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Hebbian associative plasticity in the visuo-tactile domain: A cross-modal paired associative stimulation protocol

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ABSTRACT

We developed and assessed the effects of a novel cross-modal protocol aimed at inducing associative (Hebbian-like) plasticity in the somatosensory cortical system through vision. Associative long-term potentiation can be induced in the primary somatosensory cortex (S1) by means of paired associative stimulation (PAS), in which a peripheral electrical stimulation of the median nerve is repeatedly paired with a transcranial magnetic stimulation (TMS) pulse over S1. Considering the mirror proprieties of S1, the cross-modal PAS (cm-PAS) consists of repetitive observation of bodily tactile stimulations, paired with TMS pulses over the contralateral S1. Through three experiments in healthy participants, we demonstrate that the cm-PAS is able to induce excitatory plastic effects with functional significance in S1, improving somatosensory processing at both behavioral (tactile acuity) and neurophysiological (somatosensory-evoked potentials) levels. The plastic effects induced by cm-PAS depend on the interval (20 ms) between the visual stimulus and the magnetic pulse, the targeted cortical site (S1), and the tactile content of the visual stimulus, which must represent a touch event. Such specificity implies the involvement of cross-modal, mirror-like, mechanisms in S1, which are able to visually promote associative synaptic plasticity in S1 likely through the recruitment of predictive coding processes.

1. Introduction

In recent decades, a growing number of studies have shown that Hebbian associative plasticity may be induced noninvasively in humans by means of paired associative stimulation (PAS) protocols (Suppa et al., 2017). Original PAS protocols were developed to prove the existence of timing-dependent plasticity in the primary motor cortex (M1) and primary somatosensory cortex (S1), in healthy and pathological conditions (e.g., Battaglia et al., 2007; Castel-Lacanal et al., 2007; Litvak et al., 2007; Stefan et al., 2000; Stefan et al., 2004; Wolters et al., 2005). In PAS protocols, the induction of Hebbian associative plasticity is achieved through the repeated pairing of a peripheral and a cortical stimulation, the latter by means of transcranial magnetic stimulation (TMS). For example, in PAS protocols targeting the somatosensory system (i.e., S1-PAS), the electrical stimulation of the median nerve (MN) is repeatedly paired with a TMS pulse over the contralateral S1. Crucially, the direction of the effects (i.e., long-term potentiation, LTP, or depression, LTD) depends on the interstimulus interval (ISI) between the paired stimuli (Stefan et al., 2000; Wolters et al., 2003): for instance, in S1-PAS, LTP-like effects are induced by an ISI of 20 ms, which resembles the S1 activation due to somatosensory afference (MN stimulation) interacting with the cortical activation of S1 by TMS (Wolters et al., 2005).

Recently, in addition to sensorimotor areas, PAS protocols have been applied to induce timing-dependent plasticity within the visual system (Chiappini et al., 2018), between brain regions, in this last case by targeting cortical connectivity by pairing TMS pulses over different cortical areas (Arai et al., 2011; Buch, Johnen, Nelissen, O'Shea and Rushworth, 2011; Casula et al., 2016; Fiori et al., 2018; Koch et al., 2013; Suppa et al.,

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2015), or by pairing sensory stimulations of visual and auditory cortices with motor cortex stimulation (e.g., Sowman et al., 2014; Suppa et al., 2013, 2015; see for a review Suppa et al., 2017).

In the present study, we developed a cross-modal version of the PAS (i.e., cm-PAS) with the aim of investigating whether Hebbian LTP-like plasticity could be induced in S1 through vision. We label our PAS as 'cross-modal' because it affects somatosensory cortical activity through the visual modality.

As an operative model, we have considered the cross-modal properties of the *Tactile Mirror System*, in which the observation of tactile events (e.g., seeing someone being touched) activates a cortical network, including S1, largely overlapping the one implicated in tactile perception (Gallese et al., 2004; Gallese and Sinigaglia, 2011; Keysers et al., 2010; Keysers and Gazzola, 2009). Therefore, in our cm-PAS, the classical somatosensory MN electrical stimulation was replaced by a visual stimulus showing a hand being touched (i.e., visual-touch stimulus). The paired cortical stimulation consisted of TMS pulses delivered over S1, consistent with standard (unimodal) S1-PAS protocols (e.g., Litvak et al., 2007; Pellicciari et al., 2009; Wolters et al., 2005). Indeed, S1 is not only involved in somatosensory processing, but it is also recruited during the observation of tactile events, as shown in humans by several lines of evidence, such as functional magnetic resonance imaging (fMRI) (e.g., Blakemore et al., 2005; Ebisch et al., 2016; Kuehn et al., 2014; Kuehn et al., 2013; Schaefer et al., 2013; Schaefer et al., 2009), electroencephalography (EEG) (Pisoni et al., 2018), magnetoencephalography (Pihko et al., 2010) and noninvasive brain stimulation techniques (e.g., Bolognini et al., 2013a; Bolognini et al., 2013b; Bolognini et al., 2014; Bolognini et al., 2011; Rossetti et al., 2012). Accordingly, the repeated coupling of these two stimulations, the visual-touch stimulus plus S1-TMS, could be able to induce timing-dependent Hebbian associative plasticity in S1 through the recruitment of a visuo-tactile network, namely, the Tactile Mirror System. The effectiveness of our novel cm-PAS in inducing Hebbian plasticity in S1 was investigated in a series of three experiments using both behavioral and neurophysiological measures commonly adopted in classical S1-PAS protocols: tactile acuity (*Experiments 1, 2* and *3*) and somatosensory evoked potentials (SEPs; *Experiment 3*) (Litvak et al., 2007).

In detail, *Experiment 1* explores timing-dependent changes in tactile sensitivity as a signature of Hebbian association learning. For this purpose, we varied the ISI (i.e., 20, 60 and 100 ms) between the onset of the visual-touch stimulus (i.e., the sight of a hand being touched) and the TMS pulse delivered over S1. The ISI of 20 ms was chosen by considering the ISI of traditional S1-PAS protocols, where the MN stimulation is combined with the S1-TMS pulse (Wolters et al., 2005): the ISI of 20 ms reflects the time-course of S1 activation by tactile afferences (Cohen et al., 1991; Macerollo et al., 2018), which is optimal for inducing LTP in S1. However, since in our PAS the somatosensory stimulation was replaced with a visual stimulus, such a short ISI should not be effective, unless a direct, very fast, connection between primary visual and somatosensory areas is implied (e.g., Cappe and Barone, 2005). Rather, the activation of S1 by touch observation should occur later, within a larger time window (Bolognini et al., 2014; Kuehn et al., 2017; Martínez-Jauand et al., 2012; Pihko et al., 2010; Pisoni et al., 2018): we assessed the engagement of cross-modal, mirror-like, mechanisms by the cm-PAS using ISIs of 60 and 100 ms.

Experiment 2 explores the cortical specificity of the cm-PAS by comparing the effect of pairing a visual-touch stimulus with S1-TMS to that induced by the pairing of the same visual stimulus with the cortical stimulation of the primary visual cortex (V1); this is a sort of unimodal (visual) PAS, which should not induce cross-modal plasticity within S1, at least with the same temporal profile of S1-TMS (i.e., 20 ms of ISI) (Foxe and Simpson, 2002; Pihko et al., 2010).

Finally, *Experiment 3* assesses the neurophysiological effect of cm-PAS at the level of SEPs; moreover, we also assessed the specificity of the visual stimulus, which should have a tactile content in order to activate the mirror function of S1 (Bolognini et al., 2011). To this aim, in a control condition, the visual-touch stimulus of the cm-PAS was replaced by a visual stimulus not depicting a tactile event (i.e., the sight of an approaching hand, not delivering any tactile stimulation).

2. Experiment 1 - the effective interstimulus interval of the cm-PAS

2.1. Materials and methods

2.1.1. Participants

Eighteen healthy volunteers participated in *Experiment 1* (9 males, mean age ± standard deviation, SD: 23.5 ± 3 years). All participants were right-handed, according to the Edinburgh Handedness Inventory (Oldfield, 1971), and had no contraindication to TMS (Rossi et al., 2009). Before taking part in the study, participants gave their written informed consent. The protocol was performed in accordance with the ethical standards of the Declaration of Helsinki, and it was approved by the Ethical Committee of the IRCCS San Giovanni di Dio Fatebenefratelli (Brescia).

2.1.2. Transcranial magnetic stimulation (TMS)

TMS was delivered using a figure-of-eight 70 mm coil and a monophasic Magstim 200^2 stimulator (Magstim, Whitland, UK). The first experiment comprised 3 sessions (see below); at the beginning of every session, the participants' resting motor threshold (rMT) was assessed. The individual rMT was defined as the minimum TMS intensity (expressed as percentage of maximum stimulator output) able to elicit 5 out of 10 Motor Evoked Potentials (MEPs) of at least 50 μV in the left hand's *Abductor Pollicis Brevis* muscle (APB) during the stimulation of the right M1 (Rossi et al., 2009). For MEPs' measurement, a pair of Ag/AgCl surface electrodes in a bipolar montage was placed over the belly of the target muscle: the active electrode was placed over APB and the reference electrode over the metacarpophalangeal joint of the thumb. MEPs were visualized using BrainAmp (Brain Products GmbH, Munich, Germany). The mean participants' rMT was 40.9 ± 5.6% (mean ± SD).

After the determination of the individual rMT, the right S1 was identified by moving the coil 2 cm posterior from the APB hotspot, as usually done in PAS studies (Wolters et al., 2005). It is worth mentioning that recent evidence indicates that the scalp location of S1, at least with respect to the representation of the index finger, is lateral, not so posterior, to M1 (Holmes et al., 2019). Nonetheless, also considering that we targeted a different finger (the thumb), we preferred to be consistent with the standard localization method adopted in previous PAS experiments targeting S1 (Gorgoni et al., 2015; Litvak et al., 2007; Wolters et al., 2005).

Once the S1 location on the scalp was identified, we delivered a few TMS pulses to determine whether its stimulation could induce MEPs in the contralateral hand. None of the participants showed MEPs when TMS pulses were applied to S1 with an intensity corresponding to the rMT. For both M1 and S1 stimulation, the coil was placed tangentially to the scalp with the handle hold backward and laterally at a 45° angle to the sagittal plane, thus inducing a posterior to anterior current flow (Orth and Rothwell, 2004). TMS positioning was assisted with the SofTaxic 3.0 neuronavigation system (E.M.S., Bologna, Italy, www.softaxic.com).

2.1.3. Cross-modal paired associative stimulation (cm-PAS)

The cm-PAS consisted of a modified version of the standard S1-PAS protocol (Wolters et al., 2005), in which the electrical peripheral MN stimulation was replaced with a visual stimulus depicting a touch (i.e., visual-touch stimulus). During the cm-PAS, participants sat comfortably with their head on a chinrest to minimize movements, and they were asked to fixate a PC monitor placed at a distance of 57 cm, where the visual stimuli were presented on a black background. The visual-touch stimulus showed a left hand (contralateral with respect to the right S1-TMS) being touched on the palm by a right index finger. In particular, each trial of the cm-PAS (total duration = 10 s) started with a fixation

frame depicting the palm of a left hand (10 × 18° of visual angle), viewed from an egocentric perspective. The fixation frame was presented at the center of the screen for 9.7 s, and the participants were required to fixate a red asterisk placed in the center of the left hand. As soon as the fixation frame ended, a second, visual-touch, frame (7.5 × 8.5° of visual angle) appeared. The visual-touch frame showed an index finger of a right hand (seen from an allocentric perspective) touching the palm of the left hand (the same shown in the fixation frame). The visual-touch frame lasted 300 ms, and it started immediately after the fixation frame (0 ms of delay), in turn giving rise to an apparent motion, namely, that the right index finger moved and then touched the palm of the left hand (the index finger stopped on the red asterisk positioned on the hand used as fixation). The TMS pulse over S1 was timed with respect to the contact between the index finger and the hand (i.e., the onset of the visual-touch frame; see Supplementary Materials for an example video showing few cm-PAS trials). Actual timing of visual-touch stimuli was checked using a photodiode.

As in classical S1-PAS protocols (Wolters et al., 2005), the TMS pulses were delivered at 150% of individual rMT over S1. According to their individual rMT, participants were stimulated at a mean TMS intensity (±SD) of 61.8 ± 8.7% in the ISI-20 session, 61 ± 7.6% in the ISI-60 session and 61.4 ± 8.7% in the ISI-100 session (with no difference between sessions, $p \geq 0.49$).

Overall, the cm-PAS comprised a total of 150 paired stimulations delivered at a frequency of 0.1 Hz, for a total duration of 25 min. During the entire duration of cm-PAS, participants were told to keep their left hand on the table with their palm up, hence keeping their hand with the same posture of the left hand shown in the fixation frame (Medina and DePasquale, 2017).

To attenuate the sound made by the TMS pulse, participants heard white noise with a pair of headphones during the stimulation sessions. Noteworthy, peripheral sensations caused by TMS could not be completely avoided: during the cm-PAS, participants could still feel a slight tingling on the scalp, as well as they could have muscle twitches in the left hand given the supra-threshold intensity of the TMS (van de Ruit and Grey, 2016).

Because in PAS protocols paying attention to the stimuli is critical for the success of the protocol itself (Stefan et al., 2004), during the cm-PAS, we ensured that participants were paying attention to the visual-touch stimulus by asking them to detect rare events (presented in 15 out of 150 trials), which consisted of double visual-touch frames. In such trials, the visual-touch frame was presented twice, sequentially: a first visual-touch frame presented for 180 ms, followed by a second visual-touch frame lasting 300 ms (time interval between the two visual-touch frames = 180 ms); in this condition, the TMS pulse was applied on the second visual-touch frame, with the same parameters described above. Participants were instructed to press the PC-mouse button with their right index finger every time the double visual-touch trial was presented; detections were not analyzed.

Trial randomization, timing of the stimuli and recording of the subject's responses were under computer control (E-Prime 2.0, Psychology Software Tool, Inc.).

2.1.4. 2-Point discrimination task – 2-PDT

To assess the behavioral effect of the cm-PAS, we measured tactile acuity using the 2-point discrimination task (2-PDT), similar to the version adopted by Case et al. (2016; 2017), in a single-blind procedure. During the 2-PDT, participants were blindfolded and comfortably seated in an armchair while an experimenter touched them on the thenar eminence of the left-hand palm (i.e., the same part of the hand touched during the visual-touch trials) with 1 or 2 plastic tips using an aesthesiometer (North Coast Medical, Morgan Hill, USA). In a 2-alternative forced-choice task, participants were asked to verbally report whether they felt 1 or 2 tips; a second experimenter recorded the response on the PC. We tested 13 different distances (range 3–15 mm) in descendent blocks of 10 randomized trials comprising 5 trials with 1 tip and 5 trials with 2 tips for each distance. This procedure was repeated 3 times (with a brief break of 1 min at the end of each repetition) for a total of 30 trials for each distance (i.e., 15 with a single tip, 15 with two tips; total of 390 trials). Two experimenters alternated in the administration of the 2-PDT, both trained to always apply the same pressure for tactile delivery at a frequency of approximately 1 touch every ~2 s (total duration ~15 min). Participants were informed in advance about the occurrence of tactile stimuli, and they were asked to provide a quick response just after they felt the touch. Across experimental sessions, each participant was tested by the same experimenter. Furthermore, the stimulation site on the hand palm was marked to be consistent in the location throughout the duration of the 2-PDT and in the assessment after the cm-PAS. Task parameters, such as the number of trials, as well as the location on the hand, were selected according to a pilot study to estimate the individual psychometric function and account for inter-participants variability.

2.1.5. Experimental procedure

Experiment 1 comprises 3 sessions during which the ISI between the visual-touch frame and the S1-TMS was varied: 20 ms (ISI-20), 60 ms (ISI-60) or 100 ms (ISI-100; Fig. 1B). Each experimental session started with the administration of the 2-PDT, followed by the determination of the individual rMT and the TMS hotspot. Then, the cm-PAS was administered; immediately after its end, tactile acuity was measured again with the 2-PDT (Fig. 1A). On average, each session lasted approximately 1 h and 40 min.

In all experiments, the order of the experimental sessions was carefully counterbalanced among participants, with an intersession interval of at least 72 h; each participant was tested at the same moment of the day throughout the sessions.

2.1.6. Statistical analysis

Cm-PAS effects at the 2-PDT were assessed following the signal detection theory (Green and Swets, 1966), which allows determining the contribution of stimulus-related (i.e., perceptual sensitivity, *d'*) and subject-related (i.e., response bias, *c*) influences on tactile acuity. For sensory threshold estimation, *d'* data were linearly transformed to fit in a range between 0 and 1 and submitted to a logistic function fitting; thus, the sensory threshold was defined as the distance in mm at which performance was 50% (R, version 3.3.1 - R Core Team, 2016). In two participants, threshold estimation revealed negative values; they were therefore excluded from subsequent analyses. We also considered as a dependent variable the global performance, consisting of the mean *d'* sensitivity and response criterion regardless of the mm-distance (i.e., all distances collapsed).

The Shapiro-Wilk approach was applied to test for the normality of the distributions; sphericity requirements were assessed with Mauchly's test. Sensory threshold, response criterion and global performance were then separately analyzed via repeated-measures analysis of variance (rm-ANOVA), followed by post-hoc multiple comparisons corrected by applying Tukey honest significant difference. In *Experiment 1*, the within-subjects factors were Time (pre cm-PAS, post cm-PAS) and ISI (ISI-20, ISI-60, ISI-100).

Whenever data were not normally distributed, nonparametric tests were used: the Friedman's ANOVA and the Wilcoxon paired test.

Statistical significance was set at $p < 0.05$.

2.2. Results

The rm-ANOVA on sensory threshold (*d'* values) at the 2-PDT showed a significant ISI by Time interaction ($F_{2,\ 30} = 6.55$, $p = 0.004$, $\eta p^2 = 0.3$): post-hoc comparisons revealed a trend for a difference between pre- and post-cm-PAS only when the ISI was 20 ms ($p = 0.078$), which reached significance when further explored in a planned comparison with 2-tailed Student's paired *t*-test ($Pre_{ISI\text{-}20} = 9.35 \pm 0.52$ mm, *vs.* $Post_{ISI\text{-}20} = 8.3 \pm 0.59$ mm, $t_{15} = 2.35$, $p = 0.033$). The post-hoc comparisons also showed that the sensory threshold after the cm-PAS with 20 ms of ISI

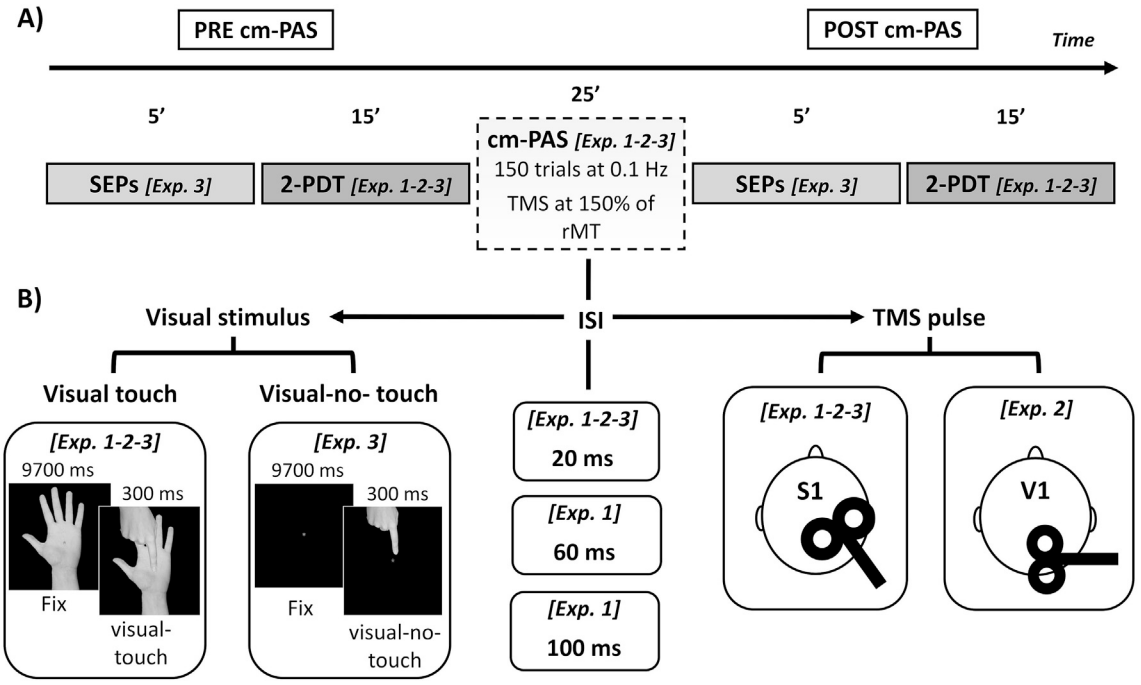

Fig. 1. *Cm-PAS*. **[A]** Experimental procedure for the 3 experiments. Before and after the cm-PAS, participants underwent the 2-PDT task and, in *Experiment 3,* SEP recording (median nerve stimulation, 32-channel EEG) before the 2-PDT. **[B]** In the cm-PAS (0.1 Hz, 25 min) the visual-touch stimulus (or visual-no-touch in *Experiment 3*) was paired with a TMS pulse over S1 (or over V1 in *Experiment 2*), with an ISI of 20 ms (or 60 or 100 ms in *Experiment 1*).

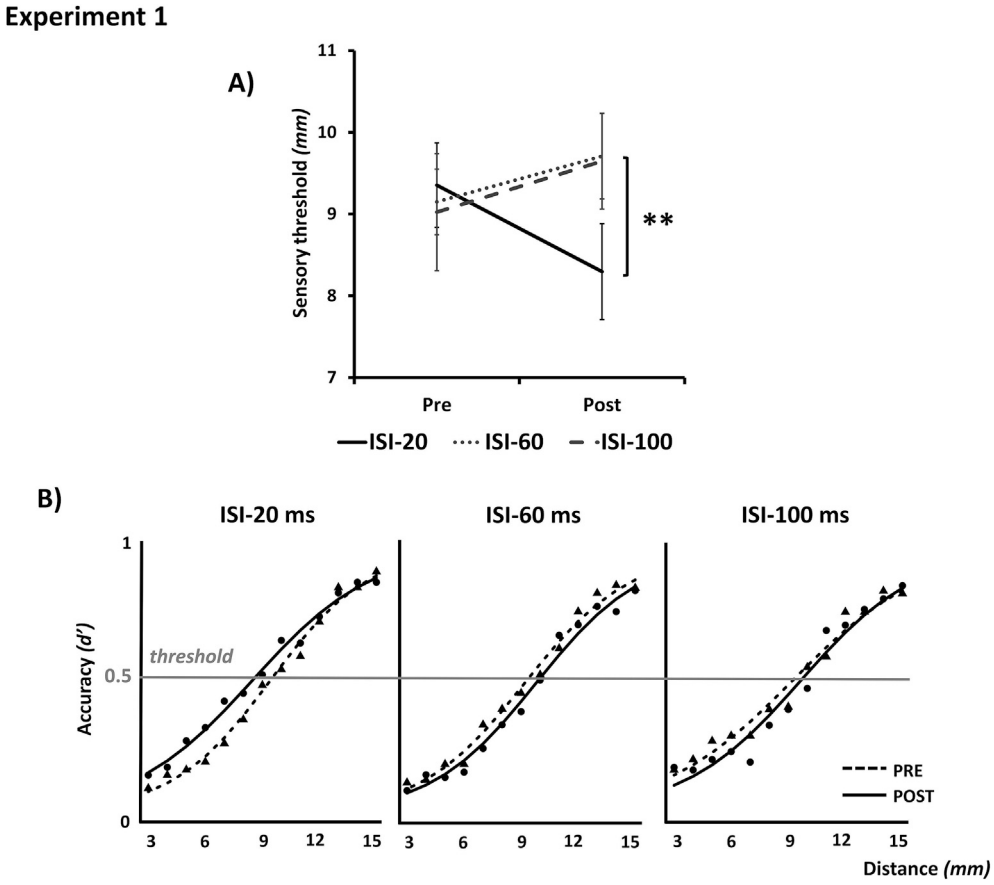

Fig. 2. *Experiment 1: Time-specific behavioral effects induced by cm-PAS*. **[A]** Effects of cm-PAS at the 2-PDT: significantly lower threshold only after ISI-20 (continuous line) compared to ISI-60 (dotted line) and ISI-100 (dashed line). Asterisks indicate statistical significance ($^{**}p < 0.01$). **[B]** Psychometric functions obtained from logistic fitting to raw data, before (dotted line, triangles) and after (continuous line, dots) cm-PAS with ISI-20, ISI-60 and ISI-100.

was significantly lower than after cm-PAS with an ISI of 60 ms ($Post_{ISI-60} = 9.71 \pm 0.53$ mm, $t = -2.37$, $p = 0.008$) or of 100 ms ($Post_{ISI-100} = 9.65 \pm 0.59$ mm, $t = -1.78$, $p = 0.012$; Fig. 2). Importantly, the threshold before cm-PAS did not differ among ISIs ($p \geq 0.947$). The main effects of ISI ($F_{2, 30} = 0.8$, $p = 0.458$, $\eta p^2 = 0.05$) and Time ($F_{1, 15} = 0.02$, $p = 0.882$, $\eta p^2 < 0.01$) were not significant.

Regarding the response criterion data, which were not normally distributed in one condition ($Pre_{ISI-100}$), the Friedmann ANOVA was used, and it did not reveal any significant effect ($\chi^2_5 = 7.93$, $p = 0.16$).

Finally, the results on global performance mirrored the previous results on sensory threshold: the significant ISI by Time interaction ($F_{2, 30} = 8.38$, $p = 0.001$) showed that performance significantly improved only after cm-PAS with 20 ms of ISI (Pre_{ISI-20}: $d' = 1.72 \pm 0.12$; $Post_{ISI-20}$: $d' = 1.94 \pm 0.11$; $t = -2.86$, $p = 0.03$; Pre_{ISI-60}: $d' = 1.78 \pm 0.1$, $Post_{ISI-60}$: $d' = 1.64 \pm 0.13$, $t = 1.98$, $p = 0.32$; $Pre_{ISI-100}$: $d' = 1.77 \pm 0.15$, $Post_{ISI-100}$: $d' = 1.68 \pm 0.12$, $t = 1.19$, $p = 0.77$). Furthermore, performance after cm-PAS with 20 ms ISI was significantly higher than that after cm-PAS at ISIs of 60 ms ($t = 2.59$; $p = 0.001$) and 100 ms ($t = 1.81$, $p = 0.008$). The main effects of ISI ($F_{2, 30} = 0.78$, $p = 0.46$, $\eta p^2 = 0.05$) and Time ($F_{1, 15} < 0.01$, $p = 0.94$, $\eta p^2 < 0.01$) were not significant.

In summary, the results of *Experiment 1* showed a timing-dependent improvement in tactile acuity after cm-PAS, only when ISI-20 was applied.

3. Experiment 2 - cortical specificity of the cm-PAS

3.1. Materials and methods

3.1.1. Participants

Ten participants, all right-handed (Oldfield, 1971), participated in *Experiment 2* (5 males, mean age ± SD: 23.7 ± 4.2 years), who were recruited using the same criteria of *Experiment 1*. Their mean rMT (±SD) was 40.2 ± 4.3%.

3.1.2. Experimental procedure and statistical analyses

Materials, methods and statistical analyses were identical to those of *Experiment 1*. The only difference pertained to the cm-PAS: now, we used only the ISI of 20 ms, which proved to be effective in *Experiment 1* (see results above), but we added a control condition during which the right V1 was stimulated to assess the cortical specificity of the cm-PAS (Fig. 1B). Hence, *Experiment 2* comprises two experimental sessions (i.e., S1 *vs.* V1 stimulation). The TMS intensity during the cm-PAS was, on average ± SD, 60.8 ± 6.1% for S1 stimulation and 59.8 ± 6.8% for V1 stimulation (not significantly different, $t = 1.5$, $p = 0.168$).

The right V1 was identified 2 cm dorsal and 0.5 cm lateral from the inion, according to previous literature (Silvanto et al., 2005). For V1 stimulation, the coil was placed tangentially to the scalp with the handle hold horizontally to the right, thus inducing a lateral from medial current flown (Kammer et al., 2001).

Data from the 2-PDT were analyzed with the same statistical approach as in *Experiment 1*: in the rm-ANOVA, the within-subjects factors were Time (pre cm-PAS, post cm-PAS) and Area (S1, V1); whenever data were not normally distributed, the Friedman's ANOVA and the Wilcoxon paired test were used.

3.2. Results

The sensory threshold and response criterion at the 2-PDT were both analyzed with non-parametric analyses since they were not normally distributed in one condition (Pre_{V1} and $Post_{V1}$, respectively). With respect to the sensory threshold, the analysis showed differences between conditions ($\chi^2_3 = 9.12$, $p = 0.028$): paired comparisons highlighted a significant decrease of the threshold only after right S1 stimulation ($Pre_{S1} = 10.56 \pm 0.42$ mm, *vs.* $Post_{S1} = 9.02 \pm 0.31$ mm, $Z = 2.70$, $p = 0.007$), which also differed from the sensory threshold after V1 stimulation ($Post_{S1}$ *vs.* $Post_{V1} = 10.82 \pm 0.53$ mm, $Z = 2.19$, $p = 0.028$; Fig. 3). No changes in sensory threshold were found after V1 stimulation ($Pre_{V1} = 10.45 \pm 0.58$ mm, *vs.* $Post_{V1} = 10.82 \pm 0.53$ mm, $Z = 1.17$, $p = 0.241$). Moreover, thresholds were comparable before S1 and V1 stimulation ($Pre_{V1} = 10.45 \pm 0.58$ mm, *vs.* Pre_{S1}, $Z = 0.25$, $p = 0.799$).

With respect to the response criterion, we found a significant difference between conditions ($\chi^2_3 = 11.30$, $p = 0.010$): response criterion values increased both after S1 stimulation ($Z = 2.60$, $p = 0.009$) and V1 stimulation ($Z = 2.67$, $p = 0.008$), while they were similar in the two experimental sessions (Pre_{S1} and Pre_{V1}) before the cm-PAS ($Z = 0.05$, $p = 0.959$).

Please note that the same results are obtained if data are analyzed with rm-ANOVAs.

The rm-ANOVA conducted on the global performance data showed a significant Area by Time interaction ($F_{1, 9} = 10.98$, $p = 0.009$, $\eta p^2 = 0.55$): performance significantly improved after the cm-PAS only when TMS was delivered over S1 (Pre_{S1}: $d' = 1.50 \pm 0.1$, $Post_{S1}$:

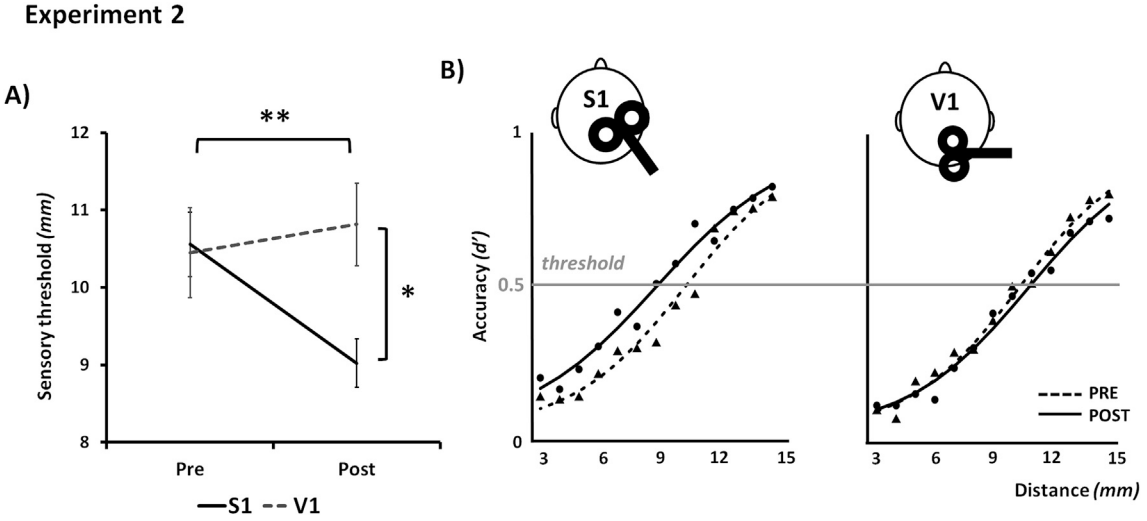

Fig. 3. Experiment 2: Cortical specificity of cm-PAS. **[A]** Effects of cm-PAS on tactile acuity at the 2-PDT: significant decrease of sensory threshold when TMS was delivered over S1 (continuous line) compared to V1 (dotted line). Asterisks indicate statistical significance in post-hoc tests corrected for multiple comparisons (*$p < 0.05$; **$p < 0.01$). **[B]** Psychometric functions obtained from logistic fitting to raw data, before (dotted line, triangles) and after (continuous line, dots) cm-PAS over S1 and V1.

$d' = 1.83 \pm 0.07$, $t = -4.23$, $p = 0.023$) but not following the stimulation of V1 (Pre_{V1}: $d' = 1.52 \pm 0.13$, $Post_{V1}$: $d' = 1.43 \pm 0.12$, $t = 1.04$, $p = 0.735$). Global performance after cm-PAS with S1 stimulation was significantly higher compared to cm-PAS over V1 ($t = 2.92$, $p = 0.008$). The main effects of Area ($F_{1,\ 9} = 3.11$, $p = 0.111$, $\eta p^2 = 0.26$) and Time ($F_{1,9} = 4.66$, $p = 0.059$, $\eta p^2 = 0.34$) did not reach the significance level.

Hence, the results of *Experiment 2* confirmed findings from *Experiment 1*, documenting the improvement in tactile acuity after cm-PAS over S1 with a 20 ms ISI between TMS and visual-touch stimuli; the effect of the cm-PAS was specific for the stimulation of S1, being ineffective when applied to V1.

4. Experiment 3: visual specificity and neurophysiological correlates of the cm-PAS

4.1. Materials and methods

4.1.1. Participants

Twenty participants, all right-handed (Oldfield, 1971), were recruited for *Experiment 3* following the same criteria of the previous experiments. One participant from *Experiment 3* dropped out and two were excluded due to EEG artifacts, so that the final sample considered in the analyses comprised 17 participants (8 males, mean age ± SD: 23.6 ± 2.1 years); their mean rMT ± SD was 48 ± 6%.

4.1.2. Experimental procedure and statistical analysis

Materials, methods and analyses of *Experiment 3* were the same as in *Experiment 1*, except for the use of a control condition concerning the visual stimulus paired to TMS and the additional recording of SEPs before and after the cm-PAS, just before the 2-PDT administration (Fig. 1A). Only the cm-PAS with 20 ms of ISI and TMS delivered over S1 was used. Moreover, to ensure the appropriate TMS intensity during the cm-PAS, the rMT was determined after the EEG cap for SEP recording was mounted (see next section) because EEG electrodes increase the distance between TMS coil and the scalp (Farzan et al., 2016).

Experiment 3 comprised two sessions, which differed for the visual stimuli displayed during the cm-PAS. In one session, the visual-touch stimuli were presented, as those used in the previous experiments; in the other session, visual-no-touch stimuli (300 ms of duration, the same of the visual-touch stimulus) were presented: now, participants viewed, from an allocentric perspective, the right index only approaching the red asterisk used as fixation point (Fig. 1A, see Supplementary Materials for an example of the visual stimulus).

Each session lasted approximately 2 h and 30 min. The TMS intensity during the cm-PAS was, on average ± SD, 72.3 ± 9.4% for the visual-touch session, and 71.7 ± 8.5% for the no-touch condition ($t = 0.81$, $p = 0.43$).

Data from the 2-PDT were normally distributed in every condition; hence, rm-ANOVAs were performed, with the within-subjects factors Time (pre cm-PAS, post cm-PAS) and Visual stimulus (visual-touch, visual-no-touch).

The same 2 (Time) by 2 (Visual stimulus) rm-ANOVA was used to analyze each SEP component.

4.1.3. Somatosensory evoked potentials - SEPs

SEPs were induced by electric stimulation of the left MN, while EEG was continuously recorded. During SEP recording, participants were comfortably seated in an armchair with their left arm lying relaxed on a desk, and they were asked to fixate a cross on a PC screen to minimize eye movements.

MN stimulation was performed using a battery-driven constant current electrical stimulator (STM140, High Technology Laboratory, Udine, Italy) using the same parameters and stimulator device of Pellicciari and coworkers (2009). Specifically, the anode was placed at the level of the wrist with the cathode proximal, and 500 pulses were delivered with a pulse width of 200 μs at a frequency of 3.3 Hz, for a total duration of approximately 3 min. Stimulation intensity was set at 200% of the individual perceptual threshold (Cruccu et al., 2008). At this stimulation intensity, none of the participants had visible muscle twitches elicited by the MN stimulation. Before the cm-PAS, the stimulator position was marked on the skin, allowing its repositioning in the same exact location after the administration of the cm-PAS. The same parameters were applied for SEP recording after the cm-PAS.

EEG was recorded from 32 channels (FP1, FP2, F3, Fz, F4, FC5, FC1, FC2, FC6, T7, T8, C3, C1, Cz, C2, C4, CP5, CP3, CP1, CP2, CP4, CP6, P7, P3, Pz, P4, P8, PO7, PO3, PO4, PO8, Oz; BrainAmp, 32 MR plus, BrainVision Recorder, Brain Products GmbH, Munich, Germany) at a frequency of 5 kHz. The ground was placed on FPz, and the signal from all electrodes was referenced online to the right mastoid. Four additional electrodes in a bipolar montage were applied for vertical and horizontal electrooculograms. Skin/electrode impedance was maintained below 5 kΩ.

Analysis of SEPs was performed using BrainVision Analyzer 2 (Brain Products GmbH, Munich, Germany). Continuous EEG data were rereferenced offline to the average of the two mastoids and high-pass filtered at 1 Hz (Butterworth zero phase filter; 12 db/oct); according to previous literature, we did not apply any low-pass filter (Pellicciari et al., 2009). The artifact induced by MN stimulation was removed by interpolating the signal in the first 4 ms after the electrical pulse, while artifacts related to eye movements were identified and corrected by means of independent component analysis (ICA; algorithm: infomax). Continuous data were then segmented into epochs from 50 ms before to 100 ms after the electrical pulse, applying a baseline correction for the 20 ms preceding the stimulation. The signal recorded from corrupted channels was interpolated (not more than 1 for each participant; mean ± SD: 0.13 ± 0.34). Epochs were visually inspected, rejected when the signal exceeded ±70 μV and/or if muscular artifacts were detected (mean ± SD: 3.09 ± 5.75%), and then averaged. SEP amplitude was measured at the peak of each component from a pooling of channels C4 and CP4 (Buchsbaum et al., 1977; Litvak et al., 2007), whose latency was identified from grand-average collapsing all conditions.

4.2. Results

4.2.1. 2-PDT

The rm-ANOVA showed a significant Stimulus by Time interaction ($F_{1,\ 16} = 33.53$, $p < 0.001$, $\eta p^2 = 0.68$), showing that the tactile threshold significantly decreased only in the visual-touch cm-PAS: $Pre_{visual\text{-}touch} = 11.99 \pm 0.59$ mm *vs.* $Post_{visual\text{-}touch} = 10.35 \pm 0.52$ mm, $t = 4.45$, $p < 0.001$. Conversely, after the cm-PAS with visual-no-touch stimuli, the sensory threshold significantly increased ($Pre_{visual\text{-}no\text{-}touch} = 11.26 \pm 0.52$ mm, *vs.* $Post_{visual\text{-}no\text{-}touch} = 12.22 \pm 0.61$ mm, $t = -2.67$, $p = 0.038$). Subjects' performance in the two sessions did not differ before the protocol ($t = 1.33$, $p = 0.141$), while it differed after the two cm-PAS ($t = -2.85$, $p < 0.001$; Fig. 4A). The main effects of Time ($F_{1,\ 16} = 1.47$, $p = 0.243$, $\eta p^2 = 0.08$) and Stimulus ($F_{1,\ 16} = 1.04$, $p = 0.323$, $\eta p^2 = 0.06$) were not significant.

A significant main effect of Time was found for the response criterion ($F_{1,\ 16} = 39.37$, $p < 0.001$, $\eta p^2 = 0.71$), with increased values after cm-PAS but independent of visual stimulus type ($Pre_{cm\text{-}PAS}$: $c = -0.54 \pm 0.07$, $Post_{cm\text{-}PAS}$: $c = -0.3 \pm 0.08$). The main effect of Stimulus ($F_{1,\ 16} = 0.29$, $p = 0.597$, $\eta p^2 = 0.02$), as well as the Stimulus by Time interaction ($F_{1,\ 16} = 2.56$, $p = 0.129$, $\eta p^2 = 0.14$), were not significant.

The results on global performance were consistent with the ones on sensory threshold: the significant Stimulus by Time interaction ($F_{1,\ 16} = 28.18$, $p < 0.001$, $\eta p^2 = 0.64$) showed that the performance improved after the cm-PAS with visual-touch stimuli ($Pre_{visual\text{-}touch}$: $d' = 1.21 \pm 0.11$ *vs.* $Post_{visual\text{-}touch}$: $d' = 1.54 \pm 0.11$, $t = -4.58$, $p < 0.001$), while it remained unchanged in the visual-no-touch ($Pre_{visual\text{-}no\text{-}touch}$: $d' = 1.3 \pm 0.1$ *vs.* $Post_{visual\text{-}no\text{-}touch}$: $d' = 1.14 \pm 0.13$, $t = 2.4$, $p = 0.102$). Global performance before cm-PAS was comparable in the two sessions ($t = -0.91$, $p = 0.484$), whereas after cm-PAS, it was higher

for the visual-touch session than for the visual-no-touch session ($t = 2.91$, $p < 0.001$). The main effects of Time ($F_{1,\ 16} = 2.53$, $p = 0.131$, $\eta p^2 = 0.14$) and Stimulus ($F_{1,\ 16} = 1.8$, $p = 0.199$, $\eta p^2 = 0.1$) were not significant.

4.2.2. SEPs

Consistent with the literature on SEPs (Desmedt et al., 1983; Macerollo et al., 2018; Mauguière et al., 1999), from grand-average collapsing all conditions, we observed 5 main peaks (mean latency in parentheses): P14 (14 ms), N20 (19 ms), P25 (25 ms), N30 (30 ms), P40 (42 ms). Significant effects were found for P40 only: the rm-ANOVA showed a significant Stimulus by Time interaction ($F_{1,\ 16} = 5.67$, $p = 0.03$, $\eta p^2 = 0.26$), and post-hoc comparisons revealed a significant increase in P40 after cm-PAS ($Pre_{visual\text{-}touch} = 0.80 \pm 0.25\ \mu V$ *vs.* $Post\text{-}_{visual\text{-}touch} = 1.57 \pm 0.29\ \mu V$, $t = -2.81$, $p = 0.038$) in the visual-touch condition only ($Pre_{visual\text{-}no\text{-}touch} = 1.34 \pm 0.22\ \mu V$ *vs.* $Post\text{-}_{visual\text{-}no\text{-}touch} = 1.24 \pm 0.27\ \mu V$, $t = 0.4$, $p = 0.983$; Fig. 4C). P40 in the two conditions did not differ before ($t = -2.13$, $p = 0.203$), nor after ($t = 1.4$, $p = 0.581$) the cm-PAS. Main effects of Stimulus ($F_{1,\ 16} = 0.39$, $p = 0.543$, $\eta p^2 = 0.02$) and Time ($F_{1,\ 16} = 3.59$, $p = 0.076$, $\eta p^2 = 0.18$) were not significant.

No significant main effects or interactions emerged from the analysis on other SEP components (see Table 1).

In sum, behavioral results from *Experiment 3* replicated those from *Experiments 1* and *2*, showing an improvement in tactile acuity after cm-

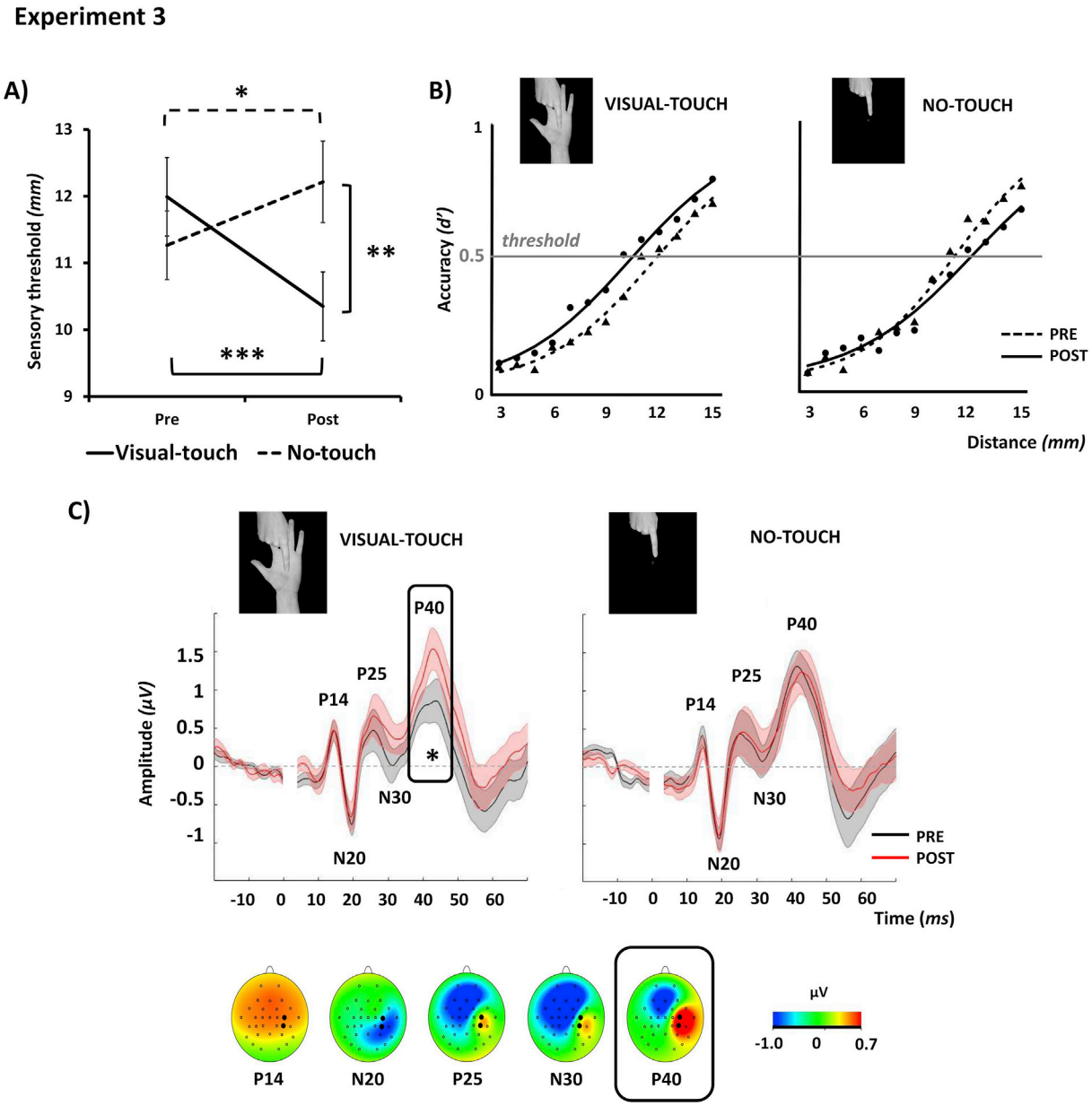

Fig. 4. *Experiment 3: Visual specificity of cm-PAS.* **[A]** Effects of cm-PAS on tactile acuity at the 2-PDT: significant decrease of sensory threshold only in the Visual-touch (continuous line) compared to No-touch (dotted line) condition. Asterisks indicate statistical significance in post–hoc tests corrected for multiple comparisons (*$p <$ 0.05, **$p < 0.01$, ***$p < 0.001$). **[B]** Psychometric functions obtained from logistic fitting to raw data, before (dotted line, triangles) and after (continuous line, dots) cm-PAS in the visual-touch and no-touch condition. **[C]** Effects of cm-PAS on SEPs. *Top*: SEPs as recorded from C4-CP4 pooling, in the visual-touch and in the no-touch condition, before (black) and after (red) cm-PAS; SE in shaded bars. The asterisk indicates the significant increase of P40 after cm-PAS ($p = 0.038$) in the visual-touch condition only. A low-pass filter at 150 Hz was applied for visualization purposes. *Bottom:* topographies of main SEP components observed (P14, N20, P25, N30, P40), taken from all conditions collapsed; amplitude range (μV) as shown in colorbar. Filled dots indicate C4-CP4 electrodes considered in the pooling.

PAS; in this last experiment, we also demonstrated that the behavioral improvement brought about by the cm-PAS was visual-specific because only participants observed a visual stimulus depicting a tactile event. *Experiment 3* also provided a neurophysiological effect of cm-PAS, consisting of an increase of the P40 SEP component, which again emerged only after the cm-PAS with visual-touch stimuli.

5. Discussion

In the present study, we developed a novel PAS protocol, the cm-PAS, targeting the somatosensory system via a cross-modal stimulation: the observation of a hand being touched (visual stimulus) was combined with a cortical stimulation over S1 (somatosensory stimulation). Overall, our results show that tactile acuity improves after the cm-PAS only when the ISI between the visual-touch stimulus and the TMS pulse is 20 ms (*Experiment 1*), TMS is delivered over S1 (*Experiment 2*), and the visual stimulus depicts a hand being touched (*Experiment 3*). Furthermore, the cm-PAS also affects SEPs, increasing P40 amplitude.

The main finding is that the cm-PAS is effective in improving tactile acuity and in modulating SEPs, effects that can be interpreted in terms of LTP-like Hebbian plasticity mechanisms (Litvak et al., 2007). Although it is well known that Hebbian learning can be induced in S1 through classical S1-PAS protocols, as well as by tactile coactivation paradigms (i.e., the repeated application of weak tactile stimuli to a body part leading to a significant modulation of tactile acuity in the stimulated skin area), much less is known about the possibility to induce similar plastic effects in a cross-modal way, for instance by pairing a tactile stimulus with a visual stimulus (Godde et al., 2000, 1996; Hodzic et al., 2004; Pleger et al., 2001; Sellien and Ebner, 2007). A first attempt in this direction was recently made by Kuehn and coworkers (2017), who presented a visual-tactile stimulation consisting of a classic tactile coactivation paradigm paired with the repeated presentation of visual stimuli showing a right index finger being touched. However, the authors did not find any significant modulation of the tactile acuity compared to the unimodal, tactile or visual, version of the paradigm (Kuehn et al., 2017). Conversely, our cm-PAS, by pairing a visual stimulus with the direct cortical stimulation of S1, was effective in modulating tactile acuity. The effectiveness of our cm-PAS compared to the study by Kuehn et al. (2017) may be due to the characteristics of the paradigm itself, combining a cortical somatosensory stimulation with touch observation in a time-specific way.

The ISI required for the interaction between the S1-TMS pulse and the visual-touch stimulus is particularly interesting. It is well known that the temporal relationship between two events is fundamental to give rise to Hebbian association effects: to induce synaptic plasticity, two neural events have to take place within a critical time range of a few tens of milliseconds (Caporale and Dan, 2008; Markram et al., 2011). In line with classical (unimodal) S1-PAS protocols (Wolters et al., 2005), the modulation of tactile acuity by our cm-PAS is time-dependent (*Experiment 1*), emerging only with an ISI of 20 ms between the visual-touch stimulus and the TMS pulse, while being absent with ISIs of 60 and 100 ms. The ISI of 20 ms matches the arrival time of the afferent input S1, and it is the same ISI effective in classical S1-PAS protocols for LTP induction (Allison et al., 1989; Macerollo et al., 2018). The fact that the same ISI is also effective in the cm-PAS, where the MN stimulation is substituted by a visual, complex, stimulus, is thought-provoking. Indeed, an interval of 20 ms seems quite short for cross-modal, visual, recruitment of S1. For instance, paired-pulse TMS and event-related potential studies have shown that S1 activation by touch observation occurs between 50 and 600 ms (Bolognini et al., 2014; Pihko et al., 2010; Pisoni et al., 2018).

A hypothesis is that such a short time course reflects an 'anticipatory' tactile effect. Considering that during the cm-PAS (as in classical PAS protocols), our participants observed for 25 min a hand being touched repetitively at a fixed frequency (0.1 Hz rate), it is possible that after a few trials, they may start to anticipate the touch stimulus before its actual occurrence (Carlsson et al., 2000; Kimura and Katayama, 2018, 2015). This, in turn, could have anticipated the mirror-like activation of S1, which then occurred rhythmically in the brain every time the new trial started. Such anticipation of the visual-touch stimulus would allow a more rapid interaction with the cortical TMS pulse occurring as soon as at 20 ms, a time that reflects the typical latency of S1 activation by direct somatosensory afference (Cohen et al., 1991; Pisoni et al., 2018). Accordingly, the timing of 20 ms does not reflect, from a temporal perspective, the real interaction between the mirror activation of S1 by touch observation and its cortical stimulation by TMS. Rather, it would reflect the interaction between an anticipated (before its actual visual occurrence) tactile mirroring and the TMS pulse in S1. From this perspective, mechanisms of prediction may also be involved. Predictive coding refers to the potential of cortical areas to actively predict their own activity. Incoming sensory signals are continuously compared with internal predictions at all levels of the cortical process hierarchy (Clark, 2013; Friston, 2010). In particular, theoretical (Friston et al., 2011; Kilner, 2011; Kilner et al., 2007; Wolpert et al., 2003) and empirical works (Aglioti et al., 2008; Avenanti et al., 2013; Kilner et al., 2004; Maranesi et al., 2014; Schippers and Keysers, 2011; Southgate et al., 2009) have proposed that the action-observation mirror network generates predictions of the observed action. Such a generative model starts with a prior expectation (prediction) about the goal of an observed action; given this prior, a prediction of the sensory consequences of the action is generated. Contextual information in which the action is embedded serves to build up a prior and offers guidance to the perceiver's expectations (Kilner et al., 2007; Maranesi et al., 2014). Based on such predictive coding mechanisms, our cm-PAS may act by generating a reafference 'tactile' prediction signal from the observed action, anticipating the time-course of interaction between the observed touch and the TMS-induced somatosensory activity.

Another account, not mutually exclusive, is suggested by studies of cross-modal interactions in primary sensory areas (Bieler et al., 2017b; Convento et al., 2013; Ghazanfar and Schroeder, 2006; Henschke et al., 2015; Iurilli et al., 2012; Murray et al., 2016). Early visuo-tactile interactions are supported by either direct (feed-forward) connections between S1 and V1, as well as by subcortical feed-forward projections from the thalamus (Cappe and Barone, 2005; Driver and Noesselt, 2008; Foxe and Simpson, 2002; Sieben et al., 2013). In particular, thalamic nuclei offer a fast pathway for information transfer between different cortical sensory areas, rapidly relaying this integrated information to the cortex by their multiple thalamo-cortical connections (Cappe et al., 2009a,b; Driver and Noesselt, 2008; Tyll et al., 2011). Through thalamo-cortical routes, the visual information can reach S1, even bypassing V1 (Bieler et al., 2017a; Sieben et al., 2013). A similar route may be invoked to explain the early latency of visuo-tactile/TMS interactions driven by the cm-PAS. However, it is important to consider that short-latency cross-modal interactions typically affect lower processing stages, insensible to the nature of the stimuli (Cappe et al., 2009a, b; Driver and Noesselt, 2008). The fact that the efficacy of the cm-PAS depends on the type of the paired visual stimulus, being present only

Table 1
Results from the analysis of SEP components.

	Main effect of *Stimulus*	Main effect of *Time*	*Stimulus* by *Time* interaction
P14	$F_{1,\ 16} = 1.62$, $p = 0.22$, $\eta p^2 = 0.09$	$F_{1,\ 16} = 1.53$, $p = 0.235$, $\eta p^2 = 0.09$	$F_{1,\ 16} = 0.9$, $p = 0.357$, $\eta p^2 = 0.05$
N20	$F_{1,\ 16} = 2.23$, $p = 0.155$, $\eta p^2 = 0.12$	$F_{1,\ 16} = 0.18$, $p = 0.673$, $\eta p^2 = 0.01$	$F_{1,\ 16} = 0.02$, $p = 0.883$, $\eta p^2 < 0.01$
P25	$F_{1,\ 16} = 0.26$, $p = 0.615$, $\eta p^2 = 0.02$	$F_{1,\ 16} = 0.81$, $p = 0.382$, $\eta p^2 = 0.05$	$F_{1,\ 16} = 0.49$, $p = 0.495$, $\eta p^2 = 0.03$
N30	$F_{1,\ 16} = 0.02$, $p = 0.88$, $\eta p^2 < 0.01$	$F_{1,\ 16} = 4.09$, $p = 0.06$, $\eta p^2 = 0.2$	$F_{1,\ 16} = 1.2$, $p = 0.291$, $\eta p^2 = 0.07$
P40	$F_{1,\ 16} = 0.39$, $p = 0.543$, $\eta p^2 = 0.02$	$F_{1,\ 16} = 3.59$, $p = 0.076$, $\eta p^2 = 0.18$	* $F_{1,\ 16} = 5.67$, $p = 0.03$, $\eta p^2 = 0.26$

when the visual stimulus conveys tactile information (*Experiment 3*), suggests further the involvement of higher-order association cortical areas, such as posterior parietal and premotor areas containing visual-tactile neurons (e.g., Duhamel et al., 1998; Fogassi et al., 1999) and showing vicarious activation by the sight of touch (for a review: Keysers et al., 2010). These high-level association cortices would be responsible for top-down influences on S1 activation involving feedback pathways, which render the cm-PAS effective only with visual stimuli with a tactile content, selectively activating mirror-touch cortical networks (Bolognini et al., 2014). On the other hand, if this is the case, ISIs longer than 20 ms would be required to support such feedback influences.

In this regard, it is worth noting the feature of the visual stimulation to be used in the cm-PAS: the visual stimulus must depict a tactile event to improve tactile perception, while the mere view of an approaching hand does not have any facilitatory effect (*Experiment 3)*. This result further supports the specific involvement of the Tactile Mirror System (e.g., Blakemore et al., 2005; Bolognini et al., 2014, 2011; Ebisch et al., 2008; Rossetti et al., 2012). Not only, observing a moving hand, without any tactile component, combined with S1-TMS at the same ISI of 20 ms tends to reverse the cm-PAS effects, impairing tactile sensitivity. This effect is reminiscent of sensory attenuation, a phenomenon associated with mechanisms of sensory feedback prediction by which the intensity of somatosensation caused by self-generated movement is reduced (e.g., Blakemore et al., 1998; Waszak, Cardoso-leite, & Hughes, 2012). Recently, it was shown that tactile attenuation may also occur during action observation (Rossi et al., 2002; Vastano et al., 2016): in this account, decreased tactile sensitivity induced by the cm-PAS with action observation stimuli could be due to the reinforcement of motor resonance mechanism, which negatively impacts somatosensory processing (Avenanti et al., 2007; Urgesi et al., 2010). This hypothesis remains a speculation because our last experiment did not control for the time- and area-specificity of this sort of inhibitory effect, at variance with the facilitatory side of cm-PAS, which was deeply explored.

We also showed that the efficacy of the cm-PAS is area-specific, not occurring if TMS is applied to V1 *(Experiment 2)*; this selectivity rules out possible interpretations of the effects as due to unspecific modulation of the participant's arousal level (Foerster et al., 1997). The inefficacy of the cm-PAS targeting the occipital cortex on tactile performance does not exclude that the same protocol could be able to modulate unimodal visual processing (e.g., visual acuity or visual evoked potentials) or its potential efficacy on tactile processing if different ISIs are used, fit the time course of functional interplay between V1 and S1 as discussed above (rapid V1–S1 feedforward connections and/or feedback influences from multisensory regions to primary cortices; Driver and Noesselt, 2008).

At the neurophysiological level, the improvement in tactile acuity after the cm-PAS was accompanied by an increase in SEP amplitude, consistent with classical S1-PAS studies describing LTP-like changes (Wolters et al., 2005). Nonetheless, our findings diverged from previous findings in terms of latency: while S1-PAS studies reported a modulation of SEPs between 20 and 30 ms after MN stimulation (Litvak et al., 2007; Pellicciari et al., 2009; Wolters et al., 2005), we observed a modulation of a later SEP component, namely, P40. Such a difference in latency is likely due to the distinct neural pathways involved in the cm-PAS compared to classical S1-PAS (Lacey and Sathian, 2016). Although most of the studies on SEPs in humans focused on earlier components evoked by MN electrical stimulation (i.e., P14–N20–P25–N30, also detected in our experiment, but not affected by cm-PAS, see Fig. 4C; e.g., Buchner et al., 1995; Macerollo et al., 2018; Mauguière et al., 1999), there is evidence suggesting that P40 originates at the cortical level, specifically in S1 (Allison et al., 1991, 1989; Gorgoni et al., 2014; Matsunaga et al., 2004) and that it could be associated with a first cognitive processing of the tactile stimulus (Desmedt et al., 1983). Interestingly, the cortical origin of P40 seems to be localized in Broadman's areas (BA) 1 and 2, while earlier components, such as N20 and P25, in BA 3b (Allison et al., 1991, 1989; Gorgoni et al., 2014). Within the human S1, BA 3b is considered the primary stage for tactile processing, while BAs 1 and, especially, 2 are involved in a secondary stage related to the integration of uni- and cross-modal stimuli (along with other brain areas such as the secondary somatosensory cortex and the insula; Cardini et al., 2010; Keysers et al., 2010; Kuehn et al., 2018, 2014, 2013; Meehan et al., 2009; Meftah et al., 2009). Importantly, fMRI studies showed that both BAs 1 and 2 are also activated by touch observation (Blakemore et al., 2005; Schaefer et al., 2009), while the mirror properties of BA 3b are more controversial (Keysers et al., 2010; Kuehn et al., 2018). We found that the increased P40 amplitude is present only after the cm-PAS involving touch observation and is absent during action observation; therefore, this electrophysiological effect might further support our proposal of a reinforcement of the mirror activity of S1 induced by the cm-PAS.

In conclusion, our findings show the efficacy of the cm-PAS in modulating tactile sensitivity and an early component of SEPs, likely through the activation of Hebbian, LTP-like, plasticity mechanisms in S1. In addition to revealing the efficacy of systematic cross-modal peripheral-cortical paired stimulations at both behavioral and neurophysiological levels, the cm-PAS may be of value in clinical settings for the treatment of various sensory or motor disorders for which classical PAS protocols, which have been shown to have therapeutic effects (for a review: Suppa et al., 2017), are not suitable (e.g., MN stimulation in deafferented patients and patients suffering from spinal injury). Future research is needed to uncover the specific neuro-functional underpinnings of the cm-PAS, as well as to track the presence and duration of its after-effects. Based on the present findings, we may only suggest that the cm-PAS likely relies on the activation of mirror mechanisms in S1, involving proactive mechanisms of prediction in perception and action.

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Declaration of interest

None.

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Appendix A. Supplementary data

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