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Published version:

DOI:10.1016/j.brs.2015.01.412

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Far Space Remapping by Tool Use: A rTMS Study Over the Right Posterior Parietal Cortex

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A B S T R A C T

Background: In previous studies, rTMS has been successfully employed to interfere with the right posterior parietal cortex (rPPC) inducing neglect-like behavior in healthy subjects. Several studies have shown that the use of tools can modulate the boundaries between near and far space: indeed when far space is reached by the stick, far space can be remapped as near.
Objective: The aim of the present study was to investigate whether once that rTMS on the rPPC has selectively induced neglect-like bias in the near space (but not in the far space), neglect can appears also in the far space when the subjects used a tool to perform the task.
Methods: Fifteen right-handed healthy subjects executed a line length judgment task in two different spatial positions (60 cm: near space and 120 cm: far space), with or without rPPC on-line rTMS. In the far space condition, subjects performed the perceptual task while holding or not a tool.
Results: During rTMS, visuospatial performance significantly shifted toward right when the task was performed in the near space and in the far space when the tool was used. No significant effect was found when rTMS was delivered in the far space condition without tool use.
Conclusions: Our results demonstrate that the application of rTMS on rPPC, specifically affect the representation of near space because it caused neglect both when the subjects acted in the near space and when they acted in a far space that was remapped as near by the use of a tool

Introduction

Spatial neglect is a disorder characterized by a variable number of clinical symptoms that share the inability to pay attention and/or to appropriately respond to stimuli coming from the space contralateral to the lesion [1,2]. It can be caused by injuries, mostly acute, to both hemispheres, but only right hemisphere lesions can cause severe and persistent deficits [3]. According to the theory by Heilman and Van Del Abell [2], the right hemisphere controls the shift of attention in both sides of the space, while the left controls attention only to the right side. Another interpretative approach is represented by the theory of interhemispheric competition proposed by Kinsbourne [4]. According to this, each hemisphere drives attention to contralateral hemispace and a balance is obtained by reciprocal inhibition mediated by transcallosal fibers. In the complex interhemispheric balance at basis of spatial attention a relevant role is played also by cortico-subcortical connections linking parietal cortex and superior colliculus (SC) [5,6]. On such bases neglect occurs because the damage to one of the competing structures produces imbalance in spatial attention shifting it toward the ipsilesional hemispace [7]. Neglect follows more frequently to right side lesions because the rightward attentional vector driven by left hemisphere is normally slightly stronger than the right one. The commonest type of left hemineglect is associated with damage to the postero-inferior parietal areas [8] or to superior temporal gyrus [9] of the right hemisphere, even if a wide range of cortical or subcortical lesions are able to cause neglect [10].

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Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) are non-invasive brain stimulation (NIBS) technologies able to interact with the underlying cortical activity. According to stimulation parameters, repetitive TMS (rTMS) is able to transiently increase or decrease cortical activity of the stimulated areas, while tDCS acts as a weak constant direct current that hyperpolarizes (cathodal stimulation) or depolarizes (anodal stimulation) the underlying tissue [11,12].

Fierro et al. [13] showed that the disruption of the right posterior parietal cortex (P6) activity through high frequency rTMS or by timed single pulse TMS (150 ms after stimulus onset) [14] induced a significant rightward bias (virtual neglect) in a line bisection judgment task in healthy subjects. More recently, Giglia et al. [15] used dual tDCS stimulation over the same areas to induce neglect-like effects in healthy subjects. Also fMRI studies supported the activation of the right parietal lobe in healthy humans during line-bisection tasks in the near space [16–18].

Among the various clinical presentations of neglect syndrome a relevant dissociation concerns the different degree of visuospatial impairment in the near or peripersonal space (the space accessible with the excursion of the upper limb) as opposed to far or extrapersonal space (the space beyond the hand reaching) [19]. Halligan and Marshall [20], for instance, described patients with a right-hemisphere stroke, who showed left spatial neglect in the near but not in the far space, while opposite dissociations (more severe in the far than in the near space) were reported by other authors [21,22]. The hypothesis inferred from these observations is that there are two distinct neural systems for the representation of near and far space. Due to their characteristics, as mentioned above, NIBS techniques are the most suitable candidates able to answer to this question.

Indeed, in healthy subjects, application of functional imaging and TMS confirms the segregation of near and far space pathways. Weiss et al. [23] found an increased activity on PET in occipital dorsal and posterior parietal cortex (PPC) near the intraparietal sulcus (IPS) when subjects performed line bisection in the near space. The same line bisection task in extrapersonal space, caused activation of ventral occipital (VO) and medial temporal regions. First, Bjoertomt et al. [24] showed differential involvement of rVO and rPPC in visuospatial perception of near and far space in healthy subjects. Indeed, functional disruption of rPPC by rTMS induced rightward bias in perceptual line bisection task in the near but not in the far space while an opposite effect was obtained by rTMS over rVO. More recently, Lane et al. [25], briefly disrupting cortical activity through TMS, provided further evidence of a dissociation between dorsal and ventral circuits in processing of near and far space. According to the functional dissociation previously attributed to the two streams, results of the study revealed a double dissociation: rPPC was involved only in processing of near space, while rVO was necessary for the task in the far space. Moreover, very recently Mahayana et al. [26] showed that also medial part of PPC, the precuneus, is involved in the near space, thus confirming the anatomical segregation of near and far space networks.

Recent studies, have suggested that the use of tools can modulate the boundaries between peripersonal and extrapersonal space. Indeed, by using a stick to reach an object in the extrapersonal space, the peripersonal space becomes expanded to include the extrapersonal one. A remapping of the body schema for which the stick becomes an extension of the hand [27] has been observed in macaque. Similar findings have been reported in studies with brain-damaged patients. Berti and Frassinetti [19] reported the case of a right brain-damaged patient showing a dissociation between near and far space neglect. The patient showed neglect in the near space in the line bisection task, the neglect extended in the far space when patient performed the task by means of a stick that could reach the line. It appeared likely that the stick determined an extension of body representation, including in the peripersonal space all the space reachable by the tool so remapping far as near space. These data, together with more recent findings by Neppi-Mòdona et al. [28], suggest that space representations can be recoded when tools change the spatial relation between the agent's body and the target object.

Taking advantage of the previous discussed data, the aim of the present study was to investigate space remapping in healthy individuals. We examined whether the on-line high frequency rTMS, through disruption of right PPC activity along intraparietal sulcus known to be involved in the perception of the peripersonal space, also affects far space representation when the action to be performed in the far space was carried out while holding the tool. Bjoertomt et al. [24], have previously demonstrated the involvement of rPPC near space in a perceptual line bisection task. The present study extends these findings by exploring remodulation of far into near space when subjects use a tool that expands hand reaching. For this purpose, normal subjects underwent a line bisection judgment task in the near and far space with or without a tool, in baseline and during real or sham repetitive stimulation. The task employed does not rely on manual responses in a way that exclude any confound between perceptual and motor neglect.

Material and methods

We studied 15 right-handed normal volunteers (7 men; mean age 28.2 $\pm$ 6.3 S.D. years). All subjects underwent to an accurate medical history and to clinical neurological evaluation in order to exclude possible brain dysfunctions. We examined their performance on a computerized visuospatial task in baseline and during real or sham repetitive stimulation delivered on-line (during task performance) at various conditions and distances from the screen: at 60 cm (near space), 120 cm (far space) and 120 cm handing and pointing a stick to touch the screen (far space with a tool). Subjects were comfortably seated on a chair in front of a 15-inch 4:3 computer screen (33 cm wide and 25 cm high). The subject's seat was positioned so that eye level was at the middle of the display monitor that was centered on his/her sagittal midplane. The experimental procedure was conducted according to Helsinki Declaration, approved by the ethical committee and all subjects gave their informed consent to participate in the experiment.

Magnetic stimulation

We used a Cadwell high frequency magnetic stimulator with a figure of eight coil. rTMS was applied over the right PPC, at P6 location (according to 10–20 EEG system) likely close to IPS according with MRI evidence as in previous work [13]. The exact point of stimulation was obtained by the method of functional localization described by Oliver et al. [29] and named "Hunting paradigm." On each trial of near condition, either an unbroken horizontal line (10% of the lines) or a line with a 'gap' of 1.5 cm at the far left (90% of the lines) were shown. The lines were presented for 50 ms. The subjects were 60 cm away from the screen; they were instructed to keep their eyes fixed on the center of the screen indicated by fixation cross and to say their perception ('gap' or 'no gap') during rTMS. The coil position at the start of the experiment was EEG 10–20 position P6 in all subjects and it was moved with a spiral movement in .5 cm steps along a path which approximated a clockwise spiral drawn through the intersections of a square grid (4 cm $\times$ 4 cm, i.e. 2 cm between all nearest points in a 9 point grid). We delivered 5 stimuli at the frequency of 10 Hz and at the intensity of 110% of the resting motor threshold (MT), starting 100 ms before the visual task. The exact point of stimulation was that in which the

Figure 1. Visual stimuli presented to the subjects. For each stimulus, the subjects have to make a judgment on the length of the line if it is equally bisected, if it is longer on the right or left longer. Sizes used in the far space are inside parentheses. Line 1: right segment 75 (150) mm; 75 (150) mm left segment (exactly bisected); visual angle: 14.32. Line 2: right segment 70 (140) mm; left segment 75 (150) mm (longer on the left); visual angle: 13.85. Line 3: right segment 75 (150) mm; left segment 80 (160) mm (longer on the left); visual angle: 14.80. Line 4: right segment 75 (150) mm; left segment 70 (140) mm (longer on the right); visual angle: 13.85. Line 5: right segment 80 (160) mm; 75 (150) mm left segment (longer right); visual angle: 14.80.

subject did not see the gap 3 times on 5 tests. The Motor Threshold (MT) was determined as the minimum stimulus intensity able to elicit a MEP of 50 μV in the contralateral hand (in at least 3 out of 6 trials) [30].

Experimental paradigm

TMS was given on-line on the stimulation point: each stimulus train consisted in 10 stimuli delivered at the repetition frequency of 25 Hz for a stimulation time of 400 ms. [13]. Magnetic stimuli were delivered at an intensity of 10% above the MT. The train started 100 ms before presentation of the line on the screen; line lasted on the screen for 50 ms. Inter-train intervals were equal to 30 s. To control unspecific effects of rTMS we performed an ineffective, sham repetitive stimulation positioning the coil on the same stimulation point on the scalp. The sham control condition was identical to the real condition, except that for the position of the coil, which was perpendicular to the scalp. The settings of stimulus intensity, frequency, duration and interval of the trains were selected according to the guidelines for preventing intracortical spread of excitation [30].

Visual stimulation

Five lines were presented, differing in the position of the transector and in the overall length of the line (see legend of Fig. 1). Line's length and thickness were modified based on the viewing distance to keep the same retinal visual angle. Subjects were seated 60 or 120 cm from the screen. The computer-generated stimulus line was back-projected on a 15-inch 4:3 (33 cm wide and 25 cm high, 1024 × 768 resolution) computer translucent screen facing the subject; the room was darkened with the mean luminance of the screen kept constant across conditions.

Irrespective of the distance, the black horizontal transected lines had a mean length of 14.32° of visual angle (range 13.85–14.80°). A short dark vertical line (.95° long) transected the horizontal lines. All lines were .09° thick. In the test the horizontal lines was always presented such that the transection mark was at the sagittal midline of the subject and the horizontal line was at the eye level (Fig. 2).

Tachistoscopic stimulus presentation of 50 ms duration was used to prevent eye scanning. Before stimulus presentation the patient was required to fixate a central target (an upward pointing arrow), that disappeared as soon as the visual stimulus was flashed. After stimulus presentation the subject made a verbal forced-choice decision about the respective length of the two segments of the pre-bisected lines with three response possibilities: equal, longer right or longer left. Visual task was performed in tree conditions in separate sessions: near space (60 cm distance), far space (120 cm) and far space (120 cm) while holding a wooden stick

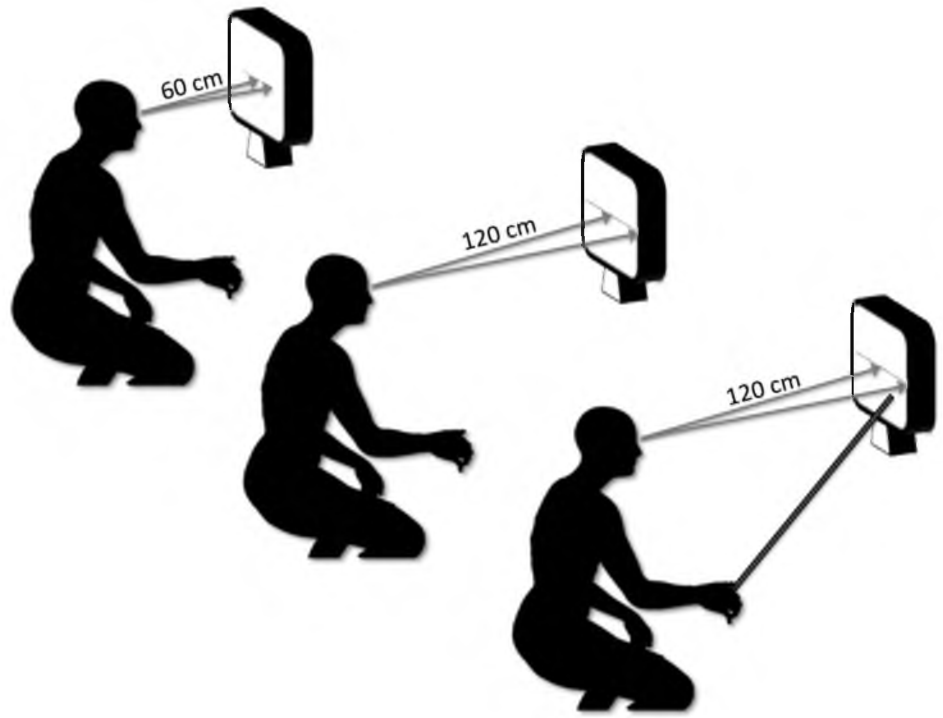

Figure 2. Graphical elaboration of the visual tasks performed in each condition.

(length: 120 cm) pointing to and touching the screen. Participants handled without moving the stick with their dominant hand. In each session subjects were given 2 blocks of 30 trials each in random order: 10 with lines centrally bisected, 10 with lines longer left and 10 with lines longer right. There was no time limit to perform the task. Whenever the participant gave the response, the experimenter marked it and the next trial started. The visual task conditions (near, far and far with stick) were explored in baseline and during real or sham rTMS in separate sessions with at least one-week interval. Each subject underwent 3 × 3 experimental sessions: 3 visual task conditions × 3 experimental conditions (baseline, sham or real rTMS). Order of visual task conditions and order of the experimental conditions were randomized.

Based on previous studies [13–15,31,32] the performance of the subjects on each trial was scored as follows: 0 = correct responses; 1 = right segment of line 1 judged longer, or left and right segments of lines 2 and 3 judged equal (left underevaluation); 2 = right segment of lines 2 and 3 judged longer (left underevaluation); −1 = left segment of line 1 judged longer, or left and right segments of lines 4 and 5 judged equal (right underevaluation); −2 = left segment of lines 4 and 5 judged longer (right underevaluation). Statistical analysis was performed using a repeated measures ANOVA test with significance level at $P < .05$.

Results

Subjects did not complain of any harmful effects of rTMS. Mean resting MT was: 63.6% ± 8.86. No evident eye movements or blinks that could have influenced the results (Figs. 2 and 3) were revealed by an observer throughout the experiment.

Because a repeated measures ANOVA comparing mean score of baseline and sham TMS with Condition (2 levels: baseline and sham) and Visual task (3 levels: near, far and far distance with stick) as within-subjects factors showed no significant main effects of Conditions [$F(1, 14) = 1.2549$, $P = .28147$] neither of interaction Condition X Visual task [$F(2, 28) = .31438$, $P = .73279$], data were pooled together in a no-TMS condition.

A repeated measures ANOVA on the mean score with Condition (2 levels: TMS and no-TMS) and Visual task (3 levels: near, far and far distance with stick) as within-subjects factors showed significant main effects of Conditions [$F(1, 14) = 9.4010$, $P = .00838$], and of Condition X Visual task interaction [$F(2, 28) = 10.186$, $P = .00047$]. Post-hoc analysis (Duncan's test) showed that in no-TMS condition the overestimation of the left segment of the line in the "near visual task" significantly reduced in the "far visual task," shifting back to the left when using the stick (near vs. far: $P < .0005$; far vs. far with stick: $P < .05$) (Fig. 3). In the TMS condition in far space while holding the stick, subjects showed a greater bias toward right, with respect to performances without stick, that approached significance at Duncan's post-hoc analysis (far vs. far with stick: $P = .052$). No other significant changes were observed in the TMS condition (near vs. far: $P = .06$; near vs. far with stick: $P = .7$).

During TMS, visuospatial performance significantly shifted toward right in the "near" and "far with stick" compared with no-TMS condition (near TMS vs. no-TMS: $P < .0005$; far with stick TMS vs. no-TMS: $P < .05$). TMS did not induce any significant change in visuospatial perception in the far space. Given that the no-TMS condition showed evident effects of the visual task, two separate analysis for baseline and sham conditions were performed, contrasting them with the TMS condition.

Repeated measures ANOVA comparing mean score in baseline vs. TMS, with Condition (2 levels: baseline and TMS) and Visual task (3 levels: near, far and far distance with stick) as within-subjects factors showed significant main effects of Conditions [$F(1, 14) = 7.1332$, $P = .01827$], and of interaction Condition X Visual Task [$F(2, 28) = 6.8879$, $P = .00369$]. Duncan's Post-hoc analysis showed that TMS induced significant changes with respect to baseline in visual task conditions: near: ($P < .005$) and far with stick ($P < .05$) while no differences between baseline and TMS emerged for the performance in far space without stick ($P = .1$). In the baseline condition, among visual tasks, Duncan's post-hoc analysis showed: near vs. far: ($P < .05$); near vs. far with stick: ($P = .3$); far vs. far with stick: ($P < .05$).

Repeated measures ANOVA comparing mean score in sham vs. TMS, with Condition (2 levels: sham and TMS) and Visual task (3 levels: near, far and far distance with stick) as within-subjects factors didn't show significant main effects of Conditions [$F(1, 14) = 4.0783$, $P = .06301$], but showed a significant main effects of interaction Condition X Visual Task [$F(2, 28) = 8.5579$, $P = .00126$]. Duncan's Post-hoc analysis showed a significant difference in the visual task "near" between TMS and baseline conditions (near TMS vs. near sham: $P < .005$; far TMS vs. far baseline: $P = .06$; far with stick TMS vs. far with stick baseline: $P < .12$). In the sham condition, among visual tasks, Duncan's post-hoc analysis showed: near vs. far: ($P < .05$); near vs. far with stick: ($P < .05$); far vs. far with stick: ($P < .1$).

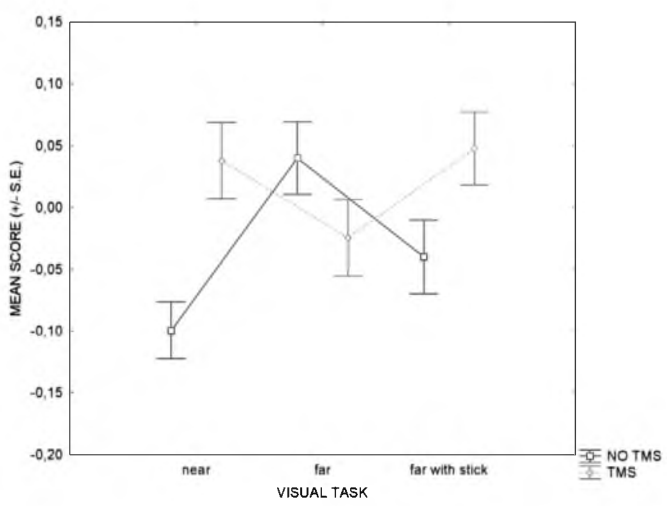

Figure 3. ANOVA comparing mean values of scores in TMS and no-TMS conditions. Vertical bars indicate standard errors (SE).

Discussion and conclusions

The aim of the present experiment was to study space coding in normal individuals through transient inhibition of PPC area, in different experimental conditions. In particular we wanted to see whether tool use could affect space representation so consistently that when near space circuits are inhibited by rTMS causing neglect in the near space, neglect also appears when stimuli are located in the far space but tool use affects space remapping.

First, our results in baseline condition are in agreement with previous findings [24,33,34] showing modulatory changes in visuospatial performance that depend on the space in which the subject performs the task (near vs. far) and on the use of the tool. Indeed, in the near space we observed a slight attentional bias toward left (pseudoneglect) that shifted toward right when the task was performed in the far space but moved back again to the left when the subject uses the tool, this latter point supporting the ability of the tool to remap far-into near space. Moreover we replicated previous findings, namely rTMS stimulation over the right intraparietal sulcus induced a transitory rightward bias in line bisection judgment task when lines were presented in the near space [13,24,35] but not in the far space [24]. The novel data of the present work concern the use of a tool in performing the task in the far space: crucially, we found that during rTMS, the rightward attentional bias, absent when the subjects acted in the far space without tool, reappeared, as in the near space, when subjects performed judgments while holding a stick long enough to touch the screen. These results not only confirmed that there is a modulation of far and near space perception also in normal subjects, and that this perception can be affected by rPPC rTMS application, but also demonstrated that the use of the tool induces space remapping both when subjects acted without TMS stimulation and even when TMS induced a virtual neglect. Even if the difference between the TMS in far space with and without tool conditions was only approaching significance, the fact that TMS induced significant change in far space with respect to no rTMS only when subjects hold a stick, speaks in favor of a far into near space remapping by the tool.

The line bisection task has been used in several experimental settings to assess the isotropy of spatial attention distribution. Subjects affected by left neglect due to a right hemispheric lesion tend to perceive the left segment of an exactly bisected line as shorter and the right one as longer than their physical size [36]. On the contrary, the healthy population shows a perceptual bias through the left hemispace that seems to be related to a physiologic hemispheric imbalance in visuospatial attention control [4]. This phenomenon defined as "pseudoneglect" has been repetitively confirmed in metanalysis studies of bisection performance [2,37,38,39] and described to be present more in the peripersonal (within reaching) than in extrapersonal (beyond reaching) space [33,24]. According to such assumption, the results of our study showed, in no-TMS condition, the natural tendency to overestimate the left side of the pre-bisected lines in the near/peripersonal space (60 cm). When lines are placed outside of reach (far/extrapersonal space condition: 120 cm), the leftward bias reversed toward a rightward bias but pseudoneglect, however, reappeared in the far space when subject used the tool. In line with previous works [13,14,31,32,40], the TMS over the right PPC was able to disrupt its activity so inducing virtual neglect in the near space.

In this study, the new result refers to the ability of rTMS to cause a virtual neglect also when the subjects judge lines in the far space when using the stick. The changes in spatial bias depending on the use of tool, in both conditions with and without rTMS, demonstrate that the tool can act by determining a remapping of far into near space. The use of tool may extend the peripersonal space to the extrapersonal one, thus filling the sensory gap between the subject's body and the far target object. According to Berti and Frassinetti [18], the limit between peripersonal and extrapersonal space is not fixed but dynamic, as an object in the far space can be brought into the 'reaching space' by use of the tool. Longo and Lourenco [34] showed a similar remapping of far into near space in healthy subjects performing a line bisection tasks at distances ranging from .3 m to 1.2 m. The pseudoneglect phenomenon was present in the near space, while a rightward bias was observed in the far space when a laser pointer was used to bisect lines. On the other hand, the leftward bias was again seen for both viewing distances when subjects used a stick. Furthermore, it is also known that the near space limit can be "shrinked" adding weights to the arms of participants during pointing [41].

Many studies [27,42–45] in humans and animals showed that the repeated manipulations of a stick to reach distant objects may change the neural representation of the body schema, so to include the tool as an elongated hand [46]. Electrophysiological studies by Iriki et al. [27] showed that in monkeys using a rake the bimodal visual-tactile neurons enlarged their receptive fields up to include all the space reachable by the tool. In agreement with these findings, changes in neural activity were observed in imaging studies during tool use in the far space in both monkeys [45] and humans [41]. Transient disruption of the right parietal cortex induced in healthy subjects by rTMS was found to affect visuospatial behavior and the effect was viewing-distance specific [24,47]. One hypothesized role for the right posterior parietal cortex (rPPC) is the coding and processing of visuospatial attention [48]. A distinction has been drawn between ventral PPC, which is part of the temporo-parietal junction (TPJ) involved in the perception of far space, and dorsal PPC areas along the intraparietal sulcus, involved in the perception of near space (e.g. [49]). The dissociation we found in visuospatial performance between near and far space during rTMS supports the contention that there is a dorsal/near and a ventral/far space relatively independent segregation of processing in the visual system [50]. In line with this view, one can argue that our TMS stimulation could have targeted the dorsal stream component of PPC areas along the intraparietal sulcus involved in the perception of near space (e.g. [49]).

It is worth noting that a common concern with TMS experiments is the very low spatial resolution and, given the spread of current following a TMS pulse [51], the exact site of stimulation. Although in our study we did not use a neuronavigation system, based on coordinates used in previous work [13], and on the application of the "hunting paradigm" [29] we are confident to have targeted the right anterior intraparietal sulcus. Very recently TMS has been used to investigate the role of this area in cognitive control [52]. The authors found that interference of IPS is able to disrupt the capacity to switch between different action rules within a given task. However, we are confident that our experiment required a very low cognitive control as the visual task conditions (near, far, far with stick) where clearly separated and presented in random order, thus excluding a different weight of switch cost in each condition.

It is interesting to observe that, in our study, we found near/far visuospatial processes dissociation by using a purely perceptual task for both distances. The finding that the rPPC was involved in purely perceptual conjunction search without any motor demands within the near space has been reported by Lane et al. [47] and is in line with previous reports [22,50,53]. This finding seems to confirm the role of rPPC in representing the actionable space, although any apparent motor action was requested. Objects located outside the reaching distance can be brought into reachable space using a rake and so processed by dorsal stream mechanisms [27].

More recently, in an fMRI study, Tomasino et al. [54] by using only imagined movements, showed that IPS may be modulated during motor imagery of tool use [55], as well as during actual execution in the far space [27,44,45,56].

In conclusion, our study demonstrate that space representation is dynamically modulated by the position of the target in space and by the use of tool. Moreover, the evidence that rTMS stimulation on PPC, causing neglect both when the subject acted in the near space and in the far space with a tool that remapped far space into near, strongly supports the idea that PPC is a fundamental component of near space coding.

A possible pitfall of TMS studies on visual attention can be the TMS-induced eye blinking, when stimulating posterior parietal cortices [57]. In the present study, we used tachistoscopic task just to prevent eye scanning and tried to avoid eye-blink chance by adjusting coil rotation on each subject. It should be noticed that no eye movements were experienced by subjects or observed by the examiner who monitored the subjects during TMS stimulation. It is worth noting that even if they had been present, they would have an effect across both distance conditions. Moreover the presented stimuli subtended the same visual angle in both near and far condition, making us confident that the effects can be considered comparable across each condition by excluding differences in search area, salience, or item density, known to affect performances in both healthy subjects and negligent patients [58].

Sham stimulation in all three conditions of visual task (near, far and far with stick) did not modify the performance obtained in baseline condition. The lack of evident effects of sham stimulation seems to exclude unspecific effect of TMS unrelated to direct cortical stimulation. Moreover, the absence of significant changes during sham stimulation would also exclude a possible improvement of performance due to learning.

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