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ORIGINAL ARTICLE

Individual susceptibility to TMS affirms the precuneal role in meta-memory upon recollection

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Abstract

A recent virtual-lesion study using inhibitory repetitive transcranial magnetic stimulation (rTMS) confirmed the causal behavioral relevance of the precuneus in the evaluation of one's own memory performance (aka mnemonic metacognition). This study's goal is to elucidate how these TMS-induced neuromodulatory effects might relate to the neural correlates and be modulated by individual anatomical profiles in relation to meta-memory. In a within-subjects design, we assessed the impact of 20-min rTMS over the precuneus, compared to the vertex, across three magnetic resonance imaging (MRI) neuro-profiles on 18 healthy subjects during a memory versus a perceptual task. Task-based functional MRI revealed that BOLD signal magnitude in the precuneus is associated with variation in individual meta-memory efficiency. Moreover, individuals with higher resting-state functional connectivity (rs-fcMRI) between the precuneus and the hippocampus, or smaller gray matter volume in the stimulated precuneal region exhibit considerably higher vulnerability to the TMS effect. These effects were not observed in the perceptual domain. Thus, we provide compelling evidence in outlining a possible circuit encompassing the precuneus and its mnemonic midbrain neighbor the hippocampus at the service of realizing our meta-awareness during memory recollection of episodic details.

Highlights

- TMS disrupts the correlation between BOLD activity and meta-memory ability.
- TMS effect is modulated by rs-fcMRI between precuneus and hippocampus.
- Individuals with greater precuneal gray matter volume more immune to TMS effect.

Keywords Transcranial magnetic stimulation · Magnetic resonance imaging · Posterior parietal cortex · Metacognition · Episodic memory

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Introduction

The ability to accurately monitor and evaluate one's own behavioral performance is a critical feature of our cognitive function. Recent studies have advanced our understanding of the neural underpinnings of metacognitive ability, mainly with a focus on the perception and memory domains. While ample neuroimaging and neuropsychological evidence from distinct modalities convergently point to the anterior prefrontal cortex (aPFC) being specifically related to perceptual metacognition, including white matter (WM) fiber tracking (Fleming et al. 2010), microstructural measures of WM concentration (Allen et al. 2017), gray matter (GM) volume (Fleming et al. 2010; McCurdy et al. 2013), task-related functional magnetic resonance imaging (fMRI) (Fleming et al. 2012; Hebart et al. 2016; Morales et al. 2018; Qiu et al. 2018), resting-state fMRI (Baird et al. 2013), neurophysiology (Kepecs et al. 2008; Middlebrooks and Sommer 2012), and lesion-based studies (Fleming et al. 2014; Rounis et al. 2010; Shekhar and Rahnev 2018), our understanding of the neural correlates of metacognition for memory is in contrast less conclusive.

Researchers have used a combination of objective memory task accuracy (usually from recognition or forced-choice tasks, known as type 1 tasks) and subsequent subjective confidence rating (type 2 tasks) to define successful decision-making (Fleming and Lau 2014), and have found that the memory-related signals and the confidence-related signals can diverge and might rely on two largely independent processes (Rutishauser et al. 2018). Neurally, other investigations have implicated the posterior parietal cortex in the subjective experiences and mnemonic metacognition of memory contents (Simons et al. 2010). Most notably, patients with lesions on the posterior parietal cortex tend to show less confidence in their source recollection even though their type 1 task appears to be executed as well as healthy controls (Ciaramelli et al. 2017; Simons et al. 2010), implying a critical role of the parietal cortex in mnemonic metacognition (Ye et al. 2018). It has also been shown that the medial parietal cortex was particularly activated during confidence rating in memory tasks (Chua et al. 2006; Morales et al. 2018).

Individual differences in mnemonic metacognition ability is correlated with resting-state connectivity between the aPFC and the right precuneus (Baird et al. 2013), as well as with variation in the volume of the precuneus (McCurdy et al. 2013). In a previous paper (Ye et al. 2018), we have confirmed the causal relevance of the precuneus in mnemonic metacognition via inhibiting the normal functioning of the precuneus temporarily with non-invasive low-frequency repetitive transcranial magnetic stimulation (1-Hz rTMS). However, we have not been able to characterize the individual neural variability affected by the neuromodulatory effects of the TMS on this critical region for this metacognitive process. Hence, here together with TMS, we used individual variability in both functional responses and structural data to elucidate the neural underpinnings of meta-memory.

Our experimental protocol utilized data from subjects' resting-state functional MRI, structural MRI, and two task-based functional MRI following stimulation on a target region, the precuneus, or a control region, the vertex. We analyzed the resting-state functional connectivity, voxel-based morphometry (VBM), and blood oxygen level-dependent (BOLD) activity by specifically comparing the putative effects of TMS on the precuneus with a control stimulation condition. Our results provided a comprehensive profile to characterize the neuromodulatory effects by the focal magnetic stimulation on the precuneus across subjects through the three different MRI analyses, and corroborated previous findings on the contribution made by the precuneus in supporting mnemonic metacognition (McCurdy et al. 2013; Ye et al. 2018).

Materials and methods

Participants

Participants were recruited from the student community of the East China Normal University and were compensated for their participation. Data came from 18 healthy adults (7 females; age 19–24 years). Each of them participated in two experiments, which refer to a memory experiment and a perceptual experiment. Each experiment included two TMS sessions, giving us a within-subjects comparison. A within-subjects TMS design gave us a statistically more powerful comparison than a between-subjects design. The number of participants was decided based on previous work adopting a similar experimental design (Wang et al. 2014). All participants had normal or corrected-to-normal vision, no reported history of neurological disease, no other contraindications for MRI or TMS, and all gave written informed consent. No subjects withdrew due to complications from the TMS procedures, and no negative treatment responses were observed.

Overview of study

Participants were first required to complete their 7-min resting-state fMRI scans acquisition in a separate session prior to the two sessions of main experiments (see below). In that pre-session, we also acquired their T1 structural images to prepare for subject-specific coordinates for stimulation site localization. The participants were then asked to complete two experimental sessions of a memory task. For each session of the memory part, participants needed to play one video game (encoding phase, out of MRI scanner), and received 20 min of rTMS (rTMS stimulation phase) before going to complete the memory retrieval task conducted in MRI scanner (memory retrieval phase). The chapters of the video game and the stimulation sites were counterbalanced across the two sessions (Fig. 1a). The same participants also participated in a perceptual experiment outside the scanner for task comparison purpose.

Stimuli

The stimuli were extracted from an action-adventure video game (Beyond: Two Souls, Quantic Dream, France; PlayStation 4 version, Sony Computer Entertainment.). The Participants played 14 chapters in total across two sessions: 7 in session 1 and then another 7 in session 2. These subject-specific videos were recorded and were used for extraction of still images in both sessions.

For the memory task, we selected still frames/images from the subject-specific recorded videos in which participants had played the day before. Each second in the video consisted of 29.97 static images. In each game-playing session, 240 pairs of images were extracted from the 7 chapters and were paired up for the task based on the following criteria: (1) the two images had to be extracted from either the same chapters or adjacent chapters (Within- vs. Across-chapter condition); (2) the temporal distance (TD) between the two images were matched between within- and across-chapter condition; (3) to maximize the range of TD, we first selected the second longest chapter of the video and determined the longest TD according to a power function

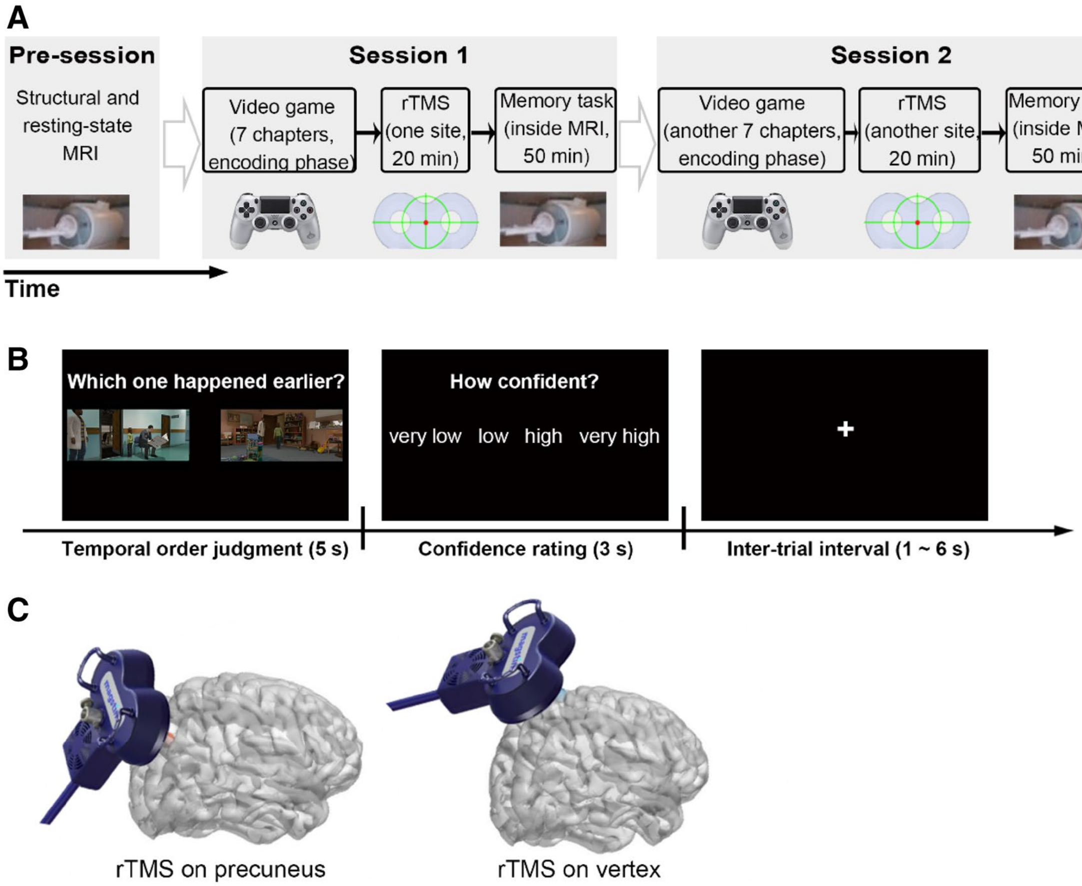

Fig. 1 **a** Memory experiment overview. Participants underwent structural and resting-state MRI scans during a pre-session. The main experiment consisted of two TMS sessions (session 1 and session 2). The two TMS sessions were conducted on different days to minimize rTMS carry-over effects (mean separation = 8 days). In both session 1 and session 2, participants played a video game containing seven related chapters on day 1; following a 24-hour retention period, they received 20 min of repetitive transcranial magnetic stimulation (rTMS) to either one of two cortical sites before performing a memory retrieval task during MRI. **b** Temporal-order memory retrieval task. Participants chose the image that happened earlier in the videoplay they had played and reported their confidence rating on how confident their judgment was correct, from very low to very high. **c** TMS to stimulation sites. Location of precuneus (target site, MNI coordinates: x, y, $z = 6, -70, 44$) is depicted with a red dot (left) and vertex with a blue dot (right)

(power = 1.5). We generated 60 progressive levels of TD among these pairs. For the perceptual task, we used the same set of subject-specific stimuli generated for the memory task to rule out any potential stimuli idiosyncrasy. The resolution of one of the paired images was changed using Python Imaging Library by resizing the image to modulate the pixel dimension; this modification of image resolution was conducted for an image-resolution comparison task (see below).

TMS: sites, protocol, and procedure

Repetitive transcranial magnetic stimulation (rTMS) was applied using a Magstim Rapid^2 magnetic stimulator connected with a 70-mm double air film coil (The Magstim Company, Ltd., Whitland, UK). The subject-specific structural T1 images were obtained and used in the Brainsight2.0 (Rogue Research Inc., Montreal, Canada), a neuronavigation system, coupled with infrared camera using a polaris optical tracking system (Northern Digital, Waterloo, Canada), to localize the target brain sites. Target stimulation sites were selected in the system by transformation of the Montreal Neurological Institute (MNI) coordinates to participant's native brain. The stimulation sites located in the precuneus at the MNI coordinates $x = 6$, $y = -70$, $z = 44$ (Kwok et al. 2012), and in a control area on the vertex, which was identified at the point of the same distance to the left and the right pre-auricular, and of the same distance to the nasion and the inion (Fig. 1c). In this study, we used a memory paradigm akin to the one reported in Kwok et al. (2012), who found a cluster of voxels activated by temporal-order memory retrieval in the precuneus. Considering several recent reports that the precuneus is involved in meta-memory processing (McCurdy et al. 2013; Morales et al. 2018), we, thus, specifically targeted at the peak voxel reported in Kwok et al. (2012) as the stimulation site coordinates to investigate the meta-cognitive component of episodic memory.

To prepare the subject-image registration and promote online processing of the neuronavigation system, four location information of each subject's head were obtained manually by touching fiducial points, which are the tip of the nose, the nasion, and the inter-tragal notch of each ear using an infrared pointer. In each session, rTMS was delivered to either the precuneus or vertex site before the participants engaged in performing the memory/perceptual tasks. Vertex stimulation is commonly used as a control site in memory tasks (Bonni et al. 2015; Yazar et al. 2017), and has little influence over fMRI BOLD signal (Jung et al. 2016). rTMS was applied at low frequency for a continuous duration of 20 min (1 Hz, 1200 pulses in total) at 110% of active motor threshold (MT). In determining the active MT, we instructed the subjects to extend their right hand fully in the air and maintain voluntary muscular contraction with their forearm and hand, while we delivered TMS over their motor cortex. The MT was defined as the lowest TMS intensity delivered over the motor cortex necessary to elicit visible twitches of the right index finger in at least 5 out of 10 consecutive pulses. The MT was measured prior to administering the stimulation (MT range: 57–80%; mean ± SD: 68.28% ± 6.19%). During stimulation, participants wore earplugs to attenuate the sound of the stimulating coil discharge. The coil was held to the scalp of the participant with a custom coil holder and the subject's head was propped with a comfortable position. Coil orientation was parallel to the midline with the handle pointing downward. Immediately after the 20 min of rTMS, subjects performed four blocks of memory retrieval task inside MRI scanner. This particular stimulation magnitude and protocols of rTMS (low-frequency stimulation of 1 Hz) are known to induce efficacious intracortical inhibitory effects for over 60 min (Iyer et al. 2003; Rossini et al. 2015). Given that each session of the memory/perceptual tasks lasted approximately 45 min, the TMS effects should have been long-lasting enough for the tasks. For safety reason and to avoid carry-over effects of rTMS across sessions, sessions 1 and 2 of both tasks were conducted on two separate days. The two TMS sessions were separated for a mean of 8 days and a mean of 3.9 days for the memory and perceptual experiments, respectively, allowing enough time for any residual TMS effects to subside.

Memory task (temporal-order judgment, TOJ), perceptual task (image-resolution judgment), and confidence ratings

The memory retrieval task required participants to choose the image that happened earlier in the video game they had played 1 day before (temporal-order judgment, TOJ). The memory retrieval task was administrated inside an MRI scanner, where visual stimuli were presented using E-prime 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA), as back-projected via a mirror system to the participant. Each trial started by a temporal-order judgment in 5 s, and immediately followed by a confidence judgment within 3 s. Participants performed the temporal-order judgment using their index and middle fingers of one of their hands via an MRI compatible five-button response keyboard (Sinorad, Shenzhen, China), and reported their confidence level ("Very Low", "Low", "High", or "Very High") regarding their own judgment of the correctness of the TOJ with four fingers (thumb was not used) of the other hand. The left/right hand response contingency was counterbalanced across participants. Participants were encouraged to report their confidence level in a relative way and make use of the whole confidence scale. Confidence judgments are one commonly used method for quantifying the sensitivity of self-reported confidence to objective discrimination performance under the signal detection theory (Maniscalco and Lau 2012). These confidence ratings will be used in our computation for metacognitive indices (see below). Following these judgments, a fixation cross with a variable duration (1–6 s) was presented (Fig. 1b). For either of the sessions, there was a practice block for participants to get familiar with the task before going into MRI scanner. In total, each participant completed 240 trials in either of the sessions (4 blocks × 60 trials).

The perceptual task required participants to choose the clearer (or blurrier, counter-balanced across participants) image among a pair of images on each trial. An identical confidence rating procedure as of the memory task was adopted immediately following each image-resolution comparison judgment. Each participant completed 240 perceptual discrimination trials in each of the two sessions.

MRI data acquisition

All the participants were scanned in a 3-Tesla Siemens Trio magnetic resonance imaging scanner using a 32-channel head coil (Siemens Medical Solutions, Erlangen, Germany). A total of 1350 fMRI volumes and 220 rs-fMRI volumes were acquired for each subject. The functional images were acquired with the following sequence: TR = 2000 ms, TE = 30 ms, field of view (FOV) = 230 × 230 mm, flip angle = 70°, voxel size = 3.6 × 3.6 × 4 mm, 33 slices, scan orientation parallel to AC–PC plane. High-resolution T1-weighted MPRAGE anatomy images were also acquired (TR = 2530 ms, TE = 2.34 ms, TI = 1100 ms, flip angle = 7°, FOV = 256 × 256 mm, 192 sagittal slices, 0.9 mm thickness, voxel size = 1 × 1 × 1 mm).

Data analysis

Behavioral data analysis

We evaluated the metacognitive ability by meta-d’ using both memory performance and confidence ratings data. Meta-d’ quantifies metacognitive sensitivity (the ability to discriminate between one’s own correct and incorrect judgments) in a signal detection theory (SDT) framework. Meta-d’ is widely used as a measure of metacognitive capacity and expressed in the same units as d’, so the type 2 sensitivity (meta-d’) can be compared with the type 1 sensitivity (d’) directly (Fleming and Lau 2014; Maniscalco and Lau 2012). If meta-d’ equals to d’, the participant makes confidence rating with maximum possible metacognitive sensitivity. If meta-d’ less than d’, the participant’s metacognitive sensitivity is suboptimal. Here, we calculated the logarithm of the ratio meta-d’/d’ (log *M*-ratio) for estimating the metacognitive efficiency (the level of metacognitive sensitivity given a particular level of performance capacity). The toolbox for the SDT-based meta-d’ estimation was available at http://www.columbia.edu/~bsm2105/type2sdt/. In short, here we measured metacognitive ability (also termed as metacognitive efficiency or accuracy) by computing the correspondence between trial-by-trial accuracy and one’s own confidence, rather than one’s own confidence *per se*.

To ensure that our results were not due to any idiosyncratic violation of the assumptions of SDT, we additionally calculated the phi coefficient index, which does not make these parametric assumptions (Fleming and Lau 2014). Rather, it evaluates how roughly “advantageously” each trial was assigned for high or low confidence based on performance in the preceding cognitive judgment, reflecting the association between the two binary variables (Miyamoto et al. 2017). The coefficient was calculated by the following equation using the number of trials classified in each case [n(case)]:

$$\text{phi coefficient } (\Phi) = \frac{n(\text{Correct High}) \times n(\text{Incorrect Low}) - n(\text{Correct Low}) \times n(\text{Incorrect High})}{\sqrt{n(\text{Correct}) \times n(\text{Incorrect}) \times n(\text{High}) \times n(\text{Low})}}.$$

Trials missing either one of the measures (memory: 2.9% of TOJ trials, 2.2% confidence rating; perception: 0.7% of perceptual trials) were excluded from the analyses. The 4-point confidence ratings were collapsed into two categories (high vs. low) for analyses.

Task-based fMRI data analysis

Preprocessing was conducted using SPM12 (http://www.fil.ion.ac.uk/spm). Scans were realigned to the middle EPI image. The structural image was co-registered to the mean functional image, and the parameters from the segmentation of the structural image were used to normalize the functional images that were resampled to 3 × 3 × 3 mm. The realigned normalized images were then smoothed with a Gaussian kernel of 8-mm full-width half-maximum (FWHM) to conform to the assumptions of random field theory and improve sensitivity for group analyses. Data were analyzed using general linear models as described below with a high-pass filter cutoff of 256 s and autoregressive AR(1) model correction for auto-correlation.

To identify brain areas in processing metacognitive information, we performed a contrast [(Correct_High–Correct_Low) > (Incorrect_High–Incorrect_Low)] at onsets of the memory phase with a duration of 5 s at single-subject level, including the following regressors: memory conditions (Correct, Incorrect, Miss) × confidence rating conditions

(High, Low, Miss). Each run consisted of six head realignment parameters and the run mean was included as parameter of no interest. These events were modeled with a canonical hemodynamic response function as an event-related response. To test the relationship between the BOLD response and the behavioral meta-memory index (log *M*-ratio) across subjects, single-subject contrast images were entered into a second-level random effects analysis using one-sample *t* tests with log *M*-ratio as a covariate separately for two TMS sessions (TMS-precuneus vs. TMS-vertex).

We extracted the parameter estimates from the individual first-level GLM analysis and then plotted the relationship between the parameter estimate and the behavioral index (log *M*-ratio) across subjects. The activation clusters were defined by the peak voxels at a threshold of $p < 0.001$ uncorrected at voxel level on the normalized structural images and labeled using the nomenclature of Talairach and Tournoux (1988). Only activation surviving multiple correction at the cluster-level FWE-corrected $p < 0.05$ threshold is reported. The anatomical mask used in the visualization was selected from the automated anatomical labeling (AAL) template using MarsBar version 0.44 software (http://marsbar.sourceforge.net/).

Resting-state functional connectivity analysis

A functional brain network was defined by a symmetric functional connectivity matrix $c = c(i,j)$, where each row(i)/column(j) of the matrix is a network node, and each matrix entry $c(i,j)$ is the weight of the network edge between node i and j. The connectivity matrices were obtained through a series of preprocessing steps on both rs-fMRI and T1 data, implemented in Python using a combination of fmriprep (Esteban et al. 2019), nipype (Gorgolewski et al. 2011) and networkx packages (https://networkx.github.io/).

T1 preprocessing consisted in correcting for bias field using N4 (Tustison et al. 2010), skull-stripping with ANTs (http://stnava.github.io/ANTs/), tissue segmentation into WM, GM and cerebral spinal fluid (CSF) with FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) FAST, and non-linear registration to MNI space with ANTs. FreeSurfer (https://surfer.nmr.mgh.harvard.edu/) was used to reconstruct the GM and WM surfaces of each subject using the brain mask previously calculated, and to parcellate the brain into 86 regions as per the Desikan–Killiany atlas.

Resting-state preprocessing consisted in slice-time corrections with AFNI (https://afni.nimh.nih.gov/) 3dTShift, motion corrections with FSL MCFLIRT, and registration to the subject native T1 volume with FreeSurfer boundary-based registration (using 9 degrees of freedom). ICA-based automatic removal of motion artifacts (AROMA) (Pruim et al. 2015) was then applied to estimate noise regressors, while physiological noise regressors were calculated from voxels in the WM and CSF masks computed previously. The data were smoothed with an 8-mm kernel excluding background voxels with FSL Susan toolbox and all the noise components regressed out using FSL regfilt. Finally, bandpass filtering between 0.008 and 0.08 Hz was implemented with AFNI. Linear detrending was included in the previous step by adding a linear sequence as additional regressor. The FreeSurfer atlas was resampled to resting-state resolution, and the connectivity matrix calculated from the correlation of the denoised signal between each pair of atlas regions. Finally, the connectivity matrix entries were Fisher transformed. To remove spurious edges while ensuring consistent edge density across subjects, a lenient wiring cost of 50% was applied to all connectivity matrices which, thus, had half the total number of possible edges.

The edge length $l(i,j)$ between two nodes was defined as the absolute inverse of the associated weight $c(i,j)$, so that strong (i.e., high) correlation corresponded to short (i.e., low) length. We investigated in each hemisphere the hippocampus–precuneus (HP) connectivity distance which was defined as the shortest path length between these two nodes (computed using Dijkstra's method) (Rubinov and Sporns 2010), that is the smallest sum of edge lengths among all the possible paths connecting them. The resulting HP connectivity distance was averaged across hemispheres.

Voxel-based morphometry (VBM) analysis

VBM preprocessing was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Following the similar protocol used in previous studies (Fleming et al. 2010; McCurdy et al. 2013), the structural images were first segmented into GM, WM and CSF in native space. For increasing the accuracy of inter-subject alignment, the GM images were aligned and wrapped to an iteratively improved template using DARTEL algorithm, while simultaneously aligning the WM images (Ashburner 2007). The DARTEL template was then normalized to MNI stereotactic space, and then GM images were modulated in a way that their local tissue volumes were preserved. Finally, images were smoothed using an 8-mm full-width at half-maximum isotropic Gaussian kernel.

The pre-processed images were analyzed in a multiple regression model to examine the relation between GM volume and difference in metacognitive efficiency between two TMS sessions (TMS-precuneus > TMS-vertex). Proportional scaling was used to account for volume variability in total intracranial volume across participants. A binary GM mask (> 0.3) was used to exclude clusters outside the brain and limit the search volume to voxels likely to contain GM.

We examined the positive and negative t-maps separately and identified clusters using an uncorrected threshold of $p < 0.001$ at voxel level. Following McCurdy et al. (2013)'s protocol, small-volume correction (SVC) was applied on a cluster of interest by centering a 10-mm sphere over the targeted site of stimulation in the precuneus (MNI: $x=6$, $y=-70$, $z=44$).

Results

Behavioral results

We first tested the hypothesis that TMS to the precuneus would reduce individual metacognitive ability in the memory task. Previous studies that have reported memory improvements following rTMS to the precuneus have typically employed relatively high frequency of stimulation (e.g., Bonni et al. (2015), three-pulse bursts at 50 Hz repeated every 200 ms; Koch et al. (2018), 40 trains of 2 s delivered at 20 Hz). In contrast, low-frequency stimulation set-up akin to the current protocols we have employed here can lead to memory reduction (e.g., Kraft et al. (2015), trains of 6 Hz for 333 ms), presumably via inducing intracortical inhibitory effects (Chen and Seitz 2001). With this a priori prediction, we hypothesized for an impairment in the cognitive process in question and made use of one-tailed t tests. Even with one-tailed t tests, we found only a trend reduction in individual metacognitive efficiency in the TMS-precuneus session compared to the TMS-vertex session (log M-ratio: paired t test t (17) = 1.63, one-tailed $p=0.061$). The trend was, however, replicated with a SDT assumption free correlation measure computed by the association between the task performances and subsequent confidence ratings (*Phi* correlation: t (17) = 1.68, one-tailed $p=0.055$) (Fig. 2), and was confirmed by another metacognitive efficiency measure, Meta-d'–d', in our previous paper (Ye et al. 2018). Moreover, we ascertained that there were no significant differences in task performance and levels of confidence rating between the two TMS sessions (accuracy: paired t test t (17) = 0.349, $p=0.640$; confidence rating: t (17) = 0.070, $p=0.780$). These results indicate that TMS to the precuneus specifically affected the individual metacognitive ability, and that no detectable effect related to their basic memory performance could be found.

Task-based fMRI analysis

While these behavioral patterns elicited by TMS have been confirmed, their relationship with the neural signals and anatomical correlates is unknown. To further test the effect of TMS on task-based BOLD responses, we first correlated the interaction term [(Correct_High–Correct_Low) > (Incorrect_High–Incorrect_Low)] (i.e., difference in activation between correct vs. incorrect trials under high vs. low confidence) with log M-ratio index across subjects separately for TMS-vertex and TMS-precuneus sessions, and compared the BOLD level of the interaction term between the two sessions. In the TMS-vertex session, there was a significant positive correlation between metacognitive efficiency and brain activation in one posterior cluster ($k=327$ voxels, Fig. 3a), extending from the precuneus (peak voxel, x, y, $z=6, -48, 14$) to the posterior cingulate cortex (peak voxel, x, y, $z=-3, -42, 14$). No significant correlation between metacognitive efficiency and brain activation was found in the TMS-precuneus session. To further visualize these results, we correlated individuals' BOLD signals with their meta-memory efficiency using an anatomical mask containing the precuneus for the two sessions separately. This mask covers the whole precuneus (e.g., containing also the ventral part of the precuneus) and we observed that there were significant correlations between metacognitive efficiency and activation in the TMS-vertex session (whole precuneus: $r=0.51$, $p=0.032$), but not in the TMS-precuneus session ($r=0.16$, $p=0.530$).

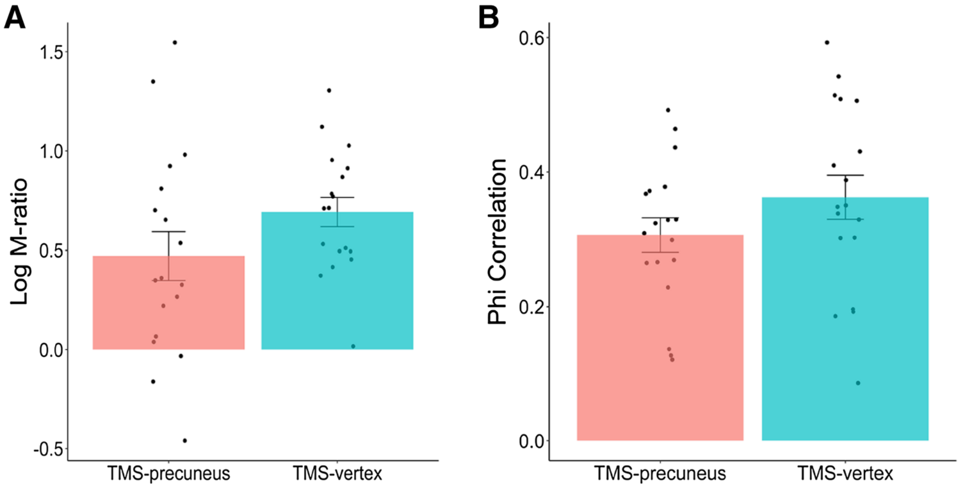

Fig. 2 Effects of TMS on meta-memory efficiency. The metacognitive ability showed a trend in reduction after TMS to precuneus compared to TMS to vertex in, **a** SDT metacognitive efficiency measure (log M-ratio, one-tailed $p=0.061$) and **b** Phi coefficient (one-tailed $p=0.055$). Black dots denote metacognitive score per subject. Error bars denote the standard error of the mean (SEM) over participants

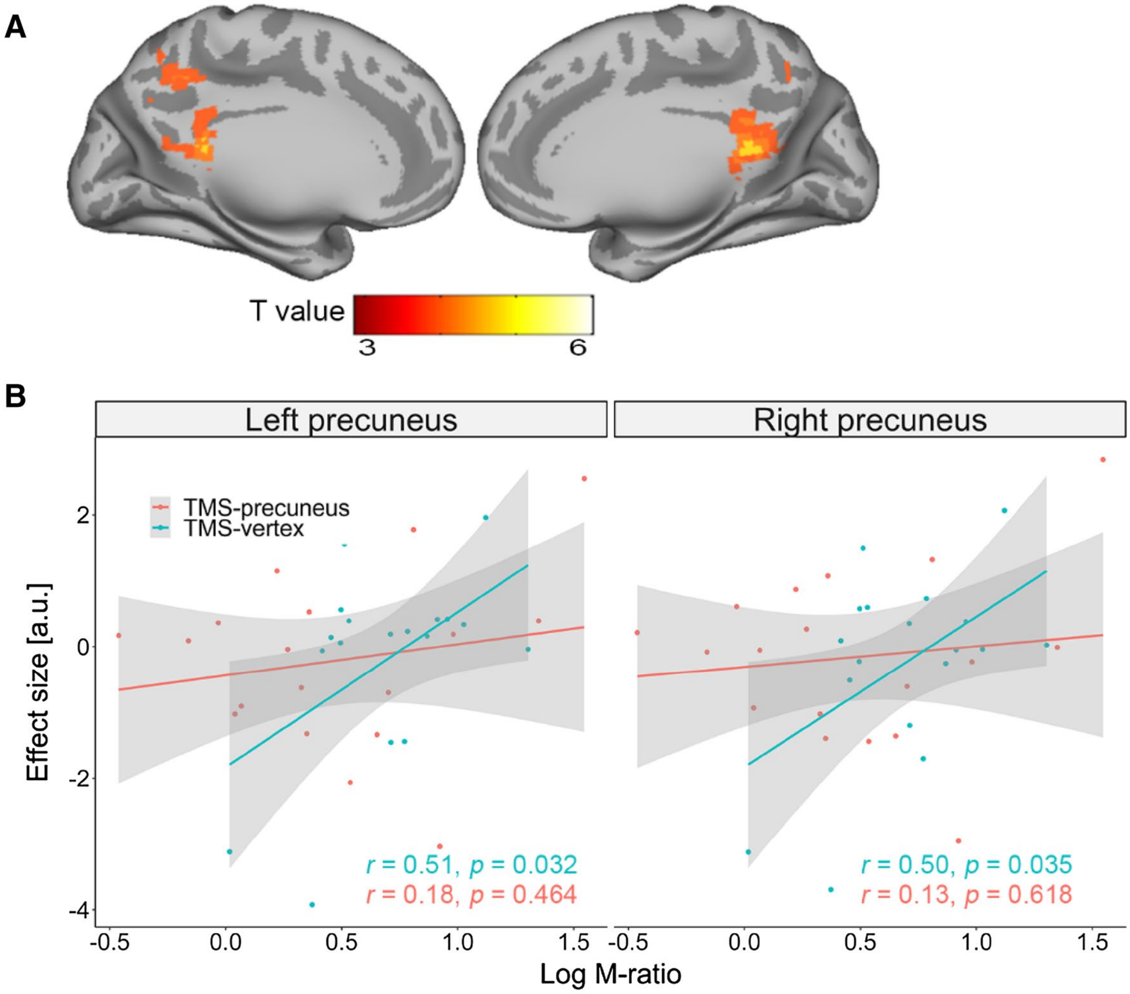

Fig. 3 **a** Significant positive correlation between meta-memory efficiency (log *M*-ratio) and activation in posterior medial region (peak voxel in precuneus: x, y, $z = 6$, -48, 14) in the TMS-vertex session. For visualization purposes, the threshold was set at voxel-level $p < 0.005$ uncorrected. **b** Individuals' BOLD effect size (arbitrary unit, a.u.) are correlated with meta-memory efficiency in the TMS-vertex session (cyan line) but not in the TMS-precuneus session (red line). The value of effect size was extracted from the individual first-level GLM analysis using unbiased anatomical precuneal masks. The data (i.e., parameter estimates) can be interpreted as average BOLD activation for processing metacognitive information. Gray regions indicate 95% confidence intervals

Resting-state functional connectivity analysis (rs-fcMRI)

In addition to task-based BOLD responses, recent works have also identified single-neuron responses in the human posterior parietal cortex which appear to code recognition confidence (Rutishauser et al. 2018), and suggested a stream that reads out meta-memory from the hippocampus in non-human primates (Miyamoto et al. 2017, 2018). To measure information communication from distributed brain regions, we estimated the measure of functional integration between precuneus and hippocampus (HP distance) over resting-state BOLD response. To aid interpretation, the shorter the HP distance is, the stronger functional integration between precuneus and hippocampus would be (Fig. 4a).

We investigated the effect of TMS on the association between HP distance and the change in log *M*-ratio between two sessions with a linear regression model, and a significant positive correlation was found (Pearson's $r = 0.49$, $p = 0.037$, Fig. 4b). Individuals with higher functional connectivity between precuneus and hippocampus showed higher vulnerability after TMS to the precuneus, compared to the vertex (TMS-precuneus > TMS-vertex). To show such effects to be specific to the memory domain, we also ran this correlational analysis with the change in metacognitive efficiency obtained from the perceptual task and found no relationship between HP distance and meta-perceptual efficiency (Pearson's $r = -0.36$, $p = 0.143$); the two correlation coefficients

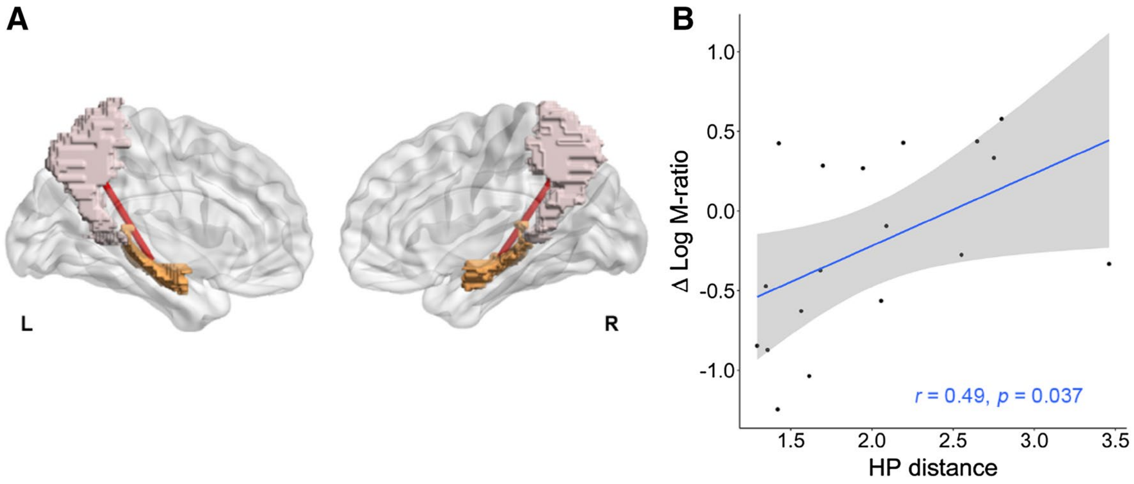

Fig. 4 **a** A cartoon image to show hippocampus–precuneus (HP) connectivity distance between hippocampus (orange color) and precuneus (pink color) separately for left- and right-hemisphere. The resulting HP distance was averaged across hemispheres. **b** Scatter plot between HP distance and the change in metacognitive efficiency (TMS-precuneus > TMS-vertex), with 95% confidence intervals

were significantly different from each other (comparison between correlations: $z = 3.27$, $p = 0.001$).

Voxel-based morphometry (VBM) analysis

Having observed that metacognitive ability was reduced by TMS to precuneus than to vertex, we then asked whether this inhibitory effect of TMS was predicted by variability in gray matter volume (GMV) in the precuneus across subjects. We investigated the association between GM volume and the change in meta-memory efficiency (TMS-precuneus > TMS-vertex) after controlling for total brain volume and gender (male/female). The results showed that change in meta-memory efficiency was positively correlated with GMV in the right precuneus ($t = 3.75$, SVC-$P_{\text{FWE}} < 0.05$ at $x, y, z = 15, -68, 43$; Fig. 5a). We also ran the same analysis on the meta-scores obtained from the perceptual task and no association between precuneal GMV and change in meta-perceptual efficiency was found (SVC-$P_{\text{FWE}} > 0.05$), again highlighting the domain-specificity of our main findings. For visualization purpose, we plotted the relationship between individual GMV and change in metacognitive efficiency across participants (Pearson's $r = 0.52$, $p = 0.027$; Fig. 5b) using the right anatomical precuneus as mask (the SVC peak is located in the right hemisphere). We should, however, note that the plotting is merely for visualization purpose

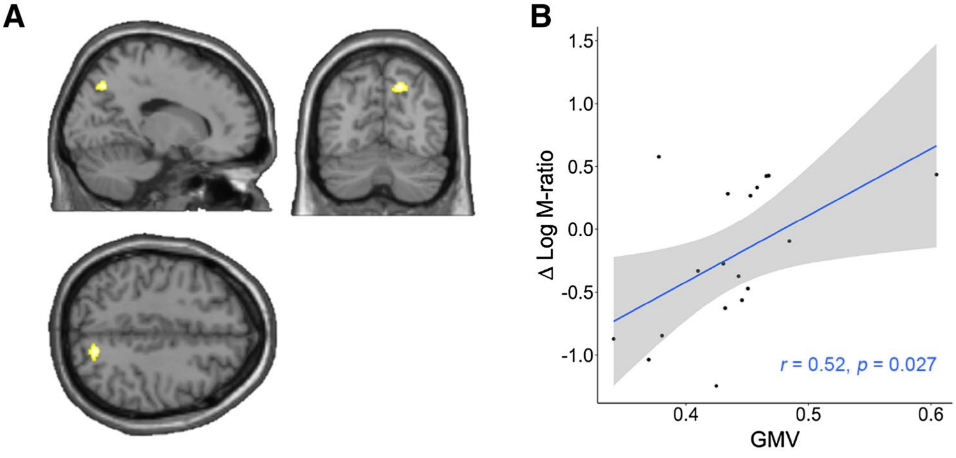

Fig. 5 **a** Brain regions with positive correlation between gray matter volume (GMV) and difference in metacognitive efficiency (log *M*-ratio in the TMS-precuneus session—log *M*-ratio in the TMS-vertex session). The significant cluster was found in the precuneal region ($P_{\text{FWE}} < 0.05$ small-volume correction). For display purpose, brain maps were thresholded at $p < 0.005$ uncorrected. (B) Scatter plot showing the relationship between individual GMV and their change in metacognitive efficiency, with 95% confidence intervals

and should not be considered in place of the SVC statistical results. These results revealed that participants with a smaller volume/density in the precuneus tend to have higher vulnerability to TMS in metacognitive ability, whereas those with a bigger volume/density in this region tend to be more immune to the TMS disruption.

Finally, we ran a control analysis correlating individuals active motor threshold with his/her delta log *M*-ratio and showed that the putative effects by TMS on meta-memory ability were not modulated by the penetrability/thickness of the individuals skull per se (Pearson's $r = 0.13$, $p = 0.611$), reinforcing our main findings that the neuromodulatory effects by TMS were specific to the precuneus-related anatomical profiles.

Discussion

TMS on the precuneus was previously found to impair metacognitive efficiency in a long-term memory retrieval task without affecting type 1 task performance (Ye et al. 2018). Although at present we obtained an insignificant reduction in individual metacognitive efficiency following TMS-precuneus, we focused primarily on elucidating the neural mechanisms that underpin the neuromodulatory effects of TMS in terms of individual differences in BOLD responses and two anatomical profiles.

We first established that the precuneal region is functionally implicated in meta-memory judgement using task-related BOLD signal measurements. To avoid the non-independent issue often seen in functional MRI studies as discussed by Vul et al. (2009), we ran an analysis using an unbiased anatomical mask including the whole precuneus. We found a significant correlation between metacognitive efficiency and meta-memory-related BOLD signal across subjects in the control session. This is in line with one recent study showing univariate activation in the precuneus and precuneal decoding accuracy with multivariate analysis are correlated with individual metacognitive efficiency (Morales et al. 2018). These findings point to a critical role of the precuneus in metacognitive ability during memory processes (Baird et al. 2013; Chua et al. 2006; Morales et al. 2018). Incidentally, neural correlates of metacognitive ability or confidence level in the precuneus have also been detected in other non-memory domains such as simple perceptual decision (Fleming et al. 2010) and visual motion discrimination (Heereman et al. 2015). Given the involvement of the precuneus in metacognitive judgments (Vaccaro and Fleming 2018), a natural question to ask is how the precuneus is involved in meta-memory processing. Here, together with TMS application, we used individual variability in functional responses to elucidate the neural underpinnings of meta-memory. While the overall BOLD level related to meta-memory judgments was equated across the two TMS sessions at the group level, we showed a relationship between meta-memory efficiency and precuneal activity during the vertex but not the precuneus stimulation session. This implies that the precuneus might be implicated to different extents across participants in subserving meta-memory assessment in face of the acute TMS disruption. These results complement and extend recent findings showing a causal role in metacognitive ability of the precuneus in temporal memory processes (Ye et al. 2018) as well as clinical findings that patients with lesions in the posterior parietal cortex tend to exhibit reduced confidence in their source recollection (Ciaramelli et al. 2017; Simons et al. 2010).

Our fMRI results implicate the more ventral portion of the precuneus, suggesting a possible fractionation within human posteromedial parietal cortex (Daitch and Parvizi 2018). The ventral region of the precuneus is found to be involved in memory-related activity and well connected to the hippocampus (Margulies et al. 2009; Ren et al. 2018; Vincent et al. 2006). To further characterize the relationship between the precuneus and the hippocampus, we revealed that individuals with higher resting-state functional connectivity between the precuneus and the hippocampus tend to exhibit higher vulnerability in metacognitive ability under the impact of TMS. By indexing the strength of functional connectivity between the precuneus and the hippocampus, we showed that subjects with higher functional connectivity were more vulnerable to the inhibitory TMS effect. Since the hippocampus is crucial for temporal-order memory judgement (Davachi and DuBrow 2015) and is known to modulate the neural activity of confidence judgments (Chua et al. 2006), we speculate that the precuneus might act as an accumulator (Wagner et al. 2005) for the strength of evidence received from the hippocampus, which was also utilized to support meta-mnemonic/meta-awareness appraisal. Although how the information is transmitted for meta-memory processing is still unknown, our results indicate that this "meta-mnemonic" accumulator during memory retrieval was dependent on its functional connectivity with the hippocampus. In fact, neuroimaging with pharmacological intervention on the monkeys has delineated a meta-memory stream consisting of information flow extracted from the hippocampus, going through the intraparietal cortex and then read-out by the prefrontal area 9 (Miyamoto et al. 2017, 2018). Using high-resolution multi-parameter mapping, researchers also found that markers of myelination and iron content in the hippocampus correlate with metacognitive ability across individuals (Allen et al. 2017). Altogether, these may help to account for the neuromodulatory effects by TMS being dependent on individuals' functional connectivity between the precuneus and the hippocampus.

We further revealed that the neuromodulatory effects by TMS were determined by the GM volume/density in the precuneus. Specifically, participants with a smaller volume/density in precuneus tend to have higher vulnerability in metacognitive ability to TMS, whereas those with a bigger volume/density in this region tend to be more immune to the TMS impact. The correlational relationship between precuneal volume and meta-memory capability has been previously established during a verbal memory task (McCurdy et al. 2013). Here, in light of the findings that the posterior parietal cortex contains two sub-groups of neurons which are differentially responsive for memory versus confidence demands during memory retrieval (Rutishauser et al. 2018), our revelation that the precuneal density/volume is a robust predictor for individuals' susceptibility might, thus, align with the possibility that participants with a bigger/denser precuneus might have a larger "missed" portion of the precuneus that can remain functional to serve to faithfully code the confidence-related signals.

We have also noted a statistical trend in the correlation between the resting-state FC between precuneus and hippocampus and the gray matter volume of the precuneus across the subjects ($r = 0.44$, $p = 0.068$). We speculate the individual variation of the precuneus gray matter volume could be related or even determining the connectivity of this area with the hippocampus, especially when such functional connectivity is known to be important for cognitive processes (cf. Kim et al. (2013)). This may help to explain the intricate inter-correlations between variation in individual difference in meta-memory efficiency and the several neural measures including functional connectivity and GM volume. However, interpreting correlations between individual differences and brain measures in a relatively small sample sizes indeed requires caution (Yarkoni 2009). Notwithstanding these caveats, adopting a within-subjects pre- vs. post-comparison may help to gain considerable power by avoiding across-subject variability (Vul and Pashler 2017) and our demonstration of brain–behavior correlations in three relatively independent neuroimaging modalities may nonetheless point to a central involvement of the precuneus in memory metacognition.

Conclusion

Taken both functional and anatomical evidence together, our study capitalized on individual variability to characterize the neuromodulatory effects of TMS during metamnemonic appraisal. Through several neuroimaging modalities, we provided compelling evidence in outlining a possible circuit encompassing the precuneus and its mnemonic midbrain neighbor the hippocampus in supporting our meta-awareness upon memory recollection of episodic details.

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Compliance with ethical standards

Conflict of interest None of the authors has any conflicts of interest to declare.

Ethical approval All procedures performed in this study involving human participants have been approved by the local ethics committee of the institute (University Committee on Human Research Protection of East China Normal University, UCHRP-ECNU) and are in agreement with the 1964 Helsinki declaration and its later amendments.

Informed consent All participants gave their informed consent to participate in the study.

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