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Hypothesis and Concept

Inter-Postsynaptic Functional Links for Associative Memory: Feasibility in a Realistic Neuropil Model

Kunjumon I. Vadakkan[1,*]

[1]Neurosearch Center, Toronto, ON M5A 2N2, Canada
*Correspondence: k.vadakkan@neurosearch.ca (Kunjumon I. Vadakkan)
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Abstract

Aim: To quantify neuronal input degeneracy and test computationally whether nanoscale (≤30 nm) spine appositions are structurally eligible sites for inter-postsynaptic functional links (IPLs) underlying associative learning, assuming plausible pathway convergence onto abutted spine pairs. **Empirical Constraint:** Neuronal firing exhibits extreme input degeneracy. Any subset of inputs arriving at ~100–200 out of ~10^4 spines can trigger an action potential; ~140 inputs yield >10^{300} possible effective input combinations. This degeneracy introduces ambiguity regarding the specific input combinations that contribute to associative encoding. **Testable Mechanism:** The semblance hypothesis proposes a spine-level conjunction code between co-active spines forming inter-postsynaptic functional links (IPLs) that operate independently of postsynaptic neuronal firing, and are proposed to maintain the fidelity of original associations during retrieval. **Computational Validation:** During retrieval, cue-induced reactivation of IPLs is hypothesized to depolarize inter-linked spines and generate semblances. Taking the depolarization of an inter-linked spine in the absence of direct presynaptic input as an "operational semblance" constituting the elemental substrate of associative recall, a computational model was implemented within a biologically realistic 1000 μm^3 neuropil volume containing 1600 dendritic spines (density 1.6/μm^3; diameter 0.6–0.7 μm) as independent dendritic segments. Of 391 crossing dendritic sites, 151 have abutted spine pairs, using ≤30 nm inter-spine distance as a candidate eligibility criterion, motivated by reported nanoscale appositions. Spine density, diameter, and separation were parameterized from electron microscopy and confocal/super-resolution imaging literature; coupling strength (0.7) was fixed and exploratory. IPL formation was implemented probabilistically across 20 learning trials (formation probability = 0.30 per trial at each of the 49 designated sites; reversal probability = 0.04), producing a gradual acquisition curve and trial-to-trial variance emerging naturally from the two-state Markov dynamics. Across 100 independent simulations, 49 of the 151 abutted pairs were designated as structurally eligible Bell–Food convergence sites; of these, 44.7 ± 2.1 developed active IPLs after 20 trials, generating operational semblances per retrieval (recall accuracy 36.93% ± 1.71%; paired *t*-test, $p < 0.001$; Cohen's d = 30.54, illustrative not calibrated). This work demonstrates that given a plausible convergence of associative pathways onto existing abutted spine pairs, the structural relations between spines in the cortical neuropil are compatible with the formation of a spine-level conjunction code as a potential substrate for associative learning.

Keywords: dendritic spine; synaptic transmission; memory; recall; cognition; neural coding

1. Introduction: The Specificity Problem in Neural Association

A central challenge in neuroscience is understanding how the nervous system encodes, stores, and retrieves information about associations between stimuli. When an animal learns that stimulus A predicts stimulus B, this association must be encoded in neural substrate changes that can later be reactivated by A alone to retrieve the memory of B. An explanation has been Hebbian plasticity [1], where coincident pre- and postsynaptic activity strengthens synaptic connections, with these strengthened weights constituting the memory trace [2]. However, this framework faces a fundamental constraint that has received insufficient attention: the extreme degeneracy of inputs capable of triggering neuronal firing.

Dendritic spines are the structural basis of information storage [3,4,5]. A typical pyramidal neuron in mammalian cortex possesses 10,000–30,000 dendritic spines [6], each representing a potential input site. Yet neuronal firing can be triggered by approximately 100–200 coincident excitatory postsynaptic potentials (EPSPs) arriving within a 10–20 ms window, regardless of which specific subset of synapses is activated [7,8,9]. Assuming that any subset of 140 inputs can trigger firing in a neuron with 10,000 input terminals, the number of distinct input combinations capable of producing an action potential is given by the binomial coefficient C (10,000,140) = 10,000! ÷ [140! (10,000-140)!] ≈ 2.79 × 10^{318} (Fig. 1). Because many distinct input combinations can generate the same output, neuronal firing alone does not uniquely specify the causal pattern of synaptic inputs. This degeneracy propagates through neural networks during learning. These simplifying assumptions treat the neuron as a basic input-integration unit and reveal the magnitude of the underlying degeneracy problem. The resulting ambiguity arises from convergent network archi-

Fig. 1. Extreme input degeneracy in neuronal firing. Pyramidal neurons possess approximately 10,000 dendritic spines (input terminals), yet only ~140 coincident excitatory postsynaptic potentials (EPSPs) are necessary to trigger an action potential. This yields ~2.79 × 10^{318} possible combinations of inputs that can produce identical neuronal output. The length of the line represents the total number of input terminals to a neuron. The red portion of the line represents the number of inputs that summate to reach the firing threshold; blue represents the number of subthreshold inputs that reach the axon hillock but are insufficient to summate for firing; the yellow area shows inputs from remote dendritic locations that attenuate before reaching the integration zone. The red region can be distributed in fragments anywhere along the line. Note that much less than the threshold value arriving at somatic locations can summate to cause firing due to reduced cable attenuation. The extreme degeneracy erases information about which specific inputs cause neuronal firing, necessitating an alternative mechanism for information storage that preserves input identity independently of neuronal firing. Figure not to scale.

tecture itself rather than from specific biological implementation details.

Consider associative learning between two sensory stimuli whose signals propagate through pathways ranging from relatively direct routes such as olfaction [10] to multistage subcortical relays [11], before converging at a common location, the hippocampus [10,12]. At each synaptic relay, the extreme input degeneracy means that the specific identity of which upstream neurons were active becomes increasingly ambiguous. By the time two associated stimulus pathways converge, the system has lost most information about the specific causal chains that linked the original sensory inputs to the convergent site [13,14].

If 140 of 10,000 inputs can determine downstream firing, a randomly selected input has only ~1.4% representation among these inputs. Across successive relays this produces progressive ambiguity of input identity; compounded over the four relays separating L1 from L5 it yields a baseline transmission probability of ~3.8 × 10^{-8} in an unstructured network. Population codes can represent information through distributed activity patterns, but they do not by themselves specify a physical mechanism for how a particular set of converging inputs could be selectively reactivated by a partial cue, which is the mechanistic gap this paper addresses (see section 2.1.6). Structured connectivity, including rich-club organization [15] and privileged pathways [16,17,18,19], raises the probability of signal propagation along particular routes and can reduce information loss in sparse networks (**Supplementary Material 1**). Preferential pairwise connectivity, however, does not guarantee that specific combinations of convergent signals arrive at the same postsynaptic neuron; higher-order convergence therefore depends on the joint organization of multiple connections. Given the probabilistic nature of cortical connectivity [20,21] even privileged pathways cannot guarantee convergence at the spine level, leaving a bottleneck for associative specificity.

This creates a dual problem for theories of associative memory. During encoding, how can the system form specific associations when input degeneracy erodes the identity of causal connections? Conversely, during retrieval, how can the system recover this lost specificity to generate accurate, context-appropriate memories? A further constraint comes from the phenomenology of memory itself. Memory retrieval generates first-person subjective experience, which is what it feels like to remember. Any viable mechanism for memory must be capable of supporting this experiential dimension, not merely producing appropriate motor outputs. This suggests that the core memory mechanism, embedded within larger memory circuits, should operate at a scale and in a manner that could plausibly give rise to content-specific internal signals [22].

The present work builds upon the semblance hypothesis [23,24], a theoretical framework developed through systematic constraint-satisfaction analysis of findings across multiple levels of the nervous system. It has previously been shown to provide interconnected mechanistic explanations for a large and diverse set of empirical observations spanning associative memory, representational drift, place cell firing, dendritic spike generation, seizure disorders, pharmacological responses to anesthetic agents, neurodegenerative conditions, perceptual phenomena, and the necessity of sleep, among others [25]. The central unresolved question within this framework is whether the physical substrate it requires, namely inter-postsynaptic functional links (IPLs) formed between abutted dendritic spines of different neurons within 30 nm of each other, is geometrically feasible within real cortical tissue as the theory predicts. The present paper addresses this question directly by providing a structural feasibility analysis and a computational proof-of-concept demonstration parameterized entirely from electron microscopy data, indicating that the anatomical configuration required by the proposed mechanism is present within cortical neuropil at the predicted scale.

2. The Inter-Neuronal Spine Link: A Candidate Structural Unit for the Engram

2.1 Deriving the IPL Mechanism From System Constraints

2.1.1 The Convergence Bottleneck

The fundamental problem facing any neural model of associative memory is ensuring that signals representing different features or stimuli can reliably converge onto a common neural substrate where their association can be encoded. This convergence must preserve sufficient information about the specific causal paths taken by each

signal. Consider the propagation of depolarization from two simultaneously presented stimuli (S_1 and S_2) from sensory receptors through approximately five neuronal layers to their convergence site. At each layer, several factors degrade signal specificity. These include the following. (a) EPSP attenuation: EPSPs generated at distal dendritic spines experience significant voltage attenuation [26,27,28] (often >50%) as they propagate to the soma due to membrane resistance and capacitance. (b) Threshold nonlinearity: The all-or-none nature of action potentials means that once summed input exceeds threshold, the resulting spike is stereotyped regardless of how far above threshold the summation was, discarding graded information about input magnitude. (c) Input degeneracy: As described above, ~10^{318} different input combinations can produce the same output, erasing information about which specific inputs were active. (d) Divergence-convergence: Each neuron typically projects to hundreds of downstream partners, while receiving inputs from hundreds of upstream partners, creating multiple possible paths between layers.

While structured networks with 'rich club' organization [15] and privileged pathways [16,17,18,19] substantially improve signal preservation (see **Supplementary Material 1**), they do not solve the fundamental problem. Even when activity patterns successfully propagate, the system must still form a specific associative link between the convergent signals. The bottleneck is not primarily in achieving signal convergence, but in creating a substrate that unambiguously links them upon convergence.

2.1.2 Lessons From Early ANN Models of Memory

Artificial neural networks (ANNs) were inspired by synaptic plasticity [29], modeling learning as changes in synaptic weights that encode memory as connection strengths between neurons. Accordingly, memories are reactivated when specific input patterns propagate through strengthened connections, engaging particular neuron ensembles. However, early ANNs had low memory efficiency. For instance, Hopfield networks [30] could store only about 0.15N (15 memories for 100 neurons) random patterns before catastrophic interference and treated memory as simple imprinting rather than generalized learning [31]. While backpropagation significantly improved learning efficiency [32], networks trained with backpropagation were prone to forgetting, exhibited poor few-shot learning, and were typically task-specific with limited generalization. Together with the lack of evidence for backpropagation in chemical synapses, these limitations motivated renewed investigation into more biologically plausible learning mechanisms for memory retrieval.

2.1.3 Core System Constraints

Any mechanism for storing associative information must satisfy multiple constraints derived from neuroscience knowledge. These include the following.

(a) Temporal constraint: Associative learning occurs rapidly, often within a single trial. The substrate must be capable of responding to coincident neural activity occurring within a millisecond timescale.

(b) Spatial constraint: To minimize information loss from EPSP attenuation, the storage site should be at or near the input terminals (dendritic spines), not the soma.

(c) Independence from firing: Given extreme input degeneracy, the storage mechanism should not depend on postsynaptic neuronal firing as a readout, since firing discards most information about input identity.

(d) Specificity constraint: The mechanism must link specific inputs, not merely strengthen a neuron's general excitability. Evidence for this comes from spine-specific plasticity: glutamate uncaging studies [33,34,35,36] demonstrate that only stimulated spines enlarge, without affecting neighboring spines on the same dendrite, despite diffusion of plasticity-related molecules.

(e) Stability and updating: Memories must persist (some for a lifetime) yet also incorporate new information. Evidence for this dual requirement comes from observations that specific spines participating in learning can persist stably while others undergo continual turnover (particularly in the hippocampus, where turnover reaches 50% per month) [37,38,39,40].

(f) Multi-output capacity: In paradigms where both conditioned stimulus (CS) and unconditioned stimulus (US) generate distinct motor outputs before learning, the system must be able to independently drive both output pathways. After learning, CS alone must be able to activate the US pathway. This requires a mechanism that bridges separate neuronal populations.

(g) Phenomenological constraint: Memory retrieval is associated with first-person subjective experience. The mechanism should plausibly provide the operational substrate for content-specific experience, though the relationship between biophysical operations and phenomenology remains beyond the scope of the present computational treatment.

2.1.4 Logical Derivation of Spine-Level Interaction

The above constraints collectively point toward a specific solution. Consider the canonical associative learning paradigm, in which an initially neutral stimulus (CS, such as sound from a bell) is paired with a biologically significant stimulus (US, such as food). After learning, CS alone can trigger behavioral and physiological responses previously elicited only by US. Now consider a variant where both CS and US generate distinct motor outputs before learning (e.g., Bell → head turn; Food → behavior such as whining). After learning, presentation of the bell alone must elicit both the original orienting response and the newly acquired behavior (Fig. 2A). This requires two key conditions. First, the bell pathway must gain the ability to activate neurons

in the food pathway. Second, this connection must form at the convergence site of the two pathways.

Given the spatial constraint (near input terminals) and the specificity constraint (between particular inputs), the mechanism must involve interaction between specific dendritic spines, protrusions from dendritic branches of neurons (Fig. 2B). Given that (a) spines on the dendrite of a neuron is spaced more than the spine diameter (Fig. 2C, Ref. [41]), and (b) the output pathways belong to different motor output systems, these interacting spines must belong to different neurons (Fig. 2D,E). The temporal constraint (millisecond-scale coincidence) suggests the mechanism should be triggered by near-simultaneous activation of abutted spines receiving the converging signals. This logic leads to a candidate mechanism, namely that IPLs must form between dendritic spines of different neurons when their presynaptic inputs are coincidentally active (Fig. 2D,E).

2.1.5 Ruling out Intra-Dendritic Coincidence Mechanisms

Given that the associative mechanism must be localized to dendritic spines (Section 2.1.3), the critical distinction becomes whether the necessary coincidence detection and information storage occur within a single neuron or between neurons.

(a) Necessity for separate motor output functions of associated stimuli: A potential alternative to an IPL is an intra-dendritic, biochemical coincidence detector that links multiple spines on the same dendritic branch via intracellular signaling cascades (e.g., calcium waves, kinase diffusion). While such a mechanism may register co-activity, it does not by itself provide the specific trans-neuronal mechanism proposed here by the necessity for two separate postsynaptic neurons to produce separate motor actions of the two associatively learned items.

(b) Failure to preserve causal specificity: An intracellular association merely creates another integrated state within the postsynaptic neuron. The core degeneracy problem remains unresolved: the neuron's somatic spike is compatible with many different combinations of active spines, making it difficult to infer which specific inputs contribute to the internal biochemical state. It provides no direct, stable linkage between the distinct presynaptic sources that originated the association. To preserve the causal chain back to the original stimuli, the physical trace must create a functional unit that explicitly spans the synaptic divide, incorporating components of both converging pathways.

(c) Lack of specificity of stimulated spines: Many molecules involved in specific spine enlargement have been shown to diffuse from that spine to the dendrite and to the nearby spines [42,43,44,45,46]. However, there is no evidence suggesting that the specific neighboring spine is activated by the associated item whose memory is being retrieved.

(d) Kinetic implausibility for rapid association and retrieval: Associative learning and memory retrieval are often observed to occur on timescales of tens to hundreds of milliseconds. Intra-cellular biochemical signaling involving second messenger diffusion, enzymatic reactions, and gene expression operates on orders of magnitude slower timescales (seconds to minutes), which challenges the existence of a timescale-matched mechanism to explain learning and memory retrieval [47,48,49]. A mechanism relying on such cascades cannot explain the millisecond precision of near-instantaneous recall of detailed memories. In contrast, an IPL can mediate sub-threshold coupling within comparable time scales, consistent with the observed speed of neural association.

Therefore, while intra-dendritic biochemical processes play crucial roles in modulating synaptic strength and cellular homeostasis, they are kinetically and logically insufficient to serve as the primary, rapid, and specific associative substrate. The conjunction of the specificity-preservation requirement and the kinetic constraint leave a direct, trans-cellular spine-to-spine link as a viable class of mechanism. These considerations motivate the formal proposal of the IPL as a candidate structural solution.

2.1.6 Operational Semblance: A Tractable Measure of Associative Recall

IPLs are activity-dependent connections, ranging from functional to structural changes, formed between dendritic spines belonging to different neurons when their presynaptic inputs are coincidentally active. IPLs provide a substrate for storing associative information with three key characteristics: (a) independence from the postsynaptic neuron's firing (thus avoiding information loss from output degeneracy), (b) localization at the convergence sites of associated stimuli (preserving causal specificity), and (c) proposed capacity to generate content-specific first-person properties during retrieval (supporting phenomenology) (Fig. 3). According to the semblance hypothesis, semblance is a distinct first-person internal state of memory. However, in this proof-of-concept study, 'operational semblance' is quantified as the count of newly activated inter-linked spines at the time of memory retrieval by the cue stimulus. Operational semblance is different from phenomenological unification, the subjective experience underlying memory (**Supplementary Material 2**). This is used as a measure of semblance during mechanistic recall, without yet establishing phenomenological unification.

2.2 Possible Molecular Mechanisms of IPL Formation

Under normal conditions, abutted dendritic spines remain electrically isolated by the extracellular matrix (ECM), which acts as an insulating medium to prevent non-specific voltage propagation or depolarization spread. The IPL mechanism describes a spectrum of potential interactions between two activated, abutted spines. Central to

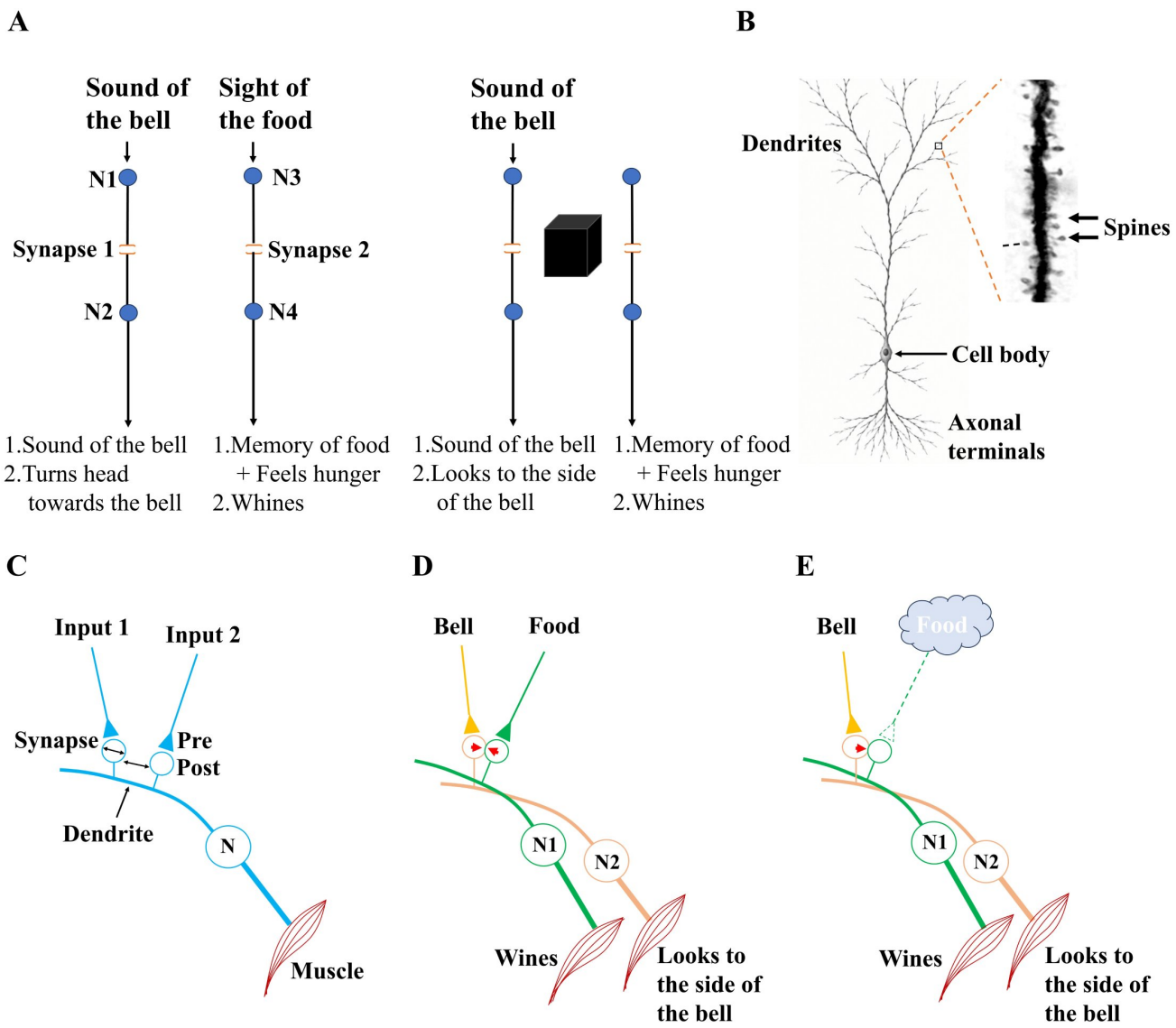

Fig. 2. A modified classical conditioning paradigm and a testable solution for behavior. (A) Modified conditioning paradigm where both the conditioned stimulus (CS) and the unconditioned stimulus (US) are capable of producing independent motor responses. After learning, the CS alone is expected to produce behavioral and perceptual responses that are normally triggered by both the CS and US. A black-box in the right panel denotes still unknown nature of the mechanism capable of generating these effects during memory retrieval. (B) A pictorial representation of a pyramidal neuron. The inset shows a Golgi-stained segment of a dendrite with several dendritic spines. (C) A dendritic branch of a pyramidal neuron (N) with two dendritic spines. When one input arrives at one spine and a second input arrives at another spine of the same neuron, with the two spines separated from each other by more than the spine diameter [41], a single neuronal output cannot independently account for the distinct motor responses elicited by CS and US in this modified paradigm. Pre: Presynaptic terminal. Post: Postsynaptic terminal. The double arrow lines indicate that mean inter-spine distance is more than the mean spine diameter. (D) A solution to the problem emerges when spines of different output neurons (along the bell and food pathways) that are abutted to each other form a link during associative learning. Red arrowheads points towards the inter-postsynaptic functional LINK (IPL). (E) Reactivation of IPL by one stimulus is proposed to transmit voltage (shown by a red arrowhead) to the inter-linked spine of the second output neuron, enabling CS-alone to drive the US pathway generating both memory of the associatively learned second item and its corresponding motor action.

the semblance hypothesis is that voltage transfer through an IPL even producing only small, subthreshold depolarizations localized to the spine head is sufficient to generate a semblance, the elemental signal of memory retrieval. This enables memory operations independent of whether the postsynaptic neuron fires, resolving the paradox of how memories can be retrieved without behavioral expression. IPL spectrum ranges from transient electrical cou-

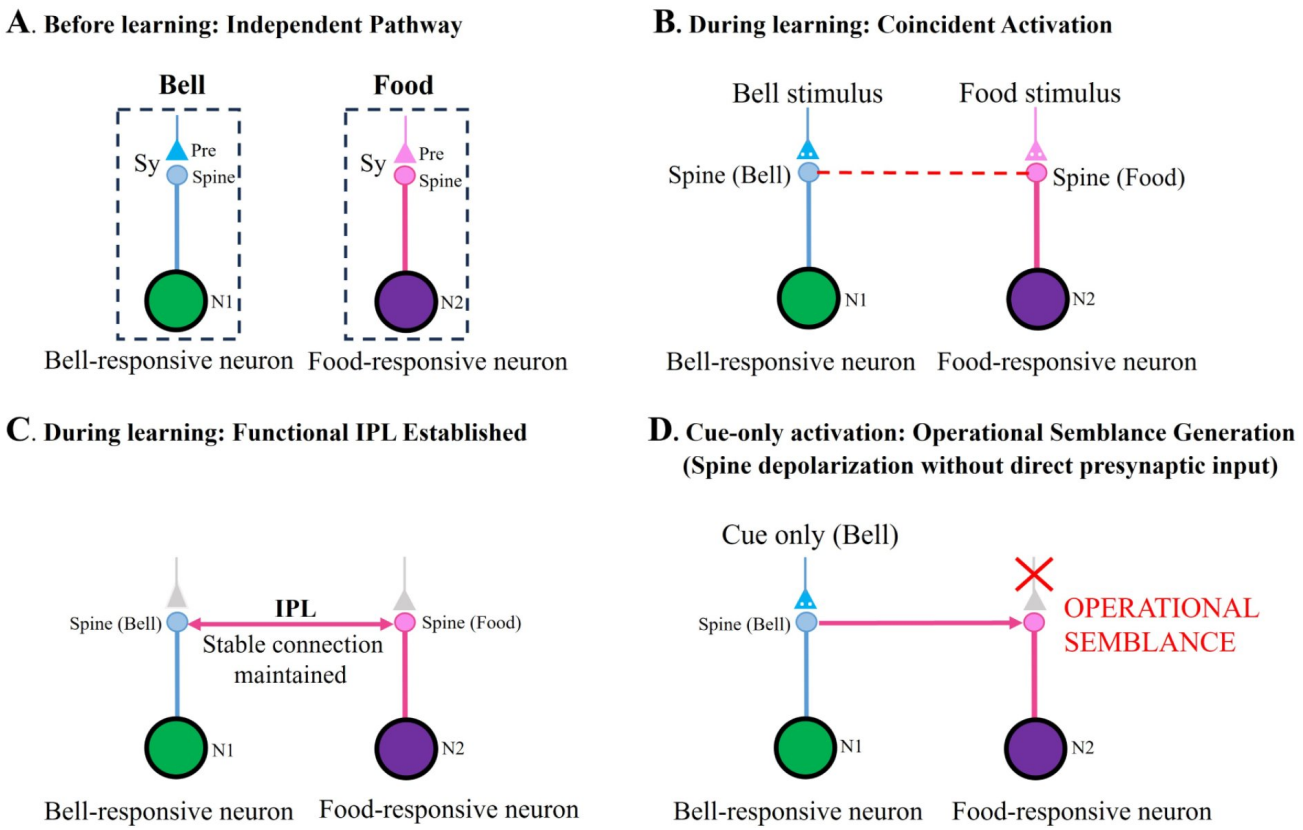

Fig. 3. Inter-postsynaptic functional link (IPL) mechanism in associative learning and memory retrieval. (A) Before learning: Abutted spines from different neurons (blue: bell pathway; purple: food pathway) receive independent inputs with no functional connection. (B) During learning: Coincident activation of both pathways triggers IPL formation (red dotted line) between spines. (C) During learning, an IPL (red line with arrows) is established between Spine (Bell) and Spine (Food), storing the Bell–Food association independently of neuronal firing. The double-arrowed red line indicates that the IPL structure is capable of operating bidirectionally, reflecting a property of the link itself rather than of the retrieval modeled here, which is strictly unidirectional as shown in (D). (D) Retrieval: Bell cue alone activates Spine (Bell), which propagates via IPL (red line with a single arrow to show the present direction of voltage flow) to Spine (Food). The count of newly depolarized inter-linked Spine (Food) instances in the absence of direct presynaptic input, at the time of memory retrieval by the cue stimulus, constitutes the 'operational semblance' as a quantifiable proxy for the phenomenological semblance at the spine level. The food pathway prior to the IPL remains silent (denoted by a red cross), yet Spine (Food) responds as if food were present, recovering specificity lost to input degeneracy. Sy = Synapse; Pre = Presynaptic terminal. N1 and N2 are postsynaptic neurons of the respective pathways.

pling that could support working memory to stable, long-lasting membrane modifications that could support long-term memory. The IPL spectrum of changes, which has features of an evolved mechanism [50], can be hypothesized to include the following possible key stages.

(1) At the most transient end of the spectrum, a localized electrical field is expected to form between inter-linked spines. Given that extracellular potentials can influence nearby neuronal membranes through ephaptic coupling [51,52], and that abutted spines at IPL-eligible sites are separated by as little as 20–30 nm of extracellular space [53,54,55,56], it is possible to infer that such fields could permit highly reversible, rapid voltage transfer between spine heads without persistent structural change.

(2) Experimental data suggest that α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-containing vesicles with small diameters fuse with spine membrane due to vesicle-associated membrane protein 2 (VAMP2) [57,58]. This fusion event is essential for AMPA receptor delivery to the postsynaptic membrane, a key process in long-term potentiation (LTP) induction that, within the present framework, can be explained in terms of IPL formation [59].

(3) A third testable mechanism involves redox-mediated inter-spine bridging. When spines become abutted more closely (e.g., due to spine expansion by released dopamine [60]), redox-active amino acids such as C103 of VAMP2 from two abutted spines become exposed to the aqueous extracellular medium. When synaptic activity in-

duces local oxygen depletion [61], this, along with the release of metal ions such as Zn^{2+} into the extrasynaptic space [62], can promote the formation of metal complexes [63] that bridge the spines and facilitate voltage transfer.

(4) Postsynaptic soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) are essential for activity-dependent membrane remodeling at dendritic spine margins [64], affecting membrane tension, curvature, and lipid organization, bringing abutted spines closer together. SNARE proteins overcome curvature-induced energy barriers, thereby initiating hemifusion [65]. SNAREs also generate force to tightly appose membranes [66], forming characteristic hemifusion intermediates [67]. SNARE-mediated fusion of AMPA receptor-containing vesicles with the spine membrane [68] potentially contributes membrane material to lateral spine regions. Based on the semblance hypothesis, SNARE proteins have a key role in IPL formation during induction of LTP by repurposing fusion machinery to facilitate inter-spine interactions [59]. During heightened synaptic activity, this may allow for transient hemifusion or restricted membrane continuity between abutted postsynaptic membranes, that stops short of full fusion.

3. The IPL Framework

3.1 Functional Definition and Biophysical Plausibility of IPLs

An IPL is defined functionally as a persistent, activity-dependent connection between two dendritic spines, belonging mostly to different neurons when both CS and US generate separate motor outputs. In rare cases, inter-linked spines may occur between two dendritic branches of the same neuron, permitting sub-threshold, input-specific associations when only the US generates a motor output. Its core function is to create a bi-directional, privileged path that allows the depolarization of one spine to directly facilitate the depolarization of its linked partner in millisecond timescales, without requiring either postsynaptic neuron to reach somatic firing threshold. This functional definition could implement the required coupling by multiple biophysical mechanisms.

From the logical derivation in Section 2.1, an IPL mechanism must satisfy the following functional properties. (a) IPL-mediated depolarization/voltage transfer is expected to increase the membrane potential of the inter-linked spine's postsynaptic neuron that is below threshold, toward generating a somatic action potential, (b) input specificity: It must form selectively between spines receiving coincidentally active, behaviorally relevant inputs, (c) bidirectionality: The link should enable depolarization propagation in either direction; the proof-of-concept model in Section 5 implements unidirectional propagation as a conservative test of the mechanism, (d) rapid engagement: It must be engaged on a timescale of milliseconds to support rapid associative learning and recall, (e) reversibility: For ordinary associative learning events, most IPLs must be reversible, (f) persistence: under threatening or beneficial contexts, and motivated states, IPLs are expected to maintain their functional state stably over time (minutes to years) to serve as a memory trace.

Critically, the IPL hypothesis does not stipulate a single unique structural implementation. Instead, it provides a framework that can be constrained by future experiments. Several known and hypothesized nanoscale biophysical mechanisms are plausible candidates for implementing one or more of the required IPL properties. These candidate mechanisms are not mutually exclusive; they could operate concurrently or in different cell types, brain regions, or developmental stages. Each candidate mechanism predicts distinct, experimentally verifiable signatures at the physiological, imaging, and ultrastructural levels. The power of the IPL framework lies in its ability to generate these specific, falsifiable predictions across multiple levels of analysis, guiding a research program to identify the physical substrate(s). For the purposes of developing the theoretical consequences of the IPL, the following sections will treat it as a functional module, independent of its exact physical instantiation.

3.2 IPL Function Independence From Neuronal Firing

A critical feature of the IPL framework is that spine-level operations can proceed independently of whether postsynaptic neurons fire action potentials. Consider a neuron receiving inputs at multiple spines, some of which arrive via IPLs. The neuron's soma integrates EPSPs from all activated spines. The neuron fires only if the summed depolarization crosses the threshold. However, the IPL-mediated depolarization transfer between spines occurs under different conditions.

When the postsynaptic neuron is far from threshold (e.g., –70 mV), IPL activation depolarizes the inter-linked spine(s), but this depolarization may not be sufficient to cross the somatic firing threshold. Hence, information processing occurs at the spine level without somatic readout. When the neuron is just below threshold (e.g., –58 mV), the additional depolarization from IPL activation may drive the postsynaptic neuron over threshold, causing it to fire, which allows the IPL operation to be reflected in the spike output (Fig. 4). When the postsynaptic neuron is strongly hyperpolarized (e.g., by inhibition), IPL operations still occur but cannot trigger firing. This situation may explain memory retrieval without overt motor output. This independence explains several observations. First, memory-related neural changes can be detected in the absence of behavioral output (e.g., during sleep or rest). Second, the same memory can be retrieved with or without associated motor action, depending on top-down control and motivational state. Third, it resolves the apparent paradox that a postsynaptic neuron can participate in encoding multiple different associations [69] because different subsets of that neuron's IPL-

connected spines are activated by different cues, enabling combinatorial encoding capacity vastly exceeding the neuron's binary firing state.

3.3 Islets of Inter-linked Spines

Continued learning does not merely form isolated inter-linked spine pairs. When an item is encountered in multiple contexts or when multiple items are associatively learned in succession, spines from different neurons are functionally connected, and are hypothesized to eventually become structurally connected, during different associative learning events, which results in networks of inter-linked spines forming islets of inter-linked spines (IILSPs) (Fig. 5). Activation of any inter-linked spine within an IILSPs can propagate through the IPL network, leading to depolarization of some or all inter-linked spines within that IILSPs, depending on the nature of postsynaptic potentials at that time. Different cues activate different subnetworks within the IILSPs, enabling context-dependent retrieval. In summary, an IILSPs represents a hub of associative memory storage.

IILSPs provides enormous storage capacity through combinatorial spine recruitment. A neuron with 10,000 spines could potentially participate in thousands of different IILSPs through different subsets of its spines. This explains how relatively modest numbers of neurons can store vast numbers of memories and why memory capacity does not saturate in the way simple weight-based models predict. The IILSPs architecture also naturally accommodates memory updating. New learning can add spines to existing IILSPs. Whether this occurs without catastrophic interference between overlapping IILSPs is not addressed by the present model and remains an open question (Section 7.5d).

3.4 Explaining Spine-Specific Plasticity Phenomena

The IPL framework provides coherent explanations for several unexplained observations about dendritic spine behavior, such as spine-specific enlargement. In glutamate uncaging experiments [33,34,35,36], only the stimulated spine enlarges. IPL formation provides a functional reason for this specificity by marking the enlarged spine as participating in a specific associative link. The spatial restriction of enlargement to the activated spine maintains the specificity of the IPL network structure. This is consistent with the findings that (a) LTP, an experimental correlate of the ability to learn, and its features can be explained in terms of the formation of IPLs [59], and (b) exocytosis of vesicles containing AMPA receptor subunits that are located at the lateral margins of spine heads [70] contributes vesicle membranes [71] increasing surface area of the spine membranes. The resulting curvature changes at the vesicle exocytotic regions [72] can contribute to early and intermediate stages of membrane fusion [73] at the lateral spine head regions favoring IPL formation.

Selective spine stability: While many spines are transient (particularly in the hippocampus), spines formed during specific learning tasks persist and their elimination leads to memory erasure. IPLs explain this selective stability, as spines participating in actively used IPL networks are stabilized, while unused spines turn over. Recruitment of new synapses and modification of pre-existing ones during fear learning [74] is an example. The high hippocampal spine turnover rate [75,76] can be inferred to reflect continuous IILSPs updating as new associations incorporate recent information.

Spine replacement at specific locations: Lost spines are frequently replaced at the same dendritic location at rates exceeding chance [75]. This is consistent with the interpretation that the location represents a functionally privileged site for forming IPLs with nearby spines from other neurons. The replacement spine can rejoin the local IILSPs structure.

Presynaptic bouton splitting: During learning, single presynaptic terminals sometimes split into multiple boutons, each forming a separate synapse [77,78,79,80]. This can be inferred to occur when the presynaptic terminal represents a stimulus that must be associated with multiple distinct stimuli that are not themselves associated. Splitting allows the terminal's signal to reach different spines that can participate in separate, non-interfering IILSPs.

3.5 Anatomical Observations Favoring Inter-Spine Apposition

(a) Structural: Several structural features provide favorable conditions satisfying the above constraints. (1) The sister branches on a neuron's dendritic tree often avoid overlapping [81]. (2) On a dendritic branch, the mean inter-spine distance exceeds the mean spine diameter [41]. (3) Synapse-dense cortical areas contain tightly packed neuropil [5,82,83]. (4) The dendritic arbors of these neurons display significant territorial overlap [84,85,86]. (5) Over half of the spine surface area lacks ensheathment by astrocytic processes [87]. These observations favor the presence of abutted spines that belong to different neurons, either in pairs, chains or clusters. They are either structurally abutted in anticipation of coincident activity from an associative learning event or are already functionally inter-linked.

(b) Imaging: Although not the primary focus, results from an electron microscopy study using ~120 nm sections [88] show hemifusion-like alterations of spine membranes at contacts with adjacent cell membranes. However, possible tissue distortion or membrane folding during preparation may limit interpretation.

4. Memory Retrieval: Semblance Generation and Integration

4.1 The Retrieval Problem Revisited

Memory retrieval requires more than the generation of a behavioral response. Presentation of a cue stimulus

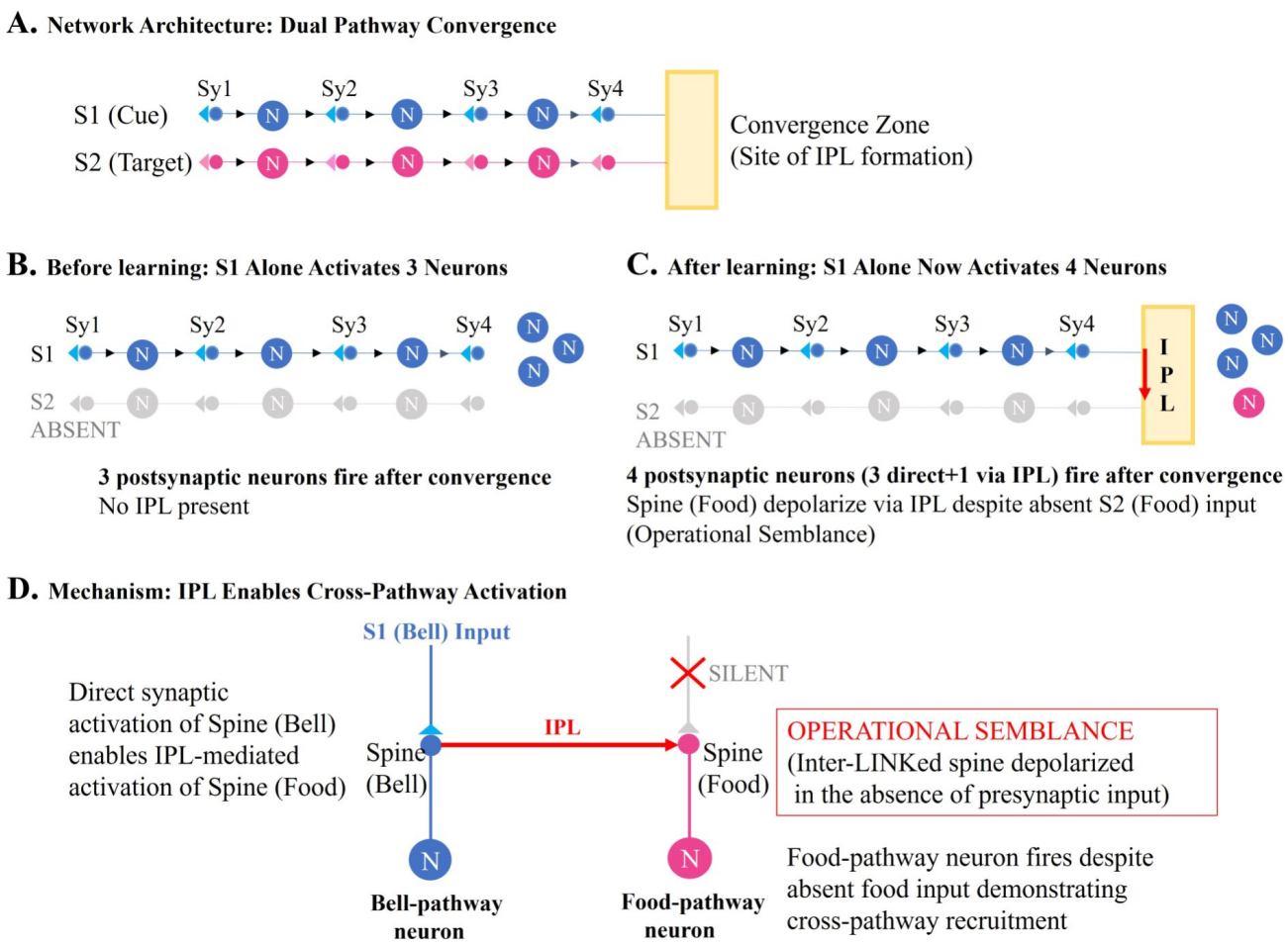

Fig. 4. Network expansion via IPL-mediated cross-pathway activation. S1 and S2 are associatively learned stimuli. Sy1 to Sy4 are synapses between the neurons. (A) Network architecture: Two sensory pathways (S1: blue/cue; S2: magenta/target) progress through five layers and converge at layer 5, where IPL formation can occur between abutted spines from different pathways. (B) Pre-learning response: S1 stimulus activates only S1-pathway neurons, resulting in 3 neurons (in blue) firing at layer 5. S2 pathway inactive. (C) Post-learning response: After associative learning (S1+S2 pairing), the same S1 stimulus now recruits an additional neuron (in magenta) from the S2 pathway via IPL-mediated activation (red arrow labelled IPL). Total firing: 4 neurons. S2 pathway still receives no direct input. (D) Spine-level mechanism: Direct S1 input activates the spine of the S1-path neuron, which propagates via IPL to the spine of the food-pathway neuron. This depolarization of spine of food-pathway neuron in the absence of the arrival of an action potential at its presynaptic terminal (the red cross denotes the silence of the food pathway) constitutes an "operational semblance". This cross-pathway activation enables the S2-path neuron to fire. This demonstrates that IPLs create functional bypass connections between pathways, enabling cue-triggered operational semblance generation at target-pathway spines and the subsequent activation of target-pathway neurons without direct target input. The recruitment of additional neurons (and suppression of others not shown) explains observed changes in ensemble activity after learning while preserving information at the spine level.

(e.g., a bell) must reinstate the specific content associated with a prior experience, including sensory features such as taste, smell, visual appearance, texture, and contextual information. In addition, retrieval is typically accompanied by a first-person quality in which the remembered content is experienced rather than merely represented. Any mechanistic account of memory retrieval must therefore explain both the restoration of specific associative content and the generation of the internal signals that support its subjective character. The IPL framework [23,24,25] addresses these requirements through a two-stage process: (1) cue-driven reactivation of IPLs generates elemental internal signals at individual spines, and (2) integration of these signals across distributed IILSPs reconstructs specific memory content.

4.2 Semblance Generation

After learning, presentation of a CS reactivates the neural pathway engaged during encoding. When action potentials evoked by the CS reach presynaptic terminals, they depolarize the corresponding postsynaptic spines. Through

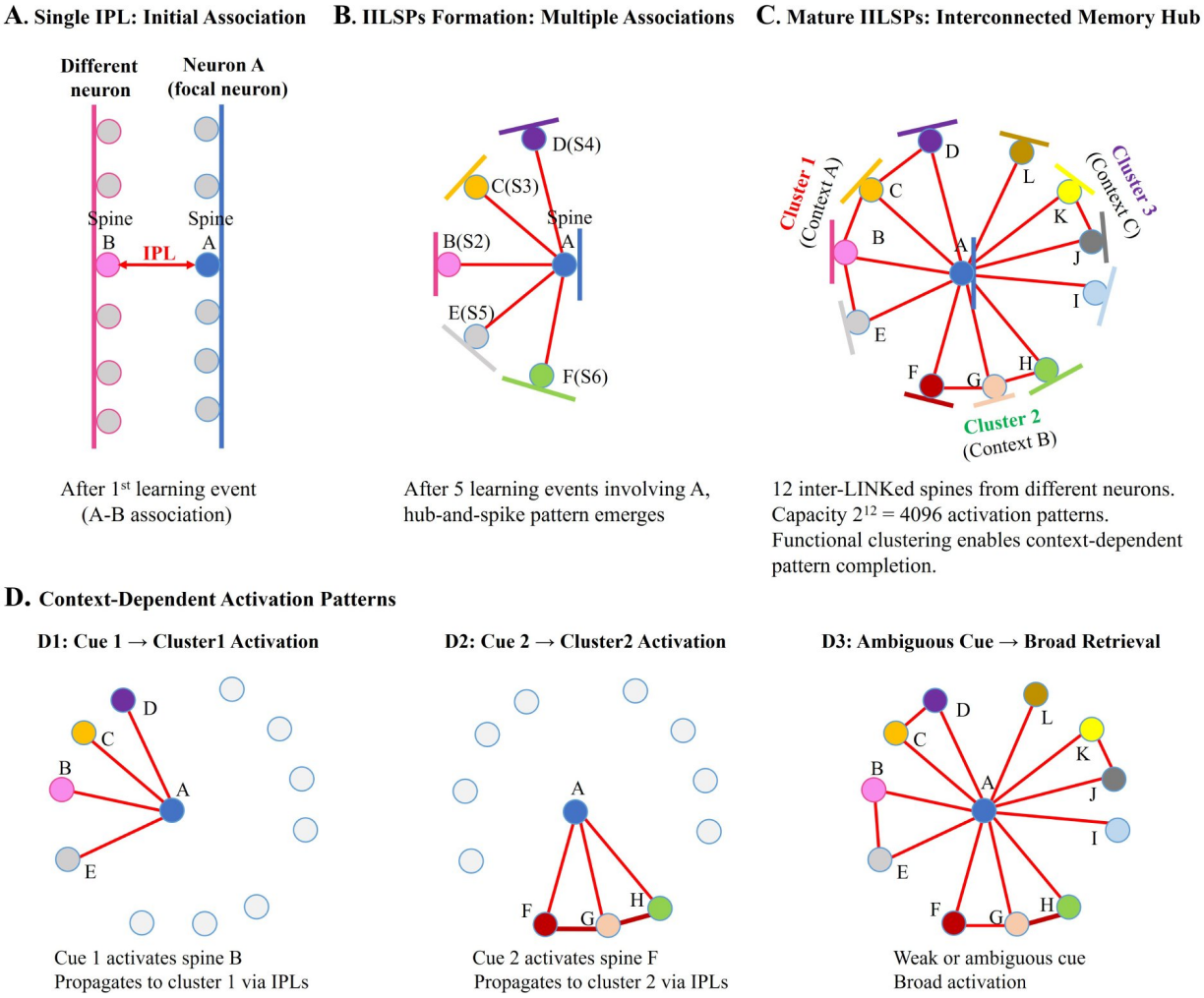

Fig. 5. Islets of inter-linked spines: networks of associative connections. Islets of inter-linked spines (IILSPs) form when a single spine participates in multiple learning events, creating interconnected memory hubs. (A) Starting point: One spine from neuron N (spine A, blue) forms a single IPL (double-arrowed red line indicating its bidirectional function) with spine B after one associative learning event. (B) Progressive recruitment: Through additional learning events pairing spine A's stimulus with different stimuli, spine A forms IPLs with multiple spines (B, C, D, E, and F) from different neurons, creating a hub structure. Each new association adds an IPL to the growing islet. (C) Mature IILSPs network: After extensive learning, spine A is inter-linked to 11 spines, some of which are also inter-linked with each other. This creates a richly connected network of 12 spines with functional clustering (related memories form denser sub-networks, indicated by colored cluster names). The structure provides: massive capacity (up to ~2^{12} activation configurations), and context-dependent retrieval mechanisms. (D) Functional dynamics: Different cues activate different subsets of the IILSPs. Cue 1 activates cluster 1 (D1); cue 2 activates cluster 2 (D2); ambiguous cues trigger broad activation across clusters (D3). This demonstrates how one IILSPs can support multiple related memories while maintaining specificity.

previously formed IPLs, this depolarization can propagate to an inter-linked spine that was originally activated by the associated US, despite the absence of direct presynaptic input to that spine. This IPL-mediated depolarization is proposed to generate units of first-person property called semblance. Operationally, a semblance is defined as spine depolarization occurring without direct presynaptic drive; phenomenologically, it is proposed to correspond to the units of first-person inner sensation of memory generated at the inter-linked spine.

A viable biological mechanism of memory should account for cue-induced internal reinstatement of associated sensory states. In this framework, semblance is the proposed first-person correlate of cue-induced internal reinstatement. Specifically, IPL-mediated voltage transfer to an inter-linked spine provides a mechanism for generating internally produced sensory-like activity in response to a cue, analogous to what Minsky described as a virtual 'hallucination' of the original event, a partial internal reinstatement that remains sensitive to the present context, in the absence of external input [89].

The sensory quality of semblance is naturally generated as a system property. The content-specificity of a semblance can be artificially derived from what is termed retrograde extrapolation, a reconstruction in representational space, not a physical backward signal or axonal transport. This is achieved as follows. Each spine occupies a specific position in the neural architecture connecting sensory receptors to a convergence site. This position can be conceptually traced back through the network layers to identify which sensory receptor population and feature space the spine represents. The spine's functional identity, specifically what sensory feature it encodes, is determined by this path. When the inter-linked spine is depolarized via IPL during retrieval, this path constitutes an internal reinstantiation of that specific sensory feature signal. The inter-linked spine becomes activated through the IPL as if the original sensory feature is present. This is proposed to provide the operational substrate for what is subjectively experienced as the hallucinatory aspect of memory, which is the reinstatement of sensory features that are no longer physically present. Critically, semblance generation does not require action potential propagation backward through the network. It is expected to be implemented naturally as a system property of systems where the propagation of potentials across the synapses and IPLs contributes vector components to the oscillating extracellular potentials. The semblances induced at the inter-linked spines are likely to couple through oscillating potentials, where temporal synchrony acts as the binding principle. In this way, the count of newly activated inter-linked spines, quantified as the operational semblance, provides a tractable measure of the inter-linked spine-level events through which semblances restore the specific content of a memory in the absence of external input.

4.3 Integration Mechanism: From Semblances to Unified Memory

A single cue typically activates hundreds to thousands of IPLs across multiple IILSPs, generating a corresponding number of simultaneous semblances. These distributed elementary signals must be integrated to produce the unified associative activation pattern that underlies coherent memory retrieval. How does this integration occur? Conscious states, when learning and memory occur, are associated with a narrow range of oscillation frequencies in the electroencephalogram (EEG) [90,91,92]. Oscillatory network dynamics, particularly theta-gamma coupling, provide the integration framework for cognitive functions during conscious states [93,94,95]. The key insight is that oscillations create temporal windows during which distributed neural events can be bound together (Fig. 6). Specifically, theta rhythm (~4–8 Hz) provides a ~125–250 ms integration window, gamma oscillations (~30–80 Hz) within each theta cycle create ~13–33 ms temporal sub-windows. IPL reactivations within the same gamma cycle can coincide and contribute lateral current components, enabling functional association through coherent summation. Their ordered sequence across a theta cycle is expected to form the temporally structured pattern underlying memory retrieval, potentially extending across multiple cycles.

This oscillatory integration mechanism explains several phenomena. Phase precession occurs as a function of an animal's position in space, causing place cells to fire at progressively earlier phases of theta. This could reflect sequential activation of spine networks, where earlier-activated IILSPs generate semblances that lead to earlier firing within the theta cycle. Additionally, theta-gamma coupling strength correlates with memory performance. Stronger coupling may reflect more effective semblance integration, which could lead to more vivid and accurate memory retrieval. The number of distinguishable gamma subcycles nested within each theta cycle (~5–8 subcycles) [96,97] closely corresponds to the well-established limit of working memory capacity. Studies indicate that working memory can maintain between 4 ± 1 and 7 ± 2 chunks of information [98,99], reflecting grouping strategies. This theta-gamma temporal architecture is expected to bind distributed semblances into coherent memory representations. The integration process itself has several critical properties. First, it is content-addressable, meaning different cues activate different subsets of semblances and thereby retrieve different memories. Second, it naturally implements generalization, as partial or degraded cues can still activate sufficient semblances for recognition. Third, it supports memory updating, since recently formed IPLs contribute new semblances that incorporate updated information into retrieved memories.

4.4 Circumventing the Convergence Bottleneck

The IPL mechanism provides a potential solution to the convergence bottleneck. Traditional Hebbian models require that signals representing associated stimuli converge onto the same neuron's soma so that coincident firing can strengthen the synaptic connections to that neuron. Given input degeneracy, somatic firing does not uniquely specify which particular combination of inputs was causally responsible for reaching threshold. IPLs bypass this requirement entirely. Association formation occurs between abutted dendritic spines, which may belong to different neurons. The convergence requirement is relaxed from 'two signals must drive the same neuron to fire' to 'two signals must arrive at abutted spines'. This relaxation increases the number of potential convergence sites by a factor of $\sim 10^4$ (the number of spines per neuron), making successful association formation vastly more probable. During retrieval, information specificity is partially recovered through the distributed semblance generation and integration process described above. The ambiguity regarding specific causal paths can be resolved within the IPL framework because information about associative relationships is proposed to

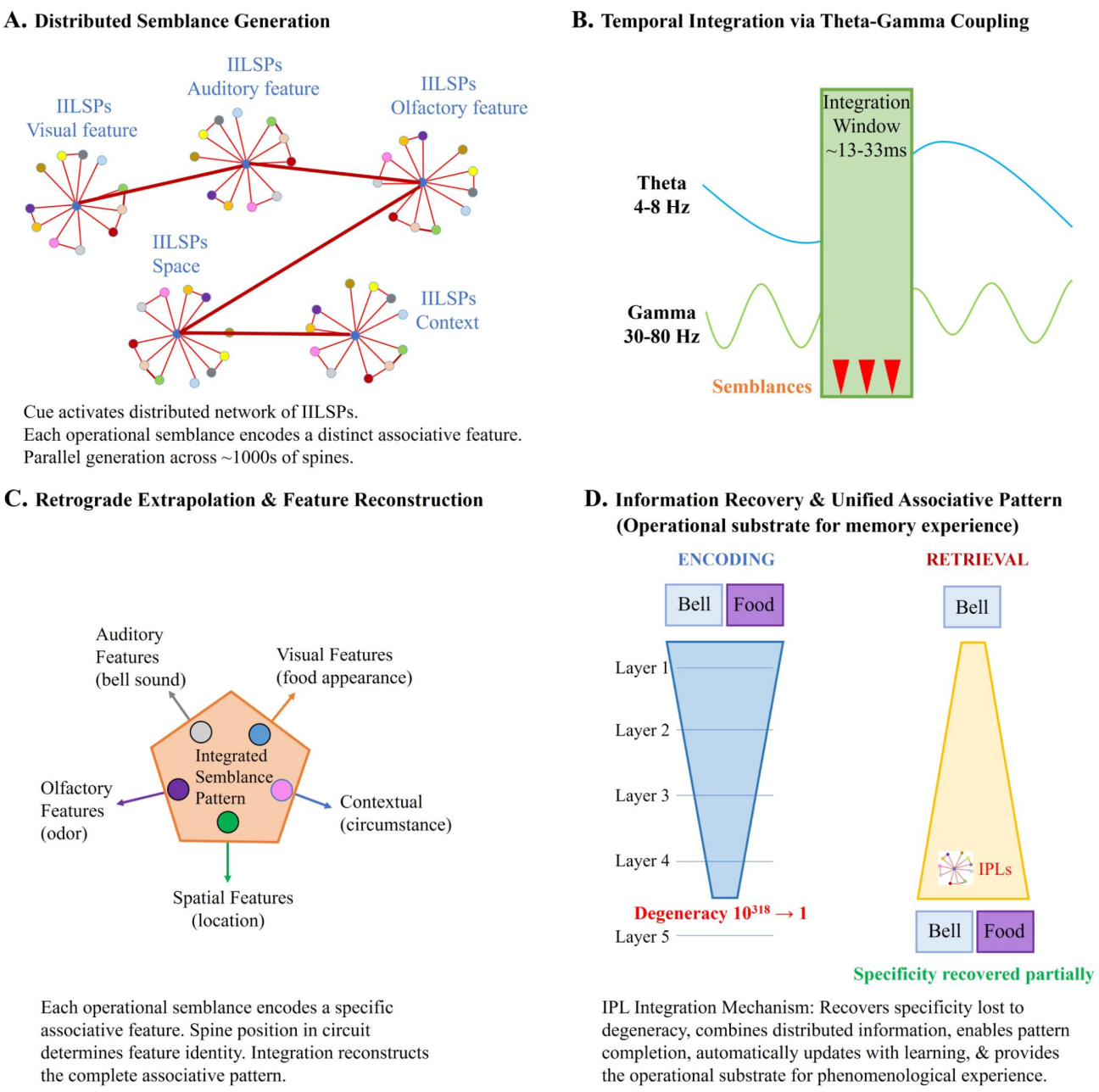

Fig. 6. Integration of distributed semblances produces unified memory retrieval. (A) Parallel semblance generation: A single cue stimulus (Bell) activates distributed IILSPs (1–5) across cortical space. At each IILSPs, one inter-linked spine (central one) undergoes depolarization by direct input from a cue stimulus and all other inter-linked spines exhibit operational semblance, encoding a different feature: visual (IILSPs$_1$), auditory (IILSPs$_2$), olfactory (IILSPs$_3$), spatial (IILSPs$_4$), contextual (IILSPs$_5$). Semblances occur simultaneously in parallel across ~1000s of spines. (B) Oscillatory integration: Theta rhythm (4–8 Hz, blue wave) creates temporal windows; gamma oscillations (30–80 Hz, green waves) nest at theta troughs. Semblances occurring within the same theta-gamma phase window (~13–33 ms, green shading) are temporally bound into a unified activation pattern. This solves the binding problem through phase synchronization. (C) Feature reconstruction: Each semblance (S_1–S_5) can be identified by retrograde extrapolation: the spine's position in neural circuits determines its sensory content. S_1→visual features, S_2→auditory, S_3→olfactory, S_4→spatial, S_5→contextual. Integration of extrapolated features reconstructs complete, multi-modal memory. (D) Information recovery: Comparison of encoding (left: forward pass with information loss) versus retrieval (right: retrograde reconstruction with information recovery). During encoding, degeneracy erases specificity (10^{318}→1). During retrieval, semblance pattern is expected to partially recover specificity via spine-level storage and oscillatory integration, reconstructing memory (Bell → Food) from the cue (Bell). Mechanism automatically incorporates updates from all learning events.

be preserved in the spatial pattern of IPL formation. Retrieval converts this spatial code (which IPLs are activated) back into temporal patterns (sequenced semblance generation), thereby reconstructing the original associative activation pattern that serves as the operational substrate for experiential content.

5. Proof-of-Concept Modeling of Associative Memory Using IPLs

The present model focuses exclusively on this operational definition: an operational semblance is defined as the depolarization of an inter-linked spine head when voltage propagates through an IPL from an activated partner spine. The relationship between this biophysical event and phenomenological experience remains an open question for future investigation. This model demonstrates structural and mechanistic feasibility of the IPL hypothesis, not experimental validation; confirmation requires the empirical tests outlined in Section 6. To demonstrate that, within this proof-of-concept model, activity-dependent inter-postsynaptic interactions are sufficient to support associative memory, a computational proof-of-concept model was developed in which learning and retrieval occur exclusively through activity-dependent interactions between postsynaptic compartments. In the model, dendritic spines are spatially distributed within a 1000 μm^3 model neuropil volume parameterized using experimentally measured spine density, spine dimensions, and IPLs form between spines of different dendritic segments when those spines are co-activated within 30 nm of each other. This geometry is compatible with several candidate biophysical mechanisms that could, in principle, mediate inter-spine interactions and matches converging empirical constraints: electron microscopy and super-resolution imaging studies document that abutted dendritic spine membranes at cortical dendritic crossing points come within membrane-to-membrane distances of ≤30 nm [53,54,55,56]. The following biologically plausible parameters reported across electron microscopy (EM) literature were incorporated into simulations of a 1000 μm^3 neuropil volume: spine density (1.6/μm^3) [100,101], spine diameter (0.6–0.7 μm) [102,103], and inter-spine separation (≤30 nm) [53,54,55,56].

At the separation of ≤30 nm, the candidate biophysical mechanisms for IPL formation, including ephaptic coupling [51,52], redox-mediated inter-spine bridging [61,62,63], and SNARE-mediated membrane apposition leading to hemifusion [64,65,66,67,68], become physically operative. Learning is driven solely by coincidence of spine depolarization. During retrieval, presentation of a cue stimulus activates only its corresponding spines via direct input, after which activation propagates unidirectionally through established IPLs to depolarize inter-linked spines associated with the paired stimulus in the absence of presynaptic input to those spines, thereby generating operational semblances (**Supplementary Fig. 1**).

Statistical validation across 100 independent runs: These parameters yielded 1600 dendritic spines as independent dendritic segments, forming a biologically realistic dendrite meshwork of 391 crossing dendritic sites, 151 of which are crossing points where both dendrites have spines that abut (subtotal 302 spines) and 240 of which have a spine on only one dendrite (subtotal 240 spines); the remaining 1058 of the 1600 total spines lie outside the ≤30 nm crossing-point framework and were not included as IPL-eligible candidates. IPL formation was probabilistic (formation probability = 0.30 per trial per eligible site; reversal probability = 0.04), following a two-state Markov updating rule at each eligible site per trial (see **Supplementary Material 3** for the formal expression), producing a gradual acquisition curve emerging naturally from the two-state Markov dynamics operating on a finite pool of eligible sites. These abutted spine pairs belong to different dendritic segments and predominantly to different neurons, as inferred from structural findings [41,81,84,85,86,87], placed at membrane-to-membrane distances of 20–30 nm within the range of separations reported for abutted spine contacts in cortical neuropil [53,54,55,56]. Of these, 49 form IPLs because they receive convergent Bell+Food inputs, and the remaining 102 background pairs do not form IPLs because they receive unrelated inputs. The formation probability (p_{form} = 0.30) and reversal probability ($p_{reversal}$ = 0.04), and coupling strength (0.7) are exploratory parameters selected to demonstrate proof-of-concept feasibility, not fitted to existing experimental data. Coupling strength specifically represents subthreshold voltage-transfer efficiency at 20–30 nm membrane apposition, applied uniformly across all structurally eligible IPL sites with no distance-dependent subdivision. Since this paper establishes the theoretical feasibility for IPL formation, direct experimental measurement of these probabilities at abutted spine pairs from different neurons using paired two-photon stimulation remains an essential empirical test that the present framework is designed to motivate.

Operational semblance generation occurs through unidirectional propagation, consistent with the semblance mechanism whereby voltage propagates from the cue-activated spine through the IPL to the inter-linked target spine. Following IPL formation, cue presentation reliably evokes spine depolarization (operational semblances) in spines corresponding to the associated stimulus, whereas no such activation occurred prior to learning in response to the cue stimulus. Pattern retrieval was tested independently in both forward (Bell→Food) and reverse (Food→Bell) directions. Results showed highly consistent performance: spine-level pattern completion accuracy improved from 0.00% ± 0.00% (before learning) to 36.93% ± 1.71% (after learning; paired *t*-test, $p < 0.001$; Cohen's d = 30.54). IPL formation was consistent across all 100 runs (44.7 ±

2.1 active IPLs per run), all representing Bell–Food interspine connections (**Supplementary Fig. 2**). Recall accuracy is expressed relative to the full 121-spine Bell or Food pathway population. The 49 IPL-eligible sites represent the subset of that population where convergence and structural eligibility coincide; of these, 44.7 ± 2.1 formed active IPLs after 20 trials, consistent with the steady-state expectation of the Markov formation model (**Supplementary Material 3**). The paired *t*-test and large Cohen's d (30.54) reflect the mathematically determined zero baseline before learning and should be interpreted as confirming a categorical pre- to post-learning difference rather than as conventional inferential statistics.

The natural variance across runs reflects probabilistic IPL formation during 20 learning trials, demonstrating that outcomes remain consistent across independent stochastic runs at these exploratory parameter values. When abutted spines at dendritic crossing points receive convergent Bell and Food inputs, IPL formation reliably creates the substrate for spine-level associative activation. All statistical results are reported as mean ± standard deviation (SD). To assess robustness to variation in these three model parameters, a three-way parameter sensitivity analysis across p_{form} (0.10–0.50), $p_{reversal}$ (0.02–0.08), and coupling strength (0.5–0.9) with 30 runs per combination. Final recall accuracy, driven primarily by p_{form} and $p_{reversal}$, ranged from 22.8% to 39.7% across all 100 parameter combinations, with no combination failing to produce associative recall; coupling strength affected the rate of approach to this range but not its final value (**Supplementary Material 3**, **Supplementary Fig. 3**). This sensitivity analysis shows robustness across the assumed parameter range, but this does not validate the range itself.

The model demonstrates that associative binding can be implemented through activity-dependent IPL formation, with pattern retrieval arising from IPL-mediated activation of postsynaptic compartments in the absence of respective presynaptic inputs. The independence of IPL-mediated spine operations from somatic firing is illustrated in **Supplementary Fig. 4**. These results establish that, within this model, networks of IPLs are sufficient to implement the operational substrate for associative memory formation and retrieval at a mechanistic level, showing that pattern completion can arise from lateral interactions between postsynaptic compartments. Code availability: see Data availability statement (Files **S1–S12**).

6. Testable Predictions

The following predictions provide decisive tests of the IPL framework. All the experiments should include appropriate temporal, spatial and behavioral controls. (a) Behavioral prediction: Associative learning should generate spine-specific, cross-neuron subthreshold coupling that is independent of postsynaptic action potentials. Selective disruption of such couplings should abolish individual learned associations. (b) Physiological prediction: During memory retrieval (e.g., recall phase of a spatial memory task), dendritic calcium imaging should reveal local calcium elevations in spine clusters (IILSPs), occurring even when some or many of their postsynaptic neurons do not fire. These 'subthreshold retrieval events' (for a subset of postsynaptic neurons of the IILSPs) should predict subsequent behavior and should be disrupted by interventions that specifically impair associative memory encoding or retrieval. (c) Computational prediction: The integration of semblances into unified memory is predicted to depend on temporal synchrony among the oscillating potentials generated by IPL-mediated propagation; disrupting this synchrony (e.g., via oscillation-desynchronizing manipulations) should impair integration without necessarily abolishing individual semblances. (d) Structural prediction: IPLs are oxygenation/oxidation state dependent functional links between abutted spines on different dendrites mostly belonging to different neurons.

7. Discussion

7.1 Relationship to Existing Frameworks

The IPL framework operates at a sub-neuronal organizational level that complements existing accounts of learning and memory. Its explanatory power derives partly from the fact that the computational model developed in Section 5 is not constructed solely on idealized or abstract parameters. The spine density, diameter, and inter-spine separation values used in the model are sourced from quantitative electron microscopy and confocal/super-resolution imaging measurements of real cortical tissue, while the site counts derived from them and the learning dynamics (formation, reversal, and coupling parameters) remain design choices and exploratory parameters, respectively. Demonstrating structural feasibility under these measured geometric constraints is precisely what gives the present proof-of-concept its empirical force. The following comparisons with established frameworks are made within this context and within the broader semblance hypothesis, which has previously provided interconnected mechanistic accounts for a large number of seemingly disparate findings spanning multiple domains, as noted in the Introduction [23,24,25]. The present model does not stand alone but contributes a structural feasibility demonstration for the substrate proposed to unify those accounts.

(a) Comparison to Hebbian plasticity: The IPL framework offers a novel reinterpretation of traditional engram theory through an operational mechanism at the subneuronal level. It proposes the principle of "abutted spines separated by ≤30 nm that depolarize together link together", which is proposed to preserve information about co-active inputs that is not explicitly represented by neuronal firing alone. This mechanism may co-occur with and reinforce traditional synaptic remodeling that enhances spine activation and facilitates IPL maintenance. While the

framework remains consistent with the core tenet that lasting memories involve persistent synaptic changes [2,104], it shifts the organizing logic of these changes from a correlative framework to one centered on spine-level associative interactions, implemented within the dendritic arbor [105]. In parallel, homeostatic synaptic changes [106,107] act to constrain network dynamics and modulate activity across different circuit levels.

(b) Comparison to dendritic computation: The IPL framework builds upon established research on dendritic nonlinear computations including N-methyl-D-aspartate (NMDA) spikes, calcium spikes, and plateau potentials [108,109,110], proposing that IPLs provide the specific substrate for associative binding that these mechanisms integrate. Plateau potentials may represent the dendritic reflection of coordinated IPL activation, a threshold-crossing event that signals successful pattern detection at the dendritic level. When sufficient spines within an IPL network are co-activated, the resulting dendritic depolarization can trigger an all-or-none plateau potential, providing an amplified and sustained dendritic readout of the distributed memory signal.

The IPL framework extends foundational dendritic clustering frameworks, which demonstrated that co-active synapses on a single branch can trigger local nonlinear events (e.g., NMDA or calcium spikes) serving as a fundamental unit of plasticity and input integration [111]. While branch-specific compartmentalization is retainedas a critical biological mechanism in this conceptual framework, the present work proposes a fundamental shift in the representational unit. Classical dendritic clustering emphasizes the branch electrical compartment as the primary locus of learning and computation [112]. In contrast, the functional engram in the present work manifests as a sparse, network-distributed assembly of clusters of spines that belong to different neurons, dynamically linked via a shared, internal generative model. This architecture allows a single neuron to simultaneously maintain multiple independent predictive schemes, a capability not fully explained by models where a branch's primary function is input segregation or synaptic cooperativity [113,114].

(c) Comparison to ensemble coding: While population-level theories accurately describe the correlation between distributed neural activity patterns and behavioral outputs [115], the IPL framework proposes a subcellular mechanism that generates these ensemble patterns. Ensemble-level descriptions face the same fundamental limitation as single-neuron accounts: each neuron's firing output is degenerate across $>10^{300}$ possible input combinations, erasing the specific causal identity of its inputs. The population code describes which neurons participate in a representation, but the precise subcellular mechanisms by which associative specificity is established and preserved remain incompletely understood. Specific IPL activation patterns are proposed to determine which neurons approach firing threshold, forming distinct cue-specific ensembles. The framework predicts that ensemble activity may reflect a downstream manifestation of underlying IPL dynamics, rather than serving as a causal driver of memory expression [116].

(d) Comparison to hippocampal indexing theory: The IPL framework can be viewed as a potential micro-architectural correlate for the hippocampal indexing theory [117], which posits that the hippocampus encodes sparse indices of distributed neocortical activity patterns. Within this view, hippocampal circuits (particularly CA3) may support associative IPL configurations driven by convergent cortical inputs, without storing full representations. During retrieval, reactivation of these hippocampal IPL configurations may facilitate pattern completion and, via hippocampal-cortical pathways, bias distributed cortical IPL networks toward reactivation, where the corresponding semblances would be generated. Crucially, the framework allows for the integration of semblances generated across distributed brain regions including cortex, offering a candidate conceptual account of memory consolidation [118]. Thus, the IPL framework provides a candidate biophysical substrate for the indexed cortical engram, bridging systems-level memory organization with cellular-level computation.

7.2 Explaining Representational Drift

Representational drift [119,120] is the observation that the specific neurons active during a learned behavior gradually change over weeks, even though the behavior remains stable. This presents a challenge for models where memory is stored in specific neuronal connections. If the participating neurons change, how does memory persist? The IPL framework offers a natural account of representational drift. Within the IPL framework, memory is proposed to be stored in IPL networks at the spine level rather than in the specific neurons that fire. A given IILSPs might include spines from 10–20 different neurons. Over time, spine turnover can result in some of those spines being lost and replaced. If a lost spine belonged to neuron A and the replacement spine belonged to neuron B, the neuronal ensemble can shift (B becomes active instead of A) even though the underlying IILSPs structure persists with minor modifications. The system can therefore tolerate substantial neuron-level drift while maintaining spine-network stability. This observation also accounts for why memories can persist despite ongoing synaptic turnover and circuit remodeling.

7.3 Rate and Temporal Coding Reconciliation

Evidence demonstrates that information is encoded in both the rate and precise timing of neuronal firing [121,122]. The IPL framework provides a natural account of both coding schemes. Firing rate is proposed to reflect the intensity of IILSPs activation. Stronger stimuli or more complete similarities to the cue activate more IPLs within relevant IILSPs, generating more semblances and thereby

increasing the probability and frequency of postsynaptic neuron firing. Thus, rate coding emerges from the statistics of semblance generation across spine populations. Temporal coding, in turn, reflects the sequence of IILSPs activation. Different features of a memory are encoded in different IILSPs subnetworks. During retrieval, these subnetworks are reactivated in a specific temporal sequence, potentially coordinated by theta-gamma coupling, a mechanism independently established in the literature [93,94,95], generating time-locked firing patterns in downstream neurons. Precise spike timing [123,124] is therefore proposed to emerge directly from the temporal unfolding of the memory representation across distributed IILSPs.

7.4 Biological Grounding of the Computational Model

A central strength of the proof-of-concept model presented in Section 5 is that its spatial and structural parameters are grounded in empirical measurements rather than abstract or idealized assumptions, while its learning dynamics are treated explicitly as exploratory, as detailed below. The geometric and density parameters used in the simulation were derived from quantitative studies of cortical neuropil, including measurements of spine density [100,101], spine dimensions [102,103], inter-spine separation [53,54,55,56], and dendritic organization obtained from electron microscopy and confocal/super-resolution imaging studies.

This biological grounding allows the model to address a specific question: whether structurally eligible sites for IPL formation exist in sufficient numbers within realistic cortical tissue to support associative memory operations. The simulations indicate that cortical-like neuropil geometries contain numerous sites that are structurally eligible for the proposed IPL mechanism and that, under the model's specified learning and coupling assumptions, these sites can support associative recall. This site count is a theoretical estimate derived from measured spine density under an assumption of random spatial distribution; the true frequency remains an open empirical question. These findings therefore represent a demonstration of structural feasibility under measured anatomical constraints and a designated convergence scenario, rather than fully permissive assumptions.

The probabilistic IPL formation framework also produced consistent associative recall across repeated simulation runs and remained robust to variation within the tested range of formation, reversal, and coupling parameters (**Supplementary Material 3**, **Supplementary Fig. 3**). While the formation and reversal probabilities, along with coupling strength, remain exploratory parameters awaiting experimental determination, the persistence of associative recall across parameter variations supports the general feasibility of the proposed mechanism. Taken together, these findings provide structural support for the IPL framework and establish a quantitative foundation for future experimental tests of the semblance hypothesis [23,24,25].

7.5 Limitations and Open Questions

Several important limitations and open questions should be acknowledged.

(a) Physical mechanism: The most critical limitation is that the precise biophysical substrate of IPLs remains hypothetical. While several candidate mechanisms are plausible, determining which (if any) actually implements IPL-like function requires focused experimental investigation using techniques such as abutted spine stimulation, super-resolution imaging of spine-spine contacts, and targeted molecular perturbations. It should be noted, however, that while the specific biophysical substrate remains unknown, the case for inter-spine coupling itself rests on an additional, independent line of evidence. The semblance hypothesis derives IPLs not from a single experimental finding but from systematic constraint-satisfaction analysis across a large number of findings at cellular, electrophysiological, associative, computational, temporal, systems, pathological, phenomenological, and evolutionary levels [23,24,25]. A mechanism that did not involve inter-spine coupling of the type proposed would need to independently account for the same interconnected set of findings that these constraints converge upon; whether such an alternative account exists remains to be established. This cross-level explanatory consistency motivates experimentally testing inter-spine coupling as a candidate mechanism, though it indicates only that some such mechanism should exist, not which specific biophysical implementation is correct.

(b) Parameter timescales: The formation probability (p_{form} = 0.30) and reversal probability ($p_{reversal}$ = 0.04) are defined per learning trial rather than per unit of real time. Biological variability in these parameters is expected, with $p_{reversal}$ likely approaching its lower bound under life-threatening conditions where one-trial learning has been reported [125], and increasing under conditions of lower motivational urgency. Both values are exploratory parameters awaiting experimental determination.

(c) Spine-to-neuron integration: While the framework explains how spine-level operations preserve information and generate semblances, the precise mechanisms by which integrated semblance activity translates into coordinated neuronal firing patterns and ultimately motor outputs require further investigation and modeling. The role of dendritic spikes and plateau potentials [108,109,110] in this integration is proposed but requires detailed modeling.

(d) Capacity and interference: While IILSPs theoretically provide substantially greater capacity than neuron-level storage, practical limits are expected to exist. How are distinct IILSPs maintained as non-overlapping entities to prevent catastrophic interference? Does spine turnover [75,76] serve to clear out obsolete associations?

(e) Developmental considerations: When and how do IPL formation mechanisms develop in the brain? A sequence of key developmental changes has been identified [50], but their experimental verification could inform un-

derstanding of critical periods and developmental memory disorders.

(f) Scope of the computational model: The present model demonstrates structural feasibility and quantifies the count of newly activated inter-linked spines as a proxy for the spine-level events where semblances are proposed to occur, but does not address the full complexity of cortical circuits, including inhibitory interneurons, neuromodulatory influences, or multi-area interactions.

(g) *In vivo* validation: The present model establishes structural feasibility but does not demonstrate that IPL-mediated coupling occurs *in vivo* at the predicted frequency or persistence.

(h) Circularity: The 49 Bell–Food sites are predesignated, and the effect size (d = 30.54) compares this against a zero baseline by construction. A null control with randomly shuffled Bell/Food labels found only 0.73 ± 0.84 sites co-activated by chance, versus 44.7 ± 2.1 in the real condition ($p < 0.001$, d = 28.1 vs. this null; **Supplementary Material 4**). The 49-site designation itself remains a modeled input, not emergent.

(i) Parameter calibration: formation probability, reversal probability, and coupling strength are unconstrained by experimental data, and the tested range is not experimentally validated; occupancy is highly sensitive outside it (91.2% → 68.8% → 33.6% under compounding 2× shifts). The reported 36.93% recall and 44.7 IPLs are illustrative, not calibrated predictions.

8. Conclusion

Given the established geometry of the neuropil [53,54,55,56], there exist widespread structural 'bottlenecks' of ≤30 nm that provide anatomically plausible sites for inter-spine interactions. Critically, the structural feasibility of the proposed mechanism is supported by a computational model in which spine geometry was parameterized from empirical ultrastructural and imaging measurements of cortical neuropil, while the learning dynamics (formation, reversal, and coupling parameters) were treated as exploratory. The simulations indicate that biologically realistic tissue volumes contain sufficient structurally eligible sites to support IPL formation and associative recall, and that these associations can emerge robustly across the range of stochastic learning parameters tested. These findings establish the structural eligibility of such sites and the computational sufficiency of the proposed mechanism under the model assumptions; they do not yet establish that IPL-mediated coupling occurs *in vivo*.

Importantly, the model generates quantitative and experimentally testable predictions. In particular, it predicts that structurally eligible IPL sites should be detectable at dendritic convergence regions where abutted spines from different neurons occur in close proximity, and that selective disruption of inter-spine coupling at such sites should impair associative recall. These predictions provide a direct framework for experimental evaluation using approaches such as paired two-photon stimulation, super-resolution imaging, serial-section electron microscopy, and dendritic voltage imaging.

The present model does not establish the link between IPL operation and first-person properties directly, as phenomenological semblances are not accessible to third-person measurement, but it does establish that the required biophysical substrate, spine-level depolarization driven by IPL reactivation in the absence of presynaptic input, is structurally feasible within real cortical tissue. Testing this substrate through serial-section electron microscopic reconstruction, super-resolution imaging of spine-spine contacts, and dendritic voltage imaging during active recall are the essential next steps. Confirmation that IPL-mediated inter-spine coupling occurs with the predicted activity-dependence and anatomical distribution would provide a testable, mechanistic account of how associative content is reinstated at the sub-neuronal level, and open a tractable experimental path toward understanding the neural basis of first-person memory experience.

Abbreviations

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANN, artificial neural network; CS, conditioned stimulus; ECM, extracellular matrix; EPSPs, excitatory postsynaptic potentials; IILSPs, islets of inter-linked spines; IPL, inter-postsynaptic functional link; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate; Pre, presynaptic terminal; Post, postsynaptic terminal; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; US, unconditioned stimulus; VAMP, vesicle-associated membrane proteins or synaptobrevins.

Availability of Data and Materials

All code and documentation are available at https://github.com/associative-memory/ipl_model and archived at https://zenodo.org/records/22311203.

Author Contributions

KIV conceived and developed the IPL theoretical framework, conducted all theoretical analysis, derived system constraints, formulated testable predictions, and wrote the manuscript. The author was responsible for the conception of ideas presented, writing, and the entire preparation of this manuscript. The author read and approved the final manuscript. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The author declares no conflicts of interest. KIV is the inventor of U.S. Patent No. 9,477,924 B2, which is an electronic circuit model of the inter-postsynaptic functional link, described in the theoretical framework presented in this manuscript. Neurosearch Center is an independent research center. KIV is a scientist working there.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the author used Claude AI (Anthropic) for code suggestions and debugging assistance in the development of the computational model to implement the author-specified theoretical framework. After using this tool, the author reviewed and edited the code as necessary and takes full responsibility for the model design, parameter selection, and interpretation.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/JIN49226.

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