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Suppression of premotor cortex disrupts motor coding of peripersonal space

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ABSTRACT

Peripersonal space (PPS) representation depends on the activity of a fronto-parietal network including the premotor cortex (PMc) and the posterior parietal cortex (PPc). PPS representation has a direct effect on the motor system: a stimulus activating the PPS around the hand modulates the excitability of hand representation in the primary motor cortex. However, to date, direct information about the involvement of the PMc–PPc network in the motor mapping of sensory events occurring within PPS is lacking. To address this issue, we used a 'perturb-and-measure' paradigm based on the combination of transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) techniques. Cathodal tDCS was applied to transiently suppress neural activity in PMc, PPc and primary visual cortex (V1; serving as an active control site); single-pulse TMS was used to induce motor-evoked potentials (MEPs) from hand muscles and so to measure the excitability of the hand motor representation. MEPs were compared when a sound was presented either near the hand or at a distance. In experimental sessions performed after sham-tDCS and after tDCS over the control area V1, we found a spatially dependent modulation of the hand motor representation: sounds presented near the hand induced an inhibitory motor response as compared to sounds presented far apart. Critically, this effect was selectively abolished after tDCS suppression of neural activity in PMc, but not when perturbing the activity of PPc. These findings suggest that PMc has a critical role in mapping sensory representations of space onto the motor system.

Introduction

When interacting with the external world, our brain integrates multisensory cues about environmental stimuli with information about the body in a coherent representation of peripersonal space (PPS). In monkeys, a network of fronto-parietal regions, involving area F4 in the premotor cortex (PMc; Fogassi et al., 1996; Graziano et al., 1994, 1997, 1999; Rizzolatti et al., 1981) and the ventral intraparietal area (VIP; Avillac et al., 2005; Duhamel et al., 1997; Schlack et al., 2005) in the posterior parietal cortex (PPC), supports this function, since neurons in these regions integrate somatosensory stimuli from the body surface with visual and acoustic stimuli in the space immediately surrounding the body (Graziano and Cooke, 2006). Neuroimaging studies support the existence of a similar fronto-parietal network with homologous functions in the human brain. Portions of PMc and PPc respond to tactile stimuli on the face (Bremmer et al., 2001) and on the hand (Gentile et al., 2011) and to visual and auditory stimuli presented near the same body part (Makin et al., 2007). Moreover, suppression of PMc and PPc activity with transcranial magnetic stimulation (TMS) impairs audio-tactile interaction within the PPS around the hand (Serino et al., 2011; see also Bassolino et al., 2010; Serino et al., 2007). Taken together, these findings suggest that in human and non-human primates a network of fronto-parietal areas underlies a multi-sensory representation of PPS.

PPS representation has not only a sensory but also a motor function. In monkeys, electrical stimulation of PPS neurons in F4 and VIP results in arm or head movements (Cooke et al., 2003; Graziano et al., 2002). In humans, auditory (Serino et al., 2009) or visual (Makin et al., 2009) stimuli presented near or far from the hand differentially modulate the excitability of the hand representation in the motor cortex (M1). More specifically, using single-pulse TMS we showed that sounds presented within PPS transiently reduce M1 excitability as compared to sounds presented in extrapersonal space, within a specific temporal-frame (Serino et al., 2009). A nearby sound, by activating PPS mechanism, might cause a defensive-like freeze, resembling that found during the presentation of noxious stimuli (Farina et al., 2001; Urban et al., 2004) or potential threats (Cantello et al., 2000; Furubayashi et al., 2000), thereby reducing the excitability of the motor cortex. This effect suggests that sensory events occurring near the body primes motor reactions, and therefore that, in humans just as in monkeys, PPS representation is functionally linked to the motor system. However, to date it is not clear whether such spatially-dependent motor modulation relies on the activity of the same fronto-parietal

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areas involved in the sensory representation of PPS. To test this hypothesis, we designed a perturb-and-measure paradigm (Avenanti et al., 2007, 2012b) in which transcranial direct current stimulation (tDCS) was applied to transiently inhibit target PPS regions in PMc and PPc, while motor-evoked potentials (MEPs) to single-pulse TMS over M1 were recorded as a measure of corticospinal excitability during presentation of task-irrelevant sounds near and far from the hand. Based on the strong functional and anatomical link between PMc and M1 (Koch et al., 2006; Matelli and Luppino, 2001), we hypothesized that suppression of PMc would specifically affect the spatially-dependent modulation of M1 due to sound presentation. To test this hypothesis, in a first experiment, we compared MEPs from hand muscles after presentation of a near or a far sound following inhibitory tDCS over PMc or sham tDCS over the same area. In a second experiment, we tested whether not only PMc but also PPc is involved in motor mapping of sensory events in PPS. To this aim, we compared MEPs associated to near and far sounds after inhibitory tDCS over PPc and over primary visual cortex (V1) chosen as an active control site.

Materials and methods

Participants

Thirty neurologically healthy subjects were tested in the study. Sixteen volunteers (7 females, mean age 22.8 years, range 20–32) were assigned to Experiment 1 and 14 to Experiment 2 (9 females, mean age 23.2 years, range 21–25). All subjects were right-handed, reported no abnormalities of touch or hearing and met the safety criteria for TMS and tDCS (Poreisz et al., 2007; Rossi et al., 2009). All the participants were naïve to the procedures and to the purpose of the experiments. A written informed consent, approved by the University of Bologna's Department of Psychology ethics committee, was obtained prior to participation. The study was conducted in accordance with the Declaration of Helsinki (1964).

Design

In two experiments, we used a 'perturb-and-measure' paradigm (Avenanti et al., 2007, 2012b) in which neural activity is assessed with single-pulse TMS (measure) within or outside the inhibitory temporal window created by cathodal tDCS over target cortical sites (perturb). In both experiments, TMS was applied to left M1 to elicit MEPs from the first dorsal interosseus (FDI) muscle of the right hand; thus MEPs were taken as a measure of excitability of the hand representation in M1. TMS was delivered 50, 175 or 300 ms after a white-noise burst that was presented either at ~5 cm from the hand (near sound) or at ~100 cm from the hand (far sound). In Experiment 1, MEP recording was performed in two post-tDCS sessions that were carried out after 15 min of either Real- or Sham-tDCS over the left PMc. In Experiment 2, MEP recording was performed in two post-tDCS sessions that were carried out after 15 min of either Real-tDCS over the left PPc (target site) or Real-tDCS over the visual cortex (V1, serving as an active control site, not involved in PPS representation). Experiments 1 and 2 were conducted on two different samples of subjects. In order to minimize carry-over effects, the two post-tDCS sessions of each experiment were performed on two different days, with an inter-session interval of at least 1 week. The order of the sessions was counterbalanced between subjects. Target sites and types of tDCS apart, procedure and stimuli were the same for the two experiments.

We predicted that different MEPs amplitude would be associated with near and far sounds after the two control conditions, Sham-tDCS (Experiment 1) and Real-tDCS over V1 (Experiment 2). In contrast, if PMc and PPc are both necessary for a motor representation of PPS, little (or no) MEPs modulation due to sound position should be found after Real-tDCS over these target areas. If PMc is necessary, and PPc is not, Real-tDCS over the former, and not the latter, area should affect the spatial modulation of MEPs.

Procedure and stimuli

Each subject sat on a chair with their right arm placed on an arm rest. Two loudspeakers were placed to the right of the subject: one was positioned close to the subject, at ≈5 cm from the right hand (at ≈50 cm from the subject's torso and at ≈60 cm from the subject head); the other was positioned far from the subject, at 100 cm away from the near loudspeaker (at ≈150 cm from the subject's torso and ≈160 cm from the subject's head). Subjects were blindfolded, were asked to keep their eyes closed during the whole experiment and their head oriented towards their front. We recorded MEPs from the right FDI muscle induced by TMS just after presenting an auditory stimulus generated either from the near loudspeaker or from the far loudspeaker. TMS pulses were delivered at 120% of resting motor threshold (rMT; see below), at one of three possible time delays after the sound onset, i.e., at 50, 175, and 300 ms (see Fig. 1). The inter-trial interval varied between 10 and 12 s. To maintain attention throughout the experimental session, subjects were requested to monitor the right hand for the infrequent occurrence of specific tactile stimuli (see below). Subjects were explicitly instructed to not pay attention to any auditory stimulation during the experimental sessions. MEPs were recorded during two experimental blocks of 42 trials each; each trial resulted in a random combination of a sound (near or far), a time delay between the sound and the TMS pulse (50, 175, 300 ms). The order of the blocks was randomized.

Auditory stimulation

Auditory stimuli consisted in 300 ms bursts of white noise, generated by two identical loudspeakers. The intensity of the near and far sounds was set to be equal (≈70 dB) as measured by a phonometer above the subject's head (over the vertex). 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.

We used white noise samples as auditory stimuli to activate PPS representation based on our previous studies on neural bases of PPS system in healthy humans (Serino et al., 2009, 2011; see also Bassolino et al., 2010; Serino et al., 2007) and on previous studies on auditory PPS in monkeys (Graziano et al., 1999) and in brain damaged patients (Farnè and Làdavas, 2002). Graziano et al. (1999) showed that white noise bursts administered close to the monkeys' body induced strong responses in F4 neurons, comparable to those elicited by more ecological sounds, such as jingling keys, claps, and crinkling paper, whereas artificial sine waves of various frequencies were ineffective (see also Schlack et al., 2005). The same difference between white noise, eliciting a strong PPS response, and pure tones, not eliciting specific response, was reported by Farnè and Làdavas (2002), in brain damaged patients suffering crossmodal extinction. Thus, although in principle more ecological sounds (see e.g. Tajadura-Jiménez et al., 2010) might induce even stronger effects, we were confident that white noise bursts were able to reliably activate the PPS system and therefore modulate the motor system.

Tactile stimulation

Tactile stimuli were delivered by means of three miniaturized solenoids (M&E Solve, Rochester, UK; http://www.me-solve.co.uk) placed under the palm of the right hand at a distance of 5 mm from one another. During inter-trial intervals, either a single solenoid was briefly activated (weak stimulus) or all solenoids were activated simultaneously (strong stimulus). Subjects were asked to only respond to the strong stimulus, by lifting the front of their left foot. Strong stimuli were rare and comprised 20% of the total trials.

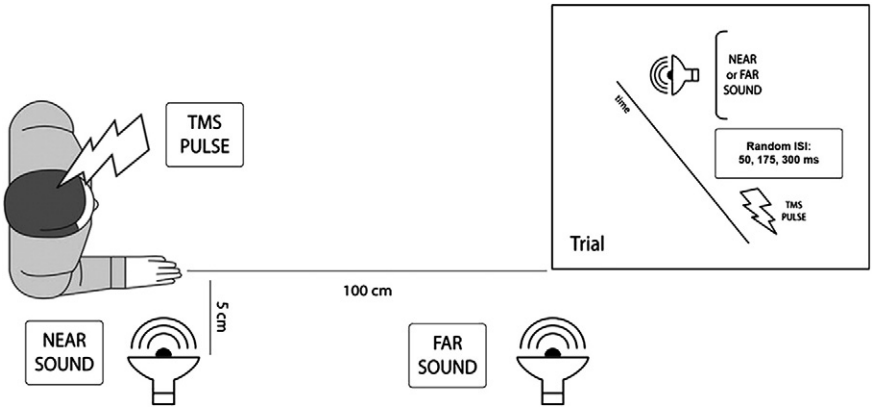

Fig. 1. Schematic representation of the experimental set up and temporal sequence of events (right panel).

Subjects' responses were visually monitored by an experimenter. Tactile stimuli were administered in the inter-trial interval at least 4–5 s apart from TMS pulses to avoid MEP contamination due to tactile stimulation or motor responses (Classen et al., 2000; Terao et al., 1995).

Electromyography and transcranial magnetic stimulation

MEPs were recorded from the first dorsal interosseus (FDI, in the region of the index finger) muscle of the right hand by means of a Biopac MP-150 (BIOPAC, USA) electromyograph. EMG signals were band-pass filtered (30–500 Hz), digitized (sampling rate: 5 kHz) and stored on a computer for off-line analysis. Electromyographic (EMG) recordings were performed through surface Ag/AgCl electrodes placed in a belly-tendon montage on the FDI muscle, with further ground electrodes on the wrist. TMS was performed by means of a figure-of-8 coil connected to a Magstim Rapid² stimulator (Magstim, Whitland, Dyfed, UK). The coil was placed over the left M1. The intersection of the two coil's wings was placed tangentially to the scalp with the handle pointing backward and laterally 45° away from the midline. In this way, the current induced in the underlying neural tissue was directed approximately perpendicular to the line of the central sulcus and was optimal for trans-synaptic activation of the corticospinal pathway (Brasil-Neto et al., 1992; Mills et al., 1992). During the recording sessions the coil was positioned in correspondence with the optimal scalp position (OSP), defined as the position from which MEPs with maximal amplitude were elicited from FDI muscle. The OSP was detected by moving the intersection of coil in 1 cm steps around the hand motor area of the left M1 and by delivering TMS pulses with a slightly suprathreshold stimulus intensity. Participants wore a bathing cap on which the OSP of the coil was marked with a pen to ensure correct coil placement throughout the experiments.

TMS intensity was calibrated at 120% of resting motor threshold (rMT) defined as the minimal intensity of the stimulator output that produces MEPs in the target muscle (the FDI) with amplitudes of at least 50 μV with 50% probability (Rossini et al., 1994). We selected this pulse intensity among the two levels of stimulation used in our previous study (i.e., 120% and 140% of rMT; see Serino et al. (2009)), in order to reduce the experimental conditions and the total length of the experimental blocks. We focused on the lower level of stimulation (120% of rMT) because this intensity showed the greatest space-dependent modulatory effects in Serino et al. (2009) and was also closer to that used by other studies investigating motor coding of PPS (e.g., Makin et al., 2009; Cardellicchio et al., 2011). It should be noted that in the present study we computed rMT by considering the target muscle FDI, while in our previous study, MEPs were collected also from the abductor digiti minimi (ADM) and rMT was computed on such muscle that showed higher threshold. Thus, in the present experiment systematically lower stimulation intensity was used to assess corticospinal excitability, although this was closer to that used in other studies investigating motor excitability changes during processing of potentially threatening visual (Cantello et al., 2000; Makin et al., 2009) or auditory stimuli (Furubayashi et al., 2000). Different TMS intensities may recruit neural populations with different activation thresholds (Chen et al., 2008). Based on previous results (Cantello et al., 2000; Furubayashi et al., 2000; Makin et al., 2009; Serino et al., 2009), low TMS intensity used in the present study is more likely to reveal inhibitory, rather than excitatory neural effects. Values of rMT were comparable in Experiment 1 (mean % of maximal stimulator output ± SD: 59% ± 11) and Experiment 2 (55% ± 7; $t_{28} = 1.09$, $p = 0.28$); thus any differential effects in the two experiments cannot be ascribed to differences in corticospinal excitability. The absence of voluntary contractions was continuously verified by visual monitoring of the EMG signal.

Transcranial direct current stimulation (tDCS) and neuronavigation

A battery-driven, constant, direct current stimulator was used to apply tDCS (Eldith DC-stimulator, Neuroconn, Germany). A pair of surface conductive rubber electrodes (35 cm²) was placed in two saline-soaked sponges and positioned over the target areas. Rubber bandages were used to hold the electrodes in place during the stimulation. For active stimulation (Real-tDCS), cathodal tDCS was applied to PMc (Experiment 1) and to PPc and V1 (Experiment 2) with the cathode positioned above the target area and the anode over the contralateral orbit. The duration of each session of tDCS was 15 min and the intensity was set at 1 mA (fade in/out duration: 20 s). This type of stimulation is known to induce a transient suppression of cortical excitability (mainly due to neural hyperpolarization and long-term depression-like mechanisms) which in turn may disrupt the function of the stimulated site (Nitsche et al., 2003a,b). It has been demonstrated that the effects of tDCS on neuronal excitability last for up to 90 min after a stimulation of 13 min only (Nitsche and Paulus, 2001). Thus we assumed that 15 min of tDCS ensured a large inhibitory window along which we run the MEP recording session.

For the Sham-tDCS, the electrodes were placed on the same locations as for Real-tDCS and the current was turned off after 15 s of stimulation (fade in/out: 20 s). This stimulation is known to induce skin sensations indistinguishable from real tDCS. These parameters for sham stimulation were chosen based on previous reports that the perceived sensations on the skin, such as mild local tingling (associated with the onset of stimulation), usually fade out in the first few seconds of tDCS (Nitsche et al., 2003c; Paulus, 2003).

The stimulation sites for correct positioning of the tDCS electrodes were identified on each participant's scalp by means of a SofTaxic Navigator system (Electro Medical Systems, Bologna, Italy) as in previous research (Avenanti et al., 2007, 2012b; Bertini et al., 2010; Serino et al., 2011). 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 and Tournoux, 1988) were automatically estimated by the SofTaxic Navigator from an MRI-constructed stereotaxic template. In Experiment 1, the PMc was targeted in the ventral aspect of the precentral gyrus (ventral premotor cortex) at the border with the posterior part of the inferior frontal gyrus (pars opercularis) (searched coordinates: $x=-52$, $y=8$, $z=25$, corresponding to Brodmann's area 6/44 in the inferior frontal cortex). Individual's Talairach coordinates corresponding to the projection of the PMc target site on brain surface were automatically estimated through the neuronavigation system. Mean PMc ± SD brain surface coordinates (corresponding to the center of the cathodal tDCS electrode placed on the scalp) were $x=-55.7\pm2.4$, $y=7.6\pm1.1$, $z=23.8\pm3.1$ (Fig. 2).

In Experiment 2, the PPc was targeted within the anterior part of the intraparietal sulcus ($x=-39$, $y=-40$, $z=43$, corresponding to Brodmann's area 40). In Experiment 2, the active control site V1 was targeted on 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). Talairach coordinates corresponding to the projection of PPc and V1 target sites on brain surface were $x=-49.1\pm1.4$, $y=-42.3\pm1.1$, $z=48.0\pm1.8$; and $x=-18.7\pm0.9$, $y=-98.2\pm0.7$, $z=0.2\pm0.7$, respectively (Fig. 2). The PMc and PPc locations were chosen by averaging the coordinates of the corresponding sites as reported in previous neuroimaging studies on PPS in humans (Bremmer et al., 2001; Makin et al., 2007). Notably, we have previously demonstrated that repetitive TMS over these sites disrupts multisensory audio-tactile representation of PPS (Serino et al., 2011).

Data analysis

MEPs were analyzed off-line with AcqKnowledge (v 4.10) software. The presence of background EMG activity prior to TMS was visually inspected. Trials with EMG activity preceding TMS were discarded from the analysis. Mean peak-to-peak MEP amplitudes (in mV) were computed for each experimental condition. In Experiment 1, we compared MEPs after Real-tDCS over PMc (test) or after Sham-tDCS over the same site (sham control), when near or far sounds were presented and were followed by a TMS pulse at 50, 175 or 300 ms. Mean raw MEP amplitudes were entered in a three-way repeated-measures ANOVA with Session (Real-tDCS PMc, Sham-tDCS PMc), Location of Sound (near, far), and TMS Delay (50, 175, 300 ms) as within-subjects factors. In Experiment 2, we compared the effect of Real-tDCS over PPc and V1. Mean raw MEP amplitudes were analyzed by means of a three-way repeated-measures ANOVA with Session (Real-tDCS PPc, Real-tDCS V1), Location of sound (near, far), and TMS delay (50, 175, 300 ms). Post hoc comparisons were performed using the Duncan's test in order to correct for multiple comparisons. A further analysis was conducted on MEP differences (near–far) recorded after the critical conditions of Real-tDCS over PMc and Real-tDCS over PPc relative to the control conditions of Sham-tDCS over PMc and Real-tDCS over V1. In this way we directly compared motor reactivity to near/far sounds across the two experiments.

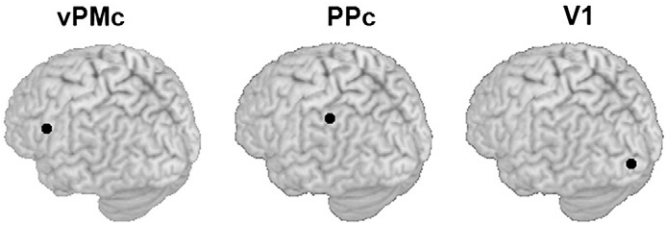

Fig. 2. Surface brain locations of transcranial direct current stimulation (tDCS).

Results

In Experiment 1, the Session × Location × TMS delay ANOVA revealed a main effect of Location ($F_{1,15}=5.33$, $p<0.05$), with lower amplitudes for MEPs recorded after near sounds (mean amplitude ± SEM: 1.72 mV ± 0.03) relative to far sounds (1.84 mV ± 0.04), and a main effect of TMS delay ($F_{2,30}=5.49$, $p<0.01$), with greater amplitudes for MEPs recorded at 175 ms (1.89 mV ± 0.03) relative to MEPs recorded at 50 (1.75 mV ± 0.03) and 300 ms (1.71 mV ± 0.05; all $p_s<0.01$). Importantly, the three-way interaction was significant ($F_{2,30}=4.03$, $p<0.05$), indicating that in the two tDCS sessions, MEPs were differently modulated as a function of the location of sounds and of the time of TMS administration. In order to identify the source of the three-way interaction, two separate Location × TMS delay ANOVAs were carried out, one for each tDCS session. In the Sham-tDCS Session, the ANOVA conducted on MEPs revealed a significant Location × TMS delay interaction ($F_{2,30}=4.10$, $p<0.05$). Post-hoc comparisons showed that MEPs recorded 300 ms after a sound's occurrence were significantly lower when sounds were presented near the hand (1.66 mV ± 0.26) than at a distance (2.00 mV ± 0.32; $p<0.0001$), thus replicating the inhibitory modulation of corticospinal excitability due to near sounds, as shown in Serino et al. (2009) (Fig. 3A, Table 1). No similar near-far difference in amplitude was found for MEPs recorded at 50 ($p=0.07$) and 175 ms ($p=0.41$). Critically, tDCS over PMc disrupted the space-dependent pattern of corticospinal modulation found after sham stimulation: in the Real-tDCS over PMc Session, the Location × TMS delay interaction was not significant ($p=0.26$). Only the main effect of TMS delay was significant ($F_{2,30}=5.55$, $p<0.01$), and post-hoc comparisons showed that MEPs recorded at 300 ms after sound presentation were lower (1.59 mV ± 0.01) as compared to those recorded at 175 ms (1.80 mV ± 0.01; $p<0.01$), but not to those recorded at 50 ms (1.69 mV ± 0.03; $p=0.12$), whereas MEPs recorded at 50 ms and 175 ms were comparable ($p=0.09$) (Fig. 3B).

In contrast to Experiment 1, the Session × Location × TMS delay ANOVA conducted on MEPs recorded during Experiment 2 showed a significant two-way Location × TMS delay interaction ($F_{2,26}=3.29$, $p<0.05$), but not a three-way interaction ($p=0.73$). These effects indicate that in both tDCS sessions, MEPs were similarly modulated as a function of the location of sound presentation and the time of TMS pulse administration. Post-hoc analysis of the two-way Location × TMS delay interaction showed that MEPs recorded at 300 ms from sound onset were lower when a near sound was presented (1.09 mV ± 0.12), as compared to a far sound (1.27 mV ± 0.13; $p<0.001$), similarly to what occurred after Sham-tDCS in Experiment 1 (Fig. 4, Table 1). Moreover, no near–far difference in amplitude was found for MEPs recorded at 50 ($p=0.93$) and 175 ms ($p=0.16$). These results show that the spatially-dependent modulation of M1 excitability (due to sound presentation) was not disrupted by interfering with neural activity in either the control area, V1, or the target area, PPc.

In sum, in the Sham-tDCS session of Experiment 1 and in both sessions of Experiment 2, MEPs recorded at 300 ms were lower when near sounds were presented as compared to when far sounds were presented. In contrast, such time-specific spatial modulation of MEPs was disrupted when Real-tDCS was applied to PMc (Experiment 1). In order to directly compare the effect of tDCS over the critical PPS areas PMc and PPc on motor reactivity to near/far sounds, we computed an index of spatial modulation of MEPs. For each tDCS session, we subtracted MEP values recorded 300 ms after administration of far sounds from those recorded 300 ms after administration of near sounds (Space-Index, SI). In this way, we could directly compare spatial effects on motor cortex excitability across the two experiments. We considered Real-tDCS sessions over PMc (Experiment 1) and over PPc (Experiment 2) as target conditions, and Sham-tDCS (Experiment 1) and Real-tDCS

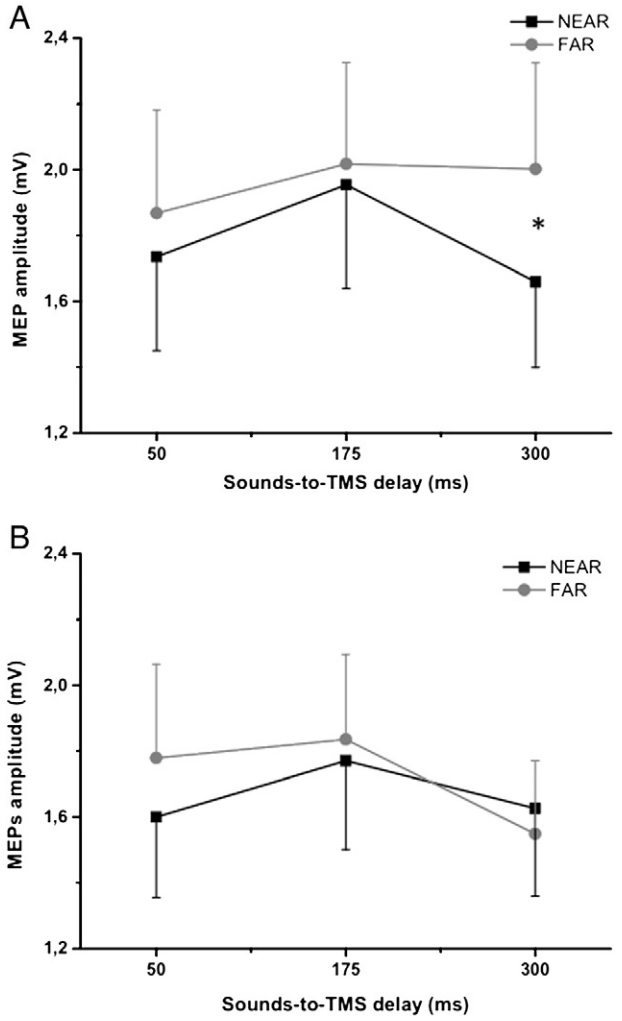

Fig. 3. Raw mean MEPs amplitude recorded during Experiment 1, after the Sham-tDCS session over the left PMc (A) and after the Real-tDCS session over the left PMc (B), when sounds were administered near (black lines) and far (gray lines) from the subject's right hand. Error bars denote SEM. Asterisks indicate significant comparisons.

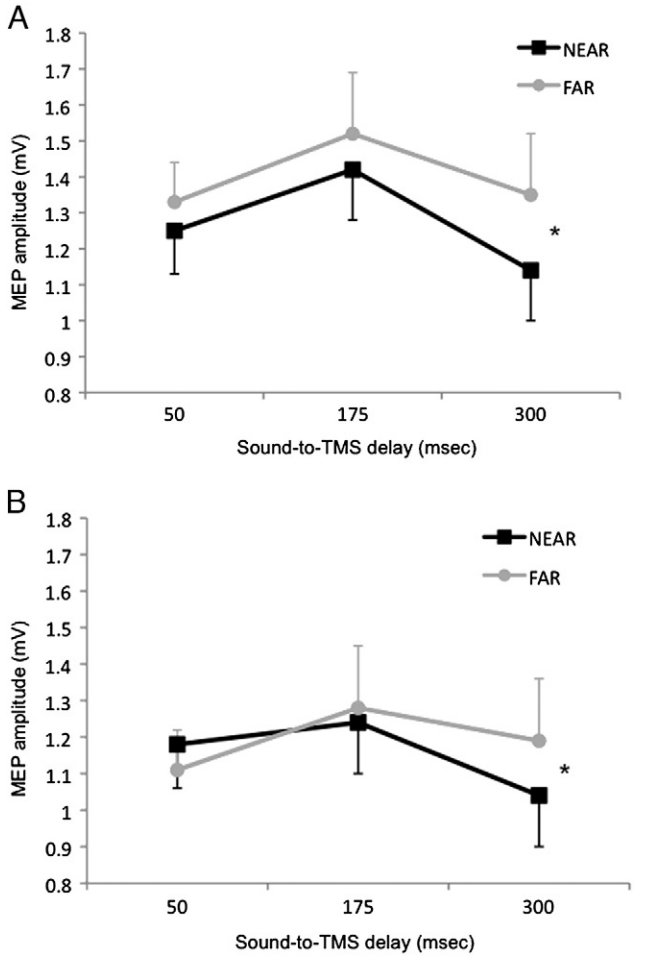

Fig. 4. Raw mean MEPs amplitude recorded during Experiment 2, after the Real-tDCS sessions over the left PPc (A) and over the left V1 (B), when sounds were administered near (black lines) and far (gray lines) from the subject's right hand. Error bars denote SEM. Asterisks indicate significant comparisons.

over V1 (Experiment 2) as respective control conditions. We entered SI at 300 ms in a 2×2 mixed-model ANOVA with Condition (Target, Control) as the within-subjects factor and Experiment (Exp1, Exp2) as the between-subjects factor. The two-way interaction was significant ($F_{1,28}=4.34$, $p<0.05$). As Fig. 5 shows, SI was negative, indicating a spatial modulation of MEPs, with lower MEPs following near sounds, for both control conditions (Sham-tDCS = −0.34 mV ± 0.11; Real-tDCS over V1 = −0.15 mV ± 0.12), as well as for the Real-tDCS over PPc condition (−0.21 mV ± 0.08). These values were not different from each other (all $p>.25$). On the contrary, no spatial modulation was evident after Real-tDCS over PMc (0.07 mV ± 0.08), and SI in this condition was significantly different from the two control conditions (all $p_s<.05$) and also, critically, from the other target condition of Real-tDCS over PPc ($p<.05$).

Table 1
MEP amplitudes (in mV) ± SEM recorded from FDI muscle in Experiment 1, after sessions of Real-tDCS over PMc and Sham-tDCS over PMc, and Experiment 2, after sessions of Real-tDCS over PPC and the Real-tDCS over V1.

Experiment 1				
Delay (ms)	SHAM-tDCS (left PMc)		Real-tDCS (left PMc)	
	Near sounds	Far sounds	Near sounds	Far sounds
50	1.74 ± 0.28	1.87 ± 0.31	1.60 ± 0.24	1.78 ± 0.28
175	1.95 ± 0.31	2.02 ± 0.31	1.77 ± 0.27	1.84 ± 0.26
300	1.66 ± 0.26	2.00 ± 0.32	1.63 ± 0.27	1.55 ± 0.22
Experiment 2				
	Real-tDCS (left PPC)		REAL-tDCS (left V1)	
50	1.25 ± 0.12	1.33 ± 0.11	1.18 ± 0.15	1.11 ± 0.16
175	1.42 ± 0.14	1.52 ± 0.17	1.24 ± 0.17	1.28 ± 0.18
300	1.14 ± 0.14	1.35 ± 0.17	1.04 ± 0.15	1.19 ± 0.16

Discussion

The brain has evolved an efficient sensorimotor mechanism, mapping sensory stimuli in the space immediately surrounding the body (i.e., in PPS) onto potential motor responses (Graziano and Cooke, 2006; Rizzolatti et al., 1997). In humans, the activation of PPS representation upon visual or auditory stimulation near the hand is associated with reduced corticospinal excitability relative to when stimuli are presented at a distance (Makin et al., 2009; Serino et al., 2009). This inhibitory, freezing-like, response resembles that found during the presentation of noxious stimuli (Farina et al., 2001; Urban et al., 2004) or unexpected events and potential threats, including loud acoustic stimuli (Furubayashi et al., 2000), unexpected visual flashes (Cantello et al., 2000) or visual stimuli depicting pain in others (Avenanti et al., 2009; Minio-Paluello et al., 2006), suggesting that motor mapping of sensory events occurring near the body primes defensive reactions (Graziano and Cooke, 2006). Using a perturb-and-measure approach (Avenanti

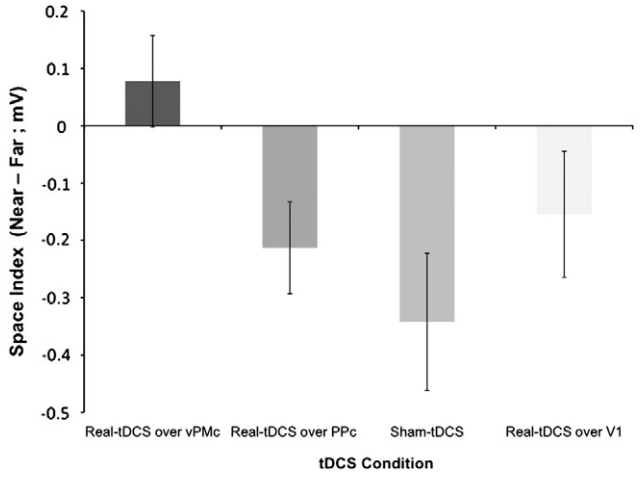

Fig. 5. Indices of spatial modulation (SI) of MEPs (amplitudes recorded at 300 ms after near sounds minus amplitudes recorded at 300 ms after far sounds) following the critical Real-tDCS sessions over PMc and over PPc and the control sessions, Sham-tDCS over PMc and Real-tDCs over V1. Error bars denote SEM Asterisks indicate significant comparisons.

et al., 2007, 2012a, 2012b), in the present study, we investigated the neural bases of this spatially-dependent modulation of motor excitability, by testing whether it relies on the fronto-parietal regions underlying multisensory representation of PPS, namely PMc (in particular its ventral sector) and PPc (Bremmer et al., 2001; Brozzoli et al., 2011; Gentile et al., 2011; Makin et al., 2007; Serino et al., 2011). We measured the excitability of the hand representation in M1 when a sound was presented either near or far from the hand, after inhibiting the target cortical sites of PMc and PPc, and V1 as a control site. In line with previous findings (Serino et al., 2009; see also Makin et al., 2009), when no neural perturbation was applied (Sham-tDCS), the hand representation in M1 was modulated as a function of sound location: MEPs recorded from the FDI muscle at 300 ms after the onset of a sound were lower if the sound was presented near the subjects' hand rather than at a distance. Analogous results were obtained when Real-tDCS was applied to the control site, V1. Importantly, the differential effect of near and far sounds on MEPs was abolished after inhibitory tDCS over PMc, showing that this area plays a critical role in the motor coding of sensory events occurring within PPS. In contrast, inhibitory tDCS over PPc did not disrupt the spatially-dependent modulation of motor excitability, as in this case, MEPs recorded at 300 ms were lower after a near than after a far sound, similarly to what occurred in the control sessions (Sham-tDCS; Real-tDCS over V1). These findings highlight the role of PPS network in modulating the human motor system when sensory stimuli are presented near or far from the body. A previous study targeting the very same brain areas showed that virtual lesions to PMc and PPc (not to V1) disrupt audio-tactile interactions within PPS (Serino et al., 2011), suggesting that in humans these two regions are similarly involved in a multisensory representation of PPS. The present data critically expand this notion by demonstrating that the two nodes of the fronto-parietal network representing PPS have partially dissociable functions, with PMc being, more than PPc, mainly involved in mapping sensory representations of space onto the motor system.

Our findings are consistent with the notion that premotor neurons are critically involved in sensory-to-motor transformations (Avenanti and Urgesi, 2011; Avenanti et al., 2007; Rizzolatti et al., 1997, 2002) supporting motor and cognitive functions. However, they may appear only partially in line with neurophysiological data in monkeys. In non-human primates, prolonged intra-cortical stimulation of both F4 (in the ventral sector of the PMc) and VIP (in PPc) areas results in overt motor behaviors, resembling defensive responses to threatening stimuli approaching the body in ecological conditions (Cooke et al., 2003; Graziano and Cooke, 2006; Graziano et al., 2002; Stepniewska et al., 2005). This would suggest that monkey premotor and parietal areas are similarly involved in implementing defensive behavior, whereas the results from the present study suggest that in humans, only PMc – and not PPc – is critically involved in processing motor reactions to sensory events occurring in the PPS.

It might be possible that the motor properties of the PPS network differ between the two species, despite the strong correspondence between the sensory properties of the posterior-parietal and premotor areas in the monkey and in the human brain (Bremmer et al., 2001). However, several pieces of evidence suggest that also in monkey, the posterior node of the fronto-parietal PPS network might be more involved in sensory processing, whereas the anterior node might be more involved in motor output (Fogassi and Luppino, 2005; Graziano and Cooke, 2006). Firstly, F4 sends direct projections to the spinal cord (Dum and Strick, 2002, 2005; Geyer et al., 2000; He et al., 1993, 1995; Rizzolatti and Luppino, 2001) as well as to M1, whereas VIP is strongly connected to PMc (Cavada and Goldman-Rakic, 1989; Matelli and Luppino, 2001), but the existence of direct connection from VIP to M1 is not well established (Luppino et al., 1999; Petrides and Pandya, 1984; Rozzi et al., 2006). Second, multimodal neurons in F4 are also active during movements of the body part where their sensory receptive fields are anchored (Rizzolatti et al., 1981), whereas evidence of motor activity associated with VIP neurons is limited to the intracortical microstimulation studies cited above (Cooke et al., 2003; Fogassi and Luppino, 2005). Third, even in the case of intracortical stimulation, evoking a motor response is much easier for F4 as compared to VIP areas: the current threshold for evoking a response is lower in F4 than in VIP; moreover in F4, but not in VIP, a response can be evoked also in an anesthetized animal; finally, responses are evoked on every trial after stimulation of F4, whereas the response generated by VIP stimulation quickly decays over repeated trials. Taken together these data suggest that in monkeys, just as in humans (Koch et al., 2010), PMc projections to the corticospinal system are more robust and direct than PPc projections. These features fit with the results of the present study showing the necessity of PMc in mediating sensory to motor representations of PPS. It is possible that information about sounds in space is processed both in PMc and in PPc cortex, through direct connections from acoustic areas. In addition, acoustic input might also modulate PMc activity through an indirect projection from PPc neurons. However, only PMc can directly modulate motor output, via the primary motor cortex (Matelli and Luppino, 2001; Rizzolatti and Luppino, 2001) and/or via direct projections to the spinal cord (Dum and Strick, 2002, 2005; Geyer et al., 2000; He et al., 1993, 1995; Rizzolatti and Luppino, 2001). Thus, when PMc cortex is inactivated, information related to the position of sounds in space cannot modulate the motor system, while when PPc is inhibited, direct projections from the auditory cortex can still reach the PMc, which in turn can affect the motor system.

An alternative hypothesis might be that stimulation of PPc through tDCS was less effective in abolishing the spatially-depended modulation of MEP, because task-relevant neurons lay in the depth of the intraparietal sulcus and tDCS was unable to target such neurons. While we cannot completely rule out this possibility, it should be noted that other brain stimulation studies using tDCS (Bolognini et al., 2010a,2010b) or TMS (Serino et al., 2011) successfully modulated multisensory integrative processing in PPc. Taken together these findings suggest that non-invasive stimulation techniques can affect intraparietal neurons. Moreover, they support the view of a greater involvement of PPc in (multi)sensory, relative to motor, processes.

Neural responses to near body stimuli in monkey area F4 and VIP are mainly excitatory (Colby & Duhamel, 1996; Graziano and Cooke, 2006; Rizzolatti et al., 2002), whereas, in the present study, inhibitory motor responses were detected. This is not surprisingly as activation of premotor or parietal regions may result not only in increased, but also in reduced motor output (Avenanti et al., 2009; Baldissera

et al., 2001; Davare et al., 2009; Tokuno and Nambu, 2000). The present data do not exclude that other facilitatory responses may occur for stimuli near the body. It may be possible that other sectors of the motor system (e.g. controlling proximal muscles or the contralateral limb) may show increased excitability for stimuli near the hand and such facilitatory responses may occur simultaneously with the freezing-like response of hand muscles, similarly to what happens during processing of real or potential noxious stimuli (Avenanti et al., 2009; Urban et al., 2004). Future studies are needed to directly test these possibilities. It is worth noting that in our previous TMS study (Serino et al., 2009), beside the inhibitory effect associated to near sounds at 300 ms, we had also found an earlier facilitatory response, detected at 50 ms after presenting near sounds (Serino et al., 2009). The failure to replicate that excitatory effect in the present study is likely to depend on the different TMS intensity used in the two studies (see Materials and Methods section). It is known that different TMS intensities may recruit neural populations with different activation thresholds (Chen et al., 2008). Therefore, it is possible that the relatively lower TMS intensity used in the present study could have disclosed the activity of inhibitory, more than of excitatory neural units, which are both present in the motor cortex (Chen et al., 2008; Serino et al., 2009; Schütz-Bosbach et al., 2009). While both these populations of neurons might be involved in the motor coding of sensory stimuli in the PPS, it is possible that early excitatory effects due to near stimuli could be detected only with higher TMS intensities (as in Serino et al. (2009)), whereas inhibitory effects can be recorded also with intensities used in the present experiment or even lower (e.g. at 110% of rMT; see Cantello et al. (2000), Furubayashi et al. (2000), and Makin et al. (2009)).

There is an additional possible limitation in the present study that it is fair to highlight when commenting our conclusions. Although we centered our stimulation over the ventral premotor cortex and intraparietal sulcus sites shown be active or critical for PPS representation by previous fMRI (Bremmer et al., 2001; Makin et al., 2007) and TMS studies (Serino et al., 2011), it is possible that additional sectors of PMc or PPc were influenced by tDCS due the relatively poor spatial resolution of this technique (Datta et al., 2009; Nitsche et al., 2008; Priori et al., 2009). Brain stimulation techniques can also modulate activity in remote interconnected regions (Avenanti et al., 2012a; Keeser et al., 2011; Stagg et al., 2009). Thus, it is possible that regions interconnected to the premotor cortex were influenced by tDCS and may have contributed to the observed effects. At any rate, our study shows a clear dissociation between the anterior (PMc) and posterior (PPc) nodes of the PPS networks in mapping sensory representations of space onto the motor system.

In conclusion, the results from the present study confirm that, if the PPS network is intact, stimuli presented near the hand inhibits the motor representation of the hand in M1, as compared to stimuli presented at a distance, within a specific time-window. This spatially-dependent modulation of the motor system depends on the activity of the PMc; inducing a "virtual lesion" to this area abolished this inhibitory effect, thus highlighting the critical role of PMc in the motor coding of PPS. It is tempting to propose a model in which the PPc and the PMc constitute two critical nodes of a parieto-frontal network underlying a sensorimotor representation of space along a postero-anterior functional gradient: the parietal node might be more involved in multisensory processing of space, whereas the premotor node is necessary to trigger or inhibit potential, appropriate motor responses to stimuli near the body, by projecting to the motor cortex and/or through direct connections to spinal cord motoneurons.

The present study offers initial support to this model, as it provides evidence for a simple dissociation in the PMc-PPc network, with the PMc, but not the PPc, being critical for implementing freezing-like responses in the motor system. A stronger support for the model would come from concurrent evidence of the opposite dissociation, which is a mainly sensory dysfunction following selective lesion to the PPc. Preliminary data from our laboratory show that structural lesions to PPc, and not to PMc, affect awareness of multisensory stimuli presented within PPS in right brain damaged patients suffering crossmodal extinction (Serino, Tomaiuolo, Quinquinio and Làdavas, Neural correlates of peripersonal space representation in humans: evidence from patients with crossmodal extinction, under revision). Providing strong evidence for such a double dissociation would definitely clarify the relationship between sensory-motor functions of PPS and their neural correlates in PMc-PPc areas.

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