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Review

A potential mechanism for first-person internal sensation of memory provides evidence for the relationship between learning and LTP induction

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ABSTRACT

Studies conducted to verify learning-induced changes anticipated from Hebb's postulate led to the finding of long-term potentiation (LTP). Even though several correlations have been found between behavioural markers of memory retrieval and LTP, it is not known how memories are retrieved using learning-induced changes. In this context, the following non-correlated findings between learning and LTP induction provide constraints for discovering the mechanism: 1) Requirement of high stimulus intensity for LTP induction in contrast to what is expected for a learning mechanism, 2) Delay of at least 20 to 30 s from stimulation to LTP induction, in contrast to mere milliseconds for associative learning, and 3) A sudden drop in peak-potentiated effect (short-term potentiation) that matches with short-lasting changes expected during working memory and occurs only at the time of delayed LTP induction. When memories are viewed as first-person internal sensations, a newly uncovered mechanism provides explanation for the relationship between memory and LTP. This work interconnects large number of findings from the fields of neuroscience and psychology and provides a further verifiable mechanism of learning.

1. Introduction

Experimental approaches to understand cellular changes responsible for learning and memory retrieval have been examining long-lasting synaptic changes postulated by Donald Hebb [1]. One experimental finding that showed long-lasting augmentation of current flow through a synapse-dense area is called long-term potentiation (LTP) [2–4]. A large number of studies have found correlations between behaviour associated with memory retrieval and LTP [5–11]. Several properties expected of a memory storage mechanism were attributed to the findings from LTP experiments and are considered as experimental correlates of the cellular mechanism for learning and memory [12–16]. To explain learning-induced changes from which behaviour indicative of retrieval of memories can take place and their relation to LTP induction, several modifications of Hebb's postulate were carried out. These include a) tagging of synapses with specific molecules during learning [17,18], b) dendritic spikes as a mechanism for co-operative LTP [19] thought to be responsible for information processing [20], c) clustering of dendritic spines on the dendritic branch of a single neuron that integrates its inputs [21], and d) proposal of sub-synaptic structural modules as the plasticity mechanism [22]. Even with all the above efforts, it was not possible to explain a learning-induced change from which memory can be retrieved [23–26].

In the search for the true mechanism, it is necessary to examine some of the following explanatory gaps that remain to be filled. 1) Based on Hebb's postulate, potentiated synapses responsible for memory storage are expected to get specifically activated during memory retrieval. In this regard, findings indicating that LTP is not specific to the synapses that were active during stimulation [27] suggest that LTP fails the "specificity requirements" for a memory mechanism [28]. 2) Transfer of locations of memory storage indicates that the brain structure used for acquiring memories is not necessarily the site for storage, a finding that suggests lack of achieving synaptic specificity [28]. This necessitates that the true mechanism should be able to maintain memory specificity using the formation of surplus operational units of similar values at different locations that can substitute each other. 3) Following LTP induction, an increase in population spike amplitude and a reduced threshold for cell firing are observed even when the magnitude of excitatory postsynaptic potential (EPSP) is held constant [4] indicating that the tetanus-induced modification is not limited to the synapses [28]. The true mechanism should be able to clarify the relationship between the operational mechanism and firing

Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ECM, extracellular matrix; EPSP, excitatory postsynaptic potential; GluR1, glutamate receptor 1; IPL, inter-postsynaptic (inter-spine) functional LINK; LTP, long-term potentiation; LTD, long-term depression; NMDA, N-methyl-d-aspartate receptor; PSD, postsynaptic density; SNARE, soluble NSF (N-ethylmaleimide sensitive fusion protein) attachment protein receptor; STP, short-term potentiation

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of neurons. 4) Modification of one synaptic input can be conditionally controlled by spatial or temporal contiguity with activity in another synaptic input to the same region [29]. This necessitates a mechanism to explain the associativity feature of LTP. 5) Inter-stimulus interval used to induce associative LTP is shorter than what is optimal for different behavioural conditioning procedures [28,30]. 6) An associative feature of LTP is simply the successful expression of what might occur "non-associatively" with repeated stimulation of a single afferent fiber and raises concerns about its relevance in associative learning [28]. 7) A long delay of at least 20 to 30 s from stimulation to LTP induction [31] occurs in contrast to mere milliseconds of time necessary for associative learning. 8) Even though qualia of inner sensations of different memories are similar, it was necessary to search for different mechanisms for working memory [32,33] due to the delayed induction of LTP that depends on protein synthesis. The above findings provide valuable constraints that can be used to derive a testable theoretical solution for the system. It is expected that the mechanism of natural learning will be able to scale up to explain LTP induction and all the uncorrelated findings between learning and LTP induction.

Interpretations of the results from experimental studies have been carried out by examining behaviour with the assumption that behaviour is an external manifestation of internal sensation of memory. In order to discover a cellular level mechanism for the relationship between memory and LTP, it is necessary to understand how the internal sensation of memory is generated. To understand the generation of first-person inner sensation of memory, to which third-person experimenters do not have access, it is necessary to use a theoretical method to derive the operating mechanism and verify it by examining whether the mechanism can a) operate in synchrony with synaptically-connected neurons, b) show the presence of comparable circuitries in remote species of animals, and c) verify its predictions. The non-sensible first-person internal sensation may be understood by seeking methods from physics that were used to understand particles and fields that cannot be sensed by our sensory systems. Accordingly, the requisites of a derived mechanism are that it should provide a) a learning-induced cellular change occurring at physiological time-scales from which inner sensations of memories are generated, and b) inter-connectable explanations for findings from different levels of the system. This necessitates arriving at a theoretical solution that can satisfy all the constraints provided by third-person findings from different levels.

During LTP stimulation at the CA3-CA1 synaptic region, a fixed number of axonal terminals (presynaptic terminals) of the Schaffer collaterals activate a fixed number of spines of the postsynaptic CA1 neuron from whose soma the patch-clamp recording is carried out. Based on the fact that there can be only a limited number of synapses between stimulated Schaffer collaterals and a recording CA1 neuron, and based on the observations made before [34], it is difficult to explain a mechanism for the arrival of increased current at the recording electrode. The explanation that delay in LTP induction by 20 to 30 s is necessary for biochemical reactions for synaptic plasticity changes to explain long-term memory necessitated a separate mechanism for working and short-term memories. Since qualia of these memories are same except for a reduction in clarity with time, and since every long-term memory has a working memory immediately after learning, a re-examination of memory as first-person internal sensations is necessary. In addition, since synaptic plasticity mechanism does not provide a mechanistic explanation for induction of internal sensation, an alternate explanation to overcome these limitations is needed.

This was begun by searching for a learning-induced change that can allow the cue stimulus to provide the source and routing of the potentials that can induce first-person internal sensations of memory and concurrently trigger motor neurons to cause behaviour. Since no cellular changes are observed during memory retrieval, memory is likely induced from a passive reactivation of the changes that occurred at the time of learning. The observed correlations between learning and LTP induction suggest that both naturally occurring learning-induced cellular mechanism and its maintenance will have similarities to the cellular-level changes during LTP induction and its persistence. To achieve this, re-examination of all the third-person observations was carried out to find a mechanism for generation of first-person internal sensation of memory by adhering to all the boundary conditions that the solution must satisfy. This resulted in the derivation of semblance hypothesis [35,36]. The hypothesis was able to explain various features associated with different higher brain functions such as memory, perception and consciousness and provided frameworks for their mechanisms [37–39]. In the present work, results from LTP experiments are re-examined in the light of the theoretically derived mechanism for the generation of first-person internal sensations.

2. Long-term potentiation

Donald Hebb postulated potential cellular changes [1] that can occur at the time of learning. In the following years, a patient named H.M. who underwent removal of both hippocampi for treating intractable seizures suffered severe memory loss following surgery. When examined for memory by testing behaviour and speech, H.M. failed to show signs of memory retrieval for the events or items learned during a certain period prior to surgery and was unable to learn anything new [40]. This indicated that hippocampi are involved in the storage and/or retrieval of memory. Since different sensory stimuli converge at the hippocampus, this brain region has been viewed as a favourable location to examine for learning-induced changes. This led to the search for an electrical marker at the synaptic regions between neuronal orders within the hippocampus that can persist for long periods. Following an initial high-frequency stimulation of the CA3 axons, a regular stimulus at the same location resulted in an augmented electrical change in the synaptic region between CA3 and CA1 neuronal orders in the hippocampal sections that lasted for several hours. This was named LTP [2–4].

Experimental steps of LTP induction are the following. Hippocampal slices are prepared by retaining connectivity between different orders of neurons (Fig. 1) and are maintained at near-physiological conditions. An electrode is used to stimulate a large number of recurrent Schaffer collaterals of excitatory CA3 layer neurons whose (presynaptic) terminals synapse with dendritic spines (spines or postsynaptic terminals) of neurons of the CA1 layer. LTP induction requires a high amount of energy, which is usually provided by high-frequency stimulation. A similar effect can be achieved by using a single burst of strong activation to induce LTP [41,42]. Recording is carried out either by placing an electrode extracellularly (for recording field potentials) at the main dendritic stem area of CA1 neurons or by patch-clamping one of the

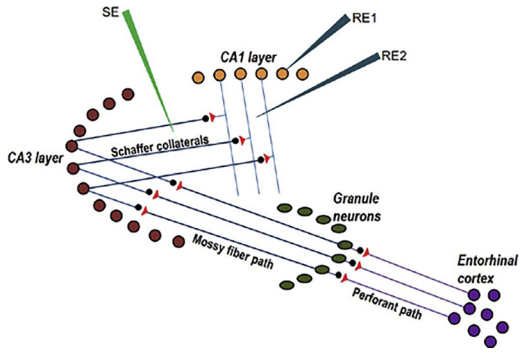

Fig. 1. Diagram showing major hippocampal pathways: Schaffer recurrent collaterals of CA3 neurons synapse with dendritic spines of CA1 neurons. Note that Schaffer collaterals cross at the middle portion of the dendritic tree of CA1 neurons (approximately 100–250 μm from soma). SE: Stimulating electrode. RE1: Recording electrode patch-clamped to CA1 neuronal cell body. RE2: Field recording electrode in the extracellular matrix space at the CA3-CA1 synaptic region.

CA1 neuronal soma. Following the application of a brief repetitive stimulation at the Schaffer collaterals, application of a regular stimulus at the same location is enough to produce an increase in the field EPSP from the baseline to up to 200% (interpretation from [43]) or 60% in EPSP amplitude by whole cell patch recordings [34] after a delay of at least 20 to 30 s [31] or even more than a minute [44]. Optimizing the locations of stimulating and recording electrodes is necessary to optimize LTP recording. By keeping the experimental preparation viable, application of a regular stimulus at the same location of stimulation continues to show a potentiated effect at the recording electrode for even up to twenty-four hours. Since comparatively more specific information can be obtained from potentiated effect recorded from patch clamping a CA1 neuron than the field recording, the results from the former method are explained in this work.

Following the initial observation of LTP that lasted for hours, several experimental studies have found a correlation between behavioural markers indicative of memory retrieval and LTP [14,45]. From these observations, it was thought that changes at a fixed number of CA3-CA1 synapses increase synaptic efficiency according to Hebb's postulate. LTP was also demonstrated in different brain regions and at non-glutamatergic [46] and inhibitory synapses [47].

3. Minimum requirements for an explanation

When memories are viewed as first-person internal sensations that occur concurrent with behavioural changes, it prompts us to ask the following questions. a) What type of a change should take place at the level of synapses during learning that will allow cue stimulus (one of the associatively-learned stimuli or its components), propagating through specific synapses, to induce the internal sensation of memory of the associatively-learned second stimulus and provide potentials to activate neurons to produce behavioural motor actions reminiscent of the second stimulus? b) Since motivation can promote learning, will it be possible to explain how motivation can augment learning-induced changes that can promote its persistence for long periods? c) Since no molecular changes were observed during memory retrieval, can passive reactivation of the change that occurs during learning induce an internal sensation of memory? d) Since memory can be retrieved instantaneously following learning, is it possible to find a learning-induced change that occurs at physiological time-scales? e) Since qualia of internal sensations of different memories classified based on the interval between learning and memory retrieval are similar, is it possible that all memories have a common mechanism of their induction? Obtaining inter-connectable answers to all the above questions is the minimum requirement to understand the operational mechanism. It is necessary to use constraints from findings at different levels to derive a mechanism responsible for learning and memory retrieval. It is then necessary to examine whether the derived mechanism can explain all the correlated and non-correlated findings between associative learning and LTP induction (Fig. 2).

4. Derivation of learning-induced change and units of internal sensations

4.1. Evidence for operation of a unitary mechanism

When a system produces a property that appears irreducible into its components, then that property is viewed as an emergent property. However, a seemingly emergent property may be subjected to reductive approaches by bringing some intuitively plausible explanations [24]. Even though first-person properties of memory evoke a sense of phenomenality as an emergent property, there is a likelihood for the presence of a unitary mechanism if it becomes possible to answer the following questions, a) What necessitates the operation of a unitary mechanism? b) At what level does unitary mechanism work? c) Is there a system property that can integrate all the unitary features at physiological time-scales? They can be answered as follows. a) An infinite number of internal sensations have to be generated in response to infinite number of items or events in the environment using a finite number of components within the nervous system. Since a unitary structure-function mechanism can provide a nearly infinite number of combinatorial possibilities, such an operational mechanism become efficient by simultaneous operations of a large number of unitary mechanisms. b) The correct level at which the unitary mechanism operates requires reaching the level at which specificity of the operations can be maintained. It is known that spatial summation of nearly one hundred and forty [48] (or temporal summation of even less than this number) EPSPs, arriving from random locations on the dendritic tree, reaching the axonal hillock can cause firing of an action potential. This indicates that for pyramidal neurons with tens of thousands of inputs (dendritic spines where EPSPs are generated), there is a huge redundancy of inputs in firing a neuron. Since different degrees of attenuation of those EPSPs occur by the time they reach the axon hillock, it further increases the degeneracy of inputs in firing a neuron. This explains why a unitary mechanism generating first-person internal sensation that can keeps specificity can operate only at the level of the dendritic spines. c) First-person internal sensations are induced only during a short range of frequencies of oscillating extracellular potentials. Traces of extracellular potentials obtained by different recording methods that reflect variations in the ionic changes caused by depolarization changes at the neuronal membranes are similar [49]. Since they are composed of a very large number of sources, it is difficult to decompose those signals [50,51]. However, oscillation of these potentials is expected to have its vector components contributed by different mechanisms. Synaptic transmission across synapses between neuronal orders can provide one vector component and it is reasonable to expect that a mechanism for induction of units of internal sensations provides a second vector component perpendicular to it.

4.2. Derivation

It is reasonable to argue that learning-induced change should be taking place at the location of convergence of sensory inputs. From the arguments explained at the section 4.1, it is clear that the interaction should be taking place between synapses through which associatively learned sensory stimuli arrive. Therefore, the interaction should take place either between the presynaptic terminals or the postsynaptic terminals of those synapses. Since neurotransmission is taking place unidirectionally, activation of postsynaptic terminal (dendritic spine) is the last step during activation of a synapse. This leads to the assumption that learning-induced changes are likely taking place between the spines. However, it should be possible to prove the presence of a sufficient operational mechanism at this level to justify this view. If the interacting synapses are present on the adjacent spines of the same neuron, both stimuli will lead to the activation (spike or firing or action potential) of this same neuron. This will not maintain the identity of the associatively-learned stimuli beyond the level of this neuron. From this, it can be inferred that ideally interaction should be taking place between spines that belong to two different neurons.

The above arguments lead to the following questions. a) Is there any evidence suggestive of an interaction between spines that belong to two different neurons? b) Can interaction between spines that belong to two different neurons generate cellular changes at the time of learning and can this be used by one of the learned stimuli to induce units of internal sensations? c) Is there a specific feature present at this level that enables integration of units of internal sensations? These can be answered as follows. a) First, there are no electrically isolated cables between adjacent spines on the dendritic branch of a neuron. Secondly, the finding that mean inter-spine distance is even greater than the mean diameter of spine heads in pyramidal CA1 neurons [52] perfectly matches with the derivation that the interaction should be taking place between spines that belong to two different neurons as a rule. Exceptions may

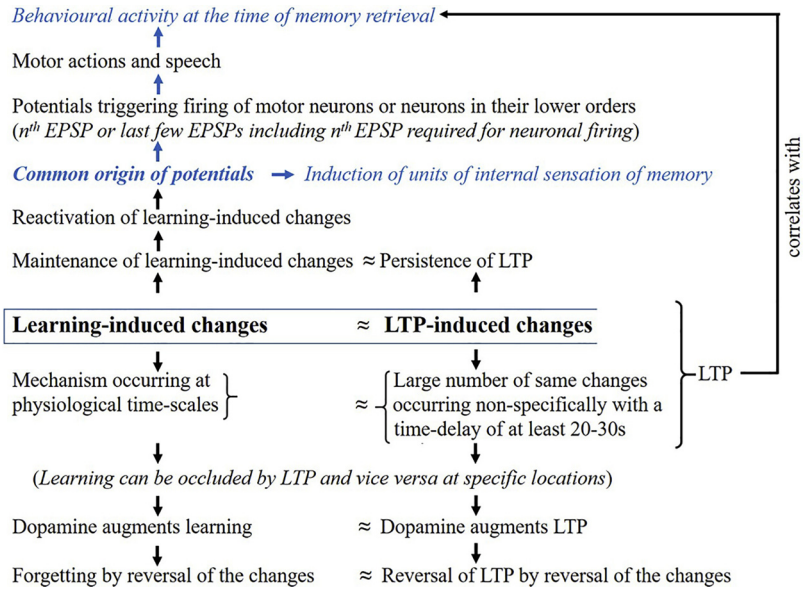

Fig. 2. Similarities and differences between learning-induced changes and LTP induction. A correlation between the ability to memorize and strength of LTP has been observed by examining behaviour as the marker of memory retrieval. This correlation needs to be re-examined when memory is viewed as an internal sensation. This leads to the search for the source of potentials necessary for the induction of internal sensation of memories occurring concurrently with behavioural motor actions. Since cellular changes are absent during memory retrieval, a mechanism for the passive reactivation of learning-induced changes is expected to occur. If learning-induced cellular changes taking place at physiological time-scales also occur following LTP stimulation, then it is necessary to discover the specific reason for the delay for LTP induction following LTP stimulation.

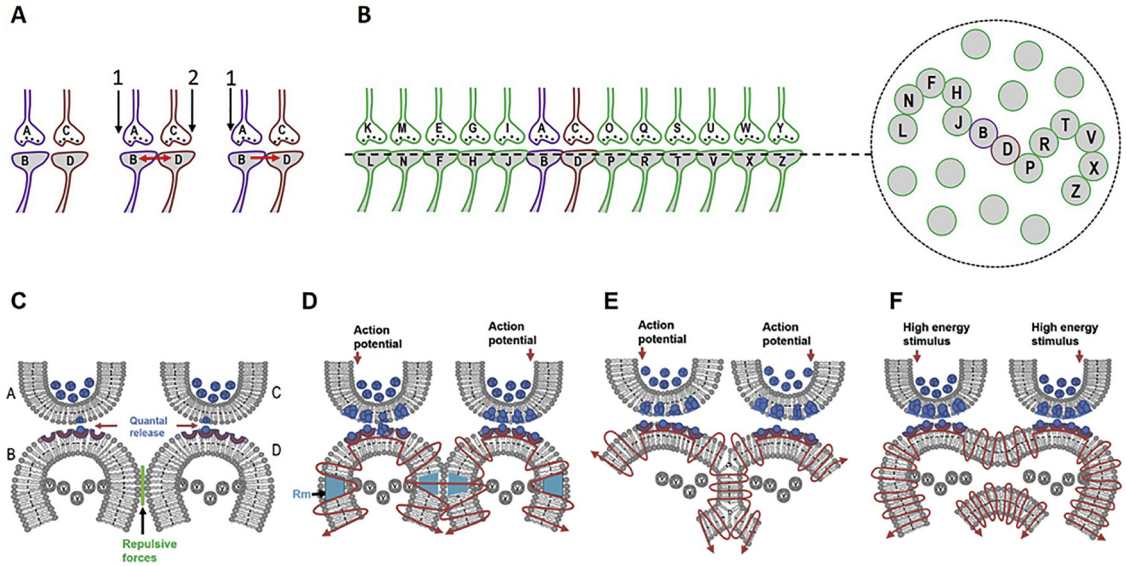

Fig. 3. Formation, types and clustering of inter-postsynaptic functional LINKs (IPLs). **A**) Left: Two synapses A–B and C–D are shown side by side whose postsynaptic terminals (spines) B and D are abutted to each other. Middle: Simultaneous arrival of stimuli 1 and 2 at presynaptic terminals A and C during learning leads to the formation of an IPL between their postsynaptic terminals B and D. Right: During memory retrieval in the presence of one of the stimuli (stimulus 1) IPL is reactivated, resulting in the activation of postsynaptic membrane D. This leads to induction of a semblance of activity arriving from presynaptic terminal C as an intrinsic system property. Synaptic activities at synapses A–B and C–D are essential during learning and synaptic activity at synapse A–B is essential for reactivation of IPL B–D to induce a unit of internal sensation. **B**) Left: Inter-LINKed spines B and D form additional IPLs with spines L, N, F, H, J, P, R, T, V, X and Z during additional learning events to form an islet (for convenience, spines are drawn in a line). Right: A cross-sectional view through spine heads within the above islet of inter-LINKed spines. Here, spines are assumed to be located in one plane. Nine other independent spines are shown. **C-F**: Different types of IPLs. Presynaptic terminals A and C with synaptic vesicles (in blue color) inside them. Postsynaptic terminals B and D contain vesicles with AMPAR subunits inside them. **C**) Continuous quantal release is represented by the presence of a single vesicle at the synaptic junction. Repulsive forces (in green) keep the spines separate and prevent depolarization spread between them. The simultaneous arrival of activity at the synapses leads to enlargement of spines B and D and removal of the hydrophilic region between them that leads to an electrically connected close contact between them (not shown). Since it is a high energy requiring process, it forms a rapidly reversible IPL and can be used to explain working memory and short-term potentiation (STP). **D**) Further enlargement of spines and membrane reorganization (at membrane segments marked Rm) secondary to AMPAR subunit vesicle exocytosis at the lateral borders of spines B and D can lead to reversible partial hemi-fusion between them. It can be used to explain short-term memory and early LTP. Rm: Lateral spine regions where rapid membrane reorganization takes place. The spread of depolarization between the spines shown as a waveform indicates electrical continuity. **E**) Complete hemifusion between spines B and D that can be reversed and also stabilized. This change is responsible for short- and long-term memories and LTP maintenance. The spread of depolarization between the spines shown as a waveform indicates electrical continuity. **F**) High energy stimulation arriving at presynaptic terminals A and C can lead to inter-spine fusion between spines B and D. Small areas of fusion may reverse back (for example, during LTP). The spread of depolarization between the spines is still present and is shown as a waveform indicates electrical continuity (Figures modified from [36,53]).

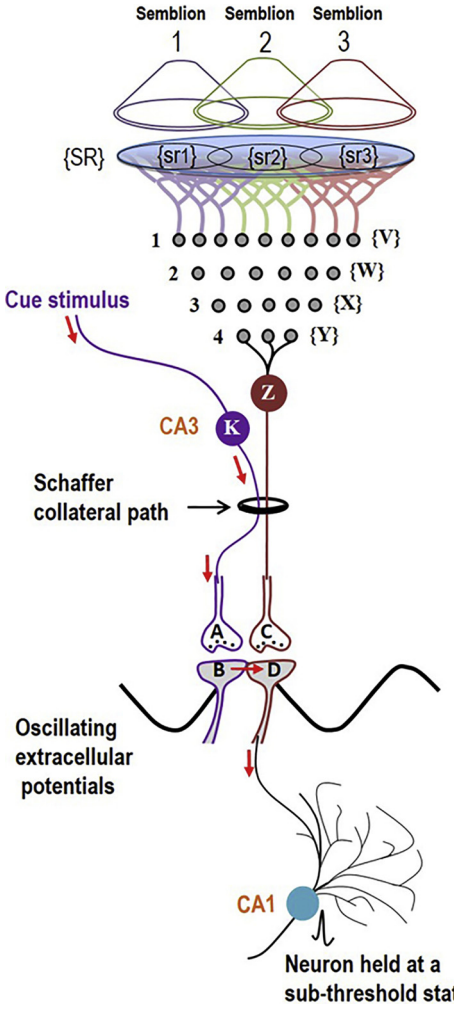

Fig. 4. Induction of units of internal sensation and concurrent firing of a sub-threshold neuron. Gray circles placed in rows (numbered from 1 to 4) represent neuronal orders. Row 1 has sensory neurons. Neurons of hippocampal CA3 layer (marked K and Z) are in neuronal order 5. When the cue stimulus re-activates IPL B–D, it activates inter-LINKed postsynaptic terminal D from a lateral direction and induces a unit of internal sensation. This systems property is expected to occur when IPL function can contribute to different vector components of the oscillating extracellular potentials (shown by a wave form). In order to estimate the sensory identity of internal sensation, a retrograde extrapolation from postsynaptic terminal D towards the sensory receptor level is made. Postsynaptic terminal D is activated by CA3 neuron Z. Spatial summation of nearly 40 EPSPs (from nearly 40 dendritic spines out of nearly tens of thousands of dendritic spines of each pyramidal neuron) or temporal summation of less than 40 EPSPs provides threshold potential that triggers an action potential at CA3 neuron's axon hillock. Since EPSPs degrade as they arrive at the cell body, the actual number of spines involved are expected to be more than the above numbers. Neuron Z is activated by a set of neurons {Y}, which in turn receives inputs from dendritic spines from a set of neurons {X}. Depolarization can also arrive through reactivation of existing IPLs at these levels. Continuation of the extrapolation arrives at a set of sensory receptors {SR}. The sensory identity of cellular hallucination is the sensory stimulus that can activate sensory receptors in set {SR}. It is likely that activation of subsets of a minimum number of sensory receptors {sr1}, {sr2}, and {sr3} from set {SR} is sufficient to activate postsynaptic terminal D. A hypothetical packet of minimum sensory stimuli capable of activating one of the above subsets of sensory receptors that can activate postsynaptic terminal D is called a semblion, which is the basic unit of internal sensation of memory. These sensory units have no orientation (Figure modified from [36]).

occur. b) To produce an interaction between the spines, the interacting spines should be readily LINKable (capitalized to denote its significance). From the interaction, an inter-postsynaptic (inter-spine) functional LINK (IPL) is expected to occur in physiological time-scales (Fig. 3A). The reactivation of IPL should be capable of activating the inter-LINKed spine and generate units of internal sensations at physiological time-scales and should provide potentials to trigger motor action. To ensure occurrence of an action potential of a motor neuron (at that or higher neuronal orders) by the arrival of a single EPSP through learning-induced inter-spine interaction, it is expected that motor neurons need to be held at a subthreshold activation state just short of the strength of potentials arriving through the IPL. This can be further regulated by inhibitory neuronal activity [36,53]. c) Both synaptic transmission and potentials propagating through the IPLs perpendicular to that of synaptic transmission contribute vector components to oscillating extracellular potentials occurring in a narrow range of frequency, which is essential for generating internal sensations.

Mechanism for establishing an IPL should match with the properties of reversibility (that explains forgetting at different time periods after associative learning), stabilization (for long-term memory), augmented stabilization in certain conditions (e.g. motivation-promoted learning), and reactivation (for memory retrieval) [53]. Associative learning of related items or events is expected to share some of the inter-LINKed spines formed during earlier learning events. In addition, it is also expected to generate new IPLs with previously inter-LINKed spines. The latter will generate groups of inter-LINKed spines called islets (groups or chains) of inter-LINKed spines (Fig. 3B). A spectrum of molecular and cellular changes can explain IPL formation [53]. These include high-energy requiring rapidly reversible close contact between the spines by removal of repulsive forces between the membranes (Fig. 3C), and formation of reversible partial and complete membrane hemifusion between the spines (Figs. 3D, E). Readily LINKable spines present at the locations of convergence can facilitate IPL formation by some of the above mechanisms. Reorganization of plasma membranes [54,55] and membrane fusion [56] are common biological events. Hemifusion is a stable intermediate stage of membrane fusion [57] (Fig. 3F). Hemifused state can reverse back to independent membranes. If a hemifused membrane region is maintained beyond a certain period, it has the potential to get stabilized by different mechanisms for different durations. These features offer a spectrum of suitable structural mechanisms expected of learning-induced changes.

4.3. Theoretical verification of the suitability of IPL

The main requirement of the correct mechanism is that at the time of memory retrieval, reactivation of IPL by the cue stimulus should induce units of virtual first-person internal sensation of the associatively-learned second stimulus. The explanation of the mechanism should be capable of providing transition from third-person findings to first-person features. It can be examined whether any specific context or logic is existing at the level of the IPLs that enables the induction of units of internal sensation. Examination shows a unique context that the spine head region is continuously being depolarized both by the continuous quantal release of neurotransmitter molecules from their presynaptic terminals and by the arrival of action potentials at the presynaptic terminal evoking EPSPs on the spine that propagate towards its neuronal soma. In this dominant context, any incidental lateral activation of the spine head by the cue stimulus is expected to induce units of internal sensation. This matches with the expectation that mechanism of memory should be capable of generating a hallucination (a sensory experience in the absence of a stimulus) [58]. If an IPL is formed between two spine head regions (outside the synapses) during learning, then arrival of one of the stimuli (cue stimulus) is expected to propagate through the IPL and spread over the inter-LINKed second spine that was previously activated by the second stimulus. In the dominant context that inter-LINKed spine head (like all other spines) is

being continuously depolarized by its presynaptic terminal, incidental lateral activation through the IPL is expected to spark a cellular hallucination (semblance) at the inter-LINKed spine that it is receiving sensory stimulus from the environment.

Content of the hallucination being sparked at the inter-LINKed spine is virtual and it constitutes units of first-person internal sensation. Since every retrieved memory within the mind has specific features that we can internally sense, the sensory qualia of virtual first-person internal sensations need to be determined. For this, it is necessary to make a retrograde extrapolation from the inter-LINKed spine towards its sensory receptors to identify minimum sensory stimulus required to activate that inter-LINKed spine (Note that there are no neural activity in this retrograde direction. This is a necessary theoretical step to identify the qualia of internal sensation of memory). The result of this examination will provide the content of what is getting internally sensed from a first-person frame of reference. This retrograde extrapolation is a transition from third-person findings towards understanding first-person features. This derivation was explained in detail before [36,53] and is summarized in Fig. 4.

Retrograde extrapolation from the inter-LINKed spine reaches at a set of sensory receptors and from that, it will be possible to understand the features of sensory stimuli that can stimulate those sensory receptors. Viewing from the opposite direction, it can be seen that only a subset of those sensory stimuli will be sufficient to stimulate a subset of those sensory receptors to activate the inter-LINKed spine (**see** Fig.4). This allows to identify the minimum sensory stimulus (called "semblion") that can be viewed as a basic operational unit of internal sensations. A cue stimulus is expected to induce a large number of semblions at every inter-LINKed spine that it will stimulate. Natural computation of all the semblions induced at different inter-LINKed spines is expected to occur as a system property during a narrow range of frequency of oscillating extracellular potentials, whose vector components have contributions from synaptic transmission and propagation of potentials through the IPLs in perpendicular directions. It is reasonable to expect that intersecting semblions induced at different inter-LINKed spines will be a major determining factor of the conformation of net semblance for memory. Computational product of all the units of internal sensations is expected to generate the qualia of a specific memory. Concurrent with the induction of internal sensations, potentials arriving at the inter-LINKed spine can activate latter's neuron if it is being held at a sub-threshold activated state. If this neuron is a motor neuron or can activate a motor neuron at its higher neuronal orders, then it can contribute towards behavioural motor action corresponding to the retrieved memory. Inhibitory interneurons and feedback circuits can regulate threshold limits of these neurons. If learning generates IPLs, then it is expected that the same mechanism should be able to explain LTP induction, but at a larger scale. If theoretically expected properties of IPLs can explain all the electrophysiological findings of LTP, its correlations and uncorrelated findings from the past, then IPL formation is a candidate mechanism of learning.

5. Suitability of IPLs in explaining features of LTP

Foremost, it is necessary to examine whether cellular changes formed during natural learning (Figs. 3**C-E**) can offer a pathway for the potentiating effect during LTP induction. In the context of IPL mechanism, one matching postsynaptic factor for LTP induction is an increase in the number of activated synapses by 63% in a modelling study [34]. This suggests that a potentiating effect can be achieved if additional routes other than the fixed number of synaptic connections through which potentials arrive from the stimulated Schaffer collaterals to the recording CA1 neuron can be generated. This becomes possible if there is formation of large numbers of IPLs in chains (islets) making electrical connection between the stimulating and recording electrodes in a time-dependent manner. Average distance between electrodes while eliciting LTP at the CA3-CA1 synaptic region is nearly 500 μm and average diameter of a spine head is nearly 400 nm. Hence, for the longest straight line route of electrical continuity between the stimulating and recording electrodes, it may need up to a thousand IPLs between the spines of different CA1 neurons. In practice, more IPLs can occur in a 3-D volume to provide electrical connections in the region between the stimulating and recording electrodes.

LTP stimulation is expected to activate all the synapses at the stimulated Shaffer collateral axonal terminals. Spines of these activated synapses are located at scattered locations between the stimulating and recording electrodes. LTP is associated with enlargement of spine heads [59,60], which is expected to take place in a time-dependent manner after the delivery of high-energy stimulation protocols. These include spines of both recorded and non-recorded CA1 neurons to which stimulated CA3 axonal terminals synapse. A reasonable expectation is that several non-stimulated spines that are interposed between stimulated spines eventually form IPLs with the enlarging spines and become part of the chain of inter-LINKed spines. Chains of inter-LINKed spines facilitate formation of large numbers of IPLs with the spines of recorded

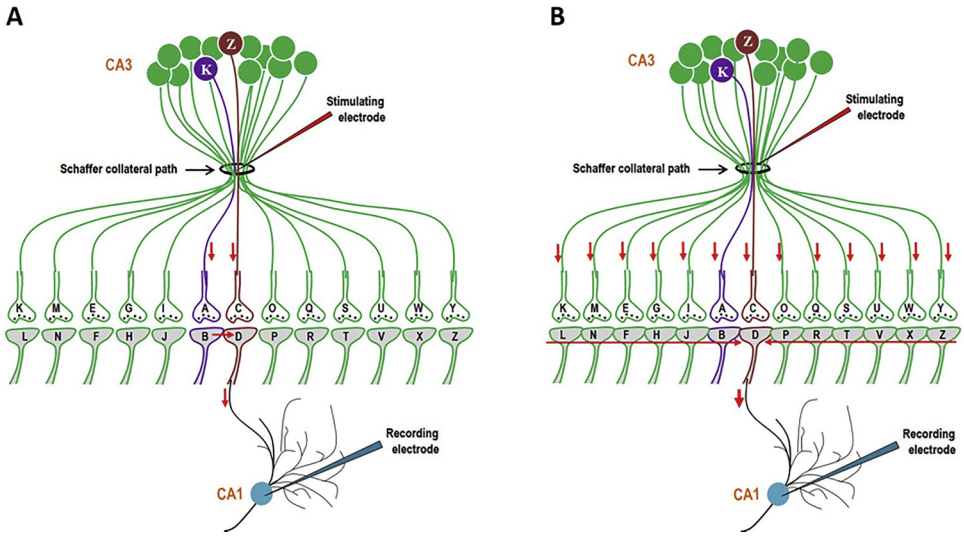

Fig. 5. The comparison showing the effect of stimulating Schaffer collaterals by a regular stimulus before and after inducing LTP. **A**) Stimulation with a regular stimulus at the Schaffer collateral path before LTP induction will only allow potentials to propagate through the existing IPL labelled B–D that will propagate through postsynaptic terminal D to its CA1 neuron. Even though all the synapses shown in the figure are activated, only the EPSPs from postsynaptic terminals B and D reach recording CA1 neuron. **B**) High-energy stimulation of LTP will lead to the formation of different types of IPLs, which is a time-consuming process. This results in increased electrical continuity between stimulating and recording electrodes. This will allow more current to propagate through all the newly formed IPLs L-N-F-H-J-B and D-P-R-T-V-X-Z (shown by two red horizontal arrows pointing to each other) and reach towards the recording CA1 neuronal soma, which explains the potentiated effect. Note that neurons K and Z are CA3 neurons through which inputs arrived during associative learning (see Fig. 4).

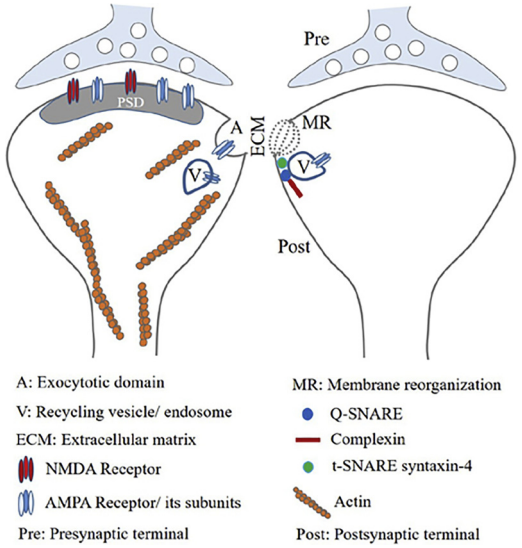

Fig. 6. Membrane changes at the lateral borders of postsynaptic terminals close to the synaptic border that can facilitate IPL formation. Two synapses whose postsynaptic terminals are separated by extracellular matrix (ECM) is shown. IPL formation is expected to take place with the same speed as that of the synaptic vesicle fusion with the presynaptic terminal during normal synaptic transmission. Exocytosis of AMPA receptor subunit containing vesicle leads to membrane reorganization at the lateral spine border. Both the thin ECM between the spines and the membrane reorganization help to overcome the repulsive forces between the membranes. This reduces the energy required for membrane interaction, which leads to IPL formation. Vesicle exocytosis involves different SNARE proteins that are regulated by other proteins. Enlargement of spines by dopamine augment the IPL formation. These changes are expected to occur both during natural learning and following LTP stimulation. Endocytosis of vesicles cause reversal of these cellular changes, reversals of IPLs and loss of learning-generated changes. Only partial features are drawn in each postsynaptic terminal. PSD: postsynaptic density.

CA1 neuron. This can provide a large number of electrical connections between the electrodes. Formation of parallel circuits among them can significantly reduce resistance to current flow. Following this, potentials generated by a regular stimulus at the stimulating electrode will be able to reach the recording electrode through multiple IPL routes. This can offer an explanation for the potentiated effect following LTP stimulation (Fig. 5).

In the field EPSP recording, stimulating electrode is placed in the axonal region of a large number of neurons of a specific neuronal order. The recording electrode is placed, after their synapses, at the dendritic regions of the next order of neurons. There is only one synaptic region (monosynaptic) between the neuronal orders at which the electrodes are placed. The recorded field EPSP reflects variations in the ionic changes caused by depolarization changes at the neuronal membranes [49]. After LTP induction that forms very large islet of inter-LINKed spines, application of a regular stimulus will allow potentials to flow through the large number of IPLs. The ionic changes of this flow will reflect in the extracellular matrix (ECM) space, which is recorded as an increase in amplitude of field EPSP. *In vivo* LTP induction where the recording electrode is located in the ECM similar to that in a field EPSP recording, can also be explained by IPL mechanism. Explanations for different features of LTP in terms of IPL mechanism are provided below.

5.1. Need for higher stimulation energy

An optimal number of IPLs will be necessary for the formation of an optimal number of routes for a regular stimulus-induced potentials to arrive at the recording electrode and show a potentiated effect in LTP experiments. This requires a large amount of energy, which is provided during LTP stimulation by high frequency stimulation. This energy will be necessary for the enlargement of small spines so that they can get abutted to the neighbouring spines and undergo IPL formation. During LTP stimulation, large number of IPLs are expected to form by hydration exclusion between the spines allowing their interaction for spread of depolarization between the spines, a process that requires a large amount of energy as evident from studies using lipid membranes [61–63]. Additional energy will be necessary for the formation of partial and complete hemifusion events between the spines. An example of direct application of energy that leads to inter-cellular fusion by the use of electrical energy is explained in section 5.6.

Since a high energy source similar to that of LTP stimulation is not available *in vivo*, how can this be compared to the IPL formation occurring in physiological conditions? Fusogenic molecules are known to overcome the energy barrier to achieve fusion [64]. SNARE (soluble NSF (N-ethylmaleimide sensitive fusion protein) attachment protein receptor) proteins are known to bring together repulsive membranes and overcome energy barriers related to curvature deformations during hemifusion formation [65,66]. SNARE proteins also generate force for pulling the abutted membranes together as tightly as possible [67]. Specifically, hemifusion intermediates are characteristic of SNARE proteins, including that of neuronal SNAREs [68,69]. SNARE proteins are known to mediate fusion of vesicles containing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) with the spine membrane [70,71]. More specifically, postsynaptic membrane t-SNARE protein syntaxin 4 defines an exocytotic zone next to the postsynaptic density (PSD) and directs membrane fusion and local membrane traffic in dendritic spines [71]. These factors favor IPL formation using less energy.

5.2. Postsynaptic terminal as final path for LTP induction

Experiments were conducted to find the final synaptic location where changes occur during the induction of LTP. This was carried out by blocking N-methyl-D-aspartate receptors (NMDARs) and by increasing postsynaptic Ca^{2+} via voltage-sensitive calcium channels. This was enough to show a potentiated effect [72,73] and indicates that the final common change that leads to potentiated effect occurs at the level of dendritic spines. This matches with the hypothesized formation of IPLs between spines as the basic cellular mechanism that follows LTP stimulation. Since the postsynaptic terminal activation is sufficient to show the potentiated effect [72,73], and since a matching postsynaptic factor for LTP induction from one modelling study is an increase in the number of activated synapses by 63% [34], IPL formation offers a suitable mechanism.

The spines were examined for cellular changes associated with LTP induction. It was found that glutamate receptor 1 (GluR1) AMPAR subunits redistribute into the cytoplasm of the spine head region after the induction of LTP [74,75] (Fig. 6). Investigations showed that the spine geometry is critical for the AMPAR expression [76]. Later, it was found that tetanic stimuli that induce LTP lead to both AMPAR insertion and generalized recycling of membrane segments from endosomes that contain GluR1 AMPAR subunits [77]. Further studies revealed that exocytosis of vesicles containing AMPAR subunits is associated with their lateral movement during LTP [78]. Exocytosis was proposed to occur at the lateral aspect of spines outside the synapses [78,79]. These findings suggest reorganization of the lateral regions of the spine heads using lipid molecules of membrane segments from the vesicles that carry AMPAR subunits during exocytosis.

The finding that both blockade of exocytosis [71,80,81] and reduction in surface expression of AMPARs [82] result in severe loss of LTP supports the hypothesized role of vesicle membranes in reorganizing spine membranes for IPL formation. The finding that surface expression of any AMPAR subunit is sufficient for inducing LTP [82] matches with the expectation that the common factor involved is the contribution of their vesicle membrane segments in reorganizing the spine membranes that can lead to the formation of IPLs. The reported

persistent curvature of the exocytotic region [83] favours formation of different types of IPLs at the locations of AMPAR subunit exocytosis. The synapses that either lack or have very few functional AMPARs are called silent synapses. During LTP induction, exocytosed AMPAR subunits get assembled to form functional AMPARs that can get inserted into the membranes of spines of these silent synapses [84,85].

In contrast to LTP induction, during learning readily available AMPAR subunit vesicles that are abutted to the inner spine membrane can undergo rapid exocytosis and transfer their lipid membrane segments for reorganization of the lateral aspects of spines for the formation of IPLs at physiological time-scales. In normal conditions, GluR1 subunits are located on the spine membrane up to 25 nm away from the synaptic junction [86]. This indicates a high probability that vesicles containing AMPAR subunits get exocytosed at this location and along with providing AMPAR subunits to form functional AMPARs, these vesicles increase spine surface areas at their lateral margins (Fig. 6) that can favour the formation of different types of IPLs.

5.3. Delay in induction of LTP

A time delay of at least 20 to 30 s [31] and even more than a minute [44], is observed before the recorded potentials reach peak level after LTP stimulation. Similar delay is also observed (through interpretation of graphs) in experiments where a transient potentiated effect was produced by a rise in the postsynaptic Ca^{2+} after blocking NMDARs [72,73], single spine LTP experiments [59], and in LTP induction by a single burst [42]. Tetanus-induced rise in the postsynaptic molar Ca^{2+} concentration lasting at most for 2 to 2.5 s was found sufficient to generate LTP [87]. The remaining time delay is not due to the emergence of filopodia or new spines as they take at least 20 min to develop [88,89]. It is also not due to multiple spine synapses between a single axon terminal and one dendrite as it takes a similar time delay as above [90]. These findings necessitate existence of a time-consuming cellular mechanism that can explain an increase in field EPSP of up to 200% from the baseline [43] or 60% increase in EPSP amplitude by whole cell patch recordings [34] after high-energy LTP stimulation.

Even though IPLs are expected to get generated at physiological time-scales, can they substantiate the long delay of up to 30 s between LTP stimulation and the peak potentiated effect? Are there any reports of similar delays in the interaction between cells following electrical stimulation in cell biological experiments? Experiments to generate membrane fusion between cells under the influence of electrical stimulation [91–93] have shown comparable delays of minutes. Delays of similar time-scales have also been observed during membrane hemifusion [94] and fusion [95,96] by using SNARE proteins. Since formation of up to a thousand IPLs between the spines of different CA1 neurons will be necessary to generate maximum electrical continuity between the stimulating and recording electrodes and since *in vitro* cell fusion is a slow process, it can explain the nearly 20–30 seconds [31] or even more than a minute [44] of delay between stimulation and LTP induction (Fig. 7).

Since LTP is associated with enlargement of spine heads [59,60], these are expected changes occurring during the delay period following stimulation and before LTP induction. Since it takes nearly 10 s for AMPARs to get recruited to spine membranes concurrent with the increase in spine volume following LTP induction [97], it can be viewed as a delayed change that reorganizes the lateral aspects of spine membranes for IPL formation. Since readily LINKable spines are responsible for the IPL formation during learning and since lipid membrane composition is a determinant of fusion [98,99] that varies between regions of the nervous system, learning-induced changes at certain locations may not even require contributions from vesicles containing AMPAR subunits and can explain certain experimental findings [100].

5.4. Sudden rise to peak potentiated effect following a delay

Rise in potentials at the recording electrode following LTP stimulation does not show a ramp-like increase before reaching its peak. Lack of slow rise is likely due to the initial formation of small islets of inter-LINKed spines that finally coalesce to form a large islet. The initial formation of small islets of inter-LINKed spones are likely to occur around the spines of synapses that receive direct stimulation. These islets will then form inter-LINKs with those unstimulated spines between them. After an optimum time, a large islet of inter-LINKed spines that establishes maximum electrical continuity between the electrodes will form. In addition, completion of several parallel circuits within the islets of inter-LINKed spines can significantly reduce resistance to current flow. Following this, a regular stimulus will be able to reach the recording electrode through multiple routes to show a peak potentiated effect.

5.5. Persistence of potentiated effect for long duration

It is most likely that high energy used in LTP stimulation leads to the generation of IPL hemifusions of large surface areas between the membranes of involved spines. These hemifusions may take several hours to reverse back to normal state. This contrasts with a few nanometers of length at which IPLs are expected to form during natural learning. In addition, following LTP stimulation several IPLs can progress to IPL fusion stage and many of them will not reverse back. From Fig. 3F, it can be seen that the fused spines can propagate potentials between them similar to other types of IPLs. These factors allow persistence of potentiated effect for long periods.

5.6. Need for AMPAR exocytosis is determined by LTP stimulation intensity

Synaptic insertion of the GluR1 subunit containing AMPARs is generally found during LTP changes [82]. Based on the present work, insertion of membrane segments during exocytosis of AMPAR subunit containing vesicles is contributing to the IPL formation responsible for LTP changes. However, it was found that a near-saturation LTP induction alone is sufficient to induce LTP without requiring GluR1 subunits, their C-tails, or their auxiliary subunits [101]. How can high energy stimulation surpass this requirement? Normally, membrane fusion requires large amounts of energy as evident from studies using lipid membranes [61–63]. However, changes in lipid membranes due to reorganization by AMPAR vesicle exocytosis are expected to reduce this energy requirement. Since electrical stimulation to achieve inter-cellular membrane fusion [91–93] is a known process and is used in applications such as hybridoma generation, delivery of high energy by methods such as high frequency stimulation is expected to generate different types of IPLs.

5.7. Sudden drop in peak-potentiated effect and working memory

LTP recordings show that after reaching the peak, potentiated effect shows a sudden drop to reach a plateau level. The short-lived component at the peak potentiation was noticed from the early days of investigations and is called short-term potentiation (STP) [102]. Studies have shown that different neurotoxins that bind to protein molecules necessary for vesicle exocytosis attenuate LTP severely, but do not attenuate STP [103,104], indicating that STP is mediated by a different mechanism than that of LTP. Earliest stage of IPL formation brings spine membranes into close contact by hydration exclusion and overcoming the repulsive forces that requires a large amount of energy. Due to the lack of continuous energy supply, most of these IPLs are expected to reverse back rapidly. Multiple inter-LINKs between spines in the volume of tissue between the electrodes occur during the delay period after stimulation eventually leads to maximal electrical continuity resulting in a peak response to a regular stimulus. Even though reversal of

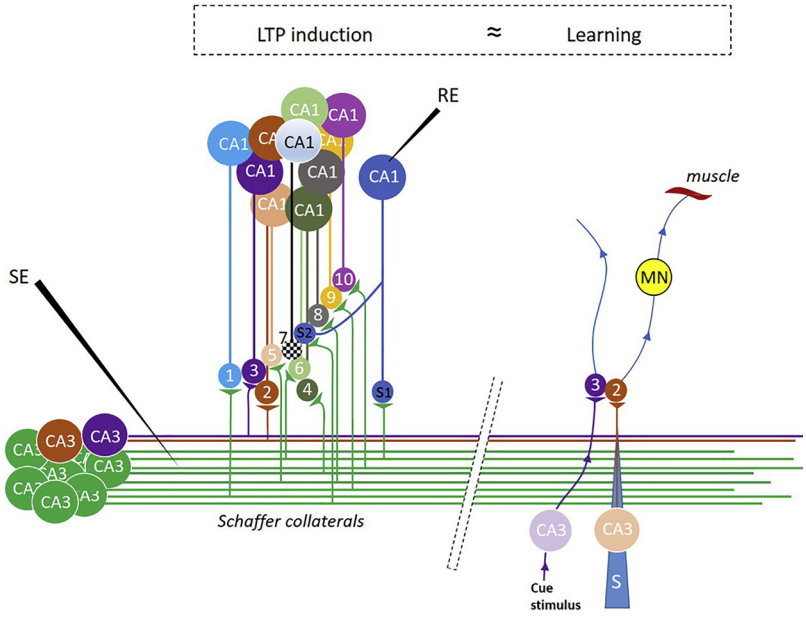

Fig. 7. Formation of inter-postsynaptic LINKs (IPLs) that lead to findings of LTP and its correlation with learning and memory retrieval. **Left side**: A group of CA3 neurons and their recurrent Schaffer collaterals are shown. Recorded CA1 neuron has only two dendritic spines S1 and S2 that synapse with axonal terminals stimulated by stimulating electrode (SE). After stimulation, LTP induction requires the arrival of increased current at recording CA1 neuronal soma after a delay, in response to a regular stimulus at the SE. Several spines (marked from 1 to 6 and 8 to 10) that belong to different CA1 neurons are activated by SE. High-energy LTP stimulus leads to slow enlargement of spines 1 to 6 and 8 to 10. This leads to the formation of different types of IPLs between them. Spine 7 (checkered spine) is located between spines 5, 6 and S2. When the latter spines enlarge, they get abutted with spine 7 and form IPLs with it. This generates a large number of electrical connections between SE and RE through dendritic spine S2. Note that electrical flow is only limited by the current carrying capacity of the spine neck of spine S2. Formation of the large number of IPLs between the spines including those with interposed non-stimulated spines is a time-requiring process as evidenced from cell fusion studies. Note that nearly a thousand spines are expected to be involved in the formation of IPLs in the volume between the electrodes. **Right side**: Learning has generated an IPL between readily LINKable spines marked 3 and 2. Following learning, the arrival of a cue stimulus at spine 3 reactivates IPL between spines 3 and 2 and induces semblance (S), the unit of internal sensation of memory (Figures of synapses are inverted compared to that of Fig. 4). Potentials from inter-LINKed spine 2 can trigger action potential of a sub-threshold activated motor neuron (MN) that leads to motor action. Figure not to scale. Distance between electrodes ~500 μm; Diameter of single spines ~400 nm. This figure has only ~12 spines between the electrodes instead of the expected nearly one thousand spines.

a proportion of early stage IPLs will continuously limit the speed of potentiating effect, a visible change can be recorded only after the total IPL effect reaches the peak. This will result in a sudden decrease in the potentiating effect and explains STP.

The observations that both long-term memory and LTP are dependent on protein synthesis led to the idea that working memory takes place by a separate method [105–107]. It was not possible to verify whether the same learning mechanism that generates working memory can get transitioned to more stabilizable forms that can persist for long durations to generate short-term and long-term memories. Since IPLs formed by hydration exclusion and removal of the repulsive forces between the membranes last only for a short period, they will be available for the cue stimulus to induce units of internal sensation only for a short period of time explaining working memory. Since the early stage of inter-spine interaction has the capability to transition to more stable forms of IPLs and since the internal sensation of memory can be induced from all these stages of the IPL, working, short-term and long-term memories can be formed by the same basic mechanism occurring at the time of learning [108].

Since AMPAR subunit vesicle exocytosis that can add membrane segments on the lateral aspect of spines is a candidate mechanism for persistent curvature at the exocytotic region [83], it can favour hydration exclusion between the abutted spine membranes and form a candidate mechanism for STP. In agreement with this expectation, experiments that blocked the steps prior to the incorporation of AMPARs into the vesicles that naturally prevent vesicle exocytosis failed to show an STP component while generating LTP [104]. It was recently reported that knockout of both postsynaptic synaptotagmins 1 and 7 (Syt1 and 7) of the exocytotic machinery shows normal maintenance of STP, while abolishing LTP [109]. Since blocking postsynaptic Syt1 and Syt7 did not reduce levels of synaptic or extra-synaptic AMPARs, or alter other AMPAR trafficking events [109], it supports the hypothesis that constitutive exocytosis of AMPARs provides membrane segments to spine membranes and supports the IPL-mediated mechanism for STP.

5.8. Role of synaptic transmission during learning and LTP induction

From Fig. 4, it can be seen that synaptic transmission at the synapses activated by associatively-learned stimuli is essential for IPL formation. Similarly, synaptic transmission at the synapses through which cue stimulus arrives is essential for reactivating the inter-LINKed spine to induce units of internal sensation. During LTP induction, stimulation of Schaffer collaterals leading to the activation of CA3-CA1 glutamatergic synapses is necessary for the activation of dendritic spines that belong to different CA1 neurons to form IPLs between them. In summary, synaptic transmission is essential for learning, memory retrieval, LTP induction and testing for the potentiated effects following LTP induction. In natural conditions, normal synaptic transmission is expected to lead to the IPL formation between readily LINKable spines at the locations of convergence of associatively-learned sensory stimuli. Contribution of activation of different neurotransmitter receptors towards the generation of IPLs may vary. At the glutamatergic synapses, exocytosis of readily available AMPAR subunits is expected to take place during natural learning. Even though NMDARs were found not required for baseline synaptic transmission, they are required for induction of LTP using specific stimulation conditions at the CA3-CA1 synaptic area *in vitro* [110].

5.9. Inhibitors of membrane fusion inhibit LTP

If partial and complete membrane hemifusion between the spines that belong to different neurons is a change occurring during learning, then blockers of membrane fusion should be able to block LTP induction. SNARE proteins are involved in membrane fusion [68] through an intermediate stage [94] that can get arrested at the stage of hemifusion [69]. When blockers of SNARE proteins that can block any membrane fusion were introduced into the neuronal cytoplasm, LTP was reduced [103]. Exocytosis of GluR1 AMPAR subunits on the membranes of spines during LTP induction requires a unique postsynaptic Q-SNARE protein for vesicle fusion [81] (Fig. 6). Postsynaptic protein complexin known to bind to SNARE proteins and block membrane fusion can control AMPAR exocytosis during LTP induction [80]. Disruption of postsynaptic plasma membrane t-SNARE syntaxin 4 impairs both AMPAR subunit containing vesicle exocytosis on the lateral borders of dendritic spine next to the postsynaptic density and LTP at hippocampal synapses [71]. Since reorganization of the lateral spine membrane is expected to occur during exocytosis of AMPAR subunit-containing vesicles and facilitate formation of different IPLs, blocking of SNARE

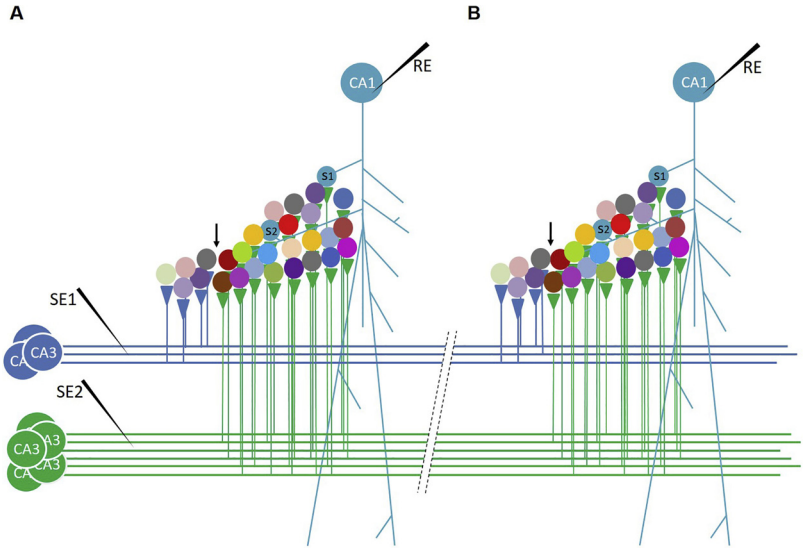

Fig. 8. Cellular-level changes of IPL formation that can explain cooperativity, associativity and input specificity. On the leftmost side are the CA3 neurons and their Schaffer collaterals that are stimulated by a weak stimulus SE1 through electrode SE1 and by a strong stimulus SE2 through electrode SE2. Note that three and six Schaffer collateral axons are activated by the weak and strong stimulus respectively. The spines (in multiple colors) of different CA1 neurons (soma not shown) are located between the stimulating and recording electrode (RE). **A**) Separate application of weak and strong stimuli provides different results. Weak stimulus SE1 results in the inter-LINKing of spines of five different CA1 neurons (soma not shown) through the IPL formation (shown on the left side of the downward pointing arrow). The formed islet of inter-LINKed spines is not connected with the recording CA1 neuron. Strong stimulus SE2 results in a large islet of inter-LINKed spines that is connected to the recording CA1 neuron. Within the islet, the spines that belong to different CA1 neurons inter-LINK with the spines (S1 and S2) of the recording CA1 neuron. Only a strong stimulus at SE2 can result in electrical continuity with the CA1 neuron and can explain the property of cooperativity. A downward pointing arrow shows that the spines within separate islets of inter-LINKed spines formed by weak and strong stimuli. **B**) The simultaneous application of weak and strong stimuli results in the formation of bridging IPLs between the islets of inter-LINKed spines that are formed when they are stimulated separately as in figure A. This is marked by a downward pointing arrow. Following this, the application of a weak stimulus at SE1 will show a potentiating effect when recorded from the CA1 neuron. Simultaneous activation of weak and strong stimuli will result in hydration exclusion between the two islets of inter-LINKed spines that are formed by the weak and strong stimuli. This explains associativity. Imagine that, another weak stimulus SE3 (not shown) is applied at a different location on the Schaffer collateral. It will share the potentiation induced by the strong stimulus SE2 only if SE3 and SE2 are applied at the same time. Input specificity depends on which weak stimulus is getting simultaneously activated with the strong stimulus S2. From the figure, it is evident that it is necessary to use optimal stimulation strengths and optimal distances between the stimulating electrodes to demonstrate the above properties.

proteins can explain the inhibition of LTP. These findings indicate that dendritic spines have an efficient machinery necessary for IPL formation and its regulation. During normal learning, SNARE proteins are expected to involve in the exocystosis of AMPAR subunit vesicles at the readily LINKable spines at physiological time-scales.

5.10. Suitability to accommodate non-Hebbian plasticity changes

Potentiated changes have been reported in the neighbouring regions of the recording CA1 neuron [27,111–113]. These findings also led to the concerns that LTP is not specific to synapses that were active during stimulation suggesting that LTP fails to meet the requirements for a memory mechanism [28]. Since the last change during LTP induction is taking place through the spines [72,73] that enlarge during LTP induction [59,60], large number of IPLs are expected to form between the spines of different CA1 neurons located between the stimulating and recording electrodes. LTP uses a very large amount of energy that results in the generation of large numbers of non-specific IPLs between the electrodes. A spectrum of IPL changes (Figs. 3**C-E**), mainly the early stages, are expected to be formed between specific spines during natural learning; whereas LTP induction is expected to generate many non-specific IPLs by the same spectrum of IPL changes, including IPL fusion (Fig. 3F). After LTP induction, a regular stimulus can propagate through all the newly formed chains of inter-LINKed spines and arrive at different CA1 neurons (Fig. 7). This can explain the observations of non-Hebbian changes and why it was interpreted that LTP fails to meet the "specificity" requirements for a memory mechanism [28].

5.11. Effect of changing locations of recording electrode

Field EPSP has shown a more potentiated effect (up to 200% from baseline) [43] than EPSP amplitude recorded from a CA1 neuron (nearly 60% from baseline) [34]. One reason may be that the recording electrode is close to the stimulating electrode in field recording setup. Secondly, more current can reach the recording electrode in the field through more IPLs formed by a large number of spines of different CA1 neurons than through the IPLs formed and connected to the spines of one CA1 neuron during patch-clamp recording. This matches with the earlier observation that intracellular EPSP is much less potentiated than field EPSP, which was interpreted as most probably due to changes in local resistance [114]. Formation of several parallel circuits by IPLs that dramatically reduce resistance matches with this interpretation.

5.12. Cooperativity, associativity and input specificity

It was demonstrated that LTP at the CA3-CA1 synaptic region exhibits properties of cooperativity, associativity and input specificity features [12–14] that are considered necessary for an ideal learning mechanism. These terms were derived from Pavlovian conditioning experiments in which two temporally contiguous stimuli get associated with one another [115]. An IPL-mediated mechanism can explain these features as follows. a) *Cooperativity*: During LTP stimulation, a critical number of presynaptic terminals are expected to be activated in a cooperative way to provide an intensity-threshold for LTP induction [13,14]. However, only a fixed fraction of these presynaptic terminals directly synapse with the CA1 neuron from which recording is carried out. Initially, it was explained in terms of the need for depolarization to reduce Mg^{2+} block of the NMDAR channels [116,117]. Later observation of a selective increase in non-NMDA component of EPSP during LTP induction [118] indicated that the latter has a role in providing additional potentials to the recording electrode. Based on the present work, reorganization of membranes at the lateral aspect of spines during AMPAR subunit vesicle exocytosis following LTP stimulation leads to formation of IPLs that result in the arrival of additional potentials (Fig. 7). Since a large number of spines are required to be inter-LINKed through IPL formation, a threshold stimulation energy will be necessary to generate sufficient number of inter-LINKed spines to get the maximum electrical connection between the electrodes. An association of two temporally contiguous stimuli during Pavlovian conditioning has led to suggestions that LTP is likely occurring from temporally and spatially contiguous events [28,29]. Gradual expansion of spines leading to continued formation of inter-LINKed spines and formation of islet of inter-LINKed spines in a 3-D space during the delay period following LTP stimulation can explain this.

Single-volley afferent EPSP paired with intracellularly applied depolarizing current pulse via the recording electrode resulted in long-

lasting potentiation within 20–30 pairing events [119]. This shows that postsynaptic depolarization of the large number of spines can facilitate formation of large numbers of IPLs for the potentiating effect. This enables the inter-LINKing of spines close to the recording electrode through IPL formation and eliminates the requirement for activation of afferent path to many synapses. This also matches with the explanation of the formation of a large islet of inter-LINKed spines as the basis of cooperativity. At certain locations, it may necessitate a delayed arrival of the second stimulus to form an optimum number of IPLs and explain temporal binding, a process that enables the association between discontiguous stimuli [120].

For demonstrating associativity and input specificity, it is necessary to apply optimum stimulation intensities at optimal distances, since the size of the islet of inter-LINKed spines depends on stimulation intensity and distance from the stimulating electrodes (Fig. 8). b) *Associativity*: This is explained as potentiation of a weak input if it is activated at the same time a strong tetanus is applied at a separate location, but as a converging input [14]. The convergent nature of the inputs allows separate islets (chains) of inter-LINKed spines from the weak and strong stimuli to become electrically connected through the IPLs that will allow both chains to get electrically connected with that of the recording CA1 neuron. Simultaneous stimulation is important for hydration exclusion between neighbouring spines that belong to different islets that can progress to the formation of different types of IPLs through enlargement of those spines. This will allow a regular stimulus applied at the location of weak stimulus to traverse through the islets of inter-LINKed spines formed by the strong stimulus, permitting increased current flow towards the recording electrode. IPL formation matches with the convergence of inputs for the associative property of LTP [14]. Formation and sequential interconnection of islets of inter-LINKed spines can explain how associativity feature is demonstrated by sequential stimulations [15]. c) *Input specificity*: Input specificity of LTP at CA3-CA1 synapses [12] can be viewed as a modification of associativity. It explains that different inputs that are not active at the arrival of strong stimulus do not share the potentiation induced by the strong stimulus. Simultaneous application of the strong and weak stimuli at optimal distances will be necessary to generate IPLs between the separate islets of inter-LINKed spines that these stimuli can generate if they are stimulated independently. This matches with the finding that the input specificity of LTP is not sustained at distances shorter than 70 μm [113], since keeping this distance between the stimuli will be necessary for the formation of separate islets of inter-LINKed spines when the stimuli are applied separately.

5.13. Occlusion of learning with LTP

Findings that learning can be occluded after LTP induction and vice versa [10,11] can be explained in terms of the IPL mechanism. LTP induction leads to the formation of large numbers of IPLs in a localized area and therefore learning following LTP induction will not to be able to generate any new IPL at that location. Moreover, at the time of memory retrieval as the cue stimulus traverses through the large number of non-specific IPLs formed by LTP induction, it leads to induction of a large number of non-specific semblances. This can explain reduced memory observed in those experiments. Single IPLs that are induced sparsely at different locations in the nervous system during learning may not always occlude LTP induced at a localized region. However, using focused experiments in the hippocampus where the strong convergence of inputs occurs, it was found that learning can occlude LTP induction [11]. Results from occlusion experiments suggest that both learning and LTP induction can be mediated through the same mechanism and IPL formation is suitable for such a mechanism. This may explain why changes similar to LTP were observed during learning [9].

5.14. Dopamine augments both motivation-promoted learning and LTP

The release of dopamine is known to be associated with motivation-promoted learning [121]. Motivation-enhanced learning can be explained in terms of enlargement of spines caused by dopamine [122] that can augment the IPL formation. Enlargement of spines is likely to increase the duration of the maintenance of IPLs, which in turn can increase the probability for the IPLs to get stabilized and remain stabilized for long periods. This in turn will determine the duration of persistence of learning-induced changes. Through a similar mechanism of enlargement of spines, it can explain how dopamine receptor activation increases the magnitude of LTP in the hippocampal slices [123].

5.15. Maintenance phase of LTP

Since energy reaching at the synapses during LTP stimulation is far higher than what is needed for natural learning, it will be difficult to make a direct correlation between their maintenance phases. However, since LTP induction generates a large number of IPLs, some of the changes following learning-induced IPL formation for long-term memory are likely to show similarities. Testing for LTP using regular stimulus at regular intervals can provide an effect similar to that of repetition of learning. In this context, biochemical pathways for implementing homeostasis to maintain the IPLs are likely triggered. These pathways are likely to initiate new protein synthesis. In normal learning, a retrieval-efficient IPL mechanism is expected to take place within milliseconds and this early stage is capable of transitioning to stabilizable forms [108]. Readily available vesicles containing AMPARs are expected to contribute to the IPL formation at physiological timescales. Since most memories are working memories, the majority of the IPLs is expected to reverse back. When there is repetition of learning or related learning or motivation-associated dopamine release that leads to spine enlargement are present, then IPLs are expected to get stabilized. Examples include activation of proteins such as calcium/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C Mζ (PKC Mζ). Entry of calcium into the postsynaptic terminal activates CaMKII that phosphorylates principal and auxiliary subunits of AMPARs [124]. All the above changes are also likely associated with a cascade of biochemical reactions that are important in replenishing the substrates needed for continued formation and stabilization of IPLs.

Even though inhibitors of PKC Mζ were found to reverse established LTP [125], later experiments showed that both LTP and memory are normal in transgenic mice lacking PKC Mζ [126]. Even though the increased concentration of PKC Mζ at the location of cell membrane abscission [127] indicates its possible role in regulating the separation of cell membranes, the finding that memory and LTP are normal in PKC Mζ knockout mice [126,128] indicates that alternate mechanisms will be sufficient to maintain the formed IPLs.

5.16. Inhibitors of NMDARs do not reverse late LTP maintenance

Even though NMDAR antagonists block the initial learning-induced changes in animals, they do not block the maintenance phase of learning-associated changes [129]. In comparison to this, it was observed that inhibitors of NMDARs do not reverse the late maintenance phase of LTP [125]. This can be explained as follows. In order to block the learning-induced changes or an already induced LTP, there should be a mechanism to reverse the formed IPLs. Since inhibition of NMDARs cannot have any effect on any type of IPLs that are already formed (see their structural organization Figs. 3**C-E**), they do not reverse either learning-induced changes or an already induced LTP.

5.17. LTP:kindling::memory:seizure

Kindling is induced by stronger stimulation energy than used for LTP induction and shows several similarities to human seizure disorders

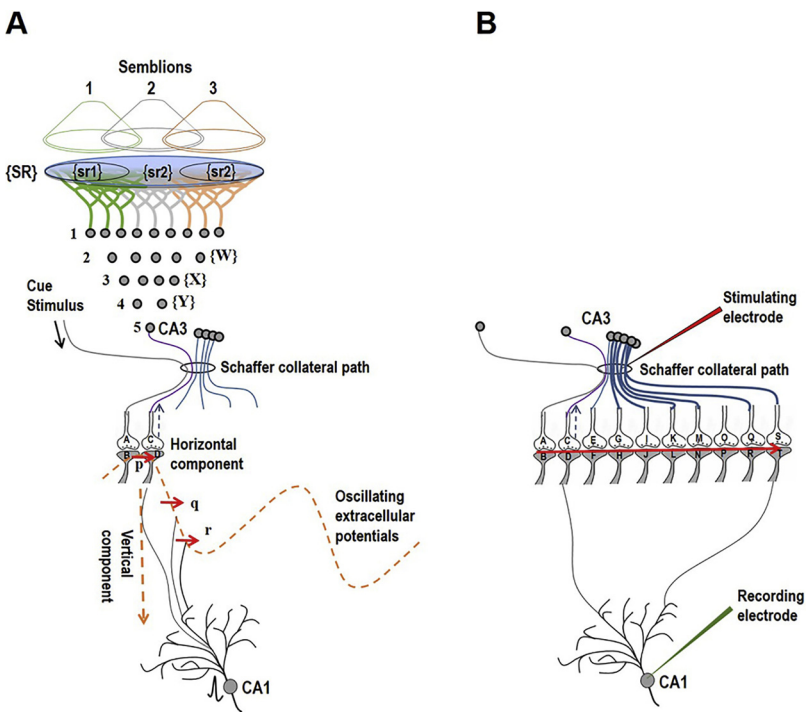

Fig. 9. Illustration comparing the structural changes during learning and memory retrieval and during LTP. **A**) Associative learning induces an IPL between spines B and D. A cue-stimulus reaching spine B, reactivates IPL marked p (red arrow) and inter-LINKed spine D, evoking a cellular illusion of an action potential reaching latter's presynaptic terminal C. Sensory identity of the semblance of activity occurring at spine D consists of semblions 1, 2, or 3 or an integral of them. Cue stimulus-induced activation of spine D reaches soma of its CA1 neuron (place cell in the context of spatial memory) which is kept at sub-threshold activation level by oscillating potentials from lower neuronal orders. Note that reactivation of IPLs (in red arrows) marked p (connecting B–D), q, and r (postsynaptic terminals not shown) contributes to one of the vector components to the oscillating extracellular potentials. **B**) Stimulation of Schaffer collaterals induces LTP through the formation of postsynaptic membrane hemi-fusion between spines that belong to islets of inter-LINKed spines B–D and F-H-J-L-N-P-R-T forming a mega-islet. Even though presynaptic terminal O (and spine P) is not activated during LTP stimulation, the enlargement of abutted spines P and T is sufficient for the formation of mega-islet that includes spine P. Note that only spines D and T belong to the recording CA1 neuron. It takes nearly 30 s for the formation of large numbers of IPLs inter-LINKing spines D to T (large red arrow). Now, a regular stimulus at the stimulating electrode has an increased probability of reaching the recording electrode through a large number of hemi-fused postsynaptic membranes within the large mega-islet, showing a potentiated effect when recorded from CA1 neuron. Neuronal orders from 1 to 5 are numbered from the sensory receptors.

[130]. Experimental findings have suggested that potentiation produced by kindling is likely based on the same mechanism as the LTP effect [102]. Kindling is expected to produce an exaggerated form of changes occurring during LTP induction and is expected to convert several of the hemifusion stages of the IPLs during LTP induction to fusion (Fig. 3**F**) [131]. Fused areas are expected to stay for a long period of time and allow the propagation of potentials between the fused spines. This can explain the findings in kindling experiments. Fusion changes can also explain the transfer of injected dye from one CA1 neuron to the neighboring ones as observed in animal models of seizures [132]. It has been observed that the gene expression profiles of adjacent CA1 are different [133,134]. Due to this reason, mixing of the cytoplasmic contents even between neurons of similar types can evoke cellular responses. This can trigger homeostatic mechanisms that can lead to spine loss as seen both after kindling [135] and in seizure disorders [136] and can be viewed as a method to protect the neurons involved.

5.18. Relationship of learning, memory and forgetting with LTP

During associative learning only specific fibers within large fiber tracks are activated, which lead to the IPL formation at unique locations of their convergence (Fig. 9A). In contrast, LTP stimulation activates many fibers around the stimulating electrode and generates a large number of IPLs between the stimulating and recording electrodes (Fig. 9B). IPLs formed during learning can have different life spans depending on several factors that lead to expansion of spines, and stabilization and reversal of IPLs. LTP induction by applying high energy at a localized area can lead to prolonged maintenance and stabilization of IPLs.

Features of different types of IPLs can explain several similarities between natural learning and LTP stimulation. IPLs formed by close contact between the spine membranes by overcoming the repulsive forces that require a large amount of energy [61–63] can reverse back very fast and can explain the short duration of maintenance of IPLs responsible for both working memory and STP. Following the occurrence of STP, LTP reverses back very slowly. This slow reversing phase has similarities to the maintenance of IPLs responsible for short-term memory that last beyond working memory. These changes can be explained in terms slowly reversing partial and complete membrane hemifusions. Potentiation of AMPA currents by single spine LTP experiments [59] that lasts only for nearly 30 min is an example of such a change. Reversal of the IPLs is expected to be associated with both endocytosis of AMPAR subunits and reduction in the size of enlarged spines that can explain LTP decay observed in experiments [137]. Long-lasting LTP can be explained by the formation of large numbers of IPLs between the electrodes having large areas of hemifusion or fusion (Fig. 3**C-F**) between spine membranes. In comparison, long-term memories can be explained by the stabilization of a specific set of IPLs (Fig. 3**C-E**).

5.19. Correlation between behavioural markers of memory retrieval and LTP

Internal sensations of memory that can be explained by the reactivation of IPLs and the concurrently occurring behavioural motor activity can be explained by continued propagation of potentials through the inter-LINKed spines towards their soma [36]. If these neurons or their downstream neurons are motor neurons remaining at subthreshold states, then the arrival of added potentials can fire them, leading to behavioural motor actions (Fig. 4). Duration of maintenance of different types of IPLs provides suitable explanation for how long a learning mechanism can persist to induce memories and produce behavioural motor actions reminiscent of memory retrieval [108]. It is very important to consider that IPL mechanism has an advantage that further associative learning events can regulate the motor outputs associated with the retrieval of a memory. In this context, it is possible that different species of animals can either involuntarily or voluntarily withhold behavioural motor action expected during a particular memory retrieval. Since animals won't undergo additional associative learning events in the midst of a specific experimental protocol, the results of focussed experiments are expected to correlate between the behaviour and generation of internal sensation of an expected memory.

5.20. Shift in memory storage locations

Lesion studies have led to the finding that memory storage locations shift across brain regions over time [138]. This was viewed as a reason against synapse specificity [28]. Based on the present work, qualia of internal sensation of memory is the computational product of units of internal sensations that can be induced at a given time. Continuous insertion of a new granule neurons into the circuitry along with repetition of learning or related learning or unrelated learning having some related components can increase the number of inter-LINKed spines at the synaptic locations of higher neuronal orders, such as at the cortices. This will increase net semblance during memory retrieval. Eventually, over time, there will be a surplus number of IPLs and their inter-LINKed spines where units of internal sensations for a specific memory can get induced. If this continues for a long period of time, a stage will reach that will allow the removal of certain areas of the nervous system that were essential in the beginning stages of a new learning, for example the hippocampus. This can explain a process that will provide an impression of transfer of memories from the hippocampus to the cortex over a long period of time [38].

5.21. Increase in size of mEPSP after LTP induction

Miniature postsynaptic currents are observed in the absence of presynaptic action potentials and are thought to correspond to the response elicited by neurotransmitter molecules from single synaptic vesicles [139]. It is found that the size of miniature EPSP (mEPSP) increases after LTP induction [140] and is thought to occur either by an increase in the number or function of AMPARs at the spines of the recording neuron [141]. Based on the present work, exocytosis of AMPAR subunit containing vesicles promotes IPL formation and increases the number of spines with which the recording electrode is electrically connected. This allows both incorporation of large numbers of AMPARs and the arrival of current through newly formed IPLs. This can explain the increase in mEPSP size following LTP induction. AMPAR subunit vesicle exocytosis, which in turn can affect either threshold or magnitude of LTP at sub-maximal stimulation [100] can also be explained in terms of increased IPL formation. Thus, IPL formation is a mechanism interconnecting AMPAR vesicle exocytosis, increase in mEPSP and robustness of LTP.

5.22. Correlation of memory with delayed changes following LTP

There are several delayed changes that occur following LTP induction that have shown correlations with learning and memory. A typical example is the action of calcium/calmodulin-dependent protein kinase II (CaMKII) in phosphorylating both principal and auxiliary subunits of AMPARs involved in contributing to the potentiating effect [124]. These biochemical changes take place at much slower time-scales than the expected mechanism occurring during natural learning from which memories can be retrieved instantaneously [108]. Since both LTP and certain slowly occurring biochemical changes correlate with the ability to memorize as shown by behaviour, it needs an explanation. Following the IPL formation during an associative learning event, the downstream cascade of biochemical changes within the neurons prepare the spines both to maintain the already formed IPLs and to generate new IPLs during subsequent learning events. Since similar IPLs are formed during LTP induction, delayed biochemical changes also occur following LTP induction. This explains the observed correlations between the ability to retrieve memories and late biochemical changes following both learning and LTP induction.

5.23. LTP and place cell firing

Place cells are a set of CA1 neurons that fire action potentials when an animal reaches a particular location in space. A possible mechanism by which IPLs trigger place cell firing was explained before [53]. LTP induction is known to modify specific sets of place cells [142] indicating that the formation of a large number of new IPLs induced by LTP can lead to the spread of potentials through these IPLs and result in firing of additional postsynaptic CA1 neurons that are held at sub-threshold states either by sub-threshold activation or by the control of inhibitory neurons (Fig. 4). A similar mechanism can explain the incremental re-mapping of the CA1 place cells to a final fully-differentiated form following environmental experience [143]. In both learning and LTP induction, the newly formed IPLs provide routes through which additional potentials arrive at those neurons that are being held at sub-threshold activated states under baseline conditions and cause them to fire.

5.24. Role of extracellular matrix (ECM) space in inducing LTP

Based on the explanation that hydration exclusion and removal of repulsive forces are necessary for the formation of IPLs between abutted spines (Fig. 3C), presence of certain protein molecules in the inter-spine space is likely to prevent IPL formation and LTP induction. Reduced ability to induce LTP at the CA2 region of the hippocampus by the presence of perineural net proteins around the spines in this region [144] is an example. Recovery of LTP after the removal of these proteins in these experiments is in agreement with the IPL formation during LTP induction. In addition, CA2 region is uniquely resistant to seizure generation [145]. This can be explained by the resistance offered by perineural net proteins to IPL formation that will prevent rapid formation of IPLs in chains expected to be responsible for seizures [131].

5.25. Single spine LTP shows features matching with IPL formation

It was possible to stimulate individual spines of CA1 neurons using a paired stimulation protocol by uncaging glutamate over that spine [59]. Recording from neuronal soma showed potentiation of AMPAR mediated currents (AMPA currents) following a delay of 3 min after stimulation and lasted for nearly 30 min. Potentiation of AMPA currents was observed only when the spine underwent enlargement, indicating the possibility that the spine has established IPLs with abutted spines (that belong to other CA1 neurons, since inter-spine distance on an average is more than the average spine diameter [52]). AMPA currents are expected to flow from inter-LINKed spines through the IPLs towards the recording CA1 soma. In single spine LTP experiments, the magnitude of potentiation was also correlated with early or long-lasting spine enlargement that matches with the possibility to form a maximum number of IPLs with abutted spines. Thus, small spines were found to be preferential sites for cellular changes causing LTP induction [59]. In contrast, large spines are likely to have existing IPLs at the baseline state and are expected to lack free surface area to form additional IPLs to show further potentiation. This can explain why large spines did not show much potentiated effect in the above experiment. The time delay of 3 min can explain the time required for spine expansion and IPL formation. Since a large amount of energy is necessary to bring the spines to close contact with each other, they can reverse back relatively quickly and this can explain why the duration of potentiated effect is limited to only 30 min in these experiments.

5.26. Dynamic nature of spine heads and IPL formation

By expressing fluorescent proteins within the cytoplasm, it was possible to view dendritic spines both in acute brain slices and in vivo. Changes of the dendritic spines were visible in many spines in late-postnatal neurons in acute slices [146]. *In vivo* examination in one study using adult mice showed that overwhelming majority of spines is remaining stable [147]. However, another study found that persistent spines grew gradually during development and into adulthood [148], in

addition to the presence of transient thin spines that appeared and disappeared. Since most of the learning-induced changes are transient and are used for working memory, it is expected that most of the IPL changes will reverse back quickly. To facilitate the early IPL change by hydration exclusion, overcoming repulsive forces and through inter-membrane protein-protein interaction [65,149] between the spine membranes within milliseconds of time [108], it is necessary to keep the spine heads dynamic (Fig. 6). Reorganization of membranes of the lateral spine head region by vesicle exocytosis and reorganization of actin are the main components of these changes.

5.27. New neurons and LTP

Potentiated effect observed by patch-recording new granule neurons was explained in terms of either an increase in the amplitude or a reduction in the threshold for inducing LTP [150,151]. This can be explained in terms of the formation of IPLs by the spines of new granule neurons with the pre-existing islets of inter-LINKed spines of existing granule neurons.

5.28. Dendritic spikes and LTP

A dendritic spike is a spike in the potentials generated in a localized area of the dendrite of a neuron. Different regions of the dendritic tree generate different types of dendritic spikes, namely NMDA, sodium, calcium spikes [152]. Dendritic sodium spikes take place in small-diameter dendrites. Dendritic NMDA spikes are generated at the regions of glutamate release and are estimated to be generated by synchronous activation of 10 to 50 neighbouring glutamatergic synapses [153]. Since there is evidence for the occurrence of dendritic spikes at physiological conditions [154], it is necessary to find out whether dendritic spikes may be involved in information processing [20]. Even though dendrites locally magnify synaptic potentials because of their high input impedance [20], it requires summated potentials from nearly 10 to 50 spines for the generation of a dendritic spike [153]. One of the requirements of LTP is postsynaptic depolarization that can result from large EPSPs that trigger dendritic spikes [155]. This study also found that dendritic spikes mediate a stronger form of LTP that requires spatial proximity of the associated synaptic inputs. These findings match with the explanations of the IPL mediated mechanism for LTP.

Since the dendritic tree has weak excitability that prevents reliable propagation of dendritic spikes through them [20] and since the longitudinal resistance of the long dendrites cause attenuation of potentials generated during a dendritic spike, it is necessary to find out whether current from a dendritic spike can flow to another location that offers less resistance and whether that can explain its functional significance. By offering an alternate route, IPLs provide a potential functional role for dendritic spikes. The explanations for LTP in terms of IPLs presented here also match with the generation of dendritic spikes. These are evident from a) findings that suggested dendritic spikes as a mechanism for co-operative LTP [19], b) finding that dendritic spikes are necessary for single-burst LTP [42], c) generation of a stronger form of LTP by local synaptic depolarization and/or dendritic spikes than alternative methods [155] and d) Ca^{2+} spikes causing long-lasting potentiation of spines that are active at the time of spike generation [156].

5.29. Dendritic spikes and place cells

Firing of a specific group of CA1 neurons forms a place field. Dendritic spikes are found in the dendrites of place cells in behaving mice. The prevalence of these events predicts spatial precision and persistence or disappearance of place fields [157]. The fact that dendritic spikes are generated by 10–50 neighbouring glutamatergic synapses [153] and that IPLs are expected to be formed between spines of different neurons show that dendritic spikes have suitable features to occur at the islets of inter-LINKed spines and contribute to the generation of internal sensation of space. Even though dendritic spikes attenuate as they propagate towards CA1 somata, they can provide necessary potentials to CA1 neurons that are maintained at the appropriate sub-threshold activated states and cause them to fire.

5.30. Non-associative learning

Permanent changes in the motor response to a single stimulus occur due to repeated exposure to that stimulus and are called non-associative form of learning. Since each sensory stimulus has a large number of stimulus components within it, the arrival of a new sensory stimulus by itself can lead to the generation of a large number of new IPLs. Therefore, repeated exposure to a single stimulus can lead to stabilization of those IPLs responsible for seemingly non-associative form of learning.

6. IPL mechanism fills the explanatory gap between learning and LTP induction

Explanatory differences between natural learning and LTP induction listed in section 1 can be explained by IPL mechanism. Here, issues that are not covered in section 5 are explained. One of the concerns is that potentiated synapses responsible for memory storage are not getting activated specifically during memory retrieval as expected from Hebb's postulate. Based on IPL mechanism, IPLs get further inter-LINKed during related associative learning events forming islets of inter-LINKed spines. It is inevitable that inter-LINKed spines will be reactivated within an islet of inter-LINKed spines during a specific memory retrieval. Since memory for an item will be the integral of semblances induced at many locations in response to a specific cue stimulus, semblance of related items induced at isolated locations will not affect the net semblance. Due to spread of potentials through large islet of inter-LINKed spines, LTP will not be specific to certain synapses [27] as expected [28]. The observation that one synaptic input can be conditionally controlled by spatial or temporal contiguity with activity in another synaptic input to the same region [29] can be explained by the formation of large islet of inter-LINKed spines. Since formation of large numbers of IPLs takes place in the 3-D volume during the delay period of at least 20 to 30 s following LTP stimulation [31], it can explain how different synaptic regions will be affected in both spatial and temporal manner.

Increase in population spike amplitude and a reduced threshold for cell firing observed after LTP induction [4] can be explained in terms of formation of large numbers of IPLs by LTP stimulation through which depolarization can reach several sub-threshold activated neurons. Short inter-stimulus intervals of the stimulus used in LTP induction is to deliver more energy from its high frequency that leads to IPL formation. This is not to compare with the long intervals between stimuli used in behavioural conditioning experiments [28,30]. Dendritic spine enlargement similar to that occur in a time-dependent manner following LTP stimulation is expected to occur in behavioural conditioning procedure following first stimulus that facilitates the IPL formation at the arrival of the second stimulus.

Repeated stimulation of a single afferent fiber during LTP stimulation raised concerns about its relevance in associative learning [28]. The hippocampus is a brain region where inputs from all the sensory modalities converge. Since a) IPL formation occurs during associative learning at random locations where inputs converge, b) area of an IPL is expected to be nearly 10 nm^2 [53], and c) the majority of IPLs results from removal of repulsive forces and hydration exclusion, focussed and specialized experiments to search for their formation will be necessary. Until now, experiments to show that natural learning and LTP induction share the same mechanism was limited to occlusion experiments [10,11]. Since IPLs form at random locations during learning, the experimental demonstration of LTP by repeated stimulation of the afferent fiber region can be viewed as a crude method of scaling up the

changes that occur during learning. Knowing these limitations, the derived working mechanism of IPL formation between spines that belong to different neurons during learning can still offer an explanation for a) need for delivering high energy for LTP stimulation, b) observation of potentiating effect after a long delay, accounting for spine enlargement and incremental increase in the number of IPLs interconnecting stimulating and recording electrodes, and c) spine enlargement by dopamine receptor activation that increases the magnitude of LTP [123].

7. Long-term depression

Long-term depression (LTD) is an experimental electrophysiological finding with properties that are opposite to that of LTP. When only modest energy is applied at the stimulating electrode by a low-frequency stimulation, it leads to modest activation of NMDARs that trigger LTD [158]. In contrast to exocytosis of AMPAR subunits during LTP induction using strong depolarization of spines, modest depolarization used in LTD cause AMPAR endocytosis [159]. LTD can also be induced using a given tetanic stimulation that can induce LTP by keeping postsynaptic depolarization below a threshold related to NMDAR-gated conductance [160]. Since it was possible to explain LTP in terms of IPL formation, the following IPL-related changes can explain LTD induction. Since animals undergo many associative learning events during their life, it is expected that the recording brain tissue already has a large number of IPLs between the stimulating and recording electrodes. Therefore, LTD stimulation is expected to reverse some of the existing IPLs located between the electrodes. Following findings support this. There are two distinct forms of LTD that can co-exist [161]. It was demonstrated that surface AMPARs are removed during induction of both NMDAR-dependent LTD [162,163], and mGluR-LTD [164,165]. Since endocytosis of the AMPAR subunits and reduction in the size of enlarged spines can explain LTP decay [137], LTD can be explained in terms of reversal of already existing IPLs in the brain tissue. Furthermore, it is known that modest depolarization by LTD stimulation protocols activates phosphatase enzymes that dephosphorylate AMPARs and cause AMPAR endocytosis during LTD [159]. These can reverse several IPLs leading to a drop in the baseline potentials arriving at the recording electrode.

LTD can also occur by an active mechanism that lowers the potentials reaching the recording electrode. Since LTP induction in the cortical regions often requires low doses of GABAA antagonist bicuculline [166] for concomitant reduction of GABAergic inhibition, it shows that inhibitory synapses are also activated by the stimulating electrode. In this context, it can be examined whether it will be possible to explain LTD at the synaptic region (input region) of medium spiny neurons in the nucleus accumbens [167] that receive both excitatory and inhibitory inputs. Based on the present work, the probability of IPL formation between the spines of medium spiny neurons that receive excitatory and inhibitory inputs is high. When inhibitory synapses are activated by LTD protocols, the resulting hyperpolarization of their spines is expected to propagate to the inter-LINKed spines of excitatory spines. This will cause depression of the net potentials arriving at the recording electrode resulting in LTD.

8. Key difference between synaptic plasticity model and IPL-mediated mechanism

Synaptic plasticity thesis assumes that plasticity changes occur at the synapses through which associatively learned stimuli propagate. In studies, electrophysiological changes indicative of synaptic plasticity changes were correlated with behaviour (Fig. 10**A, B**). In contrast, semblance hypothesis was developed from asking the question "At the time of memory retrieval, when the cue stimulus propagates through its path, how can it induce an inner sensation of memory of the associatively learned second stimulus (that moved through a second pathway during learning) and generate behavioural motor activity reminiscent of associatively learned second stimulus?" It focused on identifying the locus of interaction between two neuronal pathways and more specifically, the sub-synaptic locations between which this interaction leads to learning-induced changes from which the cue stimulus can induce inner sensations of memory of the second stimulus (Fig. 10**C, D**).

9. Testable predictions

Based on LTP experiments, three key experiments can be carried out to further verify IPL mechanism. a) A spectrum of IPL changes are expected to take place during LTP induction between the spines of different CA1 neurons. These include highly reversible stage of hydration exclusion and removal of repulsive forces between the membranes of abutted spines, intermediate stages of partial and complete hemifusion and possible fusion between the abutted spines. b) Kindling induced at the Schaffer collateral area is expected to produce more inter-spine fusions than by LTP induction at the same location. Area of inter-spine fusion between the spine surfaces is expected to be larger following kindling than LTP stimulation. Kindling-generated large inter-spine fusions are expected to be irreversible when compared to the mostly small and reversible IPLs formed by LTP-inducing stimulus. c) Strength of LTP induced at different locations of the nervous system using a fixed stimulation intensity for a given distance between the stimulating and recording electrodes depends on 1) the number of converging inputs, 2) spine density, 3) number of inter-LINKed spines formed during the delay period after the stimulation, which is responsible for conducting current to the recording electrode, 4) lipid composition of spine membranes, and 4) properties of ECM at the inter-spine region.

10. Conclusion

Hebb's postulate [1] was necessary to start experimenting that led to the finding of LTP and its correlations with behaviour indicative of memory retrieval. These findings provided an opportunity to re-examine them when a testable mechanism for the generation of internal sensations of memory become available. It was in this context that findings from a very large number of studies that used behaviour as marker of memory retrieval were used to derive a mechanism for the induction of inner sensation of memory and the re-examination of the relationship between learning and LTP induction was carried out.

The term "potentiation" was used to explain the augmented current flow through single synapses of the recording CA1 neuron that receive inputs from CA3 Shaffer collateral presynaptic terminals, matching with the expectations of Hebb's postulate. The potentiating effect through the fixed number of existing synapses were explained by using probable mechanisms at different sub-synaptic regions. They were a) enhancement of neurotransmitter release [168], b) increased postsynaptic sensitivity to glutamate [169], c) expression mechanisms [170], and d) unsilencing of silent synapses. However, they were not able to explain their relationship with a mechanism that generates the internal sensation of memory and how the latter is correlated with LTP. In the early studies of LTP, an increase in amplitude of the population spike following LTP induction [4] was observed. This was thought to be due to an increase in the number and synchrony of neuronal discharges [171]. In addition to the above, the finding of non-Hebbian plasticity changes [27,111–113] and the necessity for more than one mechanism to explain LTP [34] indicated the possibility of a yet unknown mechanism for learning.

Formation of IPLs involves spines that belong to different CA1 neurons, in contrast to the fixed number of spines of the recording CA1 neuron. In this regard, LTP can be viewed as "a long-lasting conductance path generation through IPLs" instead of "potentiation" of a fixed number of synapses. The reduced threshold for cell firing [4] during LTP induction can be explained by the arrival of additional potentials at the soma through the large number of IPLs formed in the

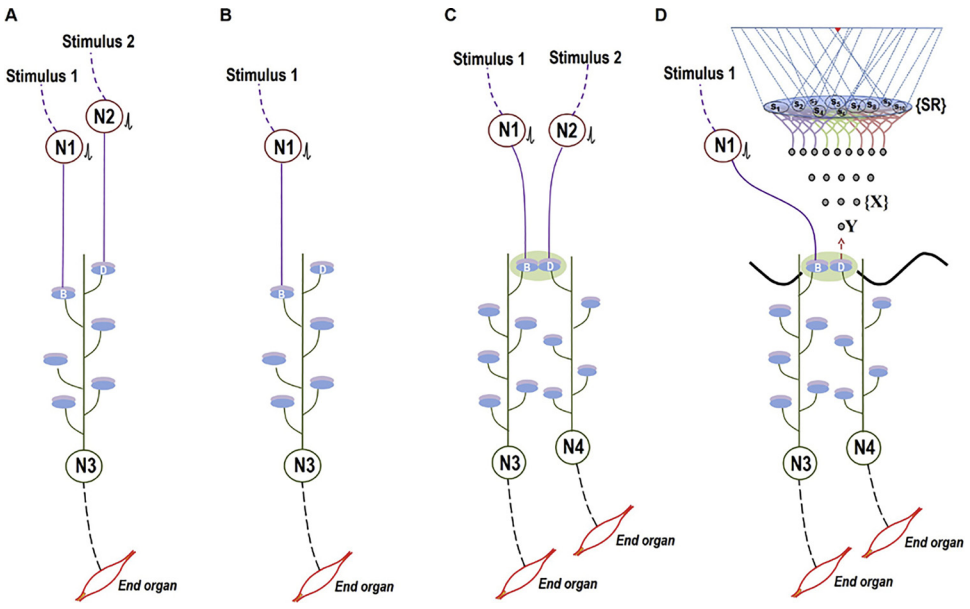

Fig. 10. The difference between learning-associated changes from which memory can be retrieved using monosynaptic changes proposed by Hebb and IPL-mediated mechanism. Only postsynaptic terminals (spines) of corresponding synapses are shown. Neurons are expected to reach a sub-threshold level either by an active mechanism or by regulating potentials arriving to it. The arrival of a cue stimulus following learning generates the n^{th} potential, which is expected to fire an action potential (axonal spike) and lead to activation of the end organ (here, a motor unit is shown). A, B: These are drawn to incorporate a modification of Hebb's postulate namely clustering of dendritic spines of a neuron. **A**) Monosynaptic activation by two associatively-learned stimuli 1 and 2. Inputs arrive at the same neuron N3. **B**) When stimulus 1 (cue stimulus) activates a synapse (whose postsynaptic terminal is B) a mechanism capable of inducing memory is expected to occur. Modifications of Hebb's postulate such as tagging of synapses or sub-synaptic structural modules within a synapse were not able to provide a mechanistic explanation for retrieval of memory at physiological time-scales. C, D: These are drawn to incorporate interaction between spines that belong to two different neurons. Note that stimuli 1 and 2 activate their independent end organs before learning. **C**) Before learning, there is no interaction between postsynaptic terminals B and D (this is not shown). Associative learning between sensory stimuli 1 and 2 leads to the formation of an IPL between postsynaptic terminals B and D. **D**) At the arrival of stimulus 1 (cue stimulus), IPL between B and D is reactivated to induce units of internal sensations at inter-LINKed spine D at physiological time-scales. This is expected to form as a system property where synaptic transmission at synapse A–B (presynaptic terminal A is not shown) and perpendicular transmission of potentials at IPL B–D form vector components of the oscillating extracellular potentials (shown by a wave shape). Semblions are overlapped at a region marked by a red triangle. SR: sensory receptor set. For details of semblance formation, refer to Fig. 4.

synaptic region between the electrodes. The increase in amplitude of the population spike during LTP [171] can be explained by the formation of large numbers of IPLs. IPL-mediated mechanism alleviates the concerns of both saturation of synapses [172] and overwriting of learning-induced changes [173]. Islets of inter-LINKed spines formed during previous learning events are expected to be shared by new learning events having shared features. They are also expected to induce semblances that are shared during their memory retrieval, an explanation that matches with the results from behavioural experiments [174].

IPLs form the alphabets of a "writable" code at the electrically isolated interface between membranes of spines that are activated by two associated stimuli during natural learning. LTP experiments artificially made a large number of similar, but non-specific, changes at one location and allowed to make several correlations between learning and LTP induction. The constraints provided by the non-correlated findings allowing to seek for alternate explanations on one side and the necessity to view memories as first-person internal sensations on the other side led to the derivation of IPL mechanism. Even though induction of units of internal sensations at the inter-LINKed spine will continue to remain non-sensible to third-person observers, it is a) the unique features at the inter-LINKed spine for inducing internal sensations, b) the substantive nature of sleep in actively maintaining this evolved mechanism on a planet with day and night [175], and c) the ability to operate in agreement with all the previous findings in an interconnected way that qualifies it as a further testable mechanism.

IPL mechanism matches with the expectation of a single mechanism expressed ubiquitously throughout the nervous system for inducing different types of memories [28]. It also matches with several expectations of K-lines, a hypothesized change during learning that can provide cellular hallucinations of partial features of the item whose memory is getting retrieved [58]. Ability to form a spectrum of learning-induced changes from which internal sensation of memory can be induced at different time periods after learning and its ability to explain the different features of LTP make the IPL mechanism a further verifiable hypothesis. If arguments, derivation and findings in this work can be justified, then it is eligible to undergo further experimental verification. This will offer an opportunity to cross the current explanatory chasm between the observations in psychology, neuroscience and related fields.

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Conflict of interest

U.S. patent: number 9477924 pertains to an electronic circuit model of the inter-postsynaptic functional LINK.

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