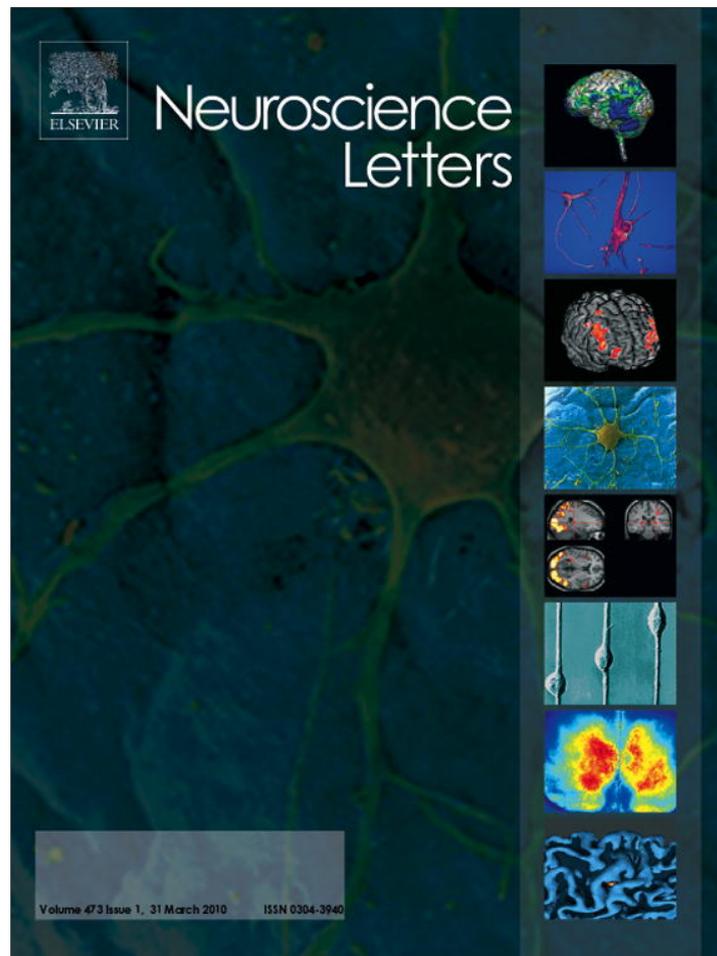


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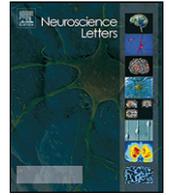
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Visuotactile empathy within the primary somatosensory cortex revealed by short-latency afferent inhibition

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ABSTRACT

Intersubjectivity entails the taking of another's perspective in order to understand their experience of the world. This perspective taking capacity extends to the intra-individual sharing of tactile experience. Previous studies have shown modulation of motor cortex excitability in response to the observation of aversive tactile stimulation to the hand of another person. Here we used transcranial magnetic stimulation (TMS) and peripheral stimulation to induce a short-latency afferent inhibition (SAI) effect, which we then sought to modulate via observation of non-noxious tactile stimulation to the hand of a model. Side congruency between the observed (model) and the recorded (participant) hand induced an increase of SAI and this effect was found to hold for motor-evoked potentials (MEPs) recorded from both left and right hands. Inhibition was not found with MEPs evoked using unconditioned pulses of TMS. These results demonstrate a sensorimotor response to observed non-noxious stimulation and suggest an empathic matching system for the tactile experiences of others.

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Intersubjectivity requires shared experience and the capacity to take others' perspectives. A number of studies have demonstrated that the neural structures underlying sensation processing are recruited when observing the sensory experiences of others. fMRI studies of the effects of touch observation [3,9,11] found activation of secondary or primary somatosensory cortex when participants experienced touch and when they observed another person or object being touched. These findings support the notion of shared neural circuits for first and third person experiences of touch. This direct matching mechanism bears strong analogies with the mirror systems, where observation of an action automatically activates parts of corresponding neural circuits in the observer, neural circuits that would be recruited if she were performing the action herself [7,10].

Visual activation of somatosensory cortical circuits for touch observation occurs regardless of the animacy of the entity being touched (i.e. object or person), is independent of the observer's perspective (i.e. ego- or allo-centric) and is not restricted to the domain of intentional touch [9]. This suggests that the observation of any touch can activate shared somatosensory circuits, although intentional touches appear to elicit a greater response in SI (BA 2) than accidental touches. Visuotactile mirroring may thus provide an embodied mechanism to support the interpretation of any

touch (regardless of animacy or intentionality) via processes of multimodal integration.

Aside from empathy for touch, some studies have addressed the issue of empathy for somatosensory sensation that carries a much stronger affective implication: cutaneous pain. Avenanti et al. [1] were able to demonstrate modulation of sensorimotor activity in response to pain observation using a single-pulse transcranial magnetic stimulation (TMS) paradigm. Motor-evoked potentials in the muscle participants saw being subjected to painful stimulation were significantly reduced. Inhibition was correlated to the intensity of the pain observed but not to task instructions, indicating that the sensorimotor component of empathy for pain may be stimulus driven, i.e., predicated on the perceived intensity of the aversive stimulation received by the observed other [1].

Observation of touch is known to elicit both perceptual and neurophysiological changes in the observer [4,14–16]. The observation of painful stimulation has been shown to produce a motor response in the observer, however this effect has not previously been found for non-painful stimuli. Thus, we used a short-latency afferent inhibition (SAI) paradigm [17] to test the primary sensory and motor cortices for an effect analogous with that found for noxious touch during the observation of non-noxious touch.

The SAI technique tests the effects of an afferent somatosensory stimulus on the excitability of the motor cortex. TMS alone at stimulation intensities just above motor threshold is capable of probing the excitability state of the motor cortex by depolarizing cortical interneurons and ultimately exciting corticospinal neurons

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trans-synaptically. In the SAI paradigm electrical stimuli are delivered to one hand and subsequently TMS is delivered over the contralateral motor cortex. The effect is that of inhibition of M1 excitability, as measured by a decrease in amplitude of motor-evoked potentials (MEPs). This effect is commonly measured by obtaining a ratio of the amplitude of MEPs induced by TMS preceded by a peripheral somatosensory stimulus to the amplitude of MEPs obtained by TMS alone.

The time window in which the motor cortex is susceptible to SAI is very early, starting 2 ms after the arrival of the afferent volley in S1, hence the term “short latency”. The neuronal circuit that subserves the phenomenon of SAI is not entirely clear but, due to the extremely short latency of the effect, it probably resides entirely in somatosensory and motor cortices. [17] The physiological role of the short-latency inhibitory effects on the motor cortex is not known. In this experiment we sought to use the phenomenon of SAI as an indirect index of excitability of the somatosensory cortex by testing its capacity for modulation of the motor cortex. In particular we investigated whether changes in SAI can reveal changes in cortical excitability associated with observation of touch.

A total of 16 right-handed volunteer participants (eight male) aged 24–41 years (mean 28 years) took part in the experiment. Eight of them were stimulated on the left hemisphere and the remaining eight were stimulated on the right hemisphere. The experiment was carried out in the Universities of Parma and Trento. Participants had no contraindications to TMS and gave their informed consent. The study was approved by the local ethical committees and carried out in accordance with the 1964 Declaration of Helsinki. No discomfort during the application of TMS or adverse effects of TMS were noticed or reported.

Monophasic TMS pulses were applied using a figure-of-eight coil, 7 cms in diameter, connected to a Magstim 200 Stimulator (Magstim, Whitland, UK). The coil was placed over motor cortex contralateral to the recorded muscle with the handle angled at 45° to the midline pointing inferiorly and backwards. The coil was attached to a mechanical arm in order to ensure that it was held firmly in place. Scalp position was chosen so as to produce maximum amplitude MEPs in the recorded FDI muscle. Pulse intensity was set to evoke MEPs with a mean peak-to-peak amplitude of 1 mV. The absence of voluntary contraction before the pulse was verified visually on the ongoing recording. MEPs were recorded from the first dorsal interosseus (FDI) muscle with surface Ag–AgCl electrodes with a bipolar belly-tendon montage. The signal was amplified 1000× by means of a CED 1902 amplifier (Cambridge Electronic Design, Cambridge, UK). The signal was digitized at 4 kHz and stored for offline analysis by means of the CED 1401 unit and the Signal software (Cambridge Electronic Design, Cambridge, UK). All subjects received TMS over right or left M1 while MEPs were recorded from the contralateral FDI muscles. EMG recordings were all digitally filtered with a band-pass of 10–2 kHz prior to any further analysis.

Since the aim of the experiment was to modulate SAI with visual stimuli, in a first set of eight subjects we explored the relation between intensity of cutaneous stimulation and SAI in order to identify an intensity of peripheral stimulation that elicits sub-maximal inhibition. The right hemisphere only was stimulated in this preliminary phase. Stimulus intensity was defined as multiples of individual perceptive threshold (PTh) for peripheral electrical stimulation assessed as a descending threshold by means of a staircase algorithm. Electrical stimulation was applied to the index finger of the recorded hand using a pair of ring electrodes with the cathode positioned just above the metacarpo-phalangeal articulation and the anode positioned just above the proximal interphalangeal joint. Electrodes were connected to a Digitimer DS7AH stimulator (Digitimer Ltd., Welwyn Garden City, UK) that delivered single square-wave stimuli, 0.2 ms in duration. Intensity was varied

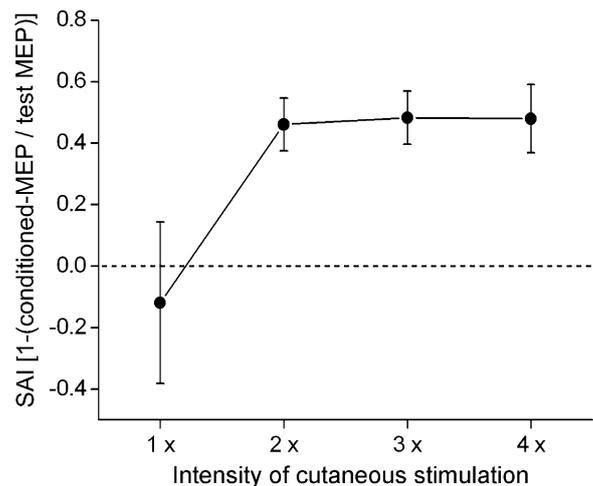


Fig. 1. Results of the preliminary testing of the recruitment curve of SAI. The SAI values are plotted against the intensity of cutaneous stimulation expressed as multiples of the individual perceptual threshold.

at steps of 1 × PTh. The interval between electrical stimulation and TMS (interstimulus interval, ISI) was set at a fixed value of 26 ms. On the basis of this preliminary experiment (Fig. 1) a stimulus intensity of 1.5 × PTh was chosen for the main experiment. During the main experiment MEPs were acquired using TMS preceded by the peripheral conditioning stimulus delivered as described above. Trials with conditioned-TMS pulses were interleaved with test-TMS trials in a pseudo random order.

Visual stimuli used in the main experiment consisted of video clips 3000 ms in duration presented on a 21-in. screen located 60 cm from participants. Videos showed a dorsal view of a male right or left hand, seen from a first person point of view, resting on a white surface. A small blue or pink brush was also present brushing either the medial aspect of the index finger or making brushing movements on the surface close to but not touching the inner edge of the hand. In all cases single brushing movements were repeated three times in every clip. The experiment was programmed using the Psychophysics Toolbox extensions of the Matlab software [5,13] to present stimuli and to synchronize them with TMS.

Each trial started with a fixation cross presented for 1000 ms. Thereafter the 3000 ms videos were presented. Subjects were required to identify the color of the brush at the end of each movie. TMS was delivered in correspondence with the first or second passage of the brush over the metacarpo-phalangeal joint. The movies that were presented belonged to three categories named in accordance with the hemisphere to which magnetic stimulation was applied: (a) the contralateral hand being brushed (congruent stimuli) (b) the ipsilateral hand being brushed (incongruent stimuli) or (c) the contralateral hand with the brush moving next to it (no-touch stimuli). For each subject each of these three conditions were repeated in a random order 32 times, 16 of which were associated with a test-TMS pulse and the other 16 with a conditioned-TMS pulse. The interval between trials was 5 s.

The data from the preliminary experiment were visually assessed to identify a “ceiling” for the SAI effect. In the main experiment subjects not showing SAI in a grand average of conditions were discarded from analysis. As a cutoff for SAI presence we chose an inhibition of at least 10%. Two different analyses were carried out: one on test-TMS trials only, in order to assess a possible effect of visual stimuli on single pulses and the second one on the reciprocal of the ratio between conditioned-TMS MEPs and test-TMS MEPs, which expresses the amount of SAI.

MEP amplitude was calculated peak-to-peak and averaged within conditions. The analysis of test-TMS trials was carried out

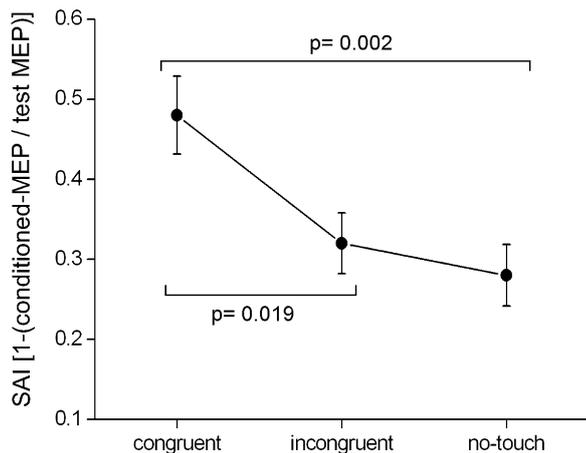


Fig. 2. results of the main experiment: SAI values are plotted against the modality of visual stimulation. The data from left and right hemisphere stimulation are collapsed; *p*-values refer to post hoc comparisons.

using an ANOVA with the video conditions as a within-subjects variable (three levels: congruent, incongruent and no-touch) and stimulation side as a between subjects variable (two levels, left and right hemisphere).

The analysis of SAI required the calculation of the SAI ratio. For each experimental condition this was taken to be: $SAI = [1 - ((\text{mean MEP amplitude from conditioned-TMS}) / (\text{within-subject grand mean of MEP amplitude from test-TMS}))]$ [8]. These values were then fed into an ANOVA again with the video conditions as a within-subjects variable (three levels: congruent, incongruent and no-touch) and stimulation side as a between subjects variable (two levels, left and right hemisphere). Post hoc comparisons were made with Tukey's honestly significant difference test (HSD). Statistical analysis was carried out with Statistica Software.

The results of the preliminary intensity assessment are shown in Fig. 1. In the main experiment four participants were discarded for not showing SAI over the cutoff limit of 10%. The analysis of single-pulse TMS did not show any differential distribution of MEP amplitudes between experimental conditions. The ANOVA neither yield any significant effect of the video condition ($F(2, 28) = 0.18$, $p = 0.83$) nor of side ($F(1, 14) = 2.13$, $p = 0.17$) and it did not show any significant interaction between the two ($F(2, 28) = 2.05$, $p = 0.15$).

The results of the analysis of SAI values showed a higher level of inhibition associated with the congruent visual condition with respect to incongruent and no-touch. Side did not influence SAI significantly. The ANOVA showed a significant effect of the video condition ($F(2, 28) = 7.72$, $p = 0.002$), and no effect of side ($F(1, 14) = 2.14$, $p = 0.17$) nor interaction between the two factors ($F(2, 28) = 0.23$, $p = 0.80$). The data and the relevant post hoc comparisons are shown in Fig. 2. No difference was found between the incongruent hand and the no-touch conditions ($p = 0.68$).

The results of the present experiment show that observation of a hand being touched gives rise to an increase in SAI on the hemisphere that is congruent with the laterality of the hand being touched, i.e. seeing a right hand being brushed favors SAI from right hand stimulation in the left hemisphere and vice-versa seeing a left hand being brushed favors SAI from left hand stimulation in the right hemisphere. MEPs from single pulses were not modulated by touch observation, showing that the effect we saw was not due to the efferent limb of the SAI circuit. The SAI technique benefits from a quite precise spatial resolution. The SAI circuit is made of very few synaptic relays, which accounts for its very short latency. These relay stations are located in the thalamus, SI and M1 [17]. The effect we observe therefore probably resides in thalamocortical projections or more probably in the somatosensory cortex.

These results support previous findings of SI modulation by touch observation [9,14–16]. It is known that SAI can be modulated by nonspecific arousal-related subcortical structures [12]. In our work however, the strict lateralization of the effect together with the congruity to the visual stimulus are likely due to specific, empathy-related changes of excitability in SI, that become evident in a greater capacity to inhibit M1. It is worth mentioning that though congruity between the observed body part and the observer's empathic representation has been described [2,6], to our knowledge no clear comparison between different body parts has been performed.

In our paradigm stimulation took place well after the onset of the visual stimulus. Therefore we do not have clear information on the chronometry of the cortical effect of increased SAI with respect to the observed stimuli. Therefore we cannot know whether it is the product of an automatic resonance or if it is mediated by semi-voluntary simulation of the observed scene. However the irrelevance of the task with respect to the touch (participants were asked to identify the color of the brush) should make less likely the presence of voluntary simulation.

The current results provide a first demonstration of a sensorimotor response to observed non-noxious stimulation whereas previous work has focused on responses to observation of another person undergoing painful stimulation. Our results show that resonant effects induced by touch observation are not limited to aversive events thus providing further support for the notion of an empathic matching mechanism for others' tactile experiences. In this study we show a modulation of the excitability of sensorimotor circuitry induced by the sight of another person being touched. Embodied simulation theory (i.e. [9]) proposes that the neural structures that mediate our own sensorimotor experiences of the world also contribute to our understanding of others' experience. By this view, the same processes that underpin individual subjectivity also provide embodied mechanisms for intersubjectivity.

The capacity to understand the tactile experience of others, and by extension to understand others as experiencing selves, thus appears to depend on the re-use of mechanisms that mediate our capacity to interact with the world of objects. From this perspective social cognition can be understood as a being continuous with more general cognitive mechanisms and to be founded on the individual's embodied capacity for action.

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