30 |
| 4 | **G.A.** | 28 | 26 | 30 | 30 | 30 | 30 | 12 | P | P | 30 | 30 | 30 | 30 | 30 | 30 |
| 5 | **L.L.** | 23 | 25 | 30 | 30 | 30 | 30 | 12 | P | P | 30 | 30 | 30 | 30 | 30 | 30 |
| 6 | **P.G.** | 26 | 28 | 30 | 30 | 30 | 30 | 12 | P | P | 30 | 30 | 30 | 30 | 30 | 30 |
| 7 | **D.G.** | 27 | 9* | 30 | 4* | 30 | 5* | 0* | P | F* | 30 | 22* | 30 | 29 | 30 | 13* |
| 8 | **B.S.** | 26 | 20* | 30 | 25* | 30 | 17* | 8 | P | F* | 27 | 25 | 30 | 30 | 30 | 24* |
| 9 | **Z.G.** | 27 | 11* | 30 | 25* | 30 | 20* | 3* | P | F* | 28 | 26 | 30 | 30 | 30 | 19* |
| 10 | **DG.F** | 21* | 17* | 30 | 25* | 30 | 26* | 12 | P | F* | 27 | 25 | 30 | 30 | 30 | 30 |
| 11 | **C.G.** | 27 | 28 | 30 | 30 | 30 | 30 | 12 | P | P | / | / | 30 | 30 | 30 | 30 |
| 12 | **T.** | 17* | 5* | / | / | / | / | / | / | / | / | / | / | / | / | / |

**Tab. 7**. RBD patients' RASP scores. RASP subtest 1: Sharp/dull discrimination, 2: Surface pressure touch, 3: surface localization, 4: sensory extinction, 5: two point discrimination, 6: temperature discrimination, 7a: proprioception movement discrimination, 7b: proprioception movement discrimination. R: right, L: left, P: passed, F: failed *: score below the cut off

| SUBTEST: | | 1 | | 2 | | 3 | | 4 | 5 | | 6 | | 7a | | 7b | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SIDE: | | R | L | R | L | R | L | B | R | L | R | L | R | L | R | L |
| 1 | **B.E.** | 27 | 27 | 30 | 30 | 30 | 30 | 12 | P | P | 29 | 30 | 30 | 30 | 23* | 30 |
| 2 | **T.G.** | 27 | 28 | 30 | 30 | 30 | 30 | 12 | P | P | 30 | 30 | 30 | 30 | 30 | 30 |
| 3 | **L.M.** | 28 | 22 | 30 | 30 | 30 | 30 | 12 | P | P | 29 | 30 | 30 | 30 | 30 | 30 |
| 4 | **G.A.** | 28 | 26 | 30 | 30 | 30 | 30 | 12 | P | P | 30 | 30 | 30 | 30 | 30 | 30 |
| 5 | **L.L.** | 23 | 25 | 30 | 30 | 30 | 30 | 12 | P | P | 30 | 30 | 30 | 30 | 30 | 30 |
| 6 | **P.G.** | 26 | 28 | 30 | 30 | 30 | 30 | 12 | P | P | 30 | 30 | 30 | 30 | 30 | 30 |

**Tab. 8** LBD patients' RASP scores. For legend see Tab. 7

*Lesion data*

Figures 12 and 13 shows the mapping of the brain lesions for RBD and LBD patients, for whom the original brain scan (MRI or CTscan) was available, that is for 12 out of 12 RBD patients and for every LBD patient. Lesions were mapped using the software MRIcro (Rorden and Brett 2000). We reconstructed the Region Of Interest (ROI) to define the location and the size of the lesion for each patient, by using a Template Technique, i.e. by manually drawing the lesion on the standard template from the Montreal Neurological Institute. ROIs were created by mapping the regions on each and every 2D slice of a 3D volume.

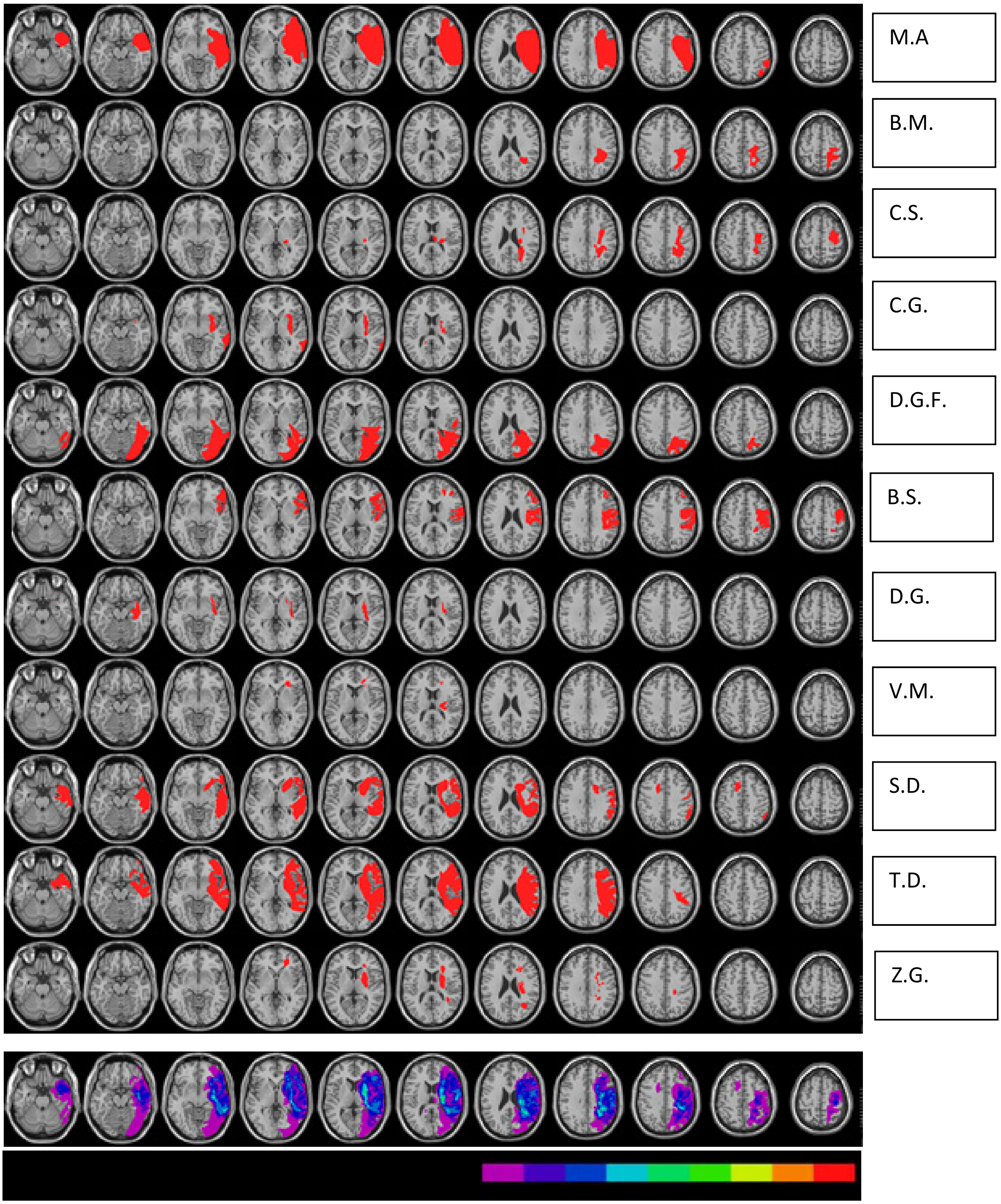

**Fig. 7.** Lesion mapping for each RBD patient: red areas represent the extension of the lesion of each single patient. In the bottom row the area of lesion overlap is shown: light blue-green areas indicate maximum overlap, pink areas minimum overlap.

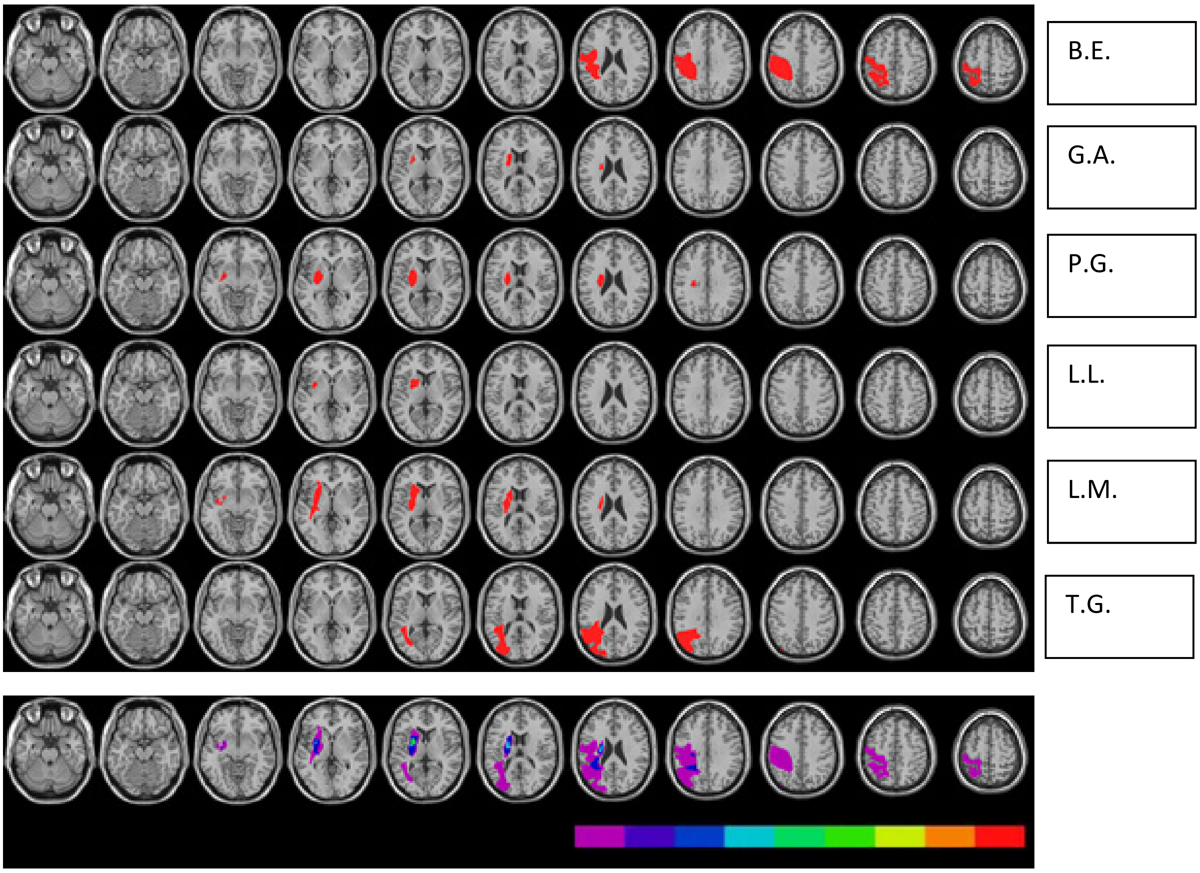

**Fig. 8.** Lesion maps of LBD patients and their lesion overlap.

*Affective go/no-go Task, Procedure, Interpersonal Reactivity index*

For a detailed description of the task, and the Interpersonal Reactivity Index see Experiment 4 (Chapter 3.1).

*Statistical analysis*

We performed a repeated-measure ANOVA on accuracy and reaction times (RTs) with the between-subject factor Group (controls, RBD, LBD) and the within-subjects factor

Condition (No-Touch vs. Touch). When appropriate, post-hoc comparisons were made with Newman-Keuls test.

**Results**

The ANOVA on the accuracy shows as significant effect the Group ($F_{2,31} = 8.47$, $p < 0.005$): post-hoc comparisons revealed that both RBD patients were significantly less accurate in the affective go-no-go task (78.5%), as compared to controls (91.4%, $p < 0.001$). No difference was found between LBD (83.8%) and RBD patients ($p = 0.17$); instead, a nearly significant difference was found between LBD patients and controls ($p = 0.052$). No other factor or interactions reached significance: Condition ($F_{1,3 1}= 1.67$, $p = 0.21$), Group × Condition ($F_{2,31} = 0.397$, $p = 068$) (Fig.9).

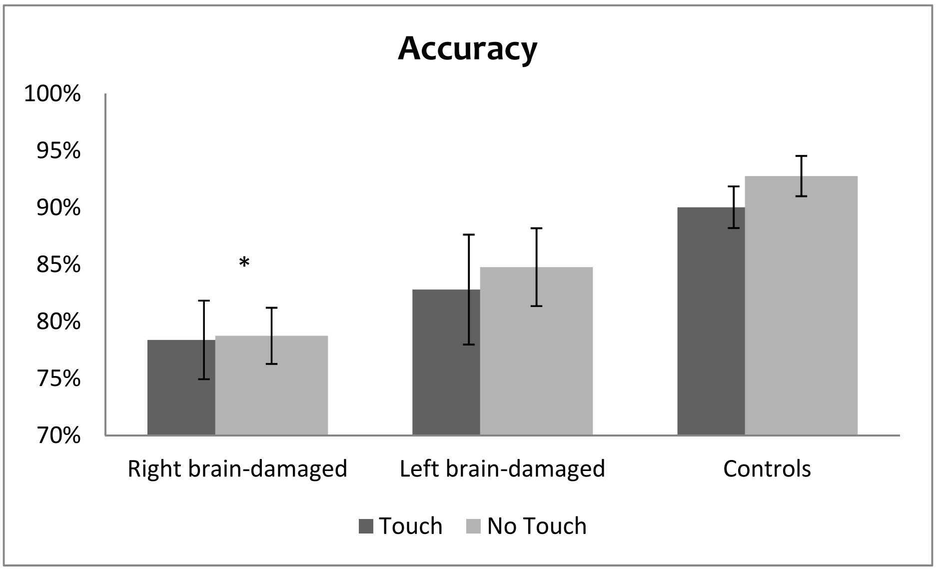

**Fig. 9.** Mean accuracy of RDB, LBD patients and controls in Touch and No-Touch conditions.

The ANOVA on RTs shows only a significant effect of the main factor Group ($F_{2,31}$ = 27.89, $p < 0.005$). The post-hoc comparisons show that RBD patients (808 ms) were slower than controls (557.8, $p < 0.001$) and LBD patients (609.8 ms, $p < 0.001$), with no differences between the last two groups ($p = 0.2$). The main effect Condition ($F_{1,31}$ = 0.11, $p = 0.7$) and the Group x Condition interaction ($F_{2,32}$ = 1.03, $p = 0.3$) did not reach significance (Fig. 10)

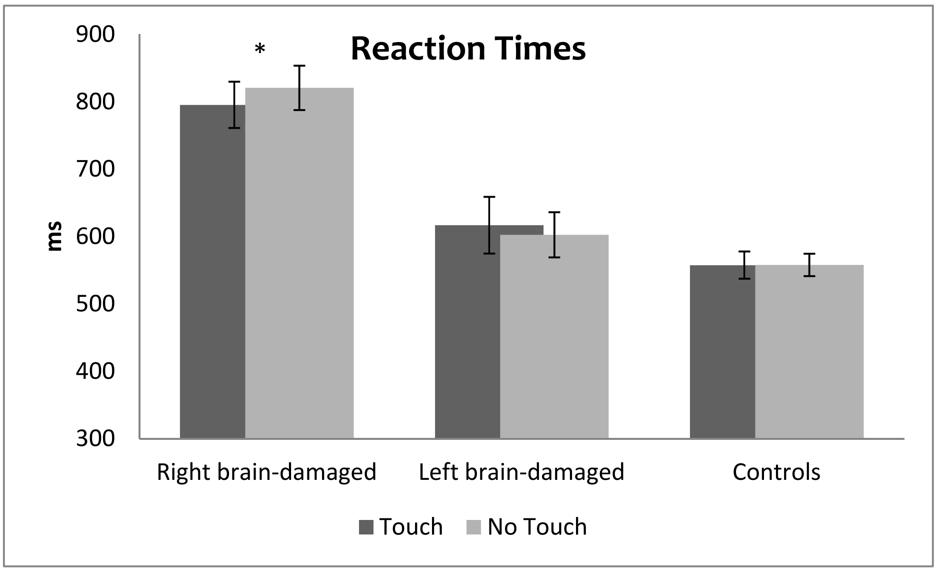

**Fig. 10.** Mean RTs of RBD patients, LBD patients and controls in touch and no touch conditions.

In order to establish whether damages to the somatosensory system would impair the ability to recognize others' somatosensations a second analysis was performed, dividing the patients according to the severity of their tactile deficit, rather than the side of the lesion as done before. Patients who had a deficit in 4 or more subtest of the RASP test were classified as patients with severe tactile deficit (i.e., T-, N=6; T+, mild/absent tactile deficit: N=12). With respect to the accuracy, the ANOVA, with Group (T+, T-, healthy controls) as between-subjects factor, and Condition (Touch, No-Touch) as within-subjects factor showed a significant effect of Group ($F_{2,31} = 7.78$, $p < 0.005$), with T- patients were less accurate (78.0%) as compared to controls (91.4%, $p < 0.005$), while no difference were found between T+ patients (81.4 %, $p = 0.4$) and controls and T-. The main effect Condition ($F_{1,31} = 1.38$, $p = 0.26$) and the Group x Condition interaction ($F_{2,31} = 0.3$, $p = 0.75$) were not significant.

The same ANOVA performed on the RTs show a significant effect of Group ($F_{2,31} = 25.28$, $p<0.001$): T- patients were slower (867.3 ms) than controls (557.8, $p < 0.001$) and T+ patients (679.3, $p < 0.001$). Moreover, T+ patients were slower than controls ($p < 0.01$). The main effect of Condition ($F_{1,31}=0.29$, $p=0.6$) and the Group x Condition interaction ($F_{2,31}=0.32$, $p=0.73$) did not reach significance.

Finally, Pearson correlational analyses were used to assess whether any difference in performance in the two experimental conditions (Touch and No-Touch) could be associated with the patients' clinical characteristics. For each patient, we calculated the difference between Touch and No-Touch condition (i.e., No-Touch minus Touch), namely the Touch Effect, for both accuracy and RTs: for accuracy, positive values indicates a better performance in the No-Touch condition, and a poorer performance in the Touch condition; viceversa for RTs (positive values= faster response in Touch condition, negative values= slower RTs in Touch condition).

First, we performed a correlation analysis between Touch Effect and the total score at the RASP; given that RASP does not provide a global score, we created an index by summing, for each patient, the number of subtests successfully completed. The correlation was not significant for the accuracy (r = 0.29, p = 0.26), nor for RTs (r= 0.07, p = 0.8). A second correlation was made between the Touch Effect and the score at Subtest 2 of RASP (surface pressure touch), which assess the ability to perceive the presence of a tactile stimulation performed by a gentle touch. This test was chosen as it appears the most suitable for measuring primary tactile defects. The correlations analysis were not significant (accuracy: r = 0.30 p=0.24; RTs: r = 0.27, p = 0.3). The Touch Effect was not associated with tactile extinction (RASP Subtest 4: accuracy, r=0.20, p = 0.43; RTs:  r= 0.18, p = 0.5).

For RBD patients, even the severity of the neglect did not correlate with the Touch Effect (Letters Cancellation: accuracy: r = -0.57, p = 0.053; RTs: r = -0.52 p = 0.079; Clock Drawing Test: accuracy: r = -0.25, p= 0.43; RTs: r = -0.39, p = 0.21; Bells Cancellation: accuracy: r = -0.17, p = 0.62; RTs: =-0.53, p=0.09). Only the mean deviation error at the Line Bisection Test was correlated with the Touch Effect indexed by RTs (r = 0.61 p < 0.05; accuracy: r=0.54 p=0.09).

A correlation analysis between IRI score and the Touch effect was performed for each group. Emphatic abilities did not correlate with the Touch Effect in RND and LBD patients and controls (accuracy: all ps > 0.05, RTs: all ps > 0.05).

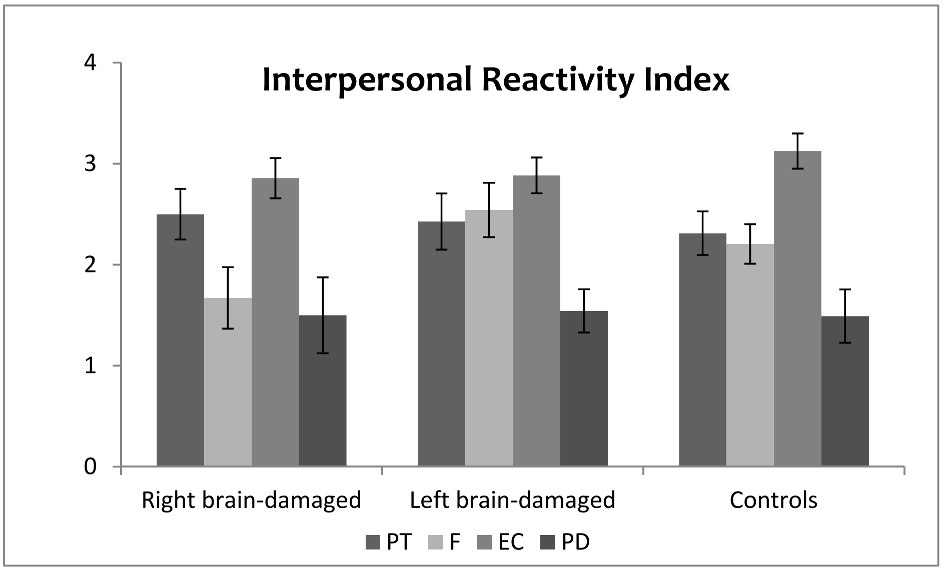

**Fig. 11.** IRI scores of RBD patients, LBD patients and controls in for each subscale (PT: perspective taking, F: fantasy, EC: emphatic concern; PD: personal distress)

Finally, the Touch Effect of every brain-damaged patient was compared of the control group with t-test, following the procedure developed by (Crawford and Garthwaite, 2005) for single case analysis. This analysis allows us to estimate the abnormality of every patient's score (i.e., the estimate of the percentage of the control population that would show a lower or larger score Touch Effect). The analysis of accuracy shows that the Touch Effect in two RBD patients (V.M., -9% and D.G.F, -9%.) and in one LBD patient (B.E., -9%) was significantly different as compared to that of the control group (3%), showing a greater accuracy in the Touch condition (t=-1.94, p<0.04) for every patient (see Fig. 12).

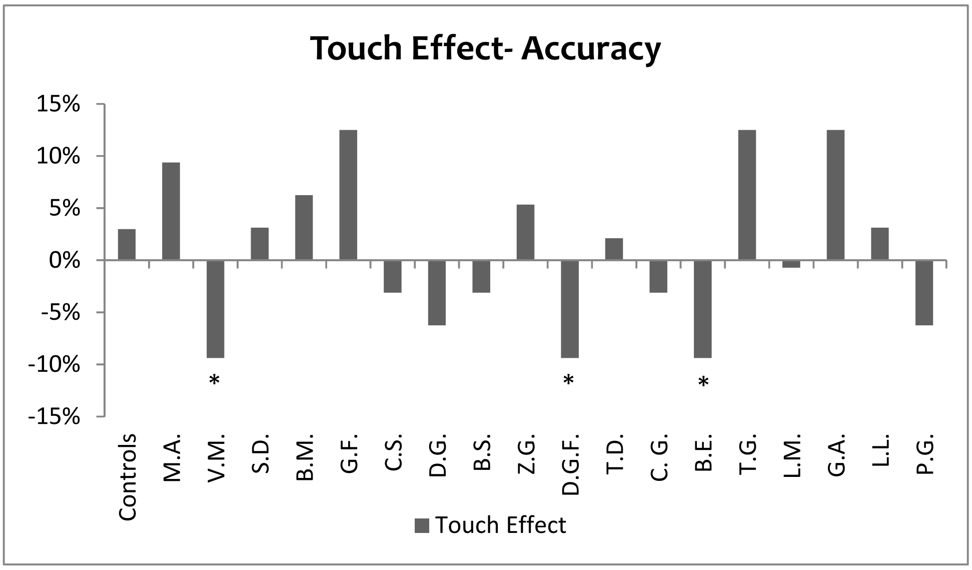

**Fig. 12.** Touch effect (RTs) for every patient and the control group

With respect to the RTs, two RBD patients, S.D. (101.0 ms, t=1.91, $p < 0.05$) and B.M. (94.67 ms, t = 1.79, $p < 0.05$) were significantly faster in responding to Touch images, as compared to controls (0.39 ms). A RBD patient, C.S. (-126.21 ms, t = 2,39 $p < 0.05$) and a LBD patient, L.M. showed the opposite effect (-113.05 ms, t = -2,152, $p < 0.05$), with slower RTs in response to Touch pictures (Fig. 13).

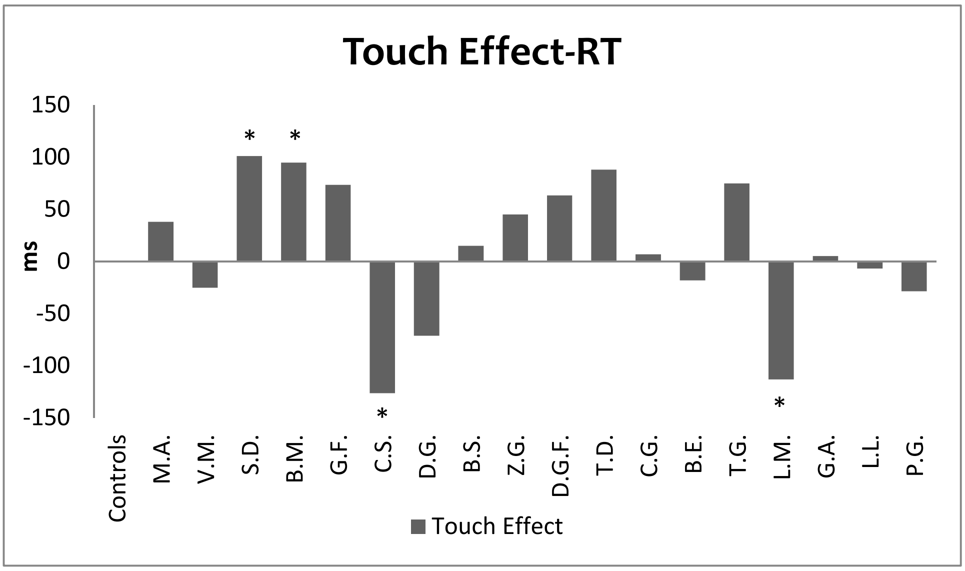

**Fig. 13.** Touch effect (RTs) for every patient and the control group

Anatomo-clinical correlations

First, in order to control whether for a possible effect of the lesion size in determining the performance at the experimental task, an analysis of the covariance (ANCOVA) was carried out on both RTs and accuracy, with the between-subjects factor Group (RBD vs LDB patients), the within-subjects factor Conditon (Touch vs No-Touch), and the Lesione size (mean volume of the lesion =61.62 ± 74cc, range= 3.5 – 241.4cc) as covariate.

The ANCOVA on Accuracy showed no significant effect: Lesion size, $F_{1,14} = 3.49$, $p = 0.08$; Group, $F_{1,14} = 0.01$, $p = 0.9$; Conditon, $F_{1,14} = 0.09$, $p = 0.76$; Condition x Lesion size: $F_{1,14} = 0.88$, $p = 0.36$; Condition X Group, $F_{1,14} = 1.09$, $p = 0.32$. The ANCOVA on RTs showed a significant effect of Group ($F_{1,14} = 9.83$, $p < 0.01$), confirming that RDB patients were slower to respond to the visual presentation of affective pictures. No other effect or interaction reached significance: Lesion size, $F_{1,14} = 0.01$, $p = 0.93$; Conditon, $F_{1,14} = 0.93$, $p = 0.35$; Condition x Lesion size, $F_{1,14} = 3.43$, $p = 0.09$; Condition X Group, $F_{1,14} = 0.05$, $p = 0.83$). These results indicate that the lesion size did not influence the performance of RBD and LBD patients.

Then, in order to verify whether the Touch Effect (No-Touch minus Touch responses), indexed by both RTs and accuracy as described above, was correlated with a damage to specific regions of the mirror-touch system, Pearson correlations analysis was conducted for each group of patients (i.e., RBD, LBD) between the Touch Effect and the lesion size (i.e., number of voxels) in the ROI of the premotor cortex (PM), the insula (I), the postcentral gyrus (PCG), the inferior parietal lobule (IPL) and the superior temporal sulcus (STS); these areas were selected as they constitute the core regions of the mirror touch system, as shown in previous brain imaging experiments (see, e.g., Blakemore et al, 2005). For the RBD patients no correlation was found between Touch Effect and the areas of the putative mirror-touch system in the right hemisphere, with respect to both the error rate (PM: r = -0.15, p = 0.67; I: r = 0.28, p = 0.4; PCG: r = 0.24, p = 0.47; IPL: r = 0.06, p = 0.86; STS: r= 0.48, p = 0.13) and the RTs (PM: r = 0.23, p = 0.52; I: r = 0.55, p = 0.1; PCG: r = 0.47, p = 0.17; IPL: r = 0.59, p = 0.07; STS: r= 0.54, p = 0.11). Similarly, for LBD patients no correlations were found between Touch effect in error rate and left mirror-touch areas (PM: r = -0.60, p = 0.21; I: r = -0.44, p = 0.38; PCG: r = -0.60, p = 0.21; IPL: r = 0.60, p = 0.21; STS: r= 0.41, p = 0.42). However, a negative correlation was found between Touch Effect indexed by RTs and the left insula (r=-0.9, p < 0.05), suggesting that that greater was the insular damage, smaller was the Touch Effect, for the RTs consisted in slower RTs in the Touch condition . No other correlation were found for the RTs (PM: r = -0.03, p = 0.96; PCG: r = 0.03, p = 0.96; IPL: r = 0.06, p = 0.96; STS: r = 0.61, p = 0.2).

## Discussion

The results of Experiment 5 do not fully support the previous finding emerged in healthy subjects (see Experiment 4a-b). RBD patients show a worst performance in the affective go-no-go task than both the LBD patients and controls, but regardless of

Touch or No-Touch condition. This may suggest that a brain damage to the right hemisphere would overall affect the ability to visually understand the valence of emotional scenes. This result is in line with neuropsychological evidence showing that a damage to right somatosensory cortices impairs recognition of basic emotions, making intensity judgments from photographs, and emotional concept retrieval (Adolphs et al., 1997, 2000; for TMS evidence see Pitcher et al., 2008; Pourtois et al., 2004). The advance from the previous study is the demonstration that the impairment induced by a right-hemisphere damage it is not restricted to the coding of emotion expressed by faces (here, mainly represented by the No-Touch condition), but also to the coding of more complex interpersonal interactions, as shown in Touch conditions.

Overall, no correlation was found between clinical features of the patients, and the responses to Touch and No-Touch stimuli. Given the role of SI in visual processing of touch that clearly emerged in the previous TMS studies, a main prediction was to find a relation between the severity of tactile deficit (i.e., an index of somatosensory cortical damage), and difference in performance in Touch and No-Touch conditions. Instead, the results showed that patients with a severe somatosensory impairment had poorer performance at the experimental task, but regardless of the tactile content of the images. It is worth to note that the patients with severe somatosensory sensory deficits were globally more impaired in other sensori-motor and cognitive domains, as shown in Table 1-2. For instance, the six patients with severe tactile deficit, all RBD, also showed motor deficits; four of them had USN, and five showed visual field deficits. This is indicative of an extensive brain lesion, which was indeed confirmed by their lesion profile. One could speculate that the functioning of this system requires the integrity of supplementary areas, such as the parietal and motor cortices. Therefore the presence of wide lesions may have indirectly affected its proper functioning.

The analysis of the lesion data show no effect of the lesion size on the patients' behavioural performance, ruling out a possible interpretation of the impairment in the experimental task shown by RBD patients as merely due to a large extension of the lesion in RBD patients, as compared to LBD patients. This evidence supports the right-hemisphere involvement in the affective go-no-go performance, in line with previous TMS evidence (Bermphol et al, 2005). However, the RBD impairment was not associated to a specific damage of one of the key areas of the mirror-touch system (Blakemore et al., 2005), nor the lesion of somatosensory cortical areas, as predicted by the results of my TMS experiments. The only effect found was a significant correlation for LBD patients between the Touch Effect in RTs and the lesion of the left insula; this may suggest that patients with a left insular damage were slower to respond to affective picture depicting a tactile experience. As discussed in Chapter 1.4, mirror-touch synaesthesia seems specifically related to the bilateral activation of the anterior insula cortex (AI); instead, such activation by the sight of touch seems absent in the non-synesthetic individuals (Blakemore et al., 2005). On the other hand, neuroimaging studies have shown the role of AI in empathy (for a review see Singer et al., 2009; Bernhardt and Singer, 2012). For instance, bilateral anterior insular activity when painful stimulation was experienced and when observing their partner in pain (Singer et al., 2004). This effect correlated with the Empathic Concern Scale of the IRI and the Balanced Emotional Empathy Scale (Mehrabian and Epstein, 1972) suggesting that subjects with marked empathic traits had stronger AI activation during pain observation. Moreover alexithymia, i.e. the difficulty to describe and recognize emotions, is linked to altered activity of insula (Ernst et al., 2013, Silani et al., 2008). Despite intriguing, this evidence did not enlightened a specific role of insula in processing painful cutaneous stimulations; moreover AI was shown to be associated with the affective but not the sensory qualities of empathic pain (Singer et al., 2004). With respect to the present findings, the association between the left insula damage, and the performance in our experimental task should be taken with cautious given our sample size is pretty small, also considering that overall LBD patients were not impaired at this task. Pearson correlation is overly sensitive to outliers, and a single outlier can result in an inaccurate summary of the data (Pernet et al., 2012). In the same way, we must be cautious about absent correlations in RBD patients.

No difference in empathic ability emerged between right and left brain-damaged patients and control group, and it does not correlate with the performance gave to experimental task.

Finally, we analyzed each patient's performance per se, comparing with the scores of the control group. Four right brain-damaged patients (V.M., D.G.F., S.D., B.M.) and a left brain-damaged patient (B.E.) scored better performance with "touch" images; on the contrary a right brain-damaged patient (C.S.) and left brain-damaged patient (L.M.) benefited from viewing "no touch" images. Again the available data are not sufficient to make certain assumptions.

In conclusion, the present TMS and neuropsychological experiments confirmed a right hemispheric specialization of S1 in coding the affective go/no-go visual tasks. The major advance is offered by the TMS experiments, which clearly show that the visual processing in SI is not restricted to the processing of emotions conveyed by facial expressions; rather this area is crucial for the encoding the pleasant and aversive consequences of others' sensations evoked by touch. The results from the neuropsychological study are, so far, inconclusive with respect to the specificity of the somatosensory cortical involvement in the understanding of others' tactile experience; this aspect would benefit of a lager sample of RBD patients.

# CHAPTER 4

# INDUCTION, CHRONOMETRY AND FUNCTIONAL CONNECTIVITY OF MIRROR-TOUCH SYNAESTHESIA

## *4.1 Experiment 6: Induction of mirror-touch synaesthetic-like responses by increasing cortical excitability of the mirror-touch system*

### Aim of the study

In previous chapters we provided evidence of the existence of a 'mirror' network for somatosensation in the human brain. So far, more direct and convincing evidence that the mere observation of others' somatosensations can really cause a somatic activation in the observer is still needed. In this perspective, the study of mirror-touch synaesthesia, an intriguing crossmodal phenomenon in which the visual perception of touch elicits conscious tactile experiences on the observer's body (Fitzgibbon et al., 2012, cfr. Chapter 1.4), offers the ideal framework for testing the existence of shared representations for viewing and experiencing touch, the neural underpinnings of these mechanisms and their involvement in social perception and empathy.

The study of a case of mirror-touch synesthesia has indeed suggested that a potential mechanism involved in the conscious feeling of being touch by viewing others' tactile experience may be related to an abnormal, hyper-activation of the mirror system for touch (Blakemore et al., 2005; Fitzgibbon et al., 2012). In particular, as discussed in Chapter 1.4, Blakemore and coworkers (2005) showed that both people with or without mirror-touch synesthesia activate overlapping areas of the brain when observing and experiencing touch, including SI and SII (Blakemore et al., 2005). However, in subjects with mirror-touch synaesthesia, the tactile mirror system, and specifically SI, appears to be overactive, above the threshold for inducing a conscious tactile perception, such that observing touch results in a conscious somatic experience (Blakemore et al., 2005). However, this hypothesis requires empirical support. Here, we aim at demonstrating the existence of a causal brain-behaviour relationship between increased excitability of SI and the emergence of synaesthesia-like responses and sensations in non-synaesthetic subjects. Furthermore, we also explored the chronometry of the processing of the visual touch in SI.

To this aim, we take advantage of a facilitatory paired-pulse transcranial magnetic stimulation (ppTMS) protocol and of a behavioural task specifically developed for assessing mirror-touch sinesthesia (Banissy and Ward, 2007), namely the visual-tactile spatial congruity task (Banissy and Ward, 2007; Bolognini et al., 2013), described in Chapter 1.4 (see below for details). In ppTMS stimulation two magnetic stimuli are delivered in close sequence to the same cortical region through a single stimulation coil. The first (conditioning) stimulus (CS) modifies the response to the second (test) stimulus (TS). The effects of the ppTMS depend on the intensity of the CS and TS, and the interval between the stimuli (Pascual-Leone et al., 1992). The intensities of the CS and TS influence the effects as different circuits are recruited by different intensities of stimulation. The ISI influences the results as the time constant of each activated circuit may differs (Kujirai et al., 1993).

In this study, we explored the relation between different aspects of empathy (i.e., cognitive vs. affective empathy) and the conscious and unconscious simulation of others' sensations.

## Materials and method

### *Participants*

Fourteen healthy, right-handed individuals (12 females; mean age= 26 ±4 years) participated in the study. All participants gave their written informed consent and were naïve to the purpose of the study.

None of the participants had neurological, psychiatric or other relevant medical problems or any contraindications to TMS (Rossi et al., 2009). The protocol was carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302: 1194) and approved by the local ethical committee.

At a preliminary interview, the participants did not report mirror-touch synaesthesia.

### *Visual-tactile spatial congruity task (adapted from Banissy and Ward, 2007; Bolognini et al., 2013)*

The subjects sat at a distance of 50 cm in front of a PC monitor (Samsung SyncMaster 1200NF) and were shown video clips of the experimental conditions on a dark screen background (luminance=0.1 cd/m$^2$). Each trial started with a fixation frame depicting a left-sided left hand and a right-sided right hand (hands size=15°X4.5°, luminance=28 cd/m$^2$), as seen from an egocentric view. Images were presented at 8° of visual angle eccentricity from the central fixation point. Then, a video clip comprising four frames (duration= 310 ms) was shown, with an index finger approaching and touching the right or left hand. Ten milliseconds after the presentation of the final frame, which depicted the touch to the hand and remained on the screen for one second, the participants received a tap (duration= 20 ms) to the back of their left or right hand, which was administered through miniature solenoid tappers (diameter= 0.8 cm, Heijo Research Electronics, UK, www.heijo.com) attached to back of each hand with a velcro strap. The tactile stimulus could be spatially congruent (i.e., visual stimulus on the same side as the actual touch) or incongruent (i.e., visual stimulus contralateral to the actual touch) with the viewed touch (Fig. 1). The participants were asked to fixate the central point and report, as quickly and accurate as possible, the location of the actual touch while ignoring the viewed touch by pressing a key on the left side of a keyboard with the index finger of their right hand when they received a touch to the left hand, or a key on the right side of the keyboard with the middle finger of their right hand in response to a touch to their right hand. As shown by Banissy and Ward (2007), individuals with mirror-touch synaesthesia are more error prone and slower in responding to incongruent vision-touch trials, as compare to subjects without mirror-touch synaesthesia, because they got confused by the synaesthetic touch (See Chap. 1.4).

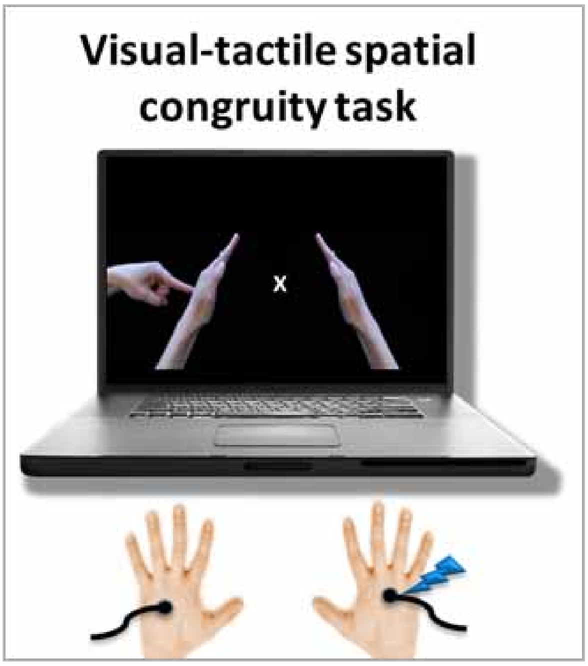

**Fig.1:** Visual-tactile spatial congruity task. An incongruent visuo-tactile trial is shown, with a left-sided visual stimulus and a right-sided touch. Subjects were asked to report the site of the actual touch on the hand while ignoring the viewed touch. .

*TMS protocols*

The individual resting motor threshold (rMT) was determined for each participant by stimulating the hand area of the right MI with single TMS pulses (cfr. Chap 2) delivered using a Magstim BiStim$^2$ transcranial magnetic stimulator (Magstim Company, Whitland, UK) connected with a figure-of-eight coil (Ø=80 mm in Experiment 1, Ø=50 mm in Experiment 2). The mean rMT was 39.7 ± 6.8% of the maximal output of the stimulator.

The appropriate location for stimulating the SI hand area of the right hemisphere was identified using the functional procedure described in Experiment 1. Almost every subject reported paresthesia in the contralateral hand; 78% of the participants showed a deficit (mean percentage of omissions = 13.21%) in detecting a contralateral touch in bilateral or unilateral trials.

Paired-pulse stimuli were delivered to SI through the figure of-eight coil (Ø=80 mm) connected to the BiStim$^2$ module. The coil was placed tangential to the skull over the SI. During the ppTMS stimulation we delivered a subthreshold CS set at 70% of the rMT. After 5 ms, the suprathreshold TS, set at 130% of the rMT, was applied. This protocol was shown to be effective for probing facilitatory intracortical circuits in somatosensory regions (Oliveri et al., 2000) (Fig 2). During the task, in each trial, a ppTMS stimulus was applied to the SI at four different ISIs with respect to the onset of the last frame of the video clip, showing the hand being touched by the finger (i.e., visual touch), namely at 50, 150, 250 and 350 ms from the onset of the visual touch.

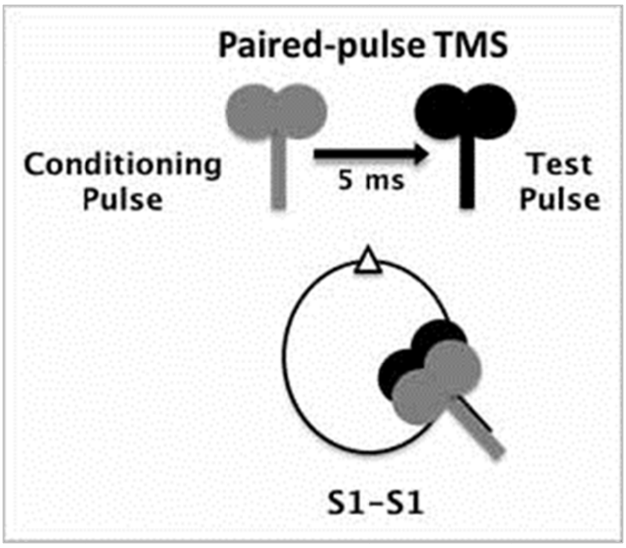

**Fig.2:** Schematic representation of the ppTMS paradigms of Experiment 6. A sub-threshold conditioning TMS pulse (CS, grey coil) was followed by the supra-threshold test TMS pulse (TS, black coil) after a delay of 5 ms. The CS intensity was 70% and the TS was 130% of the resting motor threshold. CS and TS were both applied to the right SI

*Experimental procedure*

Subjects were comfortably seated in an armchair in a quiet, dimly illuminated room. Before the experiment, the participants underwent a training session to become familiarized with the task. The experiment consisted of two experimental sessions, given in a counterbalanced order: the participants performed the task in a baseline condition, without ppTMS, and while receiving ppTMS to the right SI. The ppTMS was delivered in four randomly intermingled blocks of trials corresponding to the four ISIs.

The task comprised 12 randomly intermingled trials for each stimulus type were given, with 24 congruent vision touch trials (12 left-sided, 12 right-sided) and 24 incongruent vision-touch trials (12 left touches combined with right-sided visual stimuli, 12 right touches combined with left-sided visual stimuli), for a total of 48 trials for the baseline and each ppTMS ISI. The inter-trial interval varied between 5 and 7 seconds to prevent any carry-over effects of the ppTMS. The sequence and timing of the vision-touch stimuli and ppTMS pulses, as well as the recording of the responses, were under computer control (E-Prime, Psychology Software Tools Inc.). The total duration of each experiment was approximately 90 minutes. The participants tolerated the ppTMS well and did not report any side effects.

*Subjective reports and Interpersonal Reactivity Index*

After each experimental session, participants completed a questionnaire, comprising four measures of mirror-touch synaesthetic feelings. The items were as follows:

1. "I felt a touch on my hand when I saw the hand being touched"
2. "When I saw the hand being touched, it was more difficult to localize the actual touch"
3. "It was difficult to localize the touches on my hands"
4. "The viewed touch appeared to be very intense"

For each item, the participants rated their agreement using a five-point Likert scale: -2=strongly disagree, -1=disagree; 0=neither agree nor disagree, +1=agree, +2=strongly disagree. Values above zero indicated agreement, and therefore the presence of mirror-touch synaesthesia, whereas values below zero indicated disagreement. At the end of the experiment, participants were also required to complete the IRI (Davis, 1983, see Chap 3, Experiment 4).

*Statistical analyses*

A repeated-measures ANOVA was performed on the participants' mean percentage of errors and reaction times (RTs), with the following within-subjects factors: ppTMS interval (Baseline, ppTMS at 50 ms, 150 ms, 250 ms and 350 ms), Side (the location of the actual touch with respect to the ppTMS side, namely ipsilateral or contralateral to the right ppTMS) and Stimulus (congruent vision-touch or incongruent vision-touch).

Post-hoc multiple comparisons were conducted with the Bonferroni post-hoc test, using an $\alpha$ value divided by the number of comparisons. RTs above or below two standard deviations from the mean, computed for each experimental condition, were considered anticipations and retards respectively, and then discarded from the analyses. The effect size in the ANOVAs was measured by calculating the partial Eta Squared ($p\eta^2$).

Wilcoxon signed rank tests were used to analyze the response for the Baseline and for the ppTMS session at each item of the self-report questionnaire. Spearman's rank correlation analysis was used to explore any possible correlation between subjects' response at each item of the questionnaire compiled after the Baseline and the ppTMS session and the performance at the visuo-tactile task in the Baseline and the ppTMS session.

Finally Pearson's correlations were performed to assess the possible association between the ppTMS effect and the participants' scores at each IRI subscale.

### Results

A five (four ppTMS intervals plus the baseline) by two (Side: actual touch ipsilateral or contralateral to ppTMS) by two (Stimulus: congruent vision-touch, incongruent vision-touch) repeated-measures ANOVA was conducted on the participants' error rate.

The main factor ppTMS resulted significant ppTMS resulted significant ($F_{4,52} = 5.79$ $p < 0.001$, $p\eta^2 = 0.31$), showing that error rate during ppTMS after an ISI of 150 ms differs from Baseline. The main factor Side and Stimulus also resulted significant (Side: $F_{1,13}$= 5.65, $p < 0.05$, $p\eta^2 = 0.30$; Stimulus: $F_{1,13} = 20.30$, $p< 0.001$, $p\eta^2 = 0.61$), showing that subjects made more errors on the side ipsilateral to the TMS and in the incongruent trial. The interactions ppTMS by Side ($F_{4,52}$= 3.79, $p < 0.01$ $p\eta^2 = 0.23$) ppTMS by Stimulus ($F_{4,52}$=5.85, $p < 0.001$, $p\eta^2 = 0.31$) and Side by Stimulus ($F_{4,52}$= 6.77, $p < 0.005$, $p\eta^2 = 0.34$) also resulted significant.

Crucially, the ppTMS intervals by Side by Stimulus interaction was significant ($F_{4,52=}$ 3.93, $p < 0.01$, $p\eta^2 = 0.32$ ). As shown in Figure 3, ppTMS applied to the SI after an ISI of 150 ms from the visual touch increased the errors in the incongruent vision-touch trials (27%), but only when the actual touch was on the participant's right hand (ipsilateral to ppTMS) and the visual touch was left-sided (contralateral to ppTMS) ($p < 0.01$ for all comparisons). With the other ISIs, SI stimulation did not affect performance compared with the baseline (all $ps \geq 0.3$).

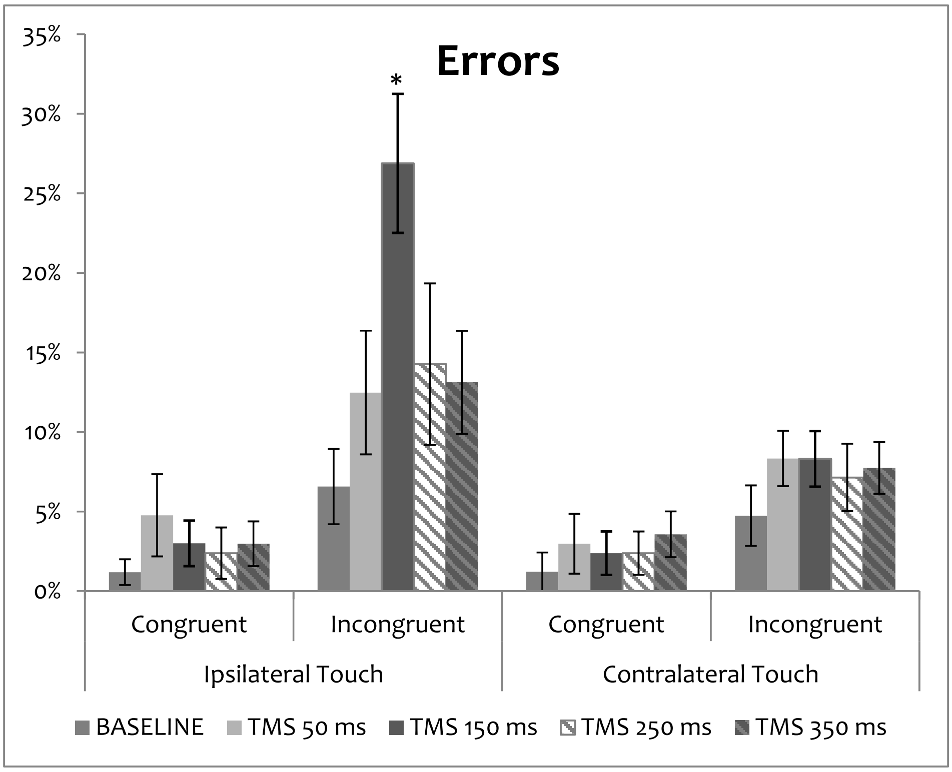

**Fig. 3** ppTMS effects on behavior. Mean error rate in each experimental condition. Error bars = S.E.

The ANOVA conducted on the participants' RTs showed the significant main factors Side ($F_{1,13}$= 12.54, p < 0.01, $p\eta^2$ = 0.49) and Stimulus ($F_{1,13}$ = 40.22, p < 0.001, $p\eta^2$ = 0.76), showing that subjects' performance was slower to respond to stimuli on the side ipsilateral to the TMS and in the incongruent trial. The analysis also showed the significant interaction ppTMS interval by Side was significant ($F_{4,52}$ = 4.39, p < 0.005, $p\eta^2$ = 0.25) as stimuli delivered to the contralateral (left) hand were slower detected (433.4) when the ppTMS was applied to SI after an ISI of 50 ms from the visual touch. No Other main effect or interaction resulted significant (ppTMS: $F_{4,52}$= 2.21, p = 0.08;

ppTMS by Stimulus: $F_{4,52}$=1.06, p = 0.39; Side by Stimulus: $F_{1,13}$= 2.06, p= 0.14) ppTMS by Side by Stimulus: $F_{4,52}$= 0.24, p = 0.92).

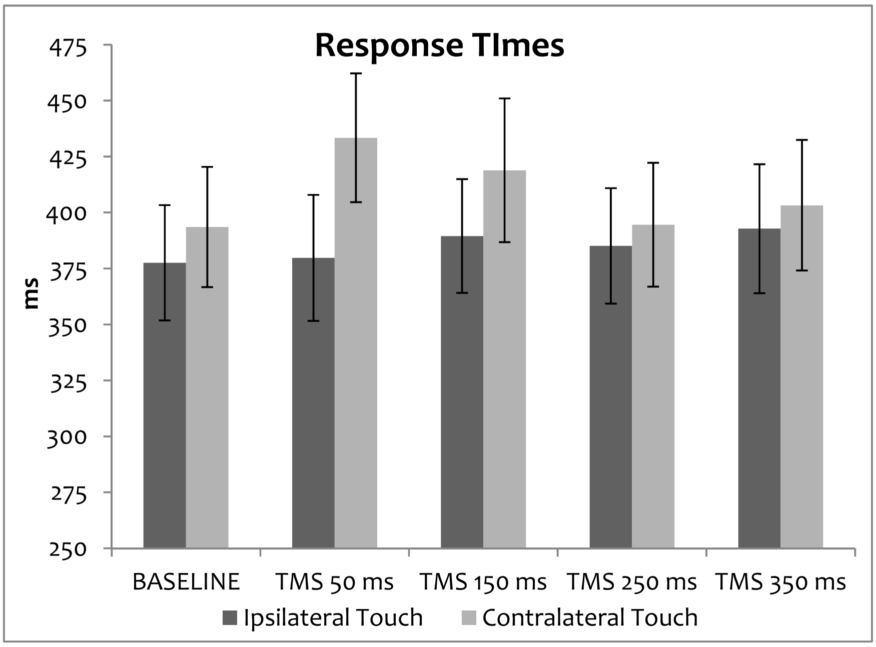

**Fig. 4** ppTMS effects on behavior. Mean RTs in each experimental condition. Error bars = S.E.

The subjective reports at the questionnaires administered after the Baseline and the ppTMS session are illustrated in Figure 4. The participants reported an increased difficulty in touch localization due to the sight of touch (Item 2) during the ppTMS of SI, compared with the baseline (Z = 2.25, $p < 0.05$). Moreover, participants were less confident that the viewed touch could not be felt on their hands (Item 1) following SI stimulation compared with the baseline (Z = 2.37, $p < 0.05$). In contrast, no changes in the subjective judgments after the ppTMS of SI emerged for questions not inquiring specifically about the visually induced sensations, namely, the overall difficulty of the tactile task (Item 3, Z = 1.78, p = 0.08) and the degree of intensity of the viewed touch (Item 4, Z = 0.94, p = 0.35). Notably, the scores on Items 1 and 2, namely the feeling of being touched by viewing a touch and the visually induced difficulty in touch localization, respectively, were both correlated with errors in the incongruent vision-touch trials (with touch ipsilateral to TMS) induced by ppTMS to SI at 150 ms (Item 1, rs = 0.85, p < 0.001; Item 2, rs = 2.15, p = 0.05). No other significant correlations were found for the SI effect at 150 ms (all ps > 0.4), nor between the subjective reports at the questionnaire and the error rates in the incongruent trials at baseline (all ps > 0.1) or during ppTMS delivered at ISIs of 50, 250 or 350 ms (all ps > 0.09).

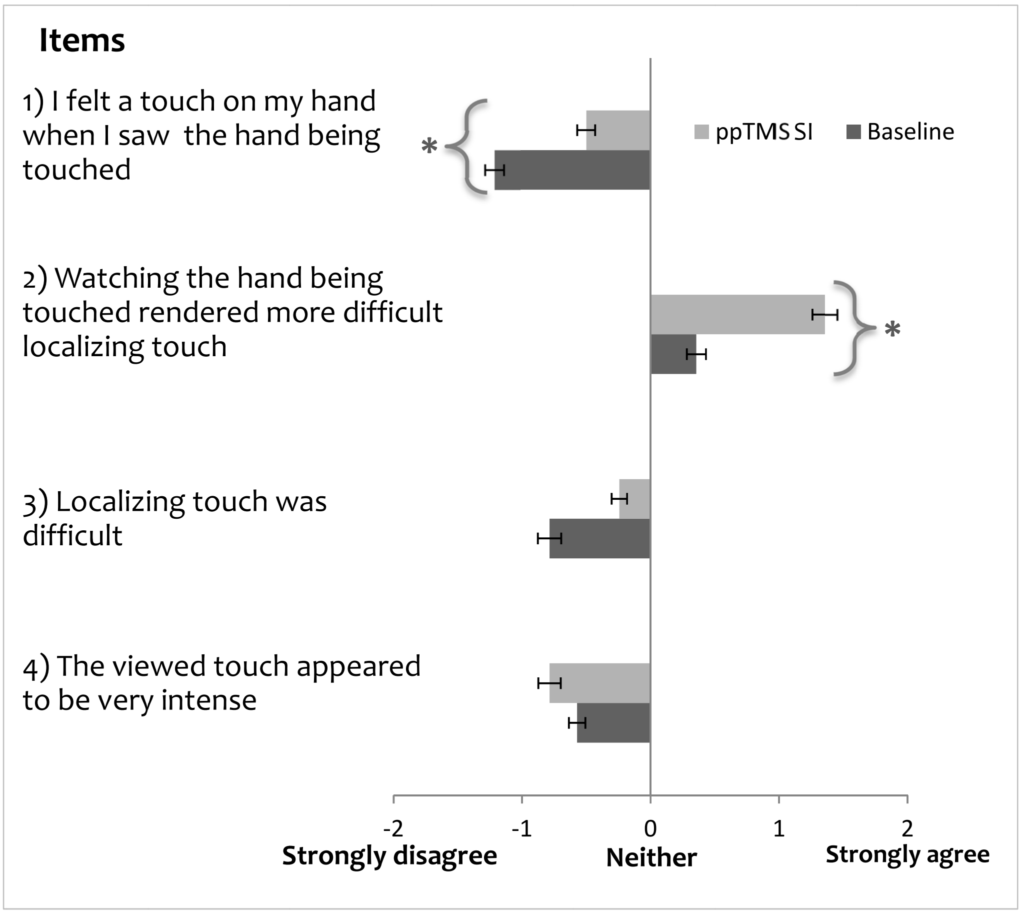

**Fig. 5**. Subjective reports of synaesthesia-like sensations assessed with a 5-points Likert scale, obtained after the baseline and the ppTMS session. Values above 0 indicate agreement and therefore the presence of mirror-touch synaesthesia, whereas values below 0 indicate disagreement. Please note that the actual Item 2 and 3 were slightly longer than what is reported in the figure, see the main text for actual questions. Error bars = S.E.

Finally, the behavioral effect of SI stimulation was also related to inter-individual differences in specific aspects of empathy, as measured by the IRI (Figure 6). The increased error rate in incongruent trials induced by ppTMS of SI at 150 ms was positively correlated with the score at the IRI's subscales PT ($r = 0.85$, $p < 0.001$) and EC ($r = 0.61$, $p < 0.05$): higher scores in these empathic measures were associated with higher vision-touch interference by SI stimulation, as shown in Figure 6a. PT measures the tendency to cognitively imagine a situation from the other person's point of view, whereas EC reflects a person's tendency to have feelings of sympathy and concern for others. Moreover, the subjective feeling of being touched by seeing touches (Item 1 reported in Figure 5) was correlated with the EC score ($rs = 0.65$, $p < 0.05$), as shown in Figure 6b, whereas visually induced difficulty in touch localization (Item 2 reported in Figure 5) was correlated with the PT score ($rs = 0.68$, $p < 0.005$), as shown in Figure 6c. No other significant correlations were found between the subjective judgments and the ppTMS effect (all $ps > 0.08$).

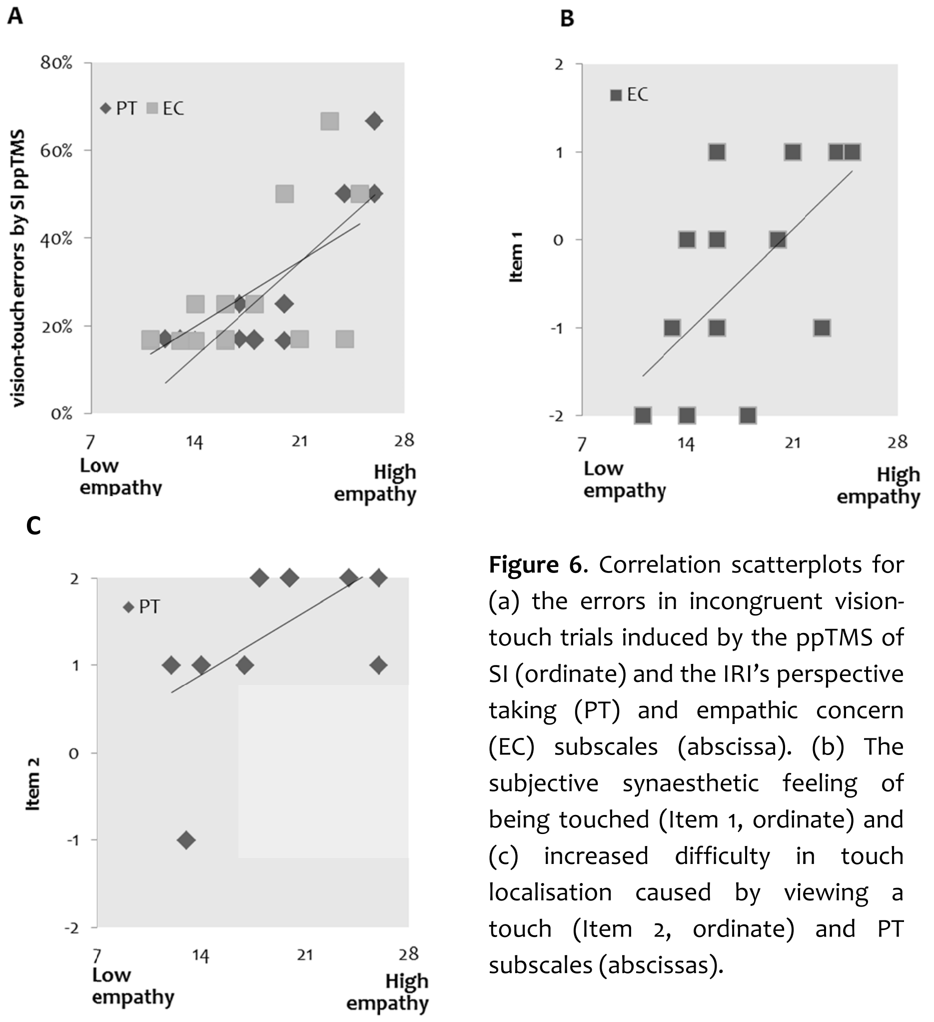

**Figure 6**. Correlation scatterplots for (a) the errors in incongruent vision-touch trials induced by the ppTMS of SI (ordinate) and the IRI's perspective taking (PT) and empathic concern (EC) subscales (abscissa). (b) The subjective synaesthetic feeling of being touched (Item 1, ordinate) and (c) increased difficulty in touch localisation caused by viewing a touch (Item 2, ordinate) and PT subscales (abscissas).

## *Control Experiment*

A control experiment was carried out to confirm that the ppTMS effect was specifically related to the processing of visual touch. We posit that no change in tactile localization during the ppTMS of SI at 150 ms should be induced if subjects viewed static images of hands, rather than video clips showing touches to a hand.

## Materials and method

The stimuli, task and TMS procedure were identical to those described for Experiment 6, but during the task, the participants watched a video clip comprising four frames depicting a static image of the left-sided left hand and the right-sided right hand. This task was performed in two experimental sessions in a counterbalanced order: a baseline without ppTMS and with ppTMS delivered to the SI with the critical ISI of 150 ms.

### *Partecipants*

Twelve participant took part at the control experiment (11 females; mean age=26 ±3 years). At a preliminary interview, the participants did not report mirror-touch synaesthesia. In this experiment, their mean rMT was 39.1 ±7.1% of the maximal output of the stimulator. With respect to the functional localization of SI, every subject reported paresthesia in the contralateral hand; 72% of the participants showed a deficit in detecting a contralateral touch in bilateral or unilateral trials.

### *Statistical analysis*

A repeated-measures ANOVA was performed on the participants' mean percentage of errors and reaction times (RTs), with the following within-subjects factors: ppTMS (Baseline, ppTMS at 150 ms) and Side (actual touch ipsilateral or contralateral to the TMS).

## Results

The ANOVA did not show any significant effects. Errors: ppTMS ($F_{1,11}$ = 0.37, p =0 .6, $p\eta^2$=0.03), Side ($F_{1,11}$ = 0.18, p = 0.7, $p\eta^2$ = 0.02), ppTMS by Side ($F_{1,11}$ = 0.98, p = 0.4, $p\eta^2$=0.06). RTs: ppTMS ($F_{1,11}$ = 0.03, p = 0.9, $p\eta^2$ = 0.01), Side ($F_{1,1\,1}$= 0.52, p = 0.48, $p\eta^2$ = 0.05), ppTMS by Side ($F_{1,11}$ = 0.27, p = 0.6, $p\eta^2$ = 0.02).

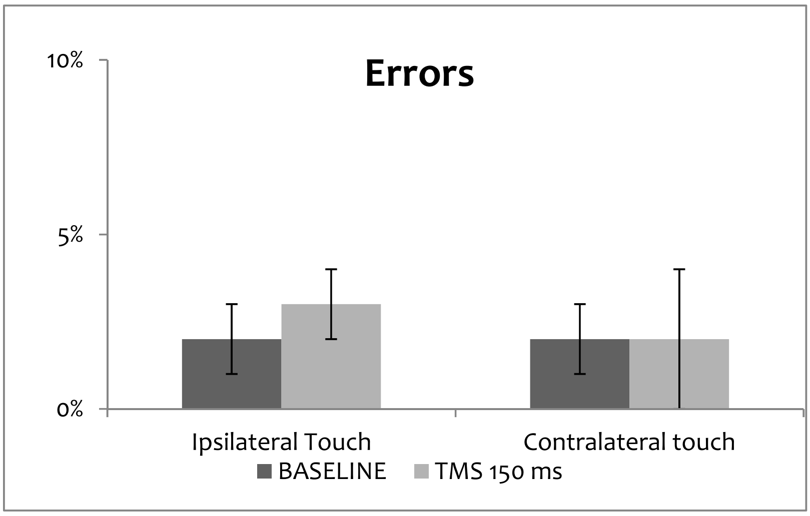

**Fig. 7** ppTMS effects on behavior. Mean values for the error rate in each experimental condition. Error bars = S.E.

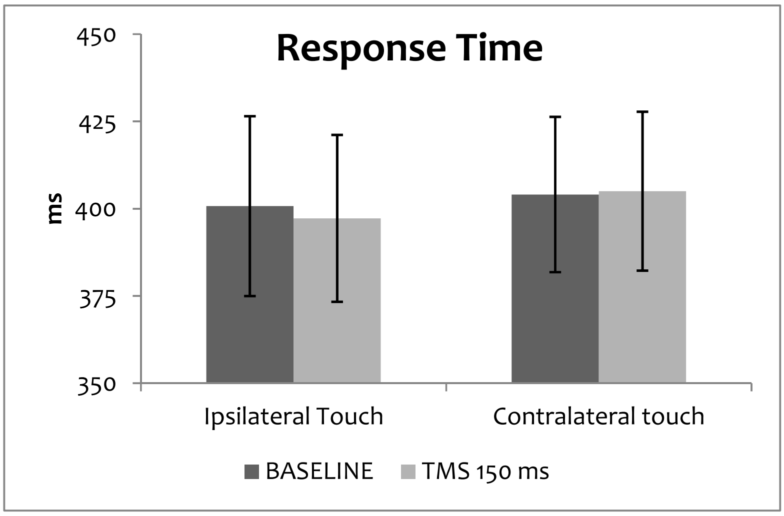

**Fig. 8 Control experiment**. Mean RTs in each experimental condition. Error bars = S.E.

## *4.2 Experiment 7: Functional connectivity in mirror-touch synesthesia*

### Aim of the study

In the current experiment we aimed to further explore the neural mechanism below mirror-touch synaesthesia, by assessing the functional connectivity between SI and the posterior parietal (PPC) and the premotor cortices (PM) in mirror-touch syaesthetic-like phenomena. These areas were chosen since both are part of the tactile mirror system and may be over-active in mirror-touch synaesthesia (Blakemore et al., 2005).

### Materials and method

*Participants*

Fourteen participants took part at the experiment (13 females; mean age=25±4 years), following the same exclusion criteria of Experiment 7. The protocol was carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302: 1194) and approved by the local ethical committee.

At a preliminary interview, the participants did not report mirror-touch synaesthesia. In this study, the mean rMT was of 40.0 ± 6.7%.

*Task, procedure*

The stimuli, task and the experimental procedure in Experiment 7 were identical to Experiment 6; Experiment 7 was different 1 only with respect to the ppTMS protocol.

TMS protocol

In different sessions: in one session, ppTMS was applied to the right SI, as in the previous study, but now using a smaller figure-of-eight coil (Ø=50 mm); in two other sessions, the sub-threshold CS was applied to the PPC (i.e., PPC-SI stimulation) or to the PM (i.e., PM-SI stimulation), and after 5 ms, the TS was applied to the SI by using two 50-mm figure-of-eight coils connected to the BiStim2 module (see Fig. 9). With respect to the functional localization of SI, almost every subject reported paresthesia in the contralateral hand; 84% of the participants showed a deficit (mean percentage of omissions=16%) in detecting a contralateral touch in bilateral or unilateral trials.

In this experiment, in every session ppTMS was delivered only with an ISI of 150 ms with respect to the onset of the visual touch, given the results from Experiment 6. For the stimulation of the right PPC the coil was placed over P4 according to the International 10/20 EEG system, a location that overlays the intraparietal sulcus (BA40 and BA7) (Herwig et al. 2003). To stimulate the right PM, the coil was placed 3 cm 0anterior to C4 electrode (Samuel et al. 1997). Throughout the experimental session, the coil/s was/were fixed in position with the aid of articulated mechanical arms. Experiment 7 consisted of four experimental sessions, given in a random order: the baseline without ppTMS and three ppTMS sessions, namely SI, PPC-SI, and PM-SI.

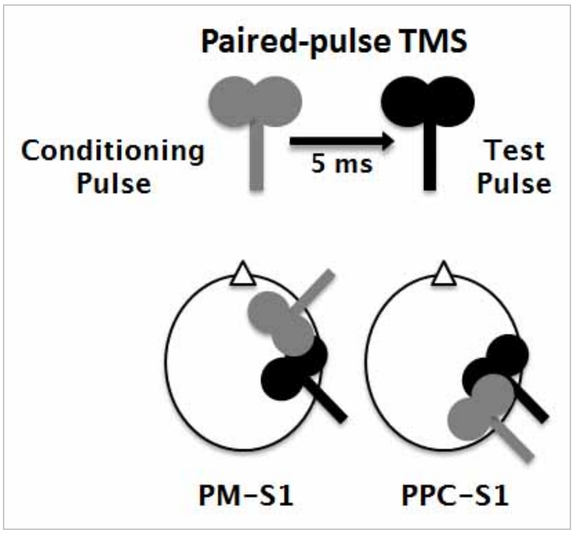

**Fig.9:** Schematic representation of the ppTMS paradigms of Experiment 7. A sub-threshold conditioning TMS pulse (CS, grey coil) delivered to PM or PPC was followed by the supra-threshold test TMS pulse (TS, black coil) after a delay of 5 ms.

### *Statistical analysis*

The participants' mean error percentage and RTs was submitted to a repeated-measures ANOVA, with the following within-subjects factors: Area (Baseline, SI-SI, PPC-SI or PM-SI), Side (ipsilateral or contralateral touch) and Stimulus (congruent vision-touch or incongruent vision-touch).

Wilcoxon signed rank test was used to compare subjects' responses to the items of the self-report questionnaire in the experimental sessions. Spearman's rank and Pearson's correlation analysis explored the association between the subjective responses at the questionnaire for mirror-touch synaesthesia and at the IRI, and the ppTMS effects, as described above.

## Results

The analysis on the participants' error rate showed as significant the main factor Side ($F_{1,13} = 12.14$ $p < 0.005$, $p\eta^2 = 0.16$) and Stimulus ($F_{1,13} = 49.73$ $p < 0.001$, $p\eta^2 = 0.79$): subjects made more errors when stimuli were delivered on the side ipsilateral to the TMS and in the incongruent trials. The interactions Area by Side ($F_{3,39}= 9.07$, $p < 0.001$ $p\eta^2 = 0.41$), Area by Stimulus ($F_{3,39}=5.59$, $p < 0.005$, $p\eta^2 = 0.30$) and Side by Stimulus ($F_{1,13} = 12.59$, $p < 0.01$, $p\eta^2 = 0.49$) also resulted significant. A significant three-way interaction Area by Side by Stimulus emerged ($F_{3,39} = 5.67$, $p < 0.005$): as shown in Figure 10, a conditioning TMS pulse over the right PPC, followed by a test pulse to the ipsilateral, right SI, increased errors in incongruent vision-touch trials (with the visual touch contralateral, and the actual touch ipsilateral to TMS) compared with all the other conditions ($p < 0.001$); this effect was analogous to that induced by the ppTMS of SI ($p = 1$), which also induced a significant increase of errors in incongruent vision-touch trials (with the visual touch contralateral, and the actual touch ipsilateral to TMS), compared with all the other conditions ($p < 0.01$). Conversely, facilitating SI via PM stimulation did not induce any changes in performance compared with the baseline ($p = 0.6$). The main factor Area did not reach significance (Area: $F_{3,39} = 1.85$, $p = 0.15$) .

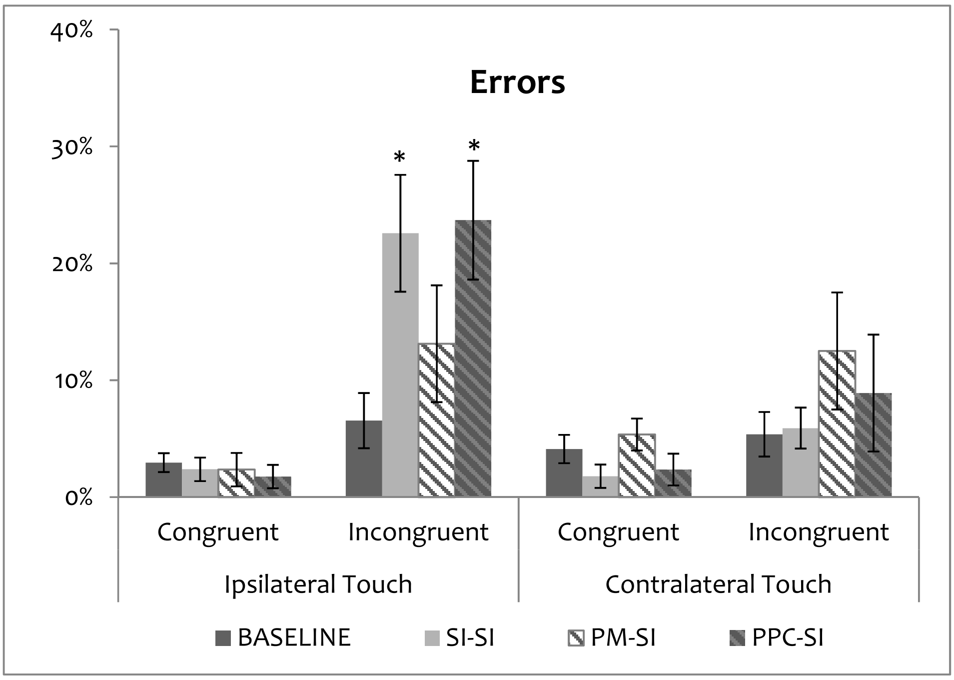

**Fig. 10** ppTMS effects on behavior in Experiment 7. Mean error rate in each experimental condition. Error bars = S.E.

The ANOVA conducted on the participants' RTs showed the significant main factors Side ($F_{1,13}$= 12.54, $p < 0.01$, $p\eta^2 = 0.49$) and Stimulus ($F_{1,13} = 40.22$, $p < 0.001$, $p\eta^2 = 0.76$), showing that subjects' performance was slower to respond to stimuli presented on the side ipsilateral to the TMS and in the incongruent trial. No other main effects of interactions reached significance (Area: $F_{3,39} = 2.44$, $p = 0.08$ Area by Side: $F_{3,39} = 2.73$, $p = 0.53$; Area by Stimulus: $F_{3,39} = 1.13$, $p = 0.28$; Side by Stimulus: $F_{1,13} = 0.57$, $p = 0.46$; Area by Side by Stimulus: $F_{3,39} = 2.71$, $p = 0.06$).

In line with the results from Experiment 6, as shown in Figure 11, the participants reported an increased difficulty in touch localization due to the sight of touch (Item 2) and were also less confident about not feeling the viewed touch on their hands (Item 1) during the SI stimulation (Item 1, $Z = 2.14$, $p = 0.05$; Item 2, $Z = 2.67$, $p < 0.01$) and PPC-SI stimulation (Item 1, $Z = 2.20$, $p < 0.05$; Item 2, $Z = 1.88$, $p < 0.05$), compared with the baseline. However, on the same items, there was no change from baseline due to the ppTMS of PM-SI (all ps > 0.3). The participants' reports on Items 3 and 4 did not change in any session (all ps > 0.3). Again, the error rates during the ppTMS to SI and to PPC-SI were associated with the post-ppTMS scores on Item 1 (SI, rs = 0.70, $p < 0.01$; PPC-SI, rs = 0.64, $p < 0.05$) and Item 2 (SI, rs = 0.61, $p < 0.05$; PPC-SI, rs = 0.55, $p < 0.05$). No other significant correlations were found (all ps > 0.08).

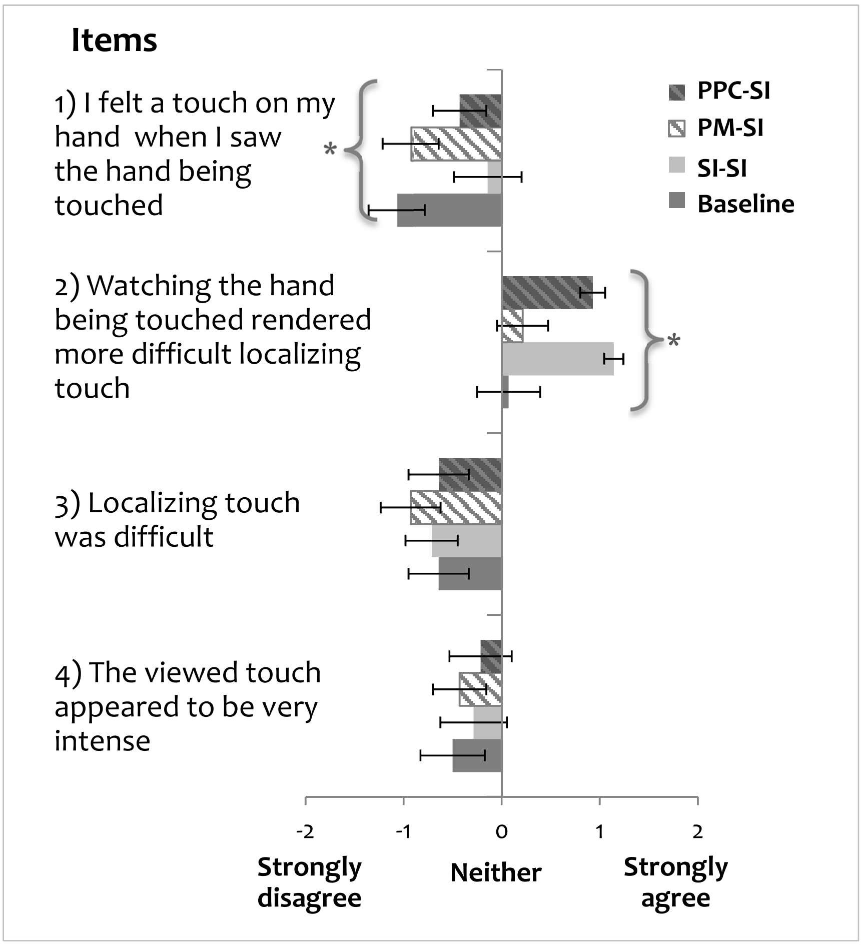

**Fig.11**. Subjective reports of synaesthesia-like sensation assessed with 5-points Likert scales, obtained after the baseline and each ppTMS sessions (SI-SI, PPC-SI, PM-SI). Error bars = S.E. For details see legend to Figure 5

Again, the scores on the empathic subscale PT were positively correlated with error rate in incongruent vision-touch trials following ppTMS of SI ($r = 0.74$, $p < 0.005$) and of PPC-SI ($r = 0.55$, $p = 0.04$). Even the subjective reports in the post-ppTMS assessment were associated with empathic abilities: the visually induced feeling of being touched (Item 1) following SI stimulation was correlated with the EC score ($rs = 2.75$, $p < 0.05$), whereas the visually induced difficulty in touch localization (Item 2) was correlated with the PT score after both SI ($rs = 2.67$, $p < 0.05$) and PPC-SI ($rs = 2.75$, $p < 0.05$) stimulations.

## Discussion

In this study, we used a ppTMS paradigm for the induction of a mirror-touch response functionally akin to mirror-touch synaesthesia. By using ppTMS, we primed facilitatory intracortical circuits in SI, promoting the emergence of localization errors in a visual-tactile spatial congruity task. This behavioural pattern is typical of mirror-touch synaesthetes and is absent when non-synaesthetes are show static images of human body parts (Bolognini et al., 2013). A similar effect was present when SI activity was boosted by priming PPC. Finally the interference effect was correlated to subjects' emphatic abilities

Regarding our first finding, the interference effect was only present when the visual touch where presented on the side contralateral to ppTMS and the actual touch ipsilateral to ppTMS. These results are in line with our previous finding, described in previous chapters, showing that SI is mainly involved in processing the contralateral visual touch; this side-specificity may be attributed to the fact that visual stimuli presented in the left (i.e., contralateral to ppTMS) visual hemifield send information to the right hemisphere, were ppTMS was applied over SI.

Moreover, mirror-touch synaesthesia-like errors were induced only when the SI was stimulated at 150 ms from the onset of the visual touch. This timing is consistent with data of the visual-tactile interactions and the consequent visually induced somatosensory activity. Indeed, Pihko and colleagues (2010) recorded event-related MEG data while finger taps were delivered to participants' dorsal right hand. Simultaneously, subjects were asked to observe an actor being touched on the same body-part. During this visual-tactile stimulation, SI was activated during the first 300 ms of tactile stimulation, and similar activations were observed during the observation of touch. More recently, an EEG study indicates that viewing a tactile stimulation induced larger amplitude responses recorded from electrodes over the somatosensory cortical areas between 100 and 250 ms, and then again between 500 and 600 ms (Streltsova and McCleery, 2012). These findings suggest that the visual processing of touch modulates somatosensory cortical activity over a time window that follows tactile processing in SI, which peaks at ~ 50 ms (Pihko et al., 2010).

In addition to modulation of the behavioural performance in the experimental task, ppTMS of the SI also changed the participants' subjective judgments about the seen touch: following SI stimulation, the participants reported confusion about touch localization and in judging whether the viewed touch could be felt or not on their own hand. Interestingly, two subjects spontaneously reported that they felt like they were touched on both hands in many trials of the task, although only unilateral touches were given. One participant spontaneously reported being confused by the viewed touch in incongruent trials.

Additionally, synaesthetic-like responses were also caused by inducing SI activity via the ipsilateral PPC. This result is not unexpected, given the functional interplay between the parietal and somatosensory cortices in mirror-touch system, and might represent the responses of bimodal cells involved in the matching of visual and somatic signals (Macaluso and Maravita 2010). As described in Chap 1.1 the caudal part of SI contains neurons with visual-tactile receptive field and is equipped with direct connections with regions of PPC containing bimodal visual-tactile neurons (Keysers et al., 2010). These neurons, first discovered in monkey, respond both to actual touched and to the see of a touch on the same body part (Ishida et al., 2010; Keysers et al., 2010; Macaluso and Maravita, 2010). Moreover, parietal areas are thought to provide visual information to the mirror system, and thus support visual activation of the tactile mirror system (Keysers et al., 2010).

On the other hand, PPC seems to play a key role in synaesthesia: under normal circumstances, the brain binds together information from different sensory modalities in order to generate a coherent representation of the world, and this binding process depends on parietal mechanisms (Robertson 2003). The hyperbinding model of synaesthesia (Esterman et al., 2006; Hubbard 2007; Robertson 2003) suggests that synaesthesia, in general, and not only mirror-touch synaesthesia, may arises through an over- activation of these same parietal binding mechanisms. In this sense anomalous binding may play an important role in the explanation of the synesthetic experiences. It is possible that hyperbinding may act in concert with the hyper activation of mirror-touch system in generate mirror-touch synaesthetic sensations.

Taken tougher our results indicate that over-activity of neural areas being part of the mirror-touch system is responsible for the emergence of mirror-touch synaesthesia-like behaviour in non-synaesthetes. Our results extended previous findings, stressing the heightened sensorimotor mirror system activity in mirror-touch synaesthetes (Banissy et al. 2011; Blakemore et al., 2005). Banissy et al. (2011) compared mirror-touch synaesthetes to non-synaesthetic control participants on measures of facial expression and identity recognition. Mirror-touch synaesthetes scored higher than controls on measures of facial expression recognition but not on identity recognition. Understanding another's facial expression requires a simulation of that same expression (e.g ., Goldman and Sripada, 2005). Accordingly, the findings of Banissy and colleagues suggest that mirror-touch synaesthetes have superior simulation mechanisms relative to people without mirror-touch synaesthesia. Such effects are consistent with the proposal of mirror-touch synaesthetes having an hyper-acivation of the mirror–touch system. The overactive hypothesis of the mirror-touch system in synaesthetes is supported by recent evidences in non-synaesthetes: using the paradigm of Banissy and Ward (2007), Bolognini and colleagues tried to induce synaesthetic-like behaviour by increasing the excitability of the mirror-touch system via transcranial direct current stimulation (tDCS). The authors found that non-synaesthetes became slower at localizing a site touched on their hands when they simultaneously viewed a touch to the opposite hand when SI was stimulated. Moreover, the interference was specific for images depicting a human touch, being absent when the touch was directed to an object. Our results represent a critical advance since Bolognini and colleagues demonstrate that using tDCS to boost SI activity was capable of slowing subjects' reactions times, but without affecting the quality of the sensations. Here subjects were confused whether seen touches were actual ones, as demonstrated by increased error rates, thus proving a more robust finding. This data was found in two independent experiments, and we also provide fundamental information regarding the chronometry of visual-touch effects.

Finally, we showed that the interaction between mechanisms for perceiving and observing touch is also relevant for the empathic sharing of the somatosensation of others. Indeed, synaesthesia-like behaviour, induced by SI activation, correlated with the emphatic subscale Perspective Taking, in line with our results of Experiment 4. In addition, the sensation of being touched in response to seeing touches correlated with the affective empathic subscale Emphatic Concern. Previous evidence in the general population indicates that PT is linked to vicarious somatosensory activity when watching others being non-painfully touched (Bolognini et al., 2013; Schafer et al., 2012b), whereas EC might be elicited when seeing others in pain and may be linked to the activation of sensorimotor areas and the insula (Avenanti et al., 2007; Singer et al., 2004). Moreover, mirror-touch synaesthetes report subjectively higher levels of affective empathy (Banissy and Ward, 2007). Therefore, one may speculate that cognitive empathy aspects, such as the ability to assume other' perspective, may be more important for the unconscious simulations of others' tactile sensations. On the other hand, the conscious sharing of touch may depend more the affective side of empathy, like the other-oriented emotions elicited by witnessing someone else in need (e.g., Stocks et al., 2011; Woltin et al., 2011).

In conclusion, mirror-touch synaesthesia-like responses can be triggered experimentally in non-synaesthetes by increasing the activity of the SI, which contains shared representations for viewing and experiencing touch. Thus, mirror-touch synaesthesia may result from disinhibited feedback in otherwise normal neural pathways. Typically, activation in mirror areas is greater when one experiences a sensation compared with when the same experience is observed in another, which is thought to reflect inhibitory processes involved in the mirror system that prevent one from experiencing or imitating the observed sensation, emotion or action (e.g., (Kraskov et al., 2009). An absence of or a reduction in normal inhibitory mechanisms within the mirror tactile system could reasonably lead to the experience that others' touch is synaesthetically felt on the observers' own body. This in turn suggests that our ability to empathize with others may rely on simulations of others somatic states in SI.

When this system is hyper activated, it is possible to consciously transfer others somatic sensations onto our own body.

# CHAPTER 5

## GENERAL CONCLUSIONS

My PhD thesis aimed at shading light into neural mechanism subtending the mirror-touch system (Keysers et al., 2004). The specific goal of my work was investigating the role of the somatosensory cortices in the embodied simulation of others' tactile sensations. According to the mirror neuron theory, understanding social interactions is supported by an internal simulation of other's experiences we are observing (Rizzolatti et al., 2001). Beside the domain of action, recent studies revealed mirror-like responses also for the observation of others' somatosensation in a network that comprises the first (SI) and second (SII) somatosensory cortices; these areas were shown to be activated not only by the self-experience of tactile sensation, but even by the sight of other people being touched (Keysers et al., 2010). The discovery of this mechanism is a building block of social science: mirror-touch mechanism may play pivotal role in social perception, providing a neural substrate to facilitate an automatic sensorimotor simulation of others' somatic state (Gallese et al., 2004). So far, convincing evidence that the somatosensory cortical areas, traditionally viewed as modality-specific, play a functional role in the visual processing of tactile events, up to a high-level of elaboration causally involved in understanding others' sensory states is still lacking. Addressing this issue was the goal of my doctoral thesis.

First, the results of experiments 1-3 (Chap. 2) provides a direct evidence that SI, but not SII, is causally involved in the visual perception of human touch. Specifically, the key role of SI in visual-touch processing is restricted to the contact between body parts: mapping others' experience into a shared neural code is possible only when the actor and the recipient of the assisted tactile stimulation are human beings. This evidence supports the hypothesis that understanding observed somatosensory stimulations is grounded on the possibility of simulating specific body-related experiences. This finding also suggests that SI is probably better suited to represent the social touch. In this perspective, by matching observed and felt touch, SI may contribute to our capacity to understand the effect of human tactile stimulations on another person, allowing us to more easily 'resonate' with the body-related experiences of both the touched person and the touching agent.

This hypothesis is in fact support by the results of experiment 4 (Chap. 3). Indeed, I demonstrated that SI is not only involved in a low-level perceptual coding of visual tactile events, but it also plays a causal role in higher-order processes, in particular in the processing of the valence of visual stimuli with emotional contents conveyed by a tactile sensation. This finding provides strong evidence for the existence of a shared representation in SI for both our own emotions and others' emotions, when the emotional meaning is conveyed by tactile sensations. In addition, there is a clear dominance of the right hemisphere in this process, which is further supported by neuropsychological evidence (experiment 5), confirming the key role of the right hemisphere in social cognition (Adolphs et al., 2000; Ruby and Decety, 2004). The implication of SI in social interaction is further supported by the association between the activation of the right SI during the coding others' somatosensation and the empathic abilities of the observer. In particular, the process of simulation of others' feeling in the right SI appears to be associated with the individual's ability to assume others' perspective: the more a person is able to "walk in others' shoes", the more the tactile sensations observed in others may be internally simulated, and ultimately understood. As a result, empathic abilities may rely upon interpersonal sharing of bodily sensations, by using a common neurophysiological code between the observer and the observed (Gallese 2007). In interpersonal relationships, in which affective states are often evoked by physical contact between people, activating a shared representation of somatic sensations in the right SI allows an automatic understanding of the consequence of others tactile experience, as we are feeling the same sensations observed in others on our body.

Finally, I also further specify the functional architecture of mirror-touch mechanism, using the phenomenon of mirror-touch synaesthesia as a framework for further explore the neural underpinnings of this mechanism and their involvement in empathy (experiments 6-7, Chap. 4). In this way, I could characterize the chronometry of the processing of the visual touch in SI, and the functional connectivity between this area and the posterior parietal and premotor cortices. The studies described in Chap. 4 provide convincing evidence that the mere observation of others' somatosensations can really cause a somatic activation in the observer. Indeed, the vicarious activation of SI by the sight of touch can induce a feeling of being touched in the observer; mirror-touch synaesthesia-like responses may be produced by the release of parietal-somatosensory mechanisms involved in the binding of viewed and felt touch to understand the somatosensation of others. Besides confirming that the behavioral effect of SI stimulation is related to inter-individual differences in empathy, a novel finding is that different aspects of empathy (i.e., cognitive vs. affective empathy) are involved in conscious and unconscious simulation of others' sensations. Indeed, synaesthesia-like errors induced by TMS are linked to more cognitive aspect of empathy, namely the ability to assume others perspective, while the sensation of being touched in response to seeing touches correlates with the affective features of empathy, like the feeling of concern for others. Thus, cognitive empathy seems to be more important for the unconscious simulations of others' tactile sensations, whereas the conscious sharing of touch may depend more on affective empathy. This finding indicates that mirror-touch synaesthesia reflects a general crossmodal mechanisms associated with empathetic abilities, rather than an abnormal neural connectivity. On a broader perspective, mirror-touch synaesthesia may be regarded as an anomalous experience of an otherwise normal perception, ranging from understanding the somatic sensation of another to the actual experience of a similar sensation; when another person's touch sensation is consciously shared, it becomes synaesthesia.

Together, my experiments support the existence in the human brain of a mirror-touch system based on the vicarious activity of a somatosensory-parietal network. This network contains shared representations of felt and viewed touch, which may allow to emphatically transfer others somatic sensations onto oneself. Our ability to empathize with others may rely on such simulation of others somatic sensations in SI.

In future it would be interesting to combine perceptual manipulation and brain stimulation to give rise to a genuine mirror-touch synaesthetic experience in non-synaesthete. Additionally it would be intriguing investigate whether interfering with SI activity would disrupt synaesthetic sensations in mirror-touch synaesthetes. These data would provide an even more robust proof of the role of SI in the emphatic simulation of others somatic states.

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