Retrodictive evidence for the structure of memory engram

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Abstract

Using constraints from findings at multiple levels, a testable description of the engram was provided by the semblance hypothesis. Its linchpin mechanism consists of inter-neuronal, inter-spine (inter-postsynaptic) interactions when associatively learned stimuli evoke their own specific motor outputs or intra-neuronal, inter-branch, inter-spine interactions when only one of the associatively learned stimuli elicits motor output before learning. Present work used several recent modifications of fear conditioning experiments that constrain the system operations, enabling further characterization of the engram. Details of a verifiable, latent, non-linear, dynamical, information storing engram capable of providing both motor outputs (behavior and speech) reminiscent of memory retrieval, and first-person property of memory are explained. Its gold standard test is replication in engineered systems.

1 Introduction

Engram consists of information bearing physical structures (Galllistel, 2021), and it provides "necessary (physical) conditions for a memory to emerge" (Moskovitch 2007). Details of what an engram is expected to explain, its components, and computation during a cognitive function were discussed (O'Sullivan and Ryan, 2024). Since information exists only in relation to or for a system in context (Brette 2018; Deacon 2021), it is expected to provide a plausible explanation for connecting biological events to information storage and retrieval. Since information stored during associative learning is part of the learning-generated change that exists at the time of recall (Schacter and Addis 2007), the engram must clearly lay out features explaining these expectations. For practical purposes, an engram consists of learning-changes that must be capable of generating first-person property of retrieved memories along with a provision for executing motor actions such as speech and behavior. Since the information-conveying symbols in the engram are extracted from experience and are expected to be computed at the time of memory retrieval (Galllistel, 2021), a detailed description of a testable mechanism is anticipated. Since the system needs to generate a near-infinite number of outputs using a finite number of cells, it is reasonable to expect the presence of a unitary operational mechanism capable of integrating its unitary outputs.

Our current search for engram has been restricted to conducting systematic examination using

various domains of behavior (Tolman, 1948, Behrens et al., 2018) such as speech and motor actions, by testing one variable at a time. Correlation between the population of firing neurons in different neuronal orders during learning and memory retrieval (called "engram neurons") provides only limited information about the engram (Chung and Abbott, 2021, Whittington et al., 2022). Neither molecular synaptic change (for e.g. post-translational modifications of proteins) nor electrophysiological changes (induction time of long-term potentiation) are timescale matched with that of the speed at which associative learning and memory retrieval takes place. For example, it is possible to associate more than one pair of stimuli in one second and retrieve the corresponding number of memories within another second, indicating millisecond time-scales of learning and memory. Furthermore, experiments to solve the system have found explanations for findings in each level in terms of findings from other levels. However, several of these explanations are not interconnected. How can we put these findings together to arrive at a solution that can provide interconnected explanations to understand the nature of the engram? A pragmatic method is to consider all the levels of the system simultaneously (Krakauer et al., 2017), and find a theoretical solution using constraints from non-redundant findings of different levels of the system (**Table 1**). This is similar to the approach of finding a unique solution for a system of linear equations. Such an attempt could constitute a search for a unified theory for the brain sciences (Frégnac, 2017).

Table 1. Major constraints that can be used to reach a solution for the engram.

Findings	**Constraints**
Engram consists of a learning mechanism from which memories in their true nature as a first-person property are generated.	Since memories can be viewed as cue induced hallucinations (inner sensation of something in the absence of the latter) (Minsky, 1980), a mechanism capable of generating cue-specific hallucinations is expected as the key property of the engram.
The first-person nature of memory may or may not be associated with behavioral motor actions.	The mechanism that generates first-person inner sensations must be connected with behavior such as motor actions or speech. It must have provisions to turn off behavior while inner sensations are being generated.
Motor actions can occur in response to sensory stimuli without producing any first-person awareness of the sensory stimuli.	When memories are retrieved in response to a cue stimulus for a long period of time, then there should be a provision to generate motoric responses without generating any first-person sense about the stimulus.
The nervous system can generate a near infinite number of inner sensations using a finite number of neurons.	Systems that generate large number of outputs using a limited number of inputs have shown the properties of degeneracy (e.g. codons of mRNA) or operate based on a combinatorial mechanism (e.g. immunoglobulin gene synthesis in response to a new infectious organism). Similarly, the nervous system is expected to have certain features for expanding the repertoire of outputs using limited inputs.

Table 1. Continued.	
Findings	**Constraints**
Learning and memory retrieval are associated with information storage.	Information exists only in relation to or for some system in context (Brette 2018; Deacon 2021). The part of the learning-imparted change in the system that exists at the time of recall constitutes an information storing mechanism (Schacter and Addis 2007). Hence, the mechanism of information storage must explain how appropriate outputs are generated.
The storage mechanism is expected to be completed in milliseconds (Miller and Matzel, 2006).	It should be possible to explain a timescale matched mechanism to explain both learning and memory retrieval mechanisms.
Information loss is prevented while, at the same time, the system is able to hypothesize, predict and respond to new stimuli arriving from the environment, which will enable it to survive.	Neurons operate in a threshold operated manner, allowing a very large number of combinations of input signals to generate the same action potential, showing extreme degeneracy of inputs in firing a neuron (Vadakkan, 2018). A neuron cannot make any additional output while receiving a new input signal while it is at a suprathreshold state. Hence, an engram should be capable of taking place independent of firing of the postsynaptic neuron.
An artificial memory could be reversibly disrupted by depression of synaptic strength (Nabavi et al., 2014). Augmented synaptic strength is not a crucial component of stored memory (Miller and Matzel, 2006; Chen et al., 2014).	A normal synaptic function is required to maintain learning changes to generate memory. Hence, the engram must operate in synchrony with the synaptically-connected neurons in the nervous system.
Some memories are short-lived, whereas others are long-lasting.	Engram must be reversible (forgetting), and stabilizable for different durations (explaining short-term and long-term memories).
Nervous systems function only in a narrow range of frequencies of oscillating extracellular potentials (Engel and Singer, 2001; Rusalova, 2006; Bagherzadeh et al., 2020).	A corresponding oscillation of intracellular potentials among interconnected neuronal processes is expected to occur. It should be possible to show the source and routes of potentials that can propagate in near perpendicular directions and provide vector components to generate oscillating potentials.

How to use constraints from findings of experiments carried out in different levels of the system to make a unification effort in solving this biological system having many variables? Here one may ask, "Is it possible to use the deep underlying principle in linear algebra? The Gauss-Jordan elimination method is used to find the solution/s for a system of linear equations (Andrilli and Hecker, 2022; Beezer, 2015). It was developed by using knowledge of solving simple systems of linear equations by trial-and-error method. Since it will take a long time and huge effort to solve a large system of linear equations by the trial-and-error method, the Gauss-Jordan matrix method was developed as a short-cut procedure for convenience. Thinking backwards, this informs us that it is possible to solve a large system by a trial-and-error method, even though it is going to be a time-consuming process. When translating this knowledge for the nervous system, it is possible to use constraints from manageable subsets of findings to reach possible solutions for each subset and eventually reach a solution point. This is carried out with the expectation that the value of each variable is constant in different equations (findings) of the system.

Since current experiments use behavior as a surrogate marker for the retrieved memories, the solution obtained by the above method will be for motor outputs. It is reasonable to expect that a mechanism generating first-person properties will be residing at or in the vicinity of that solution. The engram should have capabilities to operate in a dynamic manner and must be consistent with the expectations of an evolved property capable of protecting the system from predators and have an ability to compete with members of the same level of ecological pyramid to obtain prey. Once successful, it is possible to make testable predictions, examine comparable circuits in remote species and replicate the mechanism in engineered systems as gold standard proof. As an evolved mechanism, it is expected to be a simple one that provides survival advantage by sparking inner sensation (memory) about beneficial or deleterious stimuli from an item, in response to the fastest or first arriving stimulus, well before that item reaches close to the system.

It is suitable to use learning and memory retrieval to understand the engram since it is convenient to experimentally generate and verify learning-induced changes. Associative learning is best studied using conditioned learning paradigms. Classical experiments use an association between a stimulus with no motor response on its own (conditioned stimulus (CS)), and another stimulus that generates a motor response called unconditioned stimulus (US). After associative learning between CS and US, arrival of CS alone elicits motor response of the US (that occurred prior to learning), even though the latter is absent during memory retrieval (**Fig.1**).

From the results of many studies, it was possible to infer that the engram for fear conditioning exists in the amygdala (Fanselow and LeDoux, 1999). The lateral amygdala (LA), which is one of the nuclei in the basolateral amygdala (BLA), has a majority of excitatory neurons (nearly 80%) that fire to activate downstream neurons to elicit motor output by the US. It was found that neurons in the BLA that are activated during fear conditioning experiments are reactivated during memory retrieval (Reijmers et al., 2007), and LA neurons are involved in cue-reward association (Balleine and Killcross, 2006). Even though it is found that fear learning is mediated by distinct neural circuits, their operations remain poorly understood (Tovote et al., 2015, Li, 2019). Thus, a mechanistic explanation for the engram has been remained undiscovered. To overcome this seemingly inescapable challenge, there were suggestions to devise new methods to understand the first-person property and perception (Perl, 2011; LeDoux and Pine, 2016; Taschereau-Dumouchel et al., 2022). Even though various methods to understand cognitive processes were discussed (Cocchi et al., 2017; Song et al., 2024), a synthesis using constraints from findings at different levels of

the system is much more powerful to arrive at a testable solution. This led to the development of semblance hypothesis (Vadakkan, 2007, 2013, 2019) using available constraints and has provided a testable mechanism for behavioral motor actions along with generation of first-person features of memory. Several recent modified fear conditioning experiments provide additional constraints to undertake retrodictive verification of the hypothesis.

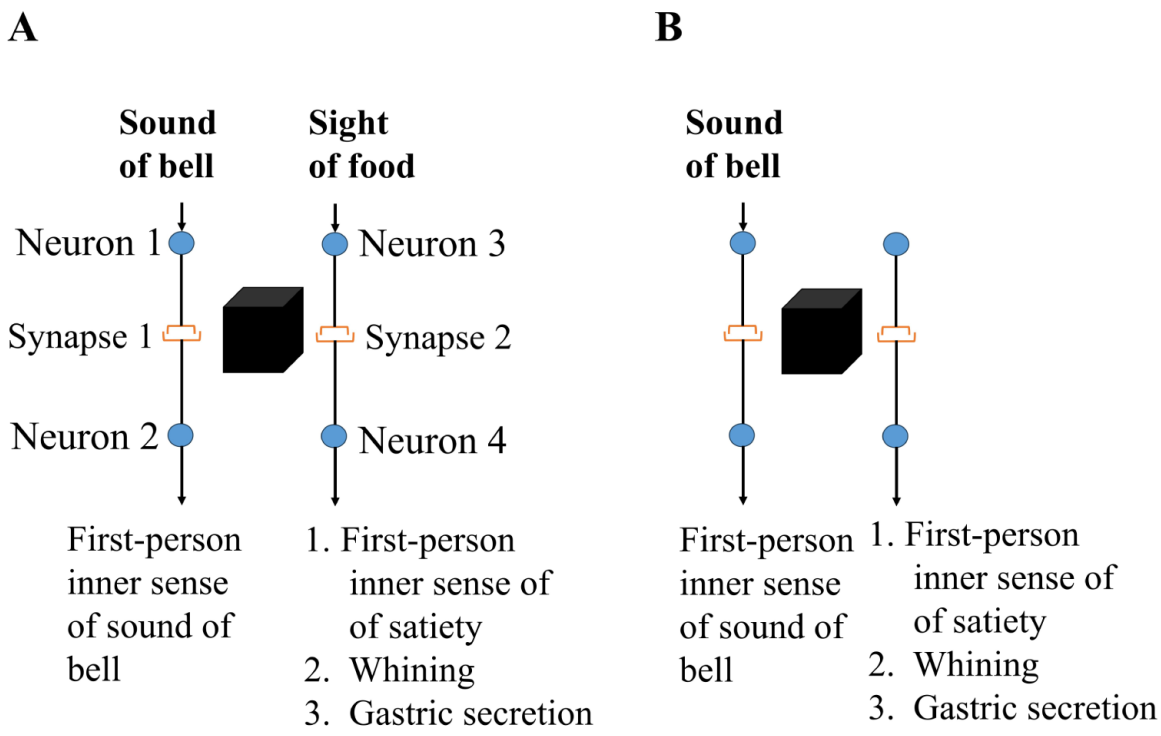

Figure 1. Necessary conditions for the conditioned learning paradigm. A) Associative learning is carried out between a stimulus that has no motor response on its own (sound of a bell) called conditioned stimulus (CS), and a stimulus that generates a motor or secretary response (e.g. whining or gastric secretion) called unconditioned stimulus (US). B) After learning, the arrival of sound from the bell (CS) alone generates motor and secretary responses reminiscent of the sight of food (US). A black box (engram) between the pathways through which CS and US stimuli propagate explains how conditioned learning takes place. An output terminal of a neuron (one of its axonal terminals) forms an input to a synapse (presynaptic terminal). An input terminal to a neuron (one of its dendritic spines or spines) forms an output from a synapse (postsynaptic terminal).

1.1 Neuronal pathway of fear conditioning

The amygdala receives sensory inputs from almost all sensory modalities (Pape H-C and Pare´, 2010). More than one division of amygdala is associated with fear conditioning (LeDoux et al., 1987; Bordi and LeDoux, 1994). LA division receives inputs from both sound (via auditory cortex), and foot shock (via thalamus) (Lanuza et al., 2008; Janak and Tye, 2015, Sun et al., 2020), and this region is thought to represent the site of convergence between discrete auditory CS and US during auditory fear conditioning (Romanski and LeDoux, 1992; Nader et al., 2001). There are projections from the amygdala to the prefrontal cortex (Likhtik et al., 2014) that send outputs to the neurons of the entorhinal cortex, which in turn synapse with CA1 neurons of the hippocampus.

The present work focuses on the input and output regions of LA neurons that have been studied extensively to find the engram. Since fear memory is affected by manipulations of different brain regions (Balderas et al., 2015, Izquierdo et al., 2016, Denny et al., 2014; Tanaka et al., 2014), a localized search around the LA neurons may only provide a subset of information about the engram. But it is hoped that details of the general principle of a unitary mechanism will become visible in this localized search.

2 Modelling the engram from a set of neurons that fire

Certain common sets of neurons fire (spike or elicit an action potential) during different cognitive functions (Whittington et al., 2022), making it difficult to understand a verifiable generative operation in terms of firing neurons (Epstein et al., 2017, Behrens et al., 2018). This has prompted the question, "How can a neural network encode many variables simultaneously (Bengio et al., 2013, Bernardi et al., 2020)? One possibility is that to facilitate generalization (Behrens et al., 2018, Yang et al., 2019), resources are being used in a shared manner at the level of input terminals. The potential from this shared hub reaches postsynaptic neurons. Depending on the regulations occurring at the input hub and the background potential arriving the postsynaptic neurons, the latter fire during different cognitive tasks. To achieve a generative property, the bases are expected to participate as common features of tasks in a manner that allows flexible recombination to generate a state definition (Behrens et al., 2018). This is possible only when there are specific interactions between input signals that fire a neuron. It is reasonable to expect that such a mechanism will be able to explain both a) firing of shared neurons in response to common features, and b) firing of specific neurons in response to specific features of the sensory inputs (Higgins et al., 2021). This necessitates the presence of a unitary mechanism for the engram and its combinatorial operation in providing appropriate neuronal outputs for motor actions. Once a solution for this unitary operation is reached, it is expected to reveal a concurrent mechanism generating first-person properties.

Since neurons of a few neighboring neuronal orders are often included in the list of "engram neurons", it is necessary to ask, "How does each neuron relate to the location/operational mechanism of the engram?" It is also necessary to verify whether firing of neurons associated with a cognitive function is a cause or effect of the engram operations. First, it is necessary to examine the conditions that make a neuron fire. A set of neurons is expected to fire repeatedly while maintaining housekeeping functions such as heartbeats (pacemaker firing of neurons in SA node), circulation, and respiration (pacemaker firing of neuros in pre-Bötzinger complex). The functions of these organs provide continuous arrival of sensory inputs to many areas of the cortex. A different set of neurons will remain short of only a fraction of the threshold potential for neuronal firing and will be able to readily respond to certain specific sensory stimuli that need quick motor responses for survival. Another set of neurons may remain short of several postsynaptic potentials, which fire only when they receive several specific inputs. Another set of neurons fires regularly and the arrival of additional inputs to these suprathreshold activated neurons do not contribute to any additional firing. Yet another set of neurons fire sporadically, but synchronously, showing sharp-wave ripples (Buzsáki, 2015, Papale et al., 2016), showing correlations with certain cognitive functions. Thus, in a background state, neurons remain in a wide spectrum of resting membrane potentials at a given time.

When a neuron fires, it activates all the synapses at its axonal terminals (presynaptic termi-

nals). But input signals arriving through only a minor fraction of a neuron's input terminals are necessary for firing (eliciting an action potential) of that neuron. This leads to the inference that an extreme degeneracy of input signals is present in firing a neuron (Vadakkan, 2017). Hence, operations that need to maintain specificity such as information storage are expected to occur at the level of spines (dendritic spines or postsynaptic terminals) and not at the level of neuronal firing. This necessitates the engram to be associated with activation of dendritic spines, irrespective of whether they are associated with firing of the latter's postsynaptic neurons or not. Since dendrites are found to have separate computational properties independent of neuronal firing (Losonczy et al., 2008; d'Aquin et al., 2022), it is most likely that the engram operates at the level of spines independent of neuronal firing. Since the brain operates only in a narrow range of frequencies of oscillating extracellular potentials (Engel and Singer, 2001; Rusalova, 2006; Bagherzadeh et al., 2020), it is necessary to explain how an inter-spine mechanism is closely associated with engram operations.

2.1 Arriving at the engram

The conventional methods towards finding a solution for the engram have been carried out by viewing behavior as a surrogate marker of memories, examining changes at the synapses, and making correlations between neuronal firing events and studying long-term potentiation (LTP). Memories were thought to result from synaptic plasticity, which is described as long-term changes in synaptic efficiency (Johansen et al., 2011). According to the studies based on synaptic plasticity thesis, two main proposals were made. These include a clustered plasticity model where neighboring spines on a dendritic branch of a neuron cluster together (Govindarajan et al., 2006, Bloss et al., 2018). However, neither cables between the adjacent spines through the dendritic shaft nor a mechanism through the extracellular matrix (ECM) space to explain an interaction between adjacent spines on a dendrite were found. Another model was that the synapses on the spines of a single neuron interact with each other using tag molecules in the cytoplasm (Frey and Morris, 1998). However, it was not possible to find matching numbers of tag molecules that could operate in matching timescales. Following these, a combination of synaptic plasticity and firing of specific neuronal ensembles was thought to be involved in the mechanism (Tonegawa et al., 2015; Bocchio et al., 2017). However, a mechanistic explanation for generating behavior at the time of memory retrieval is needed. It is necessary to replicate the mechanism in engineered systems to reliably generate first-person features.

First, it is necessary to lay out basic arguments to arrive at a foundational level. This is carried out as follows. LA neurons receive inputs from both CS and US. Before learning, CS and US are expected to propagate through separate sets of neurons. Only the US can fire LA neurons to cause foot withdrawal and CS do not generate any motor actions. The engram must explain a mechanism occurring during learning that enables the CS to trigger motor actions reminiscent of the arrival of US after learning. Excitatory postsynaptic potentials (EPSPs) evoked by stimulation of either cortical or thalamic afferents lead to increased firing responses of LA neurons after learning (Tye et al., 2008). To satisfy a minimum necessary feature of the engram, the following can be used. During learning, the engram is expected to generate a new path for the CS to propagate to make synaptic connections on to the LA output neurons of the US or cause an equivalent change in millisecond timescales. Since there is no evidence for the formation of a large number of new synapses during each learning event, it is necessary to find an equivalent change to explain the engram. This leads to the question, "After learning, how does CS generate potentials

on the spines of the pathway through which the US had propagated before learning?" A logical possibility is the occurrence of an interaction between the synapses through which signals from CS and US propagate during associative learning, which is expected to provide hints about the engram (**Fig.2**).

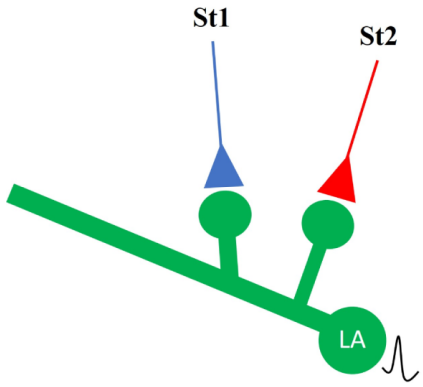

Figure 2. Configuration of locations of possible input terminals for the engram. Two associated stimuli (St1 and St2) arrive through two input terminals (blue and red) to two adjacent spines on a dendrite of one output LA neuron. Since only the US has motor action before learning, this configuration may seem suitable. However, a) it is difficult to provide an explanation of how stimulus 1 (St1) (CS) can remain without firing the LA neuron before learning, b) there is no evidence for long distance interaction between the two synapses through the extracellular matrix space, c) there is no evidence for generation of specific cables between the two spines, and d) there are no specific tag molecules operating on timescales of milliseconds.

The need for an interaction between two synapses along the pathways of CS and US leads to questions such as a) between what sub-locations of two synapses does the interaction take place? b) if two synapses do interact in a meaningful way (one evoking other's response and vice versa, what parts of the synapses must interact? The minimum statement to say that a synapse is activated is activation of its postsynaptic terminal. Hence, a mechanism that can cause interaction between the spines that synapse with axonal terminals of neurons through which CS and US propagate is expected to take place. Since the mean inter-spine distance on a dendrite of a pyramidal neuron is more than the mean spine diameter (Konur et al., 2003), interaction between two adjacent spines that have their own synapses through which CS and US arrive is not possible. The only remaining possibility is to have an interaction between abutted spines on two different dendritic branches.

Even though dendritic branches mimic branches of trees, unlike the latter, dendritic branches heavily overlap each other such that branches of one neuron go through the dendritic arbor of immediate neighboring neurons and even reach the arbor of neurons far beyond them (Cajal, 1899). Similar to that in the pyramidal neurons (Konur et al., 2003), visual inspection of images of spines on a dendrite of LA neuron (see Klenowski et al., 2017) shows that the mean spine diameter is less than the mean spine diameter. This increases the probability for the occurrence of interactions between spines that belong to different dendritic branches of either the same (rarely) or different (more often) neurons.

When only the US has motor output, and if both CS and US synapse on to the LA neurons, then interaction between the spines that belong to either different LA neurons or to different

branches of one LA neuron to which CS and US synapse can form a signature change during associative learning (**Fig.3A**). This inter-branch, interspine interaction is called inter-postsynaptic functional LINK (IPL) (Vadakkan, 2013). This will allow the arrival of CS alone (after learning) to evoke motor outputs reminiscent of the US. However, if both CS and US have their own separate motor outputs, then the above inter-spine interaction will be limited to occurring between abutted spines located on the dendritic branches of different LA neurons (**Fig.3B**).

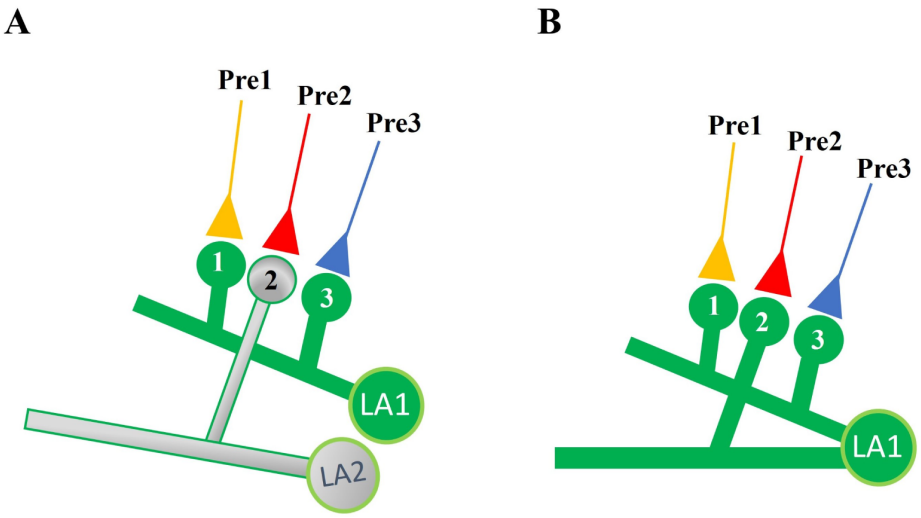

Figure 3. Two possible configurations of inter-spine interactions. These configurations can occur from a) mean inter-spine distance if more than mean-spine diameter (Konur et al., 2003), and b) there is only one motor output motor function of foot withdrawal both before and after learning. A) When the inter-spine space between spines on one dendrite (in green) of neuron LA1 is occupied by a spine of another neuron LA2, then associative learning events lead to an interaction between those inter-neuronal spines to an inter-postsynaptic functional LINK (IPL) 1-2. Such a configuration can allow associative learning when CS and US have separate motor outputs. B) When the inter-spine space between spines on one dendrite (in green) of neuron LA1 is occupied by a spine on another branch of the same neuron, then associative learning events lead to an interaction between these intra-neuronal spines to form an IPL 1-2. This configuration is suitable when only US has motor action since the output neuron LA1 is the same for both CS and US. This is possible in classical fear conditioning experiments. Since only the US has motor action and since LA neurons are output neurons from the amygdala that connects to motor neurons, both the above configurations are possible.

CS propagating across the IPL is expected to depolarize the inter-LINKed spine through which US propagated in the past, followed by firing of the latter's postsynaptic neuron. This evokes motor action reminiscent of the arrival of the US. This is suitable to explain foot withdrawal/freezing motor output of the US in classical fear conditioning experiments. This IPL formation during fear learning is a solution to the behavioral effect observed in current experimental paradigms. However, with motor action alone, this mechanism is no different from the input-output devices of present-day artificially intelligent (AI) systems. It is in this context that a thorough search for a testable mechanism that can generate first-person property in the vicinity of IPL was carried out by the semblance hypothesis. This led to the following arguments that led to a testable solution.

For the purpose of replicating the mechanism in engineered systems (Minsky, 1980), memories

have been viewed as cue induced hallucinations (inner sensation of something in its absence). Continuous quantal release of neurotransmitter molecules depolarizes the spine head. Occasional arrival of action potentials at the presynaptic terminal generates postsynaptic potentials. These events keep the postsynaptic terminal in a dominant state of being constitutively depolarized by its presynaptic terminal. While an inter-LINKed spine (through which US propagated before) maintains this dominant state, its depolarization by any spontaneous laterally arriving potentials (from the CS and through the IPL) is expected to elicit a hallucination (inner sensation of a stimulus in its absence) on the above inter-LINKed spine that it is receiving inputs through its presynaptic terminal from the environment (from the US). This hallucination forms a unitary basis of first-person property of memory and is the basis of the semblance hypothesis (Vadakkan, 2007, 2013, 2019) (**Fig.4**). This is expected to be a system property of systems where synaptic transmission and propagation of potentials across the IPLs contribute to maintaining the frequency of oscillating extracellular potentials in an optimal narrow range. Thus, a cue stimulus (CS) reactivating the IPL is expected to generate first-person internal sensation of memory (of the US) at physiological timescales and propagation of depolarization from the inter-LINKed spine towards its postsynaptic neuron can lead to motor activity reminiscent of the item or event (US) whose memory is retrieved.

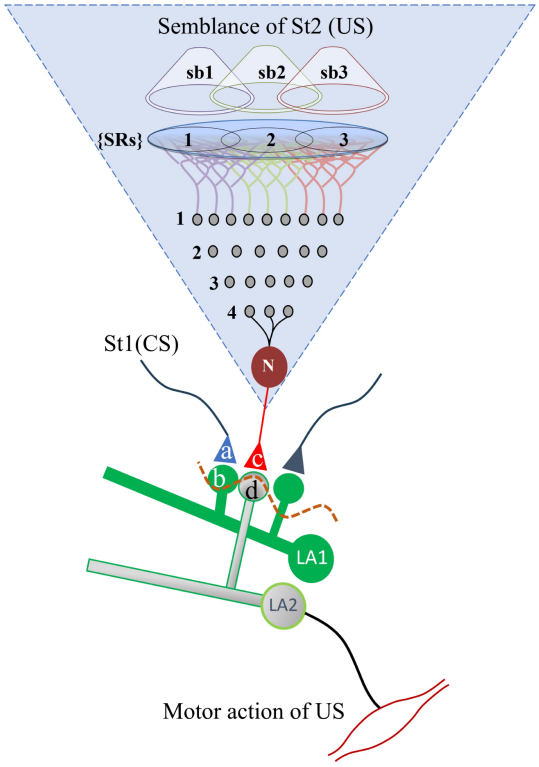

Figure 4. The solution for behavior reminiscent of the US, when CS arrives after learning, has a testable mechanism for first-person property. During associative learning between CS and US, signals propagate towards converging locations to form an inter-postsynaptic functional LINK (IPL) between spines b and d. Arrival of CS after learning reactivates IPL (b-d) and postsynaptic potentials propagates to the output neuron LA2 through which the US had propagated prior to learning, generating motor actions reminiscent of the arrival of the US. This provides a solution for fear conditioned learning being studied by examining behavior. Heads of these spines a and c are continuously being depolarized by quantally-released neurotransmitter molecules. Postsynaptic potentials are elicited on these spines occasionally when action potentials arrive at their

presynaptic terminals. These events establish a dominant state of the spines that the latter are depolarized by their presynaptic terminals that in turn receive signals from corresponding stimuli from the environment. In the above background state, arrival of CS reactivates IPL b-d to cause an incidental lateral activation of postsynaptic terminal d to spark a cellular hallucination (shown using a blue triangle with dotted lines) of US. Sensory qualia can be found out by retrograde extrapolation (blue triangle with dotted lines) (see Vadakkan, 2013). Note that the extrapolation of presynaptic terminal c to reach the sensory receptors, shown in the blue triangle with dotted lines, is virtual in nature and is a system property of systems where synaptic transmission and propagation of potentials across the IPL provide a vector component of oscillating potentials. Waveform: Synaptic transmission through synaptic junctions and propagation of depolarization through IPL b-d contribute vector components of oscillating extracellular potentials whose frequency needs to be maintained in a narrow range for generating first-person properties.

Is there a proof for the presence of IPLs? Electron microscopic (EM) examination of the cortex shows a large number of abutted spines on the dendrite of same or different neurons with a negligible ECM. Even though, fixation artifacts can be present, lack of visibility of four layers of lipid layers in several abutted spine regions of the cortex (Burette et al., 2012) indicates the presence of IPLs that need to be verified. Continued associative learning events will lead to inter-LINKing of spines that are already inter-LINKed with other spines and lead to the formation of islets of inter-LINKed spines (IILPs) (Vadakkan, 2007, 2013) (**Fig.5**). Assuming that a spine is a perfect spherical object, one spine is expected to form IPLs with thirteen to fourteen other spines (see Szpiro, 2003). Since membranes can protrude from the spine heads (Verbich et al., 2012), it is theoretically possible that each spine can make more than fourteen IPLs with its abutted spines.

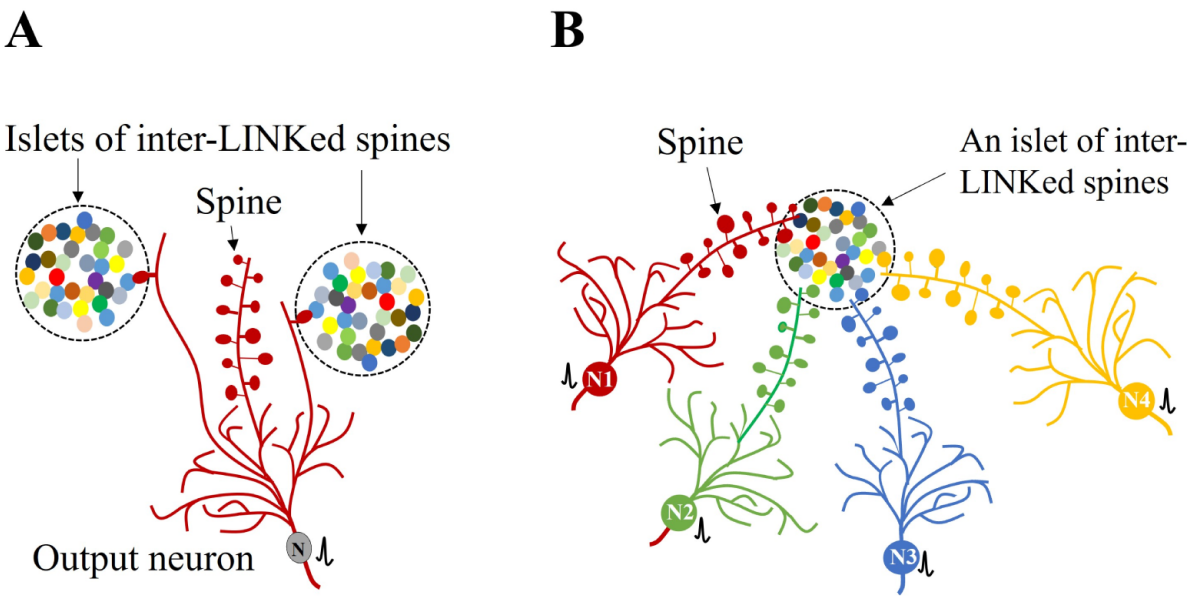

Figure 5. Structure of an islet of inter-LINKed spines (IILPs) and its relationship with dendritic branches of a single neuron. A) An IILPs (large circle with dotted lines) formed by the inter-LINKing of one spine (shown in different colors within an IILPs) each of 32 neurons. Due to space limitations, only 4 neurons, N1, N2, N3 and N4, whose spines are inter-LINKed with the IILPs are shown. Postsynaptic potentials generated on any inter-LINKed spine of an IILPs propagate through the IPLs and depolarize the inter-LINKed spine/s of an IIPLs depending on how those spines are being influenced by neighboring inter-LINKed spines at a given time. Thus,

inter-LINKed spines of an IILPs increase the possible number of circumstances under which a postsynaptic motor neuron can fire. This depends on the baseline subthreshold activation state of a given postsynaptic neuron compared to the threshold for firing and the magnitude of the sum of postsynaptic potentials arriving at the axon hillock of that neuron. Simultaneously, units of inner sensations are evoked on the inter LINKed spine heads, whose net effect generates different inner sensations. B) Three dendritic spines (in brick red) of neuron N are shown to be part of three different IIPLs (large circles with dotted lines). Summation of the potentials of inter-LINKed spines is expected to contribute to dendritic spikes (see section on dendritic spikes) that enable their propagation from remote locations on a dendrite in spite of attenuation by the distance. Different IILPs are expected to generate different first-person inner sensations for the firing of the same postsynaptic neuron (see (**Fig.4**)). Note that action potential triggered by neuron N1 can backpropagate to the IILPs and continue to propagate towards neighboring spines and to neurons N2, N3 and N4. If this potential can add to the subthreshold potentials of these neurons to cross the threshold, it can fire these neurons).

The propagation of potentials across the synapses and IPLs provide contributing vector components that contribute to oscillations within the intracellular compartments of interconnected neurons, which is observed as oscillating extracellular potentials. The latter can be recorded from two points in the ECM space. Normal cognitive functions take place only in a narrow range of frequencies of oscillating extracellular potentials (Engel and Singer, 2001; Rusalova, 2006; Bagherzadeh et al., 2020), making generation of units of first-person internal sensation as a system property of systems with the above features.

3 Constraints from modified fear conditioning experiments further characterize the engram

The comparatively less stringent conditions used in classical fear conditioning experiments is likely to restrict exploration of the details of all possible routes through which depolarization propagates to generate motor actions. Since results from several recent modified fear conditioning experiments contribute several additional constraints, present work examines weather the semblance hypothesis can provide retrodictive evidence for the engram.

3.1 Fear conditioning is associated with large synapses

It is reported that fear conditioning is associated with enlarged synapses on the LA dendritic spines (Ostroff et al., 2010; Choi et al., 2021). Since large synapses are likely to have large spines, it matches with the inference that enlarged spines promote IPL formation during associative learning (Vadakkan, 2019). In fear conditioned animals, synapses on the spines of LA dendrites show a greater ratio of the area of postsynaptic density (PSD) compared to that of the docked vesicles in the presynaptic terminals (Ostroff et al., 2012), indicating that the spines enlarge laterally during learning. This also matches with the proposal that IPL formation occurs between the lateral aspects of abutted spines. This becomes more convincing since several evidences suggest that vesicles containing glutamate receptor subunits are often observed at the lateral margins of spines (Rácz et al., 2004; Lu et al., 2007; Petrini et al., 2009; Makino and Malinow, 2009; Opazo and Choquet, 2011; Jacob and Weinberg, 2015).

3.2 Reward-learning success is proportional to the number of LA neurons responding to reward-predictive cue

EPSCs evoked by stimulation of either thalamic or cortical afferents show elevated responses of LA neurons after learning (Tye et al., 2008), indicating that the engram is likely located at the locations of convergence of pathways through which CS and US propagate. This study found that following a reward-learning association, the number of LA neurons firing in response to a specific CS is increased. This indicates that the CS pathway gets connected to the US pathway by the formation of a connection between the synapses through which CS and US propagate. The best possible location where CS can connect to the US pathway is likely at the level of the input regions of LA neurons during learning and that depolarization propagates through these connections to elicit firing of neurons of the US path. This matches with the semblance hypothesis that explains how an interaction between abutted spines to which CS and US paths synapse can generate both motor effects and first-person properties. Firing of postsynaptic neurons of inter-LINKed spines (**Fig.4**) explains how reward-learning success is proportional to the number of LA neurons responding to reward-predictive cues.

3.3 Compartmentalized activation of dendrites independent of the soma of LA PNs

Both compartmentalized and binary behavior of parallel-connected terminal dendrites have been reported (Wei et al., 2001). Several studies following this led to the view that dendrites are locations where certain computations take place (Poirazi and Papoutsi, 2020). Even though neuronal firing occurs in an "all or none" manner, examination based on the semblance hypothesis shows functional significance of each postsynaptic event on a dendrite (Vadakkan, 2016c). Using deep brain two-photon Ca2+ imaging, it is observed that fear conditioning leads to activations of dendrites and soma (cell body) at different time points by compartment-specific inhibition (d'Aquin et al., 2022). This study found events mimicking integration of dendritic sensory inputs uncoupled from the firing of LA PNs. These lead to the following questions. 1) Is there any computational principle behind local sensory inputs to the spines on the dendrites? 2) Do associatively learned sensory inputs of both CS and US are involved in the compartmentalized dendritic function? If so, how are they related to motor output? 3) Are there any possible functional explanations for the uncoupling between dendritic events and neuronal firing? 4) Are local inhibitory neurons involved in the above? 5) Can the engram provide a mechanistic explanation for fear conditioned learning whereby CS elicits responses reminiscent of the US after fear conditioning?

Interconnected explanations are possible for the above questions based on the semblance hypothesis as follows. IILPs can act as a computational hub where first-person inner sensations are generated independent of neuronal firing. If the net potential at an IILPs is more than a certain value, it can generate a dendritic spike. This is accompanied by generation and integration of units of inner sensations and firing of some of the postsynaptic neurons of spines within the IILPs to manifest motor outputs (**Fig.6**). There can be local spatial regulation within the IILPs to channelize potentials to specific postsynaptic neurons for a specific motor output. Such regulation can be brought about by inter-LINKing of a spine of one LA PN within an IILPs with the spine of another PN that synapses with an inhibitory interneuron.

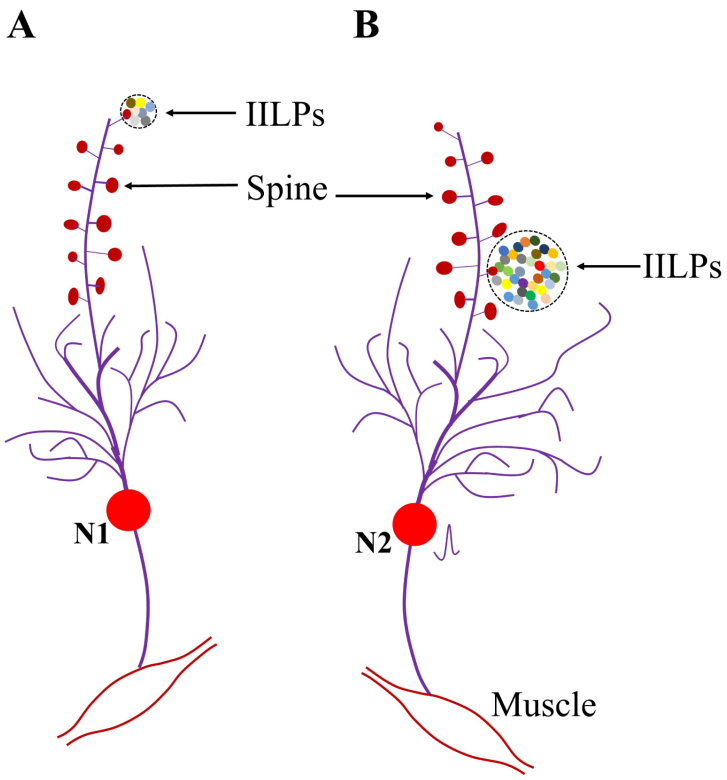

Figure 6. Dendritic computations and postsynaptic neuronal firing. Since individual postsynaptic potentials attenuate as they propagate towards the cell body, and since some of them even become extinct (Spruston, 2008), the best location for information storage is at the spine head. It also explains the disconnect between EPSPs on single spine heads and neuronal firing. In this context, islets of inter-LINKed spines (IILPs) are expected to summate the potentials to trigger dendritic spikes that can be propagated towards the cell body with comparatively lesser loss of potentials to guarantee firing of the postsynaptic neuron to do motor actions for behavior/speech. IILPs concurrently act as a computational hub where information can be retrieved as first-person inner sensations. A) Neuron N1 has been receiving 132 input signals as its baseline. Even summated EPSPs from the IILPs located at the apical segment of a cortical pyramidal neuron attenuate as they reach the axon hillock. Hence, a dendritic spike from the IILPs does not contribute sufficient potentials either for spatial or temporal summation to generate an action potential for motor output (behavior/ speech). Here, the first-person property elicited at the IILPs is independent of the firing of postsynaptic neuron N1. B) Neuron N2 has been receiving 130 input signals as its baseline. Since the IILPs that generate dendritic spikes is close to the cell body, the high potential generated gets attenuated relatively less. Arrival of additional summated input signals from the IILPs through the spine of neuron N2 fires the latter to provide motor output (behavior/ speech). Note that local inhibition of an inter-LINKed spine within an IILPs can prevent potentials from reaching the cell body of its postsynaptic neuron.

Disconnection between dendritic depolarization and neuronal firing in fear conditioning (d'Aquin et al., 2022), and activation of a spine of a synapse while its postsynaptic neuron remains in a subthreshold activated state matches with the inferences made by the semblance hypothesis that activation of an inter-LINKed dendritic spine is associated with generation of first-person property that is not always followed by LA neuronal firing for motor action (**Fig.6**). Such a disconnect

between generation of first-person property and neuronal firing occurs either naturally or when behavioral motor action is suppressed voluntarily using separate inhibitory neurons.

3.4 AMPAR incorporation into the spine membrane is necessary for fear learning

a-amino-3-hydroxy-5-methyl-isoxazole propionic acid subtype of glutamate receptor (AMPAR) is a fast kinetic glutamate receptor subtype formed from different polypeptide subunits. AMPARs are incorporated on to the spine membranes in regions that are involved in learning (Matsuo et al., 2008). Specifically, it was shown that fear conditioning drives AMPARs into the synapse of a large fraction of postsynaptic neurons in the LA (Rumpel et al., 2005; Nedelescu et al., 2010). After translation of AMPAR subunit mRNAs, the corresponding polypeptides are transported to the spine membrane using membrane-bound vesicles. At the end of this transport, AMPAR subunits get incorporated into the spine membrane, while vesicle membrane fuses with the spine membrane, leading to lateral spine expansion. It was shown that exocytosis of AMPARs is essential for maintaining a mobile pool of surface AMPARs at the lateral spine region (Petrini et al., 2009). Additional support comes from the finding that the GluR1subunit of AMPARs are located on the lateral spine membrane up to 25 nm away from the synaptic junction (Jacob and Weinberg, 2015). These inserted AMPAR subunit polypeptides undergo lateral diffusion along the membrane, assemble to form functional AMPARs, and move towards the synapse (Opazo and Choquet, 2011; van der Sluijs and Hoogenraad, 2011). The finding that fear learning increases the ratio between the area of postsynaptic density (PSD), and docked vesicles at the presynaptic terminals (Ostroff et al., 2012) matches with lateral expansion of spines.

3.5 AMPAR endocytosis leads to loss of associatively learned fear

A study showed that fear memory is reduced if synaptic incorporation of AMPARs is blocked in as few as 10 to 20% of LA neurons (Rumpel et al., 2005). It was also shown that memory erasure is associated with removal of synaptic AMPARs in the LA (Dalton et al., 2008; Clem and Huganir, 2010). Since AMPAR endocytosis necessitates removal of membrane segments from the lateral spine head regions causing reduction in spine size, it can lead to reversal of IPLs and can explain memory erasure. Hence, memory erasure can be explained in terms of reversal of IPLs due secondary to removal of membrane segments by endocytosis of receptor subunits from the lateral spine region. Once the functional role of AMPARs is completed or stopped by some regulatory mechanism, AMPARs diffuse laterally away from the postsynaptic terminal to specialized endocytic zones on the plasma membrane adjacent to the postsynaptic density (PSD) (Lu et al., 2007; Opazo and Choquet, 2011). AMPARs are then transported from the spine membrane to the cytoplasm by endocytosis, first by invagination of spine membrane followed by detachment of the endocytic vesicles from the spine membrane. AMPARs undergo both constitutive and activity-dependent translocations from the postsynaptic membrane to the cytoplasm via endocytosis (Luscher et al., 1999; Ehlers, 2000; Lee et al., 2004 Henley et al., 2011; Anggono and Huganir, 2012). The organization of endocytotic machinery at the lateral regions of spines tangential to the synapse (Rácz et al., 2004) indicates that this is the most likely membrane location at which receptor subunits are mobilized back and forth from the cytoplasm. The endocytosed AMPARs are either targeted for degradation in lysosomes or get recycled back to the spine membrane. Reversal of IPLs explains memory erasure (**Fig.7**). Fast dynamics of these processes inform on the timescale

at which learning changes occur, duration of working memory, and its rapid reversal. Stabilization of IPLs can contribute to persistence of learning-induced changes.

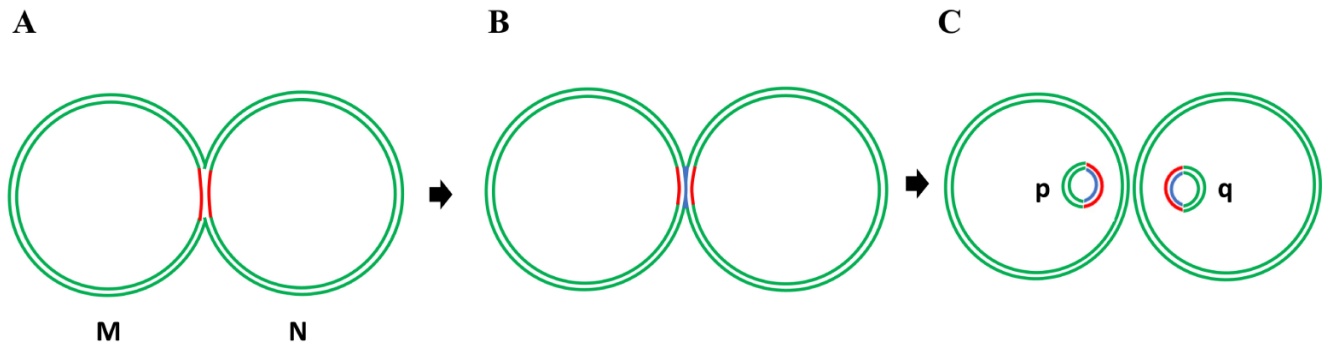

Figure 7. A figure showing how endocytosis causes reduction in the size of dendritic spines and reverses a newly formed IPL. A) Cross-section through two inter-LINKed dendritic spines that form a hemifused structure. Note that at the location of hemifusion there are only two phospholipid layers instead of four. B) When endocytosis begins, the membrane segments invaginate gradually from the spine membranes to form endosomes (not shown). In this process, the circumference of spines is reduced. The intermediate stage of the reversal of hemifused site (from two phospholipid layers) to independent membranes appears to have three layers of phospholipid layers. C) When the endosomes are fully formed, IPLs completely reverse back to form independent spines, allowing a hydration layer to appear between the spines. Note that endosome membranes are made of part of the membrane regions that were taking part in IPL structure in figure A. Red: Inner membrane segments of the spines become outer membrane segments of the endosomes. Blue: Outer membrane segments of the spines become inner membrane segments of the endosomes.

3.6 Autophagy operates to irreversibly erase fear memory

Stimulation of autophagy by tat-beclin 1 (tBC) causes the autophagosome to fuse with the endosome-lysosome system and degrades the contents of the latter, for e.g. AMPARs. It was found that stimulation of autophagy in the amygdala results in erasure of auditory fear memory due to AMPAR endocytosis (Shehata et al., 2018). This observation is expected to arise from a non-trivial mechanism. Transport of AMPAR subunits to the cytoplasm by endocytosis will inevitably use invaginated spine membranes for the formation of endosomes. Stimulation of continuous endocytosis by tBC transporting more AMPAR subunits from the lateral spine membranes to the cytoplasm will reduce the spine size specifically at the lateral spine margins and cause reversal of IPLs, leading to forgetting of the learned fear association with CS. In this situation, arrival of one of the associatively learned stimuli (CS) will not result in either generation of motor outputs or first-person inner sensation of memory of fear.

3.7 Induction of autophagy in between two specific fear learning events further constrains the engram

A modified fear conditioning study was conducted using different frequencies of sound (7 and 3 Hz) as CS in two separate learning events using the same US (Abdou et al., 2018). Erasure of associatively learned changes between a specific frequency of sound and foot shock was achieved

by inducing autophagy by injecting tBC into LA neurons after their associative learning. The study found that autophagy erases learning-induced changes that are protein synthesis resistant. Changes caused by autophagy reverse back to the background state within 5 hours and allow a new associative learning between a different frequency of sound and the same US.

Following autophagy that reverses inter-LINKed spines back to independent spines, a robust constitutive mechanism for recycling the membrane lipids back to the spine membranes is expected to take place quickly (Hao and Maxfield, 2000; Zhou et al., 2022; Wu et al., 2023). This reduces the amount of lipid molecules that need to be synthesized de novo. This allows the cell membrane of spines to restore their structure back to the normal state within five hours, at which time another specific pair of abutted spines can be inter-LINKed to accomplish a second specific associative learning between another frequency of sound and US. Since these experiments neither specified whether the same LA neuron receives inputs from both CS and US, nor identified which of the LA neurons are injected with tBC, two possible configurations of connections are possible (**Fig.8**).

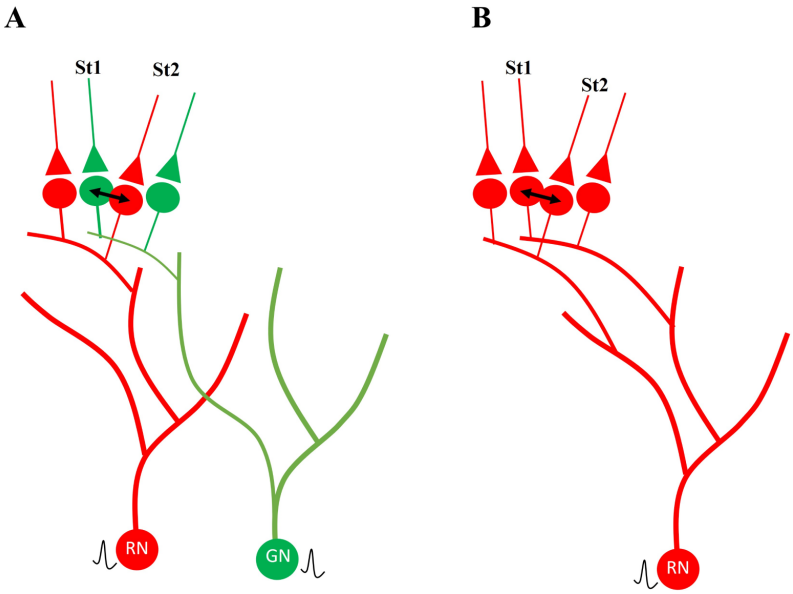

Figure 8. Two possible configurations of IPLs formed in fear conditioning using the same US. Autophagy removes membrane segments from the lateral spine region, which in turn reduces the spine diameter and facilitate reversal of the IPL, causing permanent erasure of a specific memory. A) Formation of an interneuronal interspine LINK where the same output function is generated by two different LA neurons, LA1 and LA2 (see Fig.3A). During associative learning, encoding takes place by the formation of an inter-postsynaptic functional LINK (IPL) (shown by a double arrowed line) between spines that belong to different LA neurons. It is reasonable to assume that at least one of the LA neurons whose spines are participating in IPL formation needs to get injected with tBC for the IPL to reverse back. B) Formation of an intra-neuronal inter-branch interspine LINK where the output function is generated by a single output neuron LA1 (see Fig.3B). tBC injected into an LA neuron spreads to all the spines of that neuron.

3.8 Strength of fear memory increases following experimental increase in transcription

Histones are positively charged basic proteins around which negatively charged DNA wrap in a compact manner. HAT causes acetylation of histones that will reduce the latter's affinity to DNA, exposing the latter to undergo transcription. A study found that when mice were injected with histone acetyl transferase (HAT) enzyme to increase transcription, strength of fear memory is increased (Santoni et al., 2024). The study also found a) neurons in which HAT is overexpressed are the neurons that fire during memory retrieval, and b) optogenetic silencing of these specific set of neurons prevents fear memory recall. Can any specific mechanism explain the increase in HAT-induced gene expression while associating with endangering fear-inducing events?

Even though HAT is non-specific in removing histone proteins from the DNA sequences, the presence of HAT likely increases transcription at locations where gene expression is regulated. At the time of associative learning, when membrane segments are utilized for IPL formation, exposure to HAT is expected to trigger synthesis of more phospholipid molecules to replace membrane segments used for endocytosis. This will help formation of IPLs between the spines while maintaining all the remaining essential endocytotic processes of the cell. Thus, homeostatic mechanisms to synthesize fatty acids (mainly palmitic acid) by a multienzyme complex followed by desaturase and elongase enzyme actions, synthesis of phospholipids, their transport and incorporation into the plasma membranes (Fagone and Jackowski, 2009, Exterkate et al., 2019) are expected to occur. Since IPLs are formed between spines that form synapses, several homeostatic mechanisms that are expected to occur during this transition explain findings in the above study (Santoni et al., 2024) that HAT promotes increased expression of synaptic proteins.

3.9 Retraction of astrocytic pedocytes from perisynaptic region during fear learning

Space around one spine determines the number of spines that it can inter-LINK with. In the CA1 region, less than 50% of the perisynaptic area is covered by astrocytic pedocytes (Ventura and Harris, 1999) to provide nutrition and uptake of spilled neurotransmitter molecules. It is found that during associative learning, astrocytic pedocytes move away from enlarging synaptic regions (Ostroff et al., 2014). This study found that during threat conditioning, small synapses are activated, large spines lose their surrounding astrocytic pedocytes, and large LA synapses have disproportionately long astrocyte-free perimeter. Furthermore, it was observed that glutamate application induces retraction of astrocytic processes from the vicinity of mushroom spine heads, followed by protrusions from the spine heads (Verbich et al., 2012). Based on the semblance hypothesis, these changes occur to facilitate formation of inter-LINKs between spines at the locations of convergence of sensory stimuli during associative learning.

3.10 LTP and LTD of specific input pathways have opposing effect on fear memory

LTP is an experimental finding that was observed while testing for long-lasting electrical changes in the neuronal connections following learning. When a high energy stimulation is applied in the presynaptic region, a long-lasting potentiated effect is observed at a synaptic region in the hippocampus that lasts for several hours and is called LTP (Lømo, 1971; Bliss and Lømo, 1973).

Following this, a large number of correlations were found between the ability to learn and induce LTP. Later, it was demonstrated that learning causes a change similar to LTP and learning and LTP can occlude each other (Moser et al., 1998, Whitlock et al., 2006). However, a causal link between synaptic changes and a learning mechanism that can be used for retrieving memory has been difficult to demonstrate (Stevens, 1998; Sjöström, 2021).

In an in vivo study, the thalamo-amygdala pathway was rapidly potentiated during acquisition of conditioned fear (Quirk et al., 1995, 1997). It was shown that a) fear conditioning induces changes equivalent to that of long-term potentiation (LTP) (Rogan et al., 1997), b) LTP is selectively induced in specific auditory pathways during fear memory formation (Kim and Cho, 2017), and c) fear learning can be reactivated by inducing LTP (Nabavi et al., 2014). AMPARs contribute to amygdala-dependent emotional learning and AMPAR subunit GluR1-dependent synaptic plasticity is found to be the dominant form of LTP underlying the acquisition of auditory and contextual fear conditioning (Humeau et al., 2007). Thus, it is thought that fear conditioning is mediated by changes in the strength of synapses between input terminals and spines of LA neurons (Sigurdsson et al., 2007). While on protein synthesis inhibitors, induction of optical LTP by stimulating terminals of specific AC and MGN engram cells responsible for a specific associative learning (that used 7Hz sound) allowed these mice to completely recover from amnesia to the control group's freezing level (Abdou et al., 2018). These show that a non-protein synthesis dependent mechanism is responsible for immediate millisecond timescale changes of learning. Since there is no explanation for the relationship between fear conditioning and LTP (Sun et al., 2020), a logically fitting mechanism is needed to understand the engram.

When memories were viewed as first-person property, it was possible to explain features of LTP including time delay of at least 20 seconds between LTP stimulation and LTP induction (Gustafsson and Wigström, 1990, Escobar and Derrick, 2007) by the IPL mechanism. This is explained in terms of a time-dependent scaled up exocytosis of vesicles containing AMPARs that add their membrane segments to the lateral spine regions, causing spine expansion and facilitating the formation of large number of non-specific IPLs in response to the high energy used in LTP stimulation (Vadakkan, 2019). This is supported by the observation that the density of AMPARs depends on the size of spines (Matsuzaki et al., 2001), indicating the possibility that membranes of AMPAR vesicles get added to spine membranes, enabling spine expansion. Findings that LTP induces movement of AMPARs to the synapses (Hayashi et al., 2000), and preferred sites where LTP can be induced are locations having small spines (Matsuzaki et al., 2004) further support the inference that IPL formation is responsible for LTP induction. Since the majority of AMPARs arriving at the synapses during LTP is from lateral diffusion of spine surface receptors (Makino and Malinow, 2009), it further supports the inference that exocytosis adds membrane segments of vesicles to the lateral spine region, facilitating IPL formation (see section 5). The finding that surface AMPARs are immobilized at the synapses following synaptic potentiation (Petrini et al., 2009) indicates that the IPLs are maintained intact during this period by preventing endocytosis of AMPARs from the lateral spine regions.

Depotentiation reverses conditioning-induced potentiation at the thalamic input synapses onto the LA neurons ex vivo (Kim et al., 2007), and fear conditioning is inactivated by long-term depression (LTD) (Nabavi et al., 2014). Fear extinction occludes depotentiation and blockage of AMPAR endocytosis inhibits depotentiation in vivo (Kim et al., 2007). These match with the inference that invagination of lateral spine membranes during endocytosis removes portions of

membrane segments, causing reduction in the size of spines, resulting in reversal of existing IPLs. In contrast to exocytosis of AMPAR subunits and the latter's incorporation into functional AMPA receptor channels in the synapses during LTP induction by strong depolarization of spines, modest depolarization used in LTD causes AMPAR endocytosis (Carroll et al., 2001, Waung et al., 2008, Lüscher and Malenka, 2012). Endocytosis of AMPARs is found to occur by a signaling mechanism that is shared with LTD (Beattie et al., 2000). These match with the finding that AMPAR endocytosis causes LTP decay and memory loss (Dong et al., 2015). Recent experiments validate the relationship between exocytosis and endocytosis of AMPARs in experimental LTP and LTD respectively (Sumi and Harada, 2020) (**Figs.7,8**). Thus, memory erasure and LTD induction can be explained in terms of reversal of IPLs.

Optogenetic potentiation or depotentiation of a specific CS input pathway (using either 7Hz or 4Hz frequency of sound) following its associative learning with the US affects recall only in response to the corresponding specific cue stimulus and not the other (Abdou et al., 2018). This shows that the mechanism responsible for memory storage should take place along specific routes through which optogenetic stimulation propagates to reinstate or reverse respectively the specific learning induced signature change. This is expected to be achieved by backpropagation reactivating IILPs between spines of LA neurons. According to the semblance hypothesis, LTP is generated by the formation of large number of non-specific IPLs and specificity of LTP in response to stimulation of specific pathways is described by the "associativity" and "input specificity" features attributed by specific sets of IILPs formed in response to LTP stimulation at specific loci (Vadakkan, 2019). Abdou et al.'s work provides retrodictive evidence to explain that fear learning between a specific stimulus (e.g. 7Hz sound) and US (e.g. foot shock) leads to input specific associativity between several specific spines where these inputs converge to form part of IILPs.

In the mice treated with both tBC and protein synthesis inhibitor, it was possible to elicit optical LTP (Abdou et al., 2018), which showed only a slight increase in the freezing level compared to that occurred in the unpaired control group. This can be explained as follows. tBC reverses back all the learning generated specific IPLs and even reduces the size of abutted spines to get separated from each other. Hence, after tBC treatment, optical LTP induced at the input engram cells leads to the formation of many new non-specific IPLs that can generate only non-specific semblances, which will not result in any specific memory in response to specific frequencies of sounds with which associative learning events took place in the past. However, a fraction of IPLs will inter-LINK between spines along the pathways of CS and US. Hence, in mice treated with both tBC and protein synthesis inhibitors, CS only slightly increases the freezing level.

3.11 Oscillations of extracellular potentials in LA that connects with other brain regions

When two differential electrodes are placed in the ECM space or over the brain or extracranially over the scalp, the difference in the potentials between these points shows oscillating patterns. Oscillating extracellular potentials result from ionic changes occurring across neuronal cellular membranes that cause corresponding intracellular ionic changes in connected neuronal processes. These oscillating potentials showing different amplitudes and frequencies are recorded based on the distances and depths of the tips of electrodes in the extracellular space. Oscillations between different areas of the brain take place during learning (Bauer et al., 2007, Karalis et al., 2016, Bocchio et al., 2017). Cognitive functions take place only in a narrow range of frequencies of

these oscillating extracellular potentials (Engel and Singer, 2001; Rusalova, 2006; Bagherzadeh et al., 2020). These oscillations can be explained in terms of a) IPL mechanism where synaptic transmission and near perpendicular propagation of depolarization across the IPLs provide vector components (Vadakkan, 2010) to oscillations, and b) oscillations between inhibitory interneurons connected by gap junctions (Traub et al., 2001, Fukuda et al., 2006) when an IILPs has inter-LINKed spines that synapse with inhibitory neuronal terminals. Internal and external background sensory stimuli continuously reactivate large number of IPLs to generate a net background inner sensation of "self". The finding that nasal respiration entrains limbic oscillations and modulates cognitive function (Zelano et al., 2016) is an attestation to the inferred role of the IPL mechanism in providing vector components of oscillating extracellular potentials, which is essential to keep the system operating normally.

Phasic response of LA neurons to a reward-predictive cue (Tye et al., 2008) indicates that operations through various IILPs take different durations to cause firing of LA neurons. Oscillations of potentials by IIPLs and inhibitory interneurons can contribute to phasic responses of neuronal firing. It was found that after fear conditions, firing of LA neurons increase in response to CS (Tye et al., 2008) and these firing events become more synchronized through modulating theta frequency in the LA (Pare´ and Collins, 2000). Synchronous oscillations in the theta and gamma bands occur between the BLA and interconnected structures during retrieval of fear memories and consolidation (Bauer et al., 2004; Seidenbecher et al., 2003). Furthermore, memory retrieval triggers synchronization of rhythmic activity between the BLA and interconnected structures along with reactivation of engram neurons (Bocchio et al., 2017). In BLA, neuronal membranes display intrinsic resonance at theta frequency (Pape and Driesang, 1998; Pare´ et al., 1995) contributing to theta oscillations in the local field potentials (LFP) independently of synaptic potentials. Based on the semblance hypothesis, these can be explained in terms of reactivation of inter-LINKed spines (within several IILPs) on the dendrites of LA neurons. Furthermore, if one of the inhibitory neurons among a set of oscillating inhibitory neurons synapse with a spine of one of the PN neurons that is part of an IILPs, it is expected to modulate synchronization of membrane potentials among those postsynaptic PNs.

In addition to maintaining oscillating extracellular potentials, inhibitory interneurons also have an additional role in fear conditioning. Since fear conditioning is associated with enlarged synapses on the LA dendritic spines (Ostroff et al., 2010), and since dopamine is known to cause spine expansion (Yagishita et al., 2014), it is reasonable to expect that dopamine facilitates IPL formation at the input level of LA neurons. However, in the amygdala, dopamine reduces feed-forward inhibition to LA projection neurons by increasing inhibitory inputs to the local interneurons to achieve disinhibition (Rosenkranz and Grace, 2002, Lorétan et al., 2004). Inhibition of inhibitory input (disinhibition) observed in fear learning (Ehrlich et al., 2009) can lead to an increase in the net depolarization of neighboring inter-LINKed spines within an IILPs that may allow some of the postsynaptic PN neurons to cross the threshold for firing. Fear learning is augmented by disinhibition of projection neurons causing the latter's excitation to accomplish output functions (Letzkus et al., 2015). Similar to this, the findings of both optogenetic stimulation of dopaminergic neurons (Jo et al., 2018), and facilitation of aversive learning by infusion of dopaminergic agonists in the amygdala (Guarraci et al., 1999, Frick et al., 2022) can be explained by disinhibition. Further support comes from the finding that dopamine gates LTP induction in LA by suppressing feedforward inhibition (Bisseire et al., 2003). Disinhibition targeting dendrites of CA1 PNs increases firing of the latter and augments fear learning (Lovett-Barron et al., 2024) is an additional circuit control.

4 Engram consists of a hub at the locations of interacting input terminals

All sensory inputs converge in the hippocampus (Mišić et al., 2014, Schedlbauer et al., 2014, Geib et al., 2017) after 4 to 5 neuronal orders. Specific sets of hippocampal CA1 neurons that fire when an animal reaches a specific place are called place cells (O'Keefe and Dostrovsky, 1971). They are also correlated with different extra-spatial cognitive functions such as motion trajectory (Frank et al., 2000), localization and memory retrieval in different contexts (Pastalkova et al., 2008), response to reward (Gauthier and Tank, 2018), response to auditory frequency in cognitive tasks (Aronov et al., 2017), formation of visual map (Killian et al., 2012), mental navigation (Neupane et al., 2024), organization of conceptual knowledge (Constantinescu et al., 2016), and abstract learning (Schuck and Niv, 2019; Park et al., 2020). Hippocampal neurons fire during different tasks independent of each other (Samborska et al., 2022, Tang et al., 2023, Courellis et al., 2024). In humans, visual images lead to firing of sparsely located neurons among a large population of hippocampal neurons (Waydo et al., 2006). Even though population firing of hippocampal neurons forms low-dimensional manifolds that contain a geometric representation of learned knowledge (Nieh et al., 2021), it is necessary to understand the high-dimensional detailed mechanism that can explain how the system generalizes in response to a new cue stimulus.

Firing of same set of neurons by two different types of cognitive functions severely constrains its operational mechanism that necessitates precise explanation of how and where specific information gets coded. We can ask, "What must occur to achieve both specificity of learning and firing of a common subset of neurons?" It can be inferred from studies (Palmer et al. 2014; Eyal et al., 2018) that any set of nearly 140 input signals can fire a cortical PN. Hence, PNs having thousands of input terminals can be fired by a gigantic combination of input signals arriving through those input terminals. This extreme degeneracy of input signals in firing a neuron (Vadakkan, 2019) makes neuronal firing non-specific with respect to a specific input signal. The above findings lead to the question, "How is it possible to maintain specificity of learning and memory retrieval along with a) firing of common subsets of neurons in two different learning events, and b) show the ability to generalize either in generating first-person properties or evoking motor outputs?"

One way to achieve the above is through a hub of interacting input terminals that belong to different neurons (when CS and US have different motor outputs) or on different branches of the same neuron (when only the US has motor output before learning) that can generate a combinatorial mechanism leading to firing of a specific set of output neurons that include both common shared and specific subsets (**Fig.9**). IILPs proposed by the semblance hypothesis match with the essential features of this hub. Each hub of IILPs located upstream of a neuron is expected to be capable of generating several dynamic subdomains within it that respond to different query signals. A stimulus arriving at an inter-LINKed spine of an IILPs generates motor outputs that are not formed from direct specific associative learning with other stimuli that normally generate those outputs. This is responsible for generalization. The holding of neurons at subthreshold potentials short of a few postsynaptic potentials (PSPs) or a fraction of one PSP prepares that neuron to provide output whenever sufficient cue stimuli arrive and also participates in the generalization property.

It is possible to study conditions where the same neurons are involved in different brain func-

tions. In one study, firing of hippocampal CA1 neurons during different cognitive tasks wwas examined (Chettih et al., 2024). Hippocampal neurons in chickadees show firing of a specific set of CA1 neurons in response to specific locations of hidden food and is correlated with retrieval of specific memory of the location of food, but are independent of place fields (set of CA1 neurons that fire when the bird reaches a place) (O'Keefe and Dostrovsky, 1971) for the same locations. This can be explained in terms of specific sets of input signals arriving at different sets of IILPs, leading to the firing of specific sets of postsynaptic neurons. Different spines of a neuron form part of different IILPs in different associative learning events (**Fig.5B**). Hence, firing of one neuron takes place in several circumstances when it receives sufficient input from its spines that are part of different IILPs. When plotted, the sets of neurons that fire during different cognitive events appear like different bar codes as explained by the investigators.

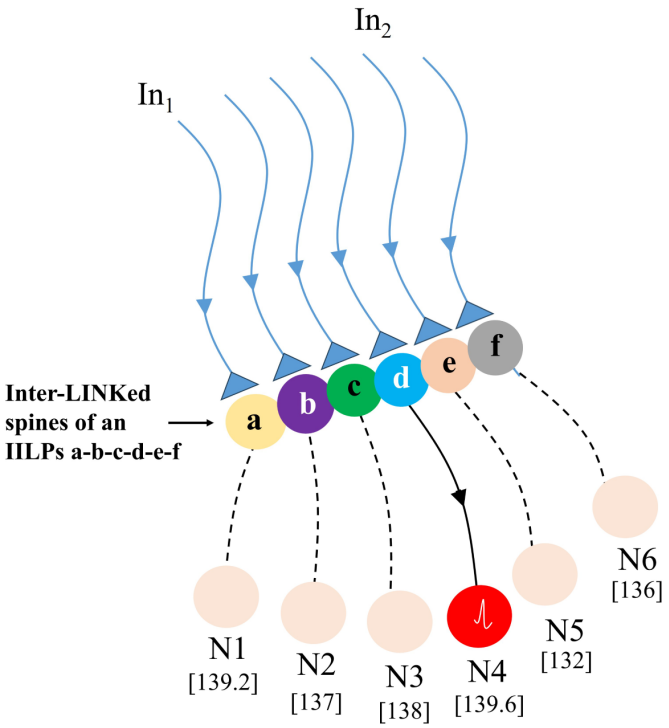

Figure 9. Operational features of a hub of IILPs where input terminals of different neurons interact. Cross-section though an IILPs formed between spine heads a, b, c, d, e and f. Summated potentials at the axon hillocks of neurons N1 to N6 are given in square brackets below their names. Postsynaptic potential (PSP) elicited by input 1 (In1) on postsynaptic terminal (spine) a provides sufficient voltage to cause firing of neuron N1. Input 2 (In2) to the postsynaptic terminal e does not lead to firing of neuron N6. However, propagation of PSPs from either input In1 or In2 to inter-LINKed spines a and e respectively will propagate across IILPs a-b-c-d-e-f and lead to the addition of required potentials to the background summated PSPs arriving at the axonal hillock of neuron N4 resulting in its firing. This shows that neuron N4 fires even when its spine within the given IILPs is not directly depolarized by an action potential arriving at its presynaptic terminal. It is the net strength of input signals that arrive at an inter-LINKed spine of the corresponding postsynaptic neuron that determines whether it can allow that neuron to cross the threshold at each moment (when the neuron is not in a refractory period). Thus, there are both specific (e.g. N1), and common (e.g. N4) postsynaptic neurons that fire in response to different stimuli arriving at a given IILPs. Any input stimulus capable of reactivating IPLs to change membrane potentials

of the inter-LINKed spines generates semblance on them.

In the absence of inhibition of inter-LINKed spines within an IILPs, depolarization of any one of its inter-LINKed spines induced by a cue stimulus is expected to propagate to neighboring inter-LINKed spines within those IILPs. However, propagation of potentials across an IPL within one IILPs can be restricted by inter-LINKing one of its spines with another spine that synapses with an inhibitory input. This can regulate regional propagation of potentials within an IILPs, generating subdomains on those IILPs. Thus, all the relations between different learned associations within the IILPs allow generation of first-person properties and associated motor actions in response to a new cue stimulus. As the number of associative learning events increases, the size of the IIPLs increases. This leads to sharing of existing relations between inter-LINKed spines formed by previous learning events. This can favor generalization of responses by any one associatively learned item (Shaban et al., 2006) that can elicit PSPs on one of the inter-LINKed spines in an IILPs.

Regulation of an IILPs hub is expected to occur as follows. Interconnected networks of inhibitory neurons have a significant role in fear conditioning (Ciocchi et al., 2010, Cummings et al., 2021). It is shown that acquisition of fear memory requires local inhibitory circuits that constitute nearly 20% of LA neurons (Spampanato et al., 2011), and that inputs from the central amygdala that contain predominantly inhibitory interneurons is essential for fear learning in LA (Yu et al., 2017). Hence, inhibition of inhibitory neurons (disinhibition) is a major regulatory mechanism (Wolff et al., 2014). Further support comes from the finding that action of dopamine that reduces feed-forward inhibition to LA projection neurons promotes fear learning (Rosenkranz and Grace, 2002, Lorétan et al., 2004). Further regulation occurs when inter-LINKed spines that inter-LINK with spines that synapse to inhibitory input terminals and generate different domains of activations within an IILPs (**Fig.10**). The finding that activation of a single dendritically targeted inhibitory interneuron prevents generation of dendritic spikes in neocortical PNs (Losonczy et al., 2008) indicates the possibility that dendritic spike is an event associated with activation of IILPs by multiple inputs that is vulnerable to inhibition. The observation that the cortex has an inhibitory blanket (Karnani et al., 2014) indicates the importance of maintaining inhibitory connections in regulating IIPLs. Oscillations of inhibitory neurons in the cortex match with the oscillations of extracellular potentials in the background state (Huang et al., 2024b), indicating an underlying role of gap junctions between interneurons in maintaining cognitive functions.

The finding that mnemonic information is present in the patterns of functional connections among neuronal ensembles during Off states (when there are no correlated neuronal firing events) (Panichello et al., 2015) matches with the operation of a hub at the origins of input terminals. The above study also found that intermittent periods of memorandum-specific spiking coexist with synaptic mechanisms during working memory. What the authors refer to as "functional connection" or "synaptic mechanism" is likely taking place by the IPL mechanism to provide explanations for both first-person property and motor actions. Association between spike-rates and brain functions can have the following alternate explanations. 1) Presynaptic neurons repeatedly fire to facilitate temporal summation of PSPs at the axonal hillocks to fire the postsynaptic output neurons. 2) This also helps to maintain the IPLs by preventing them to reverse back.

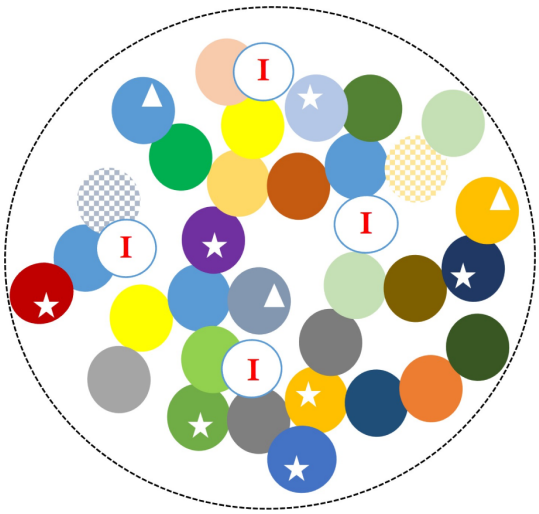

Figure 10. Inter-LINKed spines in a large IILPs respond based on the nature of neurotransmitter molecules from their input terminals. The large dotted circle represents a large islet of inter-LINKed spines (IILPs). Small circles within it represent cross-sections through different inter-LINKed spine heads. Small circles of solid color are synapsed to glutamatergic axonal terminals. Those with checkered patterns are synapsed to cholinergic inputs. Those that have no color receive inhibitory inputs. Starred spines receive dopaminergic inputs. Triangles over spines show that they receive serotonergic inputs. Activation of an inhibitory terminal to an inter-LINKed spine inhibits a sub-region of IILPs creating a subdomain of inhibition within that IILPs. Dopamine causes expansion of spines that allows them to form IPLs with neighboring abutted spines (not shown). Firing of postsynaptic neuron of each inter-LINKed spine depends on a) excitatory inputs arriving at a sub-region of inter-LINKed spines around it, b) inhibitory inputs arriving at this region of IILPs, and c) oscillations of extracellular potentials that depend on oscillation of electrically (via gap junctions) connected inhibitory interneurons. Generation of first-person inner sensations is expected to depend on the nature of variations of membrane potentials over the inter-LINKed spines from the baseline state. Conformation of semblances (first-person property) is governed by the nature of membrane potentials on inter-LINKed spines at each moment.

5 Testable prediction

The semblance hypothesis has put forward several testable predictions (Vadakkan, 2016c, 2019, 2021). The present work has allowed to add one more. Current approaches associate different types of stimuli (CS) with foot shock (US) to generate the same motor output of foot withdrawal. When the number of different types of CS that are associated with foot shock is increased in an animal, it will increase the size of the IILPs at the level of input terminals of LA neurons. Hence, following each associative learning, in a typical LTP experiment, baseline potentials generated at the recording electrode in a specific synaptic region in response to a regular stimulus will continue to increase. Hence, as the number of associative learning events is increased, relatively less LTP will be recorded with respect to the baseline potential.

6 Discussion

Experiments at different levels of the nervous system have been using behavior as a surrogate marker for retrieving memories. It is necessary to obtain a mechanistic explanation for behavior with specificity that can be interconnected with explanations for a large number of findings from all levels of the system. The semblance hypothesis has succeeded in obtaining a solution for behavior and has found a verifiable mechanism for generating first-person inner sensations as a substantive component of this solution. In the light of the re-examination findings found by the present work, the following insights can be drawn.

6.1 Re-interpreting synaptic plasticity changes

Even though experiments based on several modifications of the synaptic plasticity thesis (Tsukahara, 1981, Martin et al., 2000, Citri and Malenka, 2008, Magee and Grienberger, 2020) were carried out, a mechanistic explanation for the operation of engram is still needed. It is necessary to re-interpret the conventional way of viewing synaptic integration at the level of the synapses (Williams and Atkinson, 2008) to describe brain functions with the clarity necessary for replicating its basic principle in engineered systems. Since it is necessary to maintain synapses functioning normally for proper functioning of IPLs (see Fig.3), factors that affect normal synaptic functions will affect IPL function. Hence, some of the synaptic plasticity changes can be re-interpreted as consequences of the formation and maintenance of IPLs. Furthermore, continued quantal release of neurotransmitter molecules from the presynaptic terminals is necessary to maintain the dominant state of continued depolarization of the spine heads (Vadakkan, 2016) to generate semblances as cue-specific cue-directed hallucinations that form the basis of first-person properties of memory (Vadakkan, 2007, 2013). Since sleep is necessary to maintain the above dominant state, optimal generation of first-person properties of any brain function takes place only after sufficient sleep.

6.2 Synaptic potentiation between engram neurons in LA

It is shown that fear learning induces synaptic potentiation between engram neurons in the LA (Abatis et al., 2024). Even though this work studied direct synaptic connections between LA neurons, based on the semblance hypothesis, the results may be influenced by certain effects via the IPLs. Dendritic spikes backpropagate towards their dendritic spines as reported previously (Park et al., 2024). Hence, stimulating PN neurons with a high energy stimulus can cause backpropagation of potentials towards their dendritic spines. This causes the potential to propagate across existing IILPs and also can lead to formation of new IPLs between abutted spines. Hence, propagation of potentials across the IILPs will be interpreted as synaptic potentiation between engram neurons in the LA (**Fig.5**).

6.3 Dual role of prefrontal cortex in working memory and consolidation

The prefrontal cortex is involved in both working memory and memory consolidation (Laroche et al., 2000). These need interconnected explanations. A new associative learning event forms numerous IPLs in the prefrontal cortex generating semblance in response to one of the associated stimuli after learning. The majority of these IPLs reverse back quickly and can explain working memory. Items and events in the environment have many shared properties that can generate

sensory stimuli of shared features. During repetition of learning or associated learning events, as the new associatively learned stimuli propagate through the new circuit connections formed by newly inserted granule neurons in the circuit, they will lead to the formation of sparsely located new IPLs in several regions of the cortex such as the prefrontal cortex. Repetition of this process will lead to stabilization of the set of sparse IPLs. The net semblance on the inter-LINKed spines reactivated by the above sparse set of IPLs by a cue stimulus, a long time after learning, can explain long-term memory. Thus, the prefrontal cortex has roles in both working memory and consolidation.

6.4 More than one synapse on certain boutons

A fear conditioning study (Ostroff et al., 2012) noticed more than one synapse on certain boutons (presynaptic terminals) by splitting up one presynaptic terminal into many boutons. Similar structural findings have been reported in different locations in the cortex associated with learning (Geinisman et al., 2001; Bourne and Harris, 2012; Bloss et al., 2018), and following LTP induction (Toni et al., 1999). Dendritic spine of a synapse formed by one bouton is independent of the spine of the sister bouton even though they originate from the same presynaptic terminal. Based on the semblance hypothesis, splitting of the presynaptic bouton occurs when the stimulus propagating through a presynaptic terminal needs to be associated with several other stimuli that are not related to each other and arrive through separate presynaptic terminals. In other words, spines that synapse with sister boutons most likely remain operationally independent of each other. In other words, the spines that form synapses with boutons on the same presynaptic terminal need to remain separate from each other without forming inter-LINKs between them. However, each spine with which sister boutons synapse will form its own separate IILPs (**Fig.11**). A scaled-up change by a high energy stimulus of LTP leads to formation of multiple boutons at the axonal terminal to form more inter-LINKed spines, routes through which a regular stimulus can propagate and converge to generate a potentiated effect.

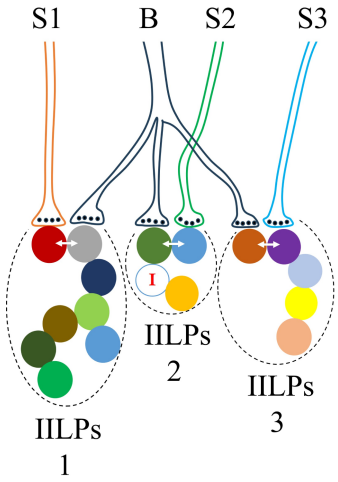

Figure 11. Splitting of an axonal terminal forming multiple boutons. This occurs when one of the associatively learned stimuli reaches only one presynaptic terminal, and it needs to be associatively learned with several other stimuli that are not related to each other. Hence, it is anticipated that spines which each of the split bouton synapsed form separate islets of inter-LINKed spines (IILPs). Splitting of a presynaptic terminal can be viewed as a means to maintain specificity of learning in

conditions where a less than necessary number of axonal terminals reach a region where they need to be associated with various other stimuli.

6.5 Potential relationship with dendritic spike

Since the postsynaptic potential of a spine by an action potential arriving at its presynaptic terminal attenuates as it propagates towards the cell body, it may not always be able to influence the postsynaptic neuronal output (Spruston, 2008). Dendritic spikes appear to be generated by local integration of synaptic activations on a dendritic branch of a cortical PN that propagates to the cell body (Williams and Atkinson, 2008). In the hippocampus, a perforant path that synapses in the apical tuft region of CA1 pyramidal neurons needs to generate dendritic spikes to fire those CA1 neurons (Jarsky et al., 2005). Dendritic spike can be viewed as a mechanism to generate a high voltage that can afford to lose a part of it as it propagates towards the cell body to add to other PSPs arriving at the axonal hillock for firing an action potential. The finding that synchronized sharp wave activity in vivo (Buzsáki, 2015, Papale et al., 2016), which is correlated with certain cognitive functions, is associated with dendritic spikes, suggests an interconnection between the latter two (Kamondi et al. 1998). Since a) cognition includes both first-person properties and behavioral motor actions, b) since the oscillating wave form of sharp wave activity is associated with a dendritic spike, and c) propagation of potentials across IPLs between two synapses provides vector components for oscillations, it is reasonable to argue that operation of inter-LINKed spines is likely associated with generation of first-person property.

It was shown that multi-site uncaging of glutamate mimics the synchronous activation of a group of synapses that generates dendritic spikes (Losonczy et al., 2008). Since uncaged glutamate diffuses in a 3-D space, is it possible to find an alternate means to explain synchronous activation of spatially clustered inputs contributing to firing? The explanation must match with the finding that dendritic spikes do not always cause firing of postsynaptic neurons (Golding and Spruston,1998). Activation of a single interneuron prevents generation of dendritic Ca2+ spikes (see section on dendritic spikes) in neocortical layer 5 PNs (Larkum et al., 1999). How is it possible to interconnect all the above findings? When dendritic spike is viewed as resulting from the activation of IILPs, which provides a route through which spines on different dendrites of the same or different neurons interact, then it is possible to interconnect the above findings. Since single-burst LTP stimulation causes dendritic spikes (Remy and Spruston, 2007), and since LTP can be explained in terms of the formation of a large number of non-specific IPLs to form IILPs (Vadakkan, 2019), it is possible to speculate that dendritic spikes originate at the IILPs. When viewed with reference to a single PN, a dendritic spike is a localized event on a dendritic shaft that can arise only from neighboring spines on the recorded single dendrite. However, based on the semblance hypothesis, IILPs involve interacting spines that belong mostly to different neurons. There is a mechanism that amplifies postsynaptic potentials within the IILPs, which is amenable to inhibition by a single interneuron.

The spiked potential of dendritic spike in an IILPs gets propagated only to certain postsynaptic neurons depending on local inhibitory inputs at different subregions on the IILPs. Hence, even though clustered synaptic activity is observed on the shaft of a dendrite, potentials on a dendritic segment may get damped by inter-LINKing of one of its spines with another spine that synapse with an inhibitory input terminal. Spiked potential of a dendric spine drains to different postsynaptic neurons of the IILPs depending on the depolarizing or hyperpolarizing state generated in the IILPs (**Fig.12**). Hence, a dendritic spike may not cause firing of all the postsynaptic neurons

of an IILPs.

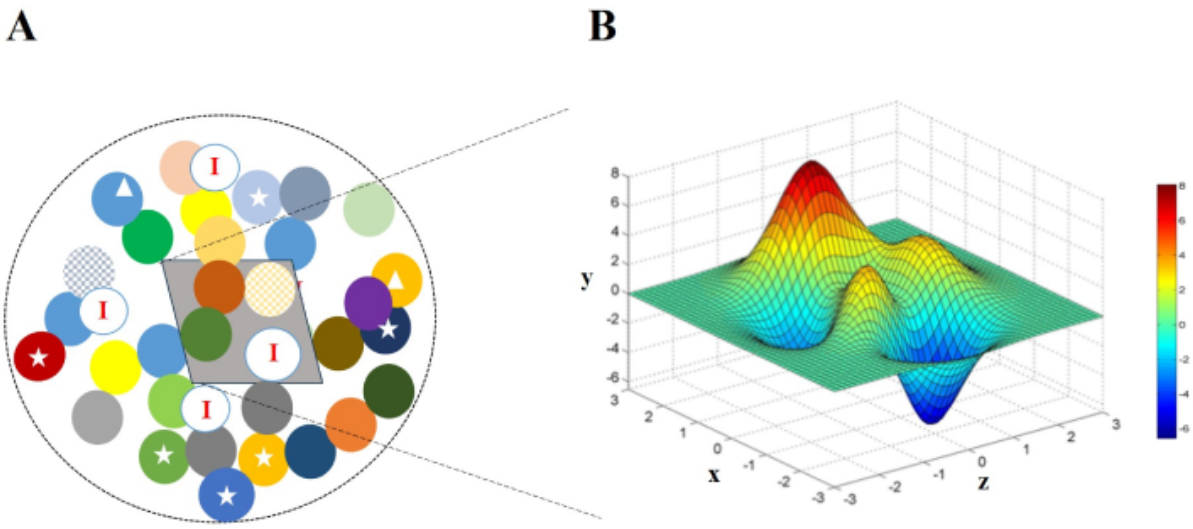

Figure 12. Representative 3D display of peaks and depressions of spatial distributions of potentials. A) An islet of inter-LINKed spines (IILPs) similar to that in Fig.10 with a square shaped surface region having four inter-LINKed spines. Three of them receive excitatory inputs and one receives inhibitory input (marked with alphabet I). B) Potentials generated on the four inter-LINKed spines in the square shaped region in figure A is shown as a 3D display. IILPs is expected to generate different domains of depolarizations depending on a) locations of arrival of different inputs that release different neurotransmitter molecules, b) number of neighboring spines that synapse with axonal terminals releasing the same neurotransmitter molecule, and c) occurrence of dendritic spikes. The width of each peak is determined by the number of similarly activated (excitatory or inhibitory) neighboring spines. Depolarization in red; Hyperpolarization in blue. x-axis: horizontal axis of the IIPLs. y-axis: Depolarization and hyperpolarization. z-axis: Either side of the center of an IIPLs in y axis (Figure modified from Kang et al., 2015).

6.6 Renewed view of engram neurons

Firing of a neuron in a threshold operated manner, lack of firing of neurons in response to arrival of input signals when those neurons are in a suprathreshold state and degeneracy of input signals in firing a neuron (Vadakkan, 2019) necessitate a renewed view of neuronal firing during a higher brain function. Since hippocampal neurons fire in response to task variables independent of each other (Samborska et al., 2022, Tang et al., 2023, Courellis et al., 2024), and since sets of engram neurons for two brain functions are shared (Ohkawa et al., 2015, Cai et al., 2016, Yokose et al., 2017, Nomoto et al., 2016), these events can occur only in the presence of a shared hub at the input terminal regions of these neurons. Operation of IILPs can lead to the firing of a postsynaptic neuron of an inter-LINKed spine within an IILPs even when its presynaptic partner is not receiving an action potential from a sensory stimulus. In other words, operation of the IILPs can lead to firing of certain postsynaptic neurons of its inter-LINKed spines even though firing of these neurons was not correlated with any previous learning or memory retrieval events. Due to the multitudes of options to summate potentials with an IILPs, postsynaptic neuronal firing events do not always have direct correlations between the arrival of sensory stimuli. Instead, firing of postsynaptic neurons in response to a stimulus depends on the strength of associations between

the inter-LINKed spines within an IILPs determined by the presence of inter-LINKed spines due to prior learning events.

Inter-LINKing a spine of a PN that synapses with an inhibitory input with one of the inter-LINKed spines (excitatory) within an IILPs can affect the strength of the IPLs between its neighboring inter-LINKed spines. This can create subdomains of different types of activations within an IILPs. It may indirectly explain why engram neurons are malleable at certain locations in the brain compared to other regions when animals are exposed to two different learning events one after another (Redondo et al., 2014). The finding that the neuronal population in the sensory cortex has spontaneous activity even without an external sensory input (Ringach, 2009) matches with the reactivation of several IPLs by background stimuli and oscillating extracellular potentials. Reactivation of inter-LINKed spines by a cue stimulus can activate a specific set of neurons unless more inter-LINKed spines are added to certain IILPs or a new sensory input evokes an inhibitory input that may reduce potentials reaching postsynaptic neurons. For neurons that are being held in a suprathreshold state, new sensory inputs have less influence on their spontaneous activation, which is associated with behavior (Stringer et al., 2019). Changes that can be brought to connection strengths between inter-LINKed spines within an IILPs by a new learning event will determine which postsynaptic neurons of the inter-LINKed spines fire. For example, inter-LINKing of a spine of an IILPs with an abutted non-LINKed spine occurs in a new learning event, then a cue stimulus that activates newly inter-LINKed spines can lead to both new downstream motor actions and first-person property from the IILPs. This can explain neuronal firing events during false memory (Ramirez et al., 2013) (**Fig.13**).

It is reasonable to assume that in the sensory cortices, the IPLs reverse back quickly after perception. Nevertheless, the relationship between the first-person property generated at the IPL level and postsynaptic neuronal firing is expected to be similar to that of cortical areas where IPLs can be stabilized. It was found that nearby neurons in the visual cortex with similar orientation tuning do not exhibit correlated variability in firing (Ecker et al., 2010) suggesting the possibilities that adjacent neurons share only a few percent of their inputs and IPL mechanism is independent of neuronal firing. The finding that while most classes of visual cortical neurons respond to specific subsets of visual stimuli, the largest class of neurons do not reliably respond to any of the stimuli (De Vries et al., 2019) also indicates that IPL mechanism for perception (Vadakkan, 2015a) takes place independent of postsynaptic neuronal firing. A study that recorded odor-evoked neuronal activity (Kehl et al., 2024) found that odor response, intensity of odor (valence), and ability to name an odor are correlated with firing of neurons in the piriform cortex (primary olfactory cortex), amygdala (a regions known for emotions), and hippocampus respectively. These indicate that the specific semblances evoked at the inter-LINKed spines of neurons in the piriform cortex, amygdala and hippocampus are responsible for the first-person property of smell, valence, and memories of associated names of odors respectively.

6.7 Information storage and retrieval

It is anticipated that features of the engram have properties suitable for information storage (O'Sullivan and Ryan, 2024). To understand the computations for the top-level output of the system from its elementary units (Marr, 1982), it is possible to argue that output functions of both a) third person accessible motor actions such as speech and behavior, and b) first-person property accessible by the owner of the system that arises from unitary mechanisms from an inter-

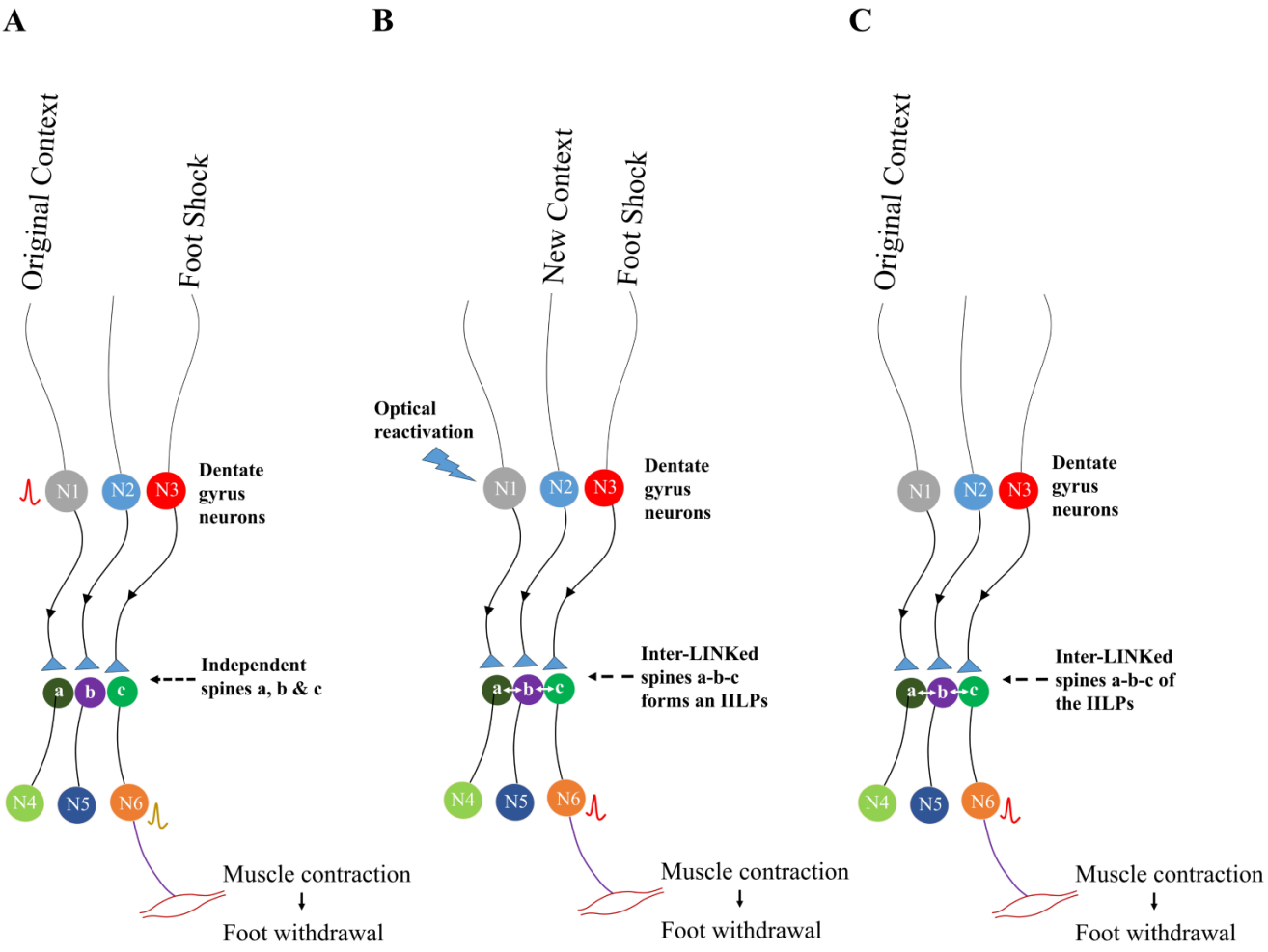

Figure 13. An explanation for false fear memory. A) Exposure to a context (called original context) leads to firing of dentate gyrus neuron N1. Foot shock alone leads to firing of dentate gyrus neuron N3 and muscle contraction for freezing. Before learning, neither the original context nor another new context cause freezing. Note that before learning, spines a, b and c from input neuron N1, N2 and N3 respectively are electrically independent from each other. B) Here, neuron N1 that fired in response to context 1 is activated optically along with conditioned learning of foot shock in the presence of a new context. Based on the semblance hypothesis, the spines a, b and c that receive inputs from the original input, new input and foot shock respectively get inter-LINKed with each other to form a new islet of inter-LINKed spines, namely a-b-c. C) After fear conditioning is carried out in B, exposure of the animal to the original context alone leads to freezing. This is explained by the propagation of potentials from the original context stimuli to the spine a, which then propagates across the newly formed islet of inter-LINKed spines a-b-c and reaches the postsynaptic neuron N6 of the inter-LINKed spine c. In a background state following fear learning, when the neuron N6 is being held at subthreshold activation state short of a fraction of one potential/ few potentials, then the depolarization initiated by the original context can become sufficient to add to the resting summated potentials arriving at neuron N6 to fire it causing freezing. In other words, original context alone becomes sufficient to cause a freezing motor action. This explains how the recall of false memory is context-specific (presence of original context, new context and foot shock), activate similar downstream neurons (N1 and N3) during a natural fear memory recall, and becomes capable of driving an active fear response (Ramirez et al., 2013).

mediate level of the system must be accounted for. The relationship between any two spines within an IILPs, which depends on previous associative learning events, makes the IPL mechanism match with the view that neural codes carry information only with reference to things with known meaning (Brette 2018). However, IILPs allows interconnection to occur between stimuli that were not directly associatively learned. Hence, operation through IILPs allows information encoding not limited to occurring between stimuli previously associated, but extends far beyond due to the network of inter-LINKs within it. This endows IILPs with the property of generalization. Furthermore, inter-LINKs in IILPs allow firing of postsynaptic neurons of several indirectly inter-LINKed spines (see Fig.9).

Different types of neurotransmitter molecules binding to receptors on the inter-LINKed spines is expected to fine-tune the conformation of units of semblance generated. Since information stored during associative learning is part of the learning-generated change that exists at the time of recall (Schacter and Addis, 2007), the engram consists of changes at the time of learning, its ability to reverse back, leading to forgetting, and mechanisms of its stabilization for long-term memory. Reversal of IPLs matches with the short duration for which working memory is held. Reversible IPL mechanism matches with both the expectations of an "activity-silent" mechanism for working memory (Stokes, 2015), and the presence of patterns of functional connections among neuronal ensembles during Off states (absence of correlated neuronal firing) for holding mnemonic information (Panichello et al., 2015).

6.8 Energy efficiency of the mechanism

One advantage of the operation of the brain is its comparatively less energy consumption. However, energy spent on maintaining the resting membrane potential (for e.g. functioning of Na/K/ATPase channels) is often discounted. Formation of IPLs by exclusion of a hydration layer between the membranes requires a huge amount of energy as inferred from experiments carried out between artificial membranes (Rand and Parsegian, 1984; Harrison, 2015, Martens and McMahon 2008). Hence, an energy efficient biological mechanism is expected to be present. Electron microscopy images of the amygdala (Klenowski et al., 2017) show very negligible ECM space between the neuronal processes. The hydration layer between the spines is expected to prevent any type of electrical connection (by depolarization spread) between them. Any physical interaction between spine membranes is expected to proceed towards the initial steps of membrane fusion, called hemifusion, which can be facilitated by the action of certain specific intracellular proteins (Kozlovsky et al., 2004; Martens and McMahon, 2008).

Introduction of blockers of membrane fusion into the postsynaptic cell prevents membrane fusion and reduces LTP (Lledo et al., 1998). The findings that a) LTP requires a unique postsynaptic soluble NSF (N-ethylmaleimide sensitive fusion protein attachment protein receptor (SNARE) fusion machinery (Jurado et al., 2013), and b) in the presynaptic terminal, this protein facilitates vesicle fusion in millisecond timescales, prompt to ask," Does postsynaptic SNARE involve in inter-spine interactions?" Since SNARE proteins are present in the postsynaptic terminals (Jurado et al., 2013), and they can form characteristic hemifusion intermediates (Lu et al., 2005; Liu et al., 2008), there is a possibility that SNARE protein is involved in inter-spine interaction. They are known to provide energy for bringing together membranes against repulsive charges and overcome an energy barrier related to curvature deformations during hemifusion between abut-

ted membranes (Martens and McMahon, 2008; Oelkers et al., 2016). They also generate force to pull together abutted membranes as tightly as possible (Hernandez et al., 2012). By initiating the fusion process by supplying energy (Jahn and Scheller, 2006), SNARE proteins can lead to the formation of characteristic hemifusion intermediates (Lu et al., 2005; Liu et al., 2008). Since fusion by SNARE proteins occurs in millisecond timescales for vesicle release at the presynaptic terminal, a mechanism of interspine fusion by postsynaptic SNAREs is a suitable mechanism for IPL formation in matching timescales. Since SNARE proteins are known to mediate fusion of intracellular vesicles containing AMPARs with the spine membrane (Lu et al., 2001; Kennedy et al., 2010), when membranes on the lateral aspects of two abutted spines undergo exocytosis of vesicles at the same time, postsynaptic SNARE proteins at the abutted region between two spines may enable interspine interactions to form a spectrum of IPL changes (Vadakkan, 2013). After their formation within milliseconds of time during associative learning, IPLs are expected to remain stable for different durations depending on several factors that affect their stability (explaining working, short and long-term memories).

6.9 IPL mechanism and framework for consciousness

The IPL mechanism provides a framework for consciousness as the net semblance generated by all the non-beneficial and non-deleterious stimuli from the environment. In this background state, beneficial and deleterious stimuli can preferably generate a first-person property to enable the system to take specific motor actions for survival in response to them (Vadakkan, 2010; Vadakkan, 2015b). An engineered system that replicates the IPL mechanism is expected to have consciousness, which is in alignment with the view that artificial general intelligence will have consciousness (Bołtuć, 2020; Butlin et al., 2023).

6.10 Limitations of current fear conditioning experiments

Since all the modified fear conditioning experiments have viewed CS as a sensory stimulus that has no motor action, it limits the minimum necessary feature of the engram to an interaction between spines on two overlapping dendritic branches of the same motor neuron (Figs.3A,8A). There are no modified fear conditioning experiments where CS has a motor action (for e.g. turning of an animal's head towards the sound of a bell). Production of separate motor actions in such an experiment necessitates the associatively learned input stimuli to converge to form an IPL between spines that belong to two different postsynaptic neurons (Figs.3B,8B). Since turning the head towards the sound of the bell is not a necessary motor action in response to the presence of CS for evoking first-person properties of US or withdrawing feet, and since it is not known whether specific LA neurons are activated by CS and US before learning, IPLs can be formed between spines on different branches of the same LA neuron.

Motor outputs using a finite number of muscles are expected to have certain methods to increase their efficiency. Different sets of motor units can be activated to cause partial contractions of muscle fibers around a hinge joint in a single plane to cause movements of different strengths in one plane. Muscles that are not attached to bones and are present around saddle shaped, condyloid, or ball and socket type of joints are able to generate numerous combinatorial movements in multiple planes to deliver speech or motor action at different forces at different angles (e.g. in sports). In classical fear conditioning, output neurons (LA neurons) are of the same type and foot withdrawal is a generic action. Hence, fear conditioning experiments offer simplicity, where IILPs at the input

levels of LA neurons operate to generate only one action – foot withdrawal. In contrast, combinatorial outputs are responsible for the enormous output repertoire of speech, which is expected to have a highly sophisticated regulatory mechanism at the input level of pyramidal neurons in the language cortex. The same reasons can be attributed to the finding that consolidation of auditory fear memory encoded in the LA is localized and rapid, whereas hippocampus-dependent memory involves a distributed, slow consolidation process (Gale et al., 2004).

7 Conclusion

Spread of potentials between spines within an IILPs in response to a new cue stimulus and the ability to generate unitary first-person semblances that are integrated by the system property of oscillating potentials enable the system to operate more efficiently than what the present-day machines do algorithmically. The finding that (in addition to stimulation frequency), electric field in a brain region impacts subthreshold and spiking properties of major cortical neuronal classes (Lee et al., 2024) matches with the anticipated ability of the IPL mechanism in providing vector components of oscillating potentials necessary for both first-person property and motor actions. Arrival of any new set of stimuli will alter relations between inter-LINKed spines within an existing IILPs. Operation at the IILPs explains how certain non-corresponding postsynaptic neurons of some of its inter-LINKed spines get fired in the absence of sensory inputs.

Constraints provided by the findings of modified fear conditioning experiments that use behavior (Tolman, 1948, Behrens et al., 2018) match with the operation of IIPLs. IPL operation for fear is expected to have two combinatorial mechanisms. One at the input level that operates to accommodate degeneracy of inputs in firing a neuron (Vadakkan, 2019) whereby a large number of sets of input signals are capable of firing one LA output neuron. Since depolarization of one spine has the provision to propagate to several spines of an IILPs, firing of a postsynaptic neuron will depend on previous associations that determine the strength of association between inter-LINKed spines within an IILPs. In this regard, direct correlation between firing of postsynaptic neurons and cognitive function cannot be expected. Hence, IILPs appears to operate using the priors in a unique manner than by Bayesian integration as previously thought (Körding and Wolpert, 2004). A second combinatorial mechanism is expected at the output level for executing motor actions. Since foot withdrawal is not a specialized motor action, both CS and US may synapse on to the spines on different dendrites of one LA neuron providing the same motor outputs. However, speech that needs multiple coordinated motor actions on a continuous basis is expected to have a combinatorial operation of motor units concurrent with first-person properties of the generated language.

The fact that amygdalae receive inputs from almost all sensory modalities (Pape H-C and Pare´, 2010) indicates that combinations of different inputs to this region regulate first-person properties of various emotions such as fear, anxiety etc. Furthermore, the presence of different types of neurons and neurotransmitter molecules in this brain region (Hagihara et al., 2021, Hájos, 2021, McDonald, 2023, McDonald, 2024) likely to add additional heterogeneity to the qualia and durations of inner sensations. Since firing of a set of neurons occurs during fear learning and memory retrieval in different regions of the brain other than LA (Balderas et al., 2015, Izquierdo et al., 2016), it is possible to infer that several postsynaptic neurons qualify the description of "fear engram neurons". This also matches with the finding that there is firing of neurons in many locations of the brain during a brain function (Roy et al., 2022, Chen et al., 2024, Huang et al., 2024a. Wen et al., 2024).

The finding that in adults fear memories are actively protected by ECM proteoglycans in amygdala (Gogolla et al., 2009) can be explained in terms of its ability to stabilize the structure of IILPs.

The correlation between fear learning and the strength of LTP that can be induced at the input area of LA neurons led to a proposal of four requirements to understand the engram (Stevens, 1998). Two of these are satisfied by the finding that fear conditioning is inactivated by LTD and reactivated by LTP (Nabavi et al., 2014). A third requirement is to find an increased postsynaptic response to the tone (CS) after auditory fear conditioning, which can be prevented by agents that can block LTP pharmacologically. Results from a combination of experiments (Weisskopf and LeDoux, 1999; Bauer et al., 2002; Choi et al., 2021) satisfy the expectations of this requirement. The last remaining one is to explain the persistence of learning changes for a long period. This can be explained by potential mechanisms capable of stabilizing the IPLs for a long duration, such as factors that stabilize the hemifused area. In addition to the above, the non-mentioned first-person feature of fear in response to CS after learning can be explained in terms of the IPL mechanism. By assigning a motor action to CS and examining how it can be triggered along with motor actions of the US at the time of memory retrieval, it will become possible to understand additional features of the engram. IPL is a derived testable missing connection within the connectome capable of explaining the engram. Testable predictions put forward by the semblance hypothesis and replication of the latter's models in engineered systems can be undertaken to further verify the mechanism.

Abbreviations:
BLA: Basolateral amygdala
CA1: Cornu ammonis 1
CFC: Contextual fear conditioning
CS: Conditioned stimulus
DG: Dentate gyrus
ECM: Extracellular matrix
GABA: Gamma amino butyric acid
IILPs: Islets of inter-LINKed postsynaptic terminals
IPL: Inter-postsynaptic functional LINK
LA: Lateral amygdala (one of the nuclei of BLA)
LINK: The word "link" is capitalized to denote its importance
LTP: Long-term potentiation
LTD: Long-term depression
PN: Pyramidal neuron
PSP: Postsynaptic potential
SNARE: Soluble NSF (N-ethylmaleimide sensitive fusion protein attachment protein receptor
US: Unconditioned stimulus

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