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Frequency-specific noninvasive modulation of memory retrieval and its relationship with hippocampal network connectivity

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Abstract

Episodic memory is thought to rely on interactions of the hippocampus with other regions of the distributed hippocampal-cortical network (HCN) via interregional activity synchrony in the theta frequency band. We sought to causally test this hypothesis using network-targeted transcranial magnetic stimulation. Healthy human participants completed four experimental sessions, each involving a different stimulation pattern delivered to the same individualized parietal cortex location of the HCN for all sessions. There were three active stimulation conditions, including continuous theta-burst stimulation, intermittent theta-burst stimulation, and beta-frequency (20-Hz) repetitive stimulation, and one sham condition. Resting-state fMRI and episodic memory testing were used to assess the impact of stimulation on hippocampal fMRI connectivity related to retrieval success. We hypothesized that theta-burst stimulation conditions would most strongly influence hippocampal-HCN fMRI connectivity and retrieval, given the hypothesized relevance of theta-band activity for HCN memory function. Continuous theta-burst stimulation improved item retrieval success relative to sham and relative to beta-frequency stimulation, whereas intermittent theta-burst stimulation led to numerical but nonsignificant item retrieval improvement. Mean hippocampal fMRI connectivity did not vary for any stimulation conditions, whereas individual differences in retrieval improvements due to continuous theta-burst stimulation were associated with corresponding increases in fMRI connectivity between the hippocampus and other HCN locations. No such memory-related connectivity effects were identified for the other stimulation conditions, indicating that only continuous theta-burst stimulation affected memory-related hippocampal-HCN connectivity. Furthermore, these effects were specific to the targeted HCN,

with no significant memory-related fMRI connectivity effects for two distinct control brain networks. These findings support a causal role for fMRI connectivity of the hippocampus with the HCN in episodic memory retrieval and indicate that contributions of this network to retrieval are particularly sensitive to continuous theta-burst noninvasive stimulation.

Keywords

hippocampus; neuromodulation; recognition; theta-burst stimulation; TMS

1 INTRODUCTION

The hippocampus is a crucial component of a distributed hippocampalcortical network (HCN) thought to support episodic memory (Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011; Buckner, Andrews-Hanna, & Schacter, 2008; Eichenbaum, Yonelinas, & Ranganath, 2007; Kondo, Saleem, & Price, 2005; Mesulam, 1990; Ranganath & Ritchey, 2012; Rugg & Vilberg, 2013; Squire & Zola-Morgan, 1991). The HCN includes posteromedial, lateral parietal, ventral anterior temporal, prefrontal, retrosplenial, parahippocampal, and rhinal cortex. Although interactions of hippocampus with other HCN locations are frequently observed during memory encoding and retrieval using fMRI (Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005; Ritchey, Yonelinas, & Ranganath, 2014; Spaniol et al., 2009; Staresina, Cooper, & Henson, 2013), there are few relevant causal tests involving experimental manipulation of hippocampal-HCN connectivity and measurement of corresponding changes in memory. The goal of the current study was to evaluate the role of hippocampal-HCN connectivity in memory retrieval via noninvasive brain stimulation.

Episodic memory is disrupted by lesions of key HCN components (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007; Olson & Berryhill, 2009; Scoville & Milner, 1957; Simons & Spiers, 2003) and their connections (Aggleton & Brown, 1999; Tsivilis et al., 2008; Vann, 2013; Vann et al., 2009; Warrington & Weiskrantz, 1982). Lesions can also produce changes in fMRI and MRI measures of connectivity (Henson et al., 2016; Maguire, Vargha-Khadem, & Mishkin, 2001), and disrupted HCN fMRI connectivity is associated with a variety of amnesic states (Damoiseaux, Prater, Miller, & Greicius, 2012; Greicius, Srivastava, Reiss, & Menon, 2004; Hampstead, Khoshnoodi, Yan, Deshpande, & Sathian, 2016; Jacobs, Radua, Luckmann, & Sack, 2013; McLaren, Sperling, & Atri, 2014; Peer et al., 2014; Poppenk & Moscovitch, 2011; Voets et al., 2014). However, it is difficult to determine whether the resulting memory impairments are due to disruption of the network per se versus disruption of individual key areas. One way to address this issue is by temporarily modulating HCN interregional interactions and measuring the resulting impact on memory using methods such as noninvasive brain stimulation (Fox, Halko, Eldaief, & Pascual-Leone, 2012). To our knowledge, only one study has shown that manipulating hippocampal fMRI connectivity to other HCN locations via transcranial magnetic stimulation (TMS) produces corresponding modulation of memory (Wang et al., 2014), while several other studies have suggested that TMS effects on memory may have resulted from changes in HCN connectivity (Kim et al., 2018; Nilakantan, Bridge, Gagnon, VanHaerents, & Voss, 2017;

Tambini, Nee, & D'Esposito, 2018). Further evidence to confirm the putative relationship between HCN connectivity and memory is needed.

HCN interregional interactions important for memory have been particularly associated with activity synchrony in the theta-frequency band. For instance, human intracranial recordings have shown that HCN regions exhibit neuronal synchrony and phase locking at the band frequencies (4–8-Hz) at rest (Foster & Parvizi, 2012), during memory formation (Lega, Jacobs, & Kahana, 2012; Rutishauser, Ross, Mamelak, & Schuman, 2010) and during memory retrieval (Anderson, Rajagovindan, Ghacibeh, Meador, & Ding, 2010; Burke et al., 2014; Foster, Kaveh, Dastjerdi, Miller, & Parvizi, 2013; Lega, Germei, & Rugg, 2017; Steinvorh, Wang, Ulbert, Schomer, & Halgren, 2010; Watrous, Tandon, Conner, Pieters, & Ekstrom, 2013). Likewise, invasive electrical theta-burst stimulation, whereby gamma bursts are applied in a theta cycle (“theta nested gamma”), preferentially induces long-term potentiation in the rodent hippocampus (Larson, Wong, & Lynch, 1986), putatively because this stimulation pattern mimics the endogenous activity of the hippocampus (Buzsaki, 2002). Furthermore, induction of long-term potentiation increases interregional connectivity throughout the HCN (Canals, Beyerlein, Merkle, & Logothetis, 2009). It is therefore possible that noninvasive theta-burst TMS mimicking the “theta-nested gamma” activity pattern relevant to the HCN might be particularly effective at engaging memory processing by this network (Shirvalkar, Rapp, & Shapiro, 2010). Although different rhythmic patterns of TMS exert distinct influences on local neural activity that have been generally characterized as “excitatory” versus “inhibitory” for primary motor cortex (Hoogendam, Ramakers, & Di Lazzaro, 2010; Huang, Rothwell, Chen, Lu, & Chuang, 2011; Pascual-Leone et al., 1998; Thickbroom, 2007) and the HCN has shown variable resting-state fMRI connectivity changes due to low versus high stimulation frequencies (Eldaief, Halko, Buckner, & Pascual-Leone, 2011), previous experiments have not evaluated whether HCN-related memory processing responds differently to different stimulation patterns. It is possible that theta-burst stimulation could increase activity coherence throughout the HCN and thereby improve memory processing to a greater extent than other stimulation patterns, due to the consistency of this stimulation pattern with endogenous HCN interregional activity [see (Roberts, Clarke, Addante, & Ranganath, 2018; Thut et al., 2011; Thut, Schyns, & Gross, 2011; Wang, Clouter, Chen, Shapiro, & Hanslmayr, 2018) for similar hypotheses].

Here, we tested relationships between memory retrieval and hippocampal fMRI connectivity using TMS. Our design included evaluation of whether theta-burst TMS is particularly effective for modulating hippocampal fMRI connectivity related to memory retrieval, as would be expected based on the hypotheses explicated above. Using a within-subjects design, we administered four different single-session stimulation conditions to the same parietal cortex location of the HCN and measured the aftereffects on fMRI connectivity and episodic memory retrieval (Figure 1). Stimulation was applied between word-list study and test for each experimental session, such that effects of stimulation on retrieval could be isolated.

Stimulation conditions used well-established regimens to provide safety and tolerability in healthy adults (Oberman, Edwards, Eldaief, & Pascual-Leone, 2011; Rossi et al., 2009), including theta-burst delivered in a continuous train (θ -burst), theta-burst delivered

intermittently (i θ -burst), and 20-Hz beta-frequency stimulation (β -freq). Although these regimens are normally described in terms of being locally “inhibitory” (θ -burst) versus “excitatory” (i θ -burst and β -freq) (Chen, Yung, & Li, 2003; Huang et al., 2011; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994; Thickbroom, 2007), our hypotheses concerned their differential ability to produce downstream effects on the hippocampus via the degree of consistency with its endogenous activity.

We assessed the immediate aftereffects of stimulation on resting-state hippocampal fMRI connectivity within the HCN, on memory retrieval accuracy, and on their relationships. We hypothesized that theta-burst stimulation would affect memory retrieval and fMRI connectivity to a greater extent than β -freq stimulation, as indicated above, but without strong a priori hypotheses regarding θ -burst versus i θ -burst conditions. We hypothesized that β -freq would have minimal effects on memory retrieval and hippocampal connectivity, as we previously found that multiple consecutive days of β -freq were required to influence episodic memory (Wang et al., 2014) and single-session β -freq stimulation has previously been shown to non-significantly impact hippocampal resting-state connectivity (Eldaief et al., 2011). Effects of the three active stimulation conditions were compared to those of sham stimulation applied at sub-threshold intensity as well as in direct contrasts with each other. To provide network-specific controls, we also assessed effects of stimulation on hippocampal fMRI connectivity within dorsal-attention and primary-visual networks.

2 MATERIALS AND METHODS

2.1 Participants

Data were obtained from 30 healthy adults who met the following criteria: passed MRI and TMS safety screening, reported no present use of psychoactive drugs, and were free of known neurological and psychiatric conditions. No participants withdrew due to complications or side effects. Data from six participants were excluded from all analyses: two participants for near-chance word recognition performance ($<0.5 d'$ score), two for self-reported failure to follow task instructions, and two for excessive motion during at least one of the four MRI scanning sessions (as described below). A final sample of 24 participants with complete datasets was included in all analyses (14 females, ages 19–28 years, average age = 23.5, $SD = 2.6$). Resting-state fMRI data from 47 additional participants (31 females, ages 18–34 years, average age = 25.4, $SD = 4.2$) who participated in an independent study were also used in order to independently define networks-of-interest for analysis of fMRI data in the main experiment (see below). All participants gave written informed consent approved by the Northwestern University Institutional Review Board and were paid for participation.

2.2 Experiment design

Participants completed a baseline session and then four experimental sessions on separate days using a within-subjects, counterbalanced design. During the baseline session, resting-state fMRI and structural MRI were acquired, and resting motor threshold was determined (described below). Resting-state fMRI from the baseline session was used to define the

stimulation location used during the subsequent four experimental sessions (described below). The four experimental sessions occurred at least 2 days apart, with an average interval of 3.6 days between each session (range = 2.0–5.8 days). Each experimental session consisted of a short practice, during which participants completed an abbreviated example of the different phases of the memory task (described below). After this, the actual experimental session commenced, starting with a memory-task study phase, followed by TMS, resting-state fMRI scanning, and a memory-task test phase (Figure 1).

2.2.1 Study phase—One hundred four words were presented sequentially at the center of a computer screen. Each word was shown for 2,000 ms (3,000–5,000-ms inter-stimulus interval) in one of eight font shades on a grey background. A different list of words and font shades was used each day. The same words were used in each list across subjects, but the words were randomized into trial type (old/new) for each subject. Each word list was assigned a pair of font color categories, including orange/blue, pink/yellow, red/teal, and purple/green. Each color category had four graded shades, for a total of eight possible font shades per word list. The color category pairs were assigned to the same word lists across subjects, but the font shades were assigned to words randomly for each subject. Thus, study stimuli, including word lists and colors, were unique for each experimental session. Participants intentionally studied words and their font shades with knowledge of the format of the forthcoming test.

2.2.2 TMS phase—TMS began approximately 5 min (mean = 4.8 min, $SD = 2.8$ min, range = 0–13 min) after the end of the study phase. TMS was delivered in a 20-min protocol while participants solved computerized math puzzles in order to maintain alertness/wakefulness (<https://gabrielecirulli.github.io/2048/>). TMS was delivered in a room adjacent to the MRI scanner room. All testing procedures occurred within an hour following the final TMS pulse. Theta-burst and high frequency (>5-Hz) rTMS protocols have been reported to induce aftereffects that last as long as 20–60 min post-stimulation (Hoogendam et al., 2010; Rossi et al., 2009; Thut & Pascual-Leone, 2010; Wischniewski & Schutter, 2015), but without definitive information regarding the timecourse of effects, which likely vary for different outcomes of interest.

2.2.3 MRI phase—Immediately after the final TMS pulse was delivered, participants moved into the MRI scanner for resting-state functional (scan duration 5.08-min) and structural (scan duration 6.36-min) scans. Approximately 6 min passed between the final TMS pulse and the acquisition of the first resting-state volume (mean delay = 6.3 min, $SD = 1.8$ min, range = 4–12 min). There were no significant differences in delay among the stimulation conditions (all pairwise comparison $ps > .25$). Scanning was completed in <15 min for all sessions.

2.2.4 Test phase—After scanning, the test phase was administered using 96 of the 104 studied “old” words (excluding the first four and last four words presented in the study phase to account for primacy and recency effects) and 96 “new” lure words. Each word was presented for 2,000 ms at the center of a computer screen in white font on a grey background, followed by a 1,000-ms delay before presentation of a 2,000-ms prompt to

make an old/new response mixed with confidence using a 6-point scale that was displayed as “Rem 4 3 2 1 New”. “Rem” responses were used to indicate recollection of the act of studying the word. “4 3 2 1” responses were used to indicate word familiarity without recollection, with “4” indicating the highest level of familiarity and “1” indicating the lowest. “New” responses were used to indicate detection of lure words. For all trials with old words, irrespective of the recognition response, the word was then shown in each of the eight possible font shades simultaneously and participants were given 4,000 ms to select the studied font shade, followed by a 1,000-ms confidence rating for the selected shade. Responses were registered using a mouse. Trial order (old/new words) was random, and the inter-trial interval was 1,000 ms. The mean delay from the end of Study to the beginning of Test was 44 min ($SD = 3$ min, range = 34–53) and the mean delay from the end of stimulation to the beginning of Test was 19 min ($SD = 2$ min, range = 11–25). There were no significant differences in delay among the stimulation conditions (all pairwise comparison $ps > .12$).

2.3 Stimuli

The MRC Psycholinguistic Database (Machine Usable Dictionary, Version 2.00) was used to generate a pool of words. Criteria included nouns with a length of 4–10 letters with scores within 5–120 on Kucera-Francis written frequency, 10–180 on Thorndike-Lorge written frequency, 220–600 on Concreteness, 220–600 on Imageability, and 350–630 on Familiarity. Eight hundred words from this pool were randomized into four lists. Each list included 200 words, was assigned to a pair of color categories, and was randomized to stimulation conditions across subjects, as described above. Words were displayed in the center of a computer screen using Presentation (Neurobehavioral Systems, Inc. Berkeley, CA, USA).

2.4 Transcranial magnetic stimulation

TMS was delivered with a MagPro X100 stimulator connected to a MagPro Cool-B65 liquid-cooled butterfly coil (MagVenture A/S, Farum, Denmark). A TMS navigation system that utilized the individual MRIs (Localite GmbH, St. Augustin, Germany) was used for anatomical targeting. Participants sat in an ergonomic chair with a headrest and a vacuum-conforming pillow to provide head stabilization. Resting motor threshold (RMT), the minimum percentage of stimulator output (%SO) necessary to generate a visible contraction of the right thumb (*abductor pollicis brevis*) for five out of 10 consecutive pulses, was determined during the baseline session. RMT values ranged between 34 and 68 %SO (mean = 49.2 %SO, $SD = 7.5$).

A different stimulation condition (θ -burst, $i\theta$ -burst, β -freq, or sham) was delivered in each of the four experimental sessions on different days. The order was counterbalanced across subjects. The stimulation conditions followed standard guidelines (Oberman et al., 2011; Rossi et al., 2009). Theta-burst stimulation delivered a total of 600 pulses at an intensity of 80% RMT. The pulses were arranged in bursts delivered every 200 ms (5-Hz). Each burst included three pulses delivered at 50-Hz. In θ -burst, bursts were delivered in one continuous train (40-s duration), whereas in $i\theta$ -burst, bursts were delivered in intermittent trains (2-s on, 8-s off; 190-s duration). β -freq stimulation delivered a total of 1,600 pulses at 20-Hz at an intensity of 100% RMT. In β -freq, pulses were delivered in trains (2-s on, 28-s off; 20 min

duration). The sham condition used the β -freq protocol but with intensity lowered as to be unlikely to affect neuronal activity (10% RMT; 2-s on, 28-s off; 20 min duration). To account for duration differences across the stimulation conditions, the θ -burst and $i\theta$ -burst protocols were preceded with 18.5 and 17 min, respectively, of the subthreshold sham protocol (10% RMT) prior to the onset of theta-burst stimulation at 80% RMT. Thus, every TMS session lasted 20 min to help equate subjective qualities of stimulation across conditions. Therefore, we were able to compare the effects of θ -burst to a near-zero control (sham), to an active-control with different frequency (β -freq), and to an active-control with the same stimulation frequency but disrupted patterning ($i\theta$ -burst).

Participants were told that stimulation would feel and sound different across the 4 days, and that the pattern and intensity might change throughout sessions, but otherwise had no knowledge of specific hypotheses. If a participant reported discomfort, stimulation intensity was decreased until tolerable and the adjusted intensity was used for all subsequent sessions. θ -burst was reduced in two subjects, β -freq was reduced in five subjects, and $i\theta$ -burst was reduced in three subjects. The resulting mean stimulation intensities were 78.8% RMT ($SD = 4.2$) for θ -burst, 96.6% RMT ($SD = 8.0$) for β -freq, 78.3% RMT ($SD = 4.6$) for $i\theta$ -burst, and 9.8% RMT ($SD = 0.8$) for sham. The location of the stimulation coil was held steady at the cortical stimulation target coordinates for all pulses delivered throughout each session, as confirmed via 3D positioning information provided by online tracking of the coil position (Localite GmbH, St Augustin, Germany) relative to the head (mean position variance across all pulses/sessions = 0.85 mm, $SD = 0.14$).

An electric field distribution (E-field) resulting from each of the three active stimulation conditions was modeled for each subject using SimNIBS 2.0 (Thielscher, Antunes, & Saturnino, 2015). Tetrahedral head meshes segmented by tissue class (white matter, grey matter, CSF, skull, and skin) were created for each subject from the T1-weighted MR images. The coordinates of the coil position recorded during each stimulation session were transformed to the space of the individual meshes. These coordinates, along with the recorded dI/dt from the stimulator, were used in a realistically shaped finite element model implemented in SimNIBS. The head meshes were converted to volumetric maps in each subject's native space and then spatially normalized to standardized space using the same approach as was used for fMRI analysis. The group-level mean E-field peaks were 131.0 V/m ($SD = 19.6$) for θ -burst, 131.7 V/m ($SD = 21.5$) for $i\theta$ -burst, and 160.2 V/m ($SD = 28.7$) for β -freq.

2.5 MRI acquisition

MRI data were collected using a Siemens 3 T Prisma whole-body scanner with a 64-channel head/neck coil. Functional images were acquired using a BOLD contrast sensitive gradient-echo echoplanar sequence (550 frames; TE 22-ms; TR 555-ms; flip angle 47°; voxel resolution $2.0 \times 2.0 \times 2.0$ -mm; 64 ascending 2-mm thick axial slices; 208×196 -mm FOV; multi-band factor of 8; scan duration 5.08-min). During the resting-state scan, participants 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 without thinking of anything specific. Structural images were acquired using a T1-weighted MPRAGE sequence

(176 frames; TE 1.69-ms; TR 2,170-ms; TI 1,100-ms; flip angle 7°; voxel resolution $1.0 \times 1.0 \times 1.0$ -mm; 1-mm thick sagittal slices; 256×256 -mm FOV; scan duration 6.36-min). Resting state scans were completed within 20 min from the end of the TMS for all sessions (see above). Raw data are archived in the National Database for Autism Research (<https://ndar.nih.gov/>).

2.6 MRI processing

MRI data were preprocessed using AFNI software (Cox, 1996). Structural scans were skull stripped (*3dSkullStrip*) and spatially normalized to the standardized Talairach and Tournoux Colin27 template via affine transformation (*auto_tlrc*). The first five EPI volumes were removed to achieve MR steady state (*3dTcat*), large outliers were suppressed (*3dDespike*), and corrected for motion by rigid body transformation (*3dvolreg*), co-registered to the anatomical scan via affine transformation (*align_epi_anat*), and spatially normalized to the standardized Talairach and Tournoux Colin27 template via affine transformation (*auto_tlrc*). 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 (angles and translations). Volumes with excessive motion (>0.2 -mm), as well as the previous volume, were flagged for later censoring. Data were spatially smoothed using a 4-mm full-width-at-half-maximum (FWHM) isotropic Gaussian kernel (*3dmerge*) and signal intensity was normalized by the mean of each voxel. An EPI mask was created that consisted only of voxels in the brain with stable signal across the scanning session (*3dAutomask*). Bandpass filtering (0.01–0.1-Hz), motion censoring, and nuisance time series (estimates of motion parameters and derivatives) were detrended from each voxel simultaneously as a linear regression model (*3dDeconvolve*, *3dTproject*) to yield a residual time series for analysis. Global signal was not included as a nuisance variable (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009; Saad et al., 2012). Two subjects had scans with excessive motion (>38 volumes censored) which caused *3dDeconvolve* error due to inadequate remaining degrees of freedom, and these subjects were excluded from all analyses (see above).

Average motion for included subjects did not vary by stimulation condition (all pairwise comparison $ps > .2$; overall mean motion = 0.05 mm, $SD = 0.01$). On average, 0.6% ($SD = 1.0$) of the θ -burst and the β -freq time series and 0.4% ($SD = 1.0$) of the $i\theta$ -burst and the sham time series were censored. There was no significant difference in the amount of censoring across conditions (all pairwise comparison $ps > .14$). A group EPI intersection mask was comprised of voxels included in datasets from all subjects and all analyses were constrained within this mask.

2.7 Determination of subject-specific stimulation locations

Using the baseline resting-state fMRI data, we identified a location of parietal cortex with relatively high connectivity to the hippocampus in each subject to be used for stimulation. The same location for each subject was used for all stimulation conditions. Individualized hippocampal volumes of interest and parietal cortex stimulation locations were defined for each subject via fMRI connectivity measures. The approach was to identify a set of representative hippocampal voxels by computing within-hippocampus fMRI

interconnectivity, and then identifying a cluster of parietal voxels having high fMRI connectivity with these hippocampal voxels. The Talairach and Tournoux Colin27 template and TT_Daemon Atlas were used to create a bilateral hippocampal mask and a left parietal mask (left angular gyrus and BA 39), blurred with a 4-mm FWHM Gaussian kernel. These masks were used to anatomically constrain each subject's hippocampal volume of interest and parietal cortex stimulation location definitions. Hippocampal connectedness maps were created by correlating (Pearson's r) the pre-processed activity timeseries in each hippocampus voxel with every other voxel in the bilateral hippocampus mask, averaging the correlations, and assigning the mean value to that voxel in the subject's hippocampal fMRI connectedness map (*3dTcorrMap*). Clusters of contiguous (>20) voxels with the top 25% hippocampal connectedness values were saved as the subject's hippocampus volume of interest (*3dclust*); that is, the set of the most highly interconnected voxels within the hippocampus. The spatially averaged time series of the hippocampal volume of interest was used as a seed to create hippocampal fMRI connectivity maps in the left parietal mask (*3dTcorr1D*). Clusters of contiguous (>20) voxels with the top 10% hippocampal connectivity values were identified (*3dclust*) as stimulation locations; that is, the cluster of parietal voxels with the highest connectivity to the hippocampal volume of interest. In the event that more than one cluster was identified, the more ventral/inferior and lateral sites were preferentially chosen. Within this cluster, the coordinate with peak correlation value to the hippocampal volume of interest was set as the parietal cortex stimulation location. The same subject-specific parietal-cortical location was used each for each of the four stimulation conditions.

2.8 Network-of-interest definition

Three a priori networks of interest, the HCN, the dorsal attention network (DAN), and the primary visual network (VIN), were used to assess network-specific effects of stimulation. Each network was defined as a set of regions with robust seed-based, voxel-wise, whole-brain fMRI connectivity to a network-specific seed at the group level. This analysis was performed using resting-state fMRI scans from 47 healthy young adults that participated in a separate study using the same MRI scan parameters. Thus, the networks of interest were defined independent of the data from the current experiment.

The HCN was defined via seed-based connectivity with the hippocampal targets that were identified for each subject in the main experiment. Given that there were individual differences in the hippocampal target definition, the seed was calculated as the voxels that overlapped among at least half of the subjects, for a total of 135 voxels. This seed was used for connectivity analysis in the independent sample to define the HCN network of interest. Contiguous voxels (>200) with robust fMRI connectivity with the hippocampal seed ($p < 1.0 \times 10^{-13}$ *voxel-wise threshold*) were saved as network regions. All voxels meeting this threshold were saved as the network-of-interest mask, which was dilated and eroded in order smooth and fill any holes in the mask (*3dmask_tool*), and then constrained within the EPI group intersection mask for the TMS experimental sample, to ensure that all HCN voxels were those with data from all subjects in the TMS experimental sample. The final HCN mask comprised 5,460 voxels (Figure 2a).

The control networks of interest (DAN and VIN) were created using similar methods applied to the independent sample resting-state fMRI data. The seeds for control networks were 6-mm sphere (123 voxels) centered at coordinates that have previously been identified as characteristic of the two networks (Yeo et al., 2011). The DAN seed was placed in the left superior frontal gyrus (see Table 5 from Yeo et al., 2011; dorsal attention seed “A”, MNI LPI: -22, -8, 54). The VIN seed was placed in the dorsal central part of V1 (see Table 2 from Yeo et al., 2011; seed “V1_{cd}”, MNI LPI: -9, -95, 3). Contiguous voxels (>200) with significant fMRI connectivity to each seed were saved as regions in its respective network. In order to approximately match the size of the control networks to the size of the HCN in terms of voxel count, different voxel-wise thresholds were used ($p < 1.0 \times 10^{-12}$ for DAN; $p < 1.0 \times 10^{-14}$ for VIN). As with the HCN mask, the control network masks were dilated and eroded in order smooth out and fill any holes in the mask (*3dmask_tool*), and then constrained within the EPI group intersection mask of subjects in the TMS experimental sample. The final DAN mask comprised 5,317 voxels and the final VIN mask comprised 5,416 voxels (Figure 2 b,c). The DAN and VIN mask shared 71 overlapping voxels (small portions of left fusiform gyrus and left declive of the cerebellum). Neither of the control networks included voxels that overlapped with the HCN.

2.9 Statistical analysis

Data were analyzed using AFNI software (Cox, 1996) and Matlab (The MathWorks, Inc. Natick, MA, USA), with visualization using the Brain-Net Viewer Matlab toolbox (Xia, Wang, & He, 2013).

2.9.1. Analysis of stimulation effects on memory retrieval—Trials with no registered response were eliminated from analyses (2.9 of 192 trials on average per participant, range = 0–22 trials). Word recognition proportion of hits (of any recognition level) and false alarms were used to compute d' using the log-linear approach to correct for extreme values (Stanislaw & Todorov, 1999). Source recollection (font color/shade) was calculated as the proportion of correct responses out of the total attempts. Source memory was evaluated separately for color category (i.e., red vs. blue) as well as for the eight gradient shades (four shades per color). The self-reported confidence ratings for the associated source responses were z-scored at the subject-level to minimize between-subject differences in the rating distribution. Source accuracy and confidence ratings were assessed independently and also contingent on word recognition success. Differences between stimulation conditions were evaluated at the group level using repeated-measures ANOVAs and *post-hoc* paired *t*-tests (two-tailed). Effect sizes were calculated as Cohen's d .

2.9.2 Analysis of stimulation effects on seed-based network connectivity—At the group level, effects of stimulation were evaluated on mean hippocampal fMRI connectivity and on the relationship between hippocampal fMRI connectivity and memory using ANCOVA. Analyses were performed separately within the HCN, DAN, and VIN networks of interest. For each subject, the time series of the subject-specific hippocampal target was spatially averaged and then correlated with every other voxel in the network mask to create network-specific seed-based voxel-wise connectivity maps (*3dTcorr1D*). Differences in connectivity with the hippocampus between conditions of interest were then

calculated for each subject via voxel-wise subtraction (i.e., θ -burst—sham, β -freq—sham, and $i\theta$ -burst—sham; *3dcalc*). Differences in memory performance were likewise calculated for each subject via subtraction of d' values (i.e., θ -burst—sham, β -freq—sham, and $i\theta$ -burst—sham). Increases in hippocampal connectivity were evaluated relative to zero for each voxel at the group-level using one-way ANCOVAs with the corresponding differences in memory performance included as a covariate (*3dttest++* with the option *-covariate*). These tests thus assessed: (a) the effect of stimulation on mean increases in hippocampal connectivity between two conditions, controlling for connectivity increases related to memory changes, and (b) the relationship between increased hippocampal connectivity and memory performance differences between conditions (covariate slope), thus testing individual differences in memory changes versus hippocampal connectivity changes between conditions. The opposite tests were also performed to test for decreases in hippocampal connectivity, although no significant effects were identified (see below). The voxel-wise threshold was $p < .005$ and a cluster-size threshold was determined via permutation (10,000 simulated t -tests) to achieve $\alpha < 0.05$ (*3dClustsim*). These thresholds varied by stimulation condition contrast and by network of interest, ranging from 40 to 46 voxels (mean = 42) in the HCN, 42–51 voxels (mean = 47) in the DAN, and 44–57 voxels (mean = 51) in the VIN. For each network of interest, the mean cluster-size threshold was used in all contrasts to identify clusters with significant effects. Notably, for the θ -burst analysis within the HCN, the sizes of supra-threshold clusters were substantially larger than the corresponding threshold values (203% of the threshold on average, range = 133–356%) and running the analysis with a voxel-wise threshold of $p < .001$ and cluster correction yielded supra-threshold clusters matching those in the reported analysis. This indicates that the analysis strategy yielded findings that would be robust to small variations in the methods used to determine statistical thresholding. We also ran a control set of analyses in which the same pairwise comparisons were performed as t -tests, without using d' values as a covariate (*3dttest++* without the option *-covariate*).

3 RESULTS

We hypothesized that memory retrieval would be superior following theta-burst stimulation than following β -freq stimulation or sham. Repeated-measures ANOVA of d' values for the four stimulation conditions indicated significant differences [$F(3,69) = 3.1, p = .03, \eta^2 = 0.12$]. Post-hoc pairwise comparisons indicated that d' values following θ -burst were significantly greater than sham [$t_{(23)} = 2.73, p = .01$, Cohen's $d = 0.40$], whereas d' values did not significantly differ from sham after $i\theta$ -burst [$t_{(23)} = 1.83, p = .07$] or β -freq [$t_{(23)} = 0.47, p = .73$] (Figure 3a). Further, d' values were significantly greater following θ -burst than β -freq [$t_{(23)} = 2.25, p = .03$, Cohen's $d = 0.31$] (Figure 3a). Difference between θ -burst and $i\theta$ -burst [$t_{(23)} = 0.76, p = .45$] and between $i\theta$ -burst and β -freq [$t_{(23)} = 1.14, p = .27$] were non-significant. Thus, although both θ -burst and $i\theta$ -burst conditions led to numerically higher memory performance relative to both β -freq and sham stimulation conditions (Figure 3a), these effects were only reliably greater than β -freq and sham for θ -burst.

Source memory and memory confidence measures were also assessed. There were no significant stimulation effects for measures of source memory accuracy in terms of color or shade, including no significant pairwise comparisons, whether accuracy was computed for

all trials or only for trials with successful word recognition (i.e., hits) (all RM-ANOVA p s > .25, all pairwise tests p s > .09; Table 1). Likewise, there were no significant stimulation effects on source memory confidence for either color or shade (RM-ANOVAS p s > .43) including no significant pairwise comparisons (p s > .07; Table 1). Thus, memory retrieval accuracy as measured by d' was the only memory measure to be influenced by stimulation.

To account for possible differences in the timecourse of stimulation effects, we separately assessed data collected during the first half from the second half of the memory test. As was the case for the entire test, d' values following θ -burst were significantly greater than sham in both the first [$t_{(23)} = 2.18$, $p = .04$ Cohen's $d = 0.36$] and second [$t_{(23)} = 2.15$, $p = .04$, Cohen's $d = 0.39$] half. Furthermore, d' values were marginally greater following θ -burst than β -freq in the first [$t_{(23)} = 1.87$, $p = .07$, Cohen's $d = 0.29$] half but not the second [$t_{(23)} = 1.03$, $p = .31$], suggesting that the reduced trial counts contributing to each average in this analysis weakened results relative to the full test data, for which θ -burst versus β -freq comparisons were significant. No other pairwise comparisons were significant between any condition for either the first half or the second half (all p s > .12). Critically, for the first half of data, d' values did not significantly differ from sham after i θ -burst [$t_{(23)} = 1.33$, $p = .20$] or after β -freq [$t_{(23)} = 0.31$, $p = .76$], indicating that there were no significant memory effects caused by these conditions even when focusing on the period most immediately following stimulation (first-half testing completed within ~34 min of the completion of stimulation).

To account for a possible learning effect over the four sessions, we also assessed the data sorted by day order rather than stimulation condition. Repeated-measures ANOVA of d' values for the 4 days treated sequentially irrespective of stimulation condition indicated no differences ($F(3,69) = 1.17$, $p = .33$), further supporting the findings of selective effects due to θ -burst.

To account for the possibility that subjective experiences of stimulation could have influenced memory performance, we assessed the relationship between the stimulator output intensity and memory performance. That is, stimulator output was calibrated based on the resting motor threshold of each subject in order to approximately match the effects of stimulation on neuronal excitability across subjects (Rossini et al., 2015), yielding stimulator output intensity values that varied across subjects. The subjective experience of stimulation, which includes auditory, motoric, somatosensory, and nociceptive qualities, is related to the intensity of stimulator output. There was no significant correlation between stimulator output and d' values for the θ -burst condition ($r = 0.12$, $p = .56$). Furthermore, stimulator output was higher for the β -freq condition than for θ -burst and i θ -burst, as these conditions were calibrated to different levels of resting motor threshold (see section 2), with matched intensities for θ -burst and i θ -burst. Yet, effects on memory were selective for θ -burst and significantly greater for θ -burst than for β -freq. This suggests that the effects of θ -burst on memory retrieval accuracy were not due to non-specific influences of the subjective qualities of stimulation.

Notably, five subjects varied from the group-level effect of increased d' values following θ -burst, instead showing decreases in d' relative to sham. Interestingly, four of these five subjects also showed decreased d' values relative to sham for i θ -burst and/or β -freq,

suggesting that stimulation was generally disruptive for these individuals (Figure 3b). This is consistent with previous reports of individual subject variability in response to single-session brain stimulation (Gratton, Lee, Nomura, & D'Esposito, 2014; Schilberg, Schuhmann, & Sack, 2017).

Mean hippocampal fMRI connectivity within the HCN did not increase significantly for any stimulation condition relative to sham or between the θ -burst, i θ -burst, or β -freq conditions, nor were there any significant mean decreases. Likewise, control analyses without inclusion of changes in d' values as a covariate did not yield any significant increases or decreases in hippocampal fMRI connectivity with the HCN.

The relationship between hippocampal fMRI connectivity increases and changes in d' values were assessed (covariate slope). This identified individual differences in stimulation effects on hippocampal connectivity related to memory performance changes. The only significant relationships were identified for the θ -burst condition. For θ -burst—sham, d' changes were related to increased hippocampal fMRI connectivity with posterior cingulate and medial-frontal/anterior-cingulate HCN locations (Figure 4a,b,c; Table 2). Connectivity values were extracted from supra-threshold voxels and plotted against d' values to verify the underlying data pattern producing these statistical effects. As expected, the relationship was positive, such that increases in hippocampal connectivity were associated with increases in d' values due to θ -burst relative to sham (Figure 4d), with 52% of the variance in the effects of θ -burst on d' values accounted for by variation in hippocampal connectivity (R^2). Furthermore, this finding was due to a positive relationship between hippocampal connectivity and d' for θ -burst and near-zero relationship for sham (Figure 4e). No corresponding effects were identified for i θ -burst—sham or β -freq—sham, and no regions showed the opposite pattern of decreased d' -connectivity relationships for any comparison.

For comparisons among active stimulation conditions (θ -burst, i θ -burst, and β -freq), the only increases in hippocampal fMRI connectivity with the HCN in relation to d' changes was for θ -burst— β -freq. This relationship was identified for a medial-parietal/precuneus area of the HCN (Table 2, Figure 5a), corresponding approximately to a location also identified in the comparison of θ -burst to sham (Figure 4a). As expected, increases in hippocampal fMRI connectivity were associated with increases in d' values, whereby 40% of the variance in d' values was accounted for by variation in hippocampal fMRI connectivity (Figure 5b). This finding was due to a positive relationship between hippocampal connectivity and d' for θ -burst and near-zero relationship for β -freq (Figure 5c). No corresponding effects were identified for comparisons between any other stimulation conditions.

To test the network specificity of θ -burst's effects on memory-related hippocampal fMRI connectivity, the same analyses was performed in the two control networks, DAN and VIN. This yielded no significant findings, indicating that the effects of θ -burst on memory-related hippocampal connectivity were specific to the HCN.

To further evaluate whether stimulation had any influence on connectivity within the control networks, seed-based analysis of connectivity changes due to stimulation was performed for

these networks using the seeds that were used to define them (superior frontal gyrus for DAN and V1 for V1N; as shown in Figure 2). There were no significant increases or decreases in fMRI connectivity in relation to corresponding changes in d' scores, indicating that memory-related connectivity did not vary within the control networks as it did within the HCN. However, mean effects of stimulation were identified, with increased connectivity of superior frontal gyrus to the superior parietal lobule (near the area that was stimulated) for β -freq versus θ -burst within the DAN, and increased connectivity of V1 to cuneus for θ -burst versus sham within the V1N (Table 3). Thus, there were modest connectivity changes within the control networks, but not related to the hippocampus and not related to corresponding changes in memory performance.

4 DISCUSSION

θ -burst was unique among the conditions we evaluated in its ability to affect memory retrieval success as well as memory-related hippocampal fMRI connectivity. Improvements in memory due to θ -burst were predicted by corresponding increases in hippocampal fMRI connectivity of regions within the HCN. Notably, individual differences in stimulation effects on hippocampal connectivity related to retrieval were only identified for the θ -burst condition, and only for the same conditions for which effects on memory retrieval were also identified (θ -burst vs. sham and θ -burst vs. β -freq). These findings suggest that fMRI connectivity measures of HCN synchrony are causally related to episodic memory, and that θ -burst is particularly capable of modulating this memory-related HCN synchrony relative to the other stimulation patterns. This supports the crucial role of synchronous theta activity of the hippocampus with other HCN regions for memory retrieval.

It is noteworthy that the memory-related hippocampal connectivity changes due to θ -burst were distributed in HCN regions downstream from the parietal sites of stimulation (Figures 4 and 5). Network-level effects have also been demonstrated by stimulation targeting frontal, occipital, and motor-cortical networks (Gratton, Lee, Nomura, & D'Esposito, 2013; Mastropasqua et al., 2014; Rahnev et al., 2013; Steel et al., 2016; Valchev et al., 2015), as well as the HCN (Eldaief et al., 2011; Halko, Farzan, Eldaief, Schmahmann, & Pascual-Leone, 2014; Kim et al., 2018; Wang et al., 2014), with some indications that network-level effects may be more robust than effects on local processing (Bilek et al., 2013). Notably, fMRI connectivity of the HCN is consistent with its known anatomical organization (Buckner et al., 2008; Vincent et al., 2006). This includes projections from parietal cortex to hippocampus via retrosplenial and parahippocampal cortex (Mesulam, Van Hoesen, Pandya, & Geschwind, 1977; Mufson & Pandya, 1984) that presumably allow parietal stimulation to affect downstream HCN locations. Importantly, the downstream memory-related effects due to θ -burst were specifically between the targeted portion of the hippocampus (i.e., subject-specific hippocampal targets) and medial anterior and posterior regions of the HCN. None of these effects were in the left lateral parietal region that was directly stimulated, and no memory-related hippocampal connectivity effects were found in the control networks.

Mechanisms for network-level effects of TMS are not fully understood. Compensation-oriented explanations propose that networks “compensate” against changes in local activity due to stimulation, such that local excitation of regions with positive connections to a

network will result in network connectivity reductions, and vice versa for local inhibition (Cocchi et al., 2015; Davis, Luber, Murphy, Lisanby, & Cabeza, 2017; Eldaief et al., 2011; Fox et al., 2012; Steel et al., 2016). θ -burst is considered inhibitory and $i\theta$ -burst and β -freq are both considered excitatory, based primarily on cortico-motor effects (Chen et al., 2003; Huang et al., 2005; Pascual-Leone et al., 1994), and the parietal area we stimulated has positive connectivity with the HCN. Consistent with compensation explanations, we found positive down-stream effects on the retrieval-connectivity relationship for θ -burst relative to sham and relative to β -freq. However, opposite effects did not occur for β -freq or $i\theta$ -burst relative to θ -burst, which would have been expected by compensations explanations.

Resonance-oriented explanations propose that stimulation applied at frequencies matching the targeted network's endogenous activity rhythms entrains oscillatory neural activity throughout network regions and promotes network synchrony and related functions (Chanes, Quentin, Tallon-Baudry, & Valero-Cabre, 2013; Kim, Ekstrom, & Tandon, 2016; Lea-Carnall, Trujillo-Barreto, Montemurro, El-Deredy, & Parkes, 2017; Romei, Thut, & Silvanto, 2016; Salinas, Franklin, Narayana, Szabo, & Fox, 2016; Thut, Veniero, et al., 2011; Weinrich et al., 2017). Indeed, resonance-like effects have been demonstrated by findings that noninvasive theta-patterned stimulation synchronizes theta oscillations (Li et al., 2017; Reinhart, Zhu, Park, & Woodman, 2015). Retrieval is associated with HCN theta rhythmic activity (Anderson et al., 2010; Burke et al., 2014; Foster et al., 2013; Lega et al., 2017; Steinvorth et al., 2010; Watrous et al., 2013). Consistent with entrainment explanations, memory retrieval responded specifically to θ -burst, with a numerical but nonsignificant response to $i\theta$ -burst and near-zero response to β -freq. Notably, θ -burst was not significantly more effective than $i\theta$ -burst for memory improvement, despite θ -burst being the only condition to significantly improve memory improvement relative to sham. Further, θ -burst was the only condition to significantly influence memory-related HCN synchrony. Interestingly, θ -burst and $i\theta$ -burst did not produce opposite effects on memory or hippocampal connectivity, as would have been expected based on compensation-oriented explanations of network-level TMS effects. We speculate that a continuous train of theta-burst generated greater and more sustained resonance with endogenous HCN theta activity than did the intermittent trains of $i\theta$ -burst. However, further research is needed to directly test this hypothesis.

Although individual differences in hippocampal fMRI connectivity increases due to θ -burst stimulation were associated with corresponding changes in retrieval success, there were no effects on group-level mean hippocampal connectivity for any stimulation condition relative to any other. Changing hippocampal fMRI resting-state connectivity is likely a very challenging target for noninvasive brain stimulation, given the separation of the hippocampus from the areas that are directly stimulated. Indeed, although the current results and also previous findings suggest that single-session θ -burst targeting the hippocampus can improve episodic memory (Tambini et al., 2018), previous findings suggest that single-session TMS does not change hippocampal connectivity (Eldaief et al., 2011), with several consecutive daily stimulation sessions needed to increase mean hippocampal fMRI connectivity (Wang et al., 2014). Of course, the current null result on group-level mean hippocampal connectivity does not indicate that the stimulation conditions tested here do not have any effect on mean fMRI connectivity, particularly given that fMRI connectivity can be

measured in a variety of ways. We focused on hippocampal connectivity given its relevance to our hypotheses concerning the role of theta in hippocampal-HCN activity synchrony for memory retrieval. Further-more, we focused on a specific portion of the hippocampus (i.e., subject-specific hippocampal targets) given our desire to validate the effects of stimulation via demonstration of a priori target engagement. Other effects of stimulation may have occurred that were not assessed here. Notably, we did not focus on fMRI connectivity of the stimulated parietal location because interpretation of such local effects would be ambiguous. This is because changes in connectivity due to stimulation for the stimulated region could reflect local effects on stimulated tissue, downstream effects on connected areas, or some unknown combination of both. Our analysis approach allowed us to more purely evaluate downstream effects of stimulation on the a priori hippocampal targets that could not have been directly affected by stimulation.

fMRI connectivity is a metric of activity coupling at frequencies that fall far below the theta band (Foster, Rangarajan, Shirer, & Parvizi, 2015; Hacker, Snyder, Pahwa, Corbetta, & Leuthardt, 2017). Thus, a limitation of the current study is that interregional communication was measured indirectly as fMRI connectivity, although it is possible that relatively higher frequencies such as theta contribute to low-frequency fMRI connectivity via vasomotor entrainment (Mateo, Knutsen, Tsai, Shih, & Kleinfeld, 2017). We speculate that θ -burst enhanced network-wide functional coupling in the theta band, but this mechanistic account is impossible to test in the current fMRI experiment. Evidence suggesting that theta-frequency stimulation to the fornix and entorhinal cortex may enhance memory in humans (Miller et al., 2015; Titiz et al., 2017) has likewise not been corroborated by demonstration of corresponding changes in theta-band activity. However, fornix theta-burst stimulation delivered continuously for an extended period (as in our θ -burst condition) entrains theta-frequency activity in relation to memory improvement in rodents (Shirvalkar et al., 2010). Electrophysiological recordings of HCN activity following stimulation could provide stronger evidence than possible with fMRI.

Despite the challenges associated with resting-state fMRI connectivity, it is noteworthy that the only memory-related hippocampal fMRI connectivity changes were those that corresponded to effects found on memory performance. θ -burst caused significant increase in d' relative to sham and to β -freq (Figure 3), and these were the like-wise the only effects on hippocampal-HCN connectivity related to memory (Figures 4 and 5). Memory retrieval was measured separately from fMRI connectivity in a task subsequent to the scan acquisition. Therefore, the influence of stimulation on fMRI was not confounded by corresponding changes in task performance, as would have been the case if fMRI connectivity had been measured during the retrieval task. These findings suggest that strengthening of functional connections between hippocampus and other HCN regions due to θ -burst occurs in proportion to the corresponding improvement in memory retrieval, and thus hippocampus-HCN coupling strength during rest can be an indicator of memory-related connectivity.

It is notable that θ -burst increased recognition memory success in the current study, whereas previous findings using multiple-day HCN-targeted β -freq have identified improvement in associative and recollection-specific memory expressions (Kim et al., 2018; Nilakantan et

al., 2017; Wang et al., 2014). However, a previous study using single-session θ -burst targeting the HCN identified effects on the success of spatial recall but not its precision (Tambini et al., 2018). The success component of spatial recall is thought to indicate processes that support general familiarity memory (i.e., “gist”) rather than processes that support high-fidelity recollection memory (Harlow & Yonelinas, 2016; Kolarik, Baer, Shahlaie, Yonelinas, & Ekstrom, 2018; Nilakantan, Bridge, VanHaerents, & Voss, 2018). It is therefore possible that single-session θ -burst of the HCN affects familiarity-related processes relevant to recognition and success whereas multi-session β -freq affects recollection-related processes relevant to recall and precision. Likewise, different portions of the HCN are functionally distinct, with an anterior-temporal HCN subdivision related to item-oriented familiarity memory and a posterior-medial HCN subdivision related to memory for contextual associations among items (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Ranganath & Ritchey, 2012). Previous multi-session stimulation experiments have identified effects on posterior-medial HCN fMRI activity and connectivity (Kim et al., 2018; Nilakantan et al., 2017; Wang et al., 2014). However, in the current experiment, medial-prefrontal/anterior-cingulate HCN areas changed in hippocampal connectivity in addition to posterior-medial areas in relation to retrieval success increases. Thus, the differential effects of multi-day versus single-day stimulation on familiarity-related versus recollection-related processing could relate to distinct loci of functional changes within the HCN. Additional research is needed to directly test for selective stimulation effects on putative functional subdivisions of the HCN, and particularly to compare the effects of single-session versus multiple-session stimulation.

To summarize, these findings demonstrate that downstream effects of parietal stimulation on memory-related hippocampal fMRI connectivity within the targeted HCN were specific to θ -burst. Network-specific effects on hippocampal fMRI connectivity corresponded to the coarse match between stimulation frequency and endogenous network activity rhythms. Thus, we suggest that matching stimulation frequency and endogenous network activity rhythms may be an important factor in the response of HCN to noninvasive stimulation. Research incorporating direct electrophysiological measurement of HCN theta rhythms will be needed to further test this hypothesis. Nonetheless, the current findings that only θ -burst influenced memory-related hippocampal HCN connectivity provides novel evidence in support for the causal role of HCN theta-frequency activity in memory. Although effects on memory retrieval were small in magnitude in the current study of healthy adults receiving one session of stimulation, we propose that the development of stimulation-based treatment approaches for memory and other cognitive disorders associated with HCN dysfunction will benefit from identification of stimulation parameters with maximal HCN impact.

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FIGURE 1.

Experiment overview. (a) One parietal stimulation location was selected for each subject based on high baseline resting-state fMRI connectivity with the hippocampus. Hippocampal volumes of interest are shown in an overlap map in which colorization indicates the number of subjects having each voxel included in the target volume. (b) Individualized parietal-cortex stimulation locations are shown as a green spheres for each subject. (c) Approximate timeline an experimental session with the approximate duration of each phase and transition (exact values and ranges are provided in the text). A different TMS condition was used for each of four sessions, administered in counterbalanced order across subjects. All TMS conditions were delivered to the same individualized location of parietal cortex for each subject [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2.

Networks of interest. (a) The HCN (dark purple) was defined as regions with robust fMRI connectivity to a hippocampal target volume (light purple). (b) The DAN (dark green) was defined as regions with robust fMRI connectivity to a seed in left superior frontal gyrus (light green). (c) The VIN (dark blue) was defined as regions with robust fMRI connectivity to a seed in dorsal central V1 (light blue) [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3.

Stimulation effects on retrieval. (a) Word recognition memory performance (d') for each stimulation condition (left) and the change in d' values for each active stimulation condition relative to sham (right). Error bars indicate SEM. Statistical results are given in the text and P values are replicated here for convenience. (b) Changes in d' values due to each active stimulation condition relative to sham shown for each subject. Bar plots are ordered by subject, such that each subject's change relative to sham for the three stimulation conditions can be identified by looking at the same row across the plots

FIGURE 4.

θ -Burst effects on the relationship between hippocampal-HCN connectivity and retrieval relative to sham. Relative to sham, θ -burst increased the association between hippocampal-HCN connectivity and d' for (a) posterior cingulate and retrosplenial cortex, (b) left medial frontal gyrus, and (c) right medial frontal gyrus areas of the HCN. Slices are labeled with the corresponding Talairach (RAI) slice. (d) This effect is illustrated by plotting the θ -burst versus sham difference in connectivity with the hippocampus against the difference in d' values for all subjects, averaged over all supra-threshold voxels. (e) The positive relationship of difference values shown in figure (d) was due to positive correlation of hippocampal connectivity with d' following θ -burst and essentially zero correlation following sham, which are plotted separately averaged over all supra-threshold voxels. Note that the relationships shown in figure (d) and (e) are statistically redundant with the voxel-wise analysis results and are shown for illustrative purposes only, with only descriptive statistics provided [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 5.

θ -Burst effects on the relationship between hippocampal-HCN connectivity and retrieval relative to β -freq. (a) Relative to β -freq, θ -burst increased the association between hippocampal-HCN connectivity and d' for the posterior-cingulate/precuneus area of the HCN. (b) This effect is illustrated by plotting the θ -burst versus β -freq difference in connectivity with the hippocampus against the difference in d' values for all subjects, averaged over all supra-threshold voxels. (c) The positive relationship of difference values shown in figure (b) was due to positive correlation of hippocampal connectivity with d' following θ -burst and essentially zero correlation following β -freq, which are plotted separately averaged over all supra-threshold voxels. Note that the relationships shown in figure (b) and (c) are statistically redundant with the voxel-wise analysis results and are shown for illustrative purposes only, with only descriptive statistics provided [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1

Memory performance

	Hits	Correct rejections	d	Color accuracy	Shade accuracy	Color confidence	Shade confidence
Sham	0.84 (0.02)	0.61 (0.04)	1.46 (0.10)	0.72 (0.02)	0.34 (0.02)	3.95 (0.05)	4.06 (0.04)
θ-Burst	0.86 (0.02)	0.66* (0.05)	1.66* (0.11)	0.72 (0.02)	0.35 (0.02)	3.99 (0.05)	3.96 (0.04)
iθ-burst	0.86 (0.02)	0.64 (0.04)	1.61 (0.12)	0.72 (0.02)	0.33 (0.01)	4.07 (0.05)	4.02 (0.05)
β-Freq	0.82 (0.02)	0.67* (0.03)	1.50 (0.10)	0.74 (0.02)	0.36 (0.01)	3.99 (0.06)	4.04 (0.04)

Values are means. Parentheses indicate standard error of the mean.

* $p < .05$ pairwise comparison versus sham.

TABLE 2
Increased relationships between d' and hippocampal fMRI connectivity within the HCN due to stimulation

	X	Y	Z	BA	mm ³	z(t)	p	R ²
θ-burst-sham								
Left posterior cingulate	5	53	24	31	1,224	4.1	1.8e-05	0.52
Left medial frontal Gyrus	3	-55	10	10	568	3.4	3.2e-04	0.46
Right medial frontal Gyrus	-2	-44	23	9	544	4.3	1.0e-05	0.45
θ-burst-β-freq								
Left Precuneus	0	64	24	31	456	3.5	2.1e-04	0.40

Note. The centroid Talairach (RAI) coordinates, volume (mm³), approximate Brodmann areas (BA), peak standardized *t*-statistic (*z*(*t*)), peak *p* value (*p*), and the coefficient of determination of the covariate slope (*R*²) is given for each supra-threshold cluster.

TABLE 3

Increased fMRI connectivity within the DAN and VIN control networks due to stimulation

	<i>X</i>	<i>Y</i>	<i>Z</i>	BA	mm3	<i>z(t)</i>	p
<i>DAN</i>							
β -freq— θ -burst							
Left superior parietal lobule	30	57	47	7	504	3.7	1.2e-04
<i>VIN</i>							
θ -burst—sham							
Right Cuneus	−3	77	7	18	368	3.6	1.8e-04

Note. The centroid Talairach (RAI) coordinates, volume (mm³), approximate Brodmann areas (BA), peak standardized *t*-statistic (*z(t)*), and peak *p*-value (*p*) are provided for each supra-threshold cluster.