

How Transcranial Magnetic Stimulation over Early Visual Cortex impacts short-term memory precision and guess rate

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Abstract

1 Neuroimaging studies have demonstrated that activity patterns in early visual areas
2 predict stimulus properties actively maintained in visual short-term memory. Yet, the
3 mechanisms by which such information is represented remain largely unknown. In this
4 study, observers remembered the orientations of 4 briefly presented gratings, one in each
5 quadrant of the visual field. A 10Hz Transcranial Magnetic Stimulation (TMS) triplet
6 was applied directly at stimulus offset, or midway through a 2-second delay, targeting
7 early visual cortex corresponding retinotopically to a sample item in the lower hemifield.
8 Memory for one of the four gratings was probed at random, and participants reported this
9 orientation via method of adjustment. Replication errors were smaller when the visual
10 field location targeted by TMS overlapped with that of the cued memory item, compared
11 to errors for stimuli probed diagonally to TMS. This implied topographic storage of
12 orientation information, and a memory-enhancing effect at the targeted location.
13 Furthermore, early pulses impaired performance at all four locations, compared to late
14 pulses. Next, response errors were fit empirically using a mixture model analysis to
15 characterize memory precision and guess rates. Memory was more precise for items
16 proximal to the pulse location, irrespective of pulse timing. Guesses were more probable
17 with early TMS pulses, regardless of stimulus location. Thus, whereas TMS administered
18 at the offset of the stimulus array might disrupt early-phase consolidation in a
19 topographically unspecific manner, TMS also boosts the precise representation of an item
20 at its targeted retinotopic location, perhaps by increasing attentional resources or by
21 injecting a beneficial amount of noise.

Introduction

22 Humans sense the world in a highly visual fashion – the flow of information from the
23 eyes gives rise to an ostensibly effortless and seamless picture of our external
24 environment. Despite its apparent simplicity, visual perception requires the brain to form
25 an ongoing internal representation of all the information we are perceiving and perceived
26 just moments ago, even if this information can no longer be sensed directly. Short-term
27 memory takes center stage in the process of cognition by allowing relevant information to
28 be kept online for further computation, serving as an indispensable buffer for human
29 thought. Here, we investigated short-term memory for visual information and the role of
30 early visual cortex during the maintenance of such information.

31 How might the brain meet the computational demands associated with the maintenance of
32 information to which it no longer has access? The act of keeping visual memories online
33 involves a network of frontal [1,2] and parietal [3-5] regions, as well as visual areas that
34 were involved when the information was originally sensed [6-9]. The coordinated effort
35 of higher-level and sensory brain regions during the short-term retention of visual
36 information is believed to be flexible and goal dependent [10]. The dominant view in the
37 literature on short-term memory is that higher-level areas recruit sensory areas that are
38 specialized in processing the sensory analogs of specific mnemonic contents [11-14].

39 It has been suggested that sensory recruitment during visual memory is achieved in a
40 spatially global and non-retinotopic manner: While people remembered an orientation
41 presented in the left visual field, this orientation was decodable from patterns of
42 functional Magnetic Resonance Imaging (fMRI) activity originating from *both* ipsi- and
43 contralateral primary visual cortex (V1) [1,15]. However, the task used in these studies
44 did not require subjects to maintain the relevant feature (here: orientation) bound to any
45 specific location on the screen. Therefore, the lack of retinotopic recruitment could also
46 be interpreted as a spread of feature-based attention [16-18]. Conversely, memory for
47 visual information does depend on retinotopically specific representations when stimulus
48 location is made relevant, and the explicit binding of stimulus contents to a particular

49 location is required to perform a task. For example, location matters when people
50 remember objects in a scene [19,20], when two orientations are presented one in each
51 hemifield [8], or when location is made salient by a spatial transformation during
52 memory [21,22].

53 To directly probe the causal role of sensory areas during the retention of visual stimuli, as
54 well as the spatial extent of such recruitment, brain processes during memory can be
55 actively altered by means of Transcranial Magnetic Stimulation (TMS). Previous work
56 with TMS has provided support for both the necessity of visual sensory recruitment [23],
57 as well as retinotopically specific maintenance of representations in these areas [24,25].
58 However, previous TMS studies demonstrating that the spatial extent of memory
59 representations was confined in a retinotopic manner suffered some drawbacks:
60 Specificity was only found very early during retention, probably during encoding [24], or
61 was measured indirectly via the qualitative judgment of phosphenes [25]. Thus, while
62 these studies suggest that brain stimulation has the potential to impact visual memories at
63 the level of sensory representations, it remains to be seen whether retinotopically specific
64 effects on performance can be found when TMS is applied outside of the range of
65 sensory encoding.

66 While sensory recruitment during visual short-term memory has been well documented in
67 studies measuring blood oxygenation with fMRI, the functional role of such recruitment
68 is much less understood. In addition to the issue of retinotopic specificity, a second
69 unanswered question concerns the functional role of sensory recruitment during short-
70 term memory maintenance. Given that sensory areas can represent information with a
71 degree of precision not easily achieved by less specialized areas, we hypothesized that
72 their role during memory is to maintain high-precision representations.

73 Here, questions of *specificity* and *functional relevance* were addressed by applying TMS
74 over occipital cortex while participants were remembering four oriented gratings,
75 presented one in each quadrant of the visual field. By cuing memory based on spatial
76 location, this task encouraged participants to encode and retain orientation information at
77 the spatial locations at which they were presented. This design binds object identity to

78 spatial position [26] allowing us to test for retinotopically specific recruitment of visual
79 sensory cortex during short-term visual memory. To probe the functional role of sensory
80 areas during the maintenance of orientation information, we employed a novel
81 combination of methodologies: We combined TMS with rigorous psychophysical testing
82 using the method of adjustment. This procedure involved collecting many trials per
83 participant, calculating the angular deviation between the reported and true orientation on
84 each trial, and analyzing the resultant error distributions by fitting a mixture model [27].
85 A mixture model characterizes memory errors as having two underlying sources:
86 response variability and probability of uniform responses [27]. We applied this model to
87 evaluate, respectively, the effects of TMS on memory precision and the effects of TMS
88 on the likelihood of successful memory maintenance (i.e. “guess-rate”).

89 Pulses were applied at two different time intervals to check for potential differences
90 between processes occurring at the tail end of encoding, and processes occurring well
91 within the retention phase. Previous work showed that behavioral effects of visual cortex
92 TMS during short-term memory depends on the timing of TMS [28]. In this study,
93 participants remembered a circle with two lines extending from its center, forming a
94 wedge. After a two-second delay participants judged whether a target dot appeared inside
95 or outside of the remembered wedge. When TMS over visual cortex was applied at the
96 end of the delay, responses were faster compared to vertex or no TMS stimulation. By
97 contrast, TMS over visual cortex applied at the onset of the delay slowed response times
98 [28]. Because brain stimulation interacts with ongoing neural activity at the stimulated
99 region [29,30] we expected that TMS at different stages of retention (encoding and
100 maintenance), would differentially impact behavioral outcomes.

101 Our primary hypothesis was that TMS over visual cortex would impact memory precision
102 (but not guess-rate) in a retinotopically specific manner. A change in precision is
103 expected based on the clear link that exists between information contents in visual cortex
104 (as indexed by classification performance) and mnemonic resolution (as indexed by
105 behavior), with more information predicting higher behavioral precision [6] [31]. One
106 means by which TMS could impact behavior is by locally injecting random noise. Such

107 noise could act to reduce the amount of information at the TMS location in visual cortex,
108 and consequently negatively impact behavioral precision. Alternatively, at low levels of
109 noise behavioral precision could improve: If weak neural signals are below (firing)
110 threshold, a small amount of noise can push the intensity of these weak signals above
111 threshold, enhancing signal discriminability – an idea known as ‘stochastic resonance’.
112 Note that effects of noise on information transfer are non-linear, because with no (or too
113 little) noise a threshold will not be reached, while too much noise will drown out the
114 signal. Indeed, visual sensitivity is improved with low-intensity (below phosphene
115 threshold) TMS stimulation [32], and low-intensity TMS facilitates behavior based on
116 weak, but not strong, neural signals [33]. Mnemonic signals likely rely on weak sub-
117 threshold signals, and low-intensity visual cortex TMS during short-term memory has
118 indeed been shown to benefit behavior [25,28,34].

119 Here we found that TMS applied during the short-term retention of orientation stimuli
120 improved overall behavioral performance in a retinotopically specific manner. This
121 localized improvement mirrored by an increase in memory precision at the TMS location.
122 Furthermore, TMS early during retention – at the tail end of encoding – resulted in a
123 global, non-retinotopic, reduction in overall performance compared to TMS late during
124 retention. This reduction in performance was mirrored by an increase in the likelihood of
125 guess-like responses.

Methods

Participants

126 Eight participants were recruited from Maastricht University (5 females; mean age =
127 25.13 years, SE = 0.81). All had normal or corrected-to-normal vision, provided written
128 informed consent, and passed a medical screening based on published safety guidelines
129 [36] overseen by an independent medical supervisor. The medical ethics committee of the
130 Maastricht University Medical Centre approved the study. With exception of one of the
131 authors, participants received monetary reimbursement.

Overall study design

132 We combined functional and anatomical MRI, with neuro-navigated TMS during a
133 psychophysical short-term memory task (Fig 1A). Neuroimaging was utilized for the
134 purpose of neuro-navigation [37], allowing constant TMS stimulation sites across
135 multiple psychophysical sessions based on individually localized visual cortical activity.
136 During the first (fMRI) session, anatomical and functional localizer data were obtained.
137 The second (TMS) session determined the exact TMS target points and intensities to be
138 used throughout subsequent experimental sessions, and participants furthermore
139 performed 160 practice trials of the main psychophysical task.

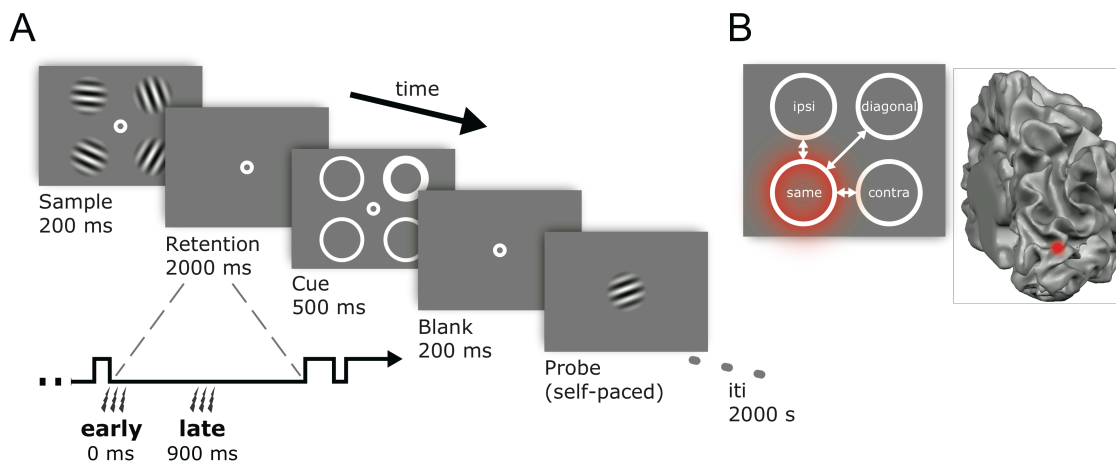


Fig 1. Trial sequence and relative locations. (A) Participants viewed a sample array displaying 4 randomly chosen orientations, and remembered these over a two-second delay. During this retention interval, participants received 3 pulses of real or sham TMS over their left or right hemisphere. The pulses arrived either directly at the offset of the sample array, or midway during the retention interval. A cue array indicated which of the four orientations was probed for recall, and after a short blank, participants rotated a test grating via button presses to match the cued orientation. **(B)** Responses at the four visual field locations were analyzed according to their position relative to the pulse. The visual field position targeted by the pulse could overlap with the memory item that was cued ('same'), the cued item could be contralateral to the affected visual field location ('contra'), it could be ipsilateral to it ('ipsi'), or diagonal to it ('diagonal'). In the example depicted here, the dorsal part of visual cortex in the right hemisphere is stimulated, targeting the lower-left visual field. Consequently, the upper left position becomes 'ipsi', the upper right position 'diagonal', the lower left 'same', and the lower right position 'contra' – relative to the visual field location affected by the TMS pulse.

140 During the last 5-6 sessions psychophysical data was collected while applying TMS over
141 visual cortex. A TMS coil (real or sham) was placed over either the left or the right dorsal
142 part of early visual cortex (V1/V2). Sham TMS was used to control for attentional

143 biasing effects that can arise simply from “clicking” sounds at different points in time
144 [37]. For half of our participants, a single session consisted of 4 blocks of 80 short-term
145 memory trials per block, of which three blocks involved triple-pulse TMS stimulation at
146 10 Hz, and one block involved triple-pulse sham stimulation at 10 Hz. Target hemisphere
147 (left or right) and type of stimulation (real or sham) were counterbalanced over blocks,
148 sessions, and participants. The other half of participants underwent the same procedure,
149 with one exception: they performed the blocks of sham-stimulation separately, several
150 months after completing the real TMS sessions.

MRI measurements

MRI acquisition

151 Scanning was performed at the Maastricht Brain Imaging Center (M-BIC) on a 3.0-Tesla
152 Siemens MAGNETOM Allegra scanner using a standard birdcage head coil. A high-
153 resolution 3D anatomical T1-weighted scan was acquired from each participant (FOV
154 256 x 256, 1 x 1 x 1 mm³ resolution, 192 slices, MPRAGE). To measure BOLD contrast,
155 standard gradient-echo echoplanar T2*-weighted imaging was used to collect 28 slices
156 covering the entire occipital lobe. Scan parameters for six participants were: TR, 2000
157 ms; TE, 30 ms; flip angle, 80°; FOV 192 x 192; slice thickness, 3 mm (no gap); in-plane
158 resolution, 3 x 3 mm². For two others scan parameters were: TR, 2000 ms; TE, 30 ms;
159 flip angle, 90°; FOV 256 x 256; slice thickness, 2 mm (no gap); in-plane resolution, 2 x 2
160 mm².

MRI data analysis

161 Preprocessing and analysis of the anatomical and functional MRI data were performed
162 using BrainVoyager QX software (version 2.3.0.1750, Brain Innovation, Maastricht, the
163 Netherlands). All anatomical data underwent inhomogeneity correction of signal intensity
164 across space, and a tissue contrast enhancement using a sigma filter (7 cycles, range 5).
165 Automatic grey-white matter segmentation was performed, after which manual
166 corrections were made to improve segmentation over occipital cortex. The borders of the
167 two resulting segmented sub-volumes were tessellated to produce surface reconstructions

168 (folded meshes) – one for each hemisphere. These reconstructions were created to
169 recover the exact spatial structure of the cortical sheet and to improve the visualization of
170 anatomical gyrification.

functional MRI

171 Localizer stimuli in the scanner were generated using MATLAB 7.10.0 (R2010a) and the
172 Psychophysics Toolbox [38]. Stimuli consisted of 5 Hz flickering black-and-white
173 checkerboards (1° radius) presented 4° from fixation in either the lower left or lower right
174 (randomly interleaved) quadrant of the screen against a uniform grey background (55.86
175 cd/m²). Stimulus locations encompassed the same visual field position as the two lower
176 Gabor patches in the short-term memory task (Fig 1A). Stimuli were viewed through a
177 mirror system on a back-projected screen (1024 x 768 resolution, 60 Hz refresh rate) at a
178 distance of 66 cm in an otherwise darkened scanner room. We presented our localizer in
179 two 5-minute functional runs, alternating twelve times between a 12 second fixation
180 period and a 12 second stimulus period. Participants fixated throughout (0.5° white bull's
181 eye) monitoring occasional dimming of the checkerboard (~5 times per block), which
182 was detected 43.18% of the time (SE=0.04).

183 After discarding the first 4 functional volumes, we applied automated 3D motion
184 correction, slice-scan time correction (sinc), and high pass temporal filtering (using a
185 GLM-Fourier basis set with 2 cycles) to correct for slow temporal drifts in signal
186 intensity. No spatial or temporal smoothing was applied directly. Next, the fMRI data
187 was aligned to the within-session anatomical scan via rigid-body transformations, with all
188 automated alignment carefully inspected and manually fine-tuned when necessary.
189 Functional data from both runs were combined and analyzed using a general linear model
190 (GLM; [39]). Activity for the left and right hemispheres was based on the statistical
191 contrast between BOLD signal [40] elicited by visual stimulation in the lower right
192 versus lower left visual field respectively.

Localization of the TMS target points

193 The anatomical reconstruction of a participant's head was co-registered with the

194 participant's head in real space using stereotaxic data recorded with an ultrasound
195 digitizer. Neuro-navigation was used to manually maneuver the TMS coil relative to a
196 participant's skull, while seeing in real-time their computer generated anatomical surface
197 reconstruction with functional localizer activity superimposed. TMS target points were
198 defined to lie within this region of activation. Specifically, each target point was chosen
199 as posteriorly as possible within this region of activation, while still eliciting a phosphene
200 overlapping the visual field location where stimuli would be presented (3–5° from
201 fixation in lower left and right quadrants). Each TMS target point was indicated on the
202 cortical surface reconstruction by a digital marker and saved to guide neuro-navigation
203 for all future sessions. Phosphene thresholds were determined for the left and right
204 hemispheres individually (at the saved TMS target points) and kept constant throughout
205 all future sessions. Two participants did not experience phosphenes: target points were
206 chosen at the peak-activity determined with fMRI, and stimulation intensity was set at the
207 average intensity of other participants in the study.

TMS protocol

208 Biphasic TMS pulses were delivered by means of a figure-of-eight coil (MCB70) and a
209 MagPro R30 stimulator (Medtronic Functional Diagnostics A/S, Skovlunde, Denmark).
210 This setup allows for pulse strengths (defined as the rate of change in the magnetic pulse)
211 up to 148 A/ μ s at 100% of stimulator output, and 52 A/ μ s at 35% stimulator output.
212 Pulses were applied at 80% of phosphene threshold to ensure that participants did not
213 perceive visual stimulation (i.e. phosphenes) due to TMS.

214 Participants received 240 TMS pulses (3 pulses * 80 trials) during each run of the short-
215 term memory task, and performed a total of 16 runs. The average pulse intensity used
216 was 34.44% (SE=0.54) of maximum stimulator output, with no significant difference
217 between the two hemispheres (mean left = 35 %, mean right = 33.88%, $t = 1.386$, $p =$
218 0.208).

Short-term memory task

Stimuli

219 Experimental stimuli were generated with MATLAB 7.10.0 (R2010a) and the
220 Psychophysics toolbox [38] under Windows XP and viewed in a dark room on a
221 luminance-calibrated 19" Dell TFT monitor (1280 x 1024 resolution, 60Hz refresh rate).
222 Communication between the experimental pc and stimulator was established using
223 PortTalk V2.0 (Beyond Logic). Stimuli consisted of randomly oriented gratings with a
224 spatial frequency of 2 cycles/°, a diameter of 2°, a 20% Michelson contrast with a wide
225 Gaussian envelope ($sd = 2^\circ$) and presented on a uniform grey background that shared the
226 mean luminance of 40.23 cd/m². Stimuli were presented at four fixed locations around a
227 central fixation point at an eccentricity of 4°. Participants viewed the stimuli from 57 cm,
228 and were instructed to maintain steady fixation throughout aided by a centrally presented
229 white bull's eye (0.5° diameter). A chinrest, forehead rest, and the tight placement of the
230 TMS coil against the back of the head assisted in maintaining head stability.

Procedure

231 Observers were presented with a 200 ms sample array of 4 to-be-remembered gratings
232 (Fig 1A). Each grating had an independently chosen random orientation (0-180°), with
233 the only constraint that simultaneously presented orientations differed by >10°. During a
234 2-second retention interval a TMS triple-pulse was applied at 10 Hz (thus taking 200 ms)
235 either directly following the offset of the sample array, or midway through the retention
236 interval (the first pulse occurring 900 ms into the interval). Next, 4 spatial cues appeared
237 for 500 ms outlining the locations of the previously presented sample stimuli. A 0.15°
238 wide white circle probed the location of the grating to be reported from memory. Non-
239 target locations had 0.05° outlines. After 200 ms a test grating was presented centrally at
240 an initially random orientation. Participants used separate buttons on a keyboard to rotate
241 the test grating clockwise or counterclockwise to match the probed orientation. Cue
242 location was conceived of as counterbalanced (with each location probed an equal
243 amount of times), but due to unforeseen circumstances the cue location was chosen
244 randomly, without exactly equal amounts of trials at each location (see also
245 supplementary information).

246 **Analyses**

247 Due to anatomical constraints, TMS can only be applied over the dorsal (and not ventral)
248 part of visual cortex. Thus, TMS can only target the two lower (and not upper) of the four
249 stimulus-locations probed during our memory task. Previous studies have relied on this
250 anatomical feature to contrast behavioral performance between a ‘TMS quadrant’
251 (usually the lower left) and a ‘control quadrant’ (usually the upper right)[24,41-43]. In
252 the current task, the memory target could be cued in all four visual field quadrants.
253 Consequently, data were analyzed according to the relationship between (1) the visual
254 field location targeted by the TMS pulse, and (2) the visual field location probed for
255 recall. To illustrate this analysis based on “relative location”, let’s assume that during a
256 given block of trials the right hemisphere was stimulated with TMS, targeting the lower-
257 left visual field (see also Fig 1B). If the target was subsequently cued in the same lower-
258 left quadrant, both TMS and stimulus were presented at the “same” relative location. On
259 trials where the target was cued in the upper-left quadrant (ipsilateral to the TMS-pulse
260 location) the relative location was “ipsilateral”. Similarly, a target cued in the lower-right
261 quadrant is at a “contralateral” relative location, whereas a target cued in the upper-right
262 quadrant is at a “diagonal” relative location. The same logic can be applied when the coil
263 is moved to the left hemisphere, targeting the lower-right visual quadrant.

264 Note that the *diagonal* location represents the *control quadrant*, as frequently employed
265 in TMS studies of visual cortex. Such a control quadrant carries two major advantages
266 over sham stimulation. One is that the diagonal location is probed randomly interleaved
267 with trials probing other locations, ensuring that participants are in the same general state
268 during both trial types. Second is that real TMS is applied even when participants are
269 probed at the control quadrant, ensuring that the acoustics and tactile experience during
270 these trials perfectly matches that of other probed locations.

271 To separately estimate the precision of memory for successfully remembered items and
272 the likelihood of memory failure we adopted a mixture-model approach following the
273 work of Zhang and Luck (2008). This model summarizes data from method-of-

274 adjustment tasks in a way that reflects the underlying assumptions of the model: on some
275 trials items are remembered with a certain degree of precision, whereas on other trials
276 items are not available for recall resulting in random guesses. This idea was implemented
277 by fitting a circular Gaussian-shaped model to the distribution of orientation errors
278 (actual orientation minus reported orientation) for each condition of interest. The model
279 consisted of two key parameters: One is the standard deviation (*SD*), or width of the
280 circular portion of the distribution, assumed to reflect the precision of short-term memory
281 for successfully remembered items (with better precision indicated by a smaller *SD*). Two
282 is the relative proportion of area under the curve corresponding to a uniform distribution
283 (*p-Uniform*), which captures the extent to which the entire distribution needed to be
284 translated along the y-axis to account for the frequency of guess-like responses, and is
285 assumed to reflect the probability of guessing responses. We rely on these summary
286 statistics throughout this paper because they provide a useful way to capture broad trends
287 in the data and because they may signify distinct types of errors. However, it is important
288 to acknowledge that the mapping between these summary statistics and underlying
289 sources of error in the short-term memory system rely on assumptions regarding the exact
290 nature of short-term memory performance, and that competing models have been
291 proposed (e.g., [44-48]).

Results

Absolute performance

292 Experimental manipulations consisted of (1) probing memory for items at various relative
293 distances from the visual field location targeted by TMS, and (2) applying TMS early or
294 late during memory retention. Moreover, TMS was applied in a counterbalanced fashion
295 either over the left- or right hemisphere, which was not expected to impact performance.
296 By performing a 3-way within-subjects ANOVA (4 relative locations x 2 pulse timings x
297 2 stimulated hemispheres) on the absolute errors (absolute difference between reported
298 and true orientation) we confirmed that the stimulated hemisphere (left or right) did not
299 affect memory accuracy ($F_{(1,7)} < 0.001$; $p = 0.986$).

300 Proximity of a memory item to the visual field location targeted by TMS while items
301 were being maintained in memory had a facilitative effect on memory performance, as
302 indexed by smaller errors for items proximal to the pulsed location (main effect of
303 relative location; $F_{(3,21)} = 3.951$; $p = 0.022$; Fig 2). Six post-hoc ANOVA's were
304 performed to investigate the origins of this main effect of location, each comparing
305 performance at two locations (each 2 relative locations x 2 pulse timings x 2 stimulated
306 hemispheres). The location effect depended on the difference between trials on which the
307 TMS pulses and probed location overlapped ('same' condition) versus when they were
308 furthest apart ('diagonal' condition, i.e. the control quadrant) ($F_{(1,7)} = 5.598$; $p = 0.050$).

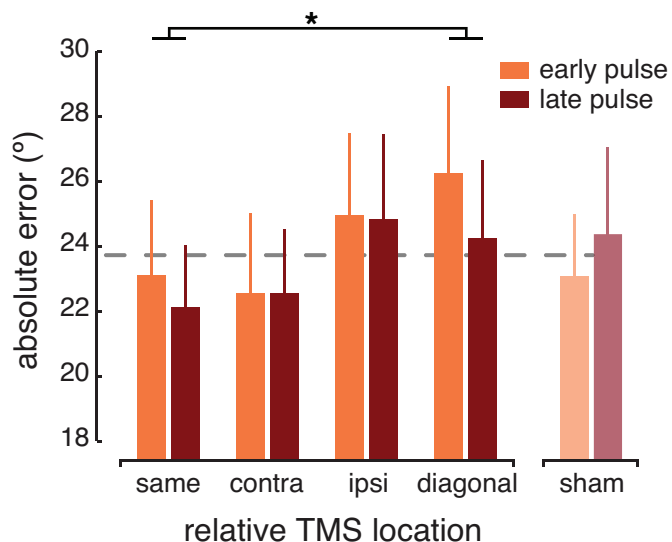


Fig 2. Absolute performance relative the TMS location. When a memory item was cued at the same location as targeted by the TMS pulses, the absolute response error was smaller than when a memory item was probed diagonally to the pulses. This indicated better performance on trials where memory cue location and TMS location overlap (compared to a cue diagonal to TMS). Early pulses resulted in worse performance compared to late pulses, irrespective of the cued visual field location. Trials during which TMS was administered are shown here after collapsing across both hemispheres, since stimulation site (left or right hemisphere) did not affect participant's performance. Sham data is shown collapsed across all conditions (dashed grey line), and separately for early and late sham pulses (orange and red bars). The time point at which audible sham clicks were delivered did not impact behavior. When data were collapsed across both hemispheres (as depicted here), a 4x2 ANOVA (relative location by pulse timing) revealed statistically reliable performance differences between the four visual field locations ($F_{(3,21)} = 3.483$; $p = 0.034$) and a marginally significant effect of pulse timing ($F_{(1,7)} = 4.820$; $p = 0.064$). Error bars depict ± 1 SEM.

309 Comparing the two pulse-timings showed that applying TMS pulses early, directly at the
310 offset of the stimulus display, resulted in larger errors than TMS applied midway through
311 the retention interval (main effect of pulse timing; $F_{(1,7)} = 6.359$; $p = 0.040$).

312 Audible ‘clicks’ from a TMS machine can have differential attentional cuing effects
313 when presented at different time points [37], with the potential to influence behavior
314 differently early and late during retention. Because sham TMS has no neural effects, we
315 collected a total of 320 sham trials (160 per pulse timing) to investigate potential effects
316 of timing. While this is the right amount of trials for looking at timing effects, note that
317 this is much less than the 1280 trials collected during real TMS, precluding analyses of
318 the sham data in a manner truly identical to analyses of the real TMS data. We analyzed
319 sham data by first looking at our condition of interest, pulse timing, while collapsing
320 across all other factors (location and hemisphere). The time point at which sham pulses
321 were applied did not impact performance ($t_{(7)} = 0.647$; $p = 0.538$). We also compared
322 performance for absolute location (comparing upper left, upper right, lower left, and
323 lower right locations) and hemisphere (left and right) collapsing across the remaining
324 factors. Again, no differences were observed ($F_{(3,21)} = 0.459$; $p = 0.714$ and $t_{(7)} = 1.013$; p
325 $= 0.345$, for location and hemisphere respectively). The finding that there were no
326 differences between any of the conditions on sham trials is important, since our
327 manipulations could have had unintended differential attentional-cuing effects,
328 mimicking the neural effects probed via TMS.

Mixture-model results

329 To gain a deeper understanding into the functional role of early visual cortex involvement
330 during the maintenance of visual memories, we fit a mixture model to data from each
331 combination of location and pulse timing conditions (collapsed across hemispheres). This
332 allowed us to decompose the absolute errors into (1) memory precision as indexed by the
333 mixture model SD (with a smaller SD indicating better precision), and (2) the likelihood
334 of guess-like responses indexed by p -Uniform (with a larger p -Uniform indicating more
335 guessing) [27].

336 When a memory target was probed at a location proximal to the location targeted by
337 TMS, memory recall was more precise (4 relative locations \times 2 pulse timings ANOVA,
338 main effect of relative location; $F_{(3,21)} = 4.102$; $p = 0.019$; Fig 3A). Specifically, six post-
339 hoc ANOVA’s (comparing all possible pairs of relative locations) showed that memory

340 was more precise on trials where the pulses and probed memory item overlapped, i.e.
341 ‘same’ condition, ($F_{(1,7)} = 7.974$; $p = 0.026$) or were ‘ipsilateral’ to one another ($F_{(1,7)} =$
342 7.658 ; $p = 0.028$), compared to trials on which the pulses and probed item were furthest
343 apart (‘diagonal’, control quadrant).

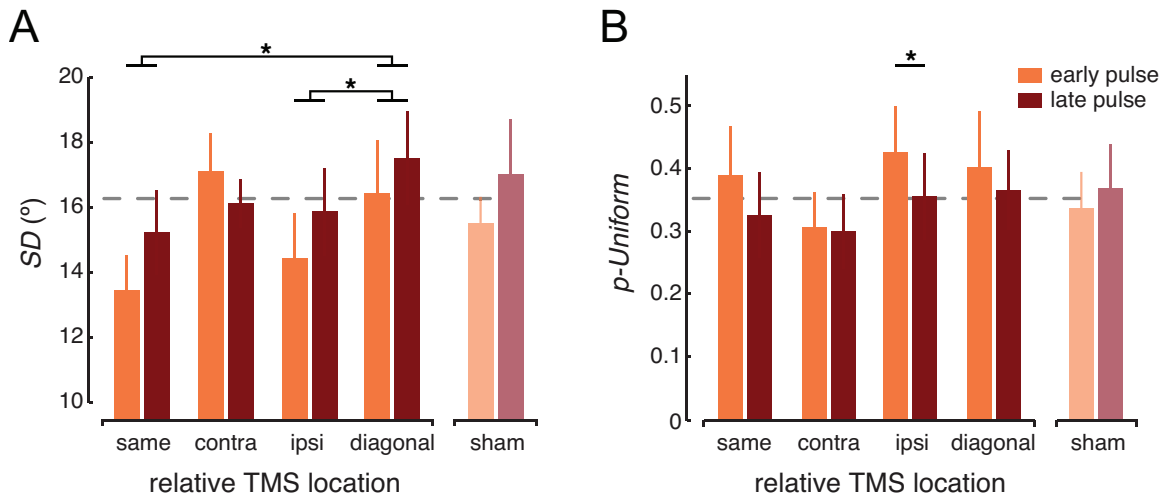


Fig 3. Model fits of TMS data. (A) Memory precision is represented by the mixed-model SD , with a smaller SD indicating more precise memory. Memory was most precise when the location of a cued memory item overlapped with the location at which TMS was applied, or was ipsilateral to it, compared to diagonally to pulses. **(B)** When pulses were delivered early during the retention interval, participants were more likely to guess compared to pulses delivered late, irrespective of their retinotopic location relative to TMS. Parameter estimates were obtained by finding the best-fitting mixture-model (centered on 0° error of report, based on the mixed model analysis) for the frequency distribution of each condition, using a bin width of 12° (mean $R^2 = 0.894 \pm 0.029$). Bin size was chosen to maximize the mean R^2 values across the different experimental conditions. Data were collapsed across hemispheres (left and right stimulation) before fitting in order to achieve a large enough number of trials per condition to obtain reliable fits. Error bars depict ± 1 SEM.

344 No retinotopic specificity was found for the probability of uniform responses, which did
345 not differ significantly between the four visual field locations ($F_{(1,7)} = 1.831$; $p = 0.172$).
346 However, participants were more likely to show guess-like responses when pulses were
347 presented early during the retention interval compared to pulses presented midway
348 through retention (main effect of pulse timing; $F_{(1,7)} = 6.594$; $p = 0.037$; Fig 3B). This
349 increase in random responses occurred irrespective of the location at which the memory
350 item was probed (no interaction; $F_{(3,21)} = 0.712$; $p = 0.555$).

351 Finally, sham data were fit with a mixture model for each condition of potential interest

352 (pulse timing, and absolute location) separately, collapsing across all other conditions.
353 Timing of the sham pulses did not affect memory variability (paired-samples $t_{(7)} = 0.822$;
354 $p = 0.438$) nor the probability of guess-like responses (paired-samples $t_{(7)} = 1.262$; $p =$
355 0.247). We found no differences between the four absolute visual field locations for
356 either memory precision ($F_{(3,21)} = 0.976$; $p = 0.423$) nor the probability of uniform
357 responses ($F_{(3,21)} = 1.272$; $p = 0.310$).

Memory performance across the visual field

358 A strength of our experimental setup was that the TMS coil was fixed over the skull,
359 which, in combination with fMRI guided neuro-navigation, ensured that the targeted
360 brain site remained stable relative to the four patches of retinotopic cortex excited by our
361 stimuli. However, this setup had the obvious side effect that the stimuli were anchored
362 onto four static visual field locations across all experimental trials. If perception and
363 memory at these static visual field locations were anisotropic, this would complicate
364 interpretation of our results. From the literature on basic human vision it is known that
365 people are generally better at performing a visual task on stimuli in the lower, compared
366 to the upper visual field. Luckily, such anisotropies are generally found for stimuli
367 presented along the cardinal meridians, and less prevalent (or even absent) for stimuli
368 presented at the obliques [49,50]. Nevertheless, any residual anisotropy would impact our
369 results by biasing performance in favor of the lower half of the visual field, incidentally,
370 the same half of the visual field targeted with TMS.

371 One crucial check was to investigate how memory on sham trials varied across the
372 stimulus locations in the upper left, upper right, lower left, and lower right parts of the
373 visual field. These results were already discussed above: During sham neither the
374 absolute error ($F_{(3,21)} = 0.459$; $p = 0.714$), memory precision ($F_{(3,21)} = 0.976$; $p = 0.423$),
375 nor the probability of uniform responses ($F_{(3,21)} = 1.272$; $p = 0.310$) varied as a function
376 of visual field location probed. While this suggests that visual field anisotropies cannot
377 explain our main findings, a null effect (absence of evidence) does not provide conclusive
378 proof (evidence of absence). A second observation arguing against anisotropies is that,
379 while results from the absolute performance seem to roughly align with the idea of upper-

380 lower visual field anisotropies (Fig 2), results from the fitted memory precision (Fig 3A)
381 imply no such distinction.

382 Finally, we also directly probed whether real TMS and sham TMS interact, as such an
383 interaction would provide the most convincing evidence against the idea that upper
384 versus lower visual field anisotropies (rather than TMS effects) might be driving
385 performance differences at the four locations. In order to perform this direct comparison,
386 we analyzed the absolute performance during sham in a manner identical to that of real
387 TMS: performance was determined at each of the four visual field locations relative to
388 the location ‘targeted’ by sham (for example, a sham coil over the right hemisphere
389 ‘targeted’ the lower left visual field). Data for both sham and real TMS were collapsed
390 across stimulated hemisphere, resulting in 160 and 40 observations per condition on
391 average for real and sham TMS respectively. An ANOVA comparing the 2 TMS
392 conditions (real and sham), 2 pulse timings (early and late), and 4 locations (‘same’,
393 ‘contra’, ‘ipsi’, and ‘diagonal’) revealed a significant interaction between pulse timing
394 and location ($F_{(3,21)} = 3.752$; $p = 0.027$). Note that neither TMS condition and location
395 ($F_{(3,21)} = 0.204$; $p = 0.893$) nor TMS condition and timing ($F_{(1,7)} = 2.007$; $p = 0.2$)
396 interacted significantly.

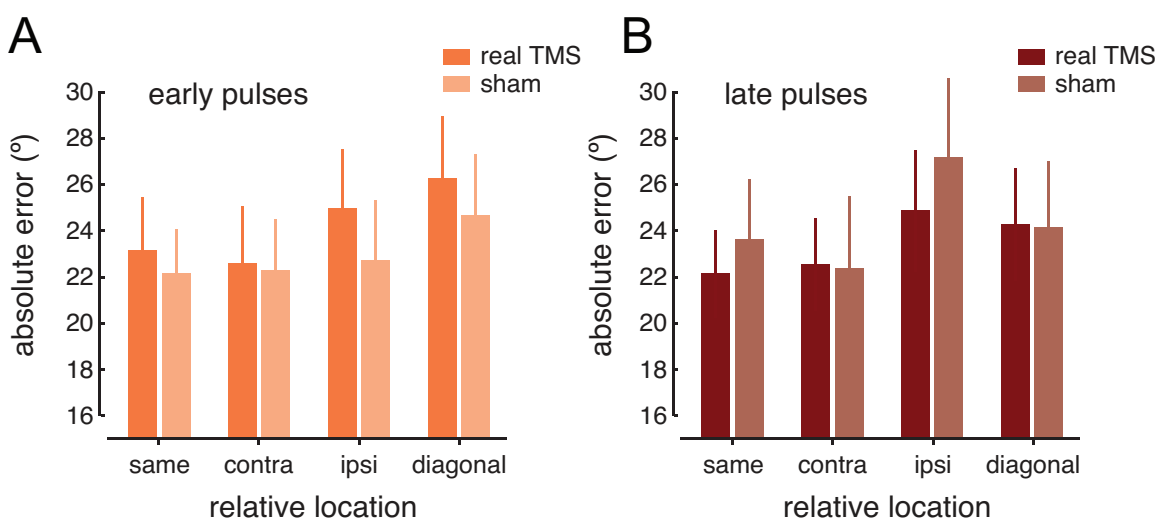


Fig 4. Absolute performance during real and sham TMS. (A) Performance when real or sham pulses were applied early during retention, directly at stimulus offset. **(B)** Performance for pulses (real or sham) applied midway through the retention interval. Error bars depict ± 1 SEM.

397 Thus, direct comparison of real and sham TMS did not yield entirely conclusive results.
398 One obvious problem is that sham data could have been more variable due to the smaller
399 number of trials, making comparisons less robust (but also note that 40 trials per
400 condition is still considerable when not performing any fitting procedures). A more
401 pertinent problem is that performance during TMS is not expected to differ from
402 performance during sham outside of the TMS-targeted location. In fact, when we only
403 considered visual field locations where real TMS is expected to yield an effect (i.e.
404 overlapping with, or ipsilateral to, the targeted location) the interaction between TMS
405 condition and timing did reach significance ($F_{(1,7)} = 5.975$; $p = 0.044$), suggesting that
406 real TMS and sham differentially affect performance at different time points of memory
407 maintenance.

Discussion

408 While participants were remembering four orientations, 10Hz triple-pulse TMS was
409 applied over early visual cortex retinotopically corresponding to the location of one of the
410 to-be-remembered items. Orientation recall differed between the four locations at which
411 stimuli had been presented, with better performance at the location targeted by TMS
412 compared to the location diagonal to TMS. Additionally, memory was impaired for early
413 (directly at stimulus offset) compared to late (midway through retention) pulses.
414 Replication errors were fit with a mixture model to reveal relative contributions of
415 changes in memory variability on the one hand, and the probability of guessing responses
416 on the other: Spatially specific improvements proximal to the pulse were attributed to
417 reduced response variability, implying that memory precision can be improved locally by
418 means of TMS. Global impairments for early compared to late pulses were due to an
419 increased likelihood of guess-like responses, implying retinotopically aspecific
420 disturbances due to TMS at the tail end of encoding. A cartoon-summary of these
421 findings is shown in Figure 5. None of these findings were observed with sham TMS.
422 While it is possible that performance at the four stimulus locations differed because of
423 visual field anisotropies, such anisotropic contributions were likely not driving the
424 observed TMS effects.

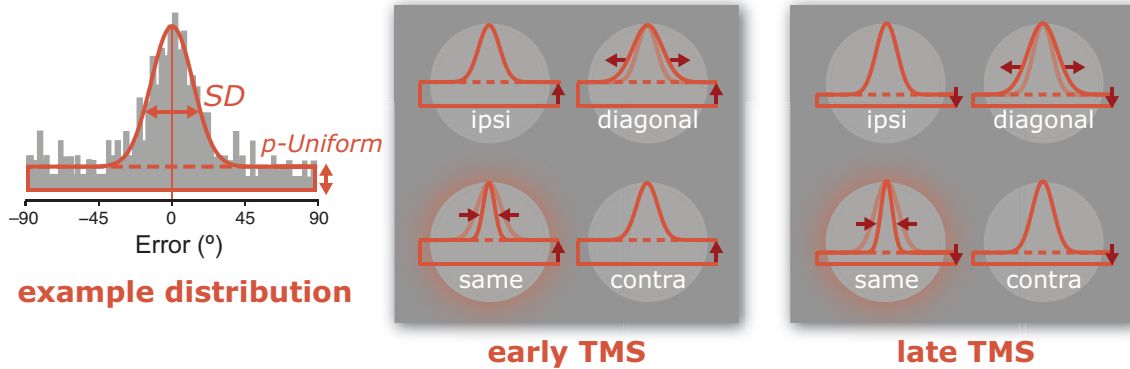


Fig 5. Cartoon summary of results. The left most panel depicts an example response distribution. The frequency of response errors (i.e. difference between cued orientation and response) is indicated by the height of the grey bars. Most responses are centered on a mean replication error of 0°, and the precision with which this replication is achieved is captured by the mixture model *SD* parameter (smaller *SD* indicates more precision). Some responses appear to be random guesses, indicated by the probability of guesses or ‘uniform responses’ (< *p-Uniform* means less guessing). A mixture model fit to the response errors is depicted in thick orange lines. The two rightmost panels provide a cartoon summary of our main results (exaggerated and simplified for illustrative purposes). First, the main effect of relative location is shown by increased memory precision (*SD*) at the location targeted by TMS (‘same’) compared to the control quadrant (‘diagonal’) for both early and late TMS pulses (compare *SD* at four visual field locations). Second, the main effect of pulse timing is shown by increased guessing when pulses were applied early compared to pulses applied late irrespective of visual field location (compare *p-Uniform* between middle and right most panels).

425 Our task encouraged binding the memorized features to their visual field positions by
426 making memory retrieval contingent upon spatial location. Limits on the spatial extent of
427 sensory recruitment have been a matter of some debate, found in some cases [8] but not
428 others [1,15]. Our findings of locally improved memory performance and precision
429 provide support for retinotopically specific sensory recruitment during visual memory.
430 What is more, this local improvement was present irrespective of the time point during
431 which TMS was applied, demonstrating that TMS can impact visual short-term memories
432 beyond the sensory encoding stage.

433 Why might early pulses lead to more guess-like responses than late pulses? Simple
434 modulations of attention or distractibility due to the timing of the three auditory clicks
435 emitted by the TMS coil could not explain this – using the same timing and sounds
436 revealed no costs for early compared to late sham TMS. Guessing responses can result
437 from forgetting, lapses of attention, or encoding failures. Since our early pulses were
438 presented at the tail end of encoding [51-54], it is possible that TMS increased random

439 guesses by prohibiting adequate encoding of the four stimuli. This finding is in line with
440 previous work showing disruptions to visual memory when TMS was applied over visual
441 cortex during the early stages of retention [24,28]. However, this earlier work observed
442 retinotopically specific disruptions. Why might we find that early pulses affected
443 performance across the visual field?

444 First, while stimulus orientations were chosen randomly and independently, accidental
445 yet strong ensemble effects probably occurred on a portion of trials by virtue of our
446 design. Anticipating the fixed trial-by-trial spatial location of memory stimuli,
447 participants could have adapted a strategy relying on the constellation of the four
448 orientations (as radial, concentric, isotropic, etc.) rather than storing features in a truly
449 independent manner. Perceptual grouping of elements allows more of them to be stored
450 in memory [55], and taking perceptual grouping and higher-order structures between
451 items into account helps explain memory performance [56,57]. Thus, early TMS pulses
452 applied while participants were extracting global shape-like representations could disrupt
453 encoding of the whole ‘object’ through the disturbance of localized ‘object features’ (i.e.
454 orientations), resulting in increased guesses for all orientations during retrieval. Such an
455 ‘object-based’ short-term memory strategy might be achieved by convergent feed-
456 forward and feedback processes at multiple stages of the visual hierarchy [58,59] – an
457 intriguing possibility that could be tested empirically in the future.

458 Second, a higher likelihood of guessing responses for early compared to late pulses
459 implied that different processes (or global cognitive ‘states’) were occurring at different
460 stages of the retention interval. A brain ‘state’ can refer to many things like general
461 arousal level, attention or inattention, being trained or untrained, adapted or unadapted,
462 etc. Acknowledging that TMS interacts with the initial brain state helps frame prior
463 studies applying TMS over visual cortex during short-term memory maintenance,
464 unveiling both performance *decrements* [23,24,28], as well as *improvements* [28,34].
465 Specifically, it has been proposed that TMS may preferentially activate neurons in low
466 initial activation states (i.e. low firing) relative to more active populations [30,60,61].
467 Alternatively, the effect of TMS on neuronal firing is monotonic, but behavioral effects

468 (facilitation versus impairment) depend on non-linearity in the input response function of
469 the sensory neurons [62]. Either way, additional mechanisms beyond global brain states
470 must be assumed to account for *local* improvements in memory precision that exist
471 independent (and in addition to) the *global* TMS timing effects reported here.

472 First, TMS might enhance processing of a memorized orientation *locally*. For example,
473 we used low-intensity TMS, which could protect local populations of neurons at the TMS
474 location against temporal decay by pushing weak signals above threshold. A related idea
475 is that TMS enhancement depends on non-monotonic intensity responses [62] as
476 mentioned above: The first basic premise is that TMS acts via a wholesale multiplication
477 of neural responses. The second premise is that while remembering an orientation, the
478 memory trace of that orientation in a population of orientation selective neurons is weak,
479 with firing rates only slightly elevated above baseline. In terms of intensity response, the
480 remembered orientation has a response that is slightly larger than that of not-remembered
481 orientations. However, because of the nonlinearity of intensive response profiles, a
482 wholesale multiplication by any factor due to TMS would result in higher signal-to-noise
483 for the remembered orientation. Conceivably, such signal-to-noise benefits could be
484 induced with TMS on a directly perceived orientation as well, as long as contrast remains
485 lower than the inflection point of the contrast response function, and intensive responses
486 undergo expansive nonlinearity.

487 Second, participants in our experiment simultaneously remembered multiple stimuli
488 presented at *distributed locations*, each stimulus competing for processing resources. This
489 raises the possibility that mnemonic representations interacted and that TMS yoked
490 competition spatially, in favor of the targeted retinotopic location. By enhancing neural
491 firing at one of multiple task-relevant locations, TMS might mimic spatial attention: It's
492 been shown that in the absence of a visual stimulus, spontaneous firing rates in V2 and V4
493 were elevated when attention was directed at a location that fell within a cell's receptive
494 field [63]. Thus, TMS might act as a bottom-up implementation of an otherwise top-
495 down biasing signal, potentially by means of a spatial gating mechanism that favors the
496 boosted location during subsequent processing stages [64].

497 Note that the results reported here seem to indicate a mixture of both improved and
498 impaired performance more proximal and distal to TMS respectively. Thus, TMS might
499 be attenuating regulatory processes that mediate competition between orientation
500 representations at distributed visual field locations. This can be framed in terms of a
501 recent population-coding model of short-term memory [14,65,66] that assumes stimulus
502 features (like orientation) are stored by probabilistic spiking activity in tuned populations
503 of neurons. Critically, this model includes a broad normalization component by keeping
504 the sum of the firing rates remains constant (across changes in set size or attentional
505 prioritization, for example) [46,65]. Normalization describes neuronal responses as
506 consisting of an input or ‘drive’, divided by the summed activity of a normalization pool
507 [67,68]. The assumption that normalization occurs between all items held in memory
508 could explain our findings via a multiplicative increase of the input drive of neurons at
509 the TMS site, biasing the overall population activity in favor of the TMS location (and
510 against non-TMS locations).

511 Alternatively, inhibitory interactions might exist between the four simultaneously
512 remembered orientations: At a local level, TMS can release orientation representations
513 from inhibitory interactions during a tilt illusion paradigm [69]. Likewise, in our study
514 TMS could have acted to depress horizontal connections between spatially distributed
515 representations, attenuating interference at the targeted location. In the brain, lateral
516 connections between neurons in posterior visual areas with relatively large aggregate
517 receptive field sizes [70], monosynaptic trans-colossal connections between the primary
518 visual hemispheres [71], or top-down influences from for example prefrontal cortex
519 [65,72] are all routes through which interactions between multiple and spatially
520 distributed stimulus representations might arise.

521 These ‘local’ and ‘distributed’ hypotheses about improved processing at the TMS
522 location, while thought-provoking, should be tested empirically in future work to
523 ascertain their true value. To that, we’d like to add some additional considerations
524 regarding the work presented here. First, noisy performance from a couple of participants
525 precluded reliable fitting using Maximum Likelihood Estimation. Instead we binned the

526 data in bins of 12° before deriving parameter estimates. While rather coarse, this bin size
527 was chosen to maximize R^2 values, and results were comparable for analyses using
528 smaller bins (i.e. 8° or 10°). Error fitting performed in this way is purely empirical, unlike
529 model fitting, and could even be considered the better choice here. However, it should be
530 noted that when applying a maximum likelihood approach the directionality of effects
531 was preserved, but neither precision differences across the visual field ($F_{(3,21)} = 1.837$; $p =$
532 0.171), nor the pulse timing effects on guessing responses ($F_{(1,7)} = 2.854$; $p = 0.135$)
533 remained significant.

534 Second, TMS effects are usually small, and people's response to TMS highly variable,
535 which is why TMS results generally benefit from large sample sizes. Instead, here we
536 opted for an in depth psychophysical approach, spanning many sessions and trials. The
537 strength of our design is that it allowed us to investigate the mechanistic underpinnings
538 memory maintenance in visual cortex. Our findings dovetail previous reports of
539 retinotopically [24] and temporally [28] specific effects of visual cortical TMS on short-
540 term memory. In addition, our findings suggest that memory precision is affected
541 retinotopically, while effects of pulse timing are likely a matter of global state-like
542 processes. The trade-off however, was a relatively smaller number of participants.

543 Despite these cautionary notes, our results provide several consistent and intriguing
544 findings. Combining the mixture-model with TMS offered novel insights into the role of
545 early visual cortex during the short-term retention of visual items in memory, while
546 affirming the involvement of these areas. We were able to uncover a double dissociation,
547 showing local changes in memory precision at the TMS location, and global changes in
548 guess rates contingent on pulse timing, with more frequent guesses for TMS applied at
549 the tail end of encoding compared to midway during the delay. Our work adds to an
550 existing literature demonstrating retinotopically specific sensory recruitment [8] and early
551 visual cortex TMS impacting visual short-term memory [24,25,28].

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