Fronto-parietal Areas Necessary for a Multisensory Representation of Peripersonal Space in Humans: An rTMS Study

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Abstract

■ A network of brain regions including the ventral premotor cortex (vPMc) and the posterior parietal cortex (PPc) is consistently recruited during processing of multisensory stimuli within peripersonal space (PPS). However, to date, information on the causal role of these fronto-parietal areas in multisensory PPS representation is lacking. Using low-frequency repetitive TMS (rTMS; 1 Hz), we induced transient virtual lesions to the left vPMc, PPc, and visual cortex (V1, control site) and tested whether rTMS affected audio–tactile interaction in the PPS around the hand. Subjects performed a timed response task to a tactile stimulus on their right (contralateral to rTMS) hand while concurrent task-irrelevant sounds were presented either close to the hand or 1 m far from the hand. When no rTMS was delivered, a sound close to the hand reduced RT-to-tactile targets as compared with when a far sound was presented. This space-dependent, auditory modulation of tactile perception was specific to a hand-centered reference frame. Such a specific form of multisensory interaction near the hand can be taken as a behavioral hallmark of PPS representation. Crucially, virtual lesions to vPMc and PPc, but not to V1, eliminated the speeding effect due to near sounds, showing a disruption of audio–tactile interactions around the hand. These findings indicate that multisensory interaction around the hand depends on the functions of vPMc and PPc, thus pointing to the necessity of this human fronto-parietal network in multisensory representation of PPS. ■

INTRODUCTION

The space immediately surrounding the body—termed *peripersonal space* (PPS)—is particularly relevant for behavior. A sensory event occurring within the PPS potentially requires fast, appropriate motor responses. Indeed, this event may represent a potential threat for the body, triggering defense or object avoidance movements, or it could be of interest, thus requiring a planned reaching movement toward the object. To interact with objects in space, the brain needs to compute where the objects are located in relation to the body parts potentially interacting with them. To this aim, visual and/or auditory information about external stimuli are integrated with tactile, proprioceptive and kinesthetic information about body parts in a multisensory representation of PPS.

Seminal studies in monkeys have suggested that neurons in the ventral premotor cortex (vPMc), specifically in area F4 (Graziano, Xu, & Gross, 1997; Fogassi et al., 1996; Graziano, Yap, & Gross, 1994; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981a, 1981b), and in the intraparietal sulcus, specifically in the ventral intraparietal area (VIP; Avillac, Denève, Olivier, Pouget, & Duhamel, 2005; Duhamel, Colby, & Goldberg, 1998), may underlie multisensory representation of PPS. These cells respond to a tactile stimulus administered on a given part of the animal's body (head, face, neck, torso, or shoulders) and to a visual (Graziano et al., 1997) and/or auditory (in case of the head; Schlack, Sterbing, Hartung, Hoffman, & Bremmer, 2005; Graziano, 1999) stimulus, only if presented close to the same body part (i.e., within a range of roughly 30 cm from the surface). Importantly, proximity to the body is defined in body part-centered reference frames: if the body part anchoring the neuron's tactile receptive field moves, then the visual or auditory receptive field also coherently shifts (Graziano & Cooke, 2006). This pattern of neural response is independent of eye position.

The existence of a similar system in humans has been initially demonstrated by neuropsychological studies on brain-damaged patients suffering from cross-modal extinction. In these patients, the detection of a tactile stimulus administered on the controlesional side of the body is reduced by the concurrent presentation of a visual (Làdavas, Farnè, & Zeloni, 2000; di Pellegrino, Làdavas, & Farnè, 1997) or auditory stimulus on the ipsilesional side (Farnè & Làdavas, 2002). Importantly, the strength of this effect depends on the distance between visual or auditory stimuli and the body: cross-modal extinction is much stronger if stimuli are presented near rather than far from the body, that is, within the limits of PPS (di Pellegrino et al., 1997; see Làdavas & Serino, 2008, for a review). Behavioral studies in healthy subjects have confirmed that multisensory integration is favored in the space around the body (see

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Spence, Pavani, Maravita, & Holmes, 2008, for a review). We have recently shown, for instance, that RT to a tactile stimulus administered to the subject's hand is fastened when concurrent task-irrelevant auditory stimuli are presented near the hand rather than in far space (Bassolino, Serino, Ubaldi, & Làdavas, 2010; Serino, Bassolino, Farnè, & Làdavas, 2007; see also Tajadura-Jimènez et al., 2009; Zampini, Torresan, Spence, & Murray, 2007).

Neuroimaging studies have tried to identify brain areas underlying PPS representation in the human brain. Bremmer, Duhamel, Ben Hamed, and Graf (2002) demonstrated that portions of the posterior parietal cortex (PPc), around the intraparietal sulcus, and the vPMc are activated by tactile stimuli administered on the head and by visual and auditory stimuli moving toward the head (see also Macaluso & Driver, 2001, 2005). Moreover, Sereno and Huang (2006) described aligned maps in the ventral part of the intraparietal sulcus responding to tactile stimuli and periface visual stimuli, which code the location of visual stimuli with respect to the face and not with respect to the eye. Finally, Makin, Holmes, and Zohary (2007) showed that PPc and vPMc activity is modulated by viewing a stimulus moving back and forth near the hand, indicating that visual and proprioceptive information about hand position affects neural response in PPc and vPMc. Taken together, these neuroimaging findings suggest that in humans, as in monkeys, a network of brain areas located in the premotor and parietal cortices might underlie a multisensory representation of the PPS. However, imaging studies do not reveal a direct causal link between brain structures and function. The aim of the present study is to test the necessary role of vPMc and PPc in multisensory representation of PPS. To this aim, we applied low-frequency (1 Hz) repetitive TMS (rTMS) to transiently interfere with vPMc and PPc processing. When applied to the motor cortex, this rTMS protocol induces a transient suppression of cortical excitability (Avenanti, Bolognini, Maravita, & Aglioti, 2007; Boroojerdi, Prager, Muellbacher, & Cohen, 2000; Chen et al., 1997). Administration of 1-Hz rTMS to other cortical areas also results in behavioral effects consistent with transient suppression of cortical excitability (Balslev et al., 2004; Hilgetag, Théoret, & Pascual-Leone, 2001). Thus, this rTMS protocol can be used to induce transient "virtual lesions" in neurologically intact participants (Ziemann, 2010; O'Shea & Walsh, 2007; Pascual-Leone, Walsh, & Rothwell, 2000).

Here we test whether the representation of PPS was altered by rTMS-induced virtual lesions to vPMc and PPc in comparison with a baseline condition of no rTMS administration. In addition, rTMS was also applied over primary visual cortex (V1), serving as a control site, to exclude possible effects due to a generic administration of TMS, rather than to a specific inhibition of the target areas.

The present study comprises two experiments. Using a behavioral paradigm, we investigated the function and the properties of PPS representation around the hand in humans (Experiment 1A and 1B), we then tested the integrity of PPS representation after the administration of rTMS over vPMc, PPc, and V1 (Experiment 2).

EXPERIMENT 1: A BEHAVIORAL MEASURE OF PPS REPRESENTATION

Experiment 1A

To assess PPS representation around the hand, we used an audio–tactile task developed by our own group (see Bassolino et al., 2010; Serino et al., 2007). Participants were asked to verbally respond as fast as they could to either a weak electrical stimulus or strong electrical stimulus on their right index finger. Tactile stimuli were either administered unimodally or together with concurrent task-irrelevant auditory stimuli. Auditory stimuli were to be ignored and were presented either near the stimulated hand (NEAR sound) or at a distance of about 100 cm from the hand (FAR sound). The rationale of the task is that stimuli from different sensory modalities interact more effectively with one another when presented within the same spatial representation (Stein & Meredith, 1993). This implies that, in normal conditions, the response to tactile stimuli administered on the hand should be more strongly affected by sounds presented near the hand (i.e., within the PPS) than by sounds presented far from the hand. Hence, we predict that the presentation of sounds should speed up tactile RT in comparison with the unimodal tactile condition. More importantly, tactile stimuli associated with near sounds should be processed faster than tactile stimuli associated with far sounds.

We also tested whether the intensity of the tactile stimulus is critical for audio–tactile interaction. Because stimuli from different sensory modalities interact more strongly when unimodal information is weak (i.e., inverse effectiveness law of multisensory integration; Stein & Meredith, 1993), stronger audio–tactile effects can be predicted in response to a weaker rather than a stronger tactile stimulus. For this reason, we compared RT for three stimulation conditions when subjects were asked to respond either to a weak or strong tactile target.

Methods

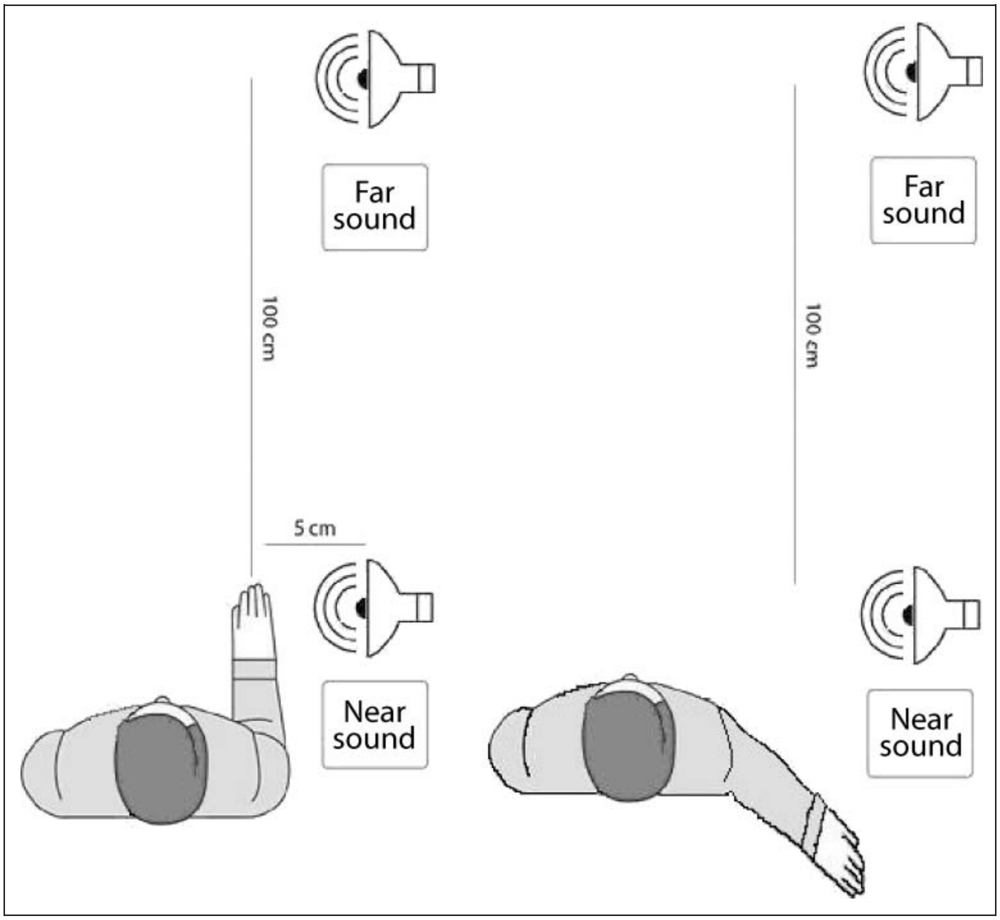
Subjects. Twelve healthy subjects (all women, mean age = 26 years) participated in the study. All participants were right-handed and had normal hearing and touch. All subjects were students at the University of Bologna and gave their informed consent to participate in the study, which was approved by the local ethics committee in accordance with the Declaration of Helsinki.

Materials. Tactile stimuli were delivered from two constant-current electrical stimulators (DS7A, Digitimer, Hertfordshire, UK) via two pairs of neurological electrodes (Neuroline, Ambu, Ballerup, Denmark) placed on the dorsal surface of the index finger. The electrical stimulus was a single, constant voltage, rectangular monophasic pulse (duration = 100 μsec). One pair of electrodes delivered weak stimuli, and the other pair delivered strong stimuli. Stimulus intensity was calibrated for each subject in a pretest session as follows: the experimenter began by administering a very low intensity stimulus (10 mA) and progressively increased the stimulus intensity until the subject reported detection. Normally, the weak stimulus was perceived around 50–80 mA, but this value was highly variable between subjects, seemingly dependent upon the placement of electrodes, the subject's skin, and individual sensitivity. After the initial detection report, the intensity was further increased by 10 mA. At that point, to ensure that the weak stimulus was actually perceived, 10 weak stimuli interspersed with 10 catch trials were administered. If the subject correctly reported the weak stimulus at least in 9 of 10 stimulations (90% of the time), the intensity of the weak stimulus was set at that value. Otherwise, the intensity of the weak stimulus was further increased and the procedure repeated. The intensity of the strong stimulus was then set at a factor of 1.5 of the intensity of the weak stimulus. The experimenter then administered 10 strong stimuli interspersed with 10 catch trials, ensuring that the strong stimulus was perceived 100% of the time. At the end of this procedure, the experimenter administered a series of five weak and five strong stimuli, in random order, and asked the subject to indicate, after presentation of each stimulus, whether it was strong or weak. If the discrimination was not perfect, the intensity setting procedure was repeated.

Auditory stimuli were 100-msec bursts of white noise. The intensity of the near and far sounds was set to be equal (≈70 dB) as measured by a sound meter above the subject's head (over the vertex). Sounds were generated by two identical loudspeakers, placed either near the subject's hand (NEAR sound, i.e., at ≈5 cm from the hand, at ≈50 cm from the subject's torso, and at ≈60 cm from the subject head) or in a far position (FAR sound, i.e., at 100 cm away from the near position, at ≈150 cm from the subject's torso, and ≈160 cm from the subject's head). Inspection of phono-spectral waves (recorded by a computer) from the two loudspeakers ensured that the sounds were equal at their origin for emitted frequencies.

Procedure. The experimental setup is illustrated in Figure 1A. On each trial, participants received either a weak or a strong electrical stimulus on their right index finger. Tactile stimuli were presented alone (NO sound) or together with a concurrent task-irrelevant sound, arising from either the near (NEAR sound) or the far loudspeaker (FAR sound). The tactile and near acoustic stimuli were delivered simultaneously. Far sound onset preceded tactile stimulus onset by 5 msec to compensate for the de-

Figure 1. Experimental setup. (A) Experimental setup for Experiment 1A and Experiment 1B in the hand forward condition. (B) Experimental setup for Experiment 1B in the hand backward condition.



layed arrival of the far sound relative to the near sound because of the difference in distance. A total of 128 trials were administered: 20 weak tactile stimuli with no sound, 20 strong tactile stimuli with no sound, 20 weak tactile stimuli with near sounds, 20 weak tactile stimuli with far sounds, 20 strong tactile stimuli with near sounds, 20 strong tactile stimuli with far sounds, and 8 catch trials (i.e., trials on which only sounds, 4 near and 4 far, were presented). Each trial lasted about 3 sec.

The task was performed in two experimental conditions, run in separate blocks, whose order was counterbalanced between subjects. In the weak target condition, subjects were asked to respond as fast as possible (saying "tah") only to the weak electrical stimulus and to refrain from responding to the strong electrical stimuli; vice versa, in the strong target condition, they were asked to respond to the strong and not to the weak electrical stimulus.

Subjects were explicitly instructed to ignore the sounds when present. RT was measured by means of a voice-activated relay. A computer running XGen (www.sph.sc.edu/comd/rorden/xgen.html) software was used to control the presentation of the stimuli and record responses. Before the experiment, 30 trials were administered to familiarize subjects with the task. Subjects performed the task blindfolded.

Data analysis. Mean RT to weak and strong tactile targets presented unimodally, with task-irrelevant near and far sounds, were calculated. RT exceeding more than 2 standard deviations from the mean RT were considered outliers and trimmed from the analyses (4% of trials). Raw RT in the different conditions were analyzed using a Sound (no sound, near sound, and far sound) × Target (weak and strong) ANOVA.

Results

The Sound × Target ANOVA on mean RT revealed a main effect of Target ($F_{1,\,11} = 7.67, p < .05, \eta^2 = .41$) with faster RT to strong relative to weak tactile targets and a main effect of Sound ($F_{2,\,22} = 15.07, p < .0001; \eta^2 = .58$). Newman–Keuls post hoc comparisons indicate that RT-to-tactile targets were faster when a near or a far sound was presented, in comparison with when no sound was presented ($p < .01$). Moreover, RT-to-tactile targets associated with near sounds were faster than those associated to far sounds ($p < .05$; Table 1A). The differences due to sound presentation were comparable for the weak and the strong target, as indicated by the lack of a significant two-way interaction ($p = .92$).

Percentage of omissions (no response to the target stimulus) and false alarms (wrong response to the nontarget stimulus) were very low and comparable across all conditions (omissions are 2%, 3%, and 2% for near sound, far sound and no sound conditions, and for both weak and strong target conditions, respectively; false alarms are <1% in all conditions).

Experiment 1B

The above results from Experiment 1A show that sounds can boost the processing of tactile stimuli presented to the hand. Critically, the audio–tactile interaction effect is stronger when sounds are presented in the space around the hand rather than in the far space. The same effect occurs for processing both relatively weaker and relatively stronger tactile stimuli. To ensure that this effect is related to a hand-centered representation of the PPS and not to a general proximity of the sound to the body, in Experiment 1B, we manipulated the relative distance between the hand and the sound sources. The task was performed in two within-subject conditions: in the hand forward condition, the subject's right hand was placed next to the near loudspeaker, as in Experiment 1A; in the hand backward condition, subjects rotated their arm so that it was off to their side, pointing slightly backward. This way, sound-to-head spatial distance was kept constant, but both near and far sounds were in far space with respect to subjects' hands. If audio–tactile interaction is coded in a hand-centered reference frame, no difference between RT associated with near and far sounds is expected in this condition.

Methods

Subjects. Eighteen new healthy subjects (13 women, mean age = 26 years) participated in Experiment 1B. All participants were right-handed and had normal hearing and touch. All subjects were students at the University of Bologna and gave their informed consent to participate in the study, which was approved by the local ethics committee in accordance with the Declaration of Helsinki.

Table 1. Experiment 1A Results

Main Effect of Sound Position			*Main Effect of Target*	
No Sound	*Near Sound*	*Far Sound*	*Weak Target*	*Strong Target*
569 ± 25	524 ± 20	541 ± 24	570 ± 26	518 ± 24
$p < .0001$, compared with near sound	$p < .05$, compared with far sound	$p < .01$, compared with no sound	$p < .05$, weak target vs. strong target comparison	

The first three columns report mean RT (±*SEM*) and Newman–Keuls post hoc comparisons when subjects responded to tactile targets associated with no sound, near sound, or far sound; the last two columns report mean RT (±*SEM*) to weak and to strong tactile targets.

Materials. The experiment was conducted with the same materials as for Experiment 1A, with the following exceptions: (a) only near and far sounds conditions were administered and (b) the tactile target was always the weak stimulus.

Procedure. The experimental setup is illustrated in Figure 1A and B. The task was performed in two experimental conditions and run in separate blocks, with order counterbalanced between subjects. Arm position was manipulated across conditions. In the hand forward condition, the subject's right hand was placed close to the near loudspeaker; therefore, the distance between the hand and the sound sources was ≈5 cm for the near loudspeaker and ≈100 cm for the far loudspeaker. In the hand backward condition, the subject's right arm was rotated and pointed slightly backward; therefore, the subject's right hand was placed at ≈80 cm from the near loudspeaker and ≈180 cm from the far loudspeaker. A total of 140 trials were administered: 30 target trials with the near sound, 30 target trials with the far sound, 30 nontarget trials with the near sound, 30 nontarget trials with the far sound, and 20 catch trials (i.e., trials on which only a sound, 10 near and 10 far, was presented). Each trial lasted about 3 sec.

Data analysis. Mean RT-to-tactile targets presented with task-irrelevant near and far sounds were calculated for the two experimental conditions of arm position. RT exceeding more than 2 standard deviations from the mean RT were considered outliers and trimmed from the analyses (3.9% of trials). Raw RT in the different conditions were analyzed using a Sound × Hand position ANOVA.

Results

The Sound × Hand position ANOVA on mean RT showed both a main effect of Sound ($F_{1,\,17} = 28.42, p < .0001, \eta^2 = .30$) and, most importantly, a two-way interaction ($F_{1,\,17} = 20.75, p < .001, \eta^2 = .18$). In the hand forward condition, RT to tactile targets were significantly shorter when task-irrelevant sounds were presented near the hand in comparison with when sounds were presented far from the hand ($p < .0005$). No similar advantage was found in the hand backward condition ($p = .40$; Table 2).

Percentage of omissions and false alarms were very low and comparable across all conditions (omissions are 2% and 3% for near sound and 2% and 2% for far sound for hand forward and hand backward conditions, respectively; false alarms are 1% and 2% for near sound and 1% and 3% for far sound for hand forward and hand backward conditions, respectively).

Discussion

Results from Experiment 1A and 1B confirm that, in normal conditions, the processing of tactile stimuli on the hand interacts with the processing of sounds presented in the environment: RT-to-tactile targets associated to sounds were faster than RT-to-unimodal tactile stimuli. Importantly, this effect is modulated by sound position in space: RT were shortened by a concurrent sound presented near the hand compared with far from the hand (Bassolino et al., 2010; Serino et al., 2007). The audio–tactile temporal advantage was sensitive to the hand's location: When subjects placed their arm backward, thus moving the hand away from the source of near sounds, while keeping the distance between the sounds and the rest of their body constant, RT associated to near and far sounds were comparable. Hence, the sound's proximity to the hand (and the tactile stimulus), not to the subject in general, was critical for modulating tactile processing.

The present data are in keeping with previous studies showing that auditory stimuli affect the perception of tactile stimuli, both in terms of detection ability (e.g., Ro, Hsu, Yasar, Elmore, & Beauchamp, 2009) and RT (e.g., Zampini et al., 2007). Notably, evidence indicates that these audio–tactile interactions require a multisensory integrative mechanism rather than a simple summation of unisensory signals (Murray et al., 2005). However, previous studies did not clearly establish whether audio–tactile integrative mechanisms are modulated by the spatial location of auditory stimuli. On the one hand, some authors reported a facilitation effect not only when auditory and tactile stimuli are delivered to the same location but also when they are widely separated (Zampini et al., 2007; Murray et al., 2005; see also Yau, Olenczak, Dammann, & Bensmaia, 2009; Gillmeister & Eimer, 2007). On the other hand, recently, Tajadura-Jiménez et al. (2009) showed a stronger auditory–tactile interaction for stimuli arising from the same sector of space (i.e., on the earlobes and near the head) rather than far apart. Moreover, we have previously shown that task-irrelevant sounds presented near the hand transiently increased the excitability of hand

Table 2. Experiment 1B Results

	Near Sounds	*Far Sounds*	*Near–Far Comparison*
Hand forward	597 ± 32	624 ± 31	$p < .0001$
Hand backward	618 ± 26	621 ± 25	$p = .40$

Mean RT (±*SEM*) and Newman–Keuls post hoc comparisons when subjects responded to tactile targets associated with sounds arising from the near or far loudspeaker (near sound and far sound), placing their right hand either close to (hand forward) or far from (hand backward) the source of near sounds.

representation in the motor cortex and that this effect was specific to a hand-centered, not a body-centered, reference frame (Serino, Annella, & Avenanti, 2009). The present study expands these findings by showing that audio–tactile interactions are sensitive to the position of the hand in space. We propose that this behavioral effect arises from the summation of multisensory inputs within the same spatial representation, that is, within representation of PPS around the hand. This effect is reminiscent of the functional properties of multimodal neurons in vPMc and PPc, as also formalized in a neural network model for PPS representation (see Magosso, Serino, di Pellegrino, & Ursino, 2010; Magosso, Ursino, di Pellegrino, Làdavas, & Serino, 2010; Magosso, Zavaglia, Serino, di Pellegrino, & Ursino, 2010).

EXPERIMENT 2: NEURAL BASIS OF PPS REPRESENTATION AROUND THE HAND

In Experiment 1, we showed a specific form of audio–tactile interaction near the hand as a sign of a multisensory representation of the PPS around the hand. A second experiment was conducted to investigate the neural basis of such representation in the human brain. We tested whether the audio–tactile interaction effect around the hand was affected by suppression of neural activity in fronto-parietal regions by means of rTMS. To this aim, the same auditory–tactile interaction task was delivered in four experimental blocks performed either within the inhibitory window created by 15 min of 1-Hz rTMS (post-rTMS blocks) or outside the influence of rTMS (baseline block). In two critical post-rTMS blocks, rTMS was applied to vPMc or PPc to test their role in PPS representation. In another post-rTMS block, rTMS was also administered on V1, serving as an active control site. As for Experiment 1, during the task, subjects received either a weak or a strong tactile stimulus on the right hand, presented concurrently with task-irrelevant sounds presented either near the hand or in far space. Subjects were instructed to respond as fast as possible to weak tactile stimuli, ignoring sounds. Because we measured the spatial modulation of audio–tactile interaction around the right hand, rTMS was delivered to critical and control areas of the contralateral, left hemisphere. The choice of the left hemisphere as a target for TMS interference is also in keeping with the finding that motor excitability in the left hemisphere shows a space-dependent modulation because of auditory (Serino et al., 2009) or visual (Makin, Holmes, Brozzoli, Rossetti, & Farnè, 2009) stimuli presented either near or far from the right hand.

The following predictions were tested. In the baseline condition with no rTMS, PPS representation should be intact, and therefore, subjects are expected to respond faster to tactile targets associated with near sounds than to those associated with far sounds. In contrast, rTMS over vPMc and PPc should interfere with brain processes representing the PPS, resulting in a reduction of the speeding effect due to near sounds when the task was administered after these two critical post-rTMS conditions. If the reduction of the speeding effect was specifically because of interfering with two putative nodes of the network underlying the PPS and not to a generic effect of rTMS, then suppression of V1 should not affect multisensory interaction within the PPS, and thus, decreased RT associated with near sounds is expected, as for the baseline condition.

To test these critical predictions, we used the same task as in Experiment 1B, but with participants' arms always placed close to the near loudspeaker. This ensured the entire task lasted for about 7–8 min, so that in each post-rTMS block all the responses were collected well within the inhibitory effect created by 1-Hz rTMS.

Methods

Subjects

Ten new subjects, all students from University of Bologna, participated in Experiment 2. All participants were right-handed and had normal hearing and touch. They gave their informed consent to participate in the study, which was approved by the local ethics committee in accordance with the Declaration of Helsinki.

Materials

The experiment was conducted with the same method as for Experiment 1B, with the exception that only forward arm position was included in the present design. Therefore, subjects received a two (tactile, weak, and strong) by two (auditory, near, and far) combination of stimuli. A total of 140 trials were administered: 30 target trials with the near sound, 30 target trials with the far sound, 30 nontarget trials with the near sound, 30 nontarget trials with the far sound, and 20 catch trials (i.e., trials on which only a sound was presented and no response was required). Each trial lasted about 3 sec; thus, each block lasted about 7 min in total.

Procedure

Participants performed the audio–tactile task in four blocks, run over 2 days. Three of four blocks were performed immediately after 15 min of 1-Hz rTMS (post-rTMS blocks) over a target area (vPMc, PPc, and V1). Studies suggest that this low-frequency rTMS protocol disrupts functions related to the targeted area for at least half the stimulation time (Pascual-Leone et al., 2000; Chen et al., 1997). Thus, all the post-rTMS blocks were performed under the interfering influence of 1-Hz rTMS. To minimize carryover effect of rTMS, in each session the interblock interval was at least 1 hr. This way, we ensured that all interferential effects of one rTMS train had faded away at the time of the following block. The very same interblock interval was used when a post-rTMS block was preceded by a baseline block (no rTMS preconditioning). Baseline blocks were performed either as the very first (in six participants) or as the last block (in the remaining subjects). The order of the post-rTMS blocks was counterbalanced.

TMS. In the preliminary part of the experiment, single-pulse TMS was used to set the intensity of low-frequency rTMS. To this aim, motor-evoked potentials (MEPs) to left motor cortex stimulation were recorded in the right first dorsal interosseous (FDI) with MP-150 Biopac EMG equipment (Biopac Corp., Goletta, CA). Pairs of Ag–AgCl surface electrodes were placed in a belly–tendon montage on the FDI muscle, with further ground electrodes on the wrist. EMG signals were band-pass filtered (30–500 Hz) and sampled at 5 kHz. A figure-of-8 coil connected to a Magstim Rapid2 Transcranial Magnetic Stimulator (Magstim, Whitland, U.K.) was placed over the left motor cortex with the handle pointing backward at 45° from the midline. In this way, the current induced in the neural tissue was directed approximately perpendicular to the line of the central sulcus, optimal for transsynaptic activation of the corticospinal pathways (Brasil-Neto et al., 1992; Mills, Boniface, & Schubert, 1992). By using a slightly suprathreshold stimulus intensity, the coil was moved over the left hemisphere to determine the optimal position from which maximal amplitude MEPs were elicited in the FDI muscle.

In the three post-rTMS blocks, the behavioral audio–tactile task was preceded by 15 min of continuous low-frequency 1-Hz rTMS over a target area (900 stimuli in total). Stimulation intensity was set at 90% of the resting motor threshold, defined as the lowest level of stimulation able to induce MEPs of at least 50 μV in the right FDI with 50% probability (Rossini et al., 1994). In the 5 min preceding rTMS, subjects were asked to rest quietly with eyes closed. Moreover, they were asked to keep this state throughout the rTMS train, as muscle contraction may reduce the effect of rTMS (Touge, Gerschlager, Brown, & Rothwell, 2001).

Coil position was identified on each participant's scalp with the SofTaxic Navigator system (Electro Medical Systems, Bologna, Italy) as in previous studies (Bertini, Leo, Avenanti, & Ladavas, 2010; Bolognini, Miniussi, Savazzi, Bricolo, & Maravita, 2009; Avenanti et al., 2007; Bolognini & Maravita, 2007). Skull landmarks (nasion, inion, and two preauricular points) and about 100 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra digitizer (Northern Digital, Inc., Ontario, Canada). Coordinates in Talairach space (Talairach & Tournoux, 1988) were automatically estimated by the SofTaxic Navigator from an MRI-constructed stereotaxic template. Figure 3 illustrates site reconstructions displayed on a standard template from MRIcro (v1.40; www.mricro.com).

The vPMc was targeted in the ventral aspect of the precentral gyrus bordering the posterior part of the inferior frontal gyrus (coordinates: $x = -52, y = 8, z = 25$, corresponding to Brodmann's area 6/44). The PPc was targeted within the anterior part of the intraparietal sulcus ($x = -39, y = -40, z = 43$, corresponding to Brodmann's area 40). These locations were chosen by averaging the coordinates of vPMc and PPc sites found in previous neuroimaging studies on PPS in humans (Makin et al., 2007; Bremmer et al., 2001). In the active control block, we identified the scalp location that corresponded best to the visual cortex ($x = 19, y = -98, z = 1$, Brodmann's area 17, in the middle occipital gyrus; Figure 2).

Data Analysis

Mean RT-to-tactile targets presented concurrently with near and far sounds was calculated for the four experimental blocks. Similar to Experiment 1, RT exceeding more than 2 standard deviations from the mean RT were considered outliers and, thus, trimmed from the analyses (2.7% of trials). Raw RT were analyzed using a mixed model ANOVA with the within-subjects factors Stimulation (no-TMS, vPMc, PPc, V1) and Sound (NEAR and FAR); moreover, because half the subjects performed the no-TMS baseline condition at the beginning of the experiment and half at the end, we included the between-subjects factor Time of Baseline (initial and final) in the ANOVA to control for potential effects of order of baseline presentation (see Table 1).

Results

The Stimulation × Sound × Time of Baseline ANOVA on RT revealed only a significant Stimulation × Sound

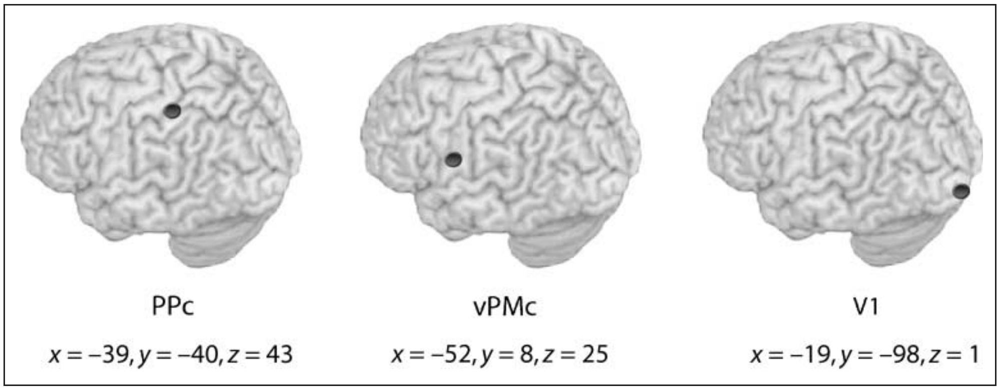
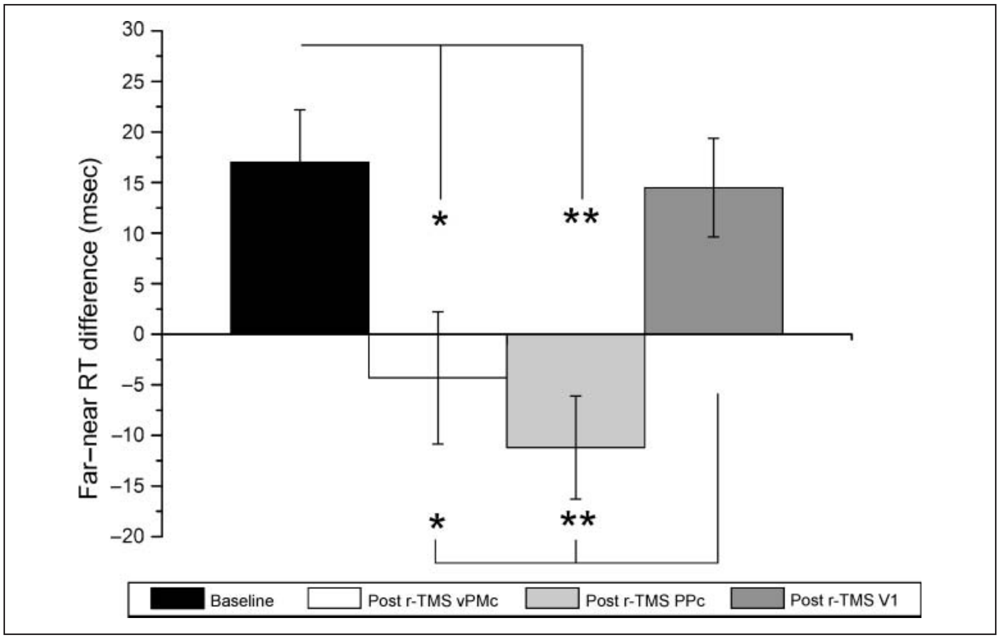


Figure 2. Brain location and mean Talairach coordinates of the coil position to induce virtual lesion by means of rTMS.

Figure 3. Experiment 2 results. The graph shows the far–near RT difference (RT for far sounds − RT for near sound) in the baseline condition (no rTMS) and after rTMS over the vPMc (post-rTMS vPMc), the PPc (post-rTMS PPc), or the primary visual cortex (post-rTMS V1). Error bars denote *SEM*. *$p < .05$.



interaction ($F_{3,\ 24} = 6.18$, $p < .01$; $\eta^2 = .44$). Newman–Keuls post hoc comparisons showed that, in normal physiological conditions (baseline block), we replicated the integrative effect found in Experiment 1: RT were significantly shorter when task-irrelevant sounds were presented near the hand in comparison with when sounds were presented far from the hand ($p < .01$). A similar speeding effect due to near sounds was also found after the inhibition of V1 ($p < .05$). In contrast, the speeding effect completely disappeared after the suppression of vPMc or PPc (all *p*s > .29; see Table 3 and Figure 3).

These findings indicate that temporal advantage of tactile processing due to the presentation of near sounds typically found in normal physiological condition (baseline block) was disrupted by suppression of vPMc and PPc, but not by suppression of V1.

Percentage of omissions and false alarms were infrequent and comparable across conditions (omissions are 4%, 5%, 4%, and 4% for near sound and 4%, 2%, 3%, and 3% for far sound for baseline, post-rTMS vPMc, post-rTMS PPc, and post-rTMS V1, respectively; false alarms are <1% in all conditions).

Discussion

In monkeys, functional properties of bimodal neurons in premotor (Graziano et al., 1994, 1997; Fogassi et al., 1996; Rizzolatti et al., 1981a, 1981b) and parietal cortex (Avillac et al., 2005; Schlack et al., 2005; Duhamel et al., 1998) have been extensively investigated, and therefore, in the last three decades, a rich picture of the neural mechanisms underlying PPS representation has emerged (see Graziano & Cooke, 2006; Rizzolatti, Fogassi, & Gallese, 2002; Matelli & Luppino, 2001, for reviews). More recently, imaging evidence in humans has shown that neural activity in vPMc and PPc is modulated by multisensory stimuli approaching the body (Makin et al., 2007; Sereno & Huang, 2006; Bremmer et al., 2001), suggesting that fronto-parietal areas are also involved in PPS representation in the human brain.

Table 3. Experiment 2 Results

	Near Sounds	*Far Sounds*	*Near–Far Comparison*
Baseline	583 ± 32	600 ± 34	$p < .01$
Post-rTMS vPMc	607 ± 31	603 ± 33	$p = .45$
Post-rTMS PPc	614 ± 24	602 ± 25	$p = .29$
Post-rTMS V1	612 ± 26	626 ± 25	$p < .05$

Mean RT (±*SEM*) and Newman–Keuls post hoc comparisons when subjects responded to tactile targets associated with near and far sounds, in the no-TMS baseline condition, or after rTMS over the vPMc (post-rTMS vPMc), the PPc (post-rTMS PPc), or the primary visual cortex (post-rTMS V1). Error bars denote *SEM*.

In the present study, we directly tested whether vPMc and PPc play a *necessary* role in audio–tactile representation of the PPS around the hand. Subjects performed a rapid response discrimination task to tactile stimuli administered on their right hand while concurrent task-irrelevant sounds were presented either close to the hand or in far space. When no TMS was applied, as in Experiment 1 and in the baseline condition of Experiment 2, RT-to-tactile targets were reduced if the auditory stimulus was presented near the hand rather than in far space. This audio–tactile effect, anchored by hand-centered reference frames (see Experiment 1), is indicative of a specific multisensory interaction within the boundaries of PPS.

Critically, the speeding effect associated to near sounds disappeared when the same task was performed after transient suppression of neural activity in vPMc or PPc: in these conditions, RT-to-tactile targets were not different when near and far sounds were administered. The absence of any difference between the effect induced by near and far sounds was not an unspecific consequence of rTMS. For when stimulation was administered over V1, RT-to-tactile target was again faster when near instead of far sounds were presented, thus showing an intact audio–tactile interaction within the space around the hand. These findings suggest that virtual lesions to vPMc and PPc, but not to V1, disrupt PPS representation mechanisms around the hand.

vPMc and PPc regions targeted in the present experiment were found to be active in two recent imaging studies during processing of tactile, visual, or auditory stimuli close to the head (Bremmer et al., 2001) or the hand (Makin et al., 2007). In addition, interference with PPc activity impairs the integration of proprioceptive information, defining upper limbs postures, with visual information presented near (Bolognini & Maravita, 2007) or tactile information presented in (Azañón, Longo, Soto-Faraco, & Haggard, 2010) the arm. These results suggest that PPc plays a critical role in discerning whether external stimuli are near or far from a part of the body, depending on the position of body parts. However, no previous studies have tested the critical role of PPc or vPMc in audio–tactile interaction near and far from the body. Bremmer and colleagues (2001) proposed a strong homology for vPMc and PPc areas of the human brain and multisensory regions in the vPMc and in the VIP of the macaque brain (see also Sereno & Huang, 2006; Grefkes & Fink, 2005). According to this view in humans as in monkeys, populations of cells within vPMc and PPc constitute two critical nodes of a fronto-parietal network underlying a multisensory representation of the space around the body. Our study expands on this by showing that interference of vPMc and PPc processing disrupts audio–tactile interactions in the perihand space, thus suggesting that fronto-parietal networks are necessary for PPS representation in humans.

Another line of evidence indicates that vPMc and PPc also play a critical role in action representation. These areas are highly interconnected (Lewis & Van Essen, 2000) and send projections to the motor cortex (Davare, Lemon, & Olivier, 2008; Koch et al., 2008; He, Dum, & Strick, 1995). Several studies indicate that vPMc and PPc are involved in action execution, observation, and imagery (Avenanti et al., 2007; Grèzes & Decety, 2001; Binkofski et al., 1998). The role of vPMc and PPc in action representation is well in keeping with the present evidence that these areas are involved in multisensory PPS representation. Studies suggest that sensory representations of space and motor representations of actions coexist within the same fronto-parietal network, which provides multimodal representation of the PPS for action (Gallese & Sinigaglia, 2010). Indeed, in monkeys, multimodal cells in F4 and VIP, beside sensory responses, also discharge during movements of the body part where their tactile receptive fields are allocated (Rizzolatti et al., 1981a). Moreover, prolonged electrical stimulation of F4 and VIP results in complex movements of the monkeys' head and arm, resembling defensive motor responses to threatening stimuli approaching the body (Cooke & Graziano, 2004; Cooke, Taylor, Moore, & Graziano, 2003; Graziano, Taylor, & Moore, 2002; see also Stepniewska, Fang, & Kaas, 2005). The strong link between action and PPS representations in humans was supported by recent single-pulse TMS studies showing that auditory (Serino et al., 2009) or visual (Makin et al., 2009) stimuli presented either near the hand or in far space differentially activate hand representation in the motor cortex. Taken together, these data suggest that vPMc and PPc represent multisensory stimuli in the space around the hand for the purpose of planning appropriate motor responses.

Finally, their role in space and action representation, an apparently alternative view, also conceives of the PPc and vPMc as two key regions in controlling spatial attention. Extensive investigations have revealed that these areas interact in shifting the focus of spatial attention both endogenously (Yantis et al., 2002; Hopfinger, Buonocore, & Mangun, 2000) and exogenously (Arrington, Carr, Mayer, & Rao, 2000; Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000). Such attentional control mechanisms in vPMc and PPc act cross-modally, because both endogenous and exogenous orienting in one sensory modality affects information processing in other sensory modalities (see Macaluso & Maravita, 2010; Macaluso & Driver, 2005, for reviews). On this view, the role of vPMc and PPc in the present experimental paradigm might be that of shifting spatial attention toward or away from the hand, depending on the location of the auditory stimulation, respectively, accelerating or slowing tactile processing at the hand. However, in contrast to classic cue-to-target experimental designs normally used to study exogenous cross-modal attention, in the present study, auditory stimulation was actually administered simultaneously to the tactile stimulation. Thus, it is unlikely that auditory stimulation acted as an attentional cue. To make a more general argument, the fact that nearly identical fronto-parietal areas are considered critical by studies both on cross-modal spatial attention and on multisensory integration within the PPS does not appear to be contradictory. In fact, it is in line with the view that vPMc and PPc might participate in representing PPS for action. According to the premotor theory of attention (Rizzolatti, Riggio, Dascola, & Umiltá, 1987), attentional control is conceived as implicit shifts of spatial representations to prepare actions. In keeping with this view, Andersen and colleagues (see Andersen & Buneo, 2002, for a review) propose a central role for the PPc in representing *intentional maps*, defined as cognitive plans for movements (see also Hu, Bu, Song, Zhen, & Liu, 2009), suggesting that pure attentional effects possibly found in PPc would be related to planning movements. A multisensory representation of the space where actions can be immediately implemented is necessary for motor intention and action planning. Therefore, it is not surprising to find overlapping spatial, motor, and attentional functions in a unique fronto-parietal network, encompassing PPc and vPMc.

In conclusion, results from the present study provide the first empirical evidence for a necessary role for vPMc and PPc in representing multisensory PPS around the hand. Further research is needed to specify the selective role of vPMc and of PPc in fronto-parietal networks representing the space around us.

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