Title: Evidence for immediate enhancement of hippocampal memory encoding by network-targeted theta-burst stimulation during concurrent fMRI

Abbreviated title: Immediate impact of theta-burst stimulation

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Abstract: The hippocampus supports episodic memory via interaction with a distributed brain network. Previous experiments using network-targeted noninvasive brain stimulation have identified episodic memory enhancements and modulation of activity within the hippocampal network. However, mechanistic insights were limited because these effects were measured long after stimulation and therefore could have reflected various neuroplastic aftereffects with extended timecourses. In this experiment with human subjects of both sexes, we tested for immediate stimulation impact on encoding-related activity of the hippocampus and immediately adjacent medial-temporal cortex by delivering theta-burst transcranial magnetic stimulation (TBS) concurrent with fMRI, as an immediate impact of stimulation would suggest an influence on neural activity. We reasoned that TBS would be particularly effective for influencing the hippocampus because rhythmic neural activity in the theta band is associated with hippocampal memory processing. First, we demonstrated that it is possible to obtain robust fMRI correlates of task-related activity during concurrent TBS. We then identified immediate effects of TBS on encoding of visual scenes. Brief volleys of TBS targeting the hippocampal network increased activity of the targeted (left) hippocampus during scene encoding and increased subsequent recollection. Stimulation did not influence activity during an intermixed numerical task with no memory demand. Control conditions using beta-band and out-of-network stimulation also did not influence hippocampal activity or recollection. TBS targeting the hippocampal network therefore immediately impacted hippocampal memory processing. This suggests direct, beneficial influence of stimulation on hippocampal neural activity related to memory and supports the role of theta-band activity in human episodic memory.

Significance Statement: Can noninvasive stimulation directly impact function of indirect, deep-brain targets such as the hippocampus? We tested this by targeting an accessible region of the hippocampal network via transcranial magnetic stimulation during concurrent fMRI. We reasoned that theta-burst stimulation would be particularly effective for impacting hippocampal function, as this stimulation rhythm should resonate with the endogenous theta-nested-gamma activity prominent in hippocampus. Indeed, theta-burst stimulation targeting the hippocampal network immediately impacted hippocampal activity during encoding, improving memory formation as indicated by enhanced later recollection. Rhythm- and

location-control stimulation conditions had no such effects. These findings suggest a direct influence of noninvasive stimulation on hippocampal neural activity and highlight that the theta-burst rhythm is relatively privileged in its ability to influence hippocampal memory function.

Introduction

The hippocampus exhibits theta-band (~4-8 Hz) oscillatory neural activity that is thought to provide a temporal framework for episodic memory (Buzsaki, 2002; Lisman and Jensen, 2013; Herweg et al., 2020). Episodic memory involves hippocampal interaction with a distributed network (Squire and Zola-Morgan, 1991; Eichenbaum et al., 2007; Ranganath and Ritchey, 2012) that exhibits interregional synchrony of memory-related activity preferentially in the theta band (Fell et al., 2001; Buzsaki and Draguhn, 2004; Foster et al., 2013; Lisman and Jensen, 2013; Staudigl and Hanslmayr, 2013). Although the functional significance of hippocampal theta activity has been tested via stimulation in rodents (Shirvalkar et al., 2010; Zutshi et al., 2018), such direct functional tests present major challenges for human experimentation.

Stimulation using a theta-rhythmic pattern, as in theta-burst stimulation (TBS; high-frequency stimulation delivered in a theta rhythm), should be capable of testing the role of theta in episodic memory. This is because TBS mimics the endogenous theta rhythm thought to support hippocampal memory processing and hippocampal network synchronization, and therefore may optimally influence this network's function via activity entrainment (Buzsaki, 2002; Thut et al., 2011b; Romei et al., 2016). Direct stimulation of the hippocampus is not possible in human subjects without neurosurgery, but noninvasive stimulation can directly test network functional properties (Fox et al., 2012). Multiple experiments using transcranial magnetic stimulation (TMS) have shown that it is possible to influence episodic memory by targeting the hippocampal network (Hebscher and Voss, 2020). In those experiments, network-targeted TMS increased hippocampal network fMRI connectivity, memory-related fMRI activity, and/or improved memory performance for hours to weeks post-stimulation e.g., (Wang et al., 2014; Kim et al., 2018; Tambini et al., 2018; Freedberg et al., 2019; Hermiller et al., 2019b; Warren et al., 2019). Consistent with the hypothesized importance of theta for memory, one study found that network-targeted TBS had greater impact on memory accuracy and memory-related hippocampal fMRI connectivity than did a non-theta (20-Hz) control frequency (Hermiller et al., 2019a). However, a weakness of previous noninvasive stimulation experiments with respect to mechanistic interpretation is that these studies measured long-lasting aftereffects of stimulation (ranging from minutes to weeks), which could be mediated by a variety of indirect neuroplasticity mechanisms (Thickbroom, 2007).

Evidence for preferred influence of TBS on memory-related neural activity would require immediate assessment of stimulation impact.

To address this, we delivered TBS to a hippocampal-network-targeted (HNT) location in the parietal cortex during concurrent fMRI while subjects performed a memory task. We developed custom fMRI parameters that allowed TBS as well as control-frequency (12.5 Hz) stimulation during scanning. These scanning parameters were suitable for our focus on the effects of TBS on hippocampus and adjacent cortex of the medial temporal lobe (MTL), as high-quality fMRI signals were obtained from these areas.

Human subjects studied complex visual scenes that were each immediately preceded by either HNT TBS or by one of several control stimulation conditions (Fig. 1). We hypothesized that HNT TBS delivered in the seconds immediately preceding individual stimuli would increase fMRI activity evoked by scenes in the hippocampus, reflecting the effects of successful entrainment of the hippocampal theta rhythm by TBS. Based on robust evidence that increased hippocampal activity during encoding is associated with later recollection (Paller and Wagner, 2002; Kim, 2011; Rugg et al., 2012) and previous findings that hippocampal network-targeted stimulation enhances recollection (Hebscher and Voss, 2020), we predicted increased recollection for scenes encoded with HNT TBS. We included various control conditions, including controls for the cognitive task (memory versus non-memory), stimulation rhythm (TBS versus non-theta), stimulation location (HNT versus out-of-network), and hemisphere (targeted left versus non-targeted right hippocampus). Because the experiment involved a randomized trial-based stimulation design, immediate and selective effects of HNT TBS on hippocampal memory-related activity would indicate that this type of stimulation impacted hippocampal neural activity, rather than longer-lasting neuroplasticity processes that would carry over to affect other trials, and would thereby support the role of theta in human memory formation.

Materials and Methods

Overview

Following a baseline session, subjects completed a two-day experiment in which they attempted to remember complex visual scenes that were each immediately preceded by different stimulation

117 conditions, performed during fMRI scanning. The main condition of interest was TBS delivered to a
118 hippocampal-network targeted (HNT) location in the parietal cortex immediately before the onset of
119 scenes. Several control conditions were used to test specificity. Subjects also received stimulation
120 immediately before the presentation of numeric judgments, interleaved randomly with the scenes
121 throughout the task (Fig. 1A). We expected no effect of stimulation on hippocampal activity for this
122 condition, as hippocampal activity is generally not evoked by numeric judgments (Stark and Squire,
123 2001) and therefore would not increase via direct effects of stimulation on hippocampal neural activity.
124 Furthermore, the same scene and number conditions were administered in three control stimulation
125 conditions: (i) a different stimulation rhythm (beta; 12.5 Hz) (Fig. 1B) applied to the same HNT location,
126 (ii) TBS applied to a control location in the supplementary motor area (SMA) outside the hippocampal
127 network (Fig. 1C), and (iii) beta stimulation of the SMA location. None of these control conditions were
128 expected to influence hippocampal activity. Finally, stimulation was not delivered for a subset of scene
129 and number trials, providing a no-stimulation ("off") control condition. Scene and number trials with and
130 without stimulation were intermixed throughout scanning sessions, guarding against confounding
131 influences such as stimulation-induced fMRI artifact and stimulation carry-over effects across trials. All
132 conditions were administered in each subject using a within-subjects counterbalanced design over two
133 experimental sessions (Fig. 1D). As indicated above, our *a priori* hypotheses were that the HNT TBS
134 encoding condition would be unique among all stimulation conditions in producing: (1) increased
135 likelihood of later recollection during the memory test, and (2) increased activity in the left (targeted)
136 hippocampus during encoding of scenes that would be later recollected during the memory test.
137
138 Subjects
139 Adult human subjects passed standard MRI and TMS safety screenings (Rossi et al., 2009), reported no
140 present use of psychoactive drugs, and were free of known neurological and psychiatric conditions.
141 Datasets from 16 subjects were included in all reported analyses (8 females, 8 males; ages 20-35 years,
142 average age=27.6, SD=4.3). Data from two additional subjects were collected but excluded from all
143 reported analyses due to poor behavioral performance (overall miss rate > 50%). In addition, data
144 collection was attempted from three additional subjects but failed due to technical malfunction (n=2) or

attrition (n=1). Subjects gave written informed consent approved by the Northwestern University Institutional Review Board and were paid for participation. The sample size of N=16 was chosen to match or exceed previous experiments that demonstrated memory improvement for stimuli encoded following short volleys of TMS (i.e., <2 s TMS immediately before stimulus onset) (Kohler et al., 2004; Demeter et al., 2016).

Baseline session

Subjects completed a baseline session to determine stimulation locations and intensity prior to two experimental sessions, performed on different days (described below).

Baseline MRI to determine stimulation locations

Resting-state fMRI and structural MRI were collected using a 3T Siemens PRISMA scanner with a 64-channel head/neck coil. Baseline resting-state functional images were acquired using a blood-oxygenation-level-dependent (BOLD) contrast sensitive gradient-echo echo-planar imaging (EPI) pulse sequence (270 frames; TE 20 ms; TR 2000.0 ms; flip angle 80°; voxel resolution 1.7 mm isotropic; 70 ascending axial slices; 210x203 mm FOV; scan duration 9 min). During the resting-state scan subjects were instructed to lie as still as possible, to keep their eyes open and focused on a fixation cross presented in the center of the screen, and to let their minds wander. Structural images were acquired using a T1-weighted MPRAGE sequence (176 frames; TE 1.69 ms; TR 2170 ms; TI 1100 ms; flip angle 7°; voxel resolution 1.0 mm isotropic; 256x256 mm FOV; GRAPPA acceleration of a factor of 2; scan duration 6.36 min).

Baseline scans were submitted to resting-state fMRI connectivity analysis to determine stimulation locations. All fMRI analyses used AFNI (Cox, 1996) and were visualized with the BrainNet Viewer Matlab (The MathWorks, Inc. Natick, MA, USA) toolbox (Xia et al., 2013) on a smoothed Colin27 template. Anatomical scans were skull-stripped (*3dSkullStrip*) and co-registered to standardized space using the Colin27 template (*auto_tlrc*). Preprocessing of the functional volumes included outlier suppression (*3dDespike*), slice timing and motion correction (*3dvolreg*), and co-registration to the anatomical scan (*align_epi_anat*). The transformations were applied simultaneously in a single

173 resampling step (*3dAllineate*). Motion parameters were calculated for each volume as the Euclidean
174 norm of the first difference of six motion estimates (three translation and three rotation). Volumes with
175 excessive motion (>0.2 mm), as well as the previous volume, were censored. On average, 0.42%
176 (SD=1.11, range=0-4.44%) of the resting-state volumes were censored. Data were spatially smoothed
177 using a 4-mm full-width-at-half-maximum (FWHM) isotropic Gaussian kernel (*3dmerge*) and signal
178 intensity was normalized by the mean of each voxel. EPI masks were created that included only voxels in
179 the brain that were not excluded due to instability by *3dAutomask*. Bandpass filtering (0.01-0.1 Hz),
180 motion censoring, and nuisance time series (estimates of motion parameters and their derivatives) were
181 detrended from each voxel simultaneously (*3dDeconvolve, 3dTproject*) to yield a residual time series
182 used in connectivity analyses.

183 Seed-based resting-state fMRI connectivity was used to determine subject-specific stimulation
184 locations used in the subsequent concurrent TMS-fMRI experimental sessions. For each subject, a 2 mm
185 seed in the left hippocampus (MNI: -30 -18 -18) was used in a seed-based functional connectivity
186 analysis (*3dTcorr1D*) to identify a left lateral parietal cortex location with robust fMRI connectivity to the
187 left hippocampal seed (mean z(r)=0.38, SD=0.05; average MNI: -53 -41 27). This was the stimulation
188 location used for hippocampal-network-targeted (HNT) stimulation (Fig. 1C). The control out-of-network
189 stimulation location was anatomically determined in the left supplementary motor area (SMA; average
190 MNI: -36 -3 67), a region outside of the targeted hippocampal network. Both the HNT and SMA locations
191 allowed the TMS coil to be positioned in the scanner without blocking the subjects' view of the screen.
192 Due to coil displacement during scanning, the actual achieved stimulation locations deviated from these
193 intended targets (see below and Fig. 1C).

194

195 *Baseline stimulation intensity determination*

196 TMS was delivered with a MagPro X100 stimulator using a MagPro MRi-B91 air-cooled butterfly
197 coil and MRI-compatible TMS setup (MagVenture A/S, Farum, Denmark). Resting motor threshold (RMT)
198 was found during the baseline session in order to determine the stimulation intensity used during the
199 experimental sessions (see below). Subjects sat at the entrance of the MRI bore with their arms resting
200 comfortably during RMT determination. The MRi-B91 TMS coil was used to determine RMT as the

minimum percentage of stimulator output (% SO) necessary to generate a visible contraction of the right thumb (*abductor pollicis brevis)* for five out of ten consecutive single pulses. Pulses were biphasic, as were pulses delivered during experimental sessions. RMT values ranged between 45.0-85.0% SO (mean=61.6, SD=10.8).

Experimental Sessions

Following the baseline session, subjects returned for two experimental TMS/fMRI sessions on separate days to complete a 2x2 crossover design. One stimulation pattern (TBS or beta) was used during each session. Within each session, there were two study phases that differed in stimulation location (HNT or SMA). The order of these conditions (TBS or beta session; HNT-then-SMA or SMA-then-HNT within each session) was counterbalanced across subjects. Memory for scenes encoded during both study phases was tested at the end of the experimental session, after subjects finished MRI scanning.

Experiment Design

There were two study phases during each of the two experimental sessions. Each study phase lasted ~70 min and comprised 144 trials (288 trials total for the session). Each trial began with a white fixation cross presented in the center of the screen, during which ~ 2 s stimulation was delivered (see TMS/fMRI acquisition methods for exact timing). Immediately following stimulation, a visual stimulus was presented for 2 s. The study item was followed by a white fixation cross that remained on the screen until the next trial for a randomly varied duration between 11-19.5 s. Different visual stimuli were presented during each study phase. Complex visual scenes (50% of trials; 144 scenes total for the session) were randomly intermixed with numeric stimuli (50% of trials; 144 numbers total for the session). During the scene presentation, subjects were instructed to imagine visiting the depicted location and to rate via button press whether they would like to visit the location (right hand button) or not (left hand button). Scenes were chosen from the SUN397 dataset (Xiao et al., 2016) based on the following criteria: complex outdoor natural scenes (e.g., mountains, beaches, forests, waterfalls, deserts) without prominent humans, animals, or man-made objects; color image; image did not include text. Subjects were told that memory would be tested for all scenes following the study phase (i.e., intentional

229 encoding). Numeric stimuli were randomly selected from the integers 1-864 and presented in white font
230 for 2 s. Subjects used a button response to indicate if the number was even (right hand button) or odd
231 (left hand button). Visual scene stimuli were randomly assigned to either a study trial stimulation
232 condition or to serve as a lure during memory testing (see below) for each subject. Stimuli were
233 presented in the center of an MRI-compatible LCD screen (Nordic Neuro Lab, Bergen, Norway)
234 positioned at the subjects' feet, on a gray background, viewed via a mirror attached to the head coil.
235 Responses were made with hand-held fiber optic button boxes (Current Designs, Inc., Philadelphia, PA,
236 USA). Subjects were told that they could make their responses during the white fixation cross following
237 each stimulus and that response times were not important (i.e., self-paced responses).

238 Stimulation was delivered for ~2 s (see TMS/fMRI acquisition methods for exact timing)
239 immediately preceding stimulus onset for 66% of scene and numeric trials (i.e., stimulation presence on),
240 with no stimulation for the remaining trials (i.e., stimulation presence off). Long inter-trial intervals (11-
241 19.5 s) were used to reduce stimulation carry-over effects (Huang et al., 2005). During one study phase
242 stimulation targeted the hippocampal network via left parietal cortex (HNT), and during the other study
243 phase stimulation targeted the SMA. Subjects came out of the scanner for a break of ~10 min between
244 study phases for TMS coil repositioning. The order of these conditions was counterbalanced across
245 subjects.

246 Prior to getting in the scanner for the study phases, MRI-navigated TMS software (Localite
247 GmbH, St. Augustin, Germany) was used to physically mark the individualized stimulation locations on
248 the participant's scalp. A conformable MRI-compatible marker was affixed to the scalp at the intended
249 stimulation location (12.7 mm x 12.7 mm re-sealable plastic bag filled with yellow-mustard MRI contrast
250 agent; Plochman, Inc., Manteno, IL, USA). The markers were used to position the TMS coil against the
251 subject's head in the scanner and coil location was recorded via MRI anatomical scans during each
252 study phase (see below).

253 One experimental session used TBS and the other used beta TMS, administered in
254 counterbalanced order across subjects. For both stimulation patterns, 30 TMS pulses were delivered
255 during the 2 s prior to stimulus onset per trial, delivered at the same intensity for each subject (80%
256 RMT). For TBS, pulses were delivered as 50 Hz triplets at 5 Hz. For beta stimulation, pulses were

delivered individually at 12.5 Hz. TMS pulses were synchronized with the MRI scan and with visual stimulus onset (see below). To acclimate subjects to the stimulation protocols and to ensure that stimulation did not cause scalp/facial twitches, a train of stimulation was applied once the subject was positioned inside the scanner and the TMS coil was positioned at the targeted location before scanning in each study phase. Stimulation intensity was lowered during one or both sessions due to technical limitations for 5 subjects. On average, TBS was delivered at 78.8% RMT (SD=1.9, range=75.0-80.0) and beta stimulation was delivered at 78.5% RMT (SD=2.2, range=74.1-80.0). The experimental sessions were scheduled at least two days apart, with an average of 27 days between sessions (range=3-84 days). For 1 subject, a session was discarded due to technical difficulties and the subject returned for a third “replacement” session. The replacement session was performed with the same location and pattern order as the discarded session, but with different visual stimuli. There were no relationships between the delay from the first to second sessions and the effect of the TBS and beta stimulation conditions on recollection memory reported below, as indicated by non-significant across-subject Pearson correlations of these variables (P’s>0.14).

At the end of each experimental session, memory was tested for the scenes that were presented during both of the study phases for that session (one study phase with HNT stimulation and one with SMA stimulation). After completing both study phases, subjects rested out of the scanner for ~15 min before taking the memory test, which was not scanned. The 144 scenes presented during the study phases were presented one at a time intermixed randomly with 144 novel lures that were not presented during study phases, in randomized order. Subjects were instructed to respond with (i) “Remember” if they specifically recalled details about the scene, (ii) “Familiar” if they recognized the scene but could not recollect details, and (iii) “New” if the scene was a lure (Yonelinas, 2002; Eichenbaum et al., 2007). Assessment of remember versus familiar responses was a key aspect of the study design, as recollection is highly related to increased hippocampal activity during encoding (Paller and Wagner, 2002; Kim, 2011; Rugg et al., 2012) and our previous experiments using hippocampal network-targeted stimulation have identified increased recollection rather than nonspecific aspects of memory performance (Hebscher and Voss, 2020). Thus, we hypothesized that the effects of HNT TBS would be specific to

284 remember responses. Trials were self paced, with the scene remaining on the screen until a response
285 was registered. The duration of the test phases was 20.8 min on average (range=14-29, SD=4.48).
286
287 *Simultaneous TMS/fMRI acquisition*
288 MRI was performed during study phases using a 3T Siemens PRISMA scanner with a single-
289 channel transmitter/receiver head coil. Fast low-angle shot (FLASH) anatomical scans were collected
290 between study phases to localize the actual location of the TMS coil relative to markers placed on the
291 scalp, including a T1 sagittal (50 slices; TE 2.42 ms; TR 311.0 ms; flip angle 80°; 1.0 mm in-plane
292 resolution; 4.0 mm thick sagittal slices with 0 mm gap; 50% phase oversampling; 256x256 mm FOV;
293 scan duration 44 sec) and a T1 oblique axial (40 slices; TE 2.42 ms; TR 249.0 ms; flip angle 80°; 1.0 mm
294 in-plane resolution; 4.0 mm thick axial slices with 0 mm gap; 60% phase oversampling; 256x256 mm
295 FOV; scan duration 36 sec). These anatomical scans were later used to localize the TMS coil targeting
296 displacement (see below).
297 We developed two fMRI scan sequences to interface with TMS pulses for the TBS and beta-
298 patterned stimulation conditions. Task-based functional images were acquired using a BOLD contrast
299 sensitive gradient echo EPI pulse sequence that contained custom programmed temporal gaps
300 interleaved between slice acquisitions. Rather than delivering stimulation during slice acquisition, which
301 causes TMS-induced artifact that requires volumes to be discarded (Bestmann et al., 2008; Siebner et
302 al., 2009), TMS was delivered between MRI slice acquisitions during the inserted temporal gaps. This
303 TMS-fMRI method did not cause artifact beyond that associated with the physical presence of the TMS
304 coil, which produces stable artifact near the coil (see Results).
305 For both stimulation patterns, 30 TMS pulses were delivered during the imaging volume
306 immediately prior to visual stimulus onset for conditions that involved stimulation. Pulses were delivered
307 over a duration of 2000 ms in the TBS condition (Fig. 2A) and 2400 ms in the beta-patterned stimulation
308 condition (Fig. 2B), for a total of 5760 pulses aggregate over the entire experimental session. For TBS,
309 107-ms temporal gaps were inserted after every two EPI slices (93 ms). During this temporal gap, a 50
310 Hz triplet burst (pulse every 20 ms) was delivered, with one triplet burst delivered every 200 ms during
311 such temporal gaps (665 frames; TE 20 ms; TR 2230.0 ms; 2442 Hz/pixel bandwidth; flip angle 90°;

312 voxel resolution 3.0 mm isotropic; 22 interleaved 3.0 mm thick axial slices angled to AC-PC alignment
313 and centered on the longitudinal axis of the temporal lobes; 50% phase oversampling in the phase-
314 encoding direction; 192x192 mm FOV; scan duration 24.83 min; 72 stimulated trials per scan) (Fig. 2A).
315 For beta-patterned stimulation, 34-ms temporal gaps were inserted after each slice (46 ms), in which a
316 single TMS pulse could be delivered, such that one pulse was delivered every 80 ms during such
317 temporal gaps (270 frames; TE 20 ms; TR 2440.0 ms; 2442 Hz/pixel bandwidth; flip angle 90°; voxel
318 resolution 3. mm isotropic; 30 interleaved 3.0 mm thick axial slices angled to AC-PC alignment and
319 centered on the longitudinal axis of the temporal lobes; 50% phase oversampling in the phase-encoding
320 direction; 192x192 mm FOV; scan duration 28.38 min; 72 stimulated trials per scan) (Fig. 2B). The scans
321 were programmed such that the last TMS pulse would occur at the end of the TR (i.e., all pulses during
322 the final 2000 ms of the 2230 ms TR for the TBS scan and during the last 2400 ms of the 2440 ms TR of
323 the beta-patterned stimulation scan). Phase oversampling in the phase-encoding direction was used in
324 both scans to shift any Nyquist ghosting induced by the presence of the TMS coil outside the brain.
325 The limited coverage in both the theta- and beta-patterned task-based scans precluded whole-
326 brain imaging but did adequately cover MTL regions of interest when the imaging volume was centered
327 at the MTL (Fig. 2AB). Notably regions imaged directly under/around the TMS coil typically exhibit
328 irreparable TMS-induced artifacts (Bestmann et al., 2008; Siebner et al., 2009), but the parietal cortex
329 and SMA stimulation locations did not fall within our limited coverage. Our hypothesis-driven regions of
330 interest were instead in downstream regions distant from the stimulation location. We confirmed image
331 quality by subject-level visual inspection, as well as validating signal quality at the group-level (see
332 Results). Two task-based scans using the same parameters were acquired per the two study phases
333 during each experimental session (~70 min per phase, 144 trials per phase). Participants wore air-
334 conduction earplugs during the scans to attenuate both scanner and TMS noise.
335 A PC in the MRI control room received transistor-transistor logic (TTL) pulses from the MR
336 scanner and, based on the experiment code, then sent TTL pulses to the TMS device to trigger
337 stimulation at appropriate times. TTL pulses were sent per EPI slice acquisition to the experiment control
338 PC, which in turn triggered the TMS device to deliver the programmed stimulation sequence. Thus,
339 stimulation delivery was trial-specific and time-locked to the slice-based MR trigger. During the study

340 phases, experiment events (e.g., pulse signals from the MRI and TMS, stimulator settings, participant
341 responses, task stimuli, etc.) were monitored and recorded in output files created by Presentation
342 (Neurobehavioral Systems, Inc. Berkeley, CA, USA), MagVenture (MagVenture A/S, Farum, Denmark),
343 and LabChart (ADInstruments, Inc. Colorado Springs, CO, USA), as well as by the experimenter in the
344 MRI control room. These records were used by the experimenter to update copies of raw output files with
345 trial-specific deviations (i.e., trials were discarded if only part of the stimulation train was delivered due to
346 coil over-heating; records reflected that the trial condition changed from “ON” to “OFF” if stimulation
347 failed entirely during the 2-s pre-stimulus period).
348
349 *TMS coil displacement during fMRI*
350 We used FLASH anatomical MRI scans (see above) collected before and after the study phase
351 fMRI scans to evaluate the actual location of the TMS coil during the experiment relative to its intended
352 location to account for possible displacement. The scans were uploaded into the MRI-navigated TMS
353 software (Localite GmbH, St. Augustin, Germany) and aligned to the subject’s high-resolution anatomical
354 scan collected during the baseline session. We utilized contrast-agent markers on the TMS coil (vitamin
355 E capsules and oil-filled tubing) and on the scalp (mustard packets, described above) to identify the
356 position, orientation, and rotation of the TMS coil inside the scanner (i.e., 4D Matrix of coordinates)
357 relative to the target that was identified based on resting-state fMRI for each subject (see above). The
358 matrices were transformed with a displacement vector to estimate the cortical coordinates directly under
359 the TMS coil. The across-participant mean MNI coordinates of the achieved HNT location was -50, -52,
360 32 (SD=4.8, 6.7, 6.8) for the TBS session and -49, -51, 33 (SD=4.8, 7.7, 7.3) for the beta stimulation
361 session. The SMA location was -31, -16, 66 (SD=5.4, 9.0, 3.7) for the TBS session and -32, -13, 63
362 (SD=6.0, 9.3, 5.5) for the beta stimulation session. For each participant and condition, the deviation in
363 achieved versus intended stimulation locations was calculated as the Euclidean distance. For the TBS
364 and beta-patterned sessions, there was an average deviation of 8.47 mm (SD=4.04) for the HNT
365 condition and a deviation of 9.02 mm (SD=4.12) for the SMA condition. The amount of deviation did not
366 significantly vary between the two locations (P>0.7). There were no relationships between location
367 deviation across sessions (i.e., TBS versus beta) and the differential effect of stimulation on the

368 recollection memory measures described below, as indicated by non-significant across-subject Pearson
369 correlations of these variables (P's>0.36).

370 To confirm that the HNT and SMA conditions differentially targeted the hippocampal network as
371 intended despite the in-scanner coil displacement, we analyzed resting-state fMRI connectivity of the
372 achieved stimulation location (considering displacement) with the hippocampal network. Using the high-
373 resolution resting-state fMRI scan collected at baseline, we calculated the hippocampal network as
374 regions with robust connectivity to the left hippocampus (defined as 2-mm spherical segments centered
375 at MNI coordinates: -23, -10, -21; -26, -14, -20; -30, -18, -18; -31 -22 -14; -30, -26, -12; see below for
376 description of these locations in the task-based fMRI analysis). The hippocampal functional connectivity
377 map for each subject was created by correlating (Pearson's *r*) the spatially averaged time series of these
378 hippocampal coordinates with every voxel's time series (*3dTcorr*). A Fisher's *z* transformation was
379 applied to yield a normally distributed correlation map for each subject (*3dcalc*). Group-level voxel-wise
380 analysis of these connectivity maps using one-sample one-tailed *t*-tests (*3dttest++*) identified clusters of
381 contiguous voxels with robust connectivity to the hippocampal seed mask (300+ voxels with *z(r)*
382 significantly greater than 0; t-threshold=5.2; P<0.0001). These clusters were saved as a hippocampal
383 network mask (*3dclust*; 6,695 voxels total). This network included locations expected based on the
384 previous literature on typical hippocampal fMRI connectivity (Kahn et al., 2008), including medial and
385 lateral temporal, lateral parietal, ventral medial prefrontal cortex areas. For each subject, we then
386 assessed resting-state connectivity between the achieved stimulation location to every voxel in the
387 hippocampal network mask (*3dTcorr*) and spatially averaged the correlation value to obtain one overall
388 network connectivity value for each stimulation condition for every subject (*3dmaskave*). A 2x2 repeated
389 measures ANOVA testing the effects of stimulation location and pattern on connectivity to the
390 hippocampal network indicated significant variation by location ($F_{1,12}$=4.83, P=0.04, η^2_p=0.24), such that
391 connectivity was significantly greater for the HNT locations (mean=0.15, SD=0.12) relative to the SMA
392 locations (mean=0.06, SD=0.07) (Fig. 1C). Thus, differential targeting of the hippocampal network by the
393 HNT and SMA locations was successful despite coil displacement during fMRI scanning.

394 To confirm that the SMA location stimulated belonged to a distinct network and therefore was a
395 suitable out-of-network control condition, we assessed the connectivity of the achieved SMA locations

using the same connectivity analysis method that was used to define the left hippocampal network but with the achieved SMA location in each subject used as the connectivity seed rather than the left hippocampus (300+ voxels with *z(r)* significantly greater than 0; t-threshold=5.2; P<0.0001; 30,275 total voxels identified). As expected, this network included canonical somatomotor regions including the majority of M1/S1, supplementary motor and somatosensory areas. The hippocampal network and SMA network had minimal overlap (7 voxels overlapping between networks out of 36,963 total voxels in both networks), confirming that the SMA location was suitable for its intended purpose as an out-of-network control.

Subject-level task-based fMRI processing

Anatomical scans were skull-stripped (*3dSkullStrip*) and co-registered to the Colin27 template (*auto_tlrc*). Preprocessing of the functional volumes included outlier suppression (*3dDespike*), slice timing and motion correction (*3dvolreg*), and co-registration to the anatomical scan (*align_epi_anat*). The transformations were applied simultaneously in a single resampling step (*3dAllineate*). Motion parameters were calculated for each volume as the Euclidean norm of the first difference of six motion estimates (three translation and three rotation). Volumes with excessive motion (>0.3 mm), as well as the previous volume, were flagged for censoring during the regression analyses, which is a typical threshold for task-based fMRI analysis. On average, 2.8% (SD=5.0) of the TBS HNT condition, 3.6% (SD=6.1) of the TBS SMA condition, 5.0% (SD=8.0) of the beta HNT condition, and 5.9% (SD=10.2) of the beta SMA condition time series were motion censored. There was no significant difference in the amount of censoring across conditions (all pairwise comparison *Ps*>0.10). Data were spatially smoothed using a 6-mm full-width-at-half-maximum (FWHM) isotropic Gaussian kernel (*3dmerge*) and signal intensity was normalized by the mean of each voxel. Task-based masks were created that consisted only of voxels in the brain with stable signal across the scanning sessions (*3dAutomask*).

Two general linear models (GLMs) incorporating hemodynamic response deconvolution were applied to the preprocessed data to estimate voxel-wise event-related activity regression coefficients for each trial type, separately for each stimulation condition (HNT TBS, SMA TBS, HNT beta, and SMA beta) (*3dDeconvolve)*. GLMs were constructed separately per condition because differences in the scan

424 parameters required for TBS versus beta stimulation precluded concatenation of all conditions into one
425 GLM. In each GLM, trials were separated based on experiment condition (scenes with TMS ON, scenes
426 with TMS OFF, numbers with TMS ON, and numbers with TMS OFF). In a second GLM, the scene trials
427 were further sorted by subsequent memory performance (Remember, Familiar, or New responses during
428 the test). Time points with motion spikes and time series outliers were censored. Polynomial trends and
429 motion estimates and their derivatives were included as nuisance regressors of no interest. Condition-
430 specific activity estimates used the duration-modulated gamma function. Each condition of interest (HNT
431 TBS, SMA TBS, HNT beta, and SMA beta) was modeled, with each event beginning at the stimulus
432 (scene or number) onset. Restricted Maximum Likelihood (REML) estimation methods were used to
433 generate voxel-wise parameter estimates and measures of variability for each trial type for each
434 stimulation condition (*3dREMLfit*). Parameter estimates from each subject were later analyzed at the
435 group-level (see below)
436
437 Data analysis
438 *Memory performance*
439 Performance on the scene recognition test was computed as the rate of hits ("Remember" and
440 "Familiar" responses for studied scenes) and correct rejections ("New" response for novel lures) for each
441 subject separately for every stimulation condition. To evaluate stimulation effects on hippocampal-
442 dependent recollection, we calculated the proportion of hits that were recollected ("Remember"
443 responses) for every stimulation condition. Accuracy was also calculated, as described in the Results
444 section.
445
446 *Group-level task-based fMRI analyses*
447 Voxel-wise analyses were performed in order to confirm that our scan parameters provided
448 sensitivity to expected fMRI correlates of cognitive processing (i.e., scenes but not numbers should
449 evoke activity in parahippocampal, fusiform, and occipital regions (Stern et al., 1996; Stark and Squire,
450 2001) and stimulation sensations (i.e., sound emitted by stimulation should evoke activity in auditory
451 cortex). The first contrast compared BOLD activity evoked by task stimuli (scenes versus numbers)

452 regardless of stimulation presence, location, or pattern; and the second contrasted activation due to
453 stimulation presence (on versus off) regardless of stimuli type or stimulation location or pattern. Subject-
454 level GLMs were used to estimate voxel-wise event-related activity regression coefficients for each trial
455 type (i.e., scenes, numbers, TMS ON, and TMS OFF) and REML estimation methods were used to
456 generate voxel-wise parameter estimates and measures of variability for each subject (*3dDeconvolve,*
457 *3dREMLfit; see above*). GLM maps were analyzed at the group-level using generalized least squares
458 with a local estimate of random effects variance (*3dMEMA*) to identify regions of significant difference
459 (P<0.001, t-threshold=4.07) for scenes versus numbers and for stimulation on versus off. Data from
460 theta-patterned and beta sessions were analyzed separately due to the differences in scan parameters.
461 To test whether differences in parameters between the TBS and beta stimulation scans did not
462 significantly affect the signal quality, the Signal-to-Fluctuation-Noise Ratio (SFNR) summary value
463 (Friedman and Glover, 2006) was assessed and compared between the two fMRI sequences. The mean
464 signal was divided by the standard deviation of the residuals (*3dTstat, 3dcalc)* and then averaged within
465 the limited task coverage mask over the whole session (*3dmaskave*) to yield one TSNR value per
466 stimulation condition per subject.
467 To measure the effect of stimulation on activity during the memory task, performance on the
468 retrieval task was used to back-sort fMRI data to analyze the effects of stimulation on encoding-related
469 activity that predicted subsequent recollection (trials that were later endorsed with "Remember"
470 responses for the main analysis, and trials later endorsed with "Familiar" and "New responses in a
471 control analysis). Subject-level GLMs estimated voxel-wise event-related activity regression coefficients
472 for each trial type (i.e., remembered scenes with TMS ON, remembered scenes with TMS OFF, scenes
473 not-recollected with TMS ON, scenes not-recollected with TMS OFF, numbers with TMS ON, and
474 numbers with TMS OFF) for each stimulation condition (*3dDeconvolve, 3dREMLfit*; see above*)*. For
475 scenes with "Remember" responses, there were 16 trials on average (range=6-33) per condition (trial
476 counts did not vary by condition; Ps>0.2). Trials with remembered scenes with TMS OFF were collapsed
477 across all study sessions to create the "combined off" condition (average number of trials=27, range=15-
478 46). For scenes with non-recollected responses ("Familiar" and "New" responses), there were 33 trials on
479 average per stimulation condition (range=16-64) and a mean of 17 trials in the "combined off" condition

480 (range=8-26). Similarly, activity for numeric judgment trials was estimated, but without respect to test
481 performance (i.e., all trials), separately for each stimulation condition, and collapsed across all study
482 sessions for the “combined off” condition.

483 The influence of stimulation conditions on fMRI activity estimates for studied scenes and numeric
484 judgment trials were tested at the group level using a region-of-interest (ROI) approach. 6-mm radius
485 spherical regions of interest (ROIs) were defined along the hippocampal longitudinal axis in each
486 hemisphere. The middle ROI in the left hemisphere was placed in the body of the hippocampus,
487 centered at the coordinate that was targeted via its connectivity with parietal cortex as measured during
488 the baseline session resting-state fMRI scan (centroid MNI coordinate: -30 -18 -18). However, because
489 the coil was displaced, this location was not accurately targeted and was instead used simply because of
490 its anatomical location in the body of the hippocampus. Two spheres were placed anterior to this location
491 (centroid MNI coordinates: -23 -10 -21; -26 -14 -20), and two posterior (centroid MNI coordinates: -31 -22
492 -14; -30, -26, -12), in 4mm increments along the longitudinal axis. These coordinates were mirrored into
493 the right hemisphere (centroid MNI coordinates: 23 -10 -21; 26 -24 -20; 30 -18 -18; 31 -22 -14; 30 -26 -
494 12. The two most anterior spheres encompassed the head of the hippocampus and the middle and two
495 posterior spheres fell in the body of the hippocampus. These spherical ROIs encompassed hippocampal
496 as well as small portions of immediately adjacent entorhinal/perirhinal and parahippocampal cortex,
497 which was necessary due to the relatively large voxel size. Spherical ROIs were used in lieu of more
498 anatomically precise methods (e.g., hippocampal subfield identification) due to the limited spatial
499 resolution imposed by the scanning parameters that are possible with the single-channel MRI head coil,
500 which was necessary to accommodate the TMS coil. The hippocampal tail was likewise not measured,
501 as very few voxels of this size can capture the hippocampal tail without also including substantial
502 portions of adjacent white matter and ventricle.

503 The primary analysis collapsed these ROIs within each hemisphere to create separate left and
504 right aggregate hippocampus ROIs, with the main hypothesis being that HNT TBS would increase
505 activity evoked by scenes only in the left hippocampus. A follow-up exploratory analysis used rmANOVA
506 to determine whether stimulation conditions had differential impact along the longitudinal axis. The goal
507 was to identify locations along the hippocampal long axis that responded to stimulation conditions, taking

508 into account potential functional distinctions along the anterior-posterior axis (Aggleton and Brown, 1999;
509 Ranganath and Ritchey, 2012; Poppenk et al., 2013) as in our previous experiments investigating the
510 variation in effects of TMS on hippocampal activity along its longitudinal axis (Wang et al., 2014;
511 Nilakantan et al., 2019).

512 Voxel-wise analysis with an intentionally liberal threshold was used to evaluate whether there was
513 any evidence for effects of stimulation in areas other than in the hippocampal ROIs, which was not
514 expected. This analysis compared activity estimates for scenes with stimulation that were later
515 recollected between stimulation conditions. Each subject's voxel-wise regression coefficients for
516 remembered scenes with TMS ON for every stimulation condition (HNT TBS, SMA TBS, HNT beta, SMA
517 beta) was entered into repeated measures ANOVA (*3dANOVA3*) to assess voxels for a significant
518 interaction between stimulation location and pattern. Clusters of significant interaction were identified
519 using a liberal threshold (two-tailed $P<0.05$ voxel-wise threshold, F-statistic=4.54, >40 contiguous supra-
520 threshold voxels) (*3dClust*).

521

522 Statistical Analysis

523 Statistical analysis was performed using AFNI and Matlab. Group-level analysis of multiple
524 conditions was performed using repeated-measures analysis of variance (rmANOVA), with partial eta
525 squared (η^2_p) reported as the effect size. The within-subject factors corresponding to each test are
526 provided in the Results. Greenhouse-Geisser correction was applied if the assumption of sphericity was
527 not met (significant Mauchly's test at $P<0.05$), with the corrected p-values and degrees of freedom
528 reported ($F_{(GG)}$). Follow-up tests avoided making all possible pairwise comparisons among the many
529 stimulation control conditions used in the experiment by focusing on the *a priori* hypothesis that the HNT
530 TBS condition would be unique among all stimulation conditions in that it alone would increase
531 hippocampal fMRI activity and recollection relative to all other control conditions. HNT TBS ON was
532 therefore the condition of interest whereas all other conditions were controls. For these follow-up
533 comparisons, we tested whether each individual stimulation condition was significantly greater than the
534 aggregate of all control conditions (other than the individual stimulation condition being tested) using
535 one-tailed Students t-tests (t) or Wilcoxon signed rank tests (z) if the assumption of normality was

536 violated (significant Shapiro-Wilk test at P<0.05), and then corrected for the number of individual
537 stimulation conditions that were tested using the Bonferroni method. Bonferroni corrected P values are
538 indicated as "P_B" throughout the manuscript. Effect size measures were calculated as Cohen's *d* (*d*) for
539 the t-tests and as rank-biserial correlation (*r*) for the Wilcoxon tests. This follow-up assessment method
540 therefore indicated whether any stimulation condition significantly increased hippocampal fMRI activity or
541 recollection relative to the control conditions, and we hypothesized that this would only be the case for
542 HNT TBS ON. For comprehensiveness, an exploratory analysis of all possible pairwise comparisons was
543 used to assess whether there was evidence that any condition increased fMRI activity or recollection
544 relative to any other condition using one-tailed Students t-tests (t) or Wilcoxon signed rank tests (z) if the
545 assumption of normality was violated (significant Shapiro-Wilk test at P<0.05), with no correction for
546 multiple comparisons and no reporting of effect sizes for the exploratory analysis.
547
548 Code and Data Accessibility
549 Raw data are freely available on the Northwestern University Neuroimaging Data Archive
550 (https://nunda.northwestern.edu/). Dataset identifiers will be provided with publication to permit
551 unrestricted access to raw data. Custom code and scripts to replicate analyses will also be available via
552 this archive.
553
554 **Results**
555 Validation of concurrent TMS-fMRI
556 The fMRI scanning methods used for TBS and beta stimulation differed in a number of critical
557 parameters, including parameters of the scan sequence as well as the timing of scan acquisition relative
558 to interleaved TMS pulses (Fig. 2AB). To test whether these differences affected signal quality, the
559 Signal-to-Fluctuation-Noise Ratio (SFNR) summary value (Friedman and Glover, 2006) was calculated
560 for each subject for the TBS and beta stimulation sessions. We expected SFNR values to be ~120, as
561 this was the approximate SFNR value obtained when we performed the same scans on an additional
562 subject who had the TMS coil at the same approximate locations but without any pulses delivered
563 (average SNFR across both scans = 120.3). Furthermore, another group using the same scanner and

564 head coil models as in this experiment reported similar SFNR values for their interleaved TMS/fMRI
565 scans (Moisa et al., 2009). The average SFNR value for the TBS sessions was 122.5 (SD=18.3,
566 range=94.8-160.2) and 123.4 for the beta sessions (SD=14.2, range=92.2-144.8), with no significant
567 difference between sessions (P=0.75). Therefore, scan stability and thus, sensitivity, did not vary by scan
568 sequence or stimulation pattern.

569 We performed two voxel-wise fMRI analyses to confirm expected neural activity correlates of
570 cognitive processing within the task. That is, scenes but not numbers should evoke activity in
571 parahippocampal, fusiform, and occipital regions (Stern et al., 1996; Stark and Squire, 2001) and
572 stimulation sensations such as TMS sounds should evoke activity in auditory cortex. The contrast of fMRI
573 activity evoked by scenes versus numbers, calculated across stimulation presence (on and off), and
574 location (HNT and SMA) identified significantly greater activity (P<0.001, t-threshold=4.07) of bilateral
575 occipital, fusiform, and posterior parahippocampal cortex as well as hippocampus for both stimulation
576 patterns (Fig. 3A). Contrasts between TBS and beta stimulation identified no voxels with significant
577 differences even at a liberal threshold (P<0.01 uncorrected). The contrast of stimulation "on" versus "off",
578 calculated across stimulation location (HNT and SMA), identified significantly greater activity for "on"
579 (P<0.001, t-threshold=4.07) in bilateral auditory cortex for both TBS and beta stimulation (Fig. 3B).
580 Again, the direct contrast identified no voxels with significantly different activity for TBS versus beta
581 stimulation at a liberal threshold (P<0.01 uncorrected). Notably, although auditory-related activity due to
582 stimulation was identified robustly, the limited imaging volume did not permit identification of likely
583 somatosensory activation. Collectively, these analyses indicate that fMRI sensitivity was sufficient for
584 identifying typical neural signals of scene viewing and auditory stimulation despite concurrent TMS and
585 that there was no obvious variation in sensitivity for TBS versus beta scan parameters.
586

587 <u>Effects of stimulation on memory encoding</u>

588 Subjects demonstrated above-chance discrimination of old/studied scenes from new scenes
589 overall across all stimulation conditions and irrespective of whether old scenes were endorsed with
590 "Remember" or "Familiar" responses (mean d'=0.81, SD=0.35; t_{15}=9.15, P<0.001 vs. chance value of 0).
591 For all stimulation conditions, the proportion of old scenes endorsed with "Remember" responses

592 (mean=0.30, SD=0.10) was greater than the proportion of new scenes endorsed with “Remember”
593 responses (mean=0.07, SD=0.05; t_{15}=21.18, P<0.001, d=2.29). Likewise, the proportion of old scenes
594 endorsed with “Familiar” responses (mean 0.34, SD=0.12) was greater than the proportion of new
595 scenes endorsed with “Familiar” responses (mean=0.28, SD=0.13; t_{15}=6.26, P<0.001, d=0.97). As
596 expected, “Remember” responses were significantly more likely to be hits to old items (mean=0.84,
597 SD=0.10) than were “Familiar” responses (mean=0.59, SD=0.10; t_{15}=6.94, P<0.001, d=1.71). Thus,
598 subjects performed the recognition task (Fig. 4A) accurately and the “Remember” responses were
599 characteristic of high-confidence, high-accuracy recognition memory, as has been linked to the
600 hippocampus in multiple previous experiments (Ranganath et al., 2004).
601 Our *a priori* hypothesis was that HNT TBS during encoding would increase subsequent
602 recollection of scenes, as quantified as the proportion of hits endorsed with “Remember” responses,
603 relative to all control stimulation conditions. Because of their different rhythms, TBS and beta could
604 produce differential effects on sensory (auditory and somatosensory) entrainment of brain activity
605 unrelated to the hypothesized effects of stimulation on hippocampal activity, and they were furthermore
606 administered during different experimental sessions/days (Fig. 1). To test for their differential effects on
607 recollection while accounting for these nonspecific differences, we compared the effects of TBS when
608 applied targeting the hippocampal network (HNT) relative to the control SMA location versus the effects
609 of beta when applied targeting HNT relative to SMA. We submitted the HNT minus SMA difference
610 scores for the proportion of recollected hits to 2x2 rmANOVA with factors TMS presence (on, off) and
611 rhythm (TBS, beta). There was a main effect of TMS presence ($F_{1,15}$=5.13, P=0.04, η^2_p=0.23) qualified by
612 significant interaction between TMS presence and rhythm ($F_{1,15}$=6.53, P=0.02, η^2_p=0.31). As indicated in
613 Figure 4B, TBS increased recollection when applied to HNT versus SMA to a greater extent than did
614 beta, which had almost no differential effect when applied to HNT versus SMA. Essentially the same
615 pattern was evident when performing this comparison without subtracting the HNT and SMA conditions.
616 Recollection varied significantly by TMS presence (on versus off), rhythm (TBS versus beta), and
617 location (HNT versus SMA) (3-way rmANOVA interaction $F_{1,11}$=6.63, P=0.02, η^2_p=0.44). Thus, TBS and
618 beta rhythms had different impacts on recollection when applied targeting the hippocampal network
619 versus the control network.

The follow-up test followed our *a priori* hypothesis that HNT TBS would be the only stimulation condition to increase recollection relative to other conditions. We tested whether the proportion of recollection hits was greater for HNT TBS versus the average of all control conditions (HNT TBS OFF, SMA TBS ON, SMA TBS OFF, HNT BETA ON, HNT BETA OFF, SMA BETA ON, SMA BETA OFF), and, for comparison, tested whether recollection hits were significantly greater for each of the control conditions versus the average of all other control conditions. Consistent with our hypothesis, HNT TBS was the only stimulation condition with significantly greater recollection relative to other conditions (t_{15}=3.59, P=0.001, P_B<0.01 corrected for 8 tests, d=0.90; P_B = 1 for each other control condition versus the average of its respective other controls) (Fig. 4C).

An exploratory analysis of all possible pairwise comparisons among stimulation conditions was also performed, although the number of comparisons is high (56 total) and this analysis does not account for possible nonspecific differences among conditions that are relatively controlled in the primary analysis. HNT TBS was the only condition for which recollection was significantly greater than all of the other individual conditions (uncorrected P = 0.007 versus HNT TBS OFF, P = 0.03 versus HNT beta ON, P = 0.008 versus HNT beta OFF, P = 0.0005 versus SMA TBS ON, P = 0.03 versus SMA TBS OFF, P = 0.03 versus SMA beta ON, and P = 0.02 versus SMA beta OFF). In contrast, no control condition was associated with greater recollection than any one other condition (range of all uncorrected P-values = 0.08-0.99).

The experiment design used trial-specific stimulation with randomized condition order and long inter-trial intervals to ensure that the effects of stimulation were specific, as any effects of stimulation that outlasted the trial (i.e., due to longer-lasting neuroplasticity) would not have been condition specific. To more directly assess whether effects of HNT TBS on recollection outlasted the trial during which it was applied, we tested whether recollection of scenes with no stimulation (OFF) varied based on whether the scene immediately followed a trial with HNT TBS (ON) versus a trial from the same study session with no stimulation (OFF). There was no difference in the proportion of recollected hits for these two categories of non-stimulated trials (t_{15}=0.66, P=0.52; two-tailed paired t-test). Thus, there was no evidence that HNT TBS continued to affect recollection on the trial after which it was applied.

647 Although our hypotheses concerned the effects of stimulation on recollection, we also examined
648 effects on overall hit rates. Overall hit rate (old items endorsed with “Remember” and “Familiar”
649 responses) did not vary by stimulation pattern, location, or presence (all 3-way rmANOVA main effects
650 and interactions P-values>0.1) (Table 1). Notably however, although effects of stimulation on hit rates
651 were not identified, overall memory strength could have been affected by stimulation, which could
652 influence both the hit rate and the false alarm rate. The format of the experiment precluded calculation of
653 false alarm rates separately for each stimulation condition because study phases for both stimulation
654 locations (HNT and SMA) were tested at the end of each experimental session using the same set of
655 novel lures (see Fig. 1D). Therefore, lures could be segregated based on stimulation pattern (TBS versus
656 beta) but not based on stimulation location. The false alarm rate was significantly lower (t_{15}=2.54,
657 P=0.02, d=0.64) for TBS (mean=0.31, SD=0.17) than beta stimulation (mean=0.38, SD=0.12). Likewise,
658 the accuracy of “Remember” responses (proportion made to old items) was significantly greater for TBS
659 (mean=0.88, SD=0.09) than for beta (mean=0.81, SD=0.13; t_{15}=2.44, P=0.03, d=0.62; two-tailed paired t-
660 test), whereas the accuracy of “Familiar” responses did not differ significantly for TBS (mean=0.61,
661 SD=0.11) compared to beta (mean=0.57, SD=0.13; t_{15}=1.89, P=0.08; two-tailed paired t-test). Although
662 we could not test for differences based on stimulation location, these findings indicate that TBS
663 increased overall memory strength and recollection accuracy to a greater extent than beta stimulation,
664 which is consistent with the primary findings that recollection was improved selectively for HNT TBS.
665
666 Effects of stimulation on recollection-related hippocampal activity during encoding
667 As outlined above, we hypothesized that HNT TBS would be unique among stimulation conditions
668 in increasing hippocampal fMRI activity evoked by later-recollected scenes, and that this would occur
669 selectively for the left hippocampus that was targeted based on its fMRI connectivity to the HNT
670 stimulation location and based on the relatively lateralized projections from lateral parietal cortex to
671 ipsilateral medial temporal lobe (Mesulam et al., 1977; Mufson and Pandya, 1984). Further, we
672 hypothesized that these effects would be specific to scenes, with no impact of stimulation conditions on
673 activity evoked by numeric-judgment trials that were randomly intermixed with scene trials during the
674 encoding periods.

675 We first evaluated the effects of stimulation on activity evoked by later-recollected scenes for the
676 left hippocampus (Fig. 5A). Activity varied significantly by stimulation condition ($F_{4,75}$=3.40, P=0.01,
677 η^2=0.18, 1x5 rmANOVA for the HNT TBS, SMA TBS, HNT beta, SMA beta, and "off" conditions). The
678 right hippocampus showed a numerically similar trend of increased activity for HNT TBS, but activity did
679 not vary significantly by stimulation condition for right hippocampus ($F_{(GG)2.3,42.2}$=0.76, P=0.49).
680 The follow-up test of left hippocampal activity followed our *a priori* hypothesis that HNT TBS
681 would be the only stimulation condition to increase activity relative to other stimulation conditions. We
682 tested whether activity evoked by later-recollection scenes was greater for HNT TBS versus the average
683 of all control conditions (SMA TBS, HNT beta, SMA beta, and off), and also tested whether activity was
684 significantly greater for each of the control conditions versus the average of all other control conditions.
685 Consistent with our hypothesis, HNT TBS was the only stimulation condition with significantly greater
686 activity relative to control conditions (z_{15}=2.61, P=0.005, P_B=0.03 corrected for 5 tests; r=0.65; P_B for
687 each control condition relative to the average of its respective other controls range = 0.67-1; Fig. 5B).
688 An exploratory analysis of all possible pairwise comparisons among stimulation conditions was
689 also performed. HNT TBS was the only condition for which left hippocampal activity evoked by later-
690 recollected scenes was significantly greater than for all of the other individual conditions (uncorrected P =
691 0.03 versus HNT beta, P = 0.002 versus SMA TBS, P = 0.02 versus SMA beta, and P = 0.03 versus
692 combined OFF). In contrast, no control condition was associated with greater activity than any other one
693 condition (range of uncorrected P-values = 0.07-0.93).
694 As shown in Fig. 5C, numeric judgments did not evoke robust activity in left or right hippocampus,
695 relative to activity evoked by scenes (Fig. 5B), as anticipated. This activity did not vary significantly by
696 stimulation condition for either left ($F_{4,75}$=1.04, P>0.4) or right ($F_{4,75}$=0.81, P>0.5) hippocampus. Focusing
697 specifically on the HNT TBS condition of interest and left hippocampus, the effect of stimulation relative
698 to the average of all control conditions was significantly greater for scene-evoked recollection-related
699 activity (difference between HNT TBS bar and adjacent white bar in Fig. 5B) than it was for activity
700 evoked by numeric judgments (difference between HNT TBS bar and adjacent white bar in Fig. 5C)
701 (z_{15}=2.30, P=0.01, r=0.58), indicating the impact of HNT TBS on activity evoked by later-recollected
702 scenes was greater than the impact of HNT TBS on activity evoked by numeric judgments. Collectively,

703 these findings indicate that HNT TBS selectively increased left hippocampal activity evoked by later-
704 recollected scenes during encoding.
705
706 Exploratory analysis of variation in stimulation effects along the hippocampal longitudinal axis
707 Based on evidence for anatomical and functional specialization along the hippocampal
708 longitudinal axis (Ranganath et al., 2004; Poppenk et al., 2013) as well as our own previous evidence
709 that network-targeted TMS can affect fMRI activity of specific hippocampal long-axis segments (Wang et
710 al., 2014; Nilakantan et al., 2019), we performed an exploratory analysis to test for variation in the effects
711 of HNT TBS along the longitudinal axis using five segments extending from anterior head to posterior
712 body (Fig. 6A) (described in Methods). For left hippocampal segments, activity varied significantly by the
713 five stimulation conditions for the two most anterior segments ($F_{(GG)1.9,36.0}$=4.14, P=0.03, η^2_p=0.28;
714 $F_{(GG)1.7,32.4}$=3.80, P=0.04, η^2_p=0.25; all other Ps>0.1) (Fig. 6B). Follow-up pairwise comparisons were
715 made among conditions using averaged activity of these two anterior segments, not corrected for
716 multiple comparisons in this exploratory analysis. Activity evoked by later-recollected scenes was greater
717 for HNT TBS relative to all control conditions (range of uncorrected P-values = 0.00009-0.03). Activity
718 was also significantly greater for OFF relative to SMA TBS (t_{15}=2.47, P=0.01, d=0.62), but no other
719 control condition significantly differed from another (range of uncorrected P-values = 0.07-0.99).
720 As expected based on findings from the primary analysis (Fig. 5), the exploratory analysis
721 performed for right (non-targeted) MTL segments yielded a numerically similar pattern of greater activity
722 following HNT TBS relative to other conditions, but there was no significant variation by stimulation
723 condition for any longitudinal segment (Ps>0.3) (Fig. 6B). Furthermore, as expected, MTL activity evoked
724 by numeric judgments was minimal along the longitudinal axis and did not vary significantly by
725 stimulation condition or segment in either the left or right hemisphere (Fig. 6C; main effect of condition
726 and interaction of condition by longitudinal segment in the left and right hemispheres Ps>0.3).
727 Collectively, this exploratory analysis provides preliminary evidence that effects of HNT TBS on activity
728 evoked by later-recollected scenes were most pronounced for relatively anterior hippocampus in the
729 targeted hemisphere.
730

731 Voxel-wise fMRI analysis to evaluate non-hippocampal stimulation effects

732 To complement the ROI-based approach that was used to assess the hypothesized effects of
733 stimulation on hippocampal activity evoked by later-recollected scenes, we performed a voxel-wise
734 analysis with an intentionally liberal statistical threshold to determine if there was any evidence for effects
735 of stimulation elsewhere within the FOV (Material and Methods). The rationale for using an exceptionally
736 liberal statistical threshold is that this provides high sensitivity to the any potential effects of stimulation,
737 with the caveat that any results would require further testing via a more rigorous approach. The voxel-
738 wise rmANOVA assessing the interaction of stimulation location (HNT, SMA) with rhythm (TBS, beta) on
739 activity evoked by later-recalled scenes did not identify supra-threshold activity anywhere outside of the
740 MTL. The only supra-threshold activity identified by this test was for the left anterior MTL (82-voxel
741 cluster, peak MNI = -20, 4, -23), and this location overlaps considerably with the anterior-left
742 hippocampal regions of interest where activity evoked by later-recollected scenes was most robustly
743 influenced by HNT TBS (Figs. 6A). This indicates that this liberal voxel-wise test had the sensitivity to
744 identify hypothesized effects of stimulation on activity (as it identified such effects in a similar area as in
745 the ROI-based analysis), yet there were no robust differential effects of stimulation location and rhythm
746 outside of the hippocampal regions of interest. The same test performed for activity evoked by numeric
747 digits did not yield any supra-threshold clusters for either the main effects or interaction.

748

749 No effects of stimulation on hippocampal activity during relatively unsuccessful scene encoding

750 In order to determine whether stimulation effects on fMRI activity evoked by scenes were specific
751 to those scenes that were later recollected, we performed the same set of fMRI analyses previously
752 described for the later-recollected scenes but for the scenes that were later endorsed with “Familiar” and
753 “New” (miss) responses. As indicated above, “Familiar” responses were significantly less accurate than
754 “Remember” responses, and “New” responses indicated memory failure. Thus, memory encoding was
755 far less successful for this combined Familiar/New condition (44% “Familiar” responses on average,
756 SD=6.49%) than it was for the “Remember” condition.

757 Stimulation condition did affect activity for this condition in the left hippocampus ($F_{4,75}$=0.34,
758 P>0.8) or right hippocampus ($F_{4,75}$=1.45, P>0.2). Considering the hippocampal longitudinal axis

759 exploratory analysis, there were also no main effects of stimulation condition or interaction of stimulation
760 condition by the five segments for either the left or right hippocampus (main effects and interaction of
761 condition by longitudinal segment in the left and right hemispheres Ps>0.2). The liberal whole-brain
762 voxel-wise analysis did not find any supra-threshold clusters with an interaction of stimulation location by
763 stimulation rhythm. Thus, the effects of HNT TBS on activity evoked by scenes were specific to the
764 scenes that were later-recollected, with no effects of stimulation on activity for scenes comprising this
765 low-memory condition.
766
767 **Discussion**
768 TBS targeting the network of the left hippocampus (HNT) during encoding selectively increased fMRI
769 activity evoked by later-recollected scenes in the targeted (left) hippocampus and increased subsequent
770 recollection memory. These increases were rhythm- and location-specific, as they were not observed for
771 HNT beta stimulation nor for either stimulation rhythm (TBS or beta) targeting an out-of-network control
772 location (SMA). Further, effects were cognitively specific, as no condition (including HNT TBS) influenced
773 hippocampal activity for scenes that were not later remembered (later-familiar and later-miss trials) nor
774 did any condition influence hippocampal activity during numeric judgments, which do not typically evoke
775 MTL activity (Stark and Squire, 2001). Effects were specific to the left hippocampus, which was targeted
776 via its connectivity to the stimulated left parietal area. A numerically similar but non-significant pattern
777 was observed for right hippocampus, which could be due to commissural connectivity and is consistent
778 with previous findings of relatively (but not completely) lateralized effects of network-targeted TMS on
779 hippocampal activity (Wang et al., 2014; Nilakantan et al., 2019). Finally, HNT TBS only influenced the
780 recollective aspect of scene memory, which supports the conclusion that hippocampal function was
781 affected, as recollection is associated with hippocampal activity during encoding (Kim, 2011; Rugg et al.,
782 2012).
783 Notably, the experiment design constrains mechanistic interpretation. Stimulation was delivered
784 as 2-sec volleys immediately before stimulus onset and with conditions intermixed across encoding trials,
785 with intentionally long inter-stimulus intervals to avoid cumulative effects of stimulation across trials
786 (Huang et al., 2005; Demeter et al., 2016). Any effects of HNT TBS versus control conditions must

787 therefore have been immediate and trial specific, and indeed a control analysis provided no evidence
788 that HNT TBS continued to affect encoding even on the subsequent trial. The experiment design and
789 pattern of findings thus suggests that HNT TBS influenced hippocampal neural activity, as opposed to
790 neuroplasticity and/or neuromodulatory mechanisms that can support persistent/long-lasting effects of
791 stimulation (Cirillo et al., 2017). Notably, the design and findings also indicate that HNT TBS effects on
792 fMRI activity were unlikely to have reflected TMS-related fMRI artefact, as different trial types were
793 intermixed and all received the same stimulation parameters, yet effects were specific to later-recollected
794 scenes.

795 The premise of the experiment was that TBS mimics endogenous theta-band neural activity
796 characteristic of the hippocampus and hippocampal network synchrony (Buzsaki, 2002; Buzsaki and
797 Draguhn, 2004; Lisman and Jensen, 2013) and therefore might optimally influence hippocampal memory
798 processing via entrainment of neural activity (Thut et al., 2011a; Hanslmayr et al., 2019). Thus, if
799 targeting hippocampal network theta activity via noninvasive TBS were successful, we expected that it
800 would cause population synchrony of theta and therefore increase the evoked fMRI BOLD response to a
801 stimulus that evokes processing by the affected region(s). Indeed, increased hippocampal theta activity
802 predicts successful memory formation, particularly for complex associative information (Rutishauser et
803 al., 2010; Fell et al., 2011; Herweg et al., 2020), including theta activity in the pre-stimulus interval
804 (Guderian et al., 2009; Fell et al., 2011; Merkow et al., 2014) when TBS was applied in our experiment.
805 Although our findings are consistent with this prediction, a weakness is that theta cannot be measured
806 with fMRI and we can only infer an impact based on fMRI activity and memory performance. Further, it is
807 also possible that recollection improvement due to HNT TBS was mediated by a mechanism other than
808 the corresponding increase in hippocampal activity, as fMRI provides a limited window on brain activity.
809 Full confirmation of our interpretation requires additional evidence, including direct measurement of
810 stimulation effects on hippocampal theta.

811 The findings inform mechanisms by which brain stimulation influences hippocampal activity.
812 Direct electrical stimulation of the hippocampus and its immediate entorhinal inputs via depth electrodes
813 in human neurosurgical cases typically disrupts memory [(Coleshill et al., 2004; Jacobs et al., 2016;
814 Goyal et al., 2018b), but see (Suthana et al., 2012; Jun et al., 2019)]. In contrast, direct/neurosurgical

815 electrical stimulation of hippocampal network areas has yielded modest evidence for memory
816 enhancement. Stimulation of lateral temporal cortex enhanced memory in four patients (Kucewicz et al.,
817 2018), and closed-loop stimulation of approximately the same location caused relative enhancement
818 compared to disruptive effects for other brain regions (Ezzyat et al., 2018). Of relevance to theta,
819 memory enhancement was achieved in four patients receiving TBS of the fornix (Miller et al., 2015), and
820 TBS with microstimulation of entorhinal cortex enhanced memory in several cases in which white matter
821 (rather than gray matter) was targeted (Titiz et al., 2017). However, demonstrations of memory
822 enhancement by invasive TBS (Miller et al., 2015; Titiz et al., 2017) did not include non-theta control
823 conditions, and therefore do not permit strong conclusions regarding the specific role of theta.

824 TMS targeting the hippocampal network can generate long-lasting and robust recollection
825 improvement and corresponding changes in hippocampal and hippocampal network activity (Hebscher
826 and Voss, 2020), with greater aftereffects using TBS (Hermiller et al., 2019a). The current findings
827 provide novel mechanistic insights by showing that hippocampal activity is immediately sensitive to
828 stimulation applied to its network and mimicking its endogenous theta activity. This suggests an impact of
829 network-targeted stimulation on hippocampal neural activity and supports the interpretation (Hebscher
830 and Voss, 2020) that effects of noninvasive stimulation targeting this network are due to the impact of
831 stimulation on the hippocampus.

832 Although sampling of activity elsewhere in the brain was limited by the fMRI methods, we found
833 no evidence for effects of HNT TBS among locations sampled outside of the left MTL. This suggests that
834 the hippocampus may be unique in its ability to be immediately impacted by stimulation. In contrast,
835 previous experiments using longer stimulation trains and/or multiple days of stimulation found effects
836 distributed throughout the network (Hebscher and Voss, 2020). Interestingly, in those studies, although
837 stimulation was delivered at a parietal network target, the most robust effects were on fMRI activity of the
838 hippocampus and network locations with highest hippocampal connectivity (Hebscher and Voss, 2020). It
839 is possible that brief TBS trains affect activity in only those areas most sensitive to this stimulation
840 pattern (hippocampus) whereas more extensive network locations are recruited with increasing
841 stimulation.

842 Functionally distinct theta bands have recently been reported along the human longitudinal
843 hippocampal axis, with slower theta (~3-5 Hz) more prevalent in the anterior and higher theta (~6-8 Hz)
844 more prevalent in the posterior hippocampus (Lega et al., 2016; Goyal et al., 2018a). TBS was delivered
845 at 5 Hz and the exploratory analysis suggested that it had relatively greater impact on the anterior
846 hippocampus. This further suggests that TBS might have affected neural activity in the matching
847 frequency band, if 5-Hz theta is more pronounced in anterior hippocampus. Formal testing of this
848 possibility is a direction for future experiments.

849 The reported effects of HNT TBS are highly unlikely to have resulted from the impact of
850 stimulation on the left parietal area where HNT stimulation was applied. This parietal location has been
851 associated with confidence and meta-memory judgments during retrieval but not with successful memory
852 encoding (Uncapher and Wagner, 2009; Kim, 2011). Stimulation in this experiment was applied at
853 encoding, not during retrieval. Moreover, because effects were condition- and trial-specific, with no
854 impact of HNT TBS even on the very next trial after it was applied, it is incredibly unlikely that stimulation
855 had any lingering impact during the delayed test period. Because hippocampus is robustly implicated in
856 encoding that produces later recollection whereas the stimulated area of parietal cortex is not, the
857 experiment affords greater confidence that the effects of HNT TBS on recollection memory were related
858 to the corresponding increases in hippocampal activity during encoding produced by HNT TBS (Tambini
859 et al., 2018).

860 A limitation of the current experiment is that the memory test was given after both study phases
861 on a given experiment session, and those study phases differed in the stimulation location (HNT versus
862 SMA), keeping stimulation rhythm constant (TBS or beta). Thus, we could not compare effects of location
863 on memory accuracy, as novel foils were not segregated by location. Nonetheless, we did find reduced
864 false alarms to novel foils for TBS versus beta as well as an increase in hit rates for HNT TBS versus
865 TBS to the SMA location. Furthermore, the accuracy of recollection, but not familiarity, responses
866 increased for TBS versus beta. These effects on accuracy are consistent with the main findings that HNT
867 TBS specifically impacted recollection, but future experiments will be necessary to directly test whether
868 TBS increases accuracy only when applied to target the hippocampus versus to any location.

869 Hippocampal network dysfunction is related to memory impairments in many disorders (Andrews-
870 Hanna et al., 2007; Buckner et al., 2008; Dickerson and Eichenbaum, 2010; Small et al., 2011). The
871 current findings suggest that memory processing by the core structure of this network can be
872 immediately and beneficially influenced via TMS of an appropriate location and rhythm. Given the
873 immediate impact and relatively precise locus of stimulation-related activity changes, concurrent TBS
874 with fMRI could be a powerful tool for testing hypotheses about normal hippocampal function as well as
875 dysfunction in memory disorders.

References:

Aggleton JP, Brown MW (1999) Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav Brain Sci 22:425-444; discussion 444-489.

Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, Buckner RL (2007) Disruption of large-scale brain systems in advanced aging. Neuron 56:924-935.

Bestmann S, Ruff CC, Blankenburg F, Weiskopf N, Driver J, Rothwell JC (2008) Mapping causal interregional influences with concurrent TMS-fMRI. Exp Brain Res 191:383-402.

Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124:1-38.

Buzsaki G (2002) Theta oscillations in the hippocampus. Neuron 33:325-340.

Buzsaki G, Draguhn A (2004) Neuronal oscillations in cortical networks. Science 304:1926-1929.

Cirillo G, Di Pino G, Capone F, Ranieri F, Florio L, Todisco V, Tedeschi G, Funke K, Di Lazzaro V (2017) Neurobiological after-effects of non-invasive brain stimulation. Brain Stimul 10:1-18.

Coleshill SG, Binnie CD, Morris RG, Alarcon G, van Emde Boas W, Velis DN, Simmons A, Polkey CE, van Veelen CW, van Rijen PC (2004) Material-specific recognition memory deficits elicited by unilateral hippocampal electrical stimulation. J Neurosci 24:1612-1616.

Cox RW (1996) AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162-173.

Demeter E, Mirdamadi JL, Meehan SK, Taylor SF (2016) Short theta burst stimulation to left frontal cortex prior to encoding enhances subsequent recognition memory. Cogn Affect Behav Neurosci 16:724-735.

Dickerson BC, Eichenbaum H (2010) The episodic memory system: neurocircuitry and disorders. Neuropsychopharmacology 35:86-104.

Eichenbaum H, Yonelinas AP, Ranganath C (2007) The medial temporal lobe and recognition memory. Annu Rev Neurosci 30:123-152.

Ezzyat Y et al. (2018) Closed-loop stimulation of temporal cortex rescues functional networks and improves memory. Nat Commun 9:365.

Fell J, Klaver P, Lehnertz K, Grunwald T, Schaller C, Elger CE, Fernandez G (2001) Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. Nat Neurosci 4:1259-1264.

Fell J, Ludowig E, Staresina BP, Wagner T, Kranz T, Elger CE, Axmacher N (2011) Medial temporal theta/alpha power enhancement precedes successful memory encoding: evidence based on intracranial EEG. J Neurosci 31:5392-5397.

Foster BL, Kaveh A, Dastjerdi M, Miller KJ, Parvizi J (2013) Human retrosplenial cortex displays transient theta phase locking with medial temporal cortex prior to activation during autobiographical memory retrieval. J Neurosci 33:10439-10446.

Fox MD, Halko MA, Eldaief MC, Pascual-Leone A (2012) Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). Neuroimage 62:2232-2243.

Freedberg M, Reeves JA, Toader AC, Hermiller MS, Voss JL, Wassermann EM (2019) Persistent Enhancement of Hippocampal Network Connectivity by Parietal rTMS Is Reproducible. eNeuro 6.

Friedman L, Glover GH (2006) Report on a multicenter fMRI quality assurance protocol. J Magn Reson Imaging 23:827-839.

Goyal A, Miller J, Qasim A, Watrous AJ, Stein JM, Inman CS, Gross RE, Willie JT, Lega B, Lin J, Sharan A, Wu C, Sperling MR, Sheth SA, McKhann GM, Smith EH, Schevon C, Jacobs J (2018a) Functionally distinct high and low theta oscillations in the human hippocampus. bioRxiv.

Goyal A, Miller J, Watrous AJ, Lee SA, Coffey T, Sperling MR, Sharan A, Worrell G, Berry B, Lega B, Jobst BC, Davis KA, Inman C, Sheth SA, Wanda PA, Ezzyat Y, Das SR, Stein J, Gorniak R, Jacobs J (2018b) Electrical Stimulation in Hippocampus and Entorhinal Cortex Impairs Spatial and Temporal Memory. J Neurosci 38:4471-4481.

Guderian S, Schott BH, Richardson-Klavehn A, Duzel E (2009) Medial temporal theta state before an event predicts episodic encoding success in humans. Proc Natl Acad Sci U S A 106:5365-5370.

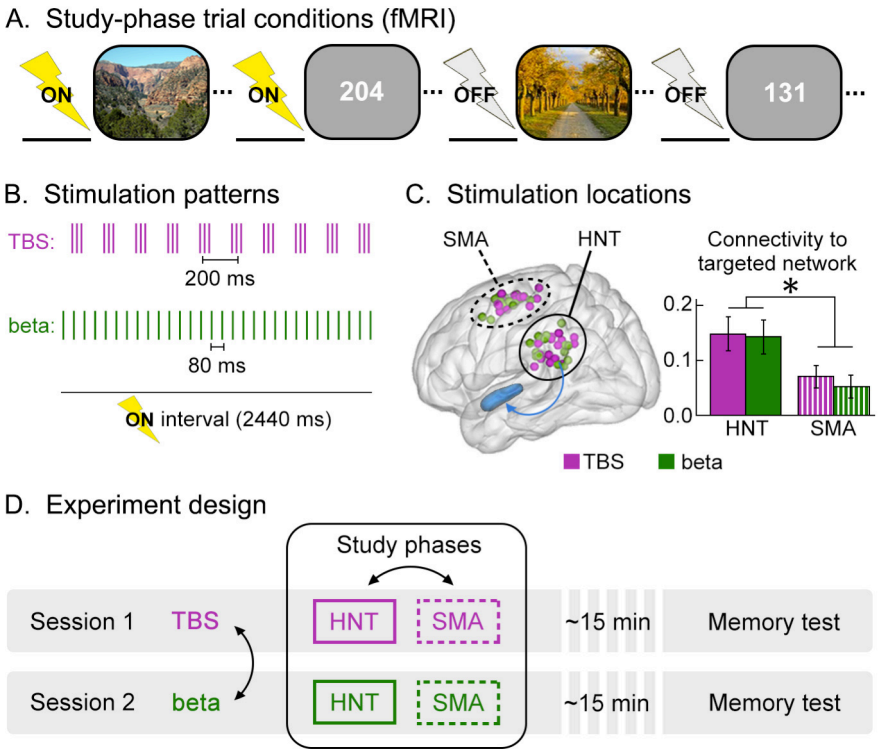
Hanslmayr S, Axmacher N, Inman CS (2019) Modulating Human Memory via Entrainment of Brain Oscillations. Trends Neurosci 42:485-499.

930 Hebscher M, Voss JL (2020) Testing network properties of episodic memory using non-invasive brain
931 stimulation. Curr Opin Behav Sci 32:35-42.
932 Hermiller MS, VanHaerents S, Raij T, Voss JL (2019a) Frequency-specific noninvasive modulation of
933 memory retrieval and its relationship with hippocampal network connectivity. Hippocampus
934 29:595-609.
935 Hermiller MS, Karp E, Nilakantan AS, Voss JL (2019b) Episodic memory improvements due to
936 noninvasive stimulation targeting the cortical-hippocampal network: A replication and extension
937 experiment. Brain Behav 9:e01393.
938 Herweg NA, Solomon EA, Kahana MJ (2020) Theta Oscillations in Human Memory. Trends Cogn Sci
939 24:208-227.
940 Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC (2005) Theta burst stimulation of the human
941 motor cortex. Neuron 45:201-206.
942 Jacobs J, Miller J, Lee SA, Coffey T, Watrous AJ, Sperling MR, Sharan A, Worrell G, Berry B, Lega B,
943 Jobst BC, Davis K, Gross RE, Sheth SA, Ezzyat Y, Das SR, Stein J, Gorniak R, Kahana MJ,
944 Rizzuto DS (2016) Direct Electrical Stimulation of the Human Entorhinal Region and
945 Hippocampus Impairs Memory. Neuron 92:983-990.
946 Jun S, Kim JS, Chung CK (2019) Direct Stimulation of Human Hippocampus During Verbal Associative
947 Encoding Enhances Subsequent Memory Recollection. Front Hum Neurosci 13:23.
948 Kahn I, Andrews-Hanna JR, Vincent JL, Snyder AZ, Buckner RL (2008) Distinct cortical anatomy linked
949 to subregions of the medial temporal lobe revealed by intrinsic functional connectivity. J
950 Neurophysiol 100:129-139.
951 Kim H (2011) Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI
952 studies. Neuroimage 54:2446-2461.
953 Kim S, Nilakantan AS, Hermiller MS, Palumbo RT, VanHaerents S, Voss JL (2018) Selective and
954 coherent activity increases due to stimulation indicate functional distinctions between episodic
955 memory networks. Sci Adv 4:eaar2768.
956 Kohler S, Paus T, Buckner RL, Milner B (2004) Effects of left inferior prefrontal stimulation on episodic
957 memory formation: a two-stage fMRI-rTMS study. J Cogn Neurosci 16:178-188.
958 Kucewicz MT, Berry BM, Miller LR, Khadjevand F, Ezzyat Y, Stein JM, Kremen V, Brinkmann BH,
959 Wanda P, Sperling MR, Gorniak R, Davis KA, Jobst BC, Gross RE, Lega B, Van Gompel J, Stead
960 SM, Rizzuto DS, Kahana MJ, Worrell GA (2018) Evidence for verbal memory enhancement with
961 electrical brain stimulation in the lateral temporal cortex. Brain 141:971-978.
962 Lega B, Burke J, Jacobs J, Kahana MJ (2016) Slow-Theta-to-Gamma Phase-Amplitude Coupling in
963 Human Hippocampus Supports the Formation of New Episodic Memories. Cereb Cortex 26:268-
964 278.
965 Lisman JE, Jensen O (2013) The theta-gamma neural code. Neuron 77:1002-1016.
966 Merkow MB, Burke JF, Stein JM, Kahana MJ (2014) Prestimulus theta in the human hippocampus
967 predicts subsequent recognition but not recall. Hippocampus 24:1562-1569.
968 Mesulam MM, Van Hoesen GW, Pandya DN, Geschwind N (1977) Limbic and sensory connections of
969 the inferior parietal lobule (area PG) in the rhesus monkey: a study with a new method for
970 horseradish peroxidase histochemistry. Brain Res 136:393-414.
971 Miller JP, Sweet JA, Bailey CM, Munyon CN, Luders HO, Fastenau PS (2015) Visual-spatial memory
972 may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation
973 with four cases. Brain 138:1833-1842.
974 Moisa M, Pohmann R, Ewald L, Thielscher A (2009) New coil positioning method for interleaved
975 transcranial magnetic stimulation (TMS)/functional MRI (fMRI) and its validation in a motor cortex
976 study. J Magn Reson Imaging 29:189-197.
977 Mufson EJ, Pandya DN (1984) Some observations on the course and composition of the cingulum
978 bundle in the rhesus monkey. J Comp Neurol 225:31-43.
979 Nilakantan AS, Mesulam MM, Weintraub S, Karp EL, VanHaerents S, Voss JL (2019) Network-targeted
980 stimulation engages neurobehavioral hallmarks of age-related memory decline. Neurology
981 92:e2349-e2354.
982 Paller KA, Wagner AD (2002) Observing the transformation of experience into memory. Trends Cogn Sci
983 6:93-102.

Poppenk J, Evensmoen HR, Moscovitch M, Nadel L (2013) Long-axis specialization of the human hippocampus. Trends Cogn Sci 17:230-240.
Ranganath C, Ritchey M (2012) Two cortical systems for memory-guided behaviour. Nat Rev Neurosci 13:713-726.
Ranganath C, Yonelinas AP, Cohen MX, Dy CJ, Tom SM, D'Esposito M (2004) Dissociable correlates of recollection and familiarity within the medial temporal lobes. Neuropsychologia 42:2-13.
Romei V, Thut G, Silvanto J (2016) Information-Based Approaches of Noninvasive Transcranial Brain Stimulation. Trends Neurosci 39:782-795.
Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Group SoTC (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 120.
Rugg MD, Vilberg KL, Mattson JT, Yu SS, Johnson JD, Suzuki M (2012) Item memory, context memory and the hippocampus: fMRI evidence. Neuropsychologia 50:3070-3079.
Rutishauser U, Ross IB, Mamelak AN, Schuman EM (2010) Human memory strength is predicted by theta-frequency phase-locking of single neurons. Nature 464:903-907.
Shirvalkar PR, Rapp PR, Shapiro ML (2010) Bidirectional changes to hippocampal theta-gamma comodulation predict memory for recent spatial episodes. Proc Natl Acad Sci U S A 107:7054-7059.
Siebner HR et al. (2009) Consensus paper: combining transcranial stimulation with neuroimaging. Brain Stimul 2:58-80.
Small SA, Schobel SA, Buxton RB, Witter MP, Barnes CA (2011) A pathophysiological framework of hippocampal dysfunction in ageing and disease. Nat Rev Neurosci 12:585-601.
Squire LR, Zola-Morgan S (1991) The medial temporal lobe memory system. Science 253:1380-1386.
Stark CE, Squire LR (2001) When zero is not zero: the problem of ambiguous baseline conditions in fMRI. Proc Natl Acad Sci U S A 98:12760-12766.
Staudigl T, Hanslmayr S (2013) Theta oscillations at encoding mediate the context-dependent nature of human episodic memory. Curr Biol 23:1101-1106.
Stern CE, Corkin S, Gonzalez RG, Guimaraes AR, Baker JR, Jennings PJ, Carr CA, Sugiura RM, Vedantham V, Rosen BR (1996) The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci U S A 93:8660-8665.
Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, Fried I (2012) Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med 366:502-510.
Tambini A, Nee DE, D'Esposito M (2018) Hippocampal-targeted Theta-burst Stimulation Enhances Associative Memory Formation. J Cogn Neurosci 30:1452-1472.
Thickbroom GW (2007) Transcranial magnetic stimulation and synaptic plasticity: experimental framework and human models. Exp Brain Res 180:583-593.
Thut G, Schyns PG, Gross J (2011a) Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. Front Psychol 2:170.
Thut G, Veniero D, Romei V, Miniussi C, Schyns P, Gross J (2011b) Rhythmic TMS causes local entrainment of natural oscillatory signatures. Curr Biol 21:1176-1185.
Titiz AS, Hill MRH, Mankin EA, Aghajan ZM, Eliashiv D, Tchemodanov N, Maoz U, Stern J, Tran ME, Schuette P, Behnke E, Suthana NA, Fried I (2017) Theta-burst microstimulation in the human entorhinal area improves memory specificity. Elife 6.
Uncapher MR, Wagner AD (2009) Posterior parietal cortex and episodic encoding: insights from fMRI subsequent memory effects and dual-attention theory. Neurobiol Learn Mem 91:139-154.
Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, Hermiller MS, Voss JL (2014) Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science 345:1054-1057.
Warren KN, Hermiller MS, Nilakantan AS, Voss JL (2019) Stimulating the hippocampal posterior-medial network enhances task-dependent connectivity and memory. Elife 8.
Xia M, Wang J, He Y (2013) BrainNet Viewer: a network visualization tool for human brain connectomics. PLoS One 8:e68910.
Xiao JX, Ehinger KA, Hays J, Torralba A, Oliva A (2016) SUN Database: Exploring a Large Collection of Scene Categories. International Journal of Computer Vision 119:3-22.

039 Yonelinas AP (2002) The nature of recollection and familiarity: A review of 30 years of research. Journal
040 of Memory and Language 46:441-517.
041 Zutshi I, Brandon MP, Fu ML, Donegan ML, Leutgeb JK, Leutgeb S (2018) Hippocampal Neural Circuits
042 Respond to Optogenetic Pacing of Theta Frequencies by Generating Accelerated Oscillation
043 Frequencies. Curr Biol 28:1179-1188 e1173.
044

045 **Figure Legends**



046

047 **Figure 1. Trial-specific stimulation during episodic memory formation.** (**A**) Scene-encoding and
048 numeric-judgment trials were randomly intermixed during each study phase, with ~2 s of stimulation
049 delivered immediately before stimulus onset for a subset of trials (ON) and no preceding stimulation for
050 remaining trials (OFF). Study phases were completed during fMRI scanning with memory test phases
051 after scanning. There were four stimulation conditions for ON and OFF trials. (**B**) Stimulation was
052 delivered as either a theta-burst pattern (TBS: 50 Hz triplet pulses delivered at 5 Hz) or at beta (single
053 pulses delivered at 12.5 Hz). These conditions had the same overall number of pulses during each
054 stimulation period delivered at the same intensity. (**C**) Stimulation was delivered to the HNT parietal
055 location (based on its fMRI connectivity with left hippocampus, as depicted by the blue arrow), or a
056 control out-of-network SMA location. Achieved stimulation locations confirmed via MRI for each condition
057 and subject are indicated by colorized spheres on a template brain. Bar plots represent mean ±s.e.m.
058 baseline resting-state fMRI connectivity of the subject-specific stimulation locations with the hippocampal
059 network, confirming relatively higher connectivity for the HNT than SMA location. *P<0.05 main effect of
060 stimulation location by one-way rmANOVA. (**D**) HNT or SMA locations were targeted for one of the two
061 study phases in each experimental session. After both study phases were complete, subjects exited the
062 scanner for a ~15 min break before taking the memory test. A different stimulation pattern (TBS or beta)
063 was used for each experimental session. Black arrows indicate stimulation conditions with order
064 counterbalanced across subjects.

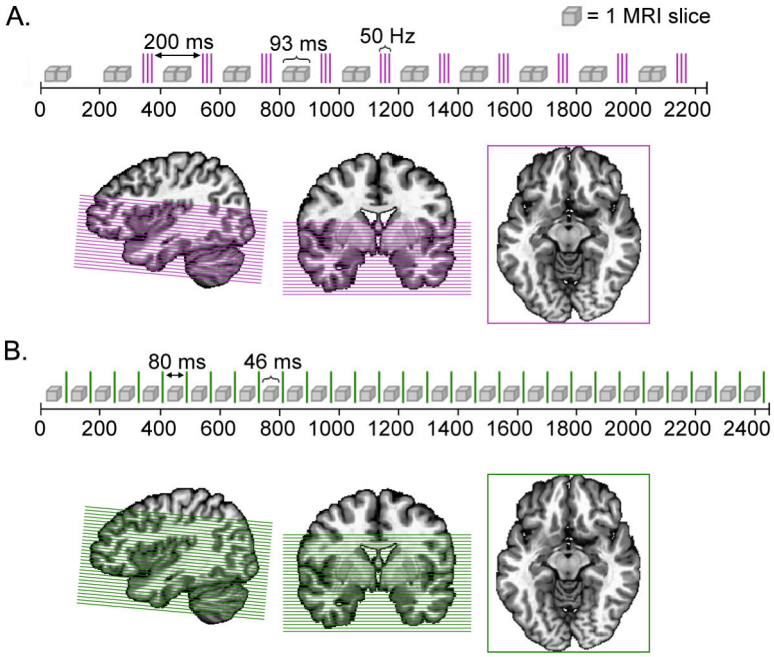


Figure 2. Interleaved TMS/fMRI scan sequences. Depiction of one imaging volume in the (**A**) TBS and (**B**) beta scan sequences. Each grey cube represents one MR EPI slice acquisition and each colored line indicates a TMS pulse (purple for TBS; green for beta). The extent of imaging coverage (22 EPI slices for TBS; 30 EPI slices for beta) is shown on a template brain, with EPI slices colorized to match the TMS pulses (purple for the TBS scan; green for the beta scan).

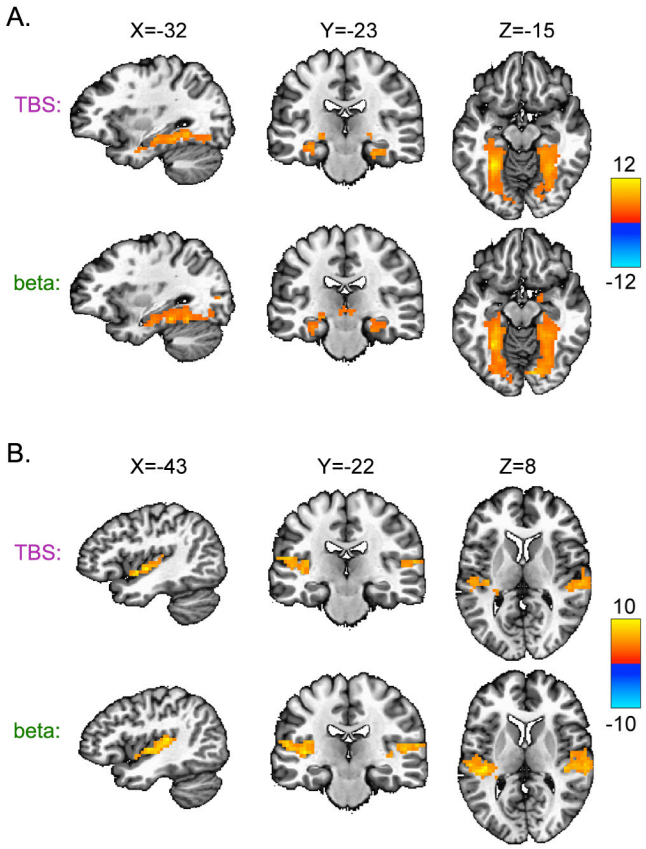


Figure 3. Expected fMRI signals of scene processing and stimulation sensations confirm fMRI data quality during concurrent TMS. Voxel-wise contrasts confirm that the fMRI signal could distinguish the task stimuli (scenes vs. numbers) and the presence of stimulation (ON vs. OFF). (**A**) Group-level contrast of scenes versus numbers, regardless of stimulation location or presence, identified significantly greater activation by scenes in areas that are typically scene-sensitive for both TBS and beta stimulation, including bilateral hippocampus and occipital, fusiform, and posterior parahippocampal cortex. (**B**) Group-level contrast of TMS ON versus OFF, regardless of stimulation location or the stimuli type (scenes and numbers) identified significantly greater activation for TMS ON in the bilateral auditory cortex for both TBS and beta stimulation. Direct contrasts of TBS versus beta did not identify significant differences for either comparison (see main text). Plots show supra-threshold voxels on a template brain. Color bars indicate t-statistic calculated by *3dMEMA*.

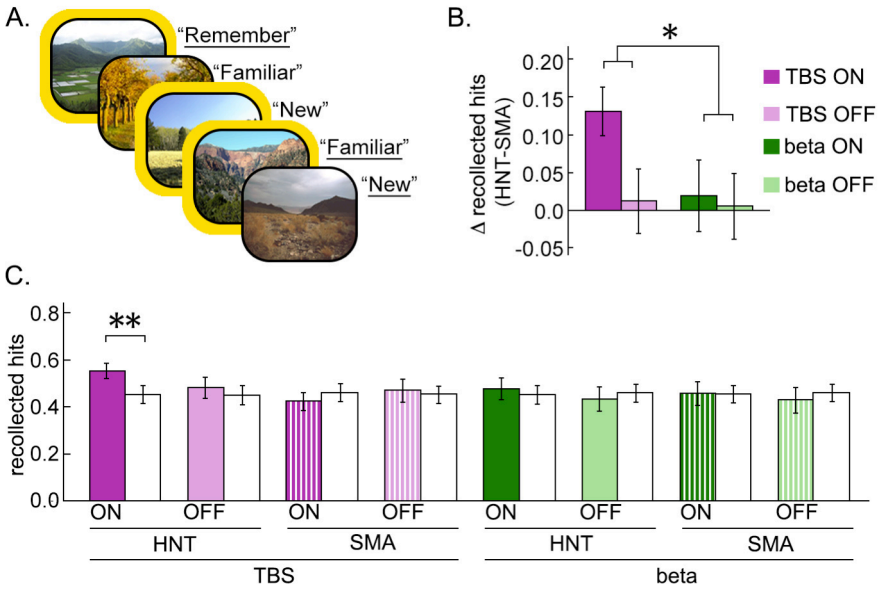


Figure 4. Theta-patterned stimulation of the hippocampal network during encoding selectively increased subsequent recollection. (**A**) Subjects discriminated studied scenes (old; depicted here with a yellow border) from randomly intermixed novel lures (new) using "Remember" responses to indicate the experience of hippocampal-dependent recollection, "Familiar" responses to indicate the experience of familiarity, and "New" responses to indicate lures. Example correct responses are underlined. (**B**) To identify stimulation effects on memory while holding sensory entrainment qualities (e.g., somatosensory, auditory) relatively constant, we compared the difference in the proportion of recollected hits for stimulation targeting HNT versus SMA for each of the stimulation patterns (TBS, beta, and off). * P=0.02 interaction between TMS presence and rhythm reported in text. (**C**) The proportion of recollected hits for HNT TBS was greater than for the aggregate of all control conditions. ** P_B=0.008 reported in text. None of the control conditions increased the proportion of recollected hits relative to the aggregate of all other control conditions (nonsignificant values reported in text). White bars next to each condition indicate the average of the control conditions that the corresponding condition of interest (colorized bars) was tested against. Bars and error bars indicate mean ± s.e.m.

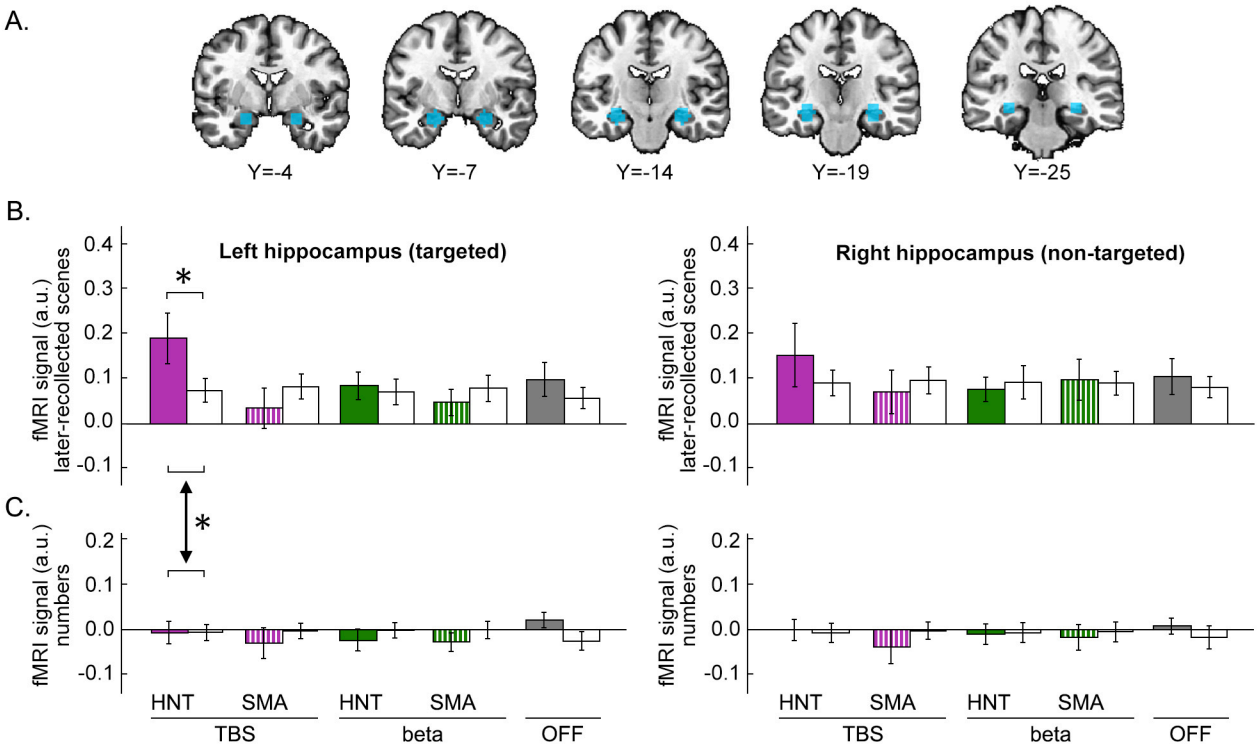


Figure 5. HNT TBS selectively increased left hippocampal activity during recollection memory formation. (**A**) Stimulation-evoked activity was measured within hippocampal/MTL units centered along the hippocampal longitudinal axis in each hemisphere, shown as colorized voxels in coronal slices of a template brain. The left hippocampus/MTL was targeted indirectly via its network functional connectivity (Materials and Methods) and the right hippocampus/MTL served as a non-targeted control. (**B**) fMRI activity evoked by later-recollected scenes for each stimulation condition (colorized bars) and the aggregate of all other control conditions (white bards adjacent to each colorized bars), plotted separately for left and right hippocampus. Bars and error bars indicate mean ± s.e.m. estimated fMRI activity (arbitrary units). Activity evoked by later-recollected scenes for HNT TBS was greater than for the aggregate of all control conditions. * P_B=0.03 reported in the text. None of the control conditions increased active relative to the aggregate of all other control conditions (nonsignificant values reported in text). (**C**) Activity evoked by numbers displayed as in panel B. Significant difference of the effect of HNT TBS relative to the average of all controls for scene-evoked recollection-related activity versus activity evoked by numeric judgments is indicated (*P=0.01 as reported in the text).

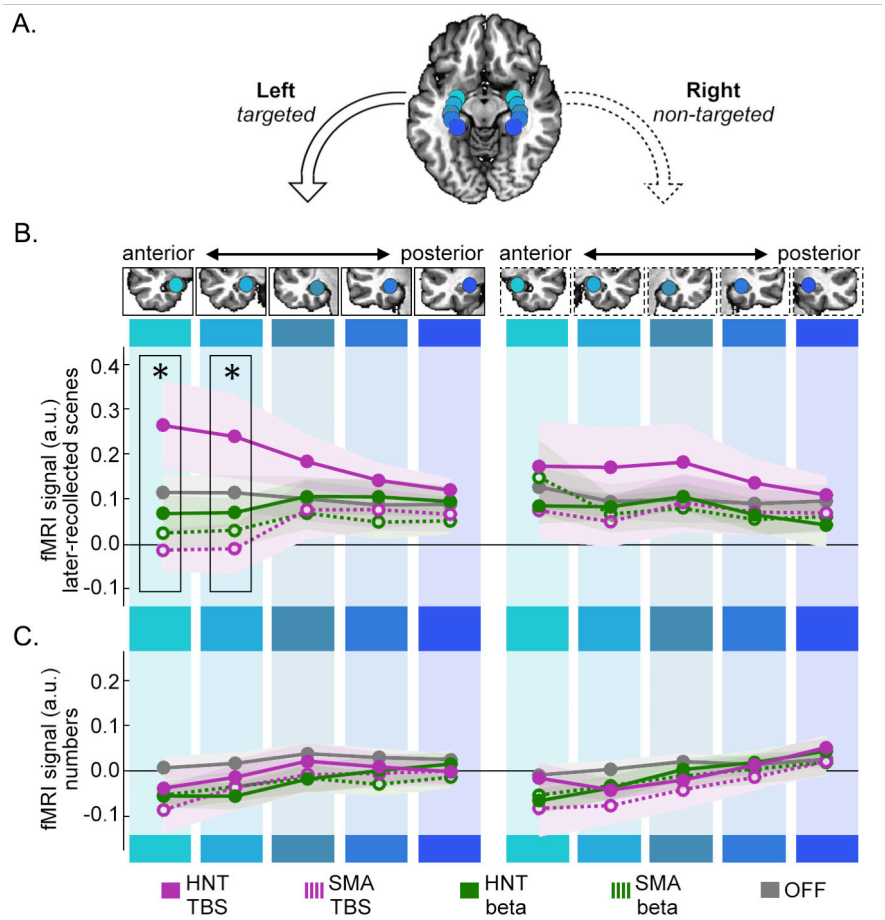


Figure 6. Exploratory analysis of differential stimulation effects on activity along the hippocampal longitudinal axis. The same fMRI analyses as described in Figure 5 are presented but segregated for longitudinal segments of the hippocampus in each hemisphere. (**A**) The five segments along the longitudinal axis in each hemisphere are shown as colorized spheres on a template brain. (**B**) fMRI activity evoked by scenes later-recollected was extracted from each of the spherical ROIs in the left and right hemisphere for each stimulation condition. Line plots indicate mean estimated fMRI activity (arbitrary units) ±s.e.m. (indicated by the shaded area), colorized for each of the five stimulation conditions. (**C**) fMRI activity evoked by numbers displayed as in panel B. * P<0.05 main effect of stimulation condition by five-way rmANOVA reported in text are outlined. Follow-up pairwise comparisons among stimulation conditions are described in the text.

Table 1. Memory performance. For the test phase in both sessions, the total hit rate (i.e., both Remember and Familiar responses) and the proportion of hits that were recollected (i.e., Remember responses; R if hit) are provided for the scenes that were presented during the study phases for the HNT and SMA location conditions, for trials with stimulation (TMS ON) and without (TMS OFF). The total false alarm rate (i.e., both Remember and Familiar responses) and the proportion of false alarms that were endorsed with recollection (R if false alarm) are provided for scenes that were not presented during the study phase (novel foils). Statistical comparisons of interest are described in the text. Values are given as across-participant means (SD).

	TBS session		Beta stimulation session	
	HNT	SMA	HNT	SMA
Total hit rate, TMS ON	0.66 (0.10)	0.61 (0.16)	0.67 (0.12)	0.66 (0.16)
Total hit rate, TMS OFF	0.63 (0.13)	0.62 (0.19)	0.62 (0.15)	0.64 (0.13)
Recollection hits, TMS ON	0.56 (0.13)	0.42 (0.15)	0.48 (0.19)	0.46 (0.21)
Recollection hits, TMS OFF	0.48 (0.18)	0.47 (0.20)	0.44 (0.21)	0.43 (0.22)
Total false alarm rate	0.31 (0.17)		0.38 (0.12)	
Recollection false alarms	0.17 (0.10)		0.21 (0.23)	