Examination of memory from a first-person frame of reference provides evidence for a relationship between learning and LTP induction

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Abstract

Correlation between behavioral markers of memory retrieval and long-term potentiation (LTP) observed at regions with groups of synapses is one of the examples of an inter-connecting bridge between the fields of psychology and neuroscience. However, several mismatches between the findings at the time of learning and LTP induction have raised concerns. This provides an opportunity to re-examine the situation and arrive at the correct cellular mechanism of learning from which retrieval of memory can occur, which will enable an explanation of both the correlations and the mismatches. Since there are no cellular-level changes observed during memory retrieval, a passive reactivation of a stably maintained learning-induced mechanism is responsible for both memory and the concurrently occurring behavioral motor actions. In this context, when memories are viewed as first-person internal sensations, the derived cellular-level mechanism provides explanations for almost all the features of LTP, its correlations and mismatches.

1 Introduction

A large number of correlations between behavior associated with memory retrieval and long-term potentiation (LTP) have been observed at various levels (Morris et al., 1986; McNaughton et al., 1986; Castro et al., 1989; Bliss and Collingridge, 1993; Moser et al., 1998; Malenka and Nicoll, 1999; Whitlock et al., 2006; Volianskis et al., 2015). In fact, this correlation is the only observation that can guide to understand the cellular-level events connecting retrieval-associated behavior, memory retrieval and learning. The source and routing of the potentials that trigger motor neurons concurrent with the actual mechanisms that induce memory are expected to provide the crucial information how the cue stimulus evokes memory. Since no cellular changes are observed during memory retrieval, the memory likely results from a passive reactivation of the changes occurred at the time of learning. In this context, the learning-induced cellular mechanism and its maintenance are expected to have similarities with the cellular-level changes during LTP induction and its persistence. Understanding this is of paramount importance in filling the explanatory gap between the experimental findings in biochemical, cellular and electrophysiological fields (Barnes

1995; Stevens 1998; Goldberg et al., 2002; Lisman et al., 2003; McEachern and Shaw 2005; Abbas et al., 2015) and their correlation with that of the motor changes via speech and behavior that are being studied by the field of psychology (Shors and Matzel, 1997). By asking the question "What are the real conditions that the solution must satisfy?," the present work has examined results from a large number of LTP-related studies and seeks to provide evidence for an interconnecting cellular mechanism.

1.1 Long-term potentiation

Donald Hebb postulated that when an axon of a neuron is near enough to excite another neuron repeatedly, some growth process or metabolic change takes place in one or both of these neurons such that the efficiency of a neuron to fire the neighboring neuron increases (Hebb, 1949). This marked the beginning of the thought process towards examining the cellular-level changes that occur during learning. Hebb's postulates describe synaptic changes that can facilitate future use of the same synapses during 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 the surgery. H.M was examined for memory loss by testing behavior and speech. Patient H.M failed to show signs of memory retrieval for the events or items learned during certain period of time prior to the surgery and was unable to learn anything new (Scoville and Milner, 1957). This indicated the involvement of the hippocampi in the storage and/or retrieval of memory. Following these findings, laboratory experiments were focused on the hippocampal tissue with the hope that any electrical event that can persist for long period of time can become a suitable marker for the increased synaptic efficiency in accordance with the Hebb's postulates. Such an electrical change called LTP was observed in the hippocampal sections (Lømo, 1966; Bliss and Lømo, 1973).

The experimental steps of LTP can be described as follows. The hippocampus is removed from the animals and slices are prepared by retaining the connectivity between the different orders of neurons (**Fig.1**) and are maintained at near-physiological conditions. When an electrode is used to stimulate a large number of recurrent collaterals (Schaffer collaterals) of the excitatory CA3 (Cornu Ammonis layer 3) layer neurons whose presynaptic terminals synapse with the dendritic spines (spines or postsynaptic terminals or postsynapses) (these terms are used interchangeably as follows: in the context of a synapse, *postsynaptic terminal* is used; in the context of a neuron, *spine* is used) of the neurons of the CA1 layer, a recording electrode placed extracellularly (for recording field potentials) at the main dendritic stem area of the CA1 neurons or intracellularly by patch-clamping one CA1 neuronal soma records electrical changes (For simplicity, mainly patch-clamping results are explained hereafter). Based on Hebb's postulates, these electrical changes are expected to be a function of changes at the CA3-CA1 synapses. It was found that if a brief repetitive stimulation is applied initially at the Schaffer collaterals, then the application of a regular stimulus at the same location is sufficient to produce a potentiated effect (125 to 300% increase in the field excitatory postsynaptic potential (field EPSP)) (interpretation from Abbas et al., 2015) following a delay period of nearly 30 seconds (Gustafsson and Wigstrm, 1990) and even more than a minute. This time-delay that does not match with the expected changes at the time of learning requires an explanation and provides an opportunity to discover the real mechanism. Moreover, interaction between the abutted synapses has not been examined since Hebbian postulates describe changes only at the individual synapses. LTP induction requires a high amount of energy, which is usually provided by high frequency stimulation. Alternatively, a similar effect can be recorded by using a single burst of strong activation to induce LTP (Remy and Spruston, 2007; Rose and Dunwiddie, 1986). By keeping the experimental preparation viable, a regular stimulus applied at

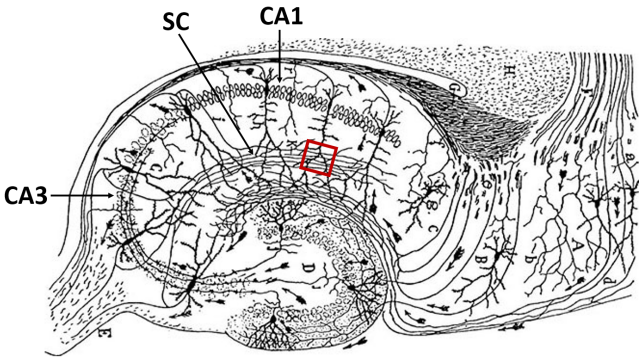

Figure 1: Diagram showing major hippocampal pathways: Schaffer recurrrent collaterals (SC) connect between the CA3 and CA1 neuronal orders. Note that Schaffer collaterals cross at the middle of the dendritic tree of the CA1 neurons (approximately 100-250 micrometers from soma (Andrasfalvy and Magee, 2001). Red square: Location of parallel Schaffer collateral axonal region where their terminals synapse with the dendritic spines (postsynaptic terminals) of one CA1 neuron. Figure modified from (Cajal, 1909).

the same location continues to induce LTP for nearly ten and even upto twenty-four hours. Several properties of LTP were examined with the goal of considering it as an experimental correlate of the cellular mechanism for learning and memory (Bliss and Collingridge, 1999). Following the initial observation of LTP, several experimental studies found a correlation between the surrogate behavioral markers indicative of memory retrieval and LTP (Levy and Steward, 1979; Teyler and Discenna, 1984). Since then, synaptic level changes that can increase synaptic efficiency in accordance with the Hebb's postulates were the focus of most investigations. Though initially discovered in the hippocampus, later experiments demonstrated LTP in different brain regions that receive different sensory inputs. LTP can also be induced at non-glutamatergic (Brown and McAfee, 1982) and inhibitory synapses (Ouardouz and Sastry, 2000).

1.2 Models related to Hebbian plasticity

Several modified mechanisms were proposed to explain synaptic changes expected from Hebb's postulates. These include: a) Synaptic tagging hypothesis: Possible intracellular mechanisms within single neurons were searched by conducting focussed electrophysiological studies. Normally, a single train of high frequency stimulation over the axonal bundles whose terminals synapse with a set of dendritic spines of a neuron elicits only an early-LTP at those synapses. However, when this is preceded by stimulating a different set of synapses at the same neuron's dendritic tree by using 3 or 4 trains of high-frequency stimulations (supra-threshold stimulations), late-LTP is induced at those synapses that receive only a single train of stimulation. A demonstration of these findings was carried out in the hippocampus (Frey and Morris, 1997) and also by using cultured Aplysia neurons (Martin et al., 1997). This was proposed to occur through the generation of specific transient local synaptic tags at the synapses activated by a single train of stimulation that is expected to capture the gene products synthesized in response to the stimulation by 3 or 4 trains of high frequency stimulation. The main drawback of this model is that the time taken for the expression of genes does not match the physiological time-scales at which learning-induced changes are occurring. b) Clustered plasticity and synaptic tagging model: According to this model, bidirectional synaptic weight changes among the synapses within a dendritic branch are achieved

through local translational enhancement (Govindarajan et al., 2006). This model incorporates synaptic tagging and capture as a mechanism for long-term memory where the dendritic branch is viewed as the location of operation of the integrative units (Govindarajan et al., 2011). Time-scale mismatch described for the synaptic tagging hypothesis also exists for the protein synthesis-dependent mechanism explained in this model. c) Modified clustered plasticity model: This view proposes that LTP at the synaptic region on the distal dendrites of the hippocampal CA1 pyramidal neurons requires cooperative synaptic inputs (Stuart and Spruston, 2015). Dendritic integration occurring at the level of the dendritic branches whose still-unknown role in information processing is the main expectation of this model. In all the above models, the specific outputs that belong to different associatively-learned stimuli are unlikely to be retained since large number of different outputs cannot be provided by the firing of the same neuron.

1.3 Minimum requirements for an explanation

The LTP experiments examined changes that lead to an increase in the synaptic efficiency in accordance with Hebb's postulates. Even though increasing the synaptic efficiency may facilitate future use of the same synapses along the stimulated pathways, it is short of providing a learning-induced change from which memory can be induced at the time of memory retrieval. For example, it does not provide an answer to the question "How can the changes at the synapses through which the cue stimulus propagates induce the memory of the associatively-learned second stimulus?" In order to understand the exact mechanism, it is necessary to view memories in their exact nature as first-person internal sensations occurring concurrent with the behavioral changes and then address the question "What type of a change should occur between two associatively-learned simuli during learning that will allow one of the stimuli (cue stimulus) to induce the internal sensation of memory of the second stimulus concurrent with behavioral motor actions reminiscent of the second stimulus?" This necessitates learning-induced changes to occur at the locations of convergence of sensory stimuli. Since no cellular changes were noticed at the time of memory retrieval, a passive reactivtion of learning-induced change is expected to occur at the time of memory retrieval. Since the internal sensations of different memories are similar in nature, maintenace of learning-induced change occurring for varying periods of time is expected to explain different memories. The maintenance of learning-induced changes and persistence of LTP for different periods of time and their capability to reverse back to the ground state suggest similarities. All the above increase the expectations for finding cellular-level changes occurring during learning and matching changes during LTP induction.

Several gene expression changes, the synthesis of new proteins and their modifications have been found related to both behavioral markers of memory retrieval and LTP (Herring and Nicoll, 2016; Madison et al., 1991), even though they occur more slowly than the physiological time-scales at which learning and memory retrieval take place. These slow changes can be viewed as homeostatic mechanisms to replenish the used molecules and to prepare the synapses for their future activations. It is necessary to separate the slowly occurring learning-induced cellular changes from those that are critical for learning and for inducing memories at physiological time-scales (Abbas et al., 2015). A flow chart diagram of the expected logical sequence of steps necessary to arrive at the explanation is given in **Fig.2**.

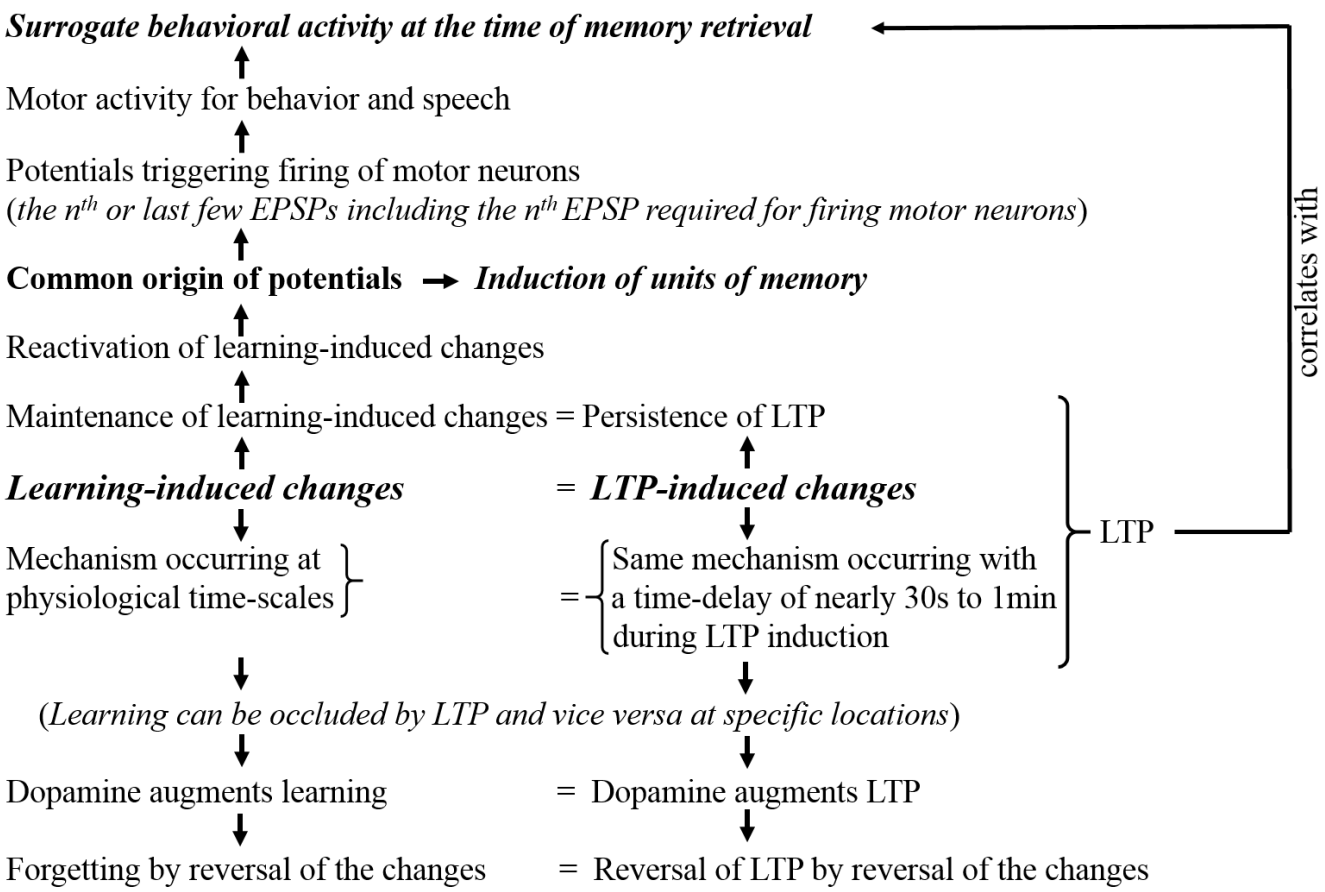

Figure 2: Steps that are necessary to prove the correlation between associative learning and LTP induction. These steps begin by searching for the source of potentials required for behavioral motor actions occurring concurrently with the induction of internal sensation of retrieved memories. Since cellular changes are absent during memory retrieval, a mechanism for passive reactivation of learning-induced changes was sought. The learning-induced cellular change is expected to correlate with LTP-induced changes occurring with a time-delay. NMDAR: N-methyl-D-aspartate receptor.

2 Derivation

2.1 Mechanism during learning from which memory can be induced

For learning-induced changes to take place at the locations of convergence of two associatively-learned stimuli, the inputs arriving through their presynaptic terminals must undergo a functional convergence at some point. Since there are only synaptic regions between the stimulating and recording electrodes in LTP experiments, the cellular mechanism of LTP is expected to take place at the level of the synapses either at the synapses or between the synapses. This also indicates that the correlation of LTP with behavioral motor actions is likely taking place through a synapse-mediated mechanism. What synaptic level changes can a) induce internal sensations of memory, b) provide additional potentials for behavioral motor action, and c) explain LTP-induced changes? From a learning perspective, this can be examined as follows. For the cue stimulus to provide the source of potentials for both the induction of internal sensation memory and concurrent motor action at the time of memory retrieval, a reactivatible interaction is expected to occur between the associatively-learned stimuli at the locations of their convergence at the time of learning. At the

locations of convergence, the axonal terminals (presynaptic terminals) of the two pathways synapse with the dendritic spines (postsynaptic terminals). Even though the importance of dendritic spines in cognition and its disorders are known (Koch et al., 1992; Penzes et al., 2011; Gonzlez-Burgos, 2012), it is not known whether the converging presynaptic terminals synapse on to the dendritic spines of the same of postsynaptic neuron or not. If they synapse to the same neuron, both stimuli will lead to the activation (spike or firing or action potential) of this same neuron and the identity of the associatively-learned stimuli beyond this neuronal level cannot be maintained. Moreover, when a neuron receives inputs during either sub-threshold or supra-threshold activations, these inputs do not contribute towards the neuronal firing and may not provide expected specific outputs. The above findings indicate that the converging presynaptic terminals are likely synapsing on to the dendritic spines of different neurons as a rule. Exceptions may be present.

The converging presynaptic terminals from two associatively-learned stimuli are expected to induce certain interactive changes at the level of their synapses during learning. These changes provide specific signatures such that at a later time when one of the stimuli arrives as a cue stimulus, it will induce the internal sensation of memory of the second stimulus. What is the ideal location between the synapses of the converging presynaptic terminals that the interaction must occur during learning? The result of the interaction must allow the cue stimulus to induce the first-person internal sensation of memory of the second stimulus and also provide potentials to activate higher order neurons that belong to the second stimulus to produce corresponding behavioural motor actions. Since neurotransmission is taking place unidirectionally, the activation of the postsynaptic terminal (dendritic spine) can be viewed as equivalent to the activation of a synapse. Hence, interaction (a link formation) between the spines that belong to different neurons (as derived from the previous paragraph) can be examined for a suitable mechanism. In this regard, an interaction between the readily LINKable (capitalized letters denote its significance) spines called inter-postsynaptic functional LINK (IPL) occurring at physiological time-scales was found to be suitable to explain the learning-induced changes (**Fig.3A**) (Vadakkan, 2013; 2016a). The finding that the mean inter-spine distance is even greater than the mean diameter of the spine heads of the pyramidal CA1 neurons (Konur et al., 2003) indicates that ideally IPL formation takes place between the spines that belong to different postsynaptic neurons. This will allow maintaining the specific motor outputs related with each of the associatively-learned stimuli at the time of memory retrieval.

The 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) (Vadakkan, 2016a). Continued associative learning events will inter-LINK additional spines with the initially inter-LINKed spines. This will generate groups of inter-LINKed spines called islets of inter-LINKed spines (**Figs.3B,C**). A spectrum of molecular and cellular changes can explain IPL formation. These include close contact between the post-synaptic membranes by hydration exclusion and inter-postsynaptic membrane hemifusion (**Figs. 3D-F**). Since hemifusion is an intermediate stage of membrane fusion (**Fig.3G**), artificial stimulation conditions such as LTP and kindling may show fusion changes that may reverse back or persist for long-period of time. IPLs are expected to last for different periods of time. Reactivation of the IPL by the cue stimulus is expected to induce an internal sensation (semblance) for the associatively-learned second stimulus. Details of the derivation and mechanism of induction of semblances were explained previously (Vadakkan, 2013) and are summarized in **Fig.4**. Briefly, it evolved from asking the question "What local and system conditions can induce the property of first-person internal sensations at the time of lateral entry of depolarization through the IPL tow-

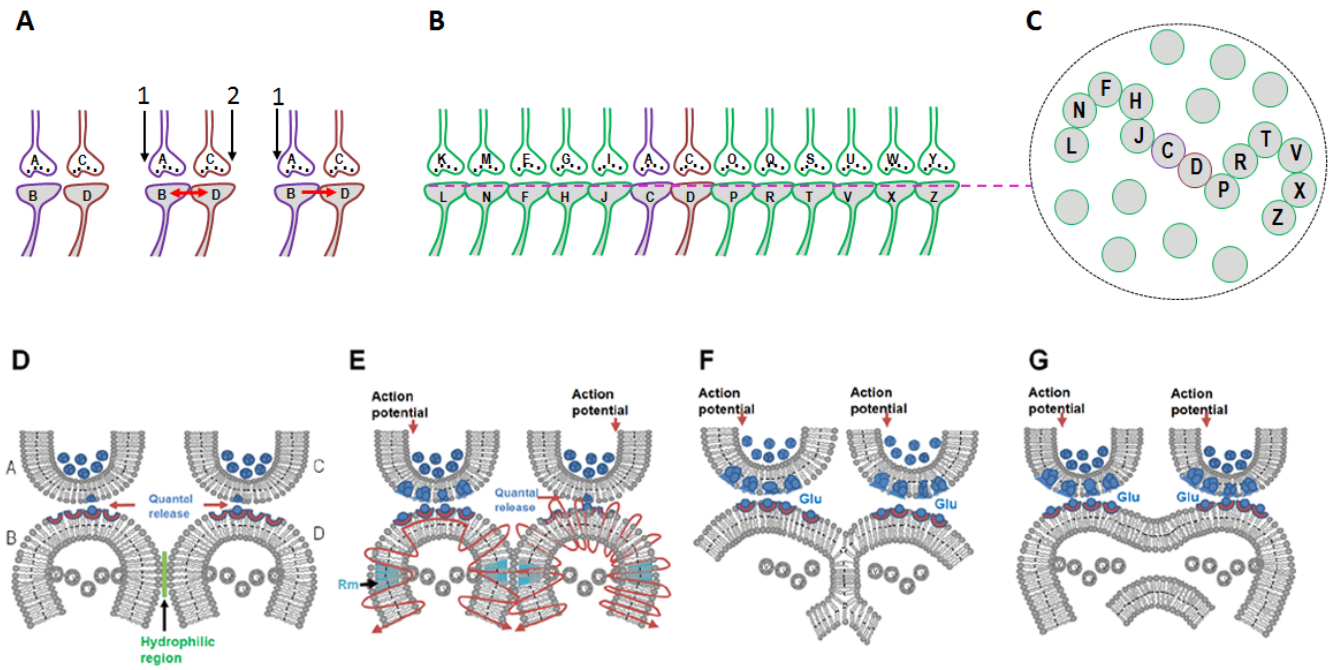

Figure 3. Inter-postsynaptic functional LINK (IPL) formation, clustering of inter-LINKed postsynaptic terminals (spines) and different types of IPLs. A) Left: Two synapses A-B and C-D are shown side by side. Note that their postsynaptic terminals B and D are abutted to each other. Middle: Simultaneous 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. The formation of the IPL is a function of simultaneous activation of postsynaptic terminals B and D. Right: During memory retrieval in the presence of one of the stimuli (stimulus 1) the IPL is re-activated, resulting in the activation of postsynaptic membrane D. This results in the induction of semblance of activity arriving from presynaptic terminal C as an intrinsic systems property. The synaptic activities at synapses A-B and C-D are essential during learning and the synaptic activity at synapse A-B is essential for the reactivation of IPL B-D to induce the unit of internal sensation. B) Formation of IPLs with spines that have already made functional LINKs with other spines during prior learning events will lead to the clustering of functionally LINKed spines. The serially inter-LINKed spines L, N, F, H, J, C, D, P, R, T, V, X, and Z form an islet. Note that the inter-LINKed spines are arranged side-by-side. C) A cross-sectional view through the postsynaptic terminals within the islet of inter-LINKed spines shown in Figure B. Note the presence of eight other independent spines in the selected region of interest (D-G): Different types of IPLs. D) Presynaptic terminals A and C with synaptic vesicles inside (in blue color). The continuous quantal release is represented by one vesicle at the synaptic junction. Spines B and D have membrane-bound vesicles marked V containing AMPA receptor GluR1 subunits inside them. Spines are normally separated by a hydrophilic region between them (in green). Simultaneous activity arriving at the synapses leads to the enlargement of the spines and removal of the hydrophilic region between them that further leads to an electrically-connected close contact between them (not shown). Since it is a process requiring large amounts of energy, it is a rapidly reversible IPL and is responsible for working memory and short term potentiation (STP). E) Further enlargement of the spines and membrane reorganization (at the membrane segments marked Rm) secondary to AMPA receptor subunit vesicle exocytosis at the lateral borders of the spines can lead to reversible partial hemifusion between the spines. It is responsible for short-term memory and early LTP. F) Complete

hemifusion between the spines that can be reversed and also stabilized. It is responsible for short- and long-term memories and LTP maintenance. G) Inter-spine fusion. Small areas of fusion may reverse back. Note that electrical continuity is maintained between the spines. Reversible fusion changes are expected to occur during LTP (Figures modified from (Vadakkan, 2013; 2016a).

ards the inter-LINKed spine?" Concurrent with the induction of internal sensations, potentials arriving at the inter-LINKed spine can lead to the activation of the latter's neuron if it is 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 the behavioral motor action corresponding to the retrieved memory. Inhibitory interneurons and feedback circuits can regulate the neurons' crossing of the threshold limits.

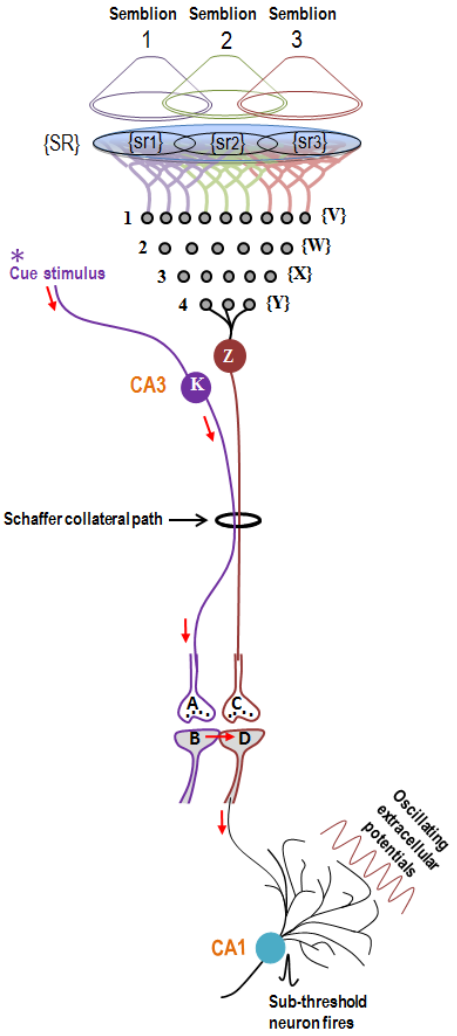

Figure 4. Induction of a unit of internal sensation and the concurrent firing of a sub-threshold neuron. The gray circles placed in rows and numbered from 1 to 4 are the different neuronal orders starting from the sensory receptor level. Neurons of the hippocampal CA3 layer (marked K and Z) are shown as neuronal order 5. When the cue stimulus reactivates IPL B-D, it activates postsynaptic terminal D from a lateral direction and induces a unit of internal sensation. In order to estimate the sensory identity of the internal sensation, a retrograde extrapolation from postsynaptic terminal D towards the sensory receptor level is undertaken. This retrograde examination constitutes the first-person approach. Postsynaptic terminal D is activated by CA3 neuron Z.

Spatial summation of nearly 40 EPSPs (from nearly 40 dendritic spines out of the nearly tens of thousands of dendritic spines of each pyramidal neuron) or temporal summation of less than 40 EPSPs triggers an action potential at the CA3 neurons axon hillock. Let the set of all combinations (for the spatial summation of EPSPs) and permutations (for the temporal summation of EPSPs) of the neurons whose activity through normal synaptic transmission and depolarization arriving through the IPLs be Y in neuronal order 4. Neurons in set Y in turn receive inputs from dendritic spines and through the re-activation of IPLs from activity arriving from a set of neurons X in neuronal order 3. By extrapolating in a retrograde fashion towards the sensory receptor level, it is possible to determine the set of sensory receptors SR and from the latter the sensory identity of the cellular hallucination can be determined. In other words, dimensions of internal sensations resulting from the activation of postsynaptic terminal D through the re-activation of IPL B-D will be related to a sensory stimulus that can activate sensory receptors in set SR. It is likely that the activation of subsets of a minimum number of sensory receptors from set of SR, for example, sr1, sr2, and sr3 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. This is considered the basic unit of the internal sensation of memory. These sensory units have no orientation. The lateral activation of postsynaptic terminal D can induce a large number of semblions (Figure modified from (Vadakkan, 2013).

2.2 Suitability of the IPLs in explaining LTP

During LTP induction, the high-energy stimulation of a group of axonal terminals induces certain changes that need to be discovered. Following a delay period of nearly 30 seconds (Gustafsson and Wigstrm, 1990) and even more than a minute, a regular stimulus applied at the same location induces a potentiated effect of up to 300% increase in the field EPSP (interpretation from Abbas et al., 2015). Since it was found that local synaptic depolarization and/or dendritic spikes can mediate a stronger form of LTP than alternative methods for its induction (Hardie and Spruston, 2009), the present work examines this direct mechanism to find its correlate at the time of learning. Since only a fixed number of spines of the postsynaptic neuron (from whose soma the recording is carried out) synapses with a fixed number of axonal terminals, the question is "Can changes occurring at these synapses alone explain the potentiated effect of up to 300%?"

arriving at the inter-LINKed spine can lead to the activation of the latter's neuron if it is 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 the behavioral motor action corresponding to the retrieved memory. Inhibitory interneurons and feedback circuits can regulate the neurons' crossing of the threshold limits.

Alternatively, are there possibilities for the origin of new routes to explain the arrival of the potentiated effect? If islets of inter-LINKed spines are formed during LTP induction that also get inter-LINKed with the spines of the recording neuron, then potentials can reach the recording electrode through multiple routes within the islet. This can provide an explanation for the potentiated effect of LTP (**Fig.5**). IPL formation necessitates spatial proximity of the converging associated synaptic inputs (Hardie and Spruston, 2009) and also matches with the convergence of inputs for the associative property of LTP (Bliss and Collingridge, 1993). In addition, such a mechanism invites several questions. Are all the spines at the localized area between the electrodes readily LINKable with the neighboring ones? If they are not, how can it influence the outcome of the experiment? Can a time-consuming mechanism lead to the formation of sufficient number of IPLs to achieve the expected result?

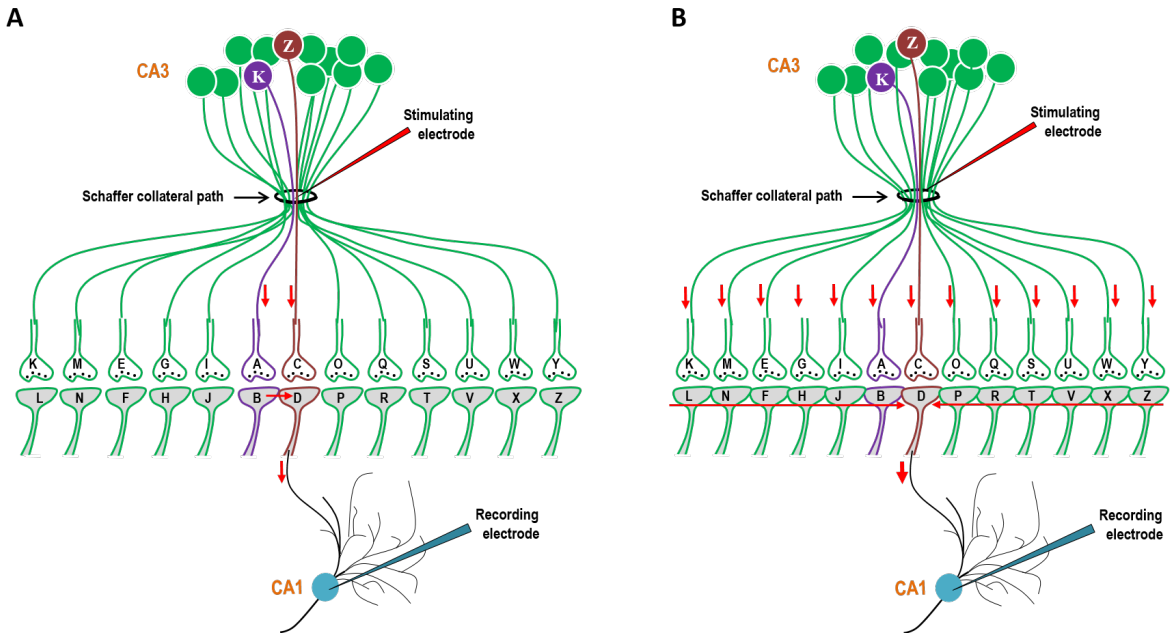

Figure 5. Comparison showing the effect of stimulating the Schaffer collaterals by a regular stimulus before and after inducing LTP. A) Stimulation with a regular stimulus at the Schaffer collateral path before LTP induction will only allow the potentials to propagate through the existing IPL labelled B-D that will propagate through postsynaptic terminal D to its CA1 neuron from which recording is carried out. Even though all the synapses are activated, the EPSPs from postsynaptic terminals B and D only reach the recording CA1 neuron. B) The effect of a regular stimulus at the Schaffer collateral path after the LTP induction will depend on different changes induced by the high-energy stimulation of LTP. The time-delayed formation of different types of IPLs produces increased electrical continuity between the 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 figure 4).

3 Evidence for the role of IPLs in LTP induction and learning

3.1 Need for higher stimulation energy

High-energy stimulation is necessary for LTP induction. During stimulation, most IPLs are expected to form by close contact with each other by excluding water of hydration, a process that requires a large amount of energy as evident from studies using lipid membranes (Rand and Parsegian, 1984; Leikin et al., 1987; Cohen and Melikyan, 2004). Additional energy will be necessary for the formation of hemifusion and fusion events as evident by the need for fusogenic molecules to achieve fusion in *in vitro* assays (Keidel et al., 2016). In contrast to the physiological conditions where most IPLs are expected to form only between readily LINKable spines, the high energy released during LTP induction is required for the enlargement of the small spines so that they can get abutted to the neighboring spines and undergo IPL formation. An optimal number of

IPLs is required to form an optimum number of routes for the regular stimulus-induced potentials to arrive at the recording neuron and show a maximal potentiated effect in LTP experiments.

3.2 Postsynaptic terminal is the final common path for LTP induction

A rise in the postsynaptic Ca^{2+} via voltage-sensitive Ca^{2+} channels shows a potentiated effect in experiments conducted after blocking the N-methyl-D-aspartate receptor (NMDA) receptors (Grover and Teyler, 1990; Kullmann et al., 1992). This shows that the final common change that leads to the potentiated effect occurs at the dendritic spines. This matches with the hypothesized formation of IPLs between the spines as the basic cellular mechanism during learning and its correlations with that of LTP. Since the aim of the above experiments was to find the final synaptic locations involved during LTP induction, they were conducted by blocking synaptic transmission. However, normal synaptic transmission will be necessary for IPL formation at physiological conditions. Studies showing that LTP is associated with the enlargement of spine heads (Lang et al., 2004; Matsuzaki et al., 2004) shows the suitability of the IPL-mediated mechanism to explain LTP induction.

3.3 Delay in the induction of LTP

A time delay of 30 seconds (Gustafsson and Wigstrm, 1990) and even more than a minute is observed before the recorded potentials reach the peak level after LTP stimulation. It is also seen (an interpretation from the graphs) in experiments where a transient potentiated effect was produced by a rise in the postsynaptic Ca^{2+} after blocking the NMDA receptors (Grover and Teyler, 1990; Kullmann et al., 1992), single spine LTP experiments (Matsuzaki et al., 2004) and in LTP induction by a single burst (Remy and Spruston, 2007). The tetanus-induced rise in the postsynaptic $[Ca^{2+}]$ lasting at most for 2-2.5 s was found sufficient to generate LTP (Malenka et al., 1992). The remaining time delay is not due to the emergence of filopodia or new spines as they take at least 20 minutes to develop (Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999). It is also not due to multiple spine synapses between a single axon terminal and a dendrite as it takes a similar time-delay as above (Toni et al., 1999). These findings necessitate the existence of a reversible cellular mechanism that can explain potentiation of up to 300% following a time delay after the induction of LTP and can also explain the correlation with the change occurring during associative learning.

Can the formation of IPLs and islets of inter-LINKed spines explain the time-delay between the LTP stimulation and the peak potentiated effect? Are there any similar delays reported in cell biological experiments? Literature search shows comparable delays of minutes during both the cell membrane fusion between cells under normal conditions (Xu et al., 2005; Hofmann et al., 2006; Brunger et al., 2015) and under the influence of electrical stimulation (Zimmermann and Vienken, 1982; Neil and Zimmermann, 1993; Rems et al., 2013). Since the average distance between the stimulating and reocording electrodes during LTP experiments is nearly 500μm and since the diameter of the spine heads are nearly 400nm, the formation of more than a thousand IPLs between the spines of different CA1 neurons is necessary to make electrical continuity through the area between the stimulating and recording electrodes (**Fig.6**). Since *in vitro* cell fusion is a slow process, the nearly 30 seconds (Gustafsson and Wigstrm, 1990) or even more than a minute of delay to obtain maximum connectivity through the CA3-CA1 synaptic area between the stimulating and recording electrodes can explain the delay during LTP induction. Not all the spines are abutted to each other within the defined space between the stimulating and recording electrodes. Therefore,

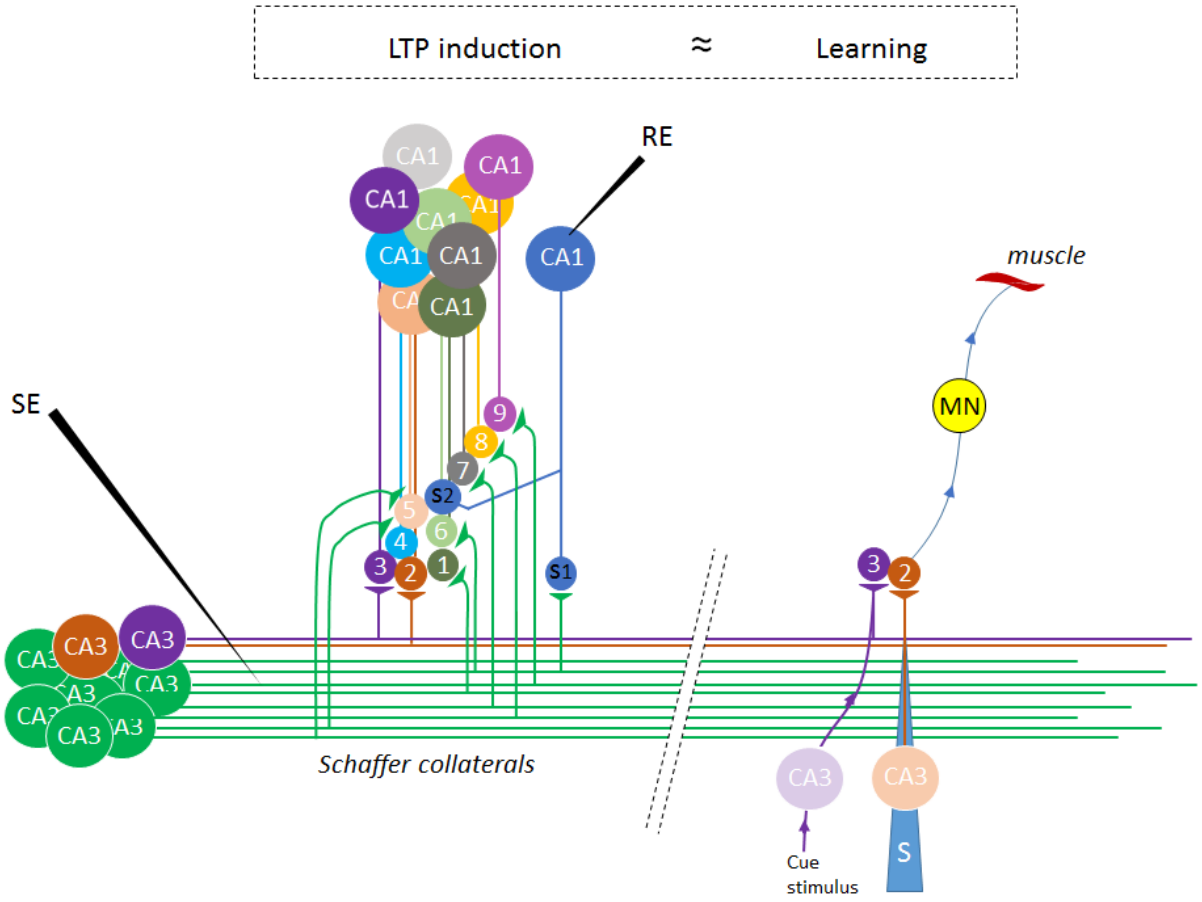

Figure 6. Formation of inter-postsynaptic functional LINKs (IPLs) resulting in LTP and its correlation with learning. Left side: A group of CA3 neurons and their recurrent collaterals (Schaffer collaterals). Before LTP induction, stimulation by a regular stimulus results in the activation of only one (this is only a representative number) dendritic spine (postsynaptic terminal) S1 of the CA1 neuron from which recording is carried out using the recording electrode (RE). It is the only synapse between the Schaffer collaterals and the dendritic tree of CA1 neuron from which recording is carried out. Regular stimuli will also activate a pre-existing learning-induced IPL between two spines marked 3 and 2 that belong to different CA1 neurons. Now, it is necessary to show that after LTP induction increased current arrives at the CA1 neuronal soma where recording is carried out, in response to a regular stimulus at the stimulating electrode (SE). Increasing synaptic efficiency of the fixed number of synapses (represented here by only the synapse of spine S1) that connects the stimulating and recording electrodes alone is not sufficient to explain the potentiated effect. There are several other synapses that are activated by the stimulating electrode. These are represented in the figure by nine synapses whose spines are marked from 1 to 9 and belong to different CA1 neurons. During LTP induction using a high-energy stimulus at the stimulating electrode, all spines marked 1 to 9 will be activated and enlarged. This leads to the formation of different types of IPLs. Note that one of the spines marked S2 of recording CA1 neuron is carried out is abutted between spines 5, 6 and 7. LTP induction will also lead to the formation of IPLs with dendritic spine S2 of the recording CA1 neuron. These events increase the electrical connection between the stimulating and recording electrodes by ten-fold and is only limited by the current carrying capacity of spine S2 and its spine neck. When a large number of IPLs need to be formed between the directly activated spines and interposed non-stimulated spines at locations between the stimulating and recording

electrodes, it takes time to obtain the required electrical connectivity between the electrodes. The time-delay of up to 30 seconds to even more than a minute to reach the potentiated effect matches with the time-delay observed in in vitro electrofusion of cells. During associative learning, several pre-formed IPLs are reused. As the animal moves through the environment, a large number of associative learning events take place and induce several IPLs. Most of the IPLs will only lead to the formation of close contact with the postsynaptic membranes by excluding water of hydration, which is a process that requires large amount of energy. Therefore, they are quickly reversed, which can explain working memory. However, the formation of a significant number of new IPLs and the repetition of learning events can lead to their stabilization explaining long-term memory. Right side: This represents the formation of a learning-induced IPL between readily LINKable spines marked 3 and 2. Following the learning, the arrival of a cue stimulus to spine 3 reactivates IPL between spines 3 and 2 and induces semblance (S) for memory. Note that the direction of the synapses is reversed compared to that in Fig.4. The potentials from inter-LINKed spine 2 can trigger the action potential of a sub-threshold activated motor neuron (MN) that leads to the motor action as described in Fig. 4. S: Semblance. Two CA3 neurons are drawn again to show the arrival of the cue stimulus and formation of semblance. Taken together, the above changes can explain the correlation between LTP and the behavioral motor actions indicative of memory retrieval.

it will take time for their enlargement and to become inter-LINKable for the IPL formation. During the delay for LTP induction, exocytosis of GluR1 receptor subunits of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors is expected to take place and facilitate formation of IPLs between the spines (see section 3.7) for achieving electrical continuity between the electrodes. In contrast during associative learning, it is the readiness of the abutted spines to form IPLs at physiological time-scales that favor learning-induced changes. This explains an IPL-mediated mechanism responsible for the correlation between LTP induction and learning.

3.4 Sudden drop in the peak-potentiated effect

LTP recordings show that after reaching the peak of the potentiated effect there is a sudden decrease in the potentiation, which is called short-term potentiation (STP). Close contact between the membranes by excluding the water of hydration that requires large amount of energy is the most common type of IPL. Therefore, several of these IPLs are expected to reverse back rapidly. This leads to a sudden loss of electrical continuity between the spines of different CA1 neurons that lead to a sudden decrease in the potentiated effect at the recording electrode. This can explain STP. Depending on different factors such as membrane composition and extracellular matrix (ECM) properties, different regions of the nervous system can exhibit different levels of STP. The rapid reversal of the close contacts is a likely mechanism for working memory and is expected to occur commonly as the animal interacts with the changing environment.

3.5 Correlation between behavioral markers of memory retrieval and LTP

How do the signs of memory retrieval by a cue stimulus and the potentiated response to a regular stimulus that demonstrate LTP match? The reactivation of IPLs that lead to the induction of internal sensations and its interconnection with the motor action (Vadakkan, 2013) (**Fig.4**) provide the cellular basis for the correlation between LTP and behaviors indicative of memory retrieval. Persisting IPLs are responsible for demonstrating both LTP in response to a regular stimulus and

the learning-induced changes that induce the interal sensations of memory and serve as the route for potentials to reach the motor neurons for motor action concurrently with memory retrieval. The different mechanisms of IPL formation are suitable for explaining different durations of their maintenance to explain working, short- and long-term memories and the corresponding behavioral markers.

3.6 Role of synaptic transmission during learning and LTP induction

From **Fig.4**, it can be seen that the synaptic transmission at the synapses activated by the associatively-learned stimuli is essential for IPL formation. Similarly, synaptic transmission at the synapses through which the cue stimulus arrives is essental for activating the inter-LINKed spine to induce units of internal sensation. The finding that blockers of the NMDA glutamate receptors block LTP (Collingridge et al., 1983; Herron et al., 1986) supports the obervation that normal glutatmatergic synaptic transmission and activation of NMDA receptors lead to the induction of LTP at the location between the CA3 and CA1 neuronal orders at specific stimulating conditions (Morris et al., 1986). Since synaptic transmission is essential for the formation and reactivation of the IPLs, normal synaptic transmission is essential for learning, LTP induction and demonstration of LTP maintanance.

3.7 Stimulation intensity determines the necessity for AMPA receptor exocytosis

Even though there is consensus that LTP is mediated by the synaptic insertion of GluR1-containing receptors (Granger et al., 2013), a near-saturation LTP induction alone is sufficient to induce LTP without requiring GluR1 AMPA receptor subunits, their C-tails, or their auxiliary subunits (Herring and Nicoll, 2016). In sub-stimulation protocols of LTP induction that have more similarities to physiological conditions, the readily available AMPA subunit vesicles are expected to contribute to the IPL formation. It was found that the GluR1 AMPA receptor subunits redistribute into the cytoplasmic volume of the spine head region after the induction of LTP (Shi et al., 1999; Passafaro et al., 2001). Investigations showed that the spine geometry is critical for AMPA receptor expression (Matsuzaki et al., 2001). Later, it was found that the tetanic stimuli that induce LTP lead to both AMPA receptor insertion and generalized recycling of membrane from endosomes that contain GluR1 AMPAR subunits (Park et al., 2004). Further studies showed that during LTP, exocytosis of the vesicles containing AMPA receptor subunits is associated with their lateral movement (Makino and Malinow, 2009). These findings suggest reorganization of the lateral regions of the postsynaptic membranes (spines) using the lipid molecules of the membrane segments from the vesicles carrying AMPA receptor subunits during exocytosis. This can also explain why blocking of the AMPA receptors alone without blocking exocytosis does not affect LTP induction (Kauer et al., 1988). The observation of GluR1 receptor subunits on the postsynaptic membrane 25nm away from the synaptic junction (Jacob and Weinberg, 2015) indicates the suitability of the lateral regions of the postsynaptic membrane for IPL formation.

IPL formation mediated by AMPA receptor subunit exocytosis can explain how AMPA receptors affect either the threshold or the magnitude of the LTP at sub-maximal stimulation (Herring and Nicoll, 2016). The propagation of potentials through the IPLs can also explain how mEPSP size is increased after LTP induction (Manabe et al., 1992), which is currently thought to occur either by an increase in the number or function of AMPA receptors at the postsynaptic terminals of the recording neuron (Malenka and Nicoll, 1999). LTP is absent at the synaptic area between

the CA3 and CA1 regions in the hippocampi when GluR1 subunits are genetically deleted (Zamanillo et al., 1999) and can be contributed by the lack of GluR1 subunit vesicles for postsynaptic membrane reorganization.

3.8 Inhibitors of membrane fusion inhibit LTP

An experiment using blockers of the soluble NSF (N-ethylmaleimide sensitive fusion protein) attachment protein receptor (SNARE) proteins introduced into the neuronal cytoplasm showed a reduction in LTP (Lledo et al., 1998). Blockers of the SNARE proteins can access and block any membrane fusion mediated through the SNARE protein. Postsynaptic exocytosis of the GluR1 receptor subunits during LTP requires a unique postsynaptic Q-SNARE protein for vesicle fusion (Jurado et al., 2013). Since the reorganization of the lateral postsynaptic membrane region occurs during exocytosis of AMPA receptor subunit-containing vesicles and is expected to facilitate formation of different IPLs, blockers of SNARE proteins are expected to inhibit LTP. In comparison, during associative learning only readily available GluR1 subunit vesicles will be contributing to the IPL formation at physiological time-scales. The action of the SNARE proteins for AMPA receptor subunit exocytosis during this period is expected to contribute to the actual physiological mechanism of learning.

Even though SNARE proteins can lead to membrane fusion through the intermediate stage of hemifusion (Xu et al., 2005), the process has the capability to get arrested at the stage of hemifusion through a specific mechanism (Liu et al., 2008). This is supported by the finding that neuronal SNARE proteins show different mechanisms of hemifusion (Xu et al., 2005; Hofmann et al., 2006; Liu et al., 2008). Furthermore, the postsynaptic protein complexin that can block fusion binds to the SNARE proteins and controls the AMPA receptor exocytosis during LTP induction (Ahmad et al., 2012). Thus, the postsynaptic terminal has an efficient machinery required for IPL formation and its regulation.

3.9 Suitability to accommodate non-Hebbian plasticity changes

Different non-Hebbian potentiation changes were reported at the neighbouring regions of the recording CA1 neuron (Schuman and Madison, 1994; Engert and Bonhoeffer, 1997). What cellular mechanism can lead to the arrival of the potentiated effect at the neighbouring CA1 neurons of the CA1 neuron where recording is carried out? From the knowledge that the final change during LTP induction is taking place through the postsynaptic terminals (Grover and Teyler, 1990; Kullmann et al., 1992) and the spines enlarge during LTP induction (Lang et al., 2004; Matsuzaki et al., 2004), we have arrived at the conclusion that a large number of IPLs are formed between the spines of different CA1 neurons located between the stimulating and recording electrodes. After LTP induction, a regular stimulus can propagate through all the inter-LINKed spines and arrive at different CA1 neurons. This can explain the observations of non-Hebbian changes.

3.10 Cooperativity, associativity and input specificity

Findings from different stimulation locations and intensities were described to exhibit the properties of cooperativity, associativity and input specificity (Bliss and Collingridge, 1999) expected of an ideal learning mechanism. These experiments have been carried at the CA3-CA1 synaptic region. An IPL-mediated mechanism can explain these observations as follows.

1) Cooperativity: A critical number of presynaptic terminals should be activated to operate in a

cooperative manner to provide an intensity-threshold for LTP induction. However, only a small fraction of these presynaptic terminals directly synapse with the CA1 neuron from which recording is carried out. How can activity reach through a fixed number of synapses to the recording CA1 soma and still show highly potentiated effects? Even though it was explained in terms of the need for depolarization to reduce the Mg^{2+} block of the NMDA receptor channels (Bliss and Collingridge, 1999), the observation of selective increase in non-NMDA component of EPSP during LTP induction (Kauer et al., 1988) indicates that a non-NMDA receptor-involved postsynaptic mechanism is providing the route for arrival of additional potentials to the recording electrode. Such mechanism is also expected during associative learning at physiological time-scales. From **Fig.6**, it can be seen that for a regular stimulus to arrive at the recording electrode in a potentiated manner, it is necessary to achieve electrical continuity by the formation of a large number of IPLs, resulting in a large islet of inter-LINKed spines (that belong to different CA1 neurons) occupying the area between the stimulating and recording electrodes (**Fig.7**). The AMPA receptor subunit vesicle exocytosis resulting in reorganization of the lateral aspects of the spine leading to the formation of IPLs fits well with these findings and requirements. In summary, a threshold stimulation energy is required to establish a large islet of inter-LINKed spines between the electrodes for LTP induction.

2) Associativity: This is explained as the potentiation of a weak input if it is activated at the same time a strong tetanus is applied at a separate but convergent input. The convergent nature of the inputs allows separate islets of inter-LINKed spines from the weak and strong stimuli to become electrically connected through IPLs that will allow both islets to get connected with that of the recording CA1 neuron. Simultaneous stimulation is important for excluding water of hydration between the neighbouring postsynaptic terminals that belong to different islets by their enlargement to form different IPLs to make electrical continuity. This will allow the regular stimulus applied at the location of the weak stimulus to traverse through the islets of inter-LINKed spines induced by the strong stimulus permitting current flow towards the recording electrode for the potentiated response.

3) Input specificity: This property explains that different inputs that are not active at the time of the strong stimulus do not share the potentiation induced by the strong stimulus. Based on the same mechanism that explains associativity, input specificity also depends on the removal of water of hydration between the islets of inter-LINKed spines formed by the activation of different pathways for the formation of different IPLs, which requires their simultaneous activation.

For the demonstration of associativity and input specificity, more than one stimulating electrode is used. In order to experimentally demonstrate these features, an optimum distance should be maintained between these stimulating electrodes. This can be explained as follows. Simultaneous activation promotes the formation of critical inter-LINKs between their independently formed islets of inter-LINKed spines to achieve the expected electrical continuity. Following the simultaneous stimulation with a strong and a weak tetanic stimulus at optimal locations, a regular stimulus at the location of application of the weak stimulus can traverse through both the islets of inter-LINKed spines to arrive at the recording electrode. Since islets of inter-LINKed spines can inter-LINK with each other only at specific stimulus intensities and by keeping optimal distances between the stimulating electrodes, experiments to demonstrate input specificity will require optimization of the above parameters. This can also explain the finding that input specificity of LTP is not sustained below a distance of 70μm in experiments using hippocampal organotypic slice cultures (Engert and Bonhoeffer, 1997).

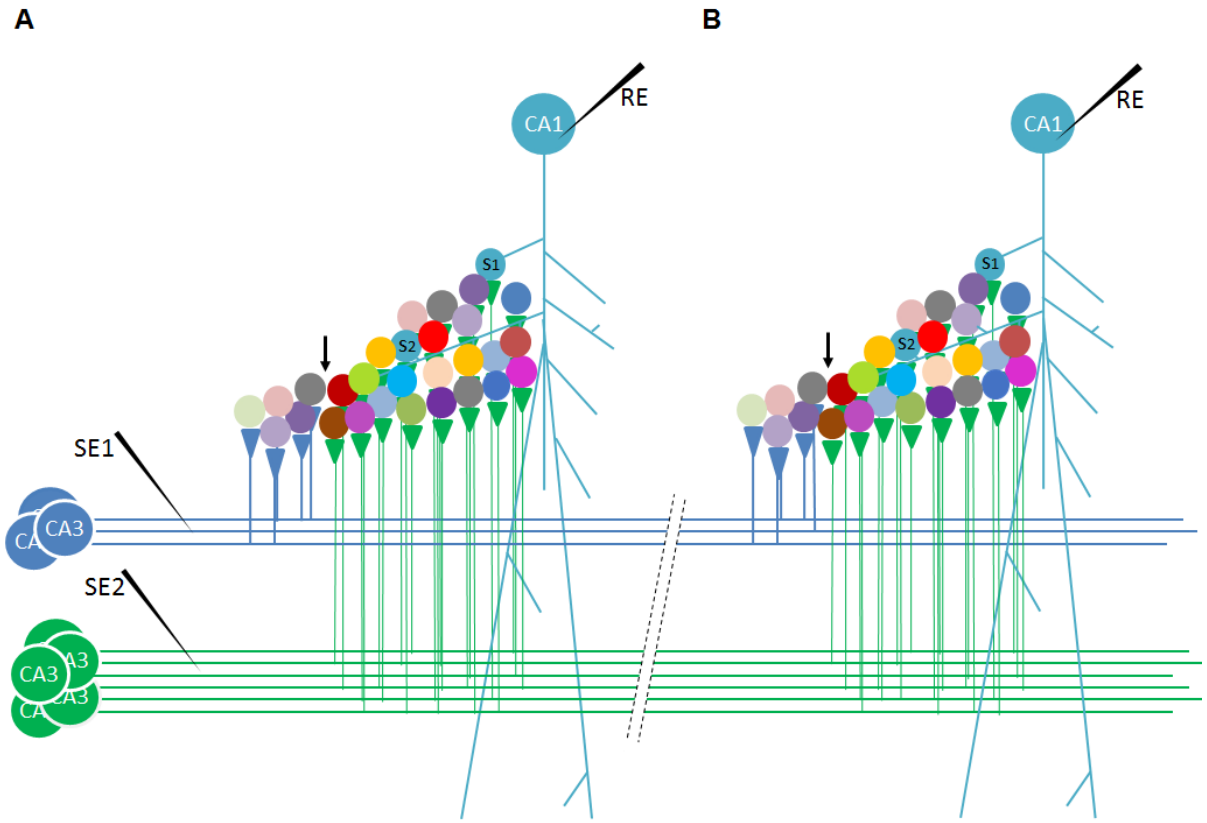

Figure 7. Cellular-level changes of IPL formation that can explain cooperativity, associativity and input specificity. On the left-most side are the CA3 neurons and their Schaffer collaterals that are stimulated by a weak stimulus SE1 through electrode SE1 and a strong stimulus SE2 through electrode SE2. Note that three and six Schaffer collateral axons are activated by the weak and strong stimulus respectively. A) Separate application of weak and strong stimuli provides different results. Weak stimulus SE1 results in the inter-LINKing of spines of 5 different CA1 neurons (not shown) through 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, spines that belong to different CA1 neurons inter-LINK with the spines of the recording neuron (S1 and S2). Only a strong stimulus can result in electrical continuity with the CA1 neuron and explains the property of cooperativity. A downward pointing arrow shows that the spines within different islet of inter-LINKed spines formed by weak and strong stimuli remain separated. B) The simultaneous application of weak and strong stimuli can result 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 to show that that the formation of bridging IPLs results in electrical continuity between the two different islets of inter-LINKed spines. Following this, the application of a weak stimulus at SE1 will show a potentiated effect when recorded from the CA1 neuron. Simultaneous activation of weak and strong stimuli will result in the removal of water of hydration 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.

3.11 Occlusion of learning with LTP

If the same mechanism is responsible for both learning and LTP induction, then by using the mechanism at a specific location by LTP induction can occlude learning, which uses that specific location and vice versa. The results of the occlusion experiments (Moser et al., 1998; Whitlock et al., 2006) can be explained in terms of the IPL mechanism. LTP induction leads to a large number of IPLs at a localized area and therefore learning following LTP induction will not to be able to induce any new IPLs at that localized region. The contribution of the semblance expected to be induced at the localized area, where LTP is induced, towards the net semblance induced by the cue stimulus (from the remaining areas in the hippocampi and the cortices) is likely very small. Therefore, memory should not be reduced for this reason alone. However, the large number of IPLs induced by LTP induction can lead to a large number of non-specific semblances at the time of memory retrieval as the cue stimulus traverses through all these non-specifically inter-LINKed spines. The large non-specific semblance can contribute to the reduced memory observed in these experiments. Occlusion of LTP after learning is likely to be difficult to demonstrate. The 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 focussed experiments in the hippocampus where a strong convergence of inputs occurs, it was found that learning can occlude LTP induction (Whitlock et al., 2006). Occlusion demonstrates that both learning and LTP induction are mediated through the same mechanism and an IPL-mediated mechanism can provide an explanation.

3.12 Dopamine augments motivation-promoted learning and LTP

Motivation can enhance learning (Wise, 2004). This can be explained by the enlargement of the spines by dopamine (Yagishita et al., 2014) released during motivation-promoted learning, which augments IPL formation. By increasing the duration of maintenance of the IPLs, the probability for the IPLs to get stabilized increases. Since dopamine takes 0.2 to 0.3 seconds for its action (Yagishita et al., 2014), it is likely that motivation is necessary prior to associative learning to have an effect. The duration of stabilization of the IPLs can determine the duration of storage of associatively-learned information. This provides a cellular-level explanation for the motivation-facilitated associative learning. Through a similar mechanism, it also explains how dopamine receptor activation can increase the magnitude of LTP in the hippocampal slices (Otmakhova and Lisman, 1996).

3.13 Inhibitors of NMDA receptors do not reverse late LTP maintenance

Even though NMDA receptor antagonists block the initial encoding of memory in animals, they do not block the maintenance phase of learning-associated changes (Day et al., 2003). In parallel to this, it was observed that inhibitors of the NMDA receptors do not reverse the late maintenance phase of LTP (Ling et al., 2002). This can be explained by the fact that in order to block the learning-induced changes or an already induced LTP, there should be a mechanism to block the

functional effect of the formed IPLs. Since inhibition of NMDA receptors cannot have any effect on any type of formed IPLs, they do not reverse either learning-induced changes or an already induced LTP.

3.14 Inhibitors of PKC Mζ can reverse maintenance phase of LTP

If LTP uses the same mechanism as that of learning, then the maintanance phase of LTP should have similarites to the maintanance stage of learning-induced changes. An established LTP can be reversed by the inhibitors of PKC Mζ (Ling et al., 2002). The cellular mechanism should be able to explain this and also the parallel results of maintenance of memory of learned spatial association in animals (Pastalkova et al., 2006). The finding that PKC Mζ is concentrated at the location of cell membrane abscission (Saurin et al., 2009) indicates its possible role in regulating the separation of cell membranes. Since LTP stimulation is expected to form different IPLs, it is likely that PKC Mζ can get concentrated at the locations of the IPLs and prevent their quick reversal.

3.15 LTP:Kindling::Memory:Seizure

Kindling is induced by stronger stimulation energy than those used for LTP induction and can cause afterdischarges. Kindling shows several similarities to human seizure disorders (Bertram, 2007). This can be explained in terms of the conversion of the IPL mechanism of hemifusion to fusion (Vadakkan, 2016b) and provides a suitable comparable change occurring *in vivo*. The fused areas allow the propagation of potentials between their postsynaptic terminals without any added resistance and can explain the findings in kindling experiments. Fusion changes can explain the transfer of injected dye from one CA1 neuron to the neighboring ones in animal models of seizures (Colling et al., 1996). Mixing of the cytoplasmic contents even between similar types of neurons that have different gene expression profiles can lead to triggering of homeostatic mechanims such as spine loss seen both after kindling (Singh et al., 2013) and in seizure disorders (Swann et al., 2000).

3.16 Forgetting and reversal of LTP

A potentiated effect caused by raising the postsynaptic Ca^{2+} via voltage-sensitive Ca^{2+} channels at the glutamatergic synapses (Kullmann et al., 1992) and potentiation of AMPA currents by single spine LTP experiments (Matsuzaki et al., 2004) lasts only for nearly 30 min. These indicate that the formed IPLs reverse back quickly. Since most IPLs are formed by close contact between the spine membranes by exclusion of the water of hydration, which requires a large amount of energy, they reverse back quickly explaining the reversal of the potentiated effect within a short period of time. This can provide a mechanism for working memory. In regular experimental protocols of inducing LTP, the IPLs reverse back slowly following the initial phase of rapid reversal responsible for STP. This slowly reversing phase has similarities to the slow reversal of changes following associative learning. This can provide a mechanism for short-term memory. It can be explained in terms of the formation of reversible spine membrane hemifusion changes. Slow reversal of these changes can include endocytosis of the AMPA receptor subunits and reduction in the enlargement of the spines responsible for LTP decay (Dong et al., 2015) and can explain forgetting.

3.17 Testing of LTP by regular stimulus may maintain the IPLs

After LTP induction, any ordinary stimulus applied at the stimulating electrode traverses through the large number of IPLs formed and reaches the recording electrode patch-clamped to the CA1 soma, which is recorded as a potentiated effect. Each of these regular stimuli at frequent intervals reactivates the already formed IPLs and may even have a role in maintaining them, which can be verified. Repeated reactivation of the existing IPLs by the regular stimulus while recording the potentiated effect is similar to the repeated retrieval of memories.

3.18 LTP and place cell firing

Role of IPLs in triggering place cell firing was explained previously (Vadakkan, 2016a). LTP induction is known to modify specific sets of place cells (Dragoi et al., 2003) 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 the firing of additional postsynaptic CA1 neurons that are held at a sub-threshold state. A similar mechanism can explain the incremental re-mapping of the CA1 place cells to a final fully-differentiated form following environmental experience (Lever et al., 2002). In both LTP induction and learning, new IPLs are formed, which can provide additional potentials to those neurons that are at a sub-threshold activated state at baseline conditions (**Fig.3**).

3.19 Blocking the extracellular matrix space blocks LTP

Based on the explanations provided by the IPL-mediated mechanisms, blocking the ECM space between the spines can prevent IPL formation and LTP induction. Perineural net proteins around the spines of the CA2 region of the hippocampus can explain the reduced LTP and how removal of these proteins improves LTP (Carstens et al., 2016). Since resistance to IPL formation can prevent rapid chain propagation of potentials (Vadakkan, 2016b), resistance offered by the perineural net proteins to IPL formation can also support the finding that CA2 region is uniquely resistant to seizures (Hatanpaa et al., 2014).

3.20 Dendritic spikes and LTP

The proposal of dendritic spikes as a mechanism for co-operative LTP (Golding et al., 2002), the finding that dendritic spikes are necessary for single-burst LTP (Remy and Spruston, 2007), and the finding that Ca^{2+} spikes cause long-lasting potentiation of spines active at the time of spike generation (Cichon and Gan 2015) can be explained on the basis of an IPL-mediated mechanism through spatially abutted spines of different neurons. The formation of a large islet of inter-LINKed spines can explain the observation of single-burst LTP. This matches with the explanation that a dendritic NMDA spike is a synchronous activation of 10 to 50 neighboring glutamatergic synapses triggering a local regenerative potential (Antic et al., 2010) and can explain the functional significance of dendritic spikes *in vivo* (Sheffield and Dombeck, 2015). If there are a large number of stabilized IPLs present at the distal dendritic compartment inter-LINKing several spines (as evident from dendritic spikes), then based on the present work the requirement for AMPA receptor subunit vesicle exocytosis and spine membrane reorganization at these locations will be less. A lesser number of AMPA receptors at the distal areas of the dendritic tree compared to the proximal area at the stratum lacunosum-moleculare region of the CA1 pyramidal neurons (Nicholson et

al., 2002) supports such an expectation. The shared physical properties of the environment in which the nervous system operates are likely responsible for the large inter-LINKed spines and the semblances induced by the dendritic spikes are likely contributing to background semblance of the system. The lateral spread of activity through the inter-LINKed spines during NMDA spikes is expected to have a significant contribution to one of the vector components of the oscillating extracellular potentials at rest.

3.21 Single spine LTP

A paired stimulation protocol by uncaging glutamate has allowed stimulation of individual spines of the CA1 neurons (Matsuzaki et al., 2004). Recording from the soma of the neuron showed potentiation of AMPA-receptor mediated currents (AMPA currents). In this experiment, the potentiation effect occurred following a delay of 3 minutes after the stimulation, which lasted nearly 30 minutes and was observed only when the spine had undergone enlargement. Potentiation of AMPA currents at the small spines was strongly correlated with the enlargement of these spines, indicating that the latter has contributed to the formation of IPLs with abutted spines (that belong to other CA1 neurons). Since recording was carried out from the CA1 soma, IPL formation with spines of other CA1 neurons is expected to result in the arrival of AMPA currents from the spines of those CA1 neurons. The magnitude of the potentiation was also correlated with early or long-lasting spine enlargement indicating the formation of a maximum number of IPLs with the abutted spines, which can increase the current flow towards the recording electrode through the newly formed IPLs. In contrast, the spines that are already large at the baseline state are likely to have existing IPLs without any free surface area to form additional IPLs and can explain why they did not show much potentiated effect. The time delay of 3 minutes can explain the time required for spine expansion and IPL formation as explained in section 3.4. The high-energy requirement for bringing the spines to close contact with each other demands reversal of this state, which can explain the limitation of the duration of potentiated effect to only 30 minutes in these experiments.

4 Discussion

In contrast to the plasticity changes proposed to occur at the single synapses based on Hebb's postulates, the semblance hypothesis proposed specific mechanisms at the level of the convergence of associatively-learned stimuli. For explaining the learning-induced changes from which internal sensation of memories concurrent with behavioral motor actions need to take place in the presence of one of the stimuli, it was necessary to arrive at the formation of IPLs between the spines that belong to different neurons. Systematic examination towards understanding the IPLs led to the derivation of the formation of different types of IPLs responsible for the maintenance of learning-induced changes for different periods of time. The corresponding formation of IPLs during experimental LTP induction taking place with a time-delay was able to explain almost all the findings associated with LTP. The retrodictive evidences used in this work are mainly from the results of the studies conducted during the search for synaptic plasticity changes at individual synapses.

The IPL-mediated mechanism removes the difficulties in finding an explanation for the potentiation occurring through the fixed number of synapses between the stimulating and recording electrodes in LTP induction studies. The potentials arriving through the IPLs also provide efficient mechanistic and functional explanations for LTP that otherwise required proposals of both

a) enhancement of neurotransmitter release (Malinow and Tsien, 1990), and b) increased postsynaptic sensitivity to glutamate (Manabe and Nicoll, 1994). IPL-mediated mechanism can provide effects similar to both an increase in the number of neurotransmitter release sites leading to an apparent increase in the quantal content and a decrease in the failure rate. Findings in LTP experiments also led to suggestions for the presence of silent synapses and their transition to active synapses (Kerchner and Nicoll, 2008; Padamsey and Emptage, 2013). When silent synapses that clearly lack functional AMPA receptors are activated by NMDA receptor activation, then it leads to spine swelling that in turn leads to IPL formation. APMA receptor subunit insertion to the postsynaptic membrane from the intracytoplasmic vesicles occurs along with postsynaptic membrane reorganization that promotes IPL formation. In this regard, IPL-mechanism also provides a suitable alternate explanation for the previously suggested expression-mechanism for LTP (Nicoll and Malenka, 1999).

The time course of the IPL formation between the spines similar to that found in cell fusion studies using electrical stimulation has provided a long-awaited explanation for the delay in LTP induction. Furthermore, the IPL-mediated mechanism provides a suitable alternative to the current explanations using the slowly occurring biochemical reactions for explaining the delay in LTP induction that do not match with the physiological time-scales of changes during either learning or memory retrieval. The different types of IPLs provide much-needed flexibility to explain different types of memories and match with the expectation of a single mechanism expressed ubiquitously throughout the nervous system for different types of memories (Shors and Matzel, 1997). Activation of the muscarinic acetylcholine receptors leading to robust potentiation of glutamatergic synaptic transmission to the CA1 pyramidal neurons (Dennis et al., 2016) can be explained in terms of IPL formation. As new granule neuron dendrites branch out towards the performant path axonal terminals, they form IPLs with the pre-existing islets of inter-LINKed spines. This can be observed either as an increase in the amplitude or a reduction in threshold for inducing LTP (Schmidt-Hieber et al., 2004; Ge, Yang et al., 2007).

Islets of inter-LINKed spines that belong to different neurons allow related learning events to share several IPLs, making the learning more efficient and allowing the avoidance of concerns about saturation of synapses or overwriting of connections (Bliss, 1998; Fusi and Abbott, 2007). These islets also provide a functional explanation for the previous suggestions of clustered plasticity necessary for long-term memory (Govindarajan et al., 2006). Schemas of previous associatively-learned items or events represented by the semblances induced at the islets of inter-LINKed spines can be used during related learning events and support the idea that schemas are important in memory consolidation (Tse et al., 2007). In summary, the present work that provides an explanation for the correlation between learning and LTP induction can answer several concerns raised previously (Shors and Matzel, 1997) and provides an opportunity for crossing the explanatory chasm between different fields of investigations of the nervous system. The presented mechanism can be verified and should be treated as unproven until further experimental verifications are carried out.

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Conflict of interest: U.S. patent: number 9,477,924 pertains to an electronic circuit model of the inter-postsynaptic functional LINK.

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