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Recollection Precision:

Neural Mechanisms and Modulation via Network-targeted Brain Stimulation

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Abstract

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Episodic memory provides a means by which we are able to reflect on the past, make decisions about the future, and form a learned identity. Even subtle changes to our memory can have a detrimental impact on our daily lives. Memory declines as we age, and clinically salient impairment is one of the defining symptoms of amnestic mild cognitive impairment and diagnosis of dementia due to Alzheimer's disease. As a result, decades of research have been dedicated to unpacking the mechanisms by which the brain, specifically the hippocampus, supports the formation and retrieval of different forms of memory. However, recollection memory is typically tested using all-or-nothing measures of general success that fail to capture the quality and details (precision) of the memory recalled. Here, I present a series of experiments combing noninvasive neuroimaging techniques with behavioral paradigms that utilize novel analysis approaches, in order to characterize the *precision of recollection*. Results from these experiments demonstrate that recollection precision is critically dependent on the hippocampus, relies on a distributed cortical network, is a sensitive measure that selectively captures impairment due to age, and can be improved via noninvasive stimulation.

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The research presented in this dissertation would not have been possible without the time, dedication, expertise, and critical feedback of my mentors and faculty committee members. To Dr. Joel Voss, Dr. M-Marsel Mesulam, Dr. Emily Rogalski, Dr. Donna Bridge, Dr. Ken Paller, and Dr. John Disdoterhoft: I admire your ability to generate, interpret, and effectively communicate impactful scientific results, and I am grateful for the opportunity to have worked with you. I would also like to express gratitude to the many postdoctoral fellows, graduate students, and research assistants at the Laboratory for Human Neuroscience and the Cognitive Neurology and Alzheimer's Disease Center (CNADC), who have encouraged my scientific curiosity and supported my research. Finally, I would like to thank my mother, father, and my brother, for their limitless words of encouragement and unwavering support.

Dedicated to my grandmothers:

Sarla Matta and Alamelu Nilakantan

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Chapter 1

Introduction

Episodic recollection reflects the retrieval of complex learned associations that comprise a specific event [1]. These events are fundamentally relational, such that seemingly arbitrary features get bound into a single episode. Recollection has typically been conceptualized as an all-or-none experience, such that individuals can either be successful or unsuccessful at recollecting all items in an event. This "thresholded" nature of recollection is often contrasted with familiarity-based recognition, in which memory for a single concept can vary in strength without specific recall of any other aspect of the event [2, 3]. However, even when recollection is successful, the amount of information that is retrieved can vary [4-7] leading to highly precise and detailed memory in some cases (e.g., "the car was parked on the left side of the street, four blocks ahead of the first stop sign") and more general memory in others (e.g., "the car was parked on the left side")[4, 5].

Patient studies have been critical in identifying the human hippocampus as necessary for recollection. Since the influential report of H.M.[8], many studies have demonstrated that insults to human hippocampal tissue lead to selective deficits of recollection, while mostly sparing familiarity-based recognition ([9-12], *but see* [13]). Moreover, patients with damage to the fornix, a major white matter track connecting the hippocampus to the thalamus, exhibit similar selective impairments to recollection[14]. Situated as a "hub" or neuroanatomical convergence zone[15, 16] for highly processed sensory information, the hippocampus has thus been hypothesized to support the high-resolution binding necessary for detailed episodic recollection[17]. However, it is

unlikely that one brain structure alone can support complex cognitive processes. Instead, recollection is likely supported by the interactions between multiple distributed cortical regions and the hippocampus[15, 16, 18].

Paired-associative memory tests, source memory tests, or remember-know paradigms are typically used to measure recollection. Paired associate tests are common because they succinctly test our ability to create and recall an episode of arbitrary features. Participants are asked to memorize a pair of words or objects ("elephant"-"shoe") and then, when cued with one item ("elephant"), participants are asked to recall the other item. In source memory tests, participants study items in a given context or with an associated source. For example, participants may memorize a list of words where each word is presented in either a male or female voice. Then after a delay, participants are asked to first determine if the word was studied before ("old/new" judgement), and then asked to recall the associated voice (male/female). Similarly, in remember-know paradigms, participants are asked to classify their responses as either old-"remembered" stimuli, where all associative content is recalled, or old-"known" stimuli where all content is not necessarily recalled. This introspective procedure is designed to segregate recollection-based processes from familiarity-based recognition processes[19, 20]. While all these tests assess the associative aspects of recollection memory success, they do not necessarily assess the varying amounts of detail that may or may not be recalled.

Many studies have accompanied these behavioral tests with noninvasive neuroimaging techniques such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) to identify characteristic neural signatures of recollection. EEG measures voltage changes derived mostly from postsynaptic potentials of apical dendrites of large pyramidal cells. Scalp potentials are direct measures of neuronal activity but are only detectable when a sufficient number

of cells are synchronous, mainly facilitated by the columnar organization of the cortex, and therefore limited in spatial resolution. Research involving theta oscillations has been particularly interesting in the context of memory, because changes in oscillatory activity provide a potential mechanism by which the hippocampus can communicate with other cortical regions to support memory. For example, in rats, neuronal spiking within the medial prefrontal cortex is phase locked with hippocampal theta oscillations, and such phase-locking is related to better spatial memory performance [21-23]. Similarly, in humans, 4-13 Hz power increases related to successful recollection has been correlated with increases in hippocampal-cortical connectivity as measured by simultaneous EEG-fMRI [24]. Collectively, many studies have demonstrated that better recollection is related to more synchronous low-frequency theta oscillations [25-27], perhaps in concert with a reduction in alpha oscillations, which allow for better encoding of complex stimuli [28], and more sensory reactivation at retrieval in humans[29, 30].

Averaging the signal obtained from EEG can produce event related potentials (ERPs), canonical waveforms consisting of positive and negative deflections, which can change in amplitude, latency, and spatial distribution during a given cognitive event. Findings from many studies suggest that recollection has a distinct ERP signature, often termed the "parietal-old/new" effect, in which remembered items elicit a larger amplitude in positive deflection ~500-700ms after stimulus onset, maximally over posterior parietal electrode recordings [31-33]. Successful source recall and "remembered" responses also elicit greater late-positive amplitudes in comparison to familiar ("know" responses) and not remembered items [33, 34]. These findings specifically contrast familiarity related ERP effects, which are typically represented as negative deflections ~300-500ms over mid-frontal electrodes ([33, 35], *but see* [36, 37]).

fMRI measures BOLD, or the increased blood oxygen level that occurs with increased metabolism as a result of cellular recruitment during a particular cognitive task. The measured hemodynamic response is slow and indirect, especially relative to the measures of EEG, but fMRI provides high spatial localization. Using fMRI, successful recollection has been associated with enhanced activity in the hippocampus [38, 39] and parahippocampal gyrus [40]. Source recollection, in particular, has been associated with parahippocampal activation[41], and functional connectivity between the parahippocampal gyrus and the hippocampus during encoding can predict whether an item will be later-remembered or forgotten [42]. In contrast, item recognition is related to perirhinal cortex activity [43]. Successful recollection has also been associated with greater activity in areas outside of the MTL, such as the retrosplenial/posterior cingulate cortex, angular gyrus and parietal cortex, especially when the associated source or context of recollection is assessed [38, 44-46]. These regions comprise a hypothesized content-independent core-recollection network [44], as many studies have consistently identified these regions as important for recollection processing, despite varied stimuli and different task demands [46].

Additional evidence for the network-basis of episodic recollection comes from functional connectivity studies at rest, in which regions consistently correlated with the hippocampus are identified despite no specific memory task demands. This network of regions, often referred to as "the default mode network," typically includes the parahippocampal gyrus, posterior cingulate, bilateral parietal cortex, and medial prefrontal cortex. High functional connectivity between these regions (strongly correlated time-series) is related to better memory performance[47-53]. Furthermore, distinct hippocampal networks have also been hypothesized such that an anterior hippocampal network, including perirhinal cortex, anterior ventral temporal cortex, amygdala, and

lateral orbitofrontal cortex, supports general item/semantic memory; while a posterior medial hippocampal network including parahippocampal gyrus, restrosplenial cortex, posterior cingulate, angular gyrus, precuneus, and medial prefrontal cortex, supports recollection for contextual information [54, 55]. It is possible that recollection success and recollection precision can likewise be associated with separate cortical networks [56].

Recollection memory declines with age [57-62], and age-related recollection impairments correspond to reductions in hippocampal integrity [63]. Large scale cross-sectional studies have revealed a decline in hippocampal function is related to memory decline across the lifespan, with significant reductions occurring after the age of 65 [64]. Longitudinal studies demonstrate that the time and rate at which this decline occurs differs across individuals. While hippocampal activity is well preserved in older adults with "maintained" memory function, hippocampal activity is altered significantly in those with memory "decline" [65, 66]. Likewise, theta power is reduced in older adults performing memory recognition and delayed recall tasks [67]. In contrast, aging minimally affects other types of memory, such as the recognition of objects seen before [58]. Indeed, abnormal function and structural connectivity of the cortical-hippocampal network thought to support recollection has also been correlated with normative memory decline in healthy aging [68-71], in individuals with amnestic mild cognitive impairment [72], and individuals with dementia due to probable Alzheimer's disease [51, 73, 74]. Furthermore, neurotoxic proteins, such as amyloid plaques and neurofibrillary tangles, accumulate and spread among regions of the distributed hippocampal-cortical network [75]. Increased pathologic load among distinct neurocognitive networks also correlates with functionally specific cognitive deficits [76-78]. Collectively, these studies provide strong evidence that memory decline in aging is related to changes in hippocampal function and disruption of hippocampal-cortical networks.

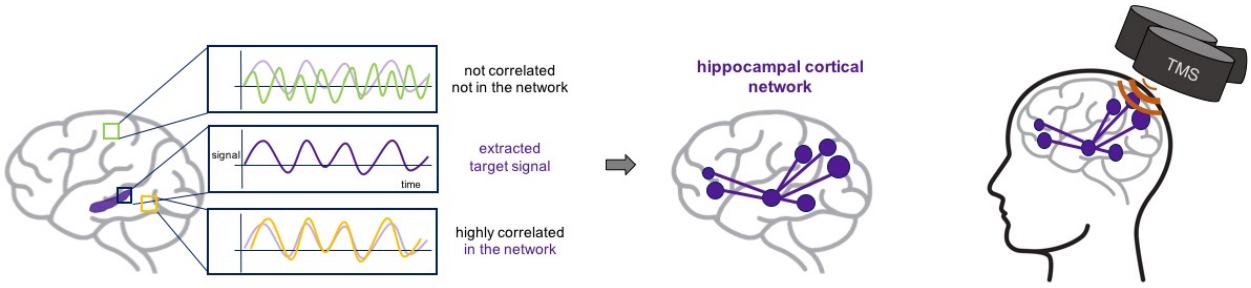
Correlative by nature, changes due to age and characteristic signals of recollection as measured by EEG and fMRI, cannot alone determine which interacting brain regions causally support recollection. One way to noninvasively address questions of network causality is to utilize transcranial magnetic stimulation (TMS). TMS generates a brief, high-intensity electro-magnetic field by passing electric current through a magnetic coil[79]. The induced changes of current, perpendicular to the magnetic field, can excite or inhibit a small superficial area of the brain below the coil. The butterfly (figure-of-eight) coil that is most commonly used in clinical and academic settings can achieve a spatial resolution of approximately $5mm^3$ of brain volume [80]. A crucial feature of stimulation through TMS, is the ability to vary pulse patterns and durations. Early in its development, most studies that utilized TMS focused on single-pulse paradigms, which are useful to measure cortical reactivity [81], and paired-pulse paradigms, which are useful for examining changes in cortical excitation as a measure of functional connectivity [82]. More recently, however, repetitive TMS (rTMS), which utilizes trains of pulses in a repetitive pattern, has been used to induce cortical effects that outlast the stimulation duration. Importantly, rTMS can modify cortical function during task performance, which can reveal causal relations between brain activity and behavior [80]. Studies utilizing TMS as a treatment for clinical depression have demonstrated that stimulation is most effective when it is guided based on individual anatomy, defined by structural magnetic resonance imaging[83]. Furthermore, effects are more robust when the cortical stimulation target, the dorsal lateral prefrontal cortex, was strongly functionally correlated [84] to the subgenual cingulate cortex, a hypothesized network "hub" of depressive symptoms [85, 86].

We therefore adapted this strategy [87, 88] to better understand the hippocampus and its interactivity with cortical network regions hypothesized to support memory (Figure 1). Individualized stimulation-accessible cortical targets are determined based on high resting state

connectivity with the hippocampus. We then applied modulatory stimulation to the lateral parietal cortex based on hypothesized interactions between the hippocampus and lateral parietal cortex during memory processing [55, 89], and robust functional connectivity between these regions measured at rest [90]. This functional connectivity is likely mediated by underlying lateral parietal projections to retrosplenial and parahippocampal cortex [91]. Our method employs high-frequency (20Hz) rTMS delivered to the parietal location for five consecutive days based on evidence that rTMS can induce changes in connectivity within stimulated networks [92, 93] and that such effects can increase over multiple-day stimulation sessions [94], perhaps due to a physiological interaction with natural fluctuations in circadian rhythm and sleep [95].

In the first study to employ this method, network-targeted stimulation increased fMRI connectivity in the targeted hippocampus and in recollection-related cortical regions such as the precuneus, retrosplenial cortex, the fusiform gyrus, parahippocampal cortex, and left parietal cortex [96]. Furthermore, changes in connectivity were related to corresponding increases in associative memory. That is, 24 hours after a final stimulation session, recall of face-word associative pairs improved, and participants that demonstrated larger changes of hippocampal connectivity also demonstrated greater memory improvement [96].These results were the first to confirm the proposed necessary role of the cortical-hippocampal interactions in associative memory in healthy young adults.

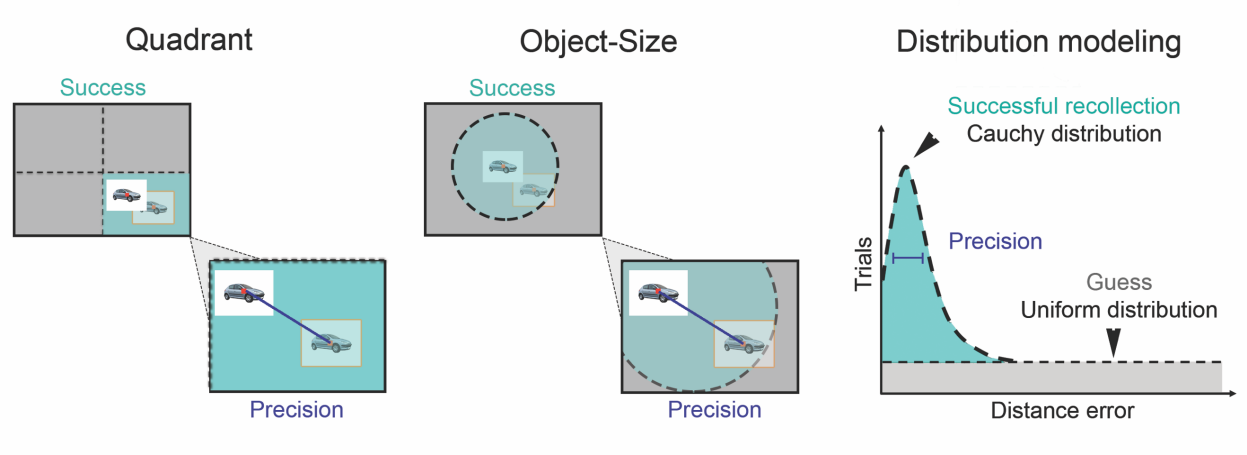
Figure 1. Hippocampal-cortical network-targeted stimulation



I utilize the targeted stimulation methods described above, along with other noninvasive neuroimaging techniques (EEG, fMRI) to measure the neural substrates that support recollection precision distinct from general success. To dissociate general memory success from precision, I used variations of a simple spatial memory task, in which participants study objects in distinct locations, and then after a delay, are asked to recall the objects and their associated location. Testing spatial locations is advantageous because it can provide objective gradations of memory performance, as opposed to typical binary assessments of memory success, or subjective confidence reports. Recollection success was defined in three complimentary ways across each experiment (Figure 2). First, success can be defined using the geometry of the screen, such that trials recalled within the same quadrant as studied are considered successfully recalled. A similar approach has also been used in other spatial memory tests of precision [97, 98], as quadrant based success is similar to rodent spatial memory tests [99, 100]. Second, success can be defined within the context of each specific experiment, such that trails recalled one-stimulus-length from the studied location are considered successfully recalled. Finally, we can also apply growth-mixture modeling to fit a Cauchy distribution (for successful recollection) and a uniform distribution (for random guessing) to distance errors adapted from previous word-location radial memory tasks [4, 5]. The modeling results in a mixture parameter (λ) denoting the proportion of success relative to

guess. Then, recollection precision is defined as the mean distance error (i.e., the distance between the studied object-location and the recalled location) for trials successfully recollected. This novel approach to objectively segregate precision from success in a spatial memory task was used with healthy young adults, healthy older adults, and individuals with mesial temporal lobe resection in order to comprehensively characterize spatial and temporal characteristics through which the hippocampus and distributed cortical regions support recollection.

Figure 2. Defining recollection precision and recollection success



In this dissertation, I present experiments that demonstrate that: precision is critically dependent on the hippocampus (Chapter 2, [101]), recollection is causally supported by hippocampal interactions with distributed posterior-medial cortical regions (Chapter 3, [102]), precision is impaired relative to general success as a result of healthy aging (Chapter 4,[101]), and noninvasive stimulation can engage the cortical network that supports recollection to improve memory in healthy older adults (Chapter 5, [103]).

Chapter 2

The mesial temporal lobe necessarily supports recollection precision

2-1 Rationale:

Damage to the hippocampus and the MTL impairs recollection [2, 104-106]. Experiments involving human MTL lesions have provided some evidence that damage to the hippocampus has a greater impact on recollection precision than success. Kolarik et al. (2016) used a virtual-reality analog of the Morris water maze task [100] in which participants were asked to explore a virtual-reality room and were trained to find and later retrieve a target location. A young adult with bilateral hippocampal damage was able to use coarse allocentric search strategies to find the target, but demonstrated significant deficits in spatial precision relative to healthy controls [98]. In a similar virtual-reality experiment, five amnestic patients with MTL damage demonstrated precision impairments without deficits of overall recollection success. They spent less time close to the target location relative to age-matched controls, but equal time in the correct general area [97]. In both studies, precision, but not success, was impaired, thereby suggesting a role for the MTL and especially the hippocampus in spatial recollection precision. However, not all results are consistent with this conclusion. Two patients with bilateral parietal lobe lesions had successful autobiographical memory for general events but showed impairments when probed for specific details [6]. It is therefore possible that precision is supported by regions outside of the MTL, such as the parietal cortex.

Because only few studies have attempted to distinguish the functional neuroanatomy of recollection success from precision, it remains unclear if and how these memory processes are

distinctly represented in the MTL and hippocampus. Furthermore, previous studies have tested memory within the same visuospatial context in which it was originally encoded. Such tests do not account for the possibility that precision and success could also be supported in part by perceptual recognition processes [107-109] rather than by relational/associative memory processes. To limit the possible contributions of perceptual memory to success and precision, we tested adults with unilateral MTL lesions using a memory task in which objects were studied at locations within a background context, and then later tested within a different background context. Importantly, the change in context ensured that recognition of the object-in-scene perceptual information alone could not support accurate performance. Instead, recollection precision and success were necessarily based on the arbitrary link between the object and its associated location. We hypothesized that if recollection precision and success were distinct processes, lesions of the MTL, specifically those that included hippocampus, would particularly disrupt precision relative to success.

2-2 Methods:

Participants: Data from 18 healthy young adults (mean age=25.0, range=18-33 years, 11 females) 8 adults with unilateral MTL resection, performed as a treatment for refractory epilepsy (mean age=39.63, range=22-50 years were included in the analyses. MTL patients participated approximately 3 years after resection surgery (mean=2.82, SE=0.26 years). Before surgery, after surgery, and on the day of the experiment, the Wechsler Abbreviated Scale of Intelligence (WASI-II,[110]) was administered to characterize verbal comprehension, perceptual reasoning and IQ (Table 1). All participants gave written informed consent and were monetarily compensated for their time, as approved by the Institutional Review Board at Northwestern University.

Table 1: Unilateral MTL resection participant demographics.

					WASI-II		
ID	Age	Hemisphere	Damage	Resection	FSIQ	VCI	PRI
1	31	L	H-	18.1	104	107	106
2	50	L	H-	2.6	99.6	103.6	99.6
3	40	R	H-	23.8	83	85.6	86.6
4	36	L	H-	3.5	108.3	107.3	120.3
5*	39	R	H-	38.6	81	82.5	84.5
6*	22	L	H+	1.7	118.5	116	118
7	49	R	H+	23.5	90.67	94	84.3
8	50	L	H+	1.3	113.3	108.6	121.3

Each resection participant is characterized based on age, hemisphere of resection (L=Left, R=Right), whether the hippocampus was intact (H+) or removed as part of the MTL resection (H-), and resection volume in milliliters (mL) in standardized space. Mean scores from the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II) including the Full-Scale Intelligence Quotient (FSIQ), Verbal Comprehension Index (VCI), and Perceptual Reasoning Index (PRI). *Participants are missing post-surgery WASI-II assessment.

Memory paradigm: Participants completed two study-test blocks of an object location memory task adapted from previous studies [111, 112]. During the study phase, participants viewed 24 objects presented at randomized locations on a specific background scene [113] on a screen (52.0x29.25 cm), viewed with an eye-to-screen distance of ~60 cm. Objects (3.25x4.06 cm [114]) were presented one at a time for 3000ms each. A red dot was centered on top of each object to identify its exact location. Participants were instructed to remember the object locations as accurately as possible. After each study phase, participants played a visuo-spatial distractor task ("Tetris") for 90 seconds. Following this filled delay, a cued recall test was administered. 24 studied objects were randomly presented one at a time in the center of the screen and participants were required to use a mouse to recall associated locations (for up to 5000ms) on a different background scene than was presented with the item during study (Figure 3A). Distance error (the distance between the location the object was originally studied and the location the object was recalled) was our main dependent variable. The change in background scene between study and test is an important manipulation because it encourages the hippocampal-dependent process of binding independent features (object and location) into an associative event and discourages other strategies involving the perceptual unitization of the object superimposed on the entire scene [107-109].

Behavioral analysis: Statistical analyses were done in R[115]. Trials were scored based on distance error (difference between recalled and studied locations). Recollection success was defined using the geometry of the screen, as the trials recalled within the same quadrant as studied. Recollection precision was defined as the mean distance error (i.e., the distance between the studied object-location and the recalled location) for trials successfully recollected. Two-sample t-tests were used to compare recollection success and recollection precision among groups. For the

targeted hippocampal analysis in n=5 of left hemisphere resection participants, a Welch- two sample t-test was used, where variance is not assumed to be equal among groups of small sample sizes. To use the modeling approach to dissociate recollection precision from success, the distribution of distance error must reliably fit the canonical Cauchy-uniform distribution (described in Figure 2). However, the distribution of distance error for individuals with MTL resections were highly variable, and limited by low trial count (48 trials per participant in this experiment). As a group, they did not demonstrate a consistent mixed cauchy-uniform distribution of distance error ($p<0.05$), and the modeling approach was not used to distinguish nor assess recollection precision from recollection success in this group.

Magnetic resonance imaging: To provide anatomical characterization of the unilateral MTL lesions, MRI structural data were collected from these participants using a Siemens 3T TIM Trio whole-body magnet with a 32-channel head coil. An MPRAGE T_1-weighted scans structural image (TR=2400ms, TE=3.16ms, FOV=256x256, flip angle=8°, with 1.0x1.0x1.0mm voxel resolution over 176 sagittal volumes) was acquired from each participant. Structural images were preprocessed using AFNI [116]. Each structural image was AC-PC aligned and transformed to Talaraich-Tournoux (stereotaxic) space. Each resection was then manually drawn as a mask using the contralateral hemisphere as reference. Whole brain-volume was estimated using a manually inspected AFNI brain segmentation from the structural scan, plus the estimated volume of resected tissue.

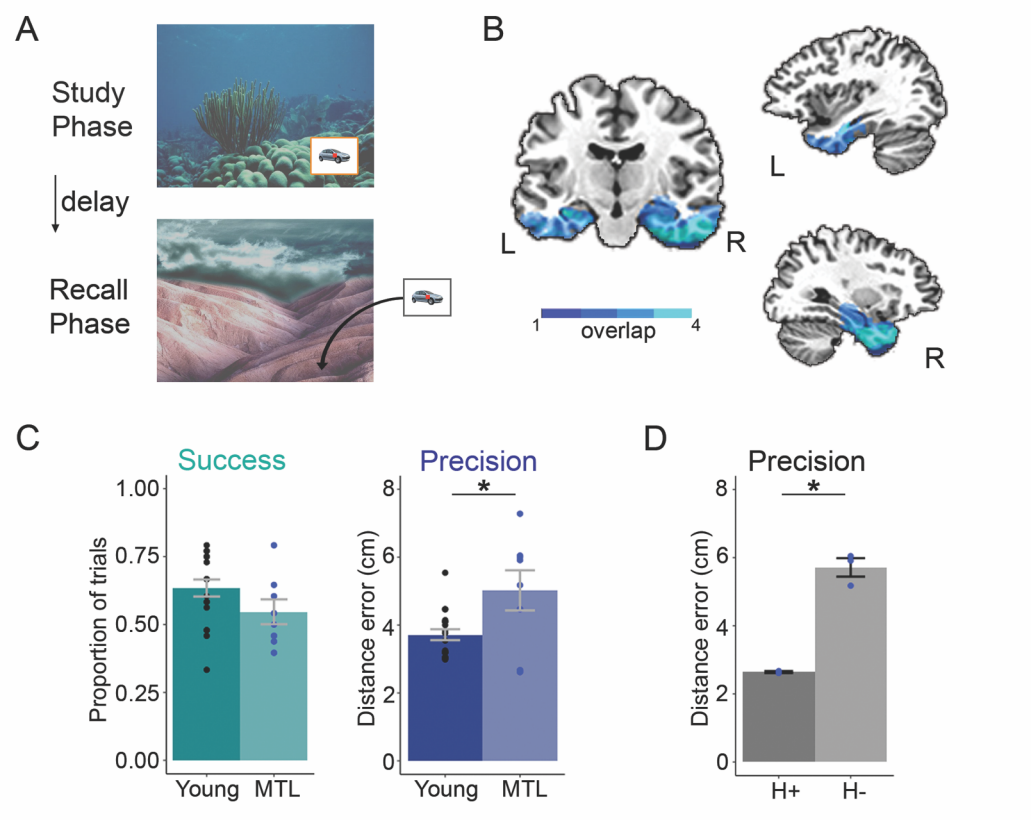
2-3 Results:

The amount of tissue resected varied among these participants, with most resections limited to the anterior third of the MTL (Table 1, Figure 3B). Overall memory performance (mean distance error) was marginally worse for individuals with MTL resection (mean=9.06 cm, SE=1.14 cm)

relative to controls (mean=6.83 cm, SE=0.50 cm; T(24)=2.1, p=0.045). Using the quadrant approach, recollection success was not significantly different for individuals with unilateral MTL resection (mean=54.69%, SE=3.13%) than for the controls (T(24)=1.56, p=0.13). However, recollection precision was significantly impaired for individuals with unilateral MTL resection participants (mean=5.02 cm, SE=0.59 cm) relative to controls (mean=3.72 cm, SE=0.16 cm; T(24)=2.87, p=0.008; Figure 3C). Notably, although participants with unilateral MTL resections were older than controls (T(24)=5.14, p<0.001), there was a wide range of ages for MTL resection participants. Furthermore, there was no significant correlation between age and recollection precision for the MTL resection participants (r=0.139, p=0.74; Table 1), suggesting that age did not contribute significantly to the precision impairments attributed to MTL lesions.

We next tested whether MTL lesions that included the hippocampus were especially disruptive for precision rather than success, compared to MTL lesions that did not include the hippocampus. The right-hemisphere resection patients overall had greater amount of tissue removed and lower IQ than left-hemisphere resection patients, and so this analysis was restricted to left-lateralized (n=5) resection patients (Figure 3D). Individuals whose left MTL resections included the hippocampus (H-, n=3, mean=5.71, SE=0.27 cm) had worse precision relative to those with no hippocampal resection (H+, n=2, mean=2.64, SE=0.03 cm) (T(2.04)=11.27, p=0.007). However, recollection success did not vary significantly for H- versus H+ participants (H-: mean=45.83%, SE=4.33%; H+: mean=71.8%, SE=7.73%) (T(1.72)=3.07, p=0.11). The amount of tissue resected did not differ for the two groups (H- mean=8.06 SE=5.03 mL; H+mean=1.53 SE=0.19 mL) (T(2.01)=1.30, p=0.32), even when corrected for estimated whole-brain volume (H- mean= 0.50, SE=0.31%; H+ mean=0.09 SE=0.38%; T(2.00)=1.32, p=0.32).

Figure 3. Precision is impaired in individuals with unilateral MTL resection.



(A) Participants studied trial-unique objects at randomly assigned locations within a background scene. Subsequent memory testing involved object-cued recall of associated locations on a different background scene. (B) Overlap map depicting resected mesial temporal lobe (MTL) tissue (with brighter colors representing more overlap across participants). (C) Mean recollection success and recollection precision of individuals with unilateral MTL resection relative to younger adults. (D). Recollection precision for left hemisphere resection participants whose hippocampus was removed (H-) as part of the MTL resection relative to participants whose hippocampus remains intact (H+). Individual participant scores are marked in blue for MTL resection participants and in black for young adults. (adapted from Nilakantan et al., 2018)

2-4 Discussion:

The necessary contribution of the MTL was assessed with individuals with unilateral surgical resections of MTL tissue, using a task that probed the associative/relational components of precision and success. In particular, the change in background scene was used to prevent perceptual recognition strategies involving encoding the object and background scene as a single unit [107-109]. While overall performance was impaired relative to controls, precision was significantly impaired with no impairment of success. Notably, resections that included hippocampal tissue produced significantly worse precision compared to resections that included only non-hippocampal MTL tissue, with no significant difference in success.

Our results are consistent with other studies of spatial episodic memory that did not limit the role of perceptual memory in success and precision. In those studies, MTL and hippocampal damage was related to impairments in recollection precision rather than in general spatial strategy or recollection success [97, 98]. There are notable caveats to our findings as well as to these previous studies. Although the change in background scene was designed to prevent perceptual recognition strategies, it could have also increased interference from the new scene background on recall performance, which could affect different memory processes [117] and have harmed MTL-resection and older adult participants more so than controls [118, 119]. Furthermore, our analysis was limited by our small sample size, which included only two individuals with resections that spared the hippocampus. Evidence demonstrating a role for the hippocampus in recollection precision would be strongest in a larger cohort with comparisons to a control group with brain lesions outside of the MTL. Precision impairments due to hippocampal damage do not rule out the possibility that other regions, such as parietal cortex, make critical contributions to precision. Indeed, there is lesion [6] and fMRI [56] evidence for parietal cortex involvement in recollection

precision, with the fMRI data indicating that parietal cortex might be particularly involved during memory retrieval [56]. Future studies could include additional perceptual controls, compare the effects of MTL lesions to parietal lesions on memory success versus precision, and fMRI studies in particular could determine whether these regions are differentially involved during memory formation versus retrieval.

The present results are also consistent with studies of visual working memory [120], which demonstrate impaired high-resolution but not low-resolution memories or general memory capacity in individuals with bilateral hippocampal damage [121, 122]. One short-term memory study demonstrated seemingly contradictory results, suggesting that the hippocampus is not necessarily involved in memory precision [123]. In this study, participants studied boxes shown in specific associated colors, and trials included one, three, or six boxes at a time. After a brief delay, cued with a box's location, participants had to select the associated color using a continuous color wheel scale. A modeling approach was then used to segregate the probability that the item was remembered relative to the quality (color precision) of the item. Amnestic patients were less likely to remember items at test overall, but showed no impairment for the quality of the associated color [123] for all trials. However, when load was matched to the other studies of precision (only one item-color association was studied at a time), four of the five amnesic patients showed no impairment of general recollection yet demonstrated reduced recollection precision relative to controls. Thus, the lack of relative precision impairment only emerged with greater loads, suggesting that precision is impaired in both amnesics and controls when high-resolution information about multiple items must be maintained (see also [124, 125]). Although the current results are agnostic to whether short versus long retention intervals are required to observe recollection precision impairments following MTL damage, they further support the conclusion

that the hippocampus is necessary to bind complex and high-resolution information [17], and that this remains the case even when perceptual qualities of the stimulus could not alone govern precision performance.

It is important to note that tissue damage can impact large-scale network function [126], including lesions of the hippocampus [127, 128]. It is therefore possible that memory precision and success are supported by different patterns of hippocampal-cortical connectivity. This idea, that a large-scale distributed network, including the hippocampus and regions of the MTL, supports recollection precision is systematically tested and described in Chapter 3.

Chapter 3

Recollection precision is supported by a distributed hippocampal network

3-1 Rationale:

While the crucial role of hippocampus in episodic memory is well-established [8], several lines of evidence suggest preferential contributions to high-precision memory by the posterior hippocampus [129]. There are smaller receptive fields for posterior compared to anterior hippocampus [130] (dorsal versus ventral in the rodent), and recent functional accounts emphasize differential anterior versus posterior hippocampal interaction with networks of distinct distributed cortical regions[55]. That is, a hippocampal-posterior-medial (HPM) network, including parahippocampal gyrus, lateral parietal, posterior cingulate, precuneus and retrosplenial cortex is associated with memory for highly precise contextual and spatial information[131], while a more anterior-temporal network is thought to support memory for semantic and global aspects of episodes. Evidence for distinct functions of these hippocampal-cortical networks is derived primarily from correlative methods (e.g., neuroimaging, recording of neural activity), and there is little direct evidence for the reliance of recollection precision on distributed functional brain networks.

Five daily sessions of repetitive high-frequency transcranial magnetic stimulation (rTMS) delivered to a stimulation-accessible parietal-cortex region enhances fMRI connectivity among hippocampal, retrosplenial, parahippocampal, medial-parietal, and lateral-parietal cortical network regions[96]. To test the hypothesized involvement of the posterior-medial network in memory precision, we used the same noninvasive stimulation regimen in conjunction with a graded

assessment of associative object-location memory, specifically designed to segregate recollection precision from general success [5]. We hypothesized that network-targeted stimulation would modulate memory precision and alter established neural correlates of recollection, as measured by EEG.

3-2 Methods:

Participants: Sixteen adults (mean age=25.7, range: 19-35 years; 11 female) participated in the experiment and were recruited based on no present use of psychoactive drugs and no history of neurological or psychiatric conditions. Participants were screened for MRI and TMS safety using standard MRI safety screening questionnaires and a TMS safety questionnaire [132]. No participants withdrew due to complications or side effects. All participants gave written informed consent and were monetarily compensated for their time. Study procedures were approved by the Institutional Review Board at Northwestern University. Two participants were excluded due to poor overall performance in which only 26.3% and 20.6% of trials, respectively, could be considered "successful recollection" (compared to 67.5% for all other participants). Few recollection trials coupled with poor EEG data quality yielded too-few trials for EEG/ERP analysis. Two additional participants were excluded for outlier change values across the week (over 2.5 standard deviations from the group mean) and were therefore not likely due to stimulation, but rather to noise-related performance variability. Thus, twelve participants (mean age=25.3, range: 19-35 years; 9 female) were included in main analyses.

Experimental Design Overview: The Stim and Sham weeks (Figure 4C) were separated by an interval of at least 4 weeks (mean delay interval=12.62 weeks, range: 4.5 – 26.1 weeks). Twenty-four hours before and after five consecutive daily stimulation sessions, participants

completed the memory task while EEG was recorded. The stimulation and sham weeks were administered in counterbalanced order across participants.

Memory assessment: One hundred and ninety-two unique color drawings of objects [133] were used as stimuli for each week (Stim and Sham). Half of the objects (96) were randomly assigned to each memory assessment session (Pre and Post), and an assessment-unique randomly assigned location was used for each object (retention of object-location associations across each week was thus not assessed in this experiment). During each assessment, participants completed an object-location memory task involving four study-test blocks. During each block (Figure 4A), participants viewed 24 objects presented at randomized locations on a blue-red-gray background grid (52.00 x 29.25 cm), viewed with an eye-to-screen distance of ~24 inches. Objects were presented one at a time for 3000 ms each (1000-ms ISI). Objects were presented within a white-box background (4.88 x 4.88 cm) and had a red dot superimposed at the object center to mark the precise location. Participants were instructed to study and remember the object-locations as accurately and precisely as possible. After each study phase, participants played a visuospatial "Tetris" distractor task [134] for 90 s. After this delay, a cued-recall test was administered. During the test, the 24 studied objects were presented one at a time in the center of the screen (in a randomized order), and participants were required to recall the studied locations. At the beginning of every trial, a gray screen with the letter "b" in the center of the screen appeared for 2000 ms. Participants were encouraged to blink freely during this period (and limit blinking for the remainder of the trial). This period was followed by a 2000 ms fixation cross at the center of the screen. Then, an object appeared at the center of the screen for 2000 ms. During this time, participants were instructed to focus on the object, and mentally recall its studied location. After

this 2000 ms period, participants were able to use the mouse to move the object from the center of the screen to its recalled location and click a button on the mouse to indicate its final location.

Behavioral analysis: Statistical analyses were done in R [135]. The distance threshold for successful recollection was determined using three converging approaches. First, the size of objects used during memory testing was 4.88x4.88 cm, and therefore in the context of our specific task "successful recollection" refers to accuracy within one stimulus length from the studied location. Second, we used mixture modeling which results in two parameters: a mixture parameter (λ) denoting the proportion of success relative to guess, and a shape parameter (s) denoting precision. The mixture parameter indicated that the most accurate 65% of trials fit the Cauchy distribution and could be considered successful recollection. For all assessment conditions and all participants (N=16), this 65% threshold corresponds to 5.41 cm in our data. Finally, we used a similar mixture-modeling approach to fit Cauchy and null distributions to distance errors in the current task, aggregated across all four testing sessions and all participants. This model provided a good fit to the distance error data (p=0.24, where p<0.05 would indicate poor fit) and indicated that 64.64% of trials fit the Cauchy distribution, which across all participants corresponded to 5.36 cm. Thus, these approaches all converge on about 65% as a reasonable threshold for successful recollection (Figure 4D). Notably, random placement of the object during memory testing would yield successful recollection for about 5.4% of trials, and so actual performance was above chance. Within the successfully recollected trials, we defined precision as the mean error of these trials.

It is important to note that random locations were selected for all objects at study, and therefore not all objects had equal error probability. For example, an object studied at an outer corner has a greater probability of higher error because its distance to all other points on the screen is greater than an object studied at the center. We excluded all trials with error greater than 19.5

cm in analyses to account for outlier values that would result from guess responses on trials with high error possibility. This left a total of 4,330 trials (93.97%) across all assessment sessions for final analysis. Excluding outlier trials within the n=12 sample used in primary analyses, the 4.88-cm cutoff resulted in an average of 67.56% (se=4.47%) successful recollection trials across all assessment conditions. Cohen's d effect size [136] tests are reported in conjunction with significant results.

A common Baseline including Pre-Stim and Pre-Sham distance error values was used for primary analyses, although effects remained consistent when using separate Pre-Stim and Pre-Sham values as baselines for each experimental week. Distance errors were slightly yet significantly greater Pre-Stim compared to Pre-Sham ($t(11)=2.40$, $p=0.036$, Cohen's d=0.690). Importantly, the primary analyses showed that Post-Stim mean error was significantly less than Post-Sham, and improvement for Stim therefore cannot be attributed to greater room for improvement for the Stim condition compared to the Sham condition or by so-called "regression to the mean". That is, despite Stim starting off slightly significantly worse than Sham, after stimulation it was significantly better. Furthermore, all primary analyses used a common Baseline in conjunction with a within-subject counterbalanced design to counteract any interpretation related to practice effects or baseline differences.

Stimulation target identification: We determined an individualized left lateral parietal stimulation location based on high resting-state fMRI connectivity with a left hippocampal seed using the same methods as in Wang et al. 2014 [96]. MRI data were collected using a Siemens 3T TIM Trio whole-body magnet with a 32-channel head coil, provided by Northwestern University Center for Translational Imaging (CTI) Facility, supported by Northwestern University Department of Radiology. To provide anatomical localization for stimulation, a structural and

resting-state scan was performed prior to any other memory assessment on the first day of participation. A MPRAGE T1-weighted structural image was acquired (with TR=2400 ms, TE=3.16 ms, FOV=25.6 cm, flip angle=8°, and 1mm^3 voxel resolution over 176 sagittal slices). Functional resting-state images were acquired using a whole-brain BOLD EPI sequence (with TR=2500 ms, TE=20 ms, FOV=22 cm, flip angle=80°, and 1.72x1.72x3-mm voxel resolution over 244 volumes). During the ~10-min resting-state scan, participants were instructed to lie still with their eyes open. Functional and structural MRI data were preprocessed using AFNI [116]. Preprocessing included motion correction, slice-timing correction (to the first slice), functional-structural co-registration, resampling to a resolution of 1.5x1.5x1.5 mm, stereotactic transformation using Montreal Neurologic Institute 305 (MNI-305) template, band-pass filtering (0.01-0.10Hz), spatial smoothing (with a 4-mm FWHM Guassian kernel), despiking, linear de-trending, and regressing out the motion time-series. A hippocampal seed voxel was located for each participant by identifying a voxel in the middle of the body nearest to MNI [-24, -18, -18] (mean distance away=6.82 mm, se=0.49). The fMRI time course data were extracted from the hippocampal seed voxel and used in a seed-based resting-state functional connectivity analysis. We identified a cluster of voxels in the left parietal cortex exhibiting the maximum connectivity within a 15 mm radius (mean=8.32 mm, se=1.04) nearest to MNI [-47, -68, 36], which was used as the Stim location. A Sham stimulation location (the vertex) was located at the MNI coordinate [0, -42, 73]. The stimulation location target for Stim and Sham were transformed from MNI space into each participant's original MRI space for anatomically guided rTMS (Figure 4B).

TMS: Nexstim eXimia NBS 4.3 air-cooled MRI Guided system (Nexstim Ltd., Helsinki, Finland) with a 70-mm figure-of-eight coil was used to apply stimulation to targeted locations marked on the structural MRI using a frameless infrared stereotactic system. Motor Threshold

(MT) was determined on the first day of participation, which was defined as the minimum stimulator output required to generate a contraction of the *abductor pollicis brevis* for 5 consecutive pulses measured either visually or via EMG contraction threshold of 50 mV. rTMS was applied at 100% MT for both Stim and Sham. For two participants, stimulation over the targeted parietal location was applied at a lower intensity (89% MT for one, and 83% MT for the other) due to reported mild discomfort for 100% MT on the first day of repetitive stimulation. The rTMS protocol consisted of 20 minutes of consecutive blocks of 20-Hz pulses for 2 s, followed by 28 s of no stimulation (1,600 pulses per session).

EEG: Continuous EEG was recorded during the test phase from 30 scalp channels (amplifier bandwidth DC to 20,000 Hz, sampled at 1,000 Hz) using active Ag/AgCl electrodes (Brain Vision LLC, actiCAP). Mean impedance across all electrodes and assessment sessions was < 10 kΩ. EEG signals were amplified and digitized online. The right mastoid was used as an online reference. The recordings were then re-referenced offline to the left and right mastoid. Electrooculography (EOG) was also used to monitor eye-movements and blinks. Bipolar electrodes at the left and right outer canthi, as well as above and below the right eye were recorded. A high-pass filter (0.1 Hz, 12 dB per octave) was applied to all channels prior to any analysis. Trials with ocular artifacts (large voltage offsets identified in 200-ms moving windows for each participant ranging between 6-20 mV) were removed from all analyses. An additional absolute voltage threshold (defined individually for each participant ranging between 100-200 μV) was applied when necessary to scalp electrodes to identify and subsequently remove trials dominated by muscle activity or movement. As with our behavioral data, our main EEG analyses concerned changes due to stimulation (Post-Stim versus Baseline) relative to control (Post-Sham versus Baseline).

Time-frequency decomposition and statistical analyses were performed using FieldTrip [137]. EEG data were epoched from -500 to 1500 ms relative to onset of the object presentation during cued-recall. For each condition, evoked oscillations were obtained via time-frequency decomposition of baseline corrected event-related averages using Mortlet wavelets (width=5) in 0.5 Hz increments of 2-30 Hz over the entire epoch in 1-ms steps with a Hanning taper. Power was analyzed with non-parametric cluster-based permutation tests[138], for the frequency band from 4-13 Hz in a latency interval of 0 to 1000 ms. For all contrasts, a channel x time dependent *t*-test was conducted for each individual sample. To control for multiple comparisons, a Monte Carlo estimate of the permutation *p*-value was calculated by randomly permuting condition comparisons over 1000 iterations. Clusters were considered significant at $p<0.05$. As with the behavioral analysis, we collapsed trials across Pre-Stim and Pre-Sham sessions as a common Baseline for each individual. Only successfully recollected trials were included in analyses. After artifact rejection, an average of 97.00 trials (range: 56-137) trials were included in Baseline, 53.91 (range: 28-69) trials were included in the Post-Stim condition and 48.75 (range: 25-66) trials were included in the Post-Sham condition. The number of trials included Post-Stim and Post-Sham did not differ significantly ($t(11)=0.63$, $p=0.54$).

To identify oscillatory changes apart from the a priori 4-13Hz range, power was also analyzed with a non-parametric cluster-based permutation test [138], averaged for 500-700ms after event onset, given a range of 2-30Hz. This latency interval was chosen because late EEG oscillatory correlates (>500ms after event onset) are thought to relate to recollection of spatial context information[33, 139, 140]. For all contrasts, a channel x frequency dependent t-test was conducted for each individual sample. To control for multiple comparisons, a Monte Carlo estimate of the permutation p value was calculated by randomly permuting condition comparisons

over 1,000 iterations, with a cluster corrected significance criterion of $p < 0.05$. To measure the phase consistency across trials, inter-trial phase coherence (ITPC) was calculated for each condition averaged across 4-13Hz.

Event-related potentials (ERP) analysis was conducted using ERPlab[141]. For ERP analyses, EEG data were re-epoched from -200 to 1000ms (shorter baseline was used here to improve trial counts, as longer baselines are not needed for ERPs). Each trial was baseline corrected using the pre-stimulus interval. An average of 107.9 (range: 64-144) trials were included in Baseline condition, 55.25 (range: 33-71) trials were included in Post-Stim condition and 57.8 (range: 29-71) trials were included in the Post-Sham condition. The number of trials included Post-Stim and Post-Sham did not differ significantly ($t(11)=0.86$, $p=0.41$). To guard against possible outliers, a robust correlation was used to test the relationship between the parietal memory effect and percent precision improvement[142]. For this correlation, we used the maximum amplitude reduction (Baseline-Post) among the central-posterior electrodes compared to the percent precision improvement calculated relative to Baseline. A 30 Hz low-pass filter was applied for waveform presentation only.

Zero-intensity Stimulation Control Experiment: The primary experiment involved full-intensity stimulation of a network-defined parietal target (Stim) compared to full-intensity stimulation of an out-of-network vertex location (Sham). To evaluate whether reported effects were due to performance reductions in the Sham condition as opposed to performance enhancements in the Stim condition, we performed an additional control experiment involving near-zero intensity stimulation of network-defined parietal locations. For this control experiment, participants (N=12; mean age=24.6 years, range: 20-34 years; 8 female) received stimulation over the lateral parietal cortex using the same parameters as in the main experiment, except that a spacer

was used to increase the distance between the coil and the target location such that the induced voltage at the stimulation location was effectively zero. The target location in the parietal cortex was determined based on functional connectivity of the posterior hippocampus using the same fMRI acquisition and analysis parameters as in the main experiment. Participants received only zero-intensity control stimulation, and so participated one week only, using the same 5-day stimulation protocol with 24-hr pre- and post-testing, as in the main experiment.

3-3 Results:

Trials were scored for distance error (difference between recalled and studied locations) and sorted into successful recollection (67.6% of trials, SE= 4.5%) and guess conditions using a two-parameter model that segregates recollection precision from general recollection success [5] (Figure 4D). We did not hypothesize effects of stimulation on general recollection success, which was tested using two complementary approaches. First, the proportion of trials categorized as reflecting successful recollection (distance errors less than the 4.88-cm threshold) did not significantly change Post-Stim ($t(11)=1.88$, $p=0.26$) or Post-Sham ($t(11)=0.18$, $p=0.86$) relative to Baseline. Second, the same growth-mixture fitting was used to define the group-level threshold for recollection success was used to estimate successful recollection for each participant and memory assessment[5]. Individualized successful recollection thresholds did not significantly differ for Pre-Stim versus Post-Stim ($t(11)=0.603$, $p=0.56$) nor for Pre-Sham versus Post-Sham ($t(11)=0.591$, $p=0.57$). Both methods thus converged to indicate that stimulation did not alter general recollection success.

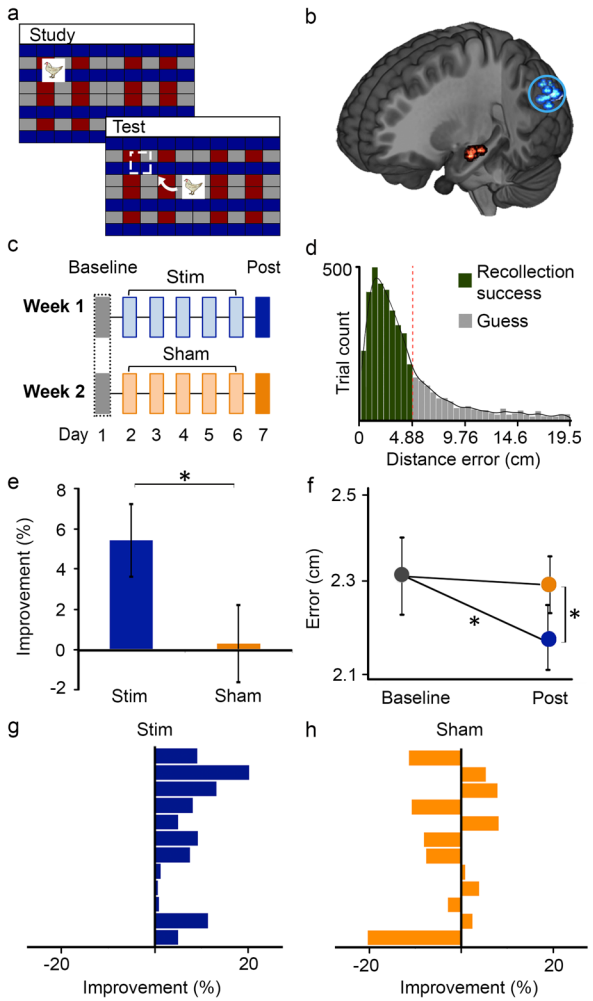
In contrast, recollection precision measured Post-Stim improved relative to Baseline ($t(11)=2.99$, $p=0.01$; Cohen's d=0.86), but not for Post-Sham relative to Baseline ($t(11)=0.14$, $p=0.89$) (Figure 4EF). The percent-improvement from Baseline was significantly greater for Post-

Stim than Post-Sham ($t(11)=2.63$, $p=0.02$; Cohen's d=0.76). Furthermore, raw distance error was less for Post-Stim than for Post-Sham ($t(11)=2.68$, $p=0.02$, Cohen's d=0.77). Thus, HPM network-targeted stimulation (and not Sham) improved recollection precision. Recollection precision improvements were highly consistent across participants due to Stim (12/12 improved; Figure 3G; Sign Test $p<0.0005$) but were at chance due to Sham (6/12 improved; Figure 3H; Sign Test $p=1.0$). To establish the specificity of this effect, we also assessed effects on distance error for guess trials. Relative to baseline, Post-Stim (mean=4.1%, se=3.9%) compared to Post-Sham (mean=1.9%, se=3.1%) was not significantly different ($t(11)=0.55$, $p=0.59$). Neither Stim ($t(11)=1.05$, $p=0.32$) nor Sham ($t(11)=0.60$, $p=0.56$) improved distance error relative to Baseline for guess trials. Therefore, effects of stimulation did not occur on guesses.

Similar effects of stimulation were identified when individual Pre-Stim and Pre-Sham values were used rather than the common Baseline. Percent-improvement for Post-Stim versus Pre-Stim (mean=7.64%, se=1.65%) was significantly greater ($t(11)=3.70$, $p=0.004$; Cohen's d=1.07) compared to Post-Sham versus Pre-Sham (mean=-2.7%, se=2.58%). Stimulation improved recall precision ($t(11)=4.6266$, $p=0.0007$; Cohen's d=1.34) whereas sham did not improve precision relative to Pre-Sham baseline ($t(11)=1.042$, $p=0.32$). These consistent results confirmed that stimulation improved precision irrespective of the choice of baseline.

The same effects were identified in the entire N=16 sample. Percent-improvement Post-Stim (mean=7.31%, se=3.54%) and percent-improvement Post-Sham (mean=2.6%, se=2.2%) were significantly different ($t(15)=2.89$, $p=0.01$; Cohen's d=0.72), as stimulation improved recall precision ($t(15)=2.38$, $p=0.03$; Cohen's d=0.60) and sham did not ($t(15)=1.31$, $p=0.21$). Precision improvements were also highly consistent (15/16 improved; Sign Test $p=0.0005$) but were at chance due to Sham (7/16 improved; Sign Test $p=0.80$).

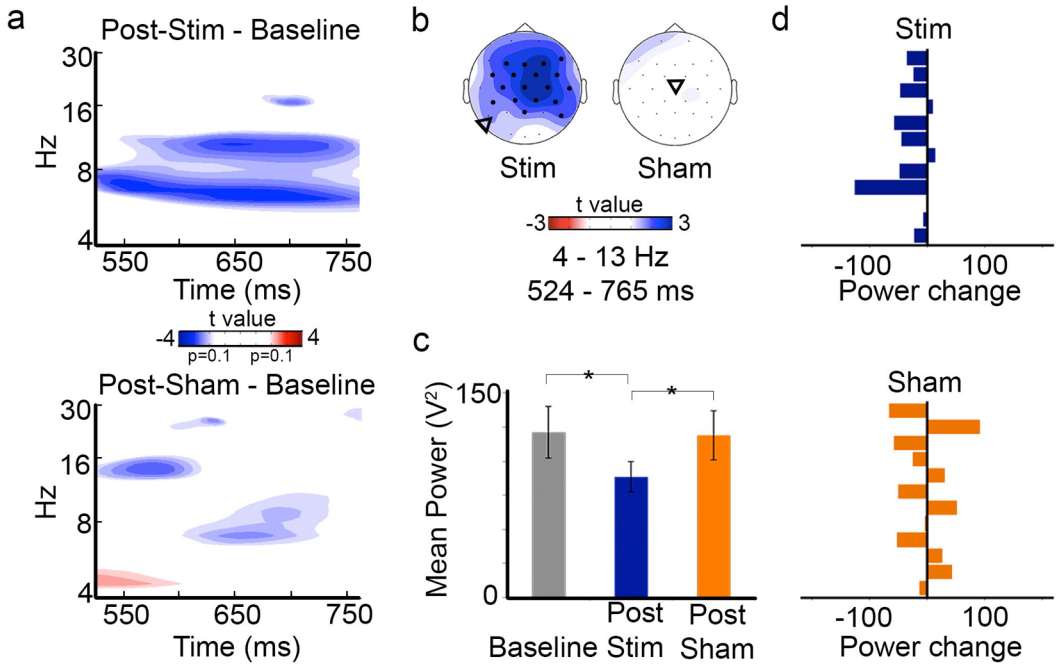
Figure 4. HPM network-targeted stimulation enhances recollection precision



(A) Participants studied trial-unique objects at randomly assigned locations. Subsequent memory testing involved object-cued recall of locations. (B) fMRI connectivity used anatomically defined hippocampal seeds (red) to define parietal-maximum stimulation locations (blue) in each participant. Each dot indicates locations for one participant. (C) Five daily sessions of Stim or Sham stimulation followed Baseline memory testing. Stim and Sham conditions were administered within-subjects in counterbalanced order. (D) Histogram of distance error for all participants and conditions. Successful recollection (green) and guessing (gray) trials were defined via converging modeling approaches. (E) Percent-improvement from Baseline was significantly above zero for Post-Stim but not Post-Sham and significantly greater for Post-Stim than Post-Sham. (F) Distance error for successful recollection was reduced Post-Stim relative to Baseline (but not Post-Sham relative to Baseline) and Post-Stim relative to Post-Sham. (G) Percent change in precision due to Stim for each participant. (H) Percent change in precision due to Sham for each participant *p<0.05 (adapted from Nilakantan et al., 2017)

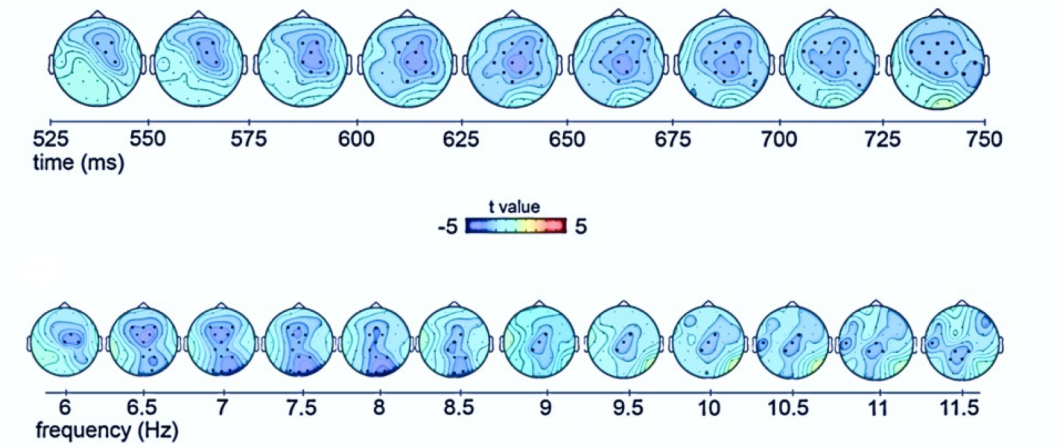
Theta-alpha frequency oscillatory activity and late-positive event-related potentials (ERP) are stimulus-evoked neural correlates of recollection [26, 33]. We hypothesized that stimulation would modulate these neural signals of memory retrieval [143], providing neural correlates of the corresponding recollection precision improvement [139]. Based on fMRI-EEG evidence linking 4-13-Hz (theta-alpha) oscillatory EEG activity to fMRI connectivity of the retrosplenial cortex and hippocampus during recollection [24], we first tested the effect of stimulation on evoked oscillatory EEG power using this a priori frequency band of interest. We compared 4-13-Hz evoked oscillations for successfully recollected trials among Post-Stim, Post-Sham, and Baseline conditions. Cluster-based non-parametric simulation testing yielded significant medial-posterior (Figure 5AB) power reduction from 524-765ms for Post-Stim relative to Baseline (Figure 5AB; *cluster-corrected* p=0.03). The same test for Post-Sham relative to Baseline identified no significant power differences (p>0.3). 4-13-Hz power averaged for all electrodes for the 524-765-ms period (Figure 5C) was significantly less Post-Stim compared to Baseline (t(11)=3.00, p=0.01, Cohen's d=0.87) and compared to Post-Sham (t(11)=2.24, p=0.05, Cohen's d=0.65), whereas the Post-Sham versus Baseline difference was not significant (t(11)=0.14, p=0.88). EEG oscillatory effects also remained consistent irrespective of choice of baseline. 4-13Hz power averaged over 524-765ms was significantly reduced Post-Stim relative to Pre-Stim baseline (t(11)=2.45, p=0.032), but remained unchanged Post-Sham relative to Pre-Sham baseline (t(11)=0.16, p=0.876). These reductions of theta-alpha power were consistent across participants due to Stim (reductions in 10/12 participants; Sign Test p=0.039; Figure 5D), but not due to Sham (reductions in 7/12 participants; Sign Test p=0.774; Figure 5D).

Figure 5. HPM network-targeted stimulation alters theta-alpha power



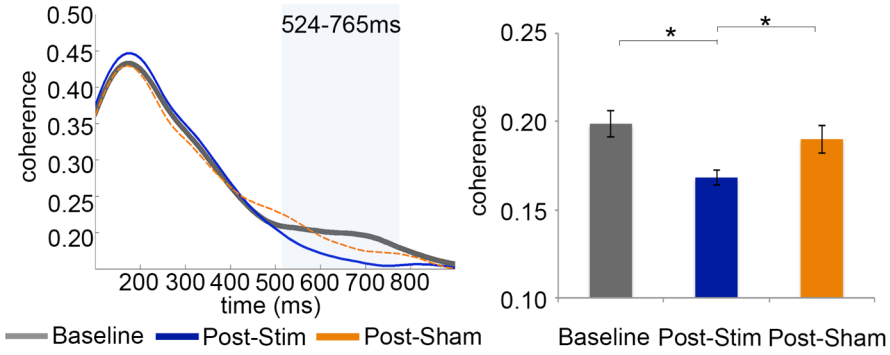
Plot indicates *t* values for pairwise comparisons of the time x frequency power spectra for (A) Post-Stim and (B) Post-Sham versus Baseline, averaged across electrodes and latency identified via cluster detection. The significant cluster of reduced power relative to Baseline is evident for Post-Stim but not Post-Sham. (C) Topographical maps of *t* values demonstrate the frontal-central distribution of these effects. Electrodes identified via cluster detection are highlighted by bold markers. Triangles indicate approximate averaged stimulation locations for each condition. (D) Mean 4-13-Hz averaged power for all electrodes was reduced for Post-Stim relative to both Baseline and Post-Sham. For each participant, mean 4-13-Hz power percent change is shown (E) Post-Stim and (F) Post-Sham, relative to baseline values. *$p<0.05$ (Adapted from Nilakantan et al., 2017)

Figure 6. Frequency x time changes due to stimulation



t value topographies displaying significant time x electrode in 25ms intervals from 525ms-750ms, and frequencies x electrodes of Post-Stim compared to Baseline defined via cluster simulation between 500-700ms. Electrodes included in the significant clusters are bolded. (Adapted from Nilakantan et al., 2017)

Figure 7. HPM network-targeted stimulation reduced inter trial phase coherence



Average inter-trial coherence (from 4-13Hz) is displayed across the epoch from 100-900ms. Bar plot displays mean coherence (and standard error) across 524-765ms time window, which is reduced Post-Stim (blue) compared to Baseline (gray) and Post-Sham (orange). *p<0.05 (Adapted from Nilakantan et al., 2017)

Further, an independent cluster-based non-parametric test for frequency across an a priori recollection latency interval [33], identified significant 6-11.5 Hz power reduction (*cluster corrected* $p<0.02$) for Post-Stim versus Baseline (Figure 6) and no significant differences for Post-Sham versus Baseline, consistent with the a priori frequency band used for primary analyses. This frequency range found via cluster-detection was consistent with the theta-alpha a priori frequency range used for primary analyses, confirming that theta-alpha oscillatory activity correlates of recollection were reduced due to stimulation. Inter-trial theta-alpha phase coherence was reduced Post-Stim relative to Baseline ($t(11) = 3.85$, $p=0.003$, Cohen's d=1.11), and Post-Sham ($t(11)=2.28$, $p=0.04$, Cohen's d=0.66), whereas there was no change Post-Sham compared to Baseline ($t(11)=0.71$, $p=0.49$, Figure 7). Collectively, these results suggest that stimulation-induced recollection precision improvement was associated with corresponding reductions in theta-alpha oscillatory activity.

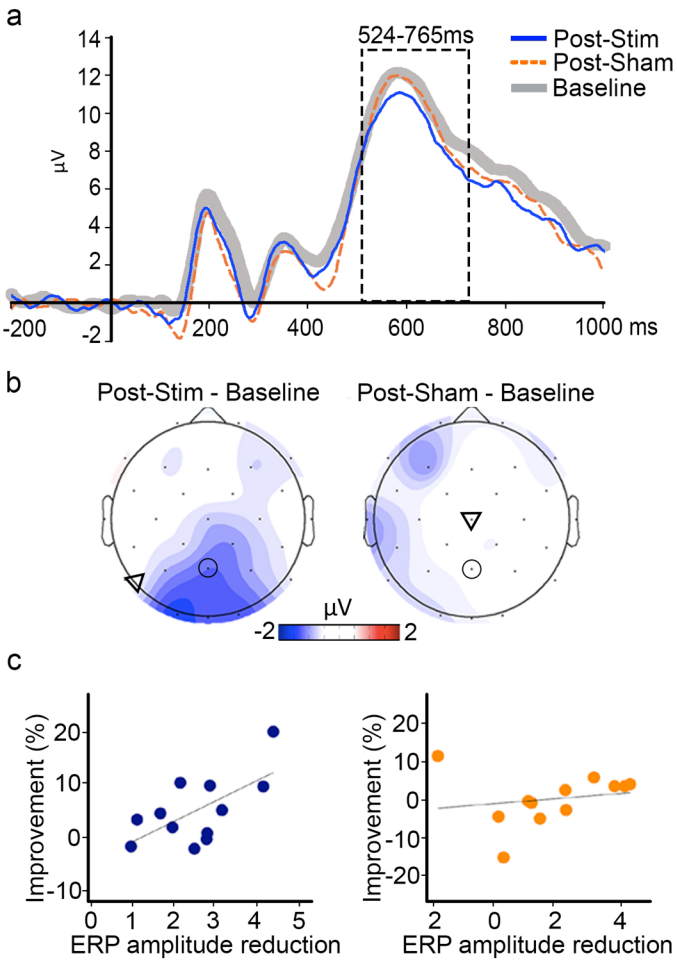
We next tested the effect of stimulation on event-related potential (ERP) correlates of successful recollection. Comparison of recollection success ERPs for both Post-Sham and Post-Stim yielded prototypical late-onset positive increases in amplitudes for successful recollected trials relative to guesses at parietal and occipital electrodes (known as the "parietal memory effect" [33]). That is, repeated-measures ANOVA of average amplitude used *condition* as a factor (success Post-Stim, success Post-Sham, and Guess). There was a main effect of condition ($F(2,22)=5.64$, $p=0.01$). ERPs were significantly greater for successful trials Post-Stim ($t(11)=2.35$, $p=0.03$) and successful trials Post-Sham ($t(11)=3.25$, $p=0.008$), relative to guess. This indicates reliable ERP correlates of successful memory irrespective of stimulation condition. For the 524-765ms latency interval of interest derived from cluster-based permutation testing, mean ERP amplitude for parietal-occipital electrodes was reduced Post-Stim relative to Baseline ($t(11)=3.31$, $p<0.01$;

Cohen's d=0.96) whereas Post-Sham amplitudes did not differ from Baseline ($t(11)=0.86$, $p=0.41$) (Figure 8AB). Further, correlation analyses using robust fitting to guard against outlier influences indicated that greater Post-Stim versus Baseline amplitude reduction was associated with greater recollection precision improvement (Robust-$r=0.659$, $p=0.02$) (Figure 8C). This relationship was not significant for Post-Sham (Robust-$r=0.023$, $p=0.94$). Stimulation thus reduced amplitudes of ERP correlates of recollection and these reductions corresponded to recollection precision improvements.

To test the possibility that the relative difference for stimulation versus sham was due to impairments for sham rather than improvements for Stim (as rTMS intensity for Stim and Sham was matched but with delivery to different locations), we also performed a separate control experiment in which zero-intensity stimulation was delivered to the HPM parietal target in an additional group of participants (N=12). Precision memory was not reliably improved in this additional control condition. There was no significant change in raw error Post-Control versus Pre-Control ($t(11)=1.57$, $p=0.145$). and percent change (mean=5.39%, se=3.39%) was not different from zero ($t(11)=1.59$, $p=0.139$). Furthermore, improvements were not consistent across participants (7/12 participants improved; Sign Test $p=0.774$). Precision improvements were therefore selective for network-targeted stimulation, and specific to full-intensity stimulation of the lateral parietal cortex. Likewise, oscillatory neural correlates of precision were not significantly different Post-Control. To evaluate changes in theta-alpha power, a cluster-based simulation of 4-13Hz over the entire epoch revealed no significant time-electrode cluster ($p>0.3$). Averaged power over 4-13Hz for 524-765-ms latency interval used in the primary analysis also did not significantly differ between Pre-Control and Post-Control ($t(11)=1.73$, $p=0.11$). Furthermore, event-related mean amplitude (ERP) for successfully recollected trials was not significantly different Pre-

Control versus Post-Control for the same latency interval ($t(11)=1.22$, $p=0.248$). Thus, precision memory improvement and an associated reduction of recollection neural correlates only occurred reliably for targeted HPM network stimulation (Stim), not for both control conditions.

Figure 8. Stimulation reduced ERP correlates of successful recollection



(A) ERPs for Post-Stim (blue), Post-Sham (dashed-orange) and Baseline (thick gray) for one representative electrode (Pz). (B) Topographical plot of the amplitude reduction relative to baseline show the posterior distribution characteristic of the parietal memory effect (the circled electrode is Pz). Triangles indicate approximate averaged stimulation locations for each condition. (C) Relative to Baseline, greater reduction in ERP amplitude (Baseline – Post) was associated with greater percent-improvement in recall precision for Stim (blue) but not Sham (orange), tested using Robust correlation. (Adapted from Nilakantan et al., 2017)

3-4 Discussion:

Targeted network stimulation improved recollection precision, but not general success. The stimulation parameters used here have previously demonstrated changes in fMRI connectivity within the posterior-medial network, particularly for hippocampus and medial aspects of parietal, occipital, and retrosplenial cortex [96]. Interestingly, just as fMRI connectivity enhancements with hippocampus were greater for medial regions than the lateral parietal regions that were stimulated[96], the changes in EEG/ERP correlates of recollection reported here occurred with medial distributions that were distal to the stimulation location (Figure 5, Figure 6). Collectively, this supports the interpretation that there were network-level effects of stimulation reflecting hippocampal-cortical network involvement in memory precision.

Targeted stimulation reduced the power and amplitude of EEG correlates of recollection precision. This reduction is consistent with the hypothesis that successful retrieval of visual details corresponds to rapid memory reactivation [29, 144] and aligns with mounting evidence that reduced theta power correlates with better item-context memory [28]. One possibility is that stimulation promotes asynchronous activity within the medial temporal lobe and the neo-cortex, which produces the flexibility for higher resolution information storage and retrieval [144-148]. Although EEG/ERP power and amplitude has been related to improved memory in many studies [26, 33, 139], EEG/ERP oscillatory enhancements versus reductions may represent a neural distinction between general/semantic memory success and visuospatial memory precision. That is, memory for general information can benefit from verbal-semantic mnemonic strategies associated with the anterior hippocampal network, with heightened verbalization of recollection content, while memory for precise perceptual details [55, 149] does not benefit substantially from semantic strategies.

Evoked activity reductions as measured by EEG may also indicate efficient processing. For example, evoked activity reductions can occur in conjunction with enhanced fMRI connectivity in experiments of priming [150], which is thought to reflect heightened processing efficiency [151]. This pattern is consistent with our findings, in which stimulation enhanced HPM network fMRI connectivity [96] and reduced recollection-related evoked activity, specifically at frequencies characteristic of HPM network communication [152]. Although effects on memory precision were robust in the entire sample, our EEG/ERP subsample was relatively small. Nonetheless, several design features enhance confidence in reported neural findings, including strong a priori hypotheses on the particular neural signals that would be affected by stimulation, effects that significantly outlasted the stimulation sessions, as well as matched-intensity control (Sham) stimulation in addition to a separate zero-intensity, site-specific control group. The current findings provide novel information on the network basis of memory because they demonstrate the link between a highly specific aspect of memory, recollection precision, and the HPM network. Isolation of stimulation effects on precision from other co-occurring memory processes such as memory success within the same task is especially crucial for validating stimulation effects on memory and network-level processing, as condition-selective effects help mitigate influences from potential nonspecific factors such as history, practice, and placebo effects.

The recollection precision improvements reported here outlasted the period of stimulation by ~24 h, consistent with our previous demonstrations of improvements lasting up to ~2 weeks after stimulation [153]. Generation of long-lasting improvement in memory ability (rather than improved retention of specific material) has implications for the many disorders related to hippocampal-cortical network dysfunction [47] (See Chapter 5).

Chapter 4

Recollection precision is impaired in aging

4-1 Rationale:

Because only few have attempted to distinguish the functional neuroanatomy of recollection success from precision, it remains unclear if and how these memory processes are distinctly represented in the MTL and hippocampus. Numerous studies have demonstrated that recollection declines with age[57, 61, 62] [58-60]. Age-related recollection impairments correspond to reductions in hippocampal integrity[63] and hippocampal-cortical network connectivity [154, 155]. However, the tests utilized in these studies predominantly measure recollection success, without corresponding measures of precision. Given that aging disproportionately impacts MTL-network function [156], we hypothesized that older adults would demonstrate greater impairments of precision relative to success.

4-2 Methods:

Participants: 20 younger and 20 older right-handed adults with no history of neurological or psychiatric conditions participated in the experiment. Data from one older adult and one younger adult were excluded for poor memory performance (at least two standard deviations below overall mean performance for each group) and data from one additional younger adult participant was excluded due to computer malfunction. Thus, data from 18 younger adults (mean age=25.0, range=18-33 years, 11 females) and 19 older adults (mean age=70.57, range=59-80 years) were included in the final analyses. The Institutional Review Board at Northwestern University approved all study procedures.

Memory paradigm: Participants completed an object location memory task adapted from [111, 112], described fully in Chapter 2. Briefly, participants studied 24 objects presented at randomized locations on a specific background scene, and were instructed to remember the object locations as accurately as possible. Following a visuo-spatial filled delay, a cued recall test was administered. 24 studied objects were randomly presented one at a time in the center of the screen and participants were required to use a mouse to recall associated locations on a different background scene than was presented with the item during study. Distance error (the distance between the location the object was originally studied and the location the object was recalled) was our main dependent variable. The change in background scene between study and test encourages the hippocampal-dependent process of binding independent features (object and location) into an associative event and discourages other strategies involving the perceptual unitization of the object superimposed on the entire scene [107-109].

Analysis: Statistical analyses were done in R[115]. Trials were scored based on distance error (difference between recalled and studied locations). The threshold for recollection success was determined using two separate approaches (Figure 2). First, we used the geometry of the screen, and defined successful recollection as the trials recalled within the same quadrant as studied. This approach was used in the experiment described in Chapter 2, and has been used in other spatial memory tests of precision[97, 98], as quadrant based success is similar to rodent spatial memory tests [99, 100]. Second, we used growth-mixture modeling [5] to fit distance error to a Cauchy distribution (for successful recollection) and a uniform distribution (representing random guessing). The modeling results in a mixture parameter (λ) denoting the proportion of success relative to guess. For all participants, the mixture-modeling approach indicated that 65.5% of trials fit the Cauchy distributions with a good fit (p=0.15). Distributions for each group

demonstrate a slightly sloped guess distribution (rather than uniform flat) due to the relatively low probability that items were either studied or recalled near the corners of the rectangular screen. Although the estimation in mixture modeling is limited by relatively low trial counts (48 trials per participant in this experiment), the fit value that was obtained is consistent with that identified in other studies using similar paradigms [4, 5, 102]. Using this modeling approach, the threshold for successful recollection corresponded to 7.66 cm. Recollection precision was then measured as the mean distance error (i.e., the distance between the studied object-location and the recalled location) for trials successfully recollected. Two-sample t-tests were used to compare recollection success and recollection precision among groups.

4-3 Results:

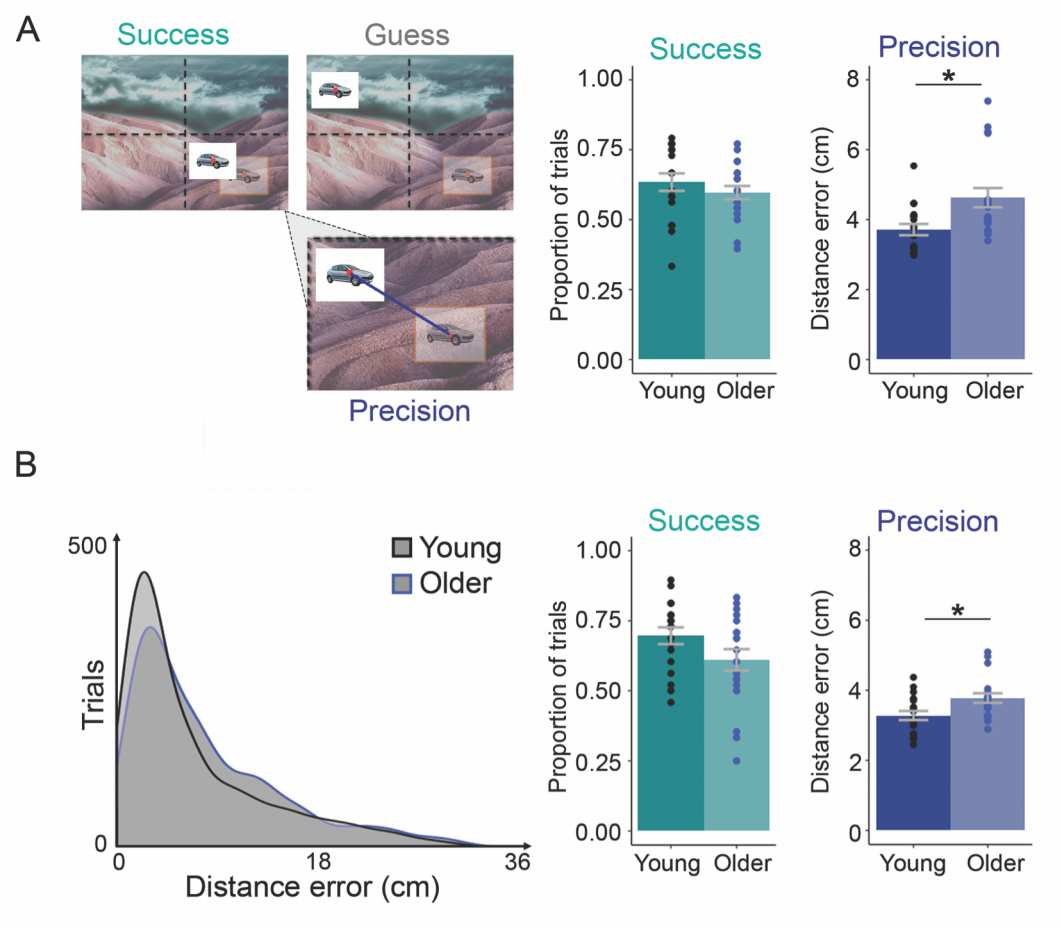
Overall memory performance (mean distance error for all trials, irrespective of any success or precision distinction) was not significantly different for younger (mean=6.83, SE=0.50 cm) compared to older adults (mean=7.94, se=0.54 cm) (T(35)=1.50, p=0.14).

We first used the geometry of the screen to characterize recollection success and precision (Figure 9A). Recollection success was not significantly different for younger adults (mean=63.43%, SE=3.13%) compared to older adults (mean=59.64%, SE=2.39%) (T(35)=0.96, p=0.34). However, recollection precision was impaired for older adults (mean=4.63, SE=0.27 cm) relative to younger adults (mean=3.72, SE=0.16 cm) (T(35)=2.82, p=0.008).

Results were consistent when we used a mixture-modeling approach to define recollection success versus precision (Figure 9B). Recollection success did not significantly differ for younger adults (mean=69.7%, SE=2.99%) compared to older adults (mean=61.1%, se=3.84%)(T(35)=1.75, p=0.09). Recollection precision was impaired for older adults (mean=3.78 cm, se=0.14 cm) relative to younger adults (mean=3.28 cm, SE=0.13 cm; T(35)=2.65, p=0.01, Figure 9B). To

further establish the specificity of these age-related effects on precision, we tested the effects of aging on distance error for guess trials. Recollection precision for younger adults (mean=14.64 SE=0.45 cm) was not significantly different compared to older adults (mean=14.35 cm, SE=0.36 cm) ($T(35)=0.51$, $p=0.61$). Therefore, we found that age selectively impaired recollection precision, but not recollection success or guess distance errors.

Figure 9. Recollection precision is impaired in older adults.



Memory testing involved object-cued recall of associated locations on a different background scene. Proportion of trials successfully recollected and mean distance error (recollection precision) of those successfully recollected trials are presented for younger and older adults determined by (A) the geometry of the screen and (B) mixture modeling (see methods). Distance error distributions for each group. Individual participant scores are plotted on each bar graph as black or blue circles. Original studied locations are outlined in yellow and quadrant demarcations are for representation in the figure only (adapted from Nilakantan et al., 2018).

4-4 Discussion:

We examined recollection precision and success in younger adults, and older adults, using a task that probed the associative/relational components of precision and success. Older adults showed a specific impairment for recollection precision but not success, and no overall memory impairment, relative to younger adults. These results demonstrate that precision is a sensitive measure, relative to overall memory and success, which selectively captures impairment due to age.

The present results are consistent with studies of visual working memory [120], which demonstrate impaired high-resolution but not low-resolution memories or general memory capacity in aging [157, 158]. Precision impairment in older adults could be related to altered MTL function and structure, as many memory impairments due to age are associated with atrophy of the hippocampus, diminished structural connectivity, and altered functional connectivity of the MTL [68, 73, 159, 160]. It is important to note that although aging disproportionately impacts MTL-network function [156], normal aging can involve a variety of neurological changes, including abnormal protein aggregation and distributed neurodegeneration [161], which also could play a role in memory performance. This cross-sectional study did not measure pathologic burden or collect accompanying neuroimaging measures to assess structural or functional integrity of our aging sample, and therefore any relation between hippocampal network function and memory performance is limited to inference. However, to address this question, we experimentally assessed whether a hippocampal-cortical network causally supports recollection, and the results are described in Chapter 5.

Chapter 5

Network-targeted stimulation improves recollection in older adults

5-1 Rationale:

Memory decline is the predominant cognitive complaint in healthy older adults [162]. On a word list recall test, it is considered normal for a 65-year-old to remember at least 25% fewer words than a 35-year-old [163], and episodic memory decline rapidly accelerates after the age of 65 [164]. There are currently no effective treatments for age-related memory impairment. With a rising global population over the age 60, the health care costs and burden to society from memory disorders of aging will continue to grow[165, 166].

Age-related memory decline is most severe for recollection[58, 61], which is often measured using word-list-recall, paired-associate, or source-memory tests. In contrast, aging minimally affects other types of memory, such as the recognition of objects seen before[1]. Abnormal function and structural connectivity of the cortical-hippocampal network thought to support recollection has been correlated with normative memory decline in healthy aging[68-71], with amnestic mild cognitive impairment[72], and with Alzheimer's disease[51, 73, 74], potentially due to similar neurologic and potentially pathologic insults across these conditions[156, 161, 167]. Age-related memory impairments have thus been hypothesized to result from cortical-hippocampal network abnormalities[51, 68, 74], but this relationship has not been causally tested.

Previous studies involving noninvasive stimulation have improved recollection accuracy and enhanced corresponding cortical-hippocampal network function in young adults. Specifically, stimulation enhanced fMRI connectivity among network regions[96], increased activity during

memory formation[168], and improved measures of recollection memory[96, 102, 168]. Older adults experience structural impairments of hippocampal-cortical network white matter connections [91], which are likely required for network-level neuroplastic responses to stimulation [70, 71]. The utility of this noninvasive stimulation method to engage the cortical-hippocampal network and mitigate age-related memory decline is therefore unknown. Moreover, because the link between cortical-hippocampal dysfunction and age-related memory impairment has not been causally validated, it is possible that modulation of this network alone could be ineffective for memory improvement in older adults.

We tested whether stimulation targeting the cortical-hippocampal network could rescue age-related recollection impairments and alter brain activity correlates of recollection in older adults. Within the same memory task, we assessed effects of stimulation on recollection separately from effects on recognition success [58, 169]. Neural target engagement was tested using fMRI to measure brain activity related to recollection and recognition memory formation.[32] We hypothesized that stimulation would improve recollection accuracy and increase fMRI activity signals of recollection memory formation in the targeted cortical-hippocampal network. We hypothesized that these effects would be selective, with greater changes due to stimulation for recollection than for recognition, with greater and more coherent[168] corresponding fMRI activity in the targeted cortical-hippocampal network, including the *a priori* targeted hippocampus[96], and without effects on either recollection or recognition fMRI activity in the control frontal-parietal network.

5-2 Methods:

Participants:18 adults were enrolled in this study. Data from two participants were excluded *post hoc* due to poor memory performance for all testing sessions due to inability to

follow instructions. Data from one participant were partially excluded due to failure to complete the full experiment. Full datasets were analyzed from the remaining fifteen participants (mean age=72.46, age-range=64-80 years, 11 female; partial dataset participant age=68 years, female). Participants were recruited from the registry of the Northwestern University Alzheimer's Disease Center or from the community via advertisements. All were cognitively normal for their age, as indicated by neuropsychological assessment (Table 2) and neurological exam with medical history review by a board-certified neurologist[170]. All participants reported no history of neurological or psychiatric disorders and passed standard MRI and TMS safety screenings, which includes exclusion of most medications with central nervous system action[171]. All participants gave written informed consent and were remunerated for their time. The Institutional Review Board at Northwestern University approved all study procedures.

Experiment design overview: The experiment used a within-subjects, sham-controlled, single-blind design. The experiment involved two distinct weeks, with each week separated by at least 4 weeks (mean delay interval = 9.05 weeks, range = 5.7-18 weeks) to ensure sufficient washout time between stimulation protocols. During each week, participants underwent five consecutive daily sessions of TMS, with full-intensity stimulation during one week and sham-intensity stimulation during the other week, in counterbalanced order. During each week, memory assessments (Figure 10A) were conducted during fMRI scanning immediately prior to the first session of stimulation, ~24 hours after the final session of stimulation (mean delay interval=22.5 hours, range=15.7-25.3 hours), and again ~1 week after the final stimulation session (mean delay = 8.8 days, range=7-8 days, except for one participant with a delay of 29 days). Data were thus collected at six assessments for each participant (Figure 10C).

Stimulation target identification: We targeted the cortical-hippocampal network with TMS. Participant- specific locations of left lateral parietal cortex were selected based on their high resting-state fMRI connectivity with the hippocampus (Figure 10B). To determine the participant-specific stimulation location, structural and resting-state scanning was performed immediately prior to any experimental procedures. A left hippocampal seed location was identified as the nearest voxel within the middle of the body of the hippocampus to MNI [-29, -25, -13] (mean distance=2.89mm, sd=1.91mm), which also demonstrated high connectivity in the contralateral right hippocampus. This location was used as center of a 2-mm spherical seed in a seed-based analysis (*InstaCor*). The stimulation location was then selected as the peak connectivity voxel, within an anatomical mask including the angular gyrus, superior and inferior parietal lobule near MNI [-47, -68, 36] (mean distance=12.43mm, sd=6.46mm), which was also stimulation-accessible. The stimulation-accessible parietal location was used because this area consistently demonstrates high resting-state connectivity with the hippocampus[53], has direct projections to mesial temporal lobe input regions in the primate [91], and is consistently engaged in episodic memory tasks[89]. Finally, the stimulation target was transformed for each participant to original space by reverse-applying the transformation matrix obtained during stereotactic normalization for participant-specific anatomically guided stimulation.

TMS: A frameless stereotactic system (Localite GmbH, St. Augustin, Germany) provided MRI-guided stimulation to the parietal locations identified in each participant. Resting motor threshold (MT) was determined visually based on the minimum stimulator output required to generate a contraction of the *abductor pollicis brevis* for 5 out of 10 consecutive single pulses. The MagPro X100 system with a 2x75mm diameter butterfly coil (MagVenture) was used to apply daily repetitive transcranial magnetic stimulation protocol (rTMS). The repetitive stimulation

sequence consisted of of 40 consecutive trains of 20-Hz pulses for 2 seconds followed by 28 seconds of no stimulation (1600 pulses per session, 20 minutes total). Repetitive TMS was applied at 100% MT for Stim and at 10% MT for Sham, for each of the five consecutive daily sessions on each week. One participant received three days of 100% MT stimulation and two days of sham 10% MT during their stimulation week, due to experimenter error. Stimulation was applied at a lower intensity for 7 participants (89.3%, 90.3%, 91.1%, 80.9%, 62.5%, 83.9%, 91.2% MT), due to reported mild discomfort at the initial session with 100% MT. Thus, the final mean stimulator output intensity was calibrated to 92.61% MT (range=62.5-100% MT) for Stim, and 9.97% MT (range=8.77-11.1% MT) for Sham. The TMS coil location and the stimulator current rate of change (dI/dt) were recorded during each session. For visualization in Figure 10C, electrical-fields (e-fields) were estimated using SimNIBS 2.0[172]. For each participant, tetrahedral head meshes segmented by tissue class (white matter, grey matter, CSF, skull, and skin) were created from the T1-weighted structural MR images. The coordinates of the coil position were transformed to the individual mesh space. These coordinates, along with dI/dt, were used in a realistic finite element model. The head meshes were converted to volumetric maps in each participant's native space and then spatially normalized to standardized space.

Memory assessment: The memory paradigm (Figure 10A) administered during fMRI scanning on each of the six assessments consisted of two blocks, and each block consisted of a study phase and a test phase, separated by ~60 second interval. During the study phase, participants studied 42 trial-unique objects paired with one of six scenes (object-scene) or one of six discrete locations (object-location). Object-scene and object-location pairs were presented for 1500ms, followed by a jittered inter-stimulus interval including a fixation (mean interval= 4000ms, range: 2000-6000ms). Participants were instructed to study and remember the object associations as

accurately as possible. During the test phase, participants were presented with 72 objects, including the original studied objects and new/unstudied objects for 2000ms each, and were asked to categorize each object as "old" or "new" (recognition). Participants had up to three seconds to make each response. To assess recollection, participants then selected one of the six scenes or one of the six discrete locations for all objects that were originally studied (recollection). The first three objects and the last three objects from each study phase were not assessed during the test phase to reduce bias from primacy and/or recency effects[173]. Each test trial was separated by a jittered inter-stimulus interval (mean interval=4000ms, range: 2000-6000ms). The mean delay between viewing an item-location or item-scene associate during study and the corresponding test trial was 5 min. The order of object-scene and object-location study-test blocks was counterbalanced across experimental conditions and sessions. Distinct sets of trial-unique objects and session-unique scene images were used for each assessment, with assignment counterbalanced across experimental conditions and sessions.

Statistical analyses were done in R[115]. Sample size was matched to our previous studies using similar methods in younger adults[96, 102, 168] such that we would have a matched-power assessment of the ability for this TMS protocol to yield effects in older adults comparable to those observed in young adults. Based on this task design, chance performance is 50% for recognition (two alternate choices "old" or "new") and 16% for recollection alone (six forced alternate choices). To focus on the construct of recollection irrespective of specific memory task details, primary analyses collapsed performance across the two test formats[174]. Recognition accuracy was assessed using the proportion of total trials in which objects were correctly identified as either old (originally studied) or as new (unstudied). To assess recollection, we computed the proportion of trials in which the object was identified correctly as old *and* the correct associate (scene or

location) was selected. One participant's Pre-Sham assessment was replaced with their Pre-Stim assessment, because their behavioral recognition accuracy performance was at chance (50% overall, and 47.2% for the object-location task, and fell two standard deviations below the rest of the group (Pre-Stim Mean: 83.04, SD=10.76%). To focus on the construct of associative recollection irrespective of specific memory task details, primary analyses collapsed performance across the two test formats[174] and subsequent fMRI analyses used data obtained from each task separately. Primary analyses, reported in the main text involved percent change scores [(Post score-Pre score)/(Pre score)] due to stimulation relative to sham for recollection relative to recognition. Cohen's d effect size tests are reported in conjunction with significant results.

fMRI analyses: To assess fMRI neural correlates of memory formation, trials during the study phase were sorted according to responses during the test phase. Study trials were assigned to one of three categories based on test performance: (1) recollection (item old/new judgment correct plus correct scene or location association selection), (2) recognition (item old/new judgment correct but incorrect scene or location association selection), or (3) item incorrect (all other trials). The first and last three trials of the study block were not tested during the test block to avoid confounds of primacy and recency. These trials were also included in the model, as a fourth category, which was not further assessed. The BOLD hemodynamic response was estimated using the general linear model incorporating signal deconvolution (*3dDeconvolve*) with the AFNI *gamma* function used as a response model. The model included onsets of all trials segregated into the four categories (item correct-association correct; item correct-association incorrect, item incorrect, and primacy/recency trials), as well as nuisance variables including six estimates of motion and their derivatives and the T1 and T0* components of the BOLD signal. Linear drift was also estimated. Volumes with over 0.3mm of displacement were censored. To isolate activity

related to recollection memory formation, we assessed activity among each network ROI (see below) using a linear contrast of item correct with source correct compared to item correct with source incorrect. To isolate activity related to recognition memory formation, we used a contrast of item correct with source incorrect versus item incorrect. Activity estimates related to recollection and activity related to recognition were extracted from ROIs and directly compared using t-tests or repeated-measures ANOVA, as described below.

We used *a priori* network regions from a previous study of older adults[68] to define the hippocampal-cortical network (default network) as the memory network we targeted, and the frontal-parietal network as a control network. Importantly, both networks have demonstrated significant age-related function impairments[68] but only one was targeted. An intersection mask of all the ROIs and a mask of all functional EPI runs from all assessments was created, such that only valid voxels across all participants were included in the analysis. Spherical ROIs at each peak coordinate are visualized for representation in Figure 11A using BrainNet Viewer[175]. The cortical-hippocampal network included four 8-mm spheres centered in medial prefrontal cortex [1,40,16], posterior cingulate/retrosplenial cortex [−1, −50, 26], and lateral parietal cortex [−45, −67, 26; 53, −65, 26], and four 4-mm spheres in hippocampus [−23, −25, −12; 23, −25, −12], and parahippocampal gyrus [−25, −39, −10; 25, −39, −10]. The frontal-parietal network included ten 8-mm spheres centered in intraparietal sulcus [−21, −71, 44; 23, −63, 50], ventral intraparietal sulcus [−27, −75, 24; 31, −79, 22], frontal eye fields [−27, −7, 50; 27, −1, 54], inferior precentral sulcus [−45, −1, 34; 45, 5, 34], and middle temporal area [−47, −75, −4; 49, −69, 4]. fMRI analyses used paired t-tests to compare activity within each network during the Post-Stim assessment relative to the activity during the Post-Sham assessment.

To measure the change in coherence of activity due to stimulation within networks[168] (Figure 11DE), we first calculated pairwise region-to-region correlations of activity change across all participants for Post-Stim and Post-Sham assessments, yielding two separate 18x18 correlation matrices (8 target network ROIs and 10 control network regions of interest). We then calculated the mean of correlation value within each network and between networks for statistical comparison.

Mean fMRI activity related to recollection and recognition was extracted from 3mm spheres placed along the long-axis of the left hippocampus centered around the selected target (MNI: -29, -25, -13; Figure 12A). Right hippocampus ROIs corresponded to the locations in the left hippocampus, and were created by reflecting each ROI about the midline. To evaluate the effect of stimulation on the hippocampus, repeated measures ANOVA was used separately for recollection and recognition and for each side of the hippocampus (left and right), each with stimulation condition (Post-Stim versus Post-Sham) and segment (nine-ROIs) as factors. Bonferroni correction was applied for the four main and interaction effects. For effects that survived Bonferroni correction, post-hoc *t* tests were used to identify particular segment ROIs within the hippocampus that demonstrated changes due to stimulation (Figure 12).

Table 2. Neuropsychological characterization of participants (N=15).

Test		Score
Years of education		15.13 ± 2.17
MOCA		0.26 ± 0.76
MINT		0.16 ± 0.72
Craft Story (verbatim)	Immediate	-0.32 ± 0.94
	Delay	-0.05± 0.90
Benson	Immediate	0.47 ± 1.04
	Delay	0.06 ± 1.26
Digit Span (total)	Forward	-0.08 ± 1.11
	Backward	0.001 ± 0.83
Trails (seconds)	A	0.06 ± 0.69
	B	0.34 ± 0.68
Category Fluency	F words	-0.13 ± 0.98
	L words	-0.39 ± 1.49

Prior to enrollment, participants were screened for healthy cognitive status using the Alzheimer's Disease Centers Uniform Dataset battery[170] including tests to assess overall cognition (Montreal Cognitive Assessment[176] (MOCA)), visual and verbal recall (Craft Story[177], Benson complex figure[178]), executive function (Trails[179], Digit Span[180]), object naming (Multilingual Naming Test[181] (MINT), and verbal category fluency[170]. Mean z-scores (normed based on age, sex, and years of education) ± standard deviations are presented for each test. All participants reported no history of neurological or psychiatric disorder and had to pass standard MRI and TMS safety requirements.

5-3 Results:

Relative to sham, stimulation improved recollection more than recognition at the ~24 hour assessment (T(14)=2.77, p=0.02; Cohen's d= 0.71; Figure 10D). There was robust recollection improvement (T(14)=3.25, p<0.01; Cohen's d=0.84), and weak yet reliable recognition improvement (T(14)=2.25, p=0.04; Cohen's d=0.58). Relative to baseline, the recollection improvement due to stimulation was 31.1% on average (T(14)=3.10, p<0.01, Cohen's d=0.80; Figure 10E) with non-significant change of -3.1% due to sham (T(14)=0.38, p=0.71). In contrast, there was non-significant recognition improvement of 2.8% (T(14)=1.55, p=0.14) and with non-significant change of -2.9% due to sham (T(14)= 1.57, p=0.14).

Primary analyses were conducted in the fifteen individuals who completed the entire experiment, however the additional participant with a partial dataset demonstrated the same increase in recollection due to stimulation (Post-Stim versus Pre-Stim comparison for N=16: T(15)=1.80, p=0.09 for recognition and T(15)=3.29, p<0.01; Cohen's d=0.82 for recollection). Recollection therefore increased in 12/16 participants (75%) due to stimulation, whereas only 5/15 participants (33%) due to sham. Improvements for recollection memory were highly consistent across participants due to stimulation but not for sham (Figure 10F). The same patterns of effects were identified when analyzed using raw values rather than percent-change values. Recollection accuracy improved significantly (Post-Stim versus Post-Sham T(14)=2.27, p=0.04; Cohen's d=0.59), whereas recognition accuracy did not change (Post-Stim versus Post-Sham T(14)=0.10, p=0.92). Furthermore, improvement after stimulation relative to sham were significantly greater for recollection than for recognition (T(14)=2.63, p=0.02; Cohen's d=0.68). Further, recollection did not differ for the Pre-Stim and Pre-Sham assessments (T(14)=1.65, p=0.12), indicating that there were no reliable carryover effects from one week to the next. Stimulation also did not affect

performance of a battery of other cognitive abilities (Table 3), with no indication of impairment, measured at the ~24 hour assessment.

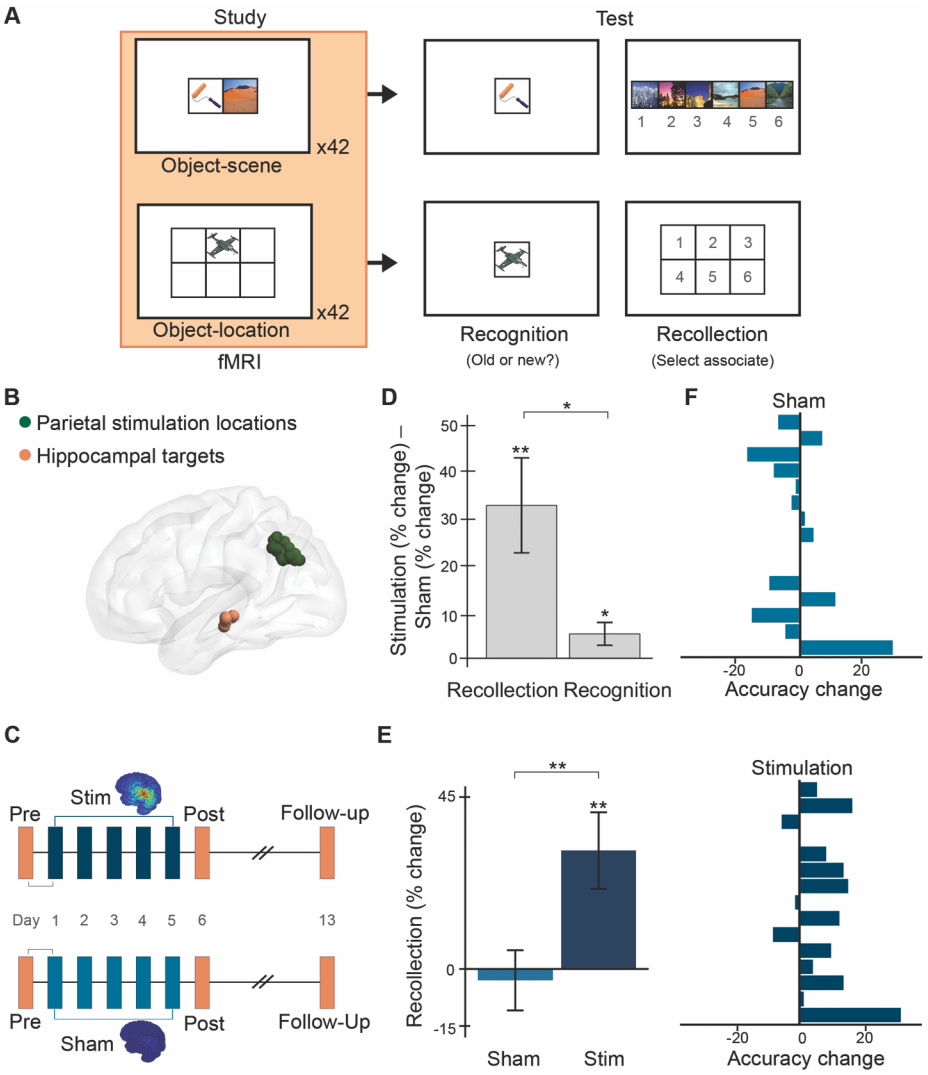
Recollection improvement was maintained at the ~1-week follow-up assessment (21.4% improvement on average ($T(14)=2.75$, $p=0.02$; Cohen's $d=0.71$), but without significant differentiation from sham ($T(14)=1.10$, $p=0.29$), indicating that the selective effects on recollection at ~24 hours only modestly persisted ~1 week later There were no changes in recognition due to stimulation ($T(14)=0.70$, $p=0.50$) or sham ($T(14)=-1.48$, $p=0.16$), with no greater change in stimulation relative to sham ($T(14)=1.64$, $p=0.12$).

Table 3. Scores on non-MRI assessments of cognition

Test		Visit 1	Post-Stim	Post-Sham
NIH Toolbox	Fluid Composite	101.47 ± 14.94	108.27 ± 14.45	110.87 ± 15.70
	Crystalized Composite	110.33 ± 13.71	111.27 ± 15.08	110.87 ± 14.92
	Total Composite	106.93 ± 14.80	111.27 ± 15.52	112.60 ±16.19
	Flanker	90.40 ± 9.92	92.47 ± 12.19	92.60 ± 10.18
	List Sorting	108.33 ± 12.36	111.07 ± 11.37	107.80 ± 13.38
	Card Sorting	102.07 ± 17.29	107.13 ± 16.62	109.00 ± 18.30
	Pattern Comparison	97.93 ± 20.50	108.87 ± 19.12	112.93 ± 19.48
	Picture Sequence	106.87 ± 16.38	108.93 ± 24.61	115.00 ± 17.54
	Picture Vocabulary Score	109.67 ± 13.45	111.47 ± 14.34	111.80 ± 13.96
	Oral Reading Score	109.53 ± 13.29	109.53 ± 14.23	108.13 ± 14.38
Category Fluency		22.27 ± 6.11	23.40 ± 5.18	22.60 ± 7.29
Georgia Complex Figure Recall		21.67 ± 9.15	22.60 ± 6.41	22.67 ± 7.76
Everyday Memory Questionnaire (EMQ)		5.27 ± 5.12	5.00 ± 5.31	4.13 ± 4.22
NeuroQOL	Fatigue	43.55 ± 6.34	43.49 ± 7.09	41.55 ± 6.29
	Depression	46.55 ± 7.64	45.41 ± 6.50	47.43 ± 8.00
	Cognition	48.83 ± 5.45	48.88 ± 6.44	48.29 ± 6.81
	Sleep **	48.39 ± 5.79	50.67 ± 5.05	46.47 ± 5.87

NIH Toolbox for Cognition[182] was administered using the web-based and iPad versions and converted to age-corrected standard scores for comparisons[183]. Alternate test versions were used during each assessment and order of administration was randomized. Category fluency[170] (cities/towns, first names, and fruits and vegetables was assessed in a randomized counterbalanced order. Three alternative versions of the Georgia Complex Figures[184] test were administered in counterbalanced order. Self-report questionnaires of everyday memory[185], Neuro-QOL domains of Fatigue, Depression (pediatric), Global Cognition, and Sleep[186] were administered using the same format for all assessments. Significant differences comparing Post-Stim to Post-Sham performance are marked (paired t-tests were not corrected for multiple comparison) **$p \leq 0.01$ uncorrected.

Figure 10. Stimulation increased recollection accuracy in older adults.



(A)For the memory assessments, participants studied trial-unique objects paired with one of six discrete scenes or locations, in separate blocks. After a delay, recognition of the objects and recollection of the associations were assessed. (B) Participant-specific stimulation locations (one sphere per participant) were selected based on high resting-state fMRI connectivity with hippocampal target locations (one sphere per participant). (C) Before and ~24 hours after five consecutive daily sessions of full-intensity or sham stimulation, participants completed fMRI memory assessments. Stimulation-induced electrical field for each stimulation condition is displayed for a representative participant with warmer colors representing peak intensity (range: 1-119 V/m) (D) Effects of stimulation on recollection and on recognition at the ~24 hr assessment. (E) Recollection changes due to stimulation and sham. (F) Each bar represents a single participant change in recollection for stimulation and sham, demonstrating consistent improvement due to stimulation. Error bars indicate SEM. *p≤0.05 **p≤0.01 (Adapted from Nilakantan et al., 2018b)

Performance was significantly worse (T(14)=4.17, p<0.001) during the object-scene task runs compared to the object-location task runs across all six sessions (mean object-scene accuracy: 0.337 (se=0.0453), mean object-location accuracy: 0.534 (se=0.057)), yielding too few trials for reliable fMRI analysis in many participants. Thus, for the fMRI analysis, we only used data from the object-location task. Nonetheless, the pattern of effects of stimulation on memory performance in the object-location task was the same as for the combined task data presented in the Results (Figure 10DE). That is, associative recollection indicated significantly over the stimulation week (Pre-Stim versus Post-Stim: T(14)=3.22, p=0.006; Cohen's d=0.83) but not over the sham week (Pre-Sham versus Post-Sham: T(14)=1.60, p=0.13), with significant recollection improvement for stimulation relative to sham (Post-Stim versus Post-Sham: T(14)=2.61, p=0.02; Cohen's d=0.67). As was the case for the primary analysis, there was consistently no effect of stimulation on recognition (Post-Stim versus Post-Sham T(14)=0.31, p=0.76). Even though the primary fMRI analyses used data from just one task, the behavioral effects of stimulation in this task closely followed those identified when pooling data across tasks, which measured associative recollection irrespective of task format.

fMRI correlates of memory formation were measured for the targeted hippocampal-cortical network and a control frontal-parietal network, defined *a priori* based on previous findings of age-related impairments[68] (Figure 11A). Stimulation increased fMRI correlates of recollection more than recognition in the targeted versus the control network (T(14)=2.10, p=0.05, Cohen's d=0.54; Figure 11B). Relative to sham, activity increases due to stimulation were greater for recollection than for recognition in the targeted network (T(14)=2.14, p=0.05, Cohen's d=0.55, Figure 11B) but not in the control network (T(14)=0.29, p=0.78), reflecting significant and consistent increase in recollection activity for the targeted network (T(14)=2.38, p=0.03, Cohen's d= 0.61) but not the

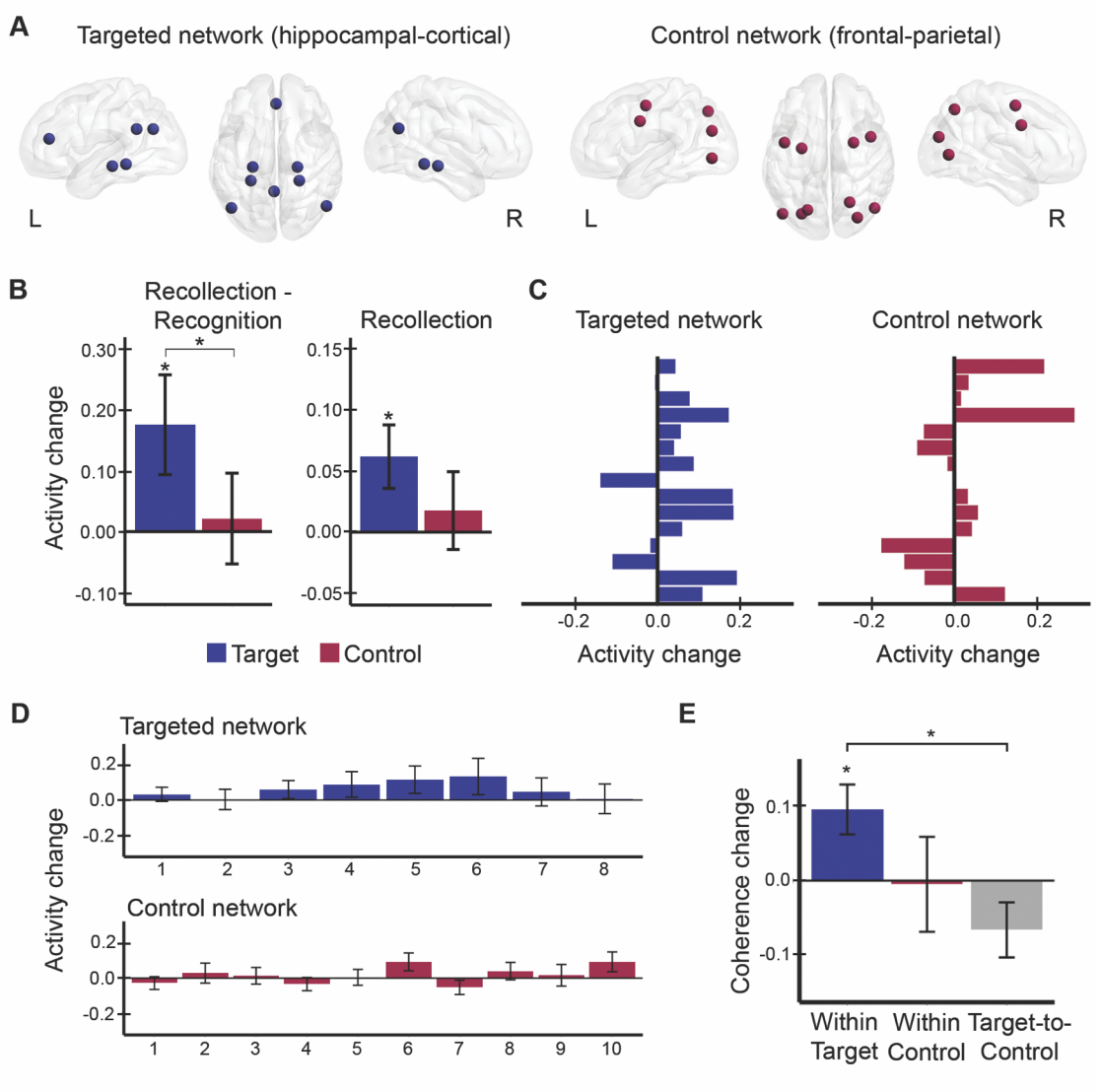
control network (T(14)=0.55, *p*=0.59), relative to sham (Figure 11C). Recognition activity did not change significantly in either network (targeted: T(14)=1.71, *p*=0.11; control: T(14)=0.07, *p*=0.95). Thus, stimulation selectively increased fMRI signals of recollection memory formation in the targeted hippocampal-cortical network, relative to recognition and to the control frontal-parietal network.

All primary fMRI analyses concerned comparisons of Post-Stim to Post-Sham sessions, and the number of available trials for fMRI analysis did not vary for these conditions (T(14)=-0.25, p=0.80). To test for possible baseline differences between weeks, the primary fMRI activity outcomes were also tested for Pre-Stim relative to Pre-Sham. This analysis was relatively weak given that fMRI data quality was relatively poor for Pre assessments, as these included the first scanning session for each participant, with significantly fewer available trials Pre-Stim compared to Post-Stim (T(14)=-2.42, p=0.03). Nonetheless, comparisons of Pre-Stim to Pre-Sham indicated no difference for recollection versus recognition accuracy in the targeted versus the control network (T(14)=0.70, p=0.50) and no difference in recollection versus recognition activity in the targeted network (T(14)=0.41, p=0.69). Thus, activity differences between recollection and recognition were selective for stimulation relative to sham.

Changes in activity coherence[168] evaluated the consistency of stimulation effects among regions comprising each network, relative to sham (Figure 11DE). Stimulation increased coherence within the targeted network (T(7)=2.85, *p*=0.02). This increase was greater than coherence changes between the targeted and control networks (T(24)=2.68, *p*=0.01). Thus, stimulation coherently increased fMRI signals of recollection memory formation among regions comprising the targeted network and these activity changes were decoupled from those occurring in the control network.

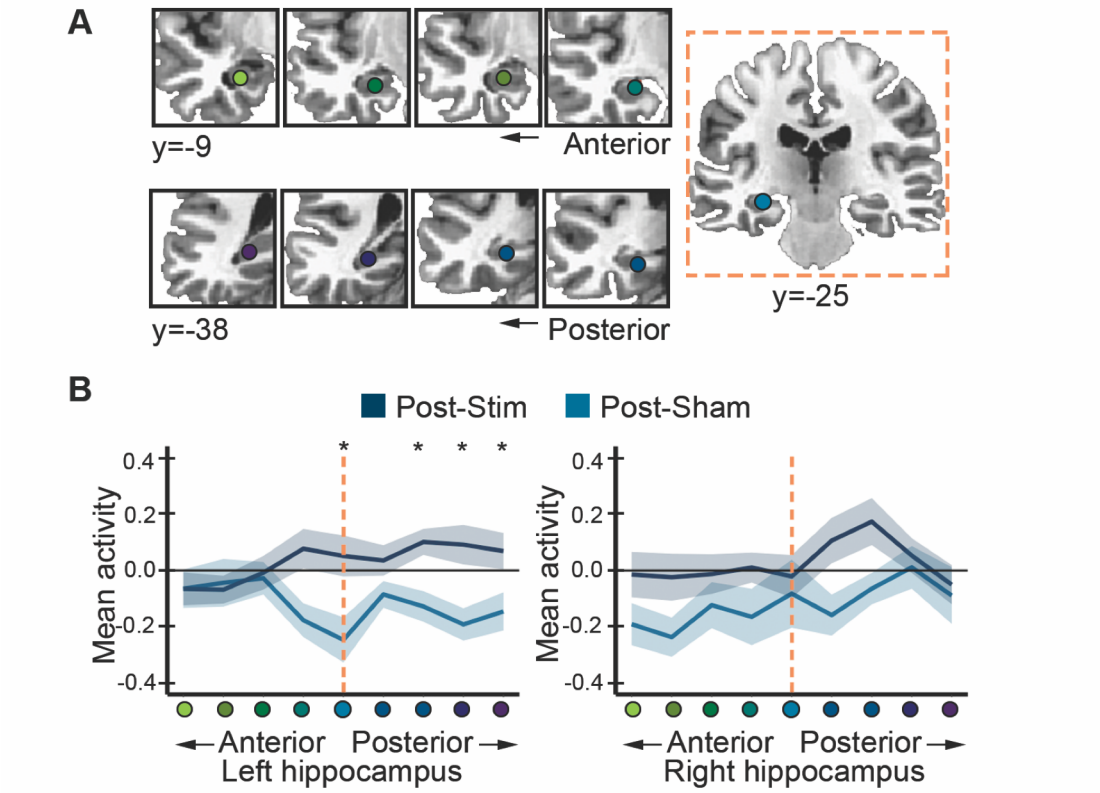
Following previous evidence for specific effects of stimulation on the targeted hippocampal segment[96], stimulation increased fMRI activity at the specific *a priori* hippocampal target (shown in Figure 10B) for recollection ($T(14)= 2.90$, $p=0.01$, Cohen's $d=0.75$), but not for recognition ($T(14)=0.43$, $p=0.68$). To assess spatial selectivity, stimulation effects were assessed along sequential segments of the anterior and posterior hippocampus relative to the target in each hemisphere (Figure 12A). For the left hippocampus, recollection activity was greater following stimulation than sham ($F(1,14)=11.06$, $p_{corr}=0.02$, $\eta_p^2=0.44$) and this relative increase for stimulation varied by segment ($F(8, 112)=2.74$, $p_{corr}=0.03$, $\eta_p^2=0.16$). Post-hoc tests indicated stimulation significantly increased activity at the target and posterior hippocampus segments (Figure 12B) relative to sham. In contrast, for recollection, there was no main effect of segment ($F(8,112)= 0.44$, $p_{corr}=1.0$) in the left hippocampus, no main effect of stimulation condition ($F(1,14)=0.63$, $p_{corr}=0.20$, main effect of segment ($F(8, 112)=1.96$, $p_{corr}=0.23$), or interaction of condition by segment ($F(8, 112)=0.77$, $p_{corr}=1.0$) in the right hippocampus. For recognition, there were no significant effects (all $p_{corr}>0.14$) in the left and right hippocampus.

Figure 11. Stimulation coherently increased network activity during memory formation.



(A) Mean fMRI activity was extracted from *a priori* selected network regions of the targeted hippocampal-cortical network and control frontal-parietal network during object-location memory formation. (B) Mean fMRI activity changes (Post-Stim versus Post-Sham) for recollection compared to recognition in the targeted network versus the control network, and for recollection alone in the targeted and control networks. (C) Each bar is a single participant's mean recollection activity change in the targeted and control networks. (D) Mean recollection fMRI activity changes (Post-Stim versus Post-Sham) for each ROI in each network (E) Mean coherence change due to stimulation within the targeted network, the control network, and between the targeted and control networks. Error bars indicate SEM. *p≤0.05 (Adapted from Nilakantan et al., 2018b)

Figure 12. Stimulation increased hippocampal activity during memory formation.



(A) Segments along the anterior-posterior long axes of the left and right hippocampus relative to the average *a priori* target in the left hippocampus (y=-25). (B) Mean recollection fMRI activity for each segment Post-Stim and Post-Sham. Error bars indicate SEM. *p≤0.05 (Adapted from Nilakantan et al., 2018b)

5-1 Discussion:

In summary, these findings demonstrate that network-targeted noninvasive brain stimulation can selectively engage the primary behavioral and neural features of memory decline in aging. In older adults, network-targeted noninvasive brain stimulation selectively improved recollection and significantly increased fMRI activity correlates of recollection memory formation in the cortical-hippocampal network. These effects on recollection were greater than the effects on recognition memory, which is not consistently impaired by aging[169], and there was no effect on fMRI activity in the control frontal-parietal network. Stimulation effects on recollection-related fMRI activity were coherent throughout the cortical-hippocampal network and occurred at the specific targeted location of the hippocampus, which is noteworthy given that recollection is strongly associated with hippocampal integrity[169] and cortical-hippocampal network function [16, 89, 174].Normative age-related reductions in cortical-hippocampal network structural and functional integrity [70, 71] therefore did not limit the ability of stimulation to affect memory functions of this network, as has been demonstrated in younger adults with presumably intact networks [96, 102, 168, 187]. These findings provide novel information on the network basis of memory function in aging because they demonstrate a causal link between recollection and a specific network in older adults. That is, alterations in cortical-hippocampal network function due to age have been hypothesized as a source of age-related memory impairments in healthy older adults, individuals with mild cognitive impairment, and those with Alzheimer's disease. These network disruptions could be caused by abnormal protein aggregation even in older adults without excessive memory impairment or dementia [188, 189]. Notably, the neurodegenerative status of our cognitively normative older adults is unknown, and this could account for some variability in stimulation outcomes. Nonetheless, the current findings validate the hypothesis that age-related

memory impairment is caused by network dysfunction by showing that functional changes of the cortical-hippocampal network due to stimulation are concomitant with corresponding changes in recollection memory. It is important to note that this study was intended to test for selective neural and behavioral target engagement, not to evaluate clinical efficacy. Indeed, our participant sample was relatively small and all testing was performed at the same site. However, our within-subject experimental design and analysis approach was intended to stringently assess the effects of stimulation. We formulated strong *a priori* hypotheses using behavioral and neural assays with high specificity to age-related decline. Similar to previous findings in young adults [96, 102, 168], effects were consistent across participants, yielding medium to large effect sizes. The effects of stimulation lasted up to 24 hours, with some evidence that it could last up to 1 week after the final stimulation session, consistent with previous findings in young adults[153]. This stimulation regimen therefore produced long-lasting improvements, especially in comparison to other studies in older adults where effects are typically measured during or immediately after the stimulation period [190]. The effects of stimulation, relative to other co-occurring memory expressions (recognition) and other cognitive networks (frontal-parietal network), are especially crucial for validating the potential for interventions of cognitive and neural function, as selective effects help mitigate influences from myriad potential confounding factors such as environment, history, material familiarity, practice, placebo, and multiple comparisons. The impact of these confounding factors can be difficult to assess in stimulation experiments that do not target specific networks or measure target engagement, and are particularly problematic for studies that combine multiple intervention modalities[190-192].

Chapter 6

Conclusions

The series of studies presented in this dissertation collectively demonstrate that recollection precision is a sensitive measure, distinct from recollection success, which is supported by the hippocampus, and can be improved via noninvasive stimulation.

Chapter 2 and Chapter 4 explore recollection precision and success in younger adults, older adults, and individuals with unilateral MTL resections. Recollection success and precision were distinguished by the functional neuroanatomical changes of healthy aging as well as by hippocampal/MTL lesions. Older adults and individuals with MTL resections demonstrated a specific impairment for recollection precision but not success, relative to younger adults. A notable strength of these studies is that we used a task that probed the associative/relational components of recollection by testing memory of associated locations in different background scenes than were studied, thereby preventing the use of perceptual recognition strategies [107-109]. In older adults, precision impairments are likely related to age-related atrophy of the hippocampus, along with possible diminished structural and functional connectivity of the MTL [68, 73, 159, 160]. Notably, resections that included hippocampal tissue produced significantly worse precision compared to resections that did not include the hippocampus, with no significant difference in success. Even though our sample size was small, these results are consistent with other patient studies that demonstrate MTL and hippocampal damage is related to impairments in precision rather than in general spatial strategy or recollection success [97, 98]. Collectively, these results support the hypothesis that that the hippocampus is responsible for high-resolution memory.

Chapter 3 and Chapter 5 use a novel experimental approach utilizing noninvasive stimulation [96], to target and unveil the causal role of hippocampal-cortical networks in recollection memory. Stimulation improved recollection precision in younger adults, and altered canonical correlates of recollection as measured as theta-alpha power, and ERP amplitude. Importantly, greater changes in correlates of recollection were related to greater memory improvements providing evidence that hippocampal-cortical network is causally related to memory precision. Remarkably, although older adults present structural and functional impairments to the network white matter connections[91] likely required for network-level responses to stimulation [70, 71], older adults also demonstrated a memory and network-activity change. That is, recollection of object-location associations improved more than object recognition after stimulation relative to sham. Moreover, stimulation increased recollection-related fMRI activity during memory encoding in the specific network that we targeted. These findings provide novel information on the network basis of memory because they demonstrate a causal link between a specific aspect of memory, recollection, and a hippocampal-cortical network in both young and older adults. The recollection precision improvements outlasted the period of stimulation by ~24 h in younger adults, and almost ~1 week in older adults, consistent with our previous demonstrations of improvements lasting up to ~2 weeks after stimulation [153]. Generation of long-lasting improvement in memory ability (rather than improved retention of specific material) has implications for the development of clinical interventions for disorders related neuro-cognitive network dysfunction [47].

The concept that the hippocampus functions to support complex bindings builds on dual-process models of memory, which are based on the idea that recollection reflects the retrieval of specific qualitative information, and is dependent on the hippocampus[19, 193, 194]. Current

computational models of hippocampal function also argue that the hippocampus is necessary for complex bindings[195]. For example, pattern separation, supported by the dentate gyrus, relies on rapid formation of distinct representations for complex configurations, and such representations are necessary for any computational system to "pattern-complete" episodic information based only on a partial cue [196, 197].

It is also important to note that recollection is usually tested using tasks that do not explicitly measure precision versus success, and such recollection tasks are consistently impaired by hippocampal damage [8, 12]. This raises the question of why performance is affected in such tasks if hippocampal impairments are relatively specific to precision. It is possible that many of these tests involve recollection of varying degrees of qualitative information, and that precision is therefore relevant to performance even though it is not specifically measured. Furthermore, although recollection precision and success are orthogonal in theory [198] and could therefore potentially be dissociated, recollection precision depends on success in our experiments and in others that have attempted to distinguish them. That is, memory for high-resolution details are not assessed (i.e., "the car was parked on the left side of the street, four blocks ahead of the first stop sign") without successful recollection (i.e., "the car was parked on the left"). Although qualitative experience of memories can vary in other sensory modalities (for example, audition, olfaction, touch), all studies that have assessed memory precision have presented and assessed stimuli in the visual domain, and it is possible that the regions and network involved may change based on stimulus modality. In addition, it may be possible to apply the concept of precision to other aspects of cognition, such as language and attention, where building distinct representations of complex models are necessary, but not typically assessed. Experiments that systematically address these questions are necessary to fully understand neural mechanisms for memory precision and how they

might relate to those of other cognitive processes. Nonetheless, the results presented in this dissertation provide evidence that precision is distinct from success, and in the case of memory, is supported by the hippocampus.

Indeed, the idea that details of recollection are quantifiable is not entirely new. A few studies have asked participants to study objects or words with increasingly number of source components, such as encoding in a male or female voice, along with color of presentation, and/or introspective semantic judgements. The amplitude of the late-positive ERP component, most associated with old/new judgements, is graded and modulated by memories with more source details [7] and less distance error in a spatial memory task [199]. Similarly, fMRI studies have shown that the magnitude of hippocampal activation correlated with the number or associated details both during encoding [200] and at retrieval [201]. However, all of these studies still assess the success of those source details in a binary manner, and do not get at the graded nature of that source content (ie., voice pitch, color gradations). Though the results from these studies align with my results, dissociating recollection precision from success is advantageous because it provides an objective and graded measure of memory in a single domain and estimates distinct memory processes within the same task.

Understanding the mechanisms of recollection precision has prompted many research studies since the start of my graduate studies. Episodic precision has been related to hippocampal function as patients with hippocampal damage were unable to recall precise locations in a virtual-maze task [97, 98], and most recently, an ECOG study related precision to high-gamma oscillatory activity in CA1 subfield of the hippocampus [202]. However, these results do contrast fMRI study that relates precision to parietal cortex activity during test [56]. A consensus position, supported by our stimulation studies [102, 103, 168], emphasizes the possible reliance of memory precision

on the distributed cortical network, rather than supported by either the parietal cortex or hippocampus alone [55].

Mechanisms that drive multi-session high-frequency stimulation effects on the cortical-hippocampal network are still unknown. TMS can only directly influence neuronal function at the cortical surface[79], however, the current findings suggest that regimens of stimulation are capable of inducing downstream trans-synaptic changes on plasticity to specific targeted networks and the cognitive functions that they support[87, 88, 94]. Increased activity due to stimulation throughout the network which has now been demonstrated in younger adults[168] and older adults[103], could suggest heightened network-specific excitability; i.e., greater response to the same category of visual stimuli during memory formation. Increased fMRI activity was also identified in the hippocampus, specifically in the targeted and posterior portions. The hippocampus has high capacity for neuroplasticity[15], and therefore could critically support these network-level changes. Stimulation induced long-term potentiation within the hippocampus has been shown to cause increased distributed cortical network excitability in rodents[203], and improved memory function has been associated with greater excitability, especially in older animals[204]. Testing the hypothesis that increased excitability in the hippocampus as a mechanism for stimulation-induced recollection improvements should be a key aim for future studies. Additional stimulation to control regions outside of the targeted network are necessary to further control potential nonspecific effects, although active control stimulation in younger adults using the same stimulation regimen had no effects on memory or its fMRI correlates[96, 102, 168]. It is also unclear if network targeting will be successful for the other large-scale networks, which may not include the hippocampus, though are critical for cognition[18] and can be negatively impacted by age and neurodegenerative disease[76].

In summary, these studies collectively demonstrate that precision is a valid measure of episodic recollection that specifically relies on the hippocampus and a distributed cortical network. Network targeted stimulation to this network improved recollection in both younger and older adults, which motivates future studies to optimize the effectiveness of noninvasive stimulation and improve our mechanistic understanding of the cortical-hippocampal networks that support episodic memory across the lifespan.

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