



Systematic Evaluation of Memory Retrieval in a Neuromorphic Model of the Hippocampus

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Abstract

Theoretical studies on memory capacity in artificial neural networks have shown the number of storable memories scale with the number of neurons and synapses in the network. As the memory capacity limit is reached, then stored memories interfere, and recall performance is reduced. A well-established neuromorphic microcircuit model was employed to systematically evaluate its recall performance as a function of stored patterns, interference, contextual information, network size, and engram cells when specific synaptic connections in the network were strengthened. The model consisted of multi-compartmental Hodgkin-Huxley-based excitatory (pyramidal) cells and two types of inhibitory neurons (bistratified cell, oriens lacunosum-moleculare (OLM) cell) firing at specific phases of a theta oscillation imposed by an external inhibitory signal targeting only the inhibitory cells in the network. Inhibitory cells inhibited specific compartments of the network's excitatory cells. Two excitatory inputs (sensory and contextual inputs) targeted dendritic compartments of cells in the network and caused cells to fire. Simulation results showed that out of six model variants tested strengthening of excitatory synapses in proximal but not basal dendrites of bistratified cells inhibiting pyramidal cells (model 1) made recall perfect. Strengthening of inhibitory synapses in pyramidal cells (model 2) made recall worst. Decreasing the number of engram cells coding for a memory pattern improved recall in a pathway-dependent way. However, increases in network size had a small effect on improving memory recall and so did increases in stored patterns. Interference between stored patterns had a detrimental effect on recall, which was reversible as the number of engram cells decreased. Changes in contextual information made recall worse confirming previous evidence that more familiar context facilitates memory retrieval.

Keywords Brain modeling · Computer model · Recall quality · Theta oscillation · Inhibition

Introduction

Memory is our most important faculty. In particular, memory retrieval enables us to retrieve our past experiences and utilize them to plan for the future. Memory retrieval has been defined as the process by which latent memory traces (engrams) are re-awakened via their interaction with external sensory or internally generated cues [1]. A memory engram

is defined as the lasting physical changes in the brain structure and state that occurred in response to an event or experience [1]. Although memory retrieval of memory engrams has been studied extensively by many notable figures (Lashley, Hebb, Milner, Penfield, McConnell, Thompson, and others) of the twentieth century memory research [2], their neurobiological substrates remained largely unknown. Very recently with the advent of cutting age molecular and circuit tools, a memory engram renaissance has been spurred [3], which allowed memory scientists to probe, target, and manipulate in rodents' distributed cell assemblies [4] (the so-called engram cells) active during memory encoding in the hippocampus and other memory-related brain areas. Suppressing engram cell activities during a memory recall test impaired memory retrieval [5–21].

Hippocampus, the site of the declarative memory engram [22, 23], has been extensively studied in the last 60 years revealing secrets about its inter- and intra-hippocampal

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anatomy, cell physiology, synaptic properties, molecular and genetic pathways, and neural network dynamics [24, 25]. Several computational brain-inspired models of hippocampal dynamics in memory formation have been proposed over the years [26–35]. Back in 2010, a neurobiologically detailed computational model of the CA1 circuit of the hippocampus was first introduced that controlled by itself memory formation (storage and recall) [34]. In the model, theta frequency-modulated inhibition was the mechanism that separated encoding and retrieval of memories in CA1 into two functionally independent processes. Different functional roles in memory formation were suggested to different forms of inhibition (somatic, axonal, dendritic). Simulation results showed that as more and more memories were stored, recall performance decreased due to interference with previously stored memories.

In this article, we systematically investigated how memory retrieval could be enhanced in the [34] model by selectively strengthening excitatory and inhibitory responses of key CA1 neurons under different experimental conditions: increases in number of stored patterns, pattern overlaps, increases in network size, and changes in engram cells' numbers coding for a memory pattern.

The remainder of this article is organized as follows:

Section [Previous Biological Models of Associative Memory](#) provides a historical overview of biological models of associative memory leading to the Cutsuridis et al. [34] study. Section [The Basis of Our Current Work](#) presents in more detail the [34] CA1 circuit model of the hippocampus. In Section [Materials and Methods](#) we present our extended version of the retrieval microcircuit of model [34], its cellular, synaptic and connectivity components, and the methods used to estimate its mean recall quality under the abovementioned conditions. Section [Results](#) provides comprehensive experiments, including performance evaluation and comparison and contrast of performance of six tested models. Section [Discussion](#) discusses the results under the prism of biological and artificial neural networks. Section [Conclusion](#) finally summarizes the work and its implications in neurodegenerative diseases.

Previous Biological Models of Associative Memory

Associative memory, the oldest artificial neural network paradigm, was first introduced by the formalism of a correlation matrix [36–40]. An exhaustive review of past computational associate memory studies is beyond the scope of this paper. Interested readers should refer to [30, 41], and [42] for reviews. Below we present a historical overview of biologically plausible computational models of hippocampal

dynamics that formed the basis of our modeling work in this paper.

In the correlation matrix, memory patterns were stored via Hebbian modification of the connections between the computing units. A memory was recalled when an activity pattern that was a partial or noisy version of a stored pattern was instantiated in the network. Network activity then evolved to the complete stored pattern as appropriate units were recruited to the activity pattern, and noisy units were removed, by threshold setting of unit activity. Memory capacity for accurate recall was strongly dependent on the form of patterns to be stored and the learning rule employed [43].

In the neural implementation of the correlation matrix in the hippocampus, formulated by Marr [44], all neurons (excitatory and inhibitory) were modeled as simple threshold neurons [45] with a resting threshold equal to one. The synaptic weights were strengthened via a Hebbian rule and the inhibitory signal that produced was proportional to the total number of nonzero elements in the input pattern and performed a division operation in the principal neuron's soma allowing this way the neurons that learned the pattern to recall it accurately.

Since Marr [44], a dramatic accumulation of knowledge about the morphological, physiological, and molecular characteristics, as well as the connectivity and synaptic properties of excitatory and inhibitory neurons in the hippocampus, has been witnessed in recent years [24, 25]. In the hippocampus, principal neurons are primarily the pyramidal neurons, which are excitatory, and they constitute 90% of all neurons in the hippocampus, whereas the remaining 10% are interneurons, primarily inhibitory, which are classified according to their morphological, physiological, molecular, and synaptic characteristics into other numerous subclasses [46, 47]. Collections of thousands of such cells then interact in microcircuits, with each microcircuit being individual machinery, which receives, processes, and transmits information. Sommer and Wennekers [48] extended the hippocampal CAM model to investigate memory capacity and retrieval under different memory loads and types of external stimulation. A clipped Willshaw learning rule [37] was utilized. Memory patterns were sequences of binary numbers (1 or 0). Each pattern was presented to a fixed number of cells in the network and each cell was active in more than one memory pattern. Inhibition worked as a global nonconstant threshold. With tonic stimulation, the addressed memory was an attractor of the network dynamics. The memory was displayed rhythmically, coded by phase-locked bursts or regular spikes. The participating neurons had rhythmic activity in the gamma frequency range (30–80 Hz). If the input was switched from one memory to another, the network activity followed this change within one or two gamma cycles. With pulsed stimulation, memories were no longer attractors and were retrieved within one or two gamma

cycles. Burst of firing became relevant for coding and its occurrence was used for discriminating related processes from background activity.

A detailed model of region CA3 of the hippocampus with pyramidal cells and two types of inhibitory neurons: basket cells and OLM cells was introduced by [26] to investigate how parameter variations affect the simulated encoding and retrieval. Nolan and colleagues [28] formulated a dentate gyrus (DG)-CA3 microcircuit model, which predicted that spike timing-dependent plasticity discriminates between known and unknown patterns by switching on and off learning. A pattern-by-pattern suppression ensured that even in unfamiliar situations, already known patterns are not relearned, whereas in familiar situations, unknown patterns could be learned. Drawing inspiration from these studies and the experimental data of Klausberger and colleagues [46, 49], Cutsuridis and colleagues [24, 29–32] advanced a series of detailed biophysical models of the hippocampal microcircuits (DG, CA3, and CA1) to investigate memory capacity, recall performance, rate and phase coding, and to propose functional roles of various types of cells in these regions under different experimental conditions (cue loading, presentation frequency, learning task, etc.). The Cutsuridis and colleagues modeling studies have been influential in computational memory research and made a number of theoretical predictions regarding the roles of various types of inhibitory interneurons in the hippocampus in memory formation (see [50] for details of these theoretical predictions).

The Basis of Our Current Work

In 2010 [34], Cutsuridis and colleagues introduced a neurobiologically detailed computational model of the CA1 circuit of the hippocampus able to control by itself the storage and

recall of patterns of new and old information arriving unpredictably. The model consisted of 100 multi-compartmental Hodgkin-Huxley-based excitatory cells (PC) and four types of inhibitory neurons (axo-axonic (AAC), basket (BC), bistratified (BSC), OLM) firing at specific phases of a theta oscillation imposed by an external inhibitory signal (medial septum (MS)) targeting only the inhibitory cells in the network. Inhibitory cells inhibited specific compartments of network's excitatory cells. Two excitatory inputs, the sensory input originating from perforant path (layer III of the entorhinal cortex (EC)) and the contextual one originating from the Schaffer collateral (CA3 input), targeted dendritic compartments of cells in the network and caused cells to fire.

The model consisted of two microcircuits: the encoding microcircuit (see Fig. 1A), and the retrieval microcircuit (see Fig. 1B), each operating at opposite and independent phases of a theta oscillation. During the encoding phase (peak of theta), the EC input had the strongest effect on the distal dendrites of AAC, BCs, and PCs [51], while the CA3 input had a weak effect on the proximal dendrites of AAC, BCs, BSC, and PCs [51]. The AAC and BCs were maximally active [49, 52] silencing the BSC and the PCs (not firing action potentials), with the latter failing to excite the OLM cells. The summed postsynaptic potentials generated in the distal PC dendrites due to the strong EC input coinciding with the postsynaptic potentials in the proximal PC dendrites due to the weak CA3 input provided a sufficient depolarized potential in the proximal PC dendrites to drive associative learning via spike timing dependent plasticity (STDP). During the retrieval phase (trough of theta), the AAC and BCs were silent [49, 52] due to MS inhibition [53]; the PCs, BSC, and OLM cells were maximally active [49, 52]; the CA3 input had the strongest effect on the proximal dendrites of the BSC and PCs [51], while the EC input had either a very weak effect on the distal dendrites of the AAC, BCs, and PCs or

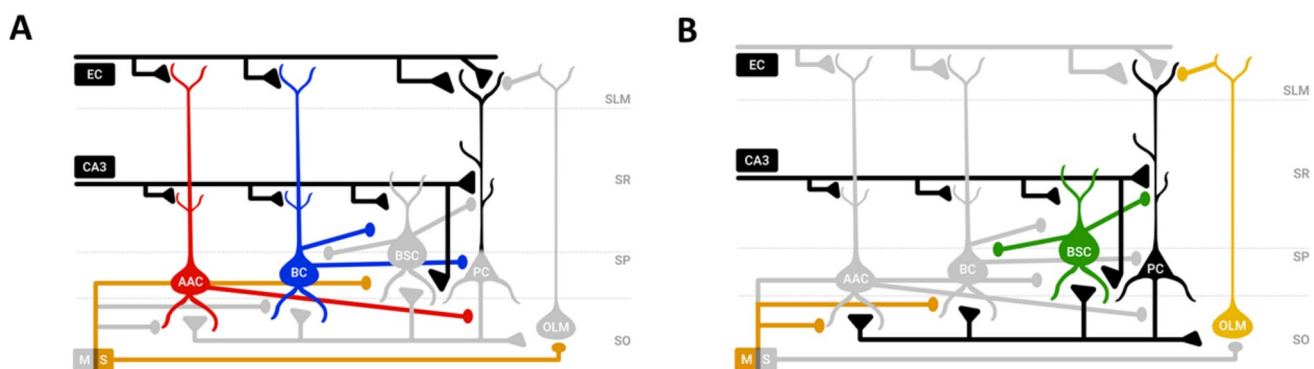


Fig. 1 Encoding (A) and retrieval (B) CA1 microcircuits showing cell types and their connectivity. Colored-filled circles, active inhibition; gray-filled circles, inactive inhibition; black-filled reverse triangles, active excitation; gray-filled reverse triangles, inactive excitation; EC, entorhinal cortex input; CA3, CA3 Schaffer collateral input; AAC,

axo-axonic cell; BC, basket cell; BSC, bistratified cell; OLM, oriens lacunosum-moleculare; MS, medial septum; SLM, stratum lacunosum moleculare; SR, stratum radiatum; SP, stratum pyramidale; SO, stratum oriens

was completely inactive [51]. During retrieval, STDP was inactive.

Cutsuridis and colleagues [34] tested the model's memory capacity and recall performance as more and more memories were stored in the network's synapses. Results showed that as more and more interfering memory patterns were stored by the network, while the network size and number of synapses remained unchanged, then its mean recall quality was reduced (see Fig. 14 in [34] and reproduced here in Fig. 2).

Materials and Methods

Starting from the results depicted in Fig. 2, the scope of this research was to uncover the extrinsic and intrinsic mechanisms and factors in the model which enhanced its memory capacity and recall performance. To do so, we extended the retrieval microcircuit (see Fig. 2) of the Cutsuridis' and colleagues' model [34] and systematically evaluated its recall performance by modulating selective excitatory and inhibitory pathways to theta-modulated cells (PCs and BSCs) active during memory retrieval.

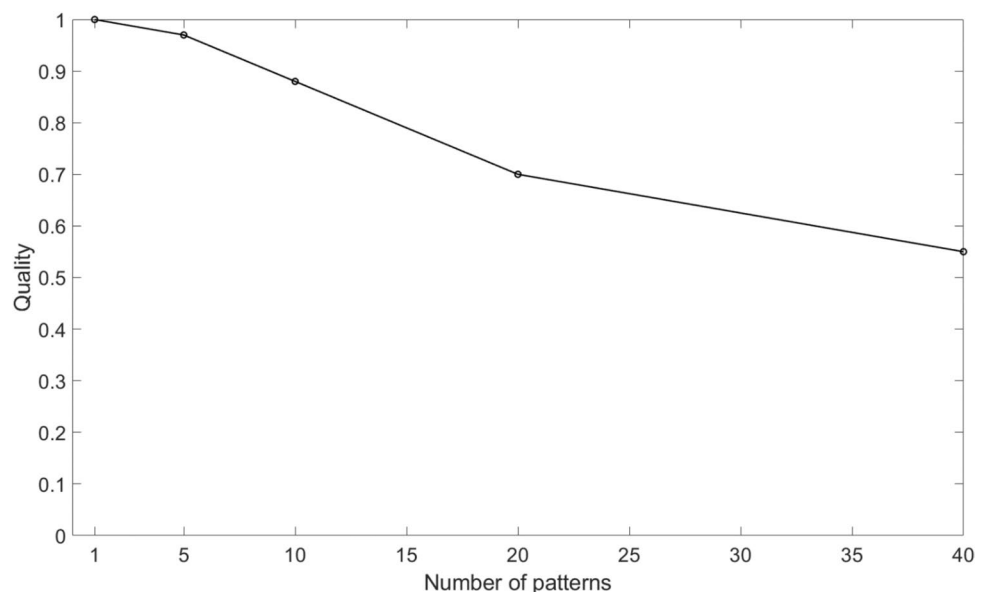
Extensions to Cutsuridis et al. (2010) CA1 Circuit Model

In this study, we removed the cellular components (AAC and BC) of the encoding microcircuit from the CA1 circuit model and kept only the cellular components (PC, BSC, and OLM) of the retrieval microcircuit. We then extended the retrieval microcircuit as follows:

- The BSC cell model had the same morphology as in the Cutsuridis et al. model [34]. For the BSC to have a fast-spiking firing pattern as in [54, 55], the A-type K^+ conductance current was removed from it. The A-type K^+ current has a fast activation and relatively fast inactivation [56]. It belongs to the threshold currents activated near the spiking threshold and it is known to produce a delay in the initiation of an action potential [56]. Thus, removal of the A-type K^+ current caused the BSC to fire action potentials faster.
- Two theta-modulated at opposite phases' populations of GABAergic MS cells were used according to the experimental evidence by [57, 58]. These two-cell population firings were added to keep in check the CA1 inhibitory cells reported to fire in opposite theta phases [46].

All other model components (PCs, OLM, EC, and CA3 inputs) remained unchanged. Simplified morphologies including the soma, apical, and basal dendrites, and a portion of the axon, were used for each cell type. The biophysical properties of each cell were adapted from cell types reported in the literature, which were extensively validated against experimental data in [54, 55, 59–61]. Details of the dimensions of cells' somatic, axonic, and dendritic compartments and distributions of passive and active conductances along these compartments can be found in Supplementary Tables 1–6 in the Supplementary Online Material (SOM). The complete mathematical formalism of the model can be found in the SOM. The parameters for the synaptic waveforms and synaptic conductances can be found in Supplementary Tables 7 and 8, respectively. Voltage traces of all cells in response to depolarizing and

Fig. 2 Average recall quality of retrieval microcircuit in [34] when recall is cued by a CA3 input alone as a function of the number of stored patterns. Recall drops with a larger number of patterns due to an increase in spurious pyramidal cell activity (reproduced with permission from [34])



hyperpolarizing current injections can be seen in Supplementary Figs. 2, 4, and 6.

Network Model

Our retrieval microcircuit model consisted of N PCs ($N=100$ (small size network) or 1000 (large size network)). The exact percentages of BSC and OLM cells in region CA1 are currently unknown. Thus, for simplicity, our retrieval microcircuit model (small size network or large size network) consisted of only 1 BSC and 1 OLM cell. Two excitatory inputs, an EC input, and a Schaffer collateral CA3 input excited the dendrites of PCs, and BSC. Inhibitory inputs from the two MS cell populations inhibited all inhibitory cells and caused them to be active in opposite phases of a theta oscillation.

Simulations were performed in NEURON [62] running on a small network of 4 personal computers with 4 CPUs each under Windows 10.

Cells

Pyramidal Cell

Each PC had 15 compartments: 1 axon, 1 soma, 3 proximal stratum radiatum (SR) dendrites, 6 distal stratum lacunosum-moleculare (SLM) dendrites, and 4 stratum oriens (SO) basal dendrites. The soma, proximal SR, and basal SO dendrites contained a passive leak current, a calcium pump and buffering mechanisms, calcium-activated slow after-hyperpolarized (AHP) and medium AHP K^+ currents, a high voltage-activated (HVA) L-type Ca^{2+} current, an HVA R-type Ca^{2+} current, a low voltage-activated (LVA) T-type Ca^{2+} current, an h current, a fast sodium and a delayed rectifier K^+ current, a slowly inactivating M-type K^+ current, and a fast-inactivating A-type K^+ current. The axon contained a passive leak current, a slowly inactivating M-type K^+ current, and a fast sodium and delayed rectifier K^+ current. The distal SLM dendrites contained a passive leak current, a fast-inactivating A-type K^+ current, and a fast Na^+ and delayed rectifier K^+ current.

Each PC received an excitatory EC input to its SLM dendrites, an excitatory input from the CA3 Schaffer collaterals to the mid-SR dendrite, an excitatory input from around 1% of other PCs in the network (recurrent collaterals) [63] in the proximal SR dendrite, six spatially distributed inhibitory inputs from the BSC in the proximal SR dendrite, and distal SLM inhibition on each distal dendritic branch from the OLM cell.

Bistratified Cell

The BSC had 13 compartments: 1 soma, 6 proximal SR dendrites, and 6 basal SO dendrites. Each compartment

contained a leak conductance, a sodium current, a fast delayed rectifier K^+ current, L- and N-type Ca^{2+} currents, a Ca^{2+} -dependent K^+ current, and a Ca^{2+} - and voltage-dependent K^+ current.

The BSC received excitation from the CA3 Schaffer collaterals in its medium SR and basal SO dendrites, excitation from active CA1 PCs in its basal SO dendrites, and inhibition from MS in its basal SO dendrites.

OLM Cell

The OLM cell had 4 compartments: 1 soma, 1 axon, and 2 basal SO dendrites. The soma contained a passive leak current, a Na^+ current, a delayed rectifier K^+ current, an A-type K^+ current, and an h-current. The axon contained a Na^+ current, and a delayed rectifier K^+ . Each basal SO dendrite contained a Na^+ current, a delayed rectifier K^+ current, and an A-type K^+ current.

The OLM cell received excitation from the PCs in its basal SO dendrites and inhibition from MS in its soma.

Model Cell Characterization

To characterize the responses of cells in the model against the responses of experimental cells, the following electrophysiological properties were calculated:

- Resting membrane potential (RMP), in units of mV , was the average membrane potential during a current injection of $0 pA$.
- Input resistance, in units of $M\Omega$, was the resistance calculated from the least hyperpolarized current injection level.
- Membrane tau, in units of ms , was computed as the time constant required for the equation $A * \exp(-t/\tau_m)$ to best fit the trajectory from the least hyperpolarized current injection level until the trace reaches steady state.
- ISI, in units of ms , was the average time interval between spike threshold time points of a regularly spiked cell when a least depolarized current level was injected to it.
- Threshold, in units of mV , was the average threshold value of the first three spikes of a regularly spiked cell when a least depolarized current level was injected to it.
- Spike amplitude, in units of mV , was the difference between the membrane potential at the peak of the action potential and the membrane potential at the threshold of the action potential, averaged for the first three spikes of a regularly spiked cell when a least depolarized current level was injected to it.
- Slow AHP amplitude, in units of mV , was the difference between the membrane potential at the most hyperpolarized potential following the action potential and the

membrane potential at the threshold of the action potential, averaged for the first three spikes of a regularly spiked cell when a least depolarized current level was injected to it.

Synaptic Properties

AMPA, NMDA, GABA-A, and GABA-B synapses were considered. GABA-A and GABA-B were present in somatic, axonic, and dendritic compartments, whereas AMPA were present only in dendritic compartments. NMDA synapses were present only in medial SR dendrites of PCs. The synaptic waveform parameter values of AMPA, NMDA, GABA-A, and GABA-B synapses can be found in Supplementary Table 7.

Inputs

An excitatory perforant path input originating from layer III of the entorhinal cortex, an excitatory input originating from CA3 Schaffer collateral PC axons and two inhibitory inputs originating from two opponent processing MS cell populations, drove the network's cells. The EC input represented the sensory input (memory pattern) to be learned during encoding (not simulated in this study). It was modeled as the firing of S ($S = 5, 10, 20$, unless otherwise stated) entorhinal cortical cells at an average gamma frequency of 40 Hz (spike trains only modeled, and not explicit cells) (see Fig. 3). The CA3 input represented the contextual information, which was associated with the sensory input during the encoding and used as “a cue” during the retrieval. It was modeled as the firing of M ($M = 5, 10, 20$, unless otherwise stated) out of N ($N = 100$ or 1000) PC at an average gamma frequency of 40 Hz (spike trains only modeled and not explicit cells) (see Fig. 3). MS inhibition was modeled as the rhythmic firing of two populations of 10 septal cells (MS_1 and MS_2) modulated at opposite phases of a theta cycle (180° out of phase) [57, 58]. Each septal cell output was modeled as bursts of action potentials using a presynaptic spike generator. Each spike train consisted of bursts of action potentials at a mean frequency of 8 Hz for a half-theta cycle (70 ms) followed by a half-theta cycle of silence. Due to 8% noise in the inter-spike intervals (ISIs), the 10 spike trains in each septal population were asynchronous.

Memory Patterns

Sets of memory patterns at different sizes (1, 5, 10, 20, 30, ..., 100, 200), pattern overlaps (0%, 10%, 20%, 40%), and number of engram cells (EngC) representing a memory pattern (5, 10, 20) were created. For example, a 0% overlap between 5 stored patterns in a set meant no overlap between any patterns (1 and 2, 1 and 3, 1 and 4, 1 and 5, 2 and 3, 2

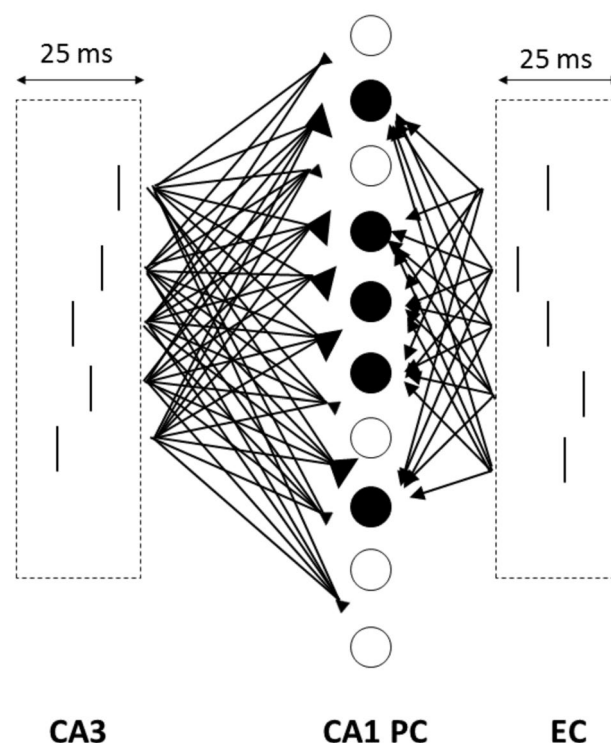


Fig. 3 Model inputs to CA1 microcircuit. EC, entorhinal cortex input (spikes) with a 25-ms jitter. A randomly selected subset of PCs (engram cells) receives the EC input. CA3, Schaffer collateral input (spikes) with a 25-ms jitter. All PCs non-selectively are excited by the CA3 input. The synaptic weights to the engram cells are stronger (large-filled reverse triangles) than the synaptic weights of other cells (small-filled reverse triangles)

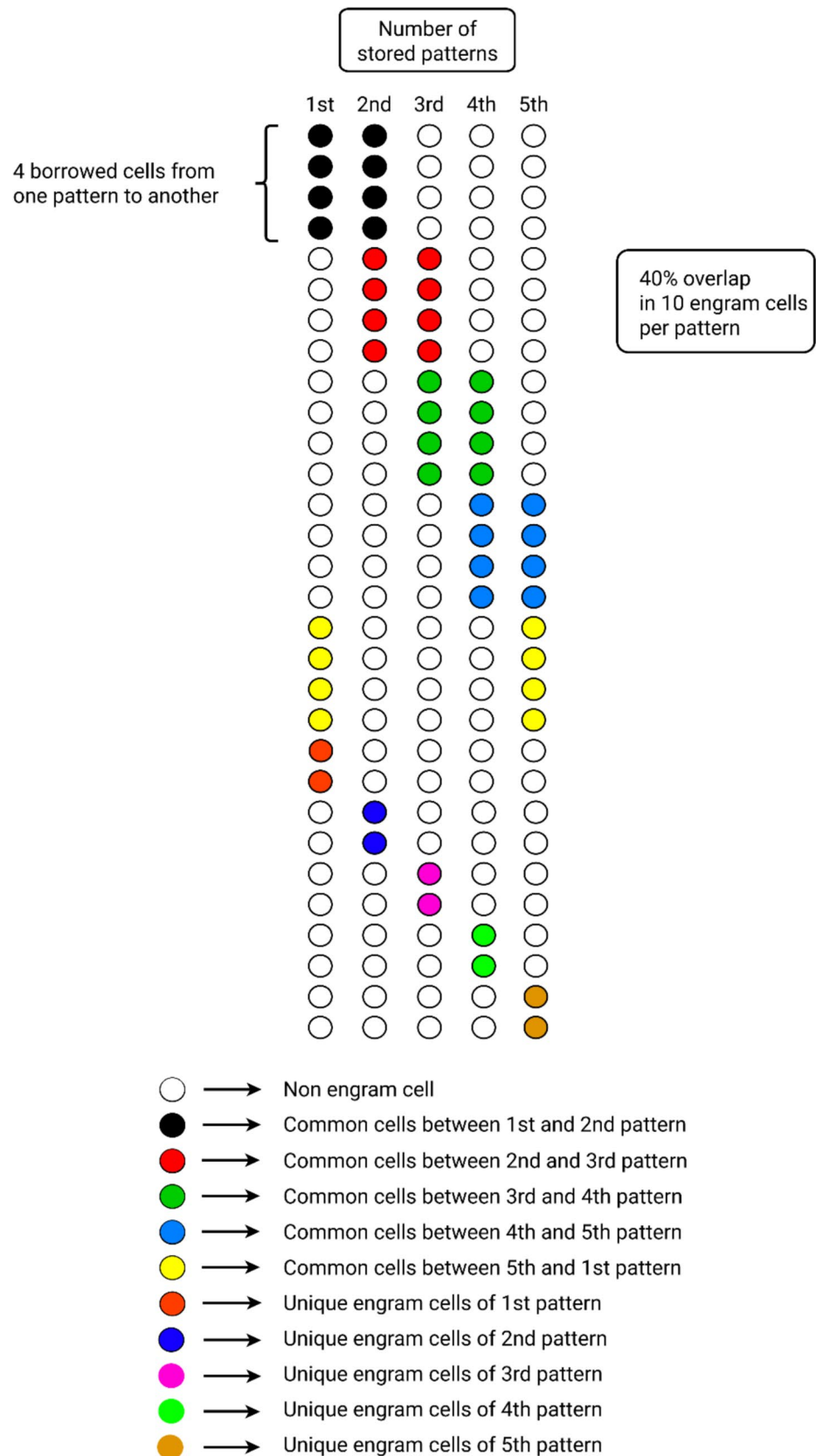
and 4, 2 and 5, 3 and 4, 3 and 5, and 4 and 5). A 40% overlap between 5 patterns in a set means that the $0.4 \cdot M$ cells shared by a pattern pair (e.g., 1 and 2) were not shared by any other pattern pair (e.g., 3 and 4 or 5 and 1) (see Fig. 4).

In a network of 1000 PCs where 20 EngCs represented a memory pattern and 40% overlap was between stored patterns, then the maximum number of patterns that could be stored by this network was 50. In a similar way, in a network of 100 PCs where 10 EngCs represented a memory pattern and 10% overlap was between stored patterns, then the maximum number of patterns that could be stored was 10. The maximum number of patterns that could be stored by these size networks (100 PCs, 1000 PCs) varied at different % overlaps and number of engram cells.

Weight Matrix

A memory pattern was stored by generating a weight matrix based on a clipped Hebbian learning rule [34]. This weight

Fig. 4 Exemplar set of five memory patterns with 40% overlap between them coded by 10 engram cells



matrix was used to pre-specify the CA3 to CA1 PC connection weights. Without loss of generality, the input (CA3) and output (CA1) patterns were assumed to be the same, with each pattern consisting of M ($M = 5, 10, 20$, unless otherwise stated) randomly chosen PCs (engram cells) out of the population of N ($N = 100$ or 1000) PCs. The $N \times N$ ($N \times N = 100 \times 100$ or 1000×1000) dimensional weight matrix was created by setting matrix entry (i, j) ; $w_{ij} = 1$ if input PC i and output PC j were both active in the same pattern pair; otherwise, weights were 0. Any number of pattern pairs could be stored to create this binary weight matrix. The matrix was applied to our network model by connecting a CA3 input to a CA1 PC with a high AMPA conductance ($g_{\text{AMPA}} = 1.5$ nS) if their connection weight was 1, or with a low conductance ($g_{\text{AMPA}} = 0.5$ nS) if their connection was 0. This approach was supported by experimental evidence favoring two-state synapses [65].

Recall Performance

To measure the recall performance of our retrieval microcircuit (network), the normalized dot product metric was used which measured the distance between the recalled output pattern, A , from the required output pattern, A^* :

$$RQ = \frac{A \cdot A^*}{\left(\sum_{i=1}^{N_A} A_i \cdot \sum_{j=1}^{N_A} A_j^* \right)} \quad (1)$$

where N_A was the number of output units. Correlation between the recalled and required output patterns took value from 0 (no correlation between output pattern $A = [1 \ 0 \ 1 \ 0 \ 1 \ 0]$ and output pattern $A^* = [0 \ 1 \ 0 \ 1 \ 0 \ 1]$) to 1 (output pattern $A = [1 \ 0 \ 1 \ 0 \ 1 \ 0]$ and output pattern $A^* = [1 \ 0 \ 1 \ 0 \ 1 \ 0]$ were identical). The higher the correlation value, the better the recall performance.

We defined mean recall quality (MRQ) of our network model as the mean value of all recall qualities estimated from each pattern presentation when a P number of patterns were already stored in the network:

$$MRQ = \frac{\sum_{i=1}^{N_p} RQ_i}{N_p} \quad (2)$$

where RQ_i was the recall quality of pattern i and N_p was total number of recalled patterns. For example, when 10 patterns ($N_p = 10$) were initially stored in the network and pattern 1 was presented to the network during recall, then a recall quality value for pattern 1 (RQ_1) was calculated. Repeating this process for each of the other patterns (pattern 2 (RQ_2), pattern 3 (RQ_3), ..., pattern 10 (RQ_{10})), a recall quality value was calculated. The MRQ of the network was then the mean value of these individual recall qualities.

Model Variation

In the retrieval microcircuit of the Cutsuridis et al. CA1 circuit model [34], the BSC inhibition to PC SR dendrites was instrumental in improving the recall performance of the model, because it acted as a global non-specific threshold machine capable of removing spurious activities (activities of cells that do not represent a memory pattern) during recall. To systematically evaluate the role of BSC inhibition in the recall performance of our extended CA1 model, we scaled the synaptic strength of selective excitatory pathways to BSC dendrites and inhibitory pathways to PC SR dendrites as more and more patterns were stored in the network:

1. Model 1: Excitatory synapse strengthening in BSC SR dendrites. These synapses are excited by feedforward excitatory Schaffer collateral CA3 input (Fig. 5A).
2. Model 2: Inhibitory synapse strengthening in PC SR dendrites. The synapses are driven by the BSC feedforward inhibition (Fig. 5B).
3. Model 3: Excitatory synapse strengthening in BSC SO basal dendrites. These synapses were driven by PC feedback excitation (Fig. 5C).
4. Model 4: Excitatory synapse strengthening in BSC SR dendrites (model 1) and inhibitory synapse strengthening in PC SR dendrites (model 2) (Fig. 5D).
5. Model 5: Excitatory synapse strengthening in BSC SR dendrites (model 1) and excitatory synapse strengthening in BSC SO basal dendrites (model 3) (Fig. 5E).
6. Model 6: Inhibitory synapse strengthening in PC SR dendrites (model 2) and excitatory synapse strengthening in BSC SO basal dendrites (model 3) (Fig. 5F).

Results

Cell Response Validation

As we mentioned in Extensions to Cutsuridis et al. (2010) CA1 circuit model section, PC and OLM cells remained unchanged. The properties (structure and ionic channel properties) are summarized in Supplementary Tables 1, 2, 5, and 6. The firing activities of PC and OLM cells in response to depolarizing pulses are depicted in Supplementary Figs. 2 and 6. On the other hand, BSC was updated to make it fire more regularly as evidenced in [54, 55]. Its properties (structure and ionic channel properties) are summarized in Supplementary Tables 3 and 4. The firing activity of BSC in response to a depolarizing pulse is depicted in Supplementary Fig. 4. Visual inspection of the simulated and biological BSC firing activities show that they are qualitatively similar. Due to lack of experimentally recorded data of a biological BSC firing activity and to quantitatively characterize

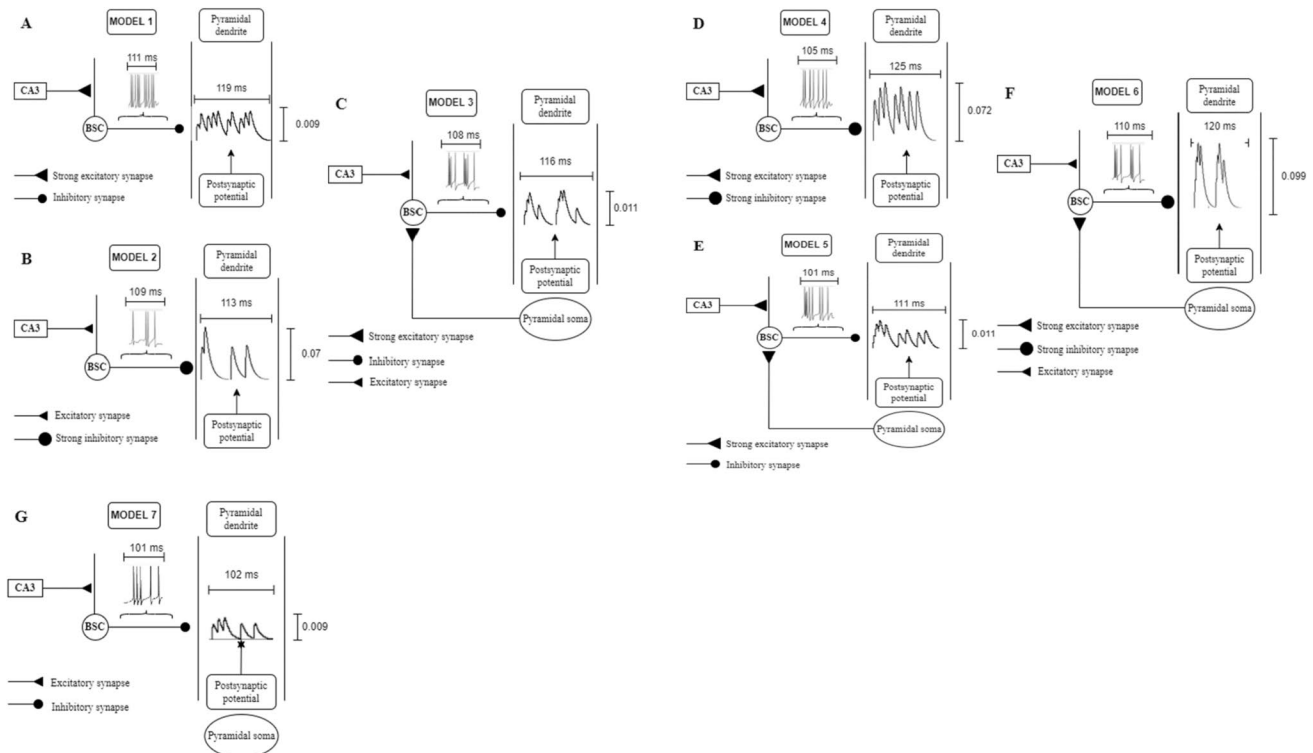


Fig. 5 Schematic drawing of “model 1” (A), “model 2” (B), “model 3” (C), “model 4” (D), “model 5” (E), “model 6” (F), and “2010 model” (G). In “model 1,” a strengthened excitatory CA3 input increases BSC firing response, which generates on PC dendrite numerous facilitated small amplitude with small duration that never decay to zero IPSPs, thus producing a very strong steady inhibitory environment which filters out spurious activities. In “model 2,” a strengthened BSC inhibitory drive to PC dendrite causes postsynaptically fewer with larger amplitude and duration IPSPs. In “model 3,” a strengthened excitatory PC feedback signal to BSC increases its firing response, which generates fewer than “model 1” IPSPs on PC dendrite, and hence a less strong, but steady inhibitory environment

its response against the response of a biological BSC, we calculated the electrophysiological properties of the simulated BSC (see Model cell characterization section) and compared/contrasted it against the properties of a biological BSC. These results are depicted in Supplementary Table 9.

Small Network Performance

Without EC Input

A set of memory patterns were stored in the PC SR dendrites of each of the six models by generating a weight matrix based on a clipped Hebbian learning rule (see “[Weight matrix](#)” section) that prespecified the CA3 to CA1 PC connection weights. To test recall of a previously stored pattern, a cue in the form of spiking of active CA3 inputs (those belonging to the pattern) distributed within a 250-ms time window is applied. The entire cue pattern was repeated at

than “model 1.” In “model 4,” a strengthened excitatory CA3 input to BSC dendrite and a strengthened BSC inhibitory drive to PC dendrite cause more with a larger amplitude and smaller duration than “model 2” IPSPs on PC dendrites. In “model 5,” a one-third in strength excitatory CA3 input and a strengthened excitatory feedback PC input to BSC dendrite cause a similar to “model 3” inhibitory environment, which removes spurious activities. In “model 6,” a strengthened BSC inhibitory drive to PC dendrite and a strengthened excitatory PC feedback signal to BSC produces the largest in amplitude and duration IPSPs in PC dendrite. In “2010 model” [34], no synapses were strengthened

40 Hz frequency (see Fig. 3). EC input to SLM dendrites was absent in these simulations. Figure 6 depicts the MRQ performance of the 2010 model [34] and models 1–6 as a function of the number of stored patterns. Error bars in Fig. 6 indicate min–max values of recall quality (RQ) (right y-axis). For small number of engram cells (EngC = 5), all models displayed perfect mean recall quality (MRQ ~ 1) regardless of percent overlap and number of patterns stored. When the number of engram cells is increased (EngC = 20), then MRQ was pathway and percent overall dependent. MRQ was nearly perfect (> 0.95) for all models at 0% overlap. However, MRQ for models 3–6 and 2010 dropped to 0.8 at 40%, whereas for model 2 the performance was approximately 0.63 at 40%. In all conditions, model 1 had the best recall performance (MRQ = 1) compared to models 2–6 regardless of the number of stored patterns (StoPat = 1, 5, 10, 20), % overlap (0% and 40%), and number of engram cells (EngC = 5 and 20) coding for a memory pattern.

Effects of Inhibitory Cloud in Recall Performance

In the previous simulations (see Fig. 6), BSC provided a strong inhibitory environment (6 GABA-A and 6 GABA-B synapses) in the PC SR dendrites. Here, we systematically varied the number of GABA (GABA-A or GABA-A/GABA-B) synaptic contacts to these dendrites of all PCs in the small network to investigate the effects of BSC dendritic inhibition in the recall performance of the six models. The synaptic waveform parameter values of GABA-A and GABA-B receptors can be found in Supplementary Table 7. The synaptic conductance values of GABA-A and GABA-B synapses in the PC medium SR dendrites can be found in Supplementary Table 8.

Figure 7 depicts the effects of 6, 4, and 2 GABA-A synaptic contacts on the MRQ performance of each of the six models as a function of % overlap between stored patterns when $\text{EngC} = 5$ or 10 and $\text{StoPatt} = 10$, respectively. In these simulations, the number of GABA-B synaptic contacts remained unchanged (6 GABA-B synaptic contacts). Simulations showed that reducing the number of GABA-A synaptic contacts had no effect on the MRQ of models 1–6 regardless of the number of stored patterns, % overlap, and number of engram cells.

Next, we varied the number of GABA-A and GABA-B synaptic contacts. Since GABA-A has no effect on the models' performances, then it is expected any effect depicted in Fig. 8 to be due to GABA-B inhibition. Figure 8 depicts the effects of 6 and 2 GABA-A/GABA-B synaptic contacts on the performances of each of the six models as a function of % overlap among stored patterns when number of stored patterns is 20 or 5 and number of EngCs is 5 or 20, respectively. When the number of EngCs was small ($\text{EngC} = 5$), reducing the number of GABA-A/GABA-B synapses had little effect on the recall performance of all six models. However, when the number of EngCs increased ($\text{EngC} = 20$), reducing the

number of GABA-A/GABA-B synapses had a detrimental effect on recall performance in a pathway-dependent manner. In models 2–6, the MRQ drop was between 1.5 and 20% particularly when overlap increased (20% or 40%).

With EC Input

In these simulations (Fig. 9), EC input to SLM dendrites was present. EC input degree of similarity with the cue pattern was set either at 0%, 40%, or 100%. In the case of $\text{EngC} = 5$, with no EC input present, MRQ for models 1–6 was perfect when 20 patterns were stored. When the EC input was 100% similar to the cue pattern, MRQ continued to be perfect for models 1–6, because the EC input operated as a boosting signal to the activity to the engram cells coding for the cue pattern. When EC was 40% similar with the cue pattern, then the MRQ dropped in all six models (see Fig. 9A). When EC was 100% dissimilar to the cue pattern, then the MRQ became almost perfect again (as in the case when EC input was absent).

When more engram cells coded for a memory pattern ($\text{EngC} = 20$) in the absence of any EC input (see Fig. 9B), models 2–6 MRQ was low (ranging from 0.65 to 0.8). Model 1 recall was perfect. When EC input 100% similar to cue pattern was presented, then the recall performance in models 2–6 improved (see Fig. 9B). When EC was 40% similar to the cue pattern, then the recall performance decreased in all six models. When EC was 100% dissimilar to the cue pattern, then the performance decreased even more.

Transfer Learning

Our task here was to examine the recall performance of all six models ("Models 1–6") on an already stored memory when exposed to a new context (transfer learning) and how the similarity of contexts affects MRQ in these models [64].

Fig. 6 Mean recall quality (MRQ) (left y-axis) as a function of stored patterns (StoPatt) with 0% (top-left), and 40% (top-right) overlap and 5 (top) and 20 (bottom) engram cells (EngC) coding for a memory pattern for the Cutsuridis et al. (2010) model (canonical model) and all six model variations (see section "K. Model variation") in a small network ($N_{\text{PCs}} = 100$). Error bars indicate min-max RQ values (right y-axis)

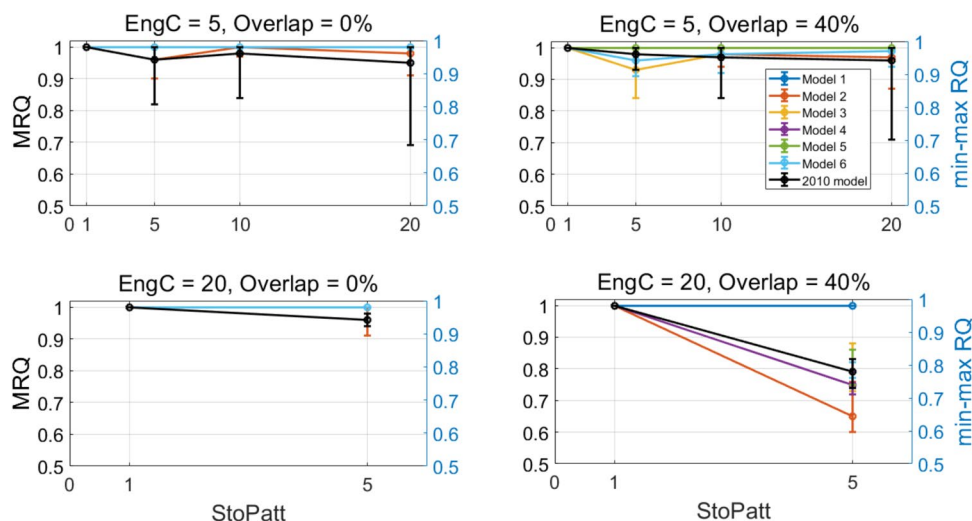
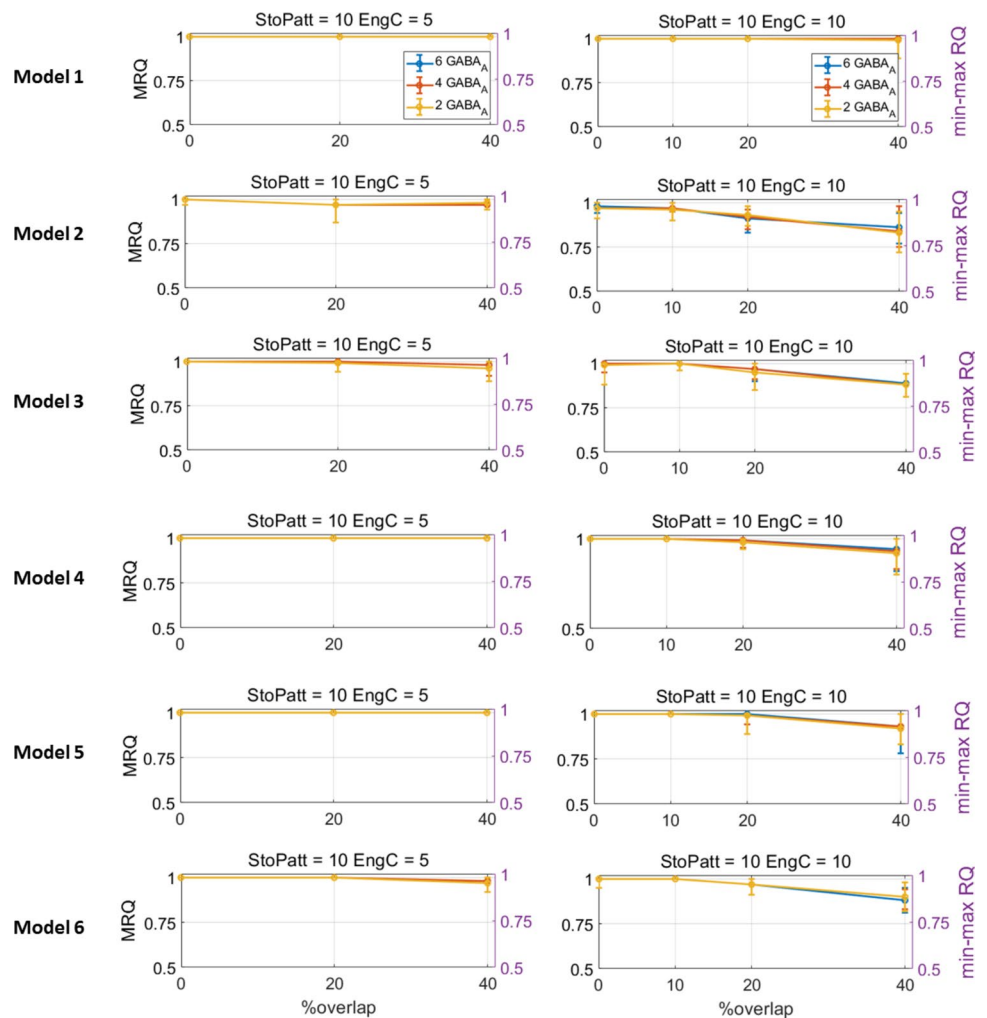


Fig. 7 Mean recall quality (MRQ) (*left y-axis*) as a function of percent overlap between stored patterns for all six models with six, four, and two GABA-A and six GABA-B synapses in the medial SR PC dendrite in a small network ($N_{PC} = 100$) when the number of stored patterns (StoPatt) and engram cells (EngC) was 10 and 5 (left column), and 10 and 10 (right column), respectively. Error bars indicate min-max RQ values (*right y-axis*)



Past studies have shown that a required memory could be retrieved more accurately when it is associated with its context [66], and disconnections between the contextual information and related memories impaired memory retrieval [67].

To quantitatively investigate the effect of different contexts on memory retrieval, we created two weight matrices as described in section “**Weight matrix**” with varied degree of similarity between them (100% similar, or 14–20% similar, or 2–10% similar) (see Fig. 10E). We considered each weight matrix to represent a different context. A set of memory patterns were extracted from one of these matrices. We then applied the other weight matrix to each model’s SR synapses as described in section “**Weight matrix**” and tested each model’s MRQ.

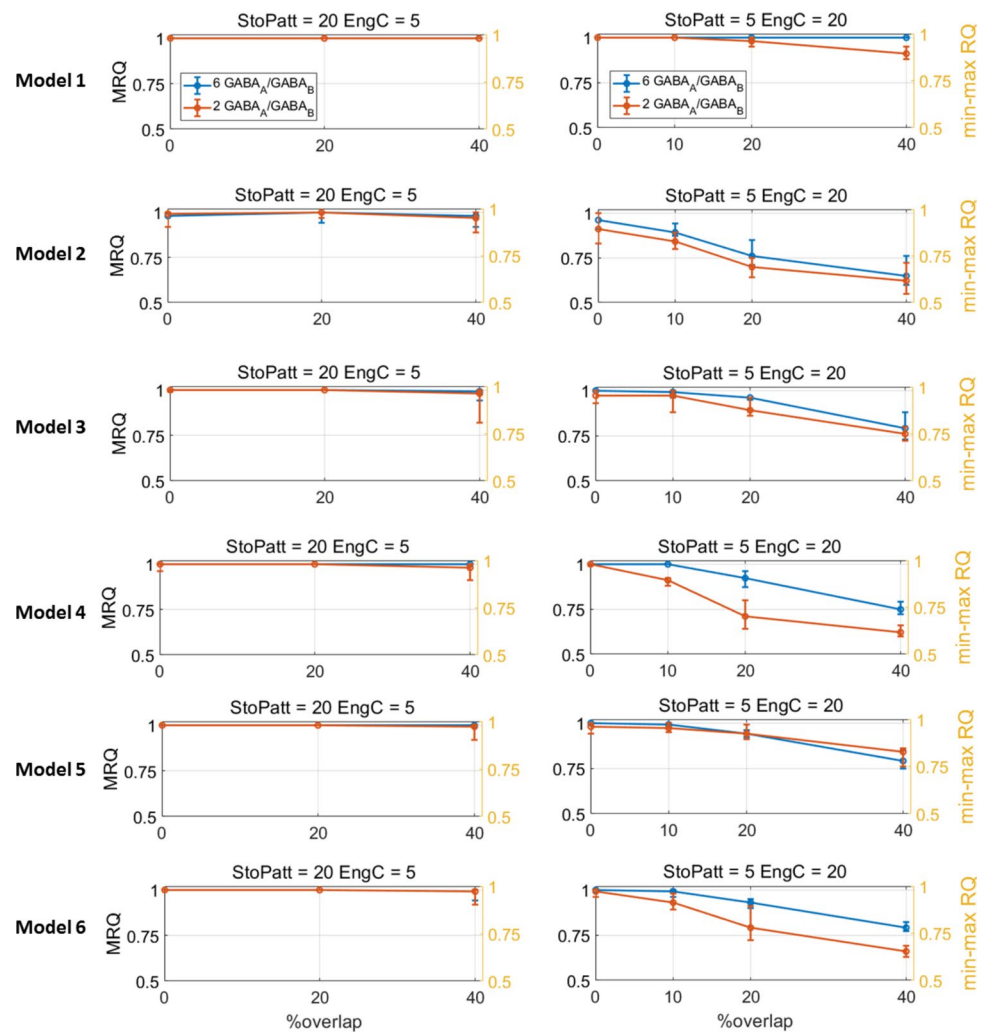
In the absence of an EC input as the similarity between the two weight matrices was reduced, then the mean recall quality decreased in all six models. How small or large was this recall quality reduction depended on how many engram cells coded for a memory. When only 5 engram cells coded for a memory and 20 patterns with 40% overlap between them were stored in the network, then mean recall quality

was very low (ranged from 0 to 15% at 14–20% similarity, and 0 to 5% at 2–10% similarity) (see Fig. 10A). When 20 engram cells coded for a memory, but only 5 patterns with 40% overlap between them were stored in the network, then mean recall quality reduction was not so severe for some models (ranged from 0 to 40% at 14–20% similarity, and 0 to 20% at 2–10% similarity) (see Fig. 10B).

When the same to the cue pattern EC input was presented, and because the EC signal acted as a booster to the activities of the engram cells, then the mean recall quality reduction trend was smaller: ranged from 20 to 75% at 14–20% similarity, and 7 to 50% at 2–10% similarity when the number of engram cells was small ($EngC = 5$) (see Fig. 10C). When the number of engram cells was large ($EngC = 20$), mean recall quality ranged from 65 to 80% at 14–20% similarity, and 50 to 70% at 2–10% similarity (see Fig. 10D).

As before, error bars represented min-max RQ values (right y-axis). It is evident from Figs. 10A and 10B that the higher the number of engram cells, the more complex is the weight matrix, then the higher is the amount of contextual information available to retrieve the required information.

Fig. 8 Mean recall quality (MRQ) (*left y-axis*) as a function of percent overlap between stored patterns for all six models with six, and two GABA-A/GABA-B synapses in the medial SR PC dendrite in a small network ($N_{PC} = 100$) when the number of stored patterns (StoPatt) and engram cells (EngC) was 20 and 5 (left column), and 5 and 20 (right column), respectively. Error bars indicate min-max RQ values (*right y-axis*)



Effects of Network Size on Recall Performance

We tested the effects of a tenfold network size increase ($N = 1000$ PCs) to the recall performance of each of the six models (see Figs. 11 and 12). The conductance parameter values (see Supplementary Table 8) remained unchanged. The findings observed in the small network were replicated in the large network. For small number of engram cells ($\text{EngC} = 5$), all six models in the small ($N_{PC} = 100$) and large ($N_{PC} = 1000$) networks displayed perfect recall quality ($\text{MRQ} \sim 1$) regardless of percent overlap and number of patterns stored. As the number of engram cells increased ($\text{EngC} = 20$), recall performance was dependent on modulated pathway (model) and % overlap. Perfect recall was maintained at only 0% overlap between stored patterns, and it was independent of the number of patterns stored. When interference between stored patterns was strong (40% overlap), then mean recall performance showed slight improvement for models 2–6 in the large network compared to the small network. Overall, we confirmed past evidence that showed the larger

the network, the less interference between stored patterns, and the better the recall quality. The positive effect of the network size to the recall quality was true only when the number of engram cells coding for a memory is large ($\text{EngC} = 20$). In the case where the number of engram cells coding a memory is small ($\text{EngC} = 5$), then any network size increase ($N = 100$ to 1000) has a minimal effect in recall performance. Instead, the number of engram cells dominates the effect on the recall performance which is always perfect regardless of modulated pathway (model), stored patterns, and % overlap between patterns.

Discussion

A number of questions present themselves. What is a memory? How many engram cells can faithfully represent a memory? Does the number of engram cells coding for a memory pattern affect memory retrieval? Do increases in the number of stored patterns, overlap, and network size

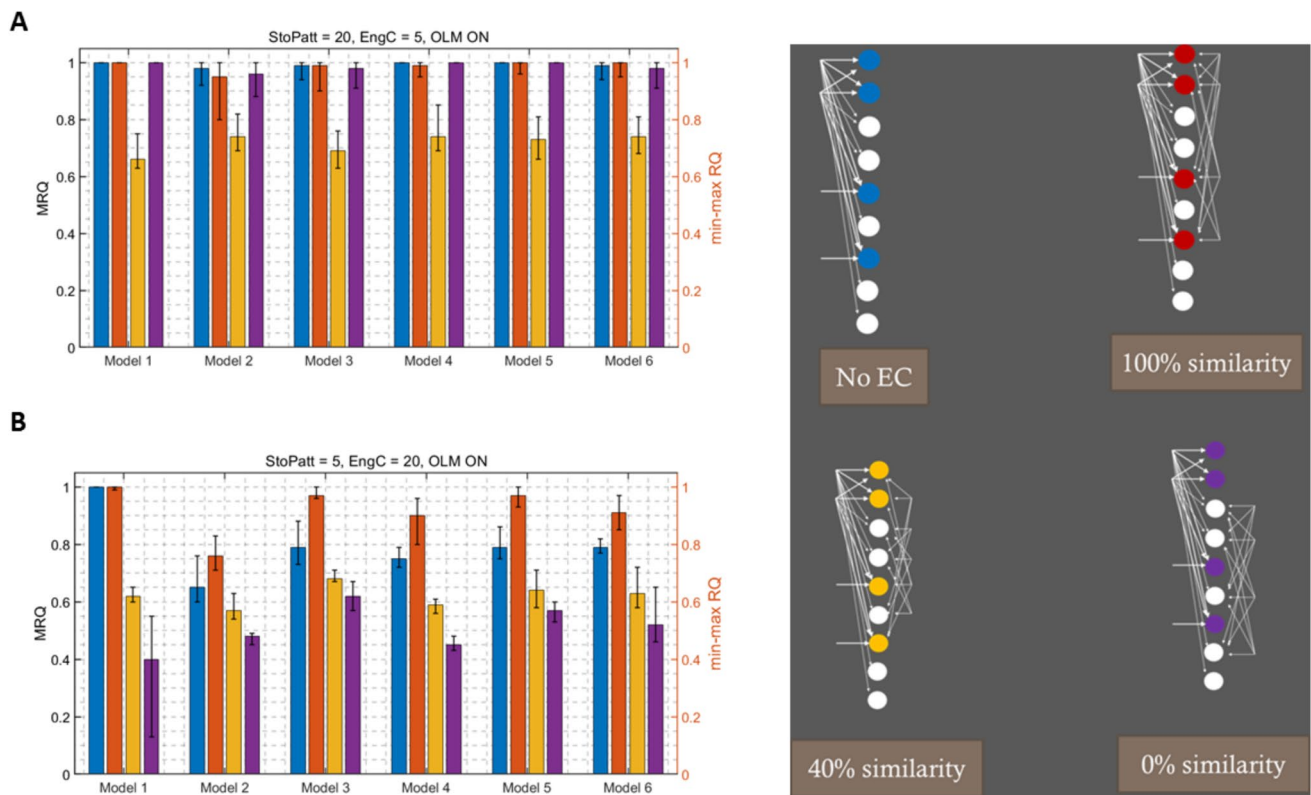


Fig. 9 Mean recall quality (MRQ) (left y-axis) for all six models when (A) 20 memory patterns with 40% overlap were stored and 5 engram cells coding each of these memory patterns, and (B) 5 memory patterns with 40% overlap were stored and 20 engram cells coding each of these memory patterns. Error bars indicate min-max RQ

values (right y-axis). *OLM ON*, OLM inhibition inhibited the LM dendrites of all PCs in the network ($N_{PC} = 100$). *Blue bar*, without EC input. *Red bar*, EC input was 100% similar to cue pattern. *Yellow bar*, EC input was 40% similar to cue pattern. *Purple bar*, EC input was 100% dissimilar to the cue pattern

affect recall? How does scaling of specific excitatory and/or inhibitory synaptic pathways affect memory retrieval? How does simultaneous encoding of a pattern and retrieval of another pattern affect the latter's retrieval process? How does transferred past acquired knowledge affect the retrieval of newly acquired knowledge? Our modeling study has provided answers to these important questions.

The nature of memory has baffled neuroscience since the dawn of time. Studies including our own [16, 24, this study] have shown that memory is the activity of the same sparse group of neurons (engram cells) activated in response to (sensory) stimuli during encoding and retrieval [68–70]. Studies have shown that the same network of neurons in the hippocampus, amygdala, and cortex active during context fear conditioning (learning) was found to be active during retrieval of the same memory 2 days later [71]. Other studies have shown that selective silencing of a neuronal population that encoded a fear memory trace has been shown to erase or inactivate the fear memory trace [12, 72, 73]. Suppressing the activities of engram cells coding for a memory, but not those of other cells, during a memory recall test impaired memory retrieval [5–18]. But how many engram

cells in a neuronal population can faithfully represent a memory? And how is memory retrieval affected when the number of engram cells changes? Computational models are instrumental at answering such experimentally challenging to control questions. Our computational study showed that as the number of engram cells coding for memories in a network decrease, then memory retrieval is improved even as the number of stored patterns increases and even when patterns strongly interfere with one another (e.g., 40% overlap) (see Figs. 11 and 12 for comparison in a small and large network). This is because as the number of engram cells decreases, then the memory capacity of the CA3-CA1 connection weight matrix increases (the weight matrix has fewer strengthened synapses) (more “0’s” and less “1’s”), so interference effects between stored patterns decrease. As the number of engram cells coding for a memory is increased, then the network weight matrix is populated with more “1’s” and fewer “0’s,” and hence, interference between stored patterns dominates and recall performance worsens. We found this finding to be depended on which type of synapse (excitatory or inhibitory) on which type of neuron (inhibitory (BSC) or excitatory (PC)) is strengthened (scaled).

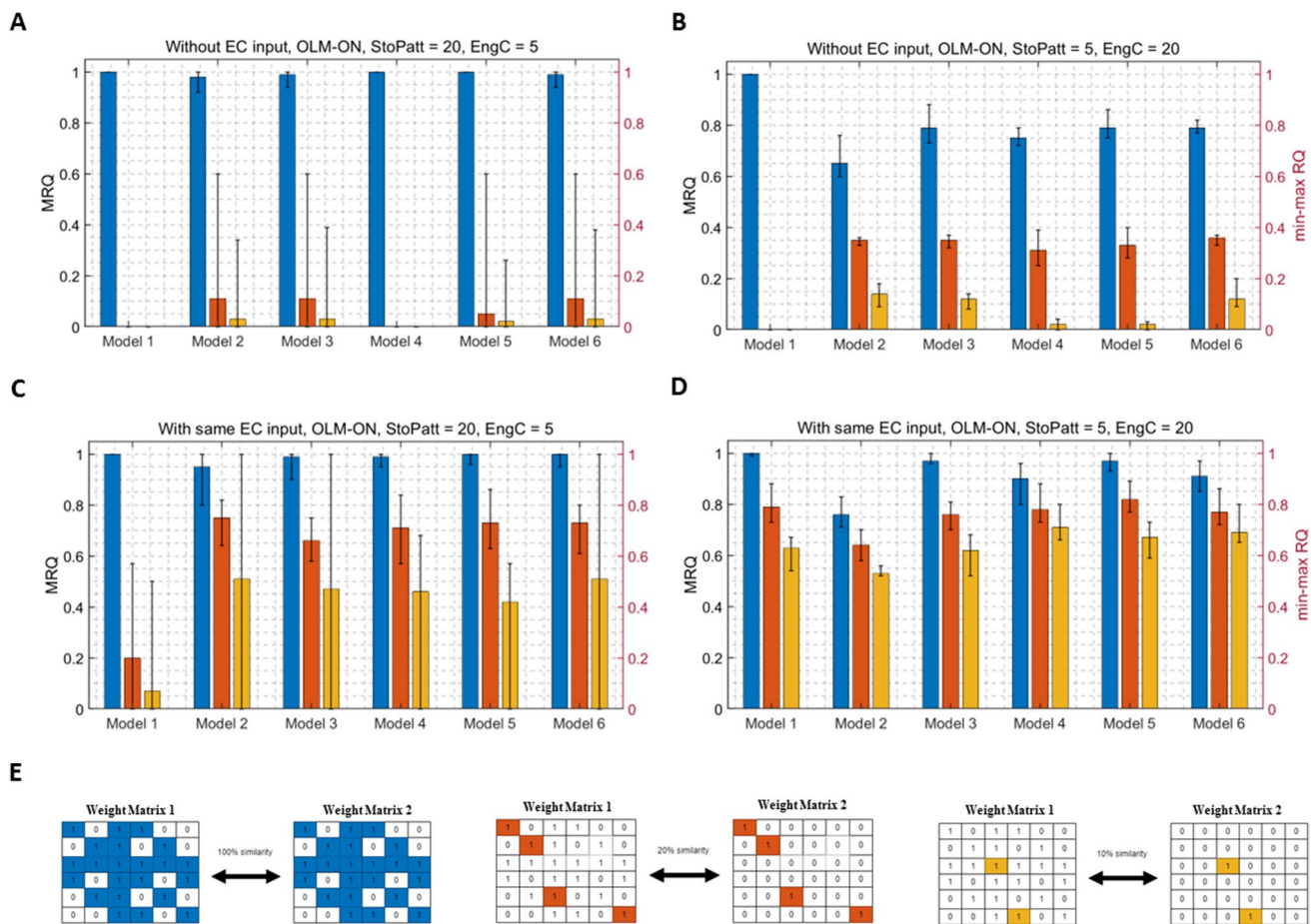


Fig. 10 Mean recall quality (MRQ) (left y-axis) during transfer learning for all six models when (top) in the absence of EC input (A) 20 memory patterns with 40% overlap were stored and 5 engram cells coding each of these memory patterns, (B) 5 memory patterns with 40% overlap were stored and 20 engram cells coding each of these memory patterns, and (bottom) when EC input exciting the LM dendrites of PCs was 100% similar to cue pattern (C) 20 memory patterns with 40% overlap were stored and 5 engram cells coding each of these memory patterns, (D) 5 memory patterns with 40% overlap were stored and 20 engram cells coding each of these memory pat-

terns. Error bars indicate min-max RQ values (right y-axis). OLM ON, OLM inhibition inhibited the LM dendrites of all PCs in the network ($N_{PC}=100$). Weight matrix, CA3-CA1 connectivity matrix. Blue bar, “Weight Matrix 1” from which cue pattern is extracted is 100% similar to “Weight Matrix 2.” Red bar, “Weight Matrix 1” from which cue pattern is extracted is 14–20% similar to “Weight Matrix 2.” Yellow bar, “Weight Matrix 1” from which cue pattern is extracted is 2–10% similar to “Weight Matrix 2.” E Examples of “Weight Matrix 1” and “Weight Matrix 2” at 100%, 20%, and 10% similarity between them

Fig. 11 Mean recall quality (MRQ) (left y-axis) as a function of stored patterns (StoPatt) with 0% (up) and 40% (down) overlap and 5 (left) and 20 (right) engram cells per pattern (EngC) for all six models in a small network ($N_{PC}=100$) (blue) and large network ($N_{PCs}=1000$) (orange). Error bars indicate min-max RQ values (right y-axis)

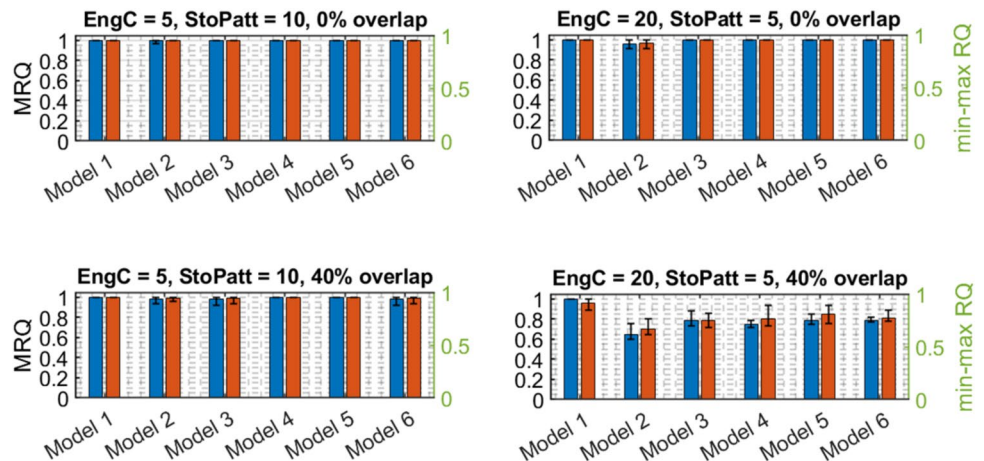
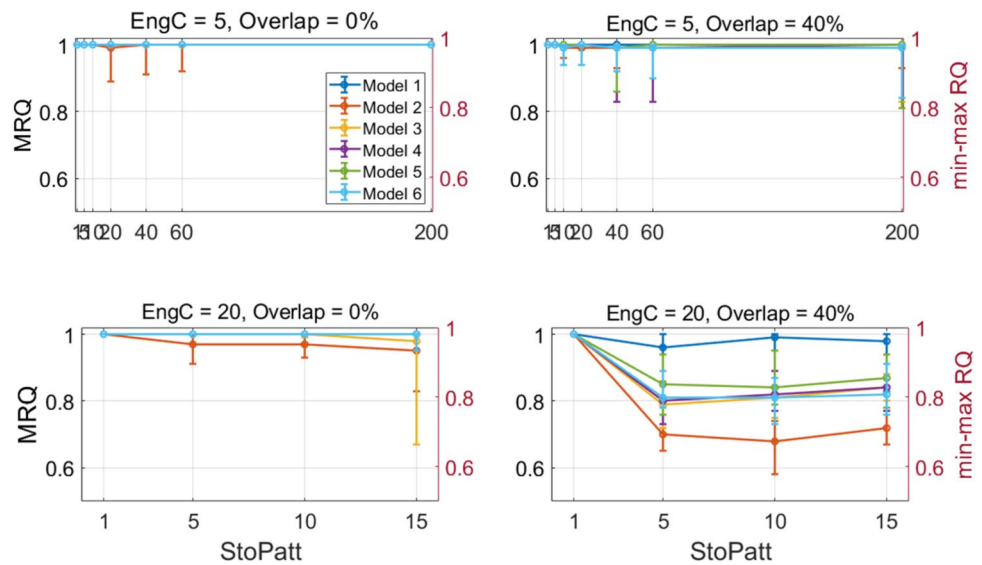


Fig. 12 Mean recall quality (MRQ) (left y-axis) as a function of stored patterns with 0% (left) and 40% (right) overlap and engram cells (EngC) coding for a memory pattern for all six models in a large network ($N_{PCs} = 1000$). Error bars indicate min-max RQ values (right y-axis)



Strengthened excitatory synapses on BSC's proximal dendrites ("model 1") led to an excellent recall performance in a network of engram cells (PCs) across all conditions ("engram cells," "stored patterns," "degree of overlap," "network size"). Strengthened inhibitory synapses on PC's proximal dendrites ("model 2") led to the worst recall performance. Models' 3–6 recall performances were somewhere between "model 1" and "model 2."

Why was "model 1" performance so consistently better than all other models across all conditions? Why the recall quality of "model 1" was always nearly perfect ($RQ \sim 1$) even when more patterns were stored in the network, more/fewer engram cells were used to represent a memory and greater interference between patterns was used? As we described in section "Model selection" and above, "model 1" was the strengthening of excitatory synapses in BSC proximal dendrites, while keeping all other synapses in the network fixed. "Model 3" was the strengthening of excitatory synapses in BSC basal dendrites, whereas "model 2" was the strengthening for inhibitory synapses in PC proximal dendrites while keeping all other synapses in the network fixed. "Model 4" was the combination of "model 1" and "model 2," "model 5" was the combination of "model 1" and "model 3," and "model 6" was the combination of "model 2" and "model 3." In all simulations, "model 1" outperformed "model 3" across all conditions (degrees of overlap and number of engram cells). This was because in "model 1," BSC was excited by CA3-PCs at high frequency (~ 40 Hz), whereas in "model 3," BSC was excited by CA1-PCs firing at theta frequency (~ 4 Hz). Since in "model 1," the BSC firing activity is higher (in frequency) than in "model 3," then the postsynaptic inhibitory effect of BSC on the PC dendrites in "model 1" is more sustained (in frequency and duration (but not in amplitude)) than in "model 3" (see Fig. 5A & 5

C). Thus, "model 1" is more successful at removing spurious activities and improving recall quality than "model 3." In "model 2," the BSC activity is lower in frequency than in "model 1" and "model 3" (see Fig. 5A, 5B, and 5C), and thus less sustained postsynaptically. The amplitude of the inhibitory postsynaptic potentials (IPSPs) on the PC dendrites compared to the IPSP amplitudes in models 1 and 3 is greater, but fewer such IPSPs are generated (see Fig. 5B). Each IPSP decayed to almost zero before another IPSP was generated. As expected, "model 4" and "model 5" performed better than "model 6" and "model 3," because their IPSPs generated on the PC dendrites showed stronger facilitation (frequency and duration) with very few decays to zero (see Fig. 5C, 5D, 5E, and 5F). In other words, a stronger and more sustained (fewer decays to zero) inhibitory cloud can remove spurious activity more efficiently than a less sustained one with greater amplitude and many zero-decays and thus improve memory retrieval.

This is further evident when looking at the models' recall performance variability (error bars in Figs. 6–12). Variability in their performances was due to noise in the ISIs of either (1) the EC excitatory input, or (2) the CA3 excitatory input, and (3) the MS inhibitory input. As described in sub-section F of Sect. 4, EC was modeled as the firing of S ECs at an average gamma frequency of 40 Hz, whereas CA3 was modeled as the firing of M out of N PCs at an average gamma frequency of 40 Hz. A 2% noise in the ISIs of the EC and CA3 spikes was considered. MS inhibition was modeled as bursts of action potentials with 8% noise in the inter-spike intervals at a mean frequency of 8 Hz for a half-theta cycle followed by a half-theta cycle of silence. Due to these sources of noise, all six models (model 1–6) tested demonstrated variability in their recall performances under various conditions (see error bars in Figs. 6–12). Error

bars indicated min–max RQ values. Model 2 demonstrated consistently the worse recall performance across all conditions and the most variable one. As we explained above, this was due to (1) BSC having on average the lowest frequency response, and (2) postsynaptically BSC produced on average fewer IPSPs with the smallest above zero duration compared to other models (see Fig. 5). ISI noise in the CA3 input exciting the BSC dendrites caused variability in the BSC firing response, at times firing fewer than average action potentials, and other times firing more than average action potentials. Thus, the majority of times the inhibitory cloud generated by “Model 2” in the PC SR dendrites was less successful at removing spurious activity, and hence, “Model’s 2” recall performance was the worst.

Which type of inhibition (GABA-A or GABA-B) is more successful at removing spurious activity and improving recall performance? Is this success depended on how many engram cells code for a memory? Systematic reduction of just GABA-A inhibition (6 GABA-A vs 4 GABA-A vs 2 GABA-A), while leaving intact GABA-B inhibition, had very little effect on the memory retrieval regardless of the number of engram cells coding for a memory (see Fig. 7 for details). This was because the strong inhibitory cloud necessary to remove any spurious activity was maintained by the intact GABA-B inhibition. On the other hand, when we systematically reduced GABA-A and GABA-B inhibition (6 GABA-A/GABA-B vs 2 GABA-A/GABA-B) (see Fig. 8 for details), as it was expected, the recall performance worsened as the number of engram cells increased (5 → 20 EngC). The effect on the recall performance was model depended, with models’ 4 and 6 performance becoming worse as interference (% overlap) between patterns increased. This was due to a combination of factors. Because GABA-B inhibition was reduced, the strong inhibitory cloud necessary to remove any spurious activity was reduced, and hence when interference and engram cells increased, then the remaining inhibition was not sufficient to remove spurious activity and hence recall performance became worse. What differentiated models 4 and 6 from all other models was that the amplitude of IPSPs in PC dendrites was higher, but less sustained with many zero-decays (see Fig. 5).

Our study provided answers to how simultaneous presentation of two patterns with varied degree of similarity between them affects the retrieval process of one of these patterns. Simultaneous presentation of an EC excitatory signal exciting the LM dendrites of the PCs in the network and recall cued by a matched to the EC signal CA3 excitatory signal targeting the SR dendrites of PCs improved memory retrieval because the EC signal worked as a boost signal to the engram cells coding for the cue pattern (see Figs. 9A and 9B). Simultaneous presentation of a 40% similar to the CA3 input EC input caused only 40% of the engram cells to have their activities boosted. Strong GABA-B inhibitory cloud

in the SR PC dendrites eliminated spurious activity including the activities of some of the remaining 60% of engram cells, whose activities were not boosted by the EC input, and hence, recall performance was reduced (see Figs. 9A and 9B). Simultaneous presentation of an 100% dissimilar EC input to the cue pattern (CA3 input) improved recall when the number of engram cells coding for a memory was small (EngC = 5) (see Fig. 9A), and worsened recall when the number of engram cells coding for a memory was bigger (EngC = 20) (see Fig. 9B). The latter finding is because when a large number of engram cells code for memories, then inference between them increases, and hence recall performance drops.

Finally, our study provided answers to how transferred past acquired knowledge affects the retrieval of newly acquired knowledge that may or may not match with the past knowledge. Past studies have shown that context is a potent cue for successful memory retrieval [74]. Information is best remembered when subjects are tested where they learned [75, 76], so that by just thinking about, it is sufficient to improve recall [77]. A context that better matches a cue may have a richer representation in memory and may elicit a more robust memory recall [78, 79]. Less familiar or unfamiliar contexts lead to less vividly remembered memories [80–84]. Memories learned in distinct contexts show better recall (less interference) than when they are learned in the same context [85]. Our simulations confirmed these findings: contextual information plays a crucial role in memory retrieval (see Fig. 10). All models improved their MRQs as similarity between contexts increased becoming nearly perfect when similarity between them was 100% (as expected). Our study made also a new prediction: the higher the number of engram cells, the higher the complexity in the weight matrix, then the higher is the amount of contextual information available to retrieve the required information even when the pattern was extracted from a different contextual information. When the number of engram cells is small (EngC = 5) and the number of patterns stored is 20 (StoPatt = 20), then the resulting weight matrix is populated with few ones (“1”) (active synapses) and many zeros (“0”) (inactive synapses) scattered throughout the weight matrix (total number of ones = 420; total number of zeros = 9580). However, when the number of engram cells is large (EngC = 20), even when a small number of patterns is stored (StoPatt = 5), then the resulting weight is populated with more ones (“1”) and fewer zeros (“0”) forming “islands” of ones throughout the weight matrix (total number of ones = 1680, total number of zeros = 8320). Comparing the number of ones in both cases, we can see a four-time increase between them. Thus, the greater the contextual complexity (more ones in the weight matrix), then some of this complexity will be shared with the patterns trying to be recalled, even if they are derived from a different weight matrix, and thus better the recall.

Conclusion

Overall, our computational study while heavily supported by experimental data at various levels of description provided a novel theoretical framework for hypothesis generation and testing in memory neuroscience. Originally designed to uncover the mechanisms of memory retrieval improvement in the hippocampus, it successfully provided novel insights about the nature of memory, engram cells, interference effects, stored patterns, network size, and transfer learning. Our study's predictions have a profound effect on neurodegenerative diseases such as Alzheimer's disease and dementia because it uncovers which synaptic pathways in the hippocampus, a brain area strongly affected in these diseases, need to be (pharmacologically) strengthened in order to enhance memory retrieval and remembering.

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Author Contribution N.A. ran simulations and analysed the data. V.C. conceived and implemented the model and wrote the manuscript. S. Y. provided comments to manuscript.

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Data Availability Upon publication of this work, the model source code will be uploaded to ModelDB.

Declarations

Competing Interest The authors declare no competing interests.

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