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The Precuneus and Visuospatial Attention in Near and far Space: A Transcranial Magnetic Stimulation Study

Indra T. Mahayana [a], Lili Tcheang [b], Chiao-Yun Chen [c], Chi-Hung Juan [a], Neil G. Muggleton [a,b,d,*]

[a] Institute of Cognitive Neuroscience, National Central University, Jhongli 320, Taiwan
[b] Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London, UK
[c] Department and Graduate Institute of Criminology, National Chung Cheng University, Chiayi, Taiwan
[d] Department of Psychology, Goldsmiths, University of London, New Cross, London, UK

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Background: There is a large body of evidence for the involvement of the parietal cortex in orientation and navigation in space. This has been supplemented by investigation of the contribution of a number of subregions using transcranial magnetic stimulation.

Objective: The role of the precuneus area, located in the medial plane of posterior parietal cortex (PPC), in visuospatial functions is not well understood. We investigated the contribution of this area using the landmark task.

Methods: Participants were asked to make forced-choice judgments of which side of prebisected line was longer for near and far viewing conditions (70 and 180 cm, respectively). Online 10 Hz, repetitive transcranial magnetic stimulation (rTMS) was delivered for 500 ms over the right precuneus, rPPC and vertex (control), in separate blocks of trials. The rPPC stimulation was used as a positive control, having previously resulted in "neglect like" spatial bias effects in a number of studies.

Results: A no-TMS condition showed a leftward spatial bias (pseudoneglect) for near space judgments but not for far space and was used as the baseline. Precuneus stimulation resulted in rightward spatial bias from the midpoint in near space similar to the rPPC neglect-like effect. No significant effects were seen with vertex stimulation.

Conclusion: This study shows that precuneus, like other parietal areas, is involved in visuospatial functions. Further work is required to clarify how the contribution of this area differs from other parietal regions.

Introduction

The function of the precuneus, or the posterior medial parietal cortex, has been the subject of relatively little investigation compared to other parietal regions. Its 'hidden' location might explain the lack of virtual lesion studies using neurodisruptive techniques and make this area less accurately mapped. It is located in the medial aspect of the posterior parietal lobe, in front of the triangular-shaped cuneus or the medial surface of the occipital lobe, and is limited by the medial portion of the parieto-occipital fissure. It is limited anteriorly and inferiorly by the marginal branch of the cingulate sulcus and subparietal sulcus, respectively [1,2].

Macaque monkeys studies have shown the precuneus to have connections to the inferior and superior parietal lobules and the intra-parietal sulcus (IPS), areas involved in visuospatial information processing [3]. It is also described as part of the *parietofrontal* network involved in control of reaching to visual targets [4] with selective connections to the dorsal portion of the frontal eye fields [5]. Furthermore, Johnson et al. [4] described evidence of a visuospatial function for precuneus, observed when the signals for visuospatial events were encountered more frequently in the ventral part of the precuneus, whereas the movement and position-related signal were distributed only within the superior parietal lobule (SPL).

In humans, the precuneus has been ascribed a role in a wide spectrum of highly integrated tasks, including visuospatial imagery, episodic memory retrieval and self-processing operations [1,2,6–11]. A resting state fMRI connectivity experiment by Zhang and Li [12] found that the dorsal precuneus showed greater connectivity with occipital and posterior parietal cortices and was also connected with areas involved in motor execution/attention and motor/visual imagery. Using positron emission tomography (PET),

* Corresponding author. Institute of Cognitive Neuroscience, National Central University, No. 300, Jhongda Rd, Jhongli City, Taoyuan County 32001, Taiwan. Tel.: +886 3 4227151x65200; fax: +886 3 4263502.
E-mail addresses: neil.muggleton@gmail.com, tri.mahayana@gmail.com (N.G. Muggleton).

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Bonda et al. [13] found significant cerebral blood flow changes in the precuneus during tasks involving spatial information about the direction of movements in an imaginary field. An fMRI experiment by Rao et al. [14] demonstrated that spatial location information activated both the angular gyrus and precuneus in the dorsal network, neither of which were involved in form discrimination. An indication of visuospatial involvement of precuneus was also described by the fMRI study by Simon et al. [15], in which they found that right precuneus activation was seen in a saccade and attention task, with greater activation for attention.

Several clinical studies have suggested the precuneus can be involved in the pathogenesis of spatial deficit conditions. In a meta-analysis across groups showing spatial neglect, precuneus damage was associated consistently with spatial neglect symptoms [16]. Precuneus has also been shown to have an important role in the improvement of patients with post-stroke visuospatial deficits, being associated with increases of neural activity during an fMRI spatial attention task bilaterally in conjunction with the middle frontal gyrus [17]. Specifically, after alertness training, the improvements in the neglect tasks were accompanied with an increase of precuneus activity as well as other right hemisphere areas such as frontal cortex, anterior cingulate cortex and angular gyrus [18]. Furthermore, in optic ataxia post-stroke patients, Karnath and Perenin [19] found parietal lesion overlap extended to the medial cortical aspect, where it affected the precuneus close to the occipito-parietal junction.

Visuospatial attention is needed not only when observing a space based on the left or right egocentric framework but also relates to the mechanism involved in calculating the spatial location based on egocentric distance, i.e. near and far space [20]. Visuospatial attention in near versus far space may have differential neural representations as task performance in near space is thought to draw differentially on the dorsal visuomotor processing stream with performance in far space drawing more on the ventral visuoperceptual stream [21,22]. Posterior parietal cortex (PPC) has been shown to have important role in visuomotor transformation behavior [23], meaning involvement of PPC may be more prominent in near space since the stimuli are within arm's reach. However the role of the medial surface of PPC, the precuneus, in the visuospatial attention mechanisms in near and far space is not yet well investigated, although it would be predicted that it may be more important for near than far space [4].

To test the visuospatial role of precuneus, we used a visuospatial task which has widely been employed in the clinical assessment of spatial neglect, the line bisection task [24]. This task presents an objective horizontal line that the patient is asked to bisect, indicating to the experimenter where their subjective line center is. A recent study by Andrade et al. [25] found that posterior cortical patients showed shifts in line bisection that correlated with hypoperfusion in the parietofrontal region. Importantly, patients with visual neglect syndrome also tend to show a rightward deviation of the subjective midpoint [26,27], and in most cases neglect patients see the left half of a centrally bisected horizontal line as shorter than the right.

Smaller and equally consistent errors of perceptual judgment are made by normal subjects, generally erring to the left of the veridical center when bisecting horizontal lines and termed *pseudoneglect* [28]. A "*neglect-like*" effect can also be produced by temporary disruption using TMS, which can reverse the pseudoneglect seen in healthy subjects into a rightward bias. This effect behaviorally mimics what can be seen in right hemisphere stroke patients. Several TMS studies have used experimentally induced spatial deficits in healthy subjects by applying TMS over right posterior parietal cortex (rPPC) [29,30] to, for example, explore the spatial role of posterior parietal cortex using repetitive TMS [31,32]. Using a landmark task, Oliveri et al. [33] showed that transient disruption of parietal regions of the unaffected hemisphere induced by focal repetitive TMS can temporarily reduce contralesional visuospatial deficits in both right and left brain damaged patients with contralesional neglect. Similarly, but using transcranial direct current stimulation (tDCS), Giglia et al. [34] also found *neglect-like* effects following dual electrode (cathodal electrode over the right PPC, and anodal electrode over the left PPC) and cathodal tDCS, by changed the lateralization bias to the right.

In the present study, in order to investigate the relationship between the precuneus and visuospatial processes, we studied the effect of repetitive TMS over right precuneus using a landmark task presented in near and far space. In the clinical setting, patients generally perform this task by manually bisecting a line drawn on paper. In the present study we used a forced-choice comparison of the length of the two segments of prebisected horizontal lines (the landmark task). We hypothesized that right precuneus TMS effect would produce a similar rightward bias in the landmark task as PPC-TMS. If the results were in line with this prediction, precuneus, like the lateral posterior parietal cortex, may be involved in the control of visuospatial function.

Materials and methods

Subjects

Fifteen participants (5 females, mean age: 23.0 $\pm$ 2.2 years) with no previous history of neurological problems, all with normal or corrected to normal vision, and without colorblindness participated in the experiment. All participants were naïve regarding the experimental task and gave informed consent prior to participation. The experiment was approved by the local ethics committee.

Apparatus

Stimuli in the near space condition were presented on a 19 inch CRT monitor with a 100 Hz refresh rate, and stimuli in the far space condition were presented by LCD projector onto a black wall. The luminance of both the monitor and the LCD projector were matched at 29 cd/m^2 and presented in the same dimly lit room. All stimuli presented were generated by an Intel-core i7 PC and were programmed using E-Prime (Psychology Software Tools Inc., Pittsburgh, PA). Subjects were seated comfortably either 70 or 180 cm away from the display with the center of the screen at eye level for both the near and far conditions. Head position was controlled with a chinrest.

Each participant's head was co-registered with his or her own T1 MRI brain scan using BrainSight™ frameless stereotaxic software (Rogue Research, Montreal, Quebec, Canada) to confirm the anatomical locus of stimulation. A Magstim Super-Rapid Stimulator (Magstim Co., Whitland, Dyfed, UK) was used to deliver the magnetic stimulation.

Stimuli and design

In each trial, the stimulus was a prebisected horizontal line with three types of such transected lines displayed in a block of trials, differing in the position of the transection: symmetrically bisected lines, right elongated lines, and left elongated lines (see Fig. 1A). The paradigm was a modified version of that used by Bjoertomt et al. [35] previously, with the lines used being similar with the exception that they averaged 19° in length (with a range of 18–20°) of length rather than 38° (with a range of 36–40°). The length of the vertical bisecting lines was 1.1° and all types of lines had a thickness of .1°. In the right and left elongated lines, the elongated segment was .5° longer than the shorter segment. All the stimuli were presented at

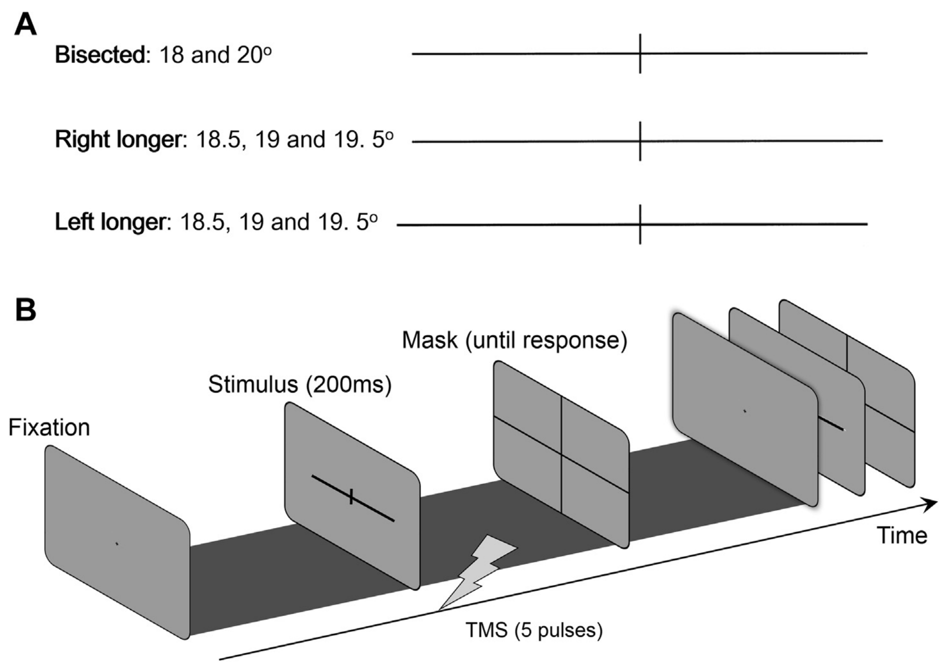

Figure 1. A. The prebisected line types and characteristics. B. The experimental procedure. A fixation was followed by presentation of a prebisected line stimulus and was masked after 200 ms, TMS pulses were delivered concurrent with the beginning of the stimulus presentation.

the eye level of the subject with the vertical bisecting line always presented at the midline of the screen and the horizontal lines at the mid-vertical of the screen. The lines were followed by a mask, which was also horizontal bisected by a vertical line in the midline, with the length of the two horizontal lines extended to the edges of the display. The configuration of the lines were set in both the near and far conditions such that they were the same in terms of degrees of visual angle.

In the current study, the distance was set at 70 cm away from the participant for near space and 180 cm for far space. The near space criterion fitted with previous research that defines it as within reaching distance [21,36]. The far space distance was in line with studies by Pitzalis et al. [37] and Lane et al. [20] which used distances of 160 and 172 cm, respectively.

Procedure

A trial consisted of a fixation cross (500 ms) followed by presentation of the prebisected line (200 ms) which was then masked until a response was made (see Fig. 1B). The train of TMS pulses began concurrent with presentation of the prebisected line. In each trial, subjects were asked to make one of two judgments, "Which side is longer, right or left?" or "Which side is shorter, right or left?" by pressing the corresponding keys with index and middle fingers of the right hand for the left and right judgments response, respectively. The stimuli were blocked according to their instruction (all "longer" judgments were made together and all "shorter" judgments were made together). Each instruction was tested in separate blocks of trials in counterbalanced order with adequate practice given for each.

The near and far space sessions were carried out in on separate days with at least 7 days between sessions and the order counterbalanced across subjects. In a session, there were 4 conditions, the right precuneus, rPPC, and vertex TMS conditions as well as a no-TMS condition. The rPPC TMS condition was used as a positive control of the "neglect like" spatial bias effect shown by Bjoertomt et al. [35]. The vertex condition served as a control site for non-specific effects of TMS such as noise (the click of the TMS coil when stimulation is delivered) and tactile sensations over the scalp and served as the negative control. The no-TMS condition was used as a baseline of the participants' performance. Therefore, we predicted that neither vertex nor no-TMS conditions would produce any significant effect on performance. The order of the TMS (precuneus, rPPC, and vertex) and no-TMS conditions were randomly assigned to subjects. For each condition, the subject had to finish 4 blocks of each of the two instruction types ("longer" or "shorter" judgments) in a counterbalanced order with a block of trials consisting of 32 trials.

rTMS procedure and site localization

rTMS procedure

Repetitive TMS was delivered during experimental sessions using a Magstim Super Rapid stimulator connected to a 70 mm figure-of-eight coil. The use of a figure-of-8 coil allows relatively focal stimulation of cortical regions [38,39] and is unlikely to result in any interference by magnetic stimulation even in areas relatively close to the target site. Each event-related train of rTMS comprised a 10 Hz, five-pulse delivery (500 ms in duration). A fixed stimulus intensity of 60% of machine output was used as previous studies have shown both that TMS is able to evoke clear responses at such intensities [40] and that there is little correlation between motor thresholds and visual cortex excitability [41].

Site localization

For all subjects, their T1 anatomical brain MRI image (which had previously been obtained) was used in conjunction with Brainsight™ neuronavigation software to localize the stimulation sites. The rPPC coordinates (*Talairach* coordinates: 42/−58/52) were taken from those used in previous TMS studies [29,35,42]. Due to a lack of neurostimulation studies investigating the precuneus, the coordinates for this site (*Talairach* coordinates: 15/−68/37) were taken from an fMRI study of spatial neglect patients by Thimm et al. [18] (see Fig. 2).

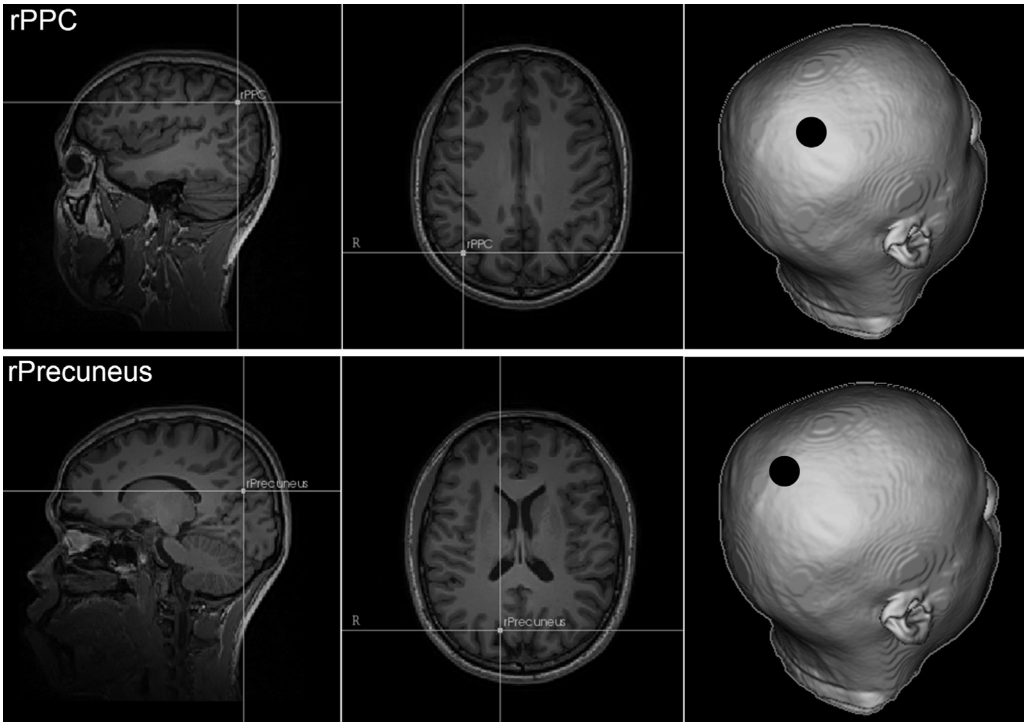

Figure 2. The coordinates of rPPC (42/-58/52, *Talairach* coordinate) and right precuneus (15/-68/37, *Talairach* coordinate) with the respective TMS coil positions (black dots).

The coordinates were transformed into the Brainsight coordinate system using the FSL software package (FMRIB, Oxford Centre for Functional MRI of the Brain, University of Oxford, Oxford, UK) and entered directly to the Brainsight™ software. Subjects were then co-registered with their structural scans using readily identifiable points on the head (nose-bridge and tip, intertragal notches of the ears) and the points on the surface of the head overlying the sites of interest were marked on a Lycra swimming cap worn by participants. To localize the vertex, the point midway between the intertragal notches and midway between the nasion and inion was measured.

Data analysis

Accuracy analysis

All accuracy data were analyzed in terms of the proportion of judgments where right was perceived to be longer. First, for the no-TMS condition a 2-way repeated measures ANOVA was employed with factors of distance (near and far) and line types (right elongated line, bisected line and left elongated line) with *post-hoc* tests of paired samples *t*-tests to analyze the effect of distance (near vs far) for each line type where appropriate to investigate baseline performance on the task.

For analysis of TMS effects, the values for the no-TMS condition served as the perceived midpoint baseline and the accuracy from rPPC, Precuneus, and Vertex TMS conditions were normalized against this baseline. For the bisected line (where it was not possible to make correct responses), the normalized values were analyzed with a 2-way repeated measures ANOVA with factors of site (rPPC, Precuneus, and Vertex) and distance (near and far viewing distance) and followed by one sample *t*-tests to test whether the midpoint shift of each mean was significant. For the right and left elongated line (where correct responses were possible), the normalized values were analyzed with a 3-way repeated measures ANOVA with factors of line (right and left elongated), site (rPPC, Precuneus, and Vertex) and distance (near and far).

Reaction time (RT) analysis

For the reaction time analysis (RT), data were grouped for elongated line analysis (mean correct RT of right elongated vs left elongated) and bisected line analysis (mean RT for left vs right judgments). The data were entered into a 3-way repeated measures ANOVA with factors of site (rPPC, Precuneus, Vertex and No-TMS), distance (near and far viewing distance) and side (left vs right).

Results

Accuracy analysis

In the No-TMS condition, the two way ANOVA revealed a significant interaction of distance and line ($F(2,28) = 6.893$, $P = .004$) as well as a significant main effect of distance ($F(1,14) = 14.910$, $P = .002$) and a significant main effect of line type ($F(2,28) = 400.189$, $P < .001$). For the bisected line condition, a significant leftward bias, a pseudoneglect effect, was seen in the near space condition (one sample *t*-test: $t(14) = -3.828$, $P = .002$) and this differed significantly from the far space condition (near vs far: $t(14) = -4.438$, $P = .001$). This effect was not observed in the right elongated and left elongated conditions ($t(14) = -1.290$, $P = .218$; and $t(14) = -1.824$, $P = .090$, respectively) (see Fig. 3). This leftward shifted perceived midpoint was the baseline for the accuracy analyses for the stimulation condition. Using the same analysis method, the vertex condition also showed similar significant leftward biased effect in the bisected line condition (one sample *t*-test: $t(14) = -2.574$, $P = .022$, distance main effect: $F(1,14) = 4.120$, $P = .062$, line main effect: $F(1,14) = 339.698$, $P < 001$).

In the normalized (perceived midpoint as the baseline) accuracy analysis for rPPC, Precuneus, and Vertex, in the bisected line condition, the ANOVA revealed no significant interaction ($F(2,28) = .123$, $P = .885$) with a significant main effect of distance ($F(1,14) = 7.353$, $P = .017$) and site ($F(2,28) = 3.731$, $P = .037$) suggesting the effect of site was the similar for both distances. One

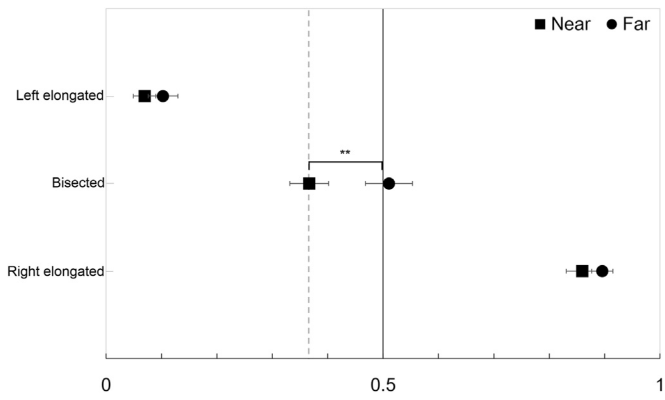

Figure 3. No-TMS condition accuracy analyses (proportion where right was perceived to be longer). Solid vertical line: midpoint: dashed gray line: perceived midpoint; **$P < .01$; error bars: standard error of the mean [SEM].

sample *t*-tests then showed a significant rightward midpoint shift in near space for precuneus ($t(14) = -2.837$, $P = .013$) similar to those observed in near space for rPPC ($t(14) = 3.332$, $P = .005$). No significant change was seen for the vertex condition ($t(14) = 1.866$, $P = .083$) (see Fig. 4). This rightward shift was a reverse of the pseudoneglect effect, i.e. a *neglect-like* effect. These results suggest that TMS over precuneus induces a *neglect-like* effect similar to that produced by rPPC in near space.

In the right and left elongated line conditions, 3 way ANOVA showed no significant 3-way interaction (line vs site vs distance: $F(2,28) = .979$, $P = .388$) as well as no significant 2-way interaction (line vs site: $F(2,28) = 1.450$, $P = .252$; line vs distance: $F(1,14) = .763$, $P = .397$; site vs distance: $F(2,28) = .472$, $P = .629$) and no main effects (line: $F(1,14) = .411$, $P = .532$; site: $F(2,28) = .031$, $P = .970$); distance: $F(1,14) = 1.325$, $P = .269$).

Reaction time (RT) analyses

In the elongated line analyses, the 3-way ANOVA revealed no significant interactions but a significant main effect of site ($F(3,42) = 2.942$, $P = .044$) was seen. *Post-hoc* Bonferroni adjusted pairwise comparisons revealed no significant differences. For the bisected line, there were no significant main effects or interactions. This lack of an RT effect on the line bisection task was in line with the previous study by Bjoertomt et al. [35] which found no significant effects on any line type in near or far space.

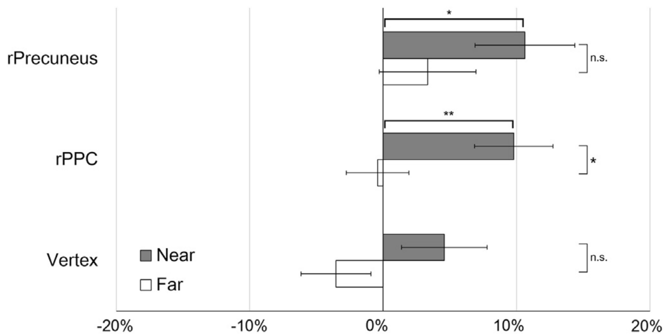

Figure 4. Normalized accuracy (perceived midpoint) in bisected line condition in near and far space viewing distances (0%: perceived midpoint from No-TMS accuracy analysis, positive values indicated rightward shift and negative values indicated leftward bias; *$P < .05$; **$P < .01$; error bars: SEM).

Discussion

The precuneus has been proposed to play a crucial role in higher cognitive control but little is known about its specific role in the visuospatial attention. The present study aimed to examine this possible role using TMS. TMS has already successfully been used to mimic the behavioral deficits following brain lesions [32] and permits causal inferences concerning the relationship between brain and behavior [43,44].

In control conditions for a line bisection task we found a leftward perceived midpoint shift (the pseudoneglect effect) in near space for both no-TMS and vertex stimulation, showing the bias in normal subject's perceptual judgment [28,34,35,45,46]. Crucially, a rightward shift of this normal bias of perceptual judgments, a "*neglect-like*" effect, was found as a consequence of TMS delivered over precuneus, specifically for near space stimuli in a bisected line condition. This pattern was consistent with the effect of stimulation of the positive control site, the rPPC. The neglect-like effect shown with precuneus stimulation could be a consequence of disruption of the controlling of task-relevant information [47] and this being controlled by both the lateral PPC and the precuneus. Therefore, this study suggests that there is similar spatial control, at least in terms of spatial bias in the landmark task, for the lateral PPC and the precuneus (medial PPC) in visuospatial attention.

The shifts of behavioral spatial bias with rPPC TMS were in line with earlier TMS work employing the landmark task [35,48,49]. A combined TMS fMRI study by Ricci et al. [50] have also observed a rightward perceptual bias in the landmark task after TMS over rPPC and this was argued to be a consequence of right parietofrontal deactivations. In our study, the near space involvement of rPPC was also consistent with previous studies investigating the role of rPPC in near and far space [20,35] and precuneus-TMS revealed a comparable effect by showing an effect that reached significance in near but not far space. This near space role of precuneus showed that precuneus may also be involved in processing associated with the dorsal visuomotor processing stream. It remains to be clarified whether the two areas can be clearly dissociated in terms of neglect in far space. If so, this may due to the role of rPPC in processing peripheral spatial locations [29,42] or specific control in far space [42], although distinguishing rPPC and precuneus more clearly requires further investigation.

Patients with lesions in the parietal cortex exhibit reaching inaccuracies which are pronounced when they attempted to reach to remembered targets without the benefit of visual guidance [51]. PPC specifically processes information from extrastriate cortex to generate a response weighted transformation into the appropriate body coordinate system required to allow action in space [23,52] and this is represented unequally due to typical right hemisphere dominance [53]. In monkeys, the medial intra-parietal area (MIP) represents immediate extrapersonal space and is specialized for responding to stimuli within reaching distance and exhibits a range of response properties [54]. In humans, it is also known that the specific area of lateral PPC, the inferior parietal lobule (IPL) which is part of the '*ventro-dorsal*' attentional network stream, is necessary for action understanding and spatial perception [55]. The fiber tract patterns of IPL, by means of probabilistic tractography, show connections to posterior medial parietal cortex, specifically the medial part of SPL [56].

To our knowledge, there is a lack of studies that specifically investigate the explicit role of precuneus in spatial attention, but the activation patterns of precuneus in spatial neglect fMRI studies employing spatial tasks [16–19] suggest that precuneus is involved in this process. The patterns of brain activation also suggest the possible functional relationship between the lateral PPC and the precuneus in spatial control. For instance a study by Loayza et al. [57]

found that, during more consistent tactile spatial localizations, the brain regions activated were bilateral clusters of SPL, intra-parietal sulcus (IPS) and IPL and an unilateral cluster specifically only to the right precuneus. Furthermore, Sturm et al. [58] investigated distributed spatial attention, with stimuli appearing at unpredictable locations within both visual fields. A contrast between distributed and focused conditions revealed activation only in the right precuneus and bilateral SPL. In investigations of higher cognitive function, testing the linguistic processing of spatial relationships, specifically the recall of spatial linguistic information relative to two non-spatial recall conditions, a distinct dorsal parietal pattern of brain responses was seen, again predominantly in precuneus and SPL [59]. These precuneus activation patterns may suggest there is parallel function between precuneus and lateral PPC in the control of spatial attention. Consequently, our TMS experiment may provide initial causal evidence related to the role of precuneus.

In conclusion, precuneus is a substantial brain area in the medial aspect of the posterior parietal cortex but its function in spatial process and relationship with the lateral part of PPC is not yet well investigated. According to our knowledge, the present study is the first neurostimulation study that explicitly investigated the role of precuneus in spatial attention. This study may shed light on the role of precuneus in visuospatial attention and allow comparison with the seemingly closely related role of the lateral posterior parietal cortex. We demonstrated that precuneus together with lateral posterior parietal cortex may be involved in visuospatial attention and in the control of the dorsal attention network. Further work is required to clarify how the contribution of this area differs from other parietal regions.

Acknowledgments

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