

Independent mechanisms for ventriloquism and multisensory integration as revealed by theta-burst stimulation

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Abstract

The visual and auditory systems often concur to create a unified perceptual experience and to determine the localization of objects in the external world. Co-occurring auditory and visual stimuli in spatial coincidence are known to enhance performance of auditory localization due to the integration of stimuli from different sensory channels (i.e. multisensory integration). However, auditory localization of audiovisual stimuli presented at spatial disparity might also induce a mislocalization of the sound towards the visual stimulus (i.e. ventriloquism effect). Using repetitive transcranial magnetic stimulation we tested the role of right temporoparietal (rTPC), right occipital (rOC) and right posterior parietal (rPPC) cortex in an auditory localization task in which indices of ventriloquism and multisensory integration were computed. We found that suppression of rTPC excitability by means of continuous theta-burst stimulation (cTBS) reduced multisensory integration. No similar effect was found for cTBS over rOC. Moreover, inhibition of rOC, but not of rTPC, suppressed the visual bias in the contralateral hemifield. In contrast, cTBS over rPPC did not produce any modulation of ventriloquism or integrative effects. The double dissociation found in the present study suggests that ventriloquism and audiovisual multisensory integration are functionally independent phenomena and may be underpinned by partially different neural circuits.

Introduction

The influence of visual cues on auditory perception has been extensively investigated and studies have documented either beneficial (i.e. multisensory integration) or detrimental (i.e. visual bias) influences of visual events on auditory localization (Corneil *et al.*, 2002; Bolognini *et al.*, 2007; Alais & Burr, 2004; Recanzone & Sutter, 2008). As far as the multisensory integration effect is concerned, it is well known that localization of an auditory stimulus is enhanced by the presence of a co-occurring spatially coincident visual stimulus (Corneil *et al.*, 2002; Bolognini *et al.*, 2007; Leo *et al.*, 2008a; Passamonti *et al.*, 2009). This perceptual enhancement can well highlight the benefit deriving from the integration of multisensory stimuli (Hairston *et al.*, 2003a; Bolognini *et al.*, 2005; Bertini *et al.*, 2008; Leo *et al.*, 2008b) and it is reminiscent of the response properties of multisensory cells in the superior colliculus, as described in several neurophysiological studies in nonhuman mammals (Meredith & Stein, 1983, 1986a,b; Stein & Meredith, 1993; Kadunce *et al.*, 2001), suggesting a pivotal role of this subcortical structure in mediating multisensory integration. Notably,

however, evidence on cats suggests that cortical areas (i.e. the anterior ectosylvian sulcus; AES) are essential for multisensory responses in collicular neurons and for multisensory mediated orienting behavior (Stein & Stanford, 2008); however, to date, information about the possible human cortical homologue of AES is meager. Primate research has focused on the properties of the superior temporal (Benevento *et al.*, 1977; Seltzer & Pandya, 1978; Barraclough *et al.*, 2005), inferior parietal (Dong *et al.*, 1994) and intraparietal (Colby *et al.*, 1993; Duhamel *et al.*, 1998; Schlack *et al.*, 2002) cortices, where sensory information from many different modalities converge. In keeping, imaging studies in humans have revealed that temporo-parietal areas (i.e. superior temporal sulcus and superior temporal gyrus, extending into inferior parietal cortex, here referred as temporoparietal cortex; TPC) and the intraparietal sulcus in the posterior parietal cortex (PPC) consistently show multisensory enhanced responses to audiovisual stimuli presented with temporal and spatial coincidence (Calvert *et al.*, 2000, 2001; Molholm *et al.*, 2002; Meienbrock *et al.*, 2007), mimicking the response properties of collicular multisensory neurons (Laurienti *et al.*, 2005). Nevertheless, to date it is not clear whether activity in these temporal and parietal cortical regions is essential for multisensory perceptual benefit or whether it reflects an epiphenomenon.

Presenting simultaneous spatial coincident auditory and visual stimuli can enhance auditory spatial localization, but presenting

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simultaneous but spatially discrepant auditory and visual stimuli is known to mostly induce a perceptual translocation of the sound towards the visual stimulus, i.e. a detrimental effect of visual events on auditory localization (Howard & Templeton, 1966; Thurlow & Jack, 1973; Welch & Warren, 1980; Bertelson & Radeau, 1981; Spence & Driver, 2000; Slutsky & Recanzone, 2001; Hairston *et al.*, 2003b; Lewald & Guski, 2003; Vroomen & de Gelder, 2004). Behavioral studies on healthy participants and brain-damaged patients suggest that mechanisms underlying this 'ventriloquism' effect are at least partially distinct from those underlying multisensory integration (Bolognini *et al.*, 2007; Leo *et al.*, 2008a; Passamonti *et al.*, 2009); indeed, reduction in perceptual saliency of visual stimuli (Hairston *et al.*, 2003b; Bolognini *et al.*, 2007) and lesions to the occipital cortex (OC; Leo *et al.*, 2008a; Passamonti *et al.*, 2009) are known to reduce ventriloquism without affecting multisensory perceptual enhancement.

In the present research we tested the hypothesis that differential neural networks are critically involved in ventriloquism and audiovisual multisensory enhancement. In three experiments we asked subjects to localize an auditory stimulus that was presented alone (unimodal stimulation) or with a concurrent hard-to-detect visual stimulus at various spatial disparities (audiovisual stimulations). In this way, we derived indices of visual bias and multisensory integration from auditory localization performance. Importantly, in each experiment the localization task was carried out in two counterbalanced sessions that were performed well within the inhibition window created by off-line repetitive transcranial magnetic stimulation (TMS) or outside the influence of TMS (baseline). Magnetic stimulation was performed by means of continuous theta-burst (cTBS), a novel TMS protocol known to suppress cortical excitability for up to 60 min (Huang *et al.*, 2005). By showing how auditory localization was affected by 'virtual lesions' to the right temporoparietal cortex (rTPC), right occipital cortex (rOC) and right posterior parietal cortex (rPPC) we were able to test the critical role of these three regions in multisensory integration and ventriloquism.

Materials and methods

Subjects

Forty-two right-handed healthy participants free from any contraindication to TMS (Wassermann, 1998) took part in the experiment and

were assigned to three experimental groups. The first group comprised 12 subjects (age range 21–28 years; seven females) who were submitted to cTBS on the rTPC (Experiment 1). The second group included 12 subjects (age range 21–27 years; nine females) submitted to cTBS on the rOC (Experiment 2). The third group comprised 18 subjects (age range 21–31 years; 11 females) submitted to cTBS on the rPPC (Experiment 3). All had normal hearing and normal or corrected-to-normal vision and were naive as to the purpose of the experiment. Participants received course credits for their participation and gave informed consent prior to beginning. The experimental procedures were approved by the Ethical Committee of the Department of Psychology, University of Bologna. The experiment was carried out according to the principles laid out in the 1964 Declaration of Helsinki.

Experimental apparatus

The apparatus consisted of a semicircular perimetry (radius 110 cm) containing an array of red light-emitting diodes (LEDs) and speakers (Fig. 1). A central LED, positioned at eye level, constituted the central fixation point (0°). A set of 26 LEDs was placed at the same level, at eccentricities ranging from 20° to 80° to the left and the right of the fixation point. Adjacent LEDs were separated by 5° of visual angle. A set of eight speakers was positioned 1.3 cm above the LED array at 20°, 40°, 60° and 80° of eccentricity to the left and the right of the central fixation point. A joystick-style yoke comprised of handles, two buttons and a laser pointer was mounted 5 cm from the center of the semicircle. A personal computer and a multifunction card controlled the stimuli display and the response acquisition, receiving input from the yoke and the buttons. The entire apparatus was enclosed in a dimly lit, sound-attenuated room.

Experimental procedure

In each experiment subjects dark-adapted for 10 min prior to beginning the testing procedure. In order to set the auditory and visual intensities, each subject's ability to localize auditory stimuli (auditory intensity setting procedure) and to detect visual stimuli (visual intensity setting procedure) was measured before the experimental task.

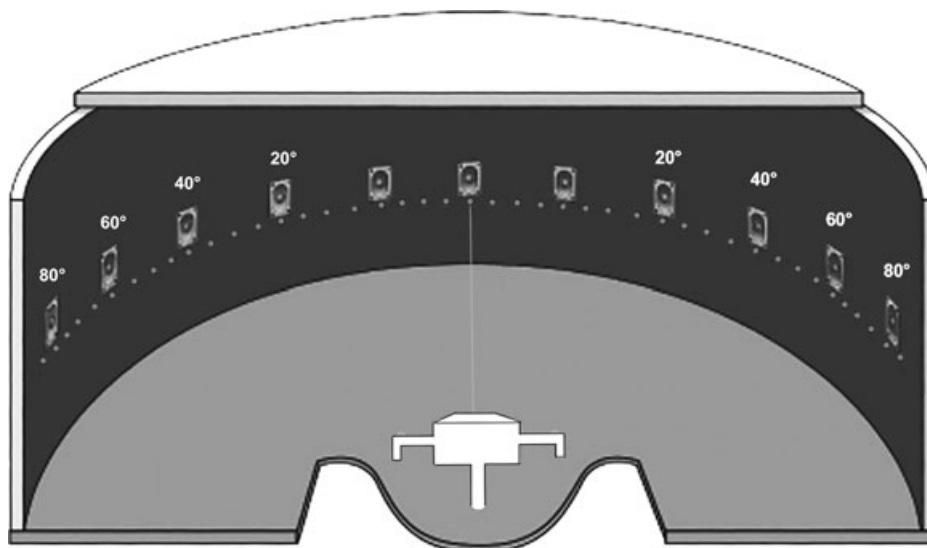


FIG. 1. Schematic view of the experimental apparatus.

In the auditory intensity setting procedure, subjects were instructed to localize a pure tone (2 kHz) delivered from a speaker, by rotating the yoke and pointing with the laser pointer. Each trial consisted of the illumination of the central fixation point for 800 ms, a random delay (100–1000 ms time window) and the presentation of the auditory stimulus (100 ms). In each block, all the eight possible auditory positions were tested and 10 trials for position were presented. After each block, auditory localization performance was evaluated by assessing the mean localization absolute error (i.e. unsigned difference between actual and reported location). The initial intensity of the pure tone was 56.1 dB and this was gradually reduced with step of 1.3 dB in each block, in order to reach a localization error within 8° in ~50% of the trials.

During the visual intensity setting procedure subjects were asked to detect the presence of a visual stimulus, consisting of the illumination of an LED, by pressing a button. In each trial, the central fixation point appeared for 800 ms and then, after a random delay (100–1000 ms time window), the visual stimulus was presented for 100 ms. The 26 visual stimulus positions were tested individually, in separate blocks. Each block consisted of 20 trials and 10 catch trials (i.e. trials in which no visual stimulus was presented). The intensity of the visual stimuli was initially set at 0.17 lux and then was gradually reduced in steps of 0.022 lux in each block, to reach a hit rate of ~50%.

Once stimuli intensities were set, subjects performed the experimental task in two counterbalanced sessions, within (post-cTBS session) and outside (baseline) the inhibition time window created by the cTBS. Participants were presented with hard-to-detect visual stimuli (100 ms illumination of a red LED, intensity range 0.011–0.17 lux) and hard-to-localize auditory stimuli (100 ms pure tone 2000 Hz, intensity range 52.2–56.1 dB).

Two possible stimuli combinations were used:

- Unisensory auditory (A-UNI): the auditory stimulus was presented alone.
- Multisensory audiovisual (AV): the auditory stimulus was presented at each location concurrently with a temporally coincident task-irrelevant visual stimulus. The visual stimulus was either spatially coincident (same position; SP-AV) or spatially disparate (SD-AV) with the auditory target. Disparities of 15° (SD-AV-15) or 30° (SD-AV-30) in the nasal (N) or temporal (T) directions were used.

For each trial, subjects were asked to fixate the central fixation point and then to judge the spatial position of the auditory stimulus, by pointing with the laser pointer, and to ignore any accompanying visual stimulus. The auditory stimuli could be presented in any of the eight possible auditory positions.

During each session of the experiment, 16 trials for each of the five stimulus combination (A-UNI, SP-AV, SD-AV-15N, SD-AV-15T, SD-AV-30) were presented at each of the four spatial positions (60° right, 40° right, 40° left, 60° left) resulting in a total of 160 trials for hemifield. Localization performance was based on data recorded at these positions. To increase uncertainty judgments we presented a total of 32 stimuli for hemifield at more central (20°) and peripheral (80°) locations (these included eight A-UNI, eight SP-AV, eight SD-AV-15 and eight SD-AV-30 stimuli for the hemifield). However, these data were not included in the analysis.

TMS

In a preliminary part of the experiments, before performing the auditory and visual intensity setting procedures (see above), we assessed the individual intensity threshold for phosphene perception in the right visual cortex. Participants wore a lycra cup, were blindfolded

and adapted to darkness for 10 min to enhance the excitability of their visual cortex (Boroojerdi *et al.*, 2000; Fernandez *et al.*, 2002). TMS was performed by means of a 70-mm figure-of-eight stimulation coil connected to a Magstim Rapid2 (The Magstim Company, Carmarthen, Wales, UK). The coil was oriented so that the induced current was lateral-to-medial, optimal for stimulating the visual cortex (Kammer *et al.*, 2001). Five participants in the rTPC experiment (42% of the total), five participants in the rOC experiment (42%) and seven participants in the rPPC experiment (39%) did not report phosphenes during single-pulse TMS. In the remaining subjects, by using a slightly suprathreshold intensity we roughly marked the scalp area in which single-pulse TMS elicited phosphenes and then, within this area, we localized the hotspot. Phosphene threshold (PT) was determined by delivering, in random order, ~10 pulses at various intensities with increments of 2–3%. PT values (mean maximum stimulator output \pm standard deviation) were similar in the three experiments (rTPC, Experiment 1: $59.4 \pm 7.5\%$; rOC, Experiment 2: $61.4 \pm 9.7\%$; rPPC, Experiment 3: $59.3 \pm 7.5\%$; $F_{2,22} = 0.14$, $P = 0.87$). After the assessment of PT and the auditory and visual intensity setting procedures (see above), participants performed the experimental task in two different sessions (post-cTBS, baseline) lasting 20–25 min each. In the post-TBS session, the task was performed within the inhibition window created by 40 s of cTBS on rTPC, rOC or rPPC; cTBS consisted of bursts of three TMS pulses delivered at 50 Hz, with each train burst repeated every 200 ms (5 Hz) for a total of 600 pulses. This TMS protocol is known to suppress the excitability of the stimulated site for ~30–60 min (Huang *et al.*, 2005; Franca *et al.*, 2006). After cTBS, participants rested for 5 min before running the task to allow the cTBS effect to reach its maximum level (Huang *et al.*, 2005). Pulse intensity was similar in the three experiments (rTPC, Experiment 1: $48.5 \pm 4.3\%$; rOC, Experiment 2: $48.7 \pm 5.0\%$; rPPC, Experiment 3: $48.4 \pm 4.3\%$; $F_{2,39} = 0.02$, $P = 0.98$) and was set as follows: (i) in those subjects with $PT < 64\%$ of maximum stimulator output (six, six and eight subjects in rTPC, rOC and rPPC experiments, respectively) the intensity was 80% of PT; (ii) in those subjects with higher PT (one, two and three in rTPC, rOC and rPPC experiments, respectively) or reporting no phosphene (five, four and seven), pulse intensity was set at the maximum allowed by the stimulator (51%).

In all the experiments, task performance in the baseline session was recorded before cTBS (in half of participants) or at least 2 h after cTBS to be sure that all the interferential effects had faded away (in the remaining subjects). This procedure was aimed at counterbalancing the two experimental sessions.

Coil position was identified on each participant's scalp with the SofTactic Navigator system (Electro Medical Systems, Bologna, Italy) as in previous research (Avenanti *et al.*, 2007; Bolognini & Maravita, 2007; Bolognini *et al.*, 2009). Skull landmarks (nasion, inion and two preauricular points) and ~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 SofTactic Navigator from an MRI-constructed stereotaxic template. Figures 2–4 illustrate site reconstructions displayed on a standard template from MRICro (v1.40; <http://www.mricro.com>). In the rTPC experiment, we targeted the superior temporal gyrus at the border with the inferior parietal cortex ($x = 63.7$, $y = -31.3$ and $z = 14.9$ mm, corresponding to Brodmann's area 42/39; Fig. 2A). This site was chosen based on imaging studies showing multisensory activity in superior temporal and inferior parietal regions (Calvert *et al.*, 2000; Wright *et al.*, 2003; Beauchamp *et al.*, 2004; Stevenson *et al.*, 2007; Noesselt *et al.*, 2007; Meinenbrock *et al.*, 2007; Werner & Noppeney,

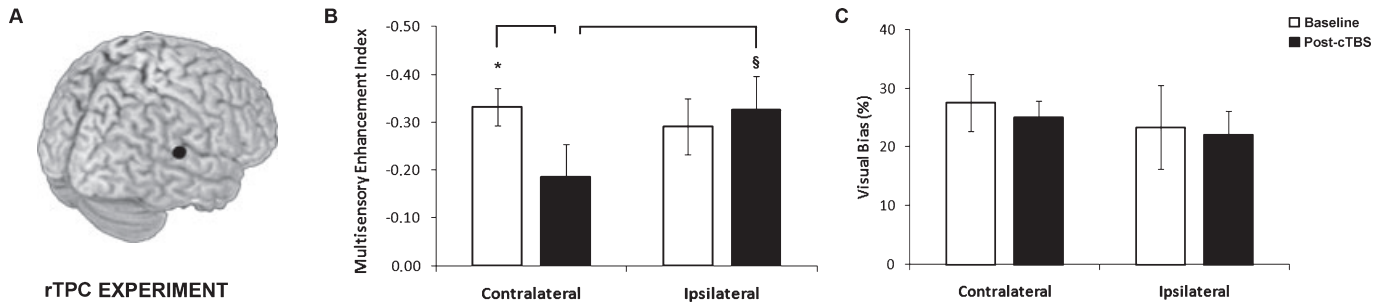


FIG. 2. Results from Experiment 1. (A) Brain location of the coil position to induce virtual lesion of the rTPC; mean Talairach coordinates, $x = 63.7$, $y = -31.3$ and $z = 14.9$ mm. (B) MEI. (C) Visual bias. White and black histograms represent MEI and visual bias during baseline and after cTBS (post-cTBS), respectively. Error bars indicate SEM. $*P < 0.05$; $§P = 0.07$.

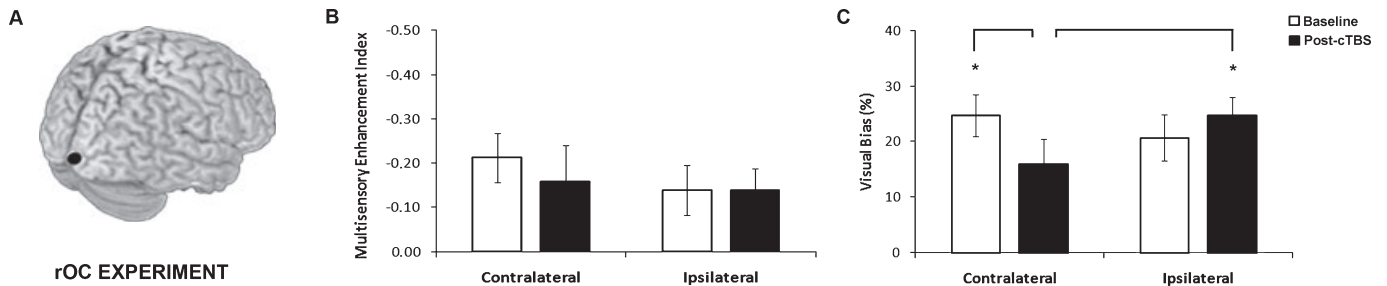


FIG. 3. Results from Experiment 2. (A) Brain locations of the coil position to induce virtual lesion of the rOC; mean Talairach coordinates, $x = 19.1$, $y = -98.2$ and $z = 0.9$ mm. (B) MEI. (C) Visual bias. White and black histograms represent MEI and visual bias during baseline and after cTBS (post-cTBS), respectively. Error bars indicate SEM. $*P < 0.05$.

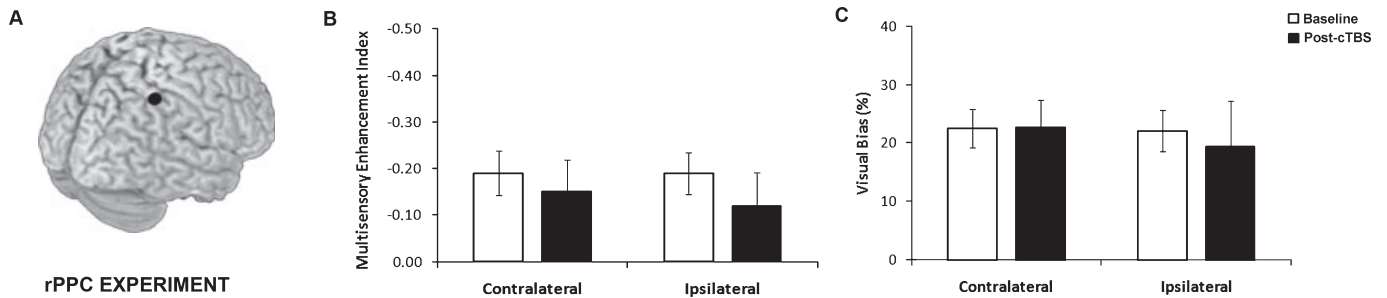


FIG. 4. Results from Experiment 3. (A) Brain locations of the coil position to induce virtual lesion of the intraparietal sulcus in the rPPC; mean Talairach coordinates, $x = 43.7$, $y = -43.3$ and $z = 47.3$ mm. (B) MEI. (C) Visual bias. White and black histograms represent MEI and visual bias during baseline and after cTBS (post-cTBS), respectively. Error bars indicate SEM.

2010). In the rOC experiment we identified the scalp locations that corresponded best to the visual cortex (coordinates: $x = 19.1$, $y = -98.2$ and $z = 0.9$ mm, corresponding to Brodmann’s area 17, in the middle occipital gyrus, see Fig. 3A). In the rPPC experiment we targeted the rPPC site where auditory and visual information are likely to be merged ($x = 43.7$, $y = -43.3$ and $z = 47.3$ mm, corresponding to Brodmann’s area 40, in the depth of the intraparietal sulcus; see Fig. 4A); this location was chosen by averaging the coordinates of the right intraparietal cortex sites found in three previous brain imaging studies (Bushara *et al.*, 2001; Bremner *et al.*, 2001; Calvert *et al.*, 2001).

Statistical analysis

Performance was evaluated for responses to auditory stimuli presented at 40° and 60° to the right and the left of the central fixation point. The

other auditory positions were not analyzed (i.e. 20° and 80°) in order to not produce a nasal or temporal response bias in the data set. In fact, auditory judgments more central than 20° and more peripheral than 80° were not possible for technical reasons. Auditory localization performances were analysed for each experiment separately according to two parameters.

Multisensory enhancement index (MEI)

The MEI for spatially coincident audiovisual stimuli was computed with the formula (modified from Meredith & Stein, 1983).

$$MEI = (\text{Err SP-AV} - \text{Err A-UNI}) / \text{Err A-UNI}$$

where Err SP-AV indicates the mean localization error for spatially coincident audiovisual stimuli and Err A-UNI represents the mean localization error in the unimodal auditory condition. Negative values

of MEI indicate that the localization error in the unimodal condition was greater than the localization error in the SP-AV condition (i.e. presence of a multisensory enhancement), while positive values indicate the opposite. This index was calculated to quantify and compare the magnitude of multisensory enhancement across the sessions.

Data were collapsed across positions (40°, 60°) to increase statistical power and analyzed with an ANOVA with Session (baseline vs. post-cTBS) and Hemifield (contralateral vs. ipsilateral to the stimulated site) as within-subjects factors.

Visual bias

The percentage of visual bias was calculated for each trial where audiovisual stimuli were presented in spatial disparity, according to the following formula (Hairston *et al.*, 2003b; Wallace *et al.*, 2004; Leo *et al.*, 2008a).

$$\% \text{Visual bias} = 100 \times (\text{Err SD-AV} - \text{Err A-UNI}) / \Delta \text{AV}$$

where Err SD-AV represents the localization error in a given trial with audiovisual disparity, Err A-UNI represents the mean localization error in the unimodal auditory condition and ΔAV represents the actual visual–auditory disparity. The resulting percentage score represents the degree of visual bias of sound location, in other words the ‘pull’ that the visual signal has over the auditory target. A score of 100% indicates a complete bias, wherein the subject localizes the sound at the visual stimulus site, while positive scores < 100% represent position judgments between the visual and auditory stimuli.

Data were collapsed across positions (40°, 60°) and disparities (15°N, 15°T, 30°) to increase statistical power and then analyzed with an ANOVA with Session (baseline vs. post-cTBS) and Hemifield (contralateral vs. ipsilateral to the stimulated site) as within-subjects factors.

Although the same experimental procedure was used in the three experiments, visual bias and multisensory enhancement indices were higher in subjects of the rTPC experiment. To eliminate differences between groups, a total of 12 subjects with no sign of multisensory enhancement (four subjects with mean MEI across conditions > 0) or with low (below the 20th percentile; six subjects) or very high visual bias (> 2 standard deviations from the mean; two subjects) were removed from the main analysis. In the following section, the results from the ANOVAs conducted on the remaining 30 participants are reported (rTPC, Experiment 1, nine subjects; rOC, Experiment 2, 10 subjects; rPPC, Experiment 3, 11 subjects). Crucially, analyses conducted on the entire sample led to the same statistical results (main effect of Session in the ANOVA performed on MEI in the rTPC

experiment, $F_{1,11} = 11.25$, $P = 0.006$; Session \times Hemifield interaction in the ANOVA performed on the visual bias in the rOC experiment, $F_{1,11} = 12.45$, $P = 0.005$. In the remaining ANOVAs, no main effect or interaction was significant: all $F < 1.49$ and $P > 0.25$ (see also Table 1).

Results

Experiment 1: Virtual lesion to rTPC

Overall, participants in Experiment 1 showed multisensory enhancement effects as indicated by the mean MEI computed across conditions (Fig. 2B): one-sample *t*-test revealed that MEI was significantly different from zero (one-sample *t*-test: $t_8 = -6.23$, $P = 0.0002$), indicating that presenting simultaneous spatially coincident visual stimuli improved localization accuracy of auditory stimuli. The Session \times Hemifield ANOVA performed on MEI revealed a significant main effect of Session ($F_{1,8} = 9.75$, $P = 0.014$), accounted for by the lower multisensory enhancement (less negative MEI) after cTBS over rTPC compared to baseline (−0.26 vs. −0.31). No main effect of Hemifield ($F_{1,8} = 1.14$, $P = 0.32$) or interaction Session \times Hemifield ($F_{1,8} = 3.34$, $P = 0.11$) were found. However, planned comparisons revealed that most of the reduction in the multisensory enhancement occurred in the left hemifield, contralateral to the stimulated site (−0.33 vs. −0.18, $P = 0.009$), while no change in MEI seemed to occur in the ipsilateral hemifield (−0.29 vs. −0.33, $P = 0.59$). After cTBS, multisensory enhancement in the left contralateral hemifield was marginally lower than in the right ipsilateral hemifield (−0.18 vs. −0.33, $P = 0.07$). Importantly, one-sample *t*-test revealed that, after cTBS over rTPC, multisensory enhancement in the left contralateral hemifield was still significantly different from 0 ($t_8 = -3.33$, $P = 0.010$), indicating that cTBS was capable of reducing but not of eliminating the multisensory enhancement.

All participants in the first experiment showed a conspicuous visual bias (one-sample *t*-test against zero calculated on mean visual bias index computed across conditions: $t_8 = 7.35$, $P < 0.0001$; see Fig. 2C). The Session \times Hemifield ANOVA on the percentage of visual bias revealed no significant effect or interaction (all $F < 0.62$ and $P > 0.45$), indicating that cTBS over rTPC did not affect ventriloquism.

In sum, this first experiment showed that in the baseline session (outside the inhibitory effect of cTBS over rTPC) auditory localization performance was strongly improved by the presentation of a spatially coincident visual stimulus (multisensory enhancement effect) and decreased by the presentation of a spatially disparate visual stimulus that induced a perceptual translocation of the sound towards the visual stimulus (visual bias effect). Crucially, suppressing the activity of

TABLE 1. Statistical values of the ANOVAs conducted on the entire sample of subjects

	Experiment 1 Virtual lesions to rTPC	Experiment 2 Virtual lesions to rOC	Experiment 3 Virtual lesions to rPPC
MEI			
Session	($F_{1,11} = 11.25$, $P = 0.006$)	($F_{1,11} = 0.08$, $P = 0.79$)	($F_{1,17} = 0.01$, $P = 0.92$)
Hemifield	($F_{1,11} = 1.32$, $P = 0.28$)	($F_{1,11} = 0.05$, $P = 0.82$)	($F_{1,17} = 0.23$, $P = 0.64$)
Session \times Hemifield	($F_{1,11} = 3.44$, $P = 0.09$)	($F_{1,11} = 0.27$, $P = 0.61$)	($F_{1,17} = 0.08$, $P = 0.79$)
Visual Bias			
Session	($F_{1,11} = 0.12$, $P = 0.74$)	($F_{1,11} = 0.40$, $P = 0.54$)	($F_{1,17} = 0.02$, $P = 0.89$)
Hemifield	($F_{1,11} = 1.49$, $P = 0.25$)	($F_{1,11} = 2.07$, $P = 0.18$)	($F_{1,17} = 0.16$, $P = 0.69$)
Session \times Hemifield	($F_{1,11} = 0.44$, $P = 0.52$)	($F_{1,11} = 12.45$, $P = 0.005$)	($F_{1,17} = 0.19$, $P = 0.67$)

MEI, multisensory enhancement index; rOC, right occipital cortex; rPPC, right posterior parietal cortex; rTPC, right temporoparietal cortex.

rTPC by means of cTBS disrupted multisensory integrative enhancement but not ventriloquism.

Experiment 2: Virtual lesions to rOC

One-sample *t*-tests against zero indicate that participants in the second experiment showed multisensory enhancement ($t_9 = -4.79$, $P = 0.0009$) and visual bias effects across sessions ($t_9 = 7.50$, $P < 0.0001$). The Session \times Hemifield ANOVA conducted on MEI showed no main effects or interaction (all $F < 1.31$, $P > 0.28$), indicating that TMS did not affect multisensory integration (Fig. 3B).

By contrast, the Session \times Hemifield ANOVA on visual bias revealed a significant double interaction ($F_{1,9} = 7.71$, $P = 0.021$; Fig. 3C), but not main effects of Session or Hemifield (all $F < 0.59$ and $P > 0.46$). *Post hoc* analysis revealed that, compared to baseline, cTBS over rOC brought about a significant decrease in the percentage of visual bias in the left (contralateral) hemifield (25% vs. 16%, $P = 0.03$). In contrast, in the ipsilateral hemifield no difference was found (21 vs. 25%, $P = 0.26$). The double interaction was also accounted for by higher visual bias after cTBS in the ipsilateral rather than the contralateral hemifield (25% vs. 16%, $P = 0.033$). No other significant comparisons were found (all $P > 0.18$). Importantly, one-sample *t*-test revealed that, after cTBS over rOC, visual bias in the left (contralateral) hemifield was still significantly different from 0 ($t_9 = 4.04$, $P = 0.003$), indicating that cTBS was capable of reducing but not of eliminating the visual bias.

These findings indicate that suppressing the excitability of the rOC led to a reduction in visual bias in the left hemifield (contralateral to the stimulated site) but did not change multisensory integration.

Experiment 3: Virtual lesions to rPPC

One-sample *t*-tests against zero indicate that participants in the third experiment showed multisensory enhancement ($t_{10} = -4.45$, $P = 0.001$) and visual bias effects across sessions ($t_{10} = 6.92$, $P < 0.0001$). However, the Session \times Hemifield ANOVAs on MEI (all $F < 1.66$ and $P > 0.23$; Fig. 4B) and on visual bias (all $F < 0.26$ and $P > 0.62$; Fig. 4C) did not show any significant main effect or interaction. Thus, suppressing the activity in the rPPC by means of cTBS did not affect multisensory integration or ventriloquism.

Discussion

The ability to determine accurately the location of a sound source has a great adaptive value in many species and represents a complex computational process, typically less accurate and reliable than visual localization (Corneil *et al.*, 2002; Bolognini *et al.*, 2007; Alais & Burr, 2004; Recanzone & Sutter, 2008). As a consequence, a visual cue is often able to either enhance (i.e. multisensory integration) or bias (i.e. ventriloquism) auditory localization performances. In three TMS experiments, we tested the causative role of rTPC, rOC and rPPC in multisensory integration and visual bias effects during an auditory localization task.

The audiovisual multisensory enhancement in auditory localization, observed in the baseline sessions, was disrupted by cTBS-induced virtual lesions of rTPC, but remained unaffected by virtual lesions to rOC or rPPC.

By contrast, the ventriloquism effect (i.e. the perceptual translocation of the sound towards the visual stimulus) found in the baseline

session was reduced by cTBS-induced virtual lesions of rOC but not by virtual lesions to rTPC or rPPC.

The present double dissociation clearly demonstrates that multisensory integration and ventriloquism are functionally independent phenomena relying on different cortical networks.

Multisensory integration

The enhanced auditory localization performance, observed in the baseline sessions when spatially coincident audiovisual stimuli were presented, attested to the presence of a multisensory integrative effect (Corneil *et al.*, 2002; Bolognini *et al.*, 2007; Leo *et al.*, 2008a; Passamonti *et al.*, 2009). This multisensory effect was reduced after cTBS over rTPC. The reduction appeared to be greater in the contralateral than the ipsilateral hemifield, although the interaction was not significant. In contrast, the multisensory effect remained unaffected by stimulation of rOC or rPPC. The finding that rTPC is involved in multisensory integration is well in keeping with previous neuroimaging evidence, showing enhanced BOLD signal during processing of a wide range of auditory and visual stimuli, including 'semantic' combinations of audiovisual stimuli (e.g. matching vocal sounds and mouth movements: Calvert *et al.*, 2001; Wright *et al.*, 2003; or visual objects that match environmental sounds: Beauchamp *et al.*, 2004; Stevenson *et al.*, 2007; Meienbrock *et al.*, 2007; Werner & Noppeney, 2010) as well as non-semantic audiovisual stimuli (Noesselt *et al.*, 2007). In keeping, additional evidence from nonhuman primates has highlighted the superior temporal and inferior parietal cortex as important multisensory sites (Stein & Stanford, 2008). Neuroanatomical and electrophysiological studies have described neurons within these temporoparietal regions receiving convergent inputs from visual, auditory and somatosensory cortices (Jones & Powell, 1970; Seltzer & Pandya, 1978; Cusick, 1997; Zhong & Rockland, 2003; Rozzi *et al.*, 2006) and responding to stimulations in more than one sensory modality (Desimone & Gross, 1979; Bruce *et al.*, 1981; Hikosaka *et al.*, 1988; Dong *et al.*, 1994). Our findings expand this evidence by showing that rTPC is critical for multisensory-related improvement in auditory localization.

The observation that rOC inhibition does not compromise the multisensory integration effect is consistent with previous studies on hemianopic patients with occipital lobe damage. These patients show an improvement of auditory localization responses when 'unseen' visual stimuli (i.e. presented in the hemianopic visual field) are presented simultaneously at the same location as the auditory stimuli (Leo *et al.*, 2008a); in a similar vein, 'unseen' visual stimuli can improve hemianopic patients' response time to simultaneous and spatially coincident sounds (Frassinetti *et al.*, 2005). In addition, a recent study on hemianopics (Passamonti *et al.*, 2009) also revealed an improvement of auditory localization after a period of passive exposure to audiovisual stimuli presented at the same location, demonstrating a perceptual learning effect due to multisensory integration. The retention of the ability to integrate audiovisual stimuli when the visual cortex is damaged or inhibited is also in agreement with neurophysiological recordings in cats, indicating that temporary deactivation of the visual cortex (Wilkinson *et al.*, 1996) and other primary cortices (Wallace & Stein, 1994) does not disrupt multisensory enhancement in the superior colliculus neurons responses or in orientation behavioral performances (Stein & Stanford, 2008).

Similarly to rOC, rPPC suppression also did not alter the multisensory enhanced localization accuracy. In keeping, in a recent TMS study, suppression of right PPC by means of low-frequency rTMS did not affect audiovisual multisensory enhancement of response time in a speeded detection task (Bolognini *et al.*, 2009).

Moreover, evidence indicates that brain-damaged patients with parietal lesions retain multisensory enhancement for spatially coincident audiovisual stimuli both in response time (Frassinetti *et al.*, 2005) and in perceptual learning (Passamonti *et al.*, 2009). Thus, previous and present findings are consistent in showing that the parietal lobe, as well as the occipital lobe, does not play a critical role in audiovisual integration.

Studies on multisensory integration in nonhuman mammals have widely reported the critical role of superior colliculus (Stein & Meredith, 1993) and the relevance of associative cortical areas (i.e. the AES), showing that the ability of superior colliculus neurons to integrate multisensory signals is disrupted after AES deactivation (Wallace & Stein, 1994; Jiang *et al.*, 2001). However, to date, a putative human homologue of AES has not been clearly identified. Imaging studies in humans suggest the involvement of several cortical areas including the temporoparietal and posterior parietal cortices in mediating audiovisual multisensory integration (for a review, see Calvert, 2001; Stein & Stanford, 2008). However, the prominent role of rTPC, but not of rPPC, in audiovisual multisensory integration described in this study suggests that neural activity in posterior parietal areas detected with functional magnetic resonance imaging or positron emission tomography during audiovisual stimulation (Bushara *et al.*, 2001; Bremmer *et al.*, 2001; Calvert *et al.*, 2001) may reflect epiphenomenic activity with no crucial behavioral consequences for auditory localization. In light of these considerations, it could be suggested that temporoparietal regions more than intraparietal cortex may represent a possible human homologue of AES.

Ventriloquism effect

The perceptual translocation of the sound towards a spatially disparate visual stimulus, observed in the baseline sessions, attested to the presence of the ventriloquism effect, a very well known phenomenon documented in previous studies (Howard & Templeton, 1966; Thurlow & Jack, 1973; Bertelson & Radeau, 1981; Spence & Driver, 2000; Slutsky & Recanzone, 2001; Hairston *et al.*, 2003b; Lewald & Guski, 2003; Vroomen & De Gelder, 2004).

This effect was reduced by cTBS over rOC, but not over rTPC or rPPC, supporting the hypothesis that cortical visual processing in the occipital cortex modulates the ventriloquism effect. Neuroimaging evidence on humans (Pekkola *et al.*, 2005; Lehmann *et al.*, 2006; Martuzzi *et al.*, 2007; Meyer *et al.*, 2007; Besle *et al.*, 2009) and intracortical recordings in animals (Bizley *et al.*, 2007; Kayser *et al.*, 2009) have suggested that visual information can have both excitatory and inhibitory effects on the activity of auditory cortex at relatively early stages, supporting the idea of the existence of direct projections from visual to auditory cortex (Bonath *et al.*, 2007). These projections and the inherent higher reliability of visual localization over auditory localization might, therefore, be responsible of the perceptual bias in auditory localization produced by spatially incongruent audiovisual stimuli. The decrease in ventriloquism effect after rOC suppression is in line with behavioural evidence showing that decreasing the saliency of visual stimuli may reduce ventriloquism (Hairston *et al.*, 2003b), at variance with multisensory integration (Bolognini *et al.*, 2007; for a review see Ládavas, 2008). In addition, it is worth remembering that hemianopic patients do not show visual bias in the hemianopic field, although they retain the multisensory integrative effects (Leo *et al.*, 2008a; Passamonti *et al.*, 2009). Based on previous evidence and on present findings, we posit that cTBS-induced suppression of rOC excitability decreases the weight of visual information in the auditory cortex and this may reduce the bias in auditory localization. Notably,

this reduction was greater in the contralateral than the ipsilateral hemifield. [A previous study has shown that cTBS over the visual cortex increases the threshold for evoking visual phosphenes by means of single-pulse TMS over the same site, demonstrating that cTBS can suppress the excitability of the visual cortex (Franca *et al.*, 2006). To the best of our knowledge, our study provides the first evidence that cTBS-induced suppression of visual cortical excitability has clear behavioural consequences. This suppressive effect of visual processing is, however, in keeping with previous TMS studies using online occipital stimulation (Amassian *et al.*, 1989; Kammer *et al.*, 2005; Romei *et al.*, 2007, 2009).]

The findings that suppression of rTPC or rPPC does not change the ventriloquism effect is in keeping with imaging studies disclosing a preferential activation in temporoparietal regions for audiovisual stimuli presented at spatial coincidence rather than at spatial disparity (Meienbrock *et al.*, 2007); moreover, brain-damaged patients with parietal lesions typically show visual bias, further suggesting that parietal regions are not critical for ventriloquism (Bertelson *et al.*, 2000; Passamonti *et al.*, 2009).

Taken together, previous studies in brain-damaged patients (Bertelson *et al.*, 2000; Leo *et al.*, 2008a; Passamonti *et al.*, 2009), neuroimaging evidence (Meienbrock *et al.*, 2007) and the present experiment in healthy subjects demonstrate the prominent role of rOC, but not of rTPC or rPPC, in modulating ventriloquism.

Concluding remarks

Overall, the present study provides causative evidence for the functional independence of multisensory integration and the ventriloquism effect during auditory localization and suggests the existence of partially different neural circuits subserving the two phenomena. Temporoparietal regions are critically involved in mediating the integration of audiovisual stimuli at the same spatial location, but not in the mislocalization of sounds towards spatially disparate visual stimuli. In contrast, suppression of occipital cortex reduces visual bias but not multisensory integration, confirming that this area is selectively involved in weighting visual information in ventriloquism. These findings further suggest that TMS represents an ideal tool for disclosing crossmodal interactions in the human brain (Romei *et al.*, 2007; Bolognini & Maravita, 2007; Romei *et al.*, 2009; Serino *et al.*, 2009; Azañón & Haggard, 2009).

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Abbreviations

AES, anterior ectosylvian sulcus; A-UNI, unisensory auditory stimulus; AV, multisensory auditory stimulus; cTBS, continuous theta-burst stimulation; LED, light-emitting diode; MEI, multisensory enhancement index; N, nasal; OC, occipital cortex; PPC, posterior parietal cortex; PT, phosphene threshold; rOC, right OC; rPPC, right PPC; rTPC, right TPC; SD-AV, spatially disparate audiovisual stimulus; SP-AV, spatially coincident audiovisual stimuli; T, temporal; TMS, transcranial magnetic stimulation; TPC, temporoparietal cortex.

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