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Review

From cells to sensations: A window to the physics of mind

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Abstract

Principles of methods for studying particles and fields that cannot be sensed by third-person observers by routine methods can be used to understand the physics of first-person properties of mind. Accordingly, whenever a system exhibits disparate features at multiple levels, unique combination of constraints offered by them direct us towards a solution that will be the first principle of that system. Using this method, it was possible to arrive at a third-person observable solution-point of brain-mind interface. Examination of this location identified a set of unique features that can allow an associatively learned (cue) stimulus to spark hallucinations that form units of first-person internal (inner) sensations reminiscent of stimuli from the associatively learned second item in timescales of milliseconds. It allows us to peep into a virtual space of mind where different modifications and integrations of units of internal sensations generate their different net conformations ranging from perception to an inner sense of hidden relationships that form a hypothesis. Since sparking of inner sensations of the late arriving (when far away) or non-arriving (when hidden) features of items started providing survival advantage, the focus of evolution might have been to optimize this property. Hence, the circuity that generates it can be considered as the primary circuitry of the system. The solution provides several testable predictions. By taking readers through the process of deriving the solution and by explaining how it interconnects disparate findings, it is hoped that the factors determining the physics of mind will become evident.

Keywords: Mind; Brain and mind; Internal sensation; First-person science; Physics of mind; Unification of brain and mind

1. Introduction

An accidental observation that a compass needle lying close to a cable carrying current got deflected when the current flowing through that cable was switched on and off led to the discovery of electromagnetism. This observation occurred at the simplest level of its emergence (first principle) and it enabled assembling large number of its operational units in different configurations to build huge systems for utilizing both its ability to generate electric current

Abbreviations: AMPAR, Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BOLD, Blood oxygenation level dependent; CS, Conditioned stimulus; ECM, Extracellular matrix; EPSP, Excitatory postsynaptic potentials; fMRI, Functional magnetic resonance imaging; GluR1, Glutamate receptor 1; IPL, Inter-postsynaptic functional LINK; LTD, Long-term depression; LTM, Long-term memory; LTP, Long-term potentiation; PDS, Paroxysmal depolarization shift; Spine, Dendritic spine or postsynaptic terminal; US, Unconditioned stimulus.

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and mechanical force. Understanding the physics of mind anticipates a sequence of events from an opposite direction - we are required to first search for reasons why unitary mechanisms should be operating in the system and if present, discover the physics behind it by using findings from the large assembly of units in the brain. If sufficient reasons for the presence of a unitary mechanism are identified, we need to find its operational mechanism using constraints from disparate findings at multiple levels of the system, explain all the remaining findings in an interconnected manner, examine comparable circuitries, make testable predictions, and transfer its principle to engineered systems. It is also necessary to examine possible evolutionary stages - circumstances that led to certain accidents that started sparking internal (inner) sensations and the nature of fine-tuning of this mechanism to reach up to the present state of mind. These can be achieved by indirect methods by using specific features of the key stages of ontogeny. Like electromagnetism, units of first-person internal sensation will always remain inaccessible to the sensory systems of third-person observers.

In the early stages of the evolutionary process, a group of excitable cells innervating muscle cells for executing reflexive motor actions continued to get synaptically connected in different configurations. An accidental circuit formation occurred at one stage when two stimuli arrived together, which later started sparking internal sensations of crude features of one of those items when the second one arrived. This started providing a survival advantage to those systems. This was important due to two reasons - animals move great distances and different types of sensory stimuli travel at different velocities. With the arrival of this new mechanism, animals were able to generate internal sensations of previously associated features of items that are either a) slow to arrive (when a predator or prey is away) than the fastest arriving visual stimulus from a distance, or b) do not arrive (predator or prey is hiding that prevents visual stimulus to travel) when sound or smell takes a curved path to reach the system. In a predator-prey environment, those animals with this new circuit feature of generating internal sensations of late or non-arriving features from an item had survival advantage and were selected over others during evolution. Over many generations, this circuit feature was optimized to generate various internal sensations along with the option to elicit behavioral motor actions as directed by those internal sensations. The purpose of this article is to review how it was possible to identify a testable location where and how the system sparks units of internal sensations, explain factors that integrate different combinations of these units, show how alteration of conformations of net internal sensations is associated with different brain functions, and provide interconnected explanations for a large number of findings from multiple levels.

First-person internal sensations generated within the mind cannot be sensed by third-person observers either directly or by indirect methods that involve only few steps. It has similarities to non-sensible particles and fields that are being studied by physics. Hence, application of deep principle behind the latter is expected to uncover the operational principle of mind. When a system exhibits disparate findings at multiple levels and are of different measurement scales, physics use methods to uncover the deep lying fundamental laws in nature that can explain all those findings. For this approach, it is necessary to set the initial and boundary conditions, arrive at the level of causation and understand the relationship between different levels while connecting them in a multi-scale nature of operation of the system [1]. Current studies use surrogate behaviors as markers to verify that internal sensations are taking place in the mind. Even though these studies maintain an implicit view that internal sensations get induced while expected behaviors are manifested, it was not possible to understand what constitutes the mental content. This is primarily because internal sensations of mind are first-person properties to which only owner of the nervous system has access. Attempts to connect behavior with observations from different levels of the nervous system could not solve the system and has been the subject of discussions [2–4]. It is necessary to use third-person observations from biochemical, cellular, electrophysiological, imaging, behavioral and system levels and derive a mechanism for the generation of internal sensations occurring from a first-person frame of reference. The derived solution should be able to provide testable predictions and once verified, it can be subjected to the gold standard test of replication in an engineered system.

Inaccessibility towards internal sensations of mind gives it the look of an apparent emergent property that appears irreducible especially since the system exhibits seemingly unrelated features at different levels. It may become possible to solve such systems by using the method of unification used in physics. It stems from the deep underlying mathematical principle that the simultaneous application of constraints offered by all the findings can lead to the discovery of a more fundamental principle capable of unifying those disparate findings. This scientific method was initiated by James Clerk Maxwell with the unification of electricity and magnetism [5]. Later, this approach led to the discovery of different fields and subatomic particles [6]. Any theoretically derived solution is verified by both its ability to triangulate different observations having their own errors and biases [7] and by confirming predictions made by the solution [8]. The necessity for a similar unification attempt towards understanding the mechanism of operation

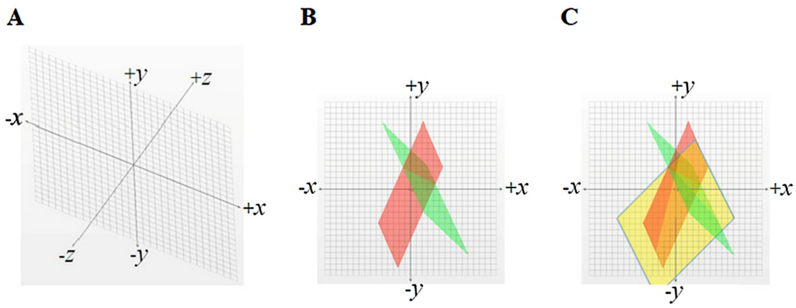

Fig. 1. Graphical representation of a system of three linear equations having one unique solution. **(A)** Real and virtual space in a 3-D graph. Note that only 1/8th of space of a 3-D graph that has all the coordinates with positive values represents real space. The remaining 7/8 portion of the graph represents virtual space. The latter has similarities to the virtual first-person internal sensations within the mind that constitutes most of the functions of the nervous system. Since virtual inner sensations are generated from an assembly of neurons, it has similarities to a system of linear equations having its solution at one of the points on x, y, or z axes. Application of this principle can guide to find the location at which inner sensations are sparked. **(B)** For a system of linear equations with three variables and having a unique solution, when we use only two equations representing only two planes (shown in green and red), the solution lies at the intersection of these two planes, which is a line. The only information that becomes available is that the unique solution can be one of the points on that line. This leaves the system unsolved. **(C)** In addition to the conditions that led to figure B, if information about an additional plane becomes available, then it is possible to find the solution. The intersection between all three planes $(x, y, z) = (0, 3, 4)$ forms a unique solution of the system of linear equations. This is an intersection between real and virtual spaces (see Fig. 8). Using information available only from real space (third person observations) we need to find the solution for the nervous system. Once we have a solution for the system of linear equations, we can predict several features of the system. Similarly, if we identify a solution for the nervous system, then we can make predictions of its properties that can be verified. Like making extensions of graphs towards the virtual space, it is reasonable to expect to make graphical representations of the internal sensations of mind. Note that in Figure C, z axis is perpendicular to the plane of this paper that we read.

of the mind was previously emphasized [9]. Since the solution of the system is expected to have features at a deep level, it is necessary to examine whether the mental content can be reduced to its elementary units. Philosophical viewpoints agree with its feasibility [10,11].

1.1. Lessons from a unique solution that binds a system of linear equations

In physics, unification uses principles of methods in mathematics [12]. For example, solving a system of linear equations that has a certain fixed number of unknown variables and a unique solution requires finding the values of variables at the solution-point. Relationship between variables within each equation provides constraints from each equation that direct towards the solution for the system. In other words, a unique solution binds (unifies) the equations within that system of linear equations. A system of linear equations can be represented graphically. Since 7/8th of the volume of a three-dimensional (3-D) graph represents virtual space (having negative coordinates) to which our senses have no direct access, it has similarities to the nervous system that forms a mind where virtual internal sensations are generated during most of the higher brain functions. In other words, a system of linear equations with a unique solution-point located at the intersection between real and virtual spaces in a graph can be compared to brain-mind relations where generation of virtual internal sensations of mind occurs at a unique intersection between third-person observed structural features. An example of a linear system of equations with three variables where the coordinates of the solution-point lies at the intersection between real and virtual space is given in Fig. 1.

Let us begin by assuming that there is a system of linear equations with a unique solution. Using observable features, it is necessary to first solve the system to find the solution-point from which extensions occur towards the virtual space. Any failure is likely to provide some information how to proceed further. For example, we are given three equations for a system with a unique solution. $3y + z = 13$, $-y + z = 1$, and $-y + 2z = 5$. We soon recognize that they are not part of a solvable system since the equations contradict each other. Furthermore, the presence of more non-redundant equations than variables indicates the likelihood that one variable is missing. Following is another situation that can lead to failure in solving a system. We are given two equations $5x + 3y + z = 13$ and $3x - y + z = 1$ for a system with a unique solution. Since a linear equation with three variables represents a plane in 3-D, solution of the above two equations is an infinite line at the intersection between those two planes. By letting x = a, it represents any value of x of a point on the line of intersection (Note: Inclusion of "a" in the solution represents parametric form of a line). Solution (x, y, z) for the system by letting $x = a$, is $(a, (6 - a)/2, (8 - 7a)/2)$. Here, the solution is an infinite line passing through any value of y on the line of intersection between the planes (Fig. 1B). Therefore, having knowledge of only two equations makes it impossible to find its unique solution. This forces us to seek at least one more equation to form a system. Let this be $2x - y + 2z = 5$. This allows solving the system and identifies its unique solution $(x, y, z) = (0, 3, 4)$ (Fig. 1C).

Do we have similar conditions of either ignoring certain variables or lacking certain required number of equations for solving the nervous system? The latter is unlikely since a very large number of findings were already made from multiple levels. Since several types of internal sensations are generated in the mind, it is most likely that we are ignoring a variable that represents or directs towards the solution-point where internal sensations are induced. Note that, when behavior alone is examined to assess the ability to retrieve memory, we are making this type of an error. In other words, only by defining properties expected from a solution-point correctly that we will be able to arrive at the solution-point where structural features essential for inducing units of internal sensations are present.

1.2. Translating to biological systems

Direct application of the principle of solving a system of linear equations requires simultaneous use of constraints provided by the findings from different levels (subsection 1.1). This is not practically possible to apply in biological systems. However, we can use abstract principles of methods used in mathematics to solve similar problems in biology. A function where two sensory stimuli can make specific changes in the location of their convergence is associative learning. Each learning is expected to leave a specific signature that can be used by a cue stimulus for inducing memory at physiological timescales. This signature is expected to have a spectrum of lifespans responsible for a range of durations during which memory can be retrieved. Related associative learning events should lead to an unambiguous clustering (grouping) of the formed associations. Ideally, addition of new associations is expected to take place without overwriting the old ones. To achieve this efficiently, it is necessary to share mechanisms when two associations have common features. In this context, each new learning event is expected to add new associations pertaining to unique features of new sensory stimuli. Continuation of this process will lead to clustering of associations and their self-organization. Those nervous systems that can stabilize the associations will have a survival advantage over others. Specific cue stimulus should be able to access specific coding for each association, so that they can be utilized for memory retrieval. There should be a robust method to keep unrelated clusters of associations isolated from each other, failure of which will lead to false conjunctions that will be expressed as "gain or loss of function" states such as hallucinations, loss of memories, and behavioral motor defects at the time of memory retrieval.

Since the system can generate very large number of internal sensations along with third person observed features, it may be possible to view this situation similar to a special mathematical problem. Third person observed findings within the real 3-D space (where coordinates are positive) can be used to derive a solution-point somewhere along the XYZ axes from where virtual internal sensations originate and extend to the virtual space of mind. First step is to identify a probable location where neuronal pathways through which different sensory inputs arrive during associative learning converge. By using constraints from observations from multiple levels (Table 1: columns one and two), careful abstractions are made to understand baseline properties necessary for the induction of units of first-person internal sensation at physiological timescales. This should also allow propagation of potentials to trigger motor action, which can be regulated by changes made by all other associative learning events. Correct solution-point operates only when the frequency of oscillating extracellular potentials is maintained within a narrow range. This indicates that the operational mechanism should be providing some of the vector components for these oscillating potentials that provide a binding property to keep all the functions interconnected within the mind.

Failure to observe any cellular change during memory retrieval indicates that internal sensation of memory is induced by passive reactivation of the learning-induced change. The latter is expected to be augmentable (for motivation-promoted learning), stabilizable (for long-term memory), and reversible (for forgetting). Since qualia of internal sensations of working, short-term and long-term memories in response to a specific cue stimulus are similar in nature, they can be expected to get induced from the same mechanism formed at the time of learning with a spectrum of reversibility features that determine their lifespans. Since items in the environment have several shared physical properties, it is expected that several of the previously formed associations in the brain will be shared by new learning events. Exposure to new environments is expected to share schemas of associations formed from exposure to the previous environments [21]. Necessary steps taken to solve the system are given in Table 2. When deriving the solution,

Table 1
List of findings from different levels of the system, constraints offered by them, and the matching findings provided by the derived solution. Constraints set boundary conditions that allow to understand the features of the solution. The derived solution is expected to explain all these features in an inter-connected manner. Note that the listed findings are so disparate, and the constraints offered by them are so strong that there can only be one unique solution. This unique solution for the system should be compatible with all the previous experimental observations. A subset of the above list of observations can be used to derive the solution and the remaining features can be used to verify its suitability. Interconnected explanations provided by the solution are expected to enable triangulation of several of these findings. These are expected of a system having an integrated operation.

Findings	Constraint provided by the finding	Explanation by the IPL mechanism
Nervous system is made of synaptically-connected circuitry	Mechanism should operate synchronous with synaptically-connected neuronal circuitry	IPL mechanism operates in synchrony with the synaptically-connected circuitry [13]
Learning-induced changes occur in physiological timescales (in milliseconds)	A learning-inducible change that occurs at physiological timescales (to explain the ability to retrieve memory instantly following learning)	Hydration exclusion between spine membranes that forms the initial stage of IPL can meet this requirement [14,15]
Memory is an internal sensation with specific sensory features	Mechanism is expected to have elements that can provide sensory features of retrieved memory	Semblances provide first-person internal sensory features [13]
Memories are virtual internal sensations of an item in the absence of that item and can be induced in response to a specific cue stimulus.	Since sensation of a stimulus in its absence is hallucination, mechanism is expected to induce cue-induced hallucinations [16]	Lateral activation of inter-LINKed spine, which is being continuously activated by its presynaptic terminal is expected to induce hallucinations (internal sensations of memory) in a cue-specific manner
Working memory lasts only for a very short period (seconds)	Learning-induced change must have a quickly reversible mechanism	IPL mechanism that overcomes repulsive forces between spines is short-lived [14]
LTM allows retrieval of memory long period after learning	A feasible mechanism for long-term maintenance of learning induced change	IPLs formed during learning get stabilized for long period that enable LTM [17]
Long-term memories (LTMs) are also capable of getting retrieved immediately after learning (working memory)	Learning-changes should be capable of getting retrieved at different timescales starting immediately after learning. Stabilization of these changes explains LTM	IPLs form in milliseconds during learning and can be used readily to retrieve memories. It can be stabilized for long period for LTM [13]
Nonexistence of learning that generates only LTM without forming working memory	Changes responsible for working memory get stabilized to generate LTM	IPLs that are formed in milliseconds during learning [14,17] have to be stabilized for LTM
Simultaneous existence of previous two conditions	Learning mechanism should have a quickly reversible change as well as a mechanism to transition it to a stable state that can last long [14]	IPLs can be stabilized individually and by their repeated activation when being part of an islet [17]
Internal sensations of working, short-term and long-term memories have similar qualia	Learning-induced change should be retained for different durations and should have the same mechanism for generating internal sensations –	Semblances induced from same set of IPLs generate same qualia. Repetition of learning with insertion of new neurons in the circuitry can introduce minor changes [13,17]
When exposed to a cue stimulus memories are retrieved in milliseconds	Cue stimulus should be capable of inducing specific internal sensation of memory in physiological timescales	Induction of semblance occurs in milliseconds [13,17]
Ability to induce the internal sensation of memory in a cue-specific manner	Specific cue features drive induction of specific internal sensation of memory	Cue stimulus reactivates a specific set of IPLs to laterally activate a specific set of inter-LINKed spines to induce a specific set of semblances [13,14]
Absence of cellular changes during memory retrieval	A passive reactivation of learning-changes should induce units of internal sensations at the time of memory retrieval	Propagation of depolarization along the IPLs inducing semblances does not require any cellular changes other than for propagation of depolarization [13].

Table 1 (*continued*)

Findings	Constraint provided by the finding	Explanation by the IPL mechanism
Storage of very large number of memories that far exceeds the finite number of neuronal processes	This becomes possible if a combinatorial operation involving unitary mechanisms are present	Semblances induced at multiple IPLs in a cue-specific manner and their integration provide this ability [13]
Large number of items in the environment have common shared physical properties	Large number of unitary mechanisms are expected to have features that enable them to be used in a shared manner	Specific IPLs can be reactivated by specific features within any cue stimuli, allowing usage of IPLs in a shared manner [14]
Ease of learning of related items or events	Learning-induced changes from previous learning should have features that enable sharing	Shared features of different cue stimuli enable reactivation of same set of IPLs [14]
Instant access to very large memory stores	Cue stimuli induce specific memories by combinatorial reactivation of learning-induced unitary changes at physiological timescales	Any cue stimulus can reactivate existing IPLs within the system in a cue-specific manner in timescales of milliseconds [13]
Motivation promotes learning and is associated with the release of dopamine [18]	Role of a specific factor and its specific action to augment learning-induced changes and possibly retain it for long period	Dopamine cause spine enlargement that can favor IPL formation [13,14]
Ability to store new memories without needing to overwrite old ones	Mechanism should have features to maintain specificity without overwriting previous learning-changes	Only shared sensory stimuli from two learning events can reactivate the same IPLs [13,14], which prevents any overwriting
Internal sensation of memory has the provision to trigger behavior	Mechanism should explain how the internal sensation of memory is related to motor action for behavior	IPL mechanism provides potentials to trigger firing of neurons that are being held at subthreshold levels [13]
Both learning and memory retrieval takes place in a narrow range of frequency of extracellularly recorded oscillating potentials	Operational mechanism is either strongly linked to or is providing vector components of oscillating extracellular potentials	IPL mechanism provides vector components to descending or ascending slopes of those potentials [13]
Brain operations take place in an energy efficient manner	Need an explanation for the seemingly energy efficient operation of the system	Energy is used to maintain a dominant state of depolarization of postsynaptic terminal by the presynaptic terminal. Minimal energy needed for memory retrieval [13]
Slow consolidation of memory is associated with transfer of locations of memory storage [19]	Mechanism for gradual transfer of locations of learning-induced changes by retaining ability to retrieve memory by the same cue stimulus	Repetition of learning or its components occurring after changes in circuitry such as the addition of new neurons will generate new IPLs at a different location for the same memory [20]
Consolidation can occur quickly if an associative “schema” into which new information is incorporated already exists [21]	It should be possible to interchangeably use segments of learning-mechanism between two learning events	Since IPLs can be shared between different learning, a related learning only requires the addition of a new set of specific IPLs, which can result in quick consolidation [20]
A constantly adapting dynamic circuit	Mechanism makes changes to accommodate large number of new learning events	Circuit changes due to the IPL formation require constant small re-adjustment of the circuitry [13]
Cue stimulus fires an additional set of neurons after learning compared to the set of neurons that were fired before learning	A cue stimulus routed through new paths generated by learning-changes cause this	Lateral activation of inter-LINKed spines by cue stimulus provides postsynaptic potentials that fires specific sub-threshold activated neurons. These are neurons that were fired by the item, whose memory is being retrieved, when stimuli from it arrived before learning [13]
Firing of a specific set of place cells in a specific place	Specific cue stimuli induce memory of a specific location along with the firing of a specific set of neurons	IPL mechanism explains this [13,14]

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Table 1 (*continued*)

Findings	Constraint provided by the finding	Explanation by the IPL mechanism
Set of place cells overlap between different places	Presence of a redundant mechanism upstream of neuronal firing to explain this	Extreme degeneracy of inputs in firing a neuron [22] and many inter-LINKed spines that can provide potentials to fire a set of sub-threshold activated neurons [13] can explain this
Dendritic spikes occur by summation of nearly 10 to 50 postsynaptic potentials [23]	System operation should accommodate this and explain its function	Lateral activation of islets of inter-LINKed spines explains dendritic spikes. It is expected to generate semblances contributing to C-semblance [16]
Regenerative dendritic events are correlated with place fields and spatial precision [24]	Explain relation between dendritic events and place fields	Generation of internal sensation of a place during activation of inter-LINKed spines cause firing of CA1 neurons [13,14]
Oscillating extracellular potentials reflect intracellular changes. Synaptic transmission between neurons of neuronal layers provides one of its vector components	There should be other vector component/s that is/are taking place at near-perpendicular direction to synaptic transmission in addition to recurrent collaterals and long-range connections	Depolarization propagating through IPLs takes place in a near perpendicular direction to that of synaptic transmission [13]
The system needs a state of sleep for nearly one third of its operational time	Mechanism for the substantive nature of sleep without which the system won't be able to continue to exist	Induction of semblances as hallucinations requires sleep for updating the dominant state [13,25]
Average inter-spine distance is more than average spine head diameter [26]	There is some functional significance for selection of this feature	IPL formation between spines that belong to different neurons allows classical conditioning [13]
Apical tuft regions of all cortical order neurons are anchored to inner pial surface and their dendritic arbors are mixed together	Mixing up of dendritic arbors of neurons from the same and different orders of neurons needs explanation for its significance	IPL formation between spines that belong to different neurons explains this [13]
The presence of a heterogeneous population of neurons in the cortex	A mechanism compatible with diverse types of neuronal processes is necessary	Neurotransmitter type determines the nature of postsynaptic membrane potential, conformation of semblance and the nature of internal sensations [27]
Integration of new neurons in the granule layer of hippocampus	There is a function for the integration of new neurons	When a learning is repeated, new neuronal connections make additional IPLs. Lack of repetition will reduce the specificity of semblances for memory [20]
Perception is a first-person internal sensation when a sensory stimulus arrives from an object	Internal sensation of perception is an event that occurs concurrent with the arrival of stimuli from an item	IPL mechanism provides an explanation for the generation of units of internal sensation of perception [28]
Flash lag delay, homogeneity of percept for stimuli above flicker fusion frequency, object borders and pressure phosphenes	Matching explanations for all these features using the mechanism of induction of units of internal sensation	Units of internal sensation of perception formed by IPL mechanism provides explanations [28]
Internal state of consciousness	A mechanistic explanation is needed for its generation	A specific reason for its formation is provided in subsection 3.1 [29,30]
Subjective nature of qualia/consciousness	Mechanism has provision to explain how previous associative learning events contribute to this	Repetition of a learning adds inter-LINKed spines to the set of inter-LINKed spines that generate C-semblance [29]
Changes in consciousness with alteration in frequency of oscillating extracellular potentials	Vector components and a specific range of frequency contribute to consciousness	Contribution of vector components by IPL mechanism is associated with the generation of a specific conformation of C-semblance [29,30]

Table 1 (*continued*)

Findings	Constraint provided by the finding	Explanation by the IPL mechanism
LTP has several correlations with behavior associated with memory	Cellular level mechanism of LTP is related to the usage of mechanism of learning at the time of memory retrieval that activates behavior	Both learning and LTP are explained by IPL formation [31]
Learning takes place in milliseconds, whereas LTP induction takes at least 20 seconds after LTP stimulation	Cellular level mechanism of learning should be able to explain this, based on special conditions in which LTP is induced	LTP stimulation generates several IPLs in a time-dependent manner [31]
Blockers of membrane fusion reduce LTP [32]	A fusion mechanism is responsible for LTP and therefore also for learning	Spectrum of changes of IPL includes inter-spine membrane hemifusion, which is an intermediate stage of fusion [31]
Stimulation with energy higher than used for inducing LTP leads to kindling that cause seizures and defects in memory [33,34]	Cellular level mechanism of learning related to that of LTP induction should be able to explain augmented changes during kindling and seizures	High energy results in rapid formation of very large numbers of IPLs producing seizures [31,35]. It adds non-specific semblances causing defects in memory
Loss of dendritic spines after kindling that uses higher stimulation energy than LTP induction (that has several correlations with learning)	Mechanism of kindling related to that of LTP and learning must have a reason to explain loss of spines	High stimulation energy used in kindling leads to IPL fusion between different neurons and can lead to spine loss [35]
Longitudinal propagation epileptic activity at a speed of nearly 0.1 m/s [36] independent of chemical or electrical synaptic transmission [37]	A mechanism for the propagation of epileptic activity independent of synaptic transmission	Rapid chain formation of IPLs can explain this [35]
CA2 area of the hippocampus is resistant to seizures	A factor capable of blocking the mechanism of seizures	Peri-neural net proteins can prevent rapid chain formation of IPLs responsible for seizures [35]
Induction of LTP at CA2 area of hippocampus becomes possible by removal of peri-neural net proteins [38]	Mechanism of LTP induction requires normal extracellular matrix (ECM) around neuronal processes	IPL formation that can explain LTP requires removable ECM between spines [31]
Seizures and memory defects in herpes simplex viral (HSV) encephalitis	HSV virus alters learning-induced changes in such a way that it can lead to seizures and loss of memory	Formation of large number of non-specific IPLs by HIV viral fusion proteins explains this [35]
Paroxysmal depolarizing shift (PDS), an electrophysiological correlate of epileptiform activity is a giant EPSP [39]	A pathological change in normal operational mechanism leads to the summation of EPSPs to form PDS	Rapid non-specific pathological IPL formation between very large number of spines in a region can explain PDS [35]
Hallucinations in schizophrenia	Continuous sensations in the absence of sensory stimuli	Ordered reactivation of non-specific IPLs can induce hallucinations [40]
Occurrence of seizures in neurodegenerative disorders	Neurodegenerative changes should generate a mechanism for seizures	Rapid formation of very large number of non-specific IPLs can explain the generation of seizures [35,41]
Contiguous lateral spread of pathology in neurodegenerative disorders	A mechanism should occur for the lateral spread of pathology	Since IPLs are generally oriented laterally compared to the vertical orientation of cortical neuronal layers, IPL fusion leads to lateral spread of pathology [41]
Sporadic occurrence of neurodegenerative disorders	A unique combination of multiple factors is necessary for the pathology	Only when multiple factors are involved, normal IPL changes can undergo IPL fusion at multiple locations [41]
Spine loss in neurodegenerative disorders [42]	There is a cause and possibly a purpose for the loss of spines	Conversion of normal IPL to IPL fusion leads to spine loss, which protects involved neurons from the continuous deleterious effect of that IPL fusion [41]

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Table 1 (*continued*)

Findings	Constraint provided by the finding	Explanation by the IPL mechanism
Dementia in neurodegenerative disorders	Specific changes that affect internal sensation of memory and motor actions	Conversion of normal IPLs to IPL fusion explains the loss of normal functions provided by them [41]
More education has a less severe impact on clinical expression of dementia	Learning-induced changes reduce dementia risk	Large number of learning events increases the number of IPLs that induce similar semblances, which can be shared during different retrieval events
Referred pain in a remote area away from that of injury	A mechanism for internal sensation of pain at a remote location	IPL-based explanation is provided in subsection 3.2
Phantom sensations and phantom pain	A mechanism for the internal sensation of a limb or painful limb after amputation	IPL-based explanation is provided in subsection 3.2
Mouse model of Huntington's disease (HD) shows neurodegenerative changes [43]	A factor that causes HD is also is responsible for neurodegeneration	Excess of dopamine in HD causes spine enlargement and augments IPL formation. Further spine enlargement leads to generation of IPL fusion
Hallucinations in both schizophrenia (usually in teenagers and young adults) and neurodegenerative disorders (usually in old age)	Mechanism for generating a train of internal sensations in the absence of external stimuli	Generation of non-specific IPLs can lead to triggering of non-specific paths to induce hallucinations in both conditions [35,41]
Loss of consciousness during generalized onset seizures	Cellular mechanism of seizure generation is related to alteration of internal sensation of consciousness	Rapid chain formation of IPLs leads to loss of conformation of C-semblance responsible for consciousness [35]
Loss of consciousness by general anaesthetic agents	Mechanism of action of anaesthetics alters mechanism of consciousness	These lipophilic agents cause the formation of a large number of non-specific IPLs, which alters conformation of C-semblance [30]
Repeated general anaesthesia can cause neurodegenerative changes [44]	Repeated mechanism of anaesthetics leads to neurodegeneration	Repeated alternation of membranes can lead to changes in membrane composition, promote IPL fusion and neurodegeneration [30]
Dopamine, known to augment motivation-promoted learning, increases anaesthetic action [45]	Dopamine augments both learning and anaesthetic action likely by the same mechanism	Spine enlargement by dopamine promotes IPL formation, which can explain both augmentation of learning and alteration in C-semblance [13,30]
System can generate hypotheses and make predictions	Learning from different fields of knowledge forms interconnections between their basic units	IPL based explanation provided in section 5
Certain functions arise from certain specific brain regions based on findings of pathologies/lesion studies	Factors that modify mechanism for inducing internal sensations are expected to be present at these locations	Circuit features and neurotransmitter types are responsible for generating semblances of different conformations for different brain functions at different regions [27]
Internal sensations of different qualia are expected to be present in different animals	Comparative circuitries are expected to be present in different animals	Overlapping of dendritic arbors of neurons for possible IPL formation is present in synaptically-connected neuronal circuitry for perception in remote species [28]
Astrocytic pedocytes cover only less than 50% of perisynaptic area in CA1 region of hippocampus [46]	This distribution of astrocytic processes should be compatible with its operational mechanism	IPL formation requires free space around postsynaptic terminals of every synapse [13]

Table 1 (*continued*)

Findings	Constraint provided by the finding	Explanation by the IPL mechanism
Present nervous systems have evolved over millions of years and resulted from certain accidental coincidences	Stages of ontogeny should show evidence for the formation of inner sensations	Accidental formation of IPLs likely produced an initial spark of internal sensations of late-arriving or non-arriving stimuli from an item that provided survival advantage. It was conserved and fine-tuned [47]
During development, dye diffusion occurs between neuronal cells as they move from periventricular region to their destination [48]	An inter-cellular fusion event is taking place either as a cause or an effect mechanism	Transient inter-cellular fusion triggers a mechanism that can arrest any future inter-cellular fusion at its beginning stage itself [47]
Significant neuronal death (70%) and spine loss (up to 20%) are observed during development [49]	It can be a change that occur either as a cause or an effect mechanism	Transient IPL fusion caused cytoplasmic content mixing between cells that led to cell death. Those cells that expressed a mechanism for arresting fusion at the stage of hemifusion survived [47]
Protein complexin blocks SNARE-mediated fusion by arresting intermediate stage of hemifusion [50]. Complexin is present in spines and no docking of vesicles is seen in spines	Complexin has a role in the spine interconnecting above findings	Since both learning and LTP induction can be explained in terms of IPL formation [31] and since blocking complexin blocks LTP [51], it indicates that complexin is essential for maintaining hemifusion stage of IPL
Artificial triggering of spikes of a cortical neuron causes spikes in a group of sparsely distributed neighboring neurons in the same neuronal order located within 25 to 70 µm from stimulated neuron [52]	Lateral spread of neuronal spikes within a cortical neuronal layer	Presence of many IPLs between spines of different neurons from same neuronal layer can lead to lateral spread of depolarization between those neurons. Neurons that are held in subthreshold activated states are prone to get fired easily

Table 2
Steps that are necessary to derive a solution for the nervous system and to verify whether it satisfies all the system requirements.

1	Examine the findings from various levels and enlist all the constraints under which the system works
2	Derive a solution that can interconnect the findings from different levels by trial and error methods and examine whether the structural details of the solution-point provide necessary logical mechanism for inducing units of internal sensations at physiological timescales
3	Since the system operates only at a narrow range of frequency of the oscillating extracellular potentials, examine whether the derived operational mechanism can contribute to the vector components of oscillating potentials that can substantiate latter's binding ability
4	Provide theoretical evidence for the solution by different methods – by triangulating observations from different normal and loss or gain of function states
5	Confirm the findings by examining whether comparable circuitries, especially in remote species of animals, have features that can accommodate the solution
6	Use the solution to make testable predictions about different features of the system that can be verified
7	Replicate the mechanism in engineered systems for demonstrating the gold standard proof

it is necessary to undertake different cycles of testing and re-testing to adjust the backbone of the principle axiom so that all other findings of the system remain interconnected with it. A solution can be reached only when it satisfies all the constraints. It is hoped that the constraints will guide us towards an inter-level mechanism (Fig. 2). While taking readers along this path, necessary explanations are provided for choosing a certain route when cross-roads are reached.

1.3. How to deal with too many constraints?

When one must solve a system having a very large number of variables and a unique solution, one is forced to look for shortcuts to find the solution quickly. Is there any shortcut method from the knowledge of solving systems of linear equations that can be applied to the nervous system? Let us take a special case of a system of large number

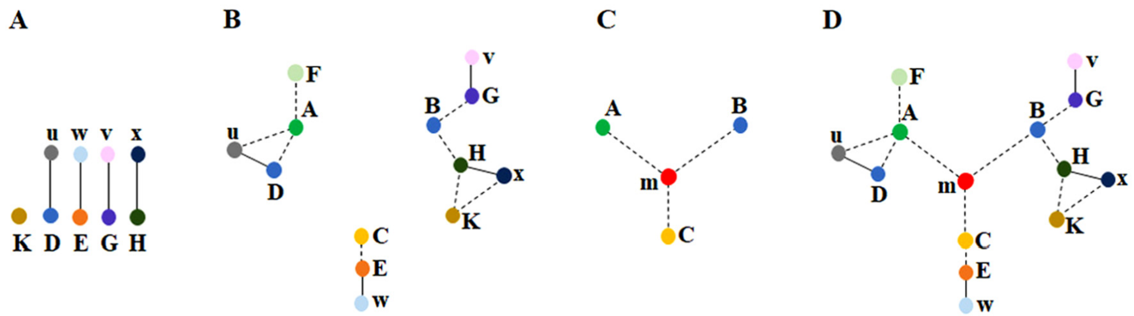

Fig. 2. Method to find a solution for the system from third person observed findings. **(A)** Features of the system are sensed either directly (represented by capital letter K) by our sensory systems or indirectly (represented by capital letters D, E, G, H) through findings such as staining of proteins, observing behavior, etc. (represented by small letters u, w, v, x). The indirectly sensed features and the method used to sense them are connected through straight lines (for example, observation of u enables sensing D). **(B)** Using both commonly used direct and indirect methods, three clusters of interconnected (represented by dotted lines) findings are found at separate levels (observations from different fields of brain science). In most cases, it was not possible to interconnect between these clusters. For example, it was not possible to interconnect between 1) learning changes and inner sensation of memory, both occurring in millisecond timescales and 2) memory, sleep and LTP. Using constraints from findings within each cluster, it is possible to arrive at overlapping common features such as A, B, and C. A solution for the system is expected to interconnect these common features from large number of clusters of findings. **(C)** Using constraints available from common features A, B and C of three clusters of findings, it is necessary to derive a deep underlying principle (a structure-function solution **m**) that allows interconnection between them and therefore all the findings within each cluster. This solution is expected to provide a mechanism for generation of internal sensations within the mind in millisecond timescales. **(D)** The solution **m** enables explaining how various findings within each cluster are interrelated with each other and with the findings from other clusters shown in B). While remaining non-sensible to our senses by any known methods used in current biological investigations, ability of the solution **m** to hold different findings from all the clusters together makes it a further verifiable solution.

of linear equations (and variables) having a unique solution with zero values for all the coordinates except one or two of the x, y, z coordinates, which have positive values (i.e. at least one of the x, y, z coordinates has zero value). Here, one method to find the solution is to plot graphs of equations containing only variables x, y and z. By this approach, one will reach the solution-point at the intersection between real and virtual spaces after plotting graphs for a minimum of three equations. A comparable approach in biology will be to draw figures of pathways through which two associatively learned stimuli are propagated to identify a converging location that can form a solution-point where learning-change can occur at physiological timescales of milliseconds. This solution-point is expected to have a mechanism for inducing hallucinations (sensation of a stimulus in its absence) of sensory features of associatively learned stimulus at the time of memory retrieval [16] in millisecond timescales. Presence of features at the solution-point to support this property is the crucial deciding factor for success (see subsection 1.2). Since both associative learning and memory retrieval take place in a narrow range of frequency of oscillating extracellular potentials, a mechanism at the solution-point is expected to contribute some vector components to the oscillations of potentials. The learning-change should be capable of lasting for a wide range of durations that can explain working, short-term and long-term memories. These are the major constraints that can be used to examine whether to move forward with a derived mechanism. These are sketched in Fig. 3.

1.4. Why should there be a unitary mechanism for the operations?

When confronted with the need to generate a very large number of outputs using limited resources, biological systems often utilize the power of combinatorial effect by using unitary mechanisms. A typical example is the capability to generate nearly 10^{11} specific antibodies in response to a diverse number of antigenic molecules that can arrive from the environment, using a finite number of variable (V), joining (J), and in some cases, diversity (D) gene segments [53,54]. By looking at the structure of immunoglobulin genes at the V_H and V_L regions alone, one can observe redundancy within different gene segments. Another example is the degeneracy of codons in the genetic code [55] that allows to retain its function even if some of its structural elements get mutated during life. Degeneracy is the ability of the elements that are structurally different to perform the same function and is viewed both necessary for, and an inevitable outcome of, natural selection [56]. In summary, whenever we observe combinatorial mechanism or degeneracy at one level in biological systems, it is likely that the basic operational units are residing in that location or in its neighborhood.

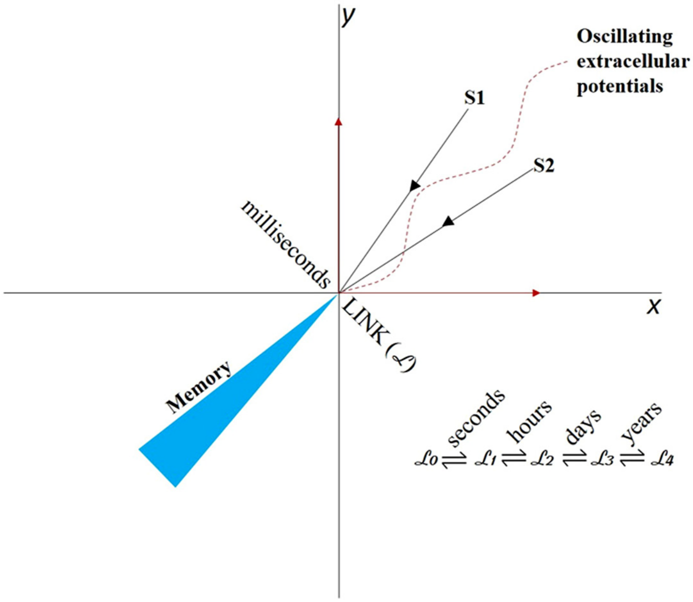

Fig. 3. Key features expected at the solution-point. Two stimuli S1 and S2 are associatively learned. The solution-point is expected to generate a change in milliseconds at a location where these pathways converge (LINK). Once formed, this LINK mechanism is expected to have different lifespans. $\mathcal{L}0$ to $\mathcal{L}4$ are different stages of the LINK mechanism that persists for a wide range of durations from a few seconds to years. Since majority of changes last only for a few seconds that explain working memory, the mechanism should have features that allow its rapid reversal. It should also have features for its maintenance for hours, days and even years. So, it is reasonable to expect a gradient of changes at this solution-point for its stabilization. Equally important is that this mechanism is reversible, which will take a course of changes in the opposite direction. The solution-point should have a mechanism for inducing hallucinations of sensory features of associatively learned stimulus at the time of memory retrieval in millisecond time scales. This should be true for all the stages of its stabilization from $\mathcal{L}1$ to $\mathcal{L}4$. The mechanism at the solution-point is expected to contribute vector components to the oscillating extracellular potentials to allow the operations to occur at a narrow range of frequency of these potentials.

Operational mechanism of the nervous system is expected to generate internal sensations in response to very large numbers of cue stimuli in an energy efficient manner. This can be accomplished if the following conditions are met. First, for providing a very large number of internal sensations using a finite number of structures within the system, a combinatorial mechanism is necessary. Secondly, since many physical properties are shared among items in the environment, there will be very large number of shared associations in a given environment. Hence, it is reasonable to expect that an efficient system will be sharing their operational units when storing and retrieving large number of information. Here, a new associative learning event will only require adding new components involved in the new learning. In this context, it is necessary to underscore the observation of the extreme degeneracy of inputs that arrive through dendritic spines (spines or postsynaptic terminals) and result in the same neuronal firing [22]. This is supported by different observations that combination of inputs arriving from any 140 randomly located spines on the dendritic tree, out of the possible thousands (and even tens of thousands) of spines can fire a neuron [57,58]. Furthermore, postsynaptic potentials attenuate as they propagate from the origin (spine head) towards the cell body. In this context, it is reasonable to expect that an operational mechanism for the generation of internal sensations will be occurring at the level of the dendritic spines that can utilize the degeneracy of inputs in firing a neuron. It is anticipated that these unitary mechanisms will be able to operate by satisfying all the constraints enlisted in column two of Table 1.

When a unitary mechanism generates internal sensations, can this mechanism also generate behavioral motor outputs using a finite number of muscle fibers? Many brain functions are associated with behavioral motor outputs that are generated by using combinations of muscles. Hence, it is reasonable to expect that the unitary mechanism for generating internal sensation has provisions to provide potentials to fire a motor neuron. Since many neurons are kept at subthreshold activation levels, providing even a fraction of one postsynaptic potential will be enough to fire neurons that are being held at certain subthreshold states. These neurons or some of their higher order neurons can be motor neurons. Thus, the unitary mechanism for internal sensation can have provisions to activate motor units (a motor unit is a motor neuron in the ventral horn or cranial nerve nucleus and all the muscle fibers innervated by it). The downstream effect of neurons can be regulated by different inhibitory neurons and feedback mechanisms to obtain appropriate behavioral outputs. Hence, firing of a set of neurons in a brain region depends on a diverse combination of factors. Since many muscle fibers are used in a shared manner for different behaviors, firing of certain combinations of motor neurons can determine the nature of behavioral motor actions.

2. Derivation of the solution

The initial approach was general in nature and was aimed at arriving a framework of a solution that can be refined later. Since the correct solution-point is expected to occur at the level of the spines (see subsection 1.4), an initial argument was made as follows. If a specific set of all the spines that are depolarized by an item can be artificially stimulated later, then the system is expected to generate an internal sensation of that item [59]. The next step was to search for a function that can be used to make changes in the system at will and can be verified. If this change can be used later to evoke internal sensations, then such a function is highly suitable to undertake experiments to study the mechanism. For this, learning and memory are highly suitable.

When living in a predator-prey environment where different sensory stimuli from an item travel at different velocities, nervous system associates these sensory stimuli when the item is close to it. Later, when the animal moves far away from the item or the item is hidden from the nervous system, if the fastest or first arriving sensory stimulus from that item can generate internal sensations about the late arriving or non-arriving stimuli from that item, then the animal will be able to utilize internal sensations of both beneficial and deleterious properties of that item. We identify the generation of first-person internal sensations as a property of "mind." This provided a survival advantage to those animals and they were selected by evolution. Later, this mechanism was fine-tuned to obtain a best possible match between virtual internal sensations of learned stimuli and the sensory stimuli that arrived from that item at the time of learning. The mechanism that generates internal sensations of mind is expected to have an option for evoking corresponding motor actions for survival. Additional learning events are expected to introduce further changes that may regulate those motor responses, depending on the nature of the cue stimulus and the context.

2.1. Which constraints should be used first to find the solution?

Similar to plotting graphs of equations in a 3-D graph to find the solution-point (see subsection 1.2), learning-induced changes during associative learning can be examined by drawing figures of the routes through which sensory stimuli propagate to reach the location where two associated stimuli converge (Fig. 4A). Whatever is the solution-point that we are reaching, it should be capable of explaining a learning-induced change that can be utilized by one of the stimuli participated in the learning to generate the internal sensation of memory of the second item. Furthermore, the learning-induced change should have a spectrum of features that will allow it to last for a range of durations during which memories can be retrieved. It should also be capable of reversing back to a state that was present before learning. Thirdly, organization of this location is expected to allow each one of the associatively learned stimuli to undergo further associative learning with different sensory stimuli. Fourth, above mechanism should allow the cue stimulus to channel enough potentials to evoke motor activity reminiscent of the arrival of the associatively learned second stimulus (Fig. 4B), if no inhibitory pathways were introduced following the initial learning. The system should be able to use information from other associative learning events to control these motor actions. Finally, the solution-point should have features for allowing its operation to tightly associate with oscillating extracellular potentials within a specific frequency range by contributing to their vector components. These constraints can be used at the initial stage to find the solution.

Before drawing figures, let us think about certain logical situations that can guide towards the correct solution. It is necessary to identify the spines between which interaction is expected to take place during learning (see subsection 1.4). Can the converging inputs synapse onto adjacent spines of a single neuron and meet all the requirements? (Fig. 4C). This can be verified by examining a classical conditioning experiment. Usually, a stimulus that does not trigger any motor response on its own is selected as a conditioned stimulus (CS). A stimulus that triggers a motor response is selected as an unconditioned stimulus (US). After repeated pairing of US and CS, it is expected that CS will trigger motor response of the US. If sensory inputs from CS and US converge to adjacent spines on a dendritic branch of one neuron, then it will not be possible to demonstrate the above feature since inter-spine interaction will

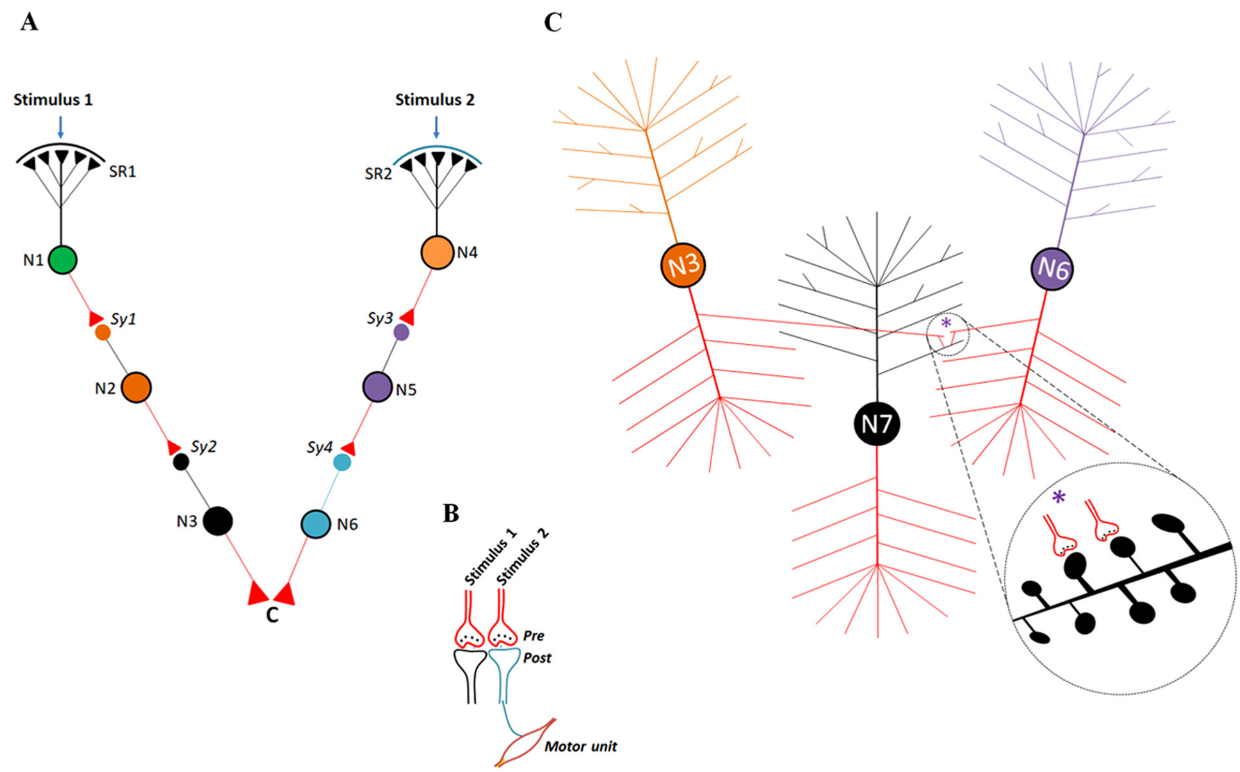

Fig. 4. Location of convergence of sensory inputs is ideal for learning-induced change. **(A)** Sensory stimuli 1 and 2 arriving at sensory receptors SR1 and SR2 respectively propagate through three neurons (N1, N2, N3 and N4, N5, N6 respectively) and two synapses each (Sy1, Sy2, and Sy3, Sy4 respectively) to arrive at the location of convergence C. Changes at the location of convergence of two stimuli (marked C) are expected to produce learning-induced changes. Note that even though changes at the synapses were studied extensively, they have not yet provided a mechanistic explanation how a stimulus propagating through one pathway can evoke the internal sensation of memories of the second stimulus after associative learning. **(B)** A pair of closely positioned synapses at the location of convergence. One synapse has received sensory input from stimulus 1 and the other from stimulus 2. Learning is expected to induce a change between some sub-synaptic locations such that the arrival of stimulus 1 following learning should activate the motor unit that is normally activated by stimulus 2. For achieving this, the shortest route that it can take necessitates the formation of a functional LINK between their postsynaptic terminals. The propagation of potentials through this route is also expected to induce units of internal sensation. Pre: presynaptic terminal; Post: postsynaptic terminal (dendritic spine). **(C)** Can the converging inputs from neurons N3 and N6 synapse on to the neighboring spines of neuron N7 (magnified view in the inset)? Since mean inter-spine distance is even more than the mean spine diameter [26], a direct physical interaction between the spines is not possible. A mechanism through the dendritic shaft that can provide specificity between the spines in electrical isolation is not feasible. A mechanism through ECM space is also not feasible. Since arrival of either one of the stimuli cause firing of the same neuron (N7), it cannot explain a learning mechanism for classical conditioning. Hence, this is not capable of providing a universal solution.

only result in the firing of the same neuron (Fig. 5B). Furthermore, since mean inter-spine distance is larger than the mean spine diameter [26], a mechanism occurring through extracellular matrix (ECM) volume between the spines of a single neuron is also not practically possible. In addition, dendritic branch shafts do not have electrically isolated conducting cables between adjacent spines of a single neuron. These reasons necessitate rejecting the feasibility of interaction between spines of a single neuron as a mechanism.

An alternative mechanism can take place as follows. Since dendritic arbor of adjacent neurons of a neuronal order mix together, some of their spines are expected to abut each other. This can lead to inter-neuronal inter-spine interactions. Since apical tuft regions of neurons of all the cortical neuronal orders are anchored to inner pial surface, dendritic arbors of many neurons including those from different cortical layers overlap and intermix. Hence, the converging inputs from associatively learned sensory stimuli are expected to synapse onto the spines that belong to different neurons as a rule (Fig. 5C) [13]. There could be exceptions. The expected inter-neuronal inter-spine interaction is called inter-postsynaptic functional LINK (IPL) and it matches with the finding that single spine synaptic inputs to the same dendrite of a neuron are highly heterogeneous [60].

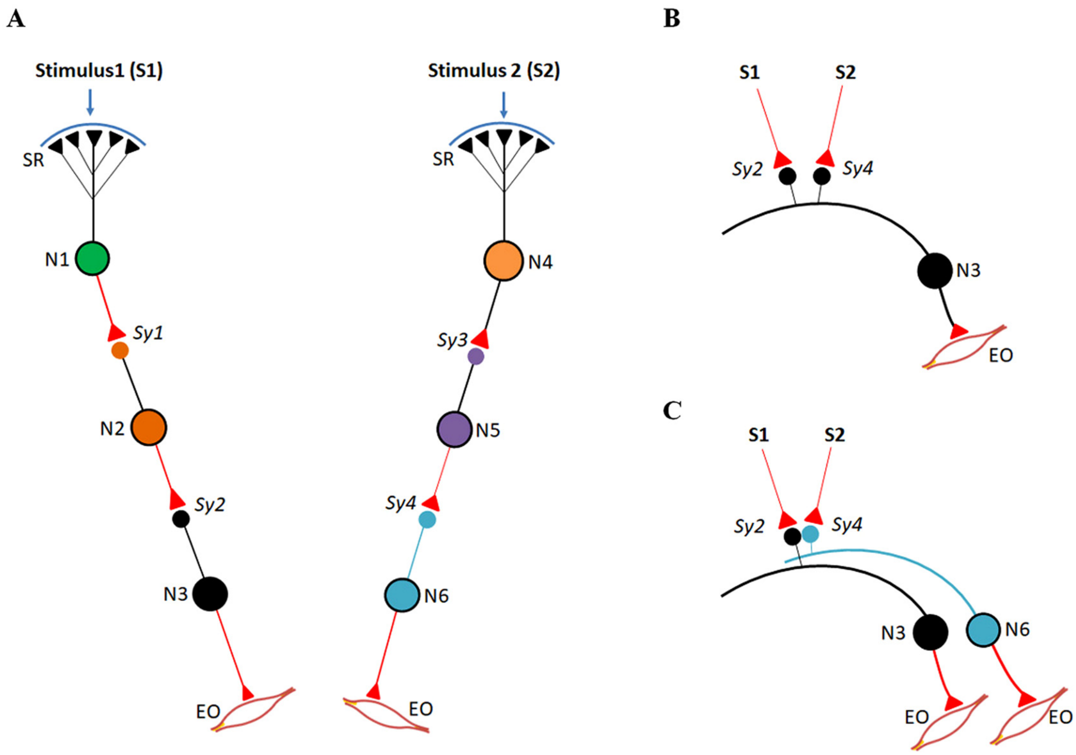

Fig. 5. Conditions that necessitate interaction between the spines that belong to two different neurons. **(A)** Associative learning between stimulus 1 and stimulus 2, where both stimuli can independently activate their own motor units. Following learning between these two stimuli, one of the stimuli is expected to activate both the motor actions. A simple pathway that can allow one of the stimuli to achieve this along with induction of internal sensation of the second stimulus at physiological timescales need to be found. **(B)** Convergence of stimulus 1 and stimulus 2 on to the adjacent spines of a neuron as shown in Fig. 4C. In this scheme, two stimuli having independent motor actions will not be able to demonstrate motor outputs expected of a learning mechanism. Hence, a learning-induced mechanism is unlikely to occur by inter-spine interaction between two adjacent spines of a single neuron. Moreover, there is no provision for a mechanistic explanation for learning-induced changes to occur between adjacent spines of a single neuron. **(C)** Convergence of stimulus 1 and stimulus 2 on to the spines of two separate neurons (N3 and N6) can provide separate motor outputs. If those spines are abutted to each other and if their interaction during learning can provide an inter-spine mechanism that can be reactivated by one of the stimuli (after learning) to induce the internal sensation of memory of the second stimulus and if the inter-spine mechanism has different lifespans to explain working, short- and long-term memories, then it is a suitable candidate mechanism. S: sensory stimulus; SR: sensory receptor set; N: neuron; Sy: synapse; EO: end organ.

IPL change can be retained for durations ranging from a few seconds to years [14] (Fig. 6) and can explain the expected relationships between working, short-term and long-term memories in previous studies [61,62]. The beginning stage of the spectrum of IPL changes is a rapidly reversible stage. Since majority of memories are working memories, this rapidly reversible stage that constitutes most of the learning-change provides a matching explanation. The other end of the spectrum of IPL mechanisms is inter-spine hemifusion that can retain the integrity of neuronal cytoplasmic compartments. It has the benefits of reversibility and capability to get stabilized for long duration. Continued learning leads to the inter-LINKing of more spines to the existing inter-LINKed spines, which can result in the formation of "islet" of inter-LINKed spines (Fig. 7). This matches with the expectation of clustering of associations between different sets of learned stimuli (see subsection 1.2). As learning continues, sizes of many islets increase.

2.2. *Memories are cue-specific hallucinations*

Since memories are internal sensations occurring in the absence of arrival of stimuli from an item, they can be viewed as cellular hallucinations [16]. Cue-induced memories are cue-specific hallucinations. Hence, it is necessary to identify a mechanism whereby a cue stimulus can utilize the learning mechanism to induce hallucination of the associatively learned sensory stimulus that moved through a second path at the time of learning. What are the elements

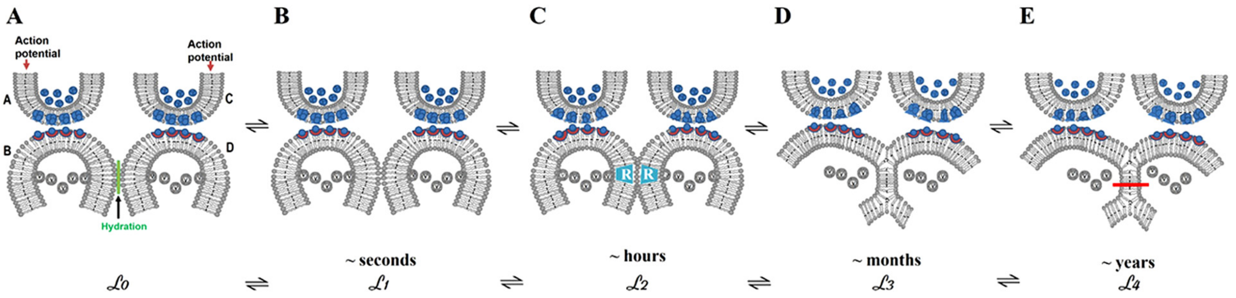

Fig. 6. IPL change that can be retained for a wide range of durations. This is an essential feature of the solution-point where units of internal sensations are generated (see Fig. 3). **(A)** The dendritic spines are electrically isolated from each other by hydration repulsion forces of the ECM. This state is $\mathcal{L}0$. **(B)** When postsynaptic potentials are generated by the arrival of sensory stimuli at their presynaptic terminals, it leads to the exclusion of hydration between the spines leading to electrical communication (LINK) generating a state $\mathcal{L}1$ between the spines. This lasts only for a few seconds and is responsible for working memory. Since majority of memories are working memories, this rapidly reversible stage that constitutes most of the learning-change provides a matching explanation. **(C)** Strong stimuli or spine enlargement by dopamine can lead to membrane reorganization (R) of the lateral spine head region and this leads to inter-spine partial hemifusion, which can last for hours ($\mathcal{L}2$). **(D)** Further continuation of this process leads to inter-spine complete hemifusion ($\mathcal{L}3$). **(E)** Stabilization of the hemifused area (marked by a red line) by different mechanisms such as membrane proteins or continuous activation of inter-LINKed spines within an islet of inter-LINKed spines can maintain these LINKs for years and even for the entire lifespan of the animal ($\mathcal{L}4$). Note that all these stages are reversible. Also note that hemifusion is an intermediate stage of fusion. For details, see [14] (Figure modified from [30]).

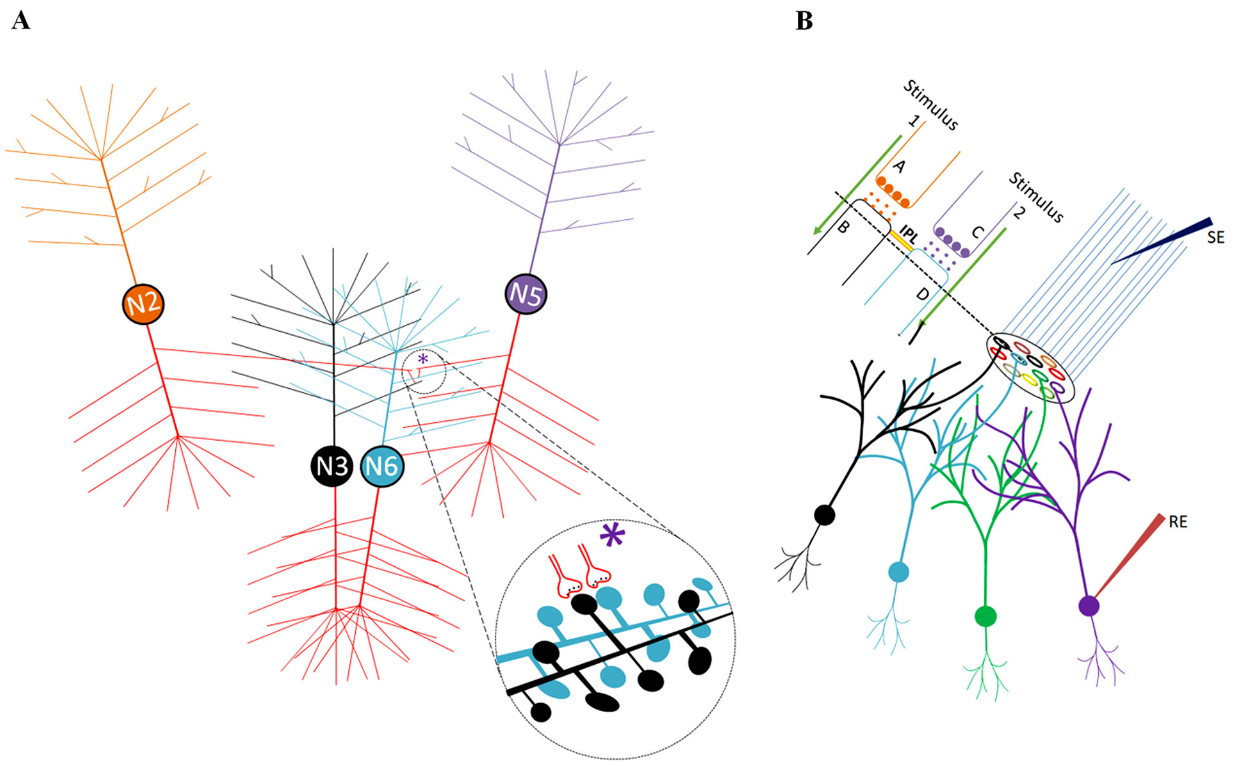

Fig. 7. Interaction between the spines of different neurons. **(A)** Associative learning stimuli arrive through neurons N2 and N5 shown in Fig. 5. Learning-induced changes are expected to take place through an interaction between the spine heads of the spines that belong to two different neurons N3 (in black) and N6 (in blue) (magnified view in the inset). This allows operation of a conditioning learning paradigm. **(B)** An islet of inter-LINKed spines (in a circle) that belong to different neurons. One pair of inter-LINKed spines B-D that belong to two neurons is shown magnified on the left side. IPL can be formed either during learning between the readily LINKable spines or by artificial stimulation using a stimulating electrode (SE). In physiological conditions, a stimulus arriving at the islet can induce related semblances and may also provide appropriate response-motor actions. Islets that are continuously activated at normal physiological conditions are expected to induce net semblances for internal sensations of common shared associations from the body and environment that contribute to C-semblance.

necessary to induce a hallucination within a system? First, the cue stimulus should be able to trick the system to hallucinate using learning-induced changes. Secondly, the path of the associatively learned item should be exhibiting some feature that makes it vulnerable to hallucinate that it is receiving input from that learned item at the arrival of cue stimulus. As an animal moves through the environment, rapidly changing cue stimuli arriving from the environment necessitate it to make several cue-specific momentary hallucinations. These hallucinations should occur when the cue stimulus propagates through the IPLs and depolarizes the corresponding inter-LINKed spines (see Fig. 7B). How does an incidental lateral activation of an inter-LINKed spine spark such a hallucination? This necessitates the presence of certain continuous events of depolarization of the inter-LINKed spine arriving from the same route through which the associatively learned second stimulus propagated in the past. Only in that context that an incidental propagation of depolarization through the IPL to laterally activate the inter-LINKed spine can generate a hallucination at the inter-LINKed spine about the sensory features of the associatively learned second stimulus. Are there any continuous events arriving at the inter-LINKed spine all the time?

Inter-LINKed spine, like any other spine, is continuously being depolarized by quantally released neurotransmitter molecules from its presynaptic terminal all the time including sleep. Occasionally, it is depolarized heavily by a volley of neurotransmitter molecules when an action potential arrives at its presynaptic terminal as a result of activation of different sets of sensory receptors by different sensory stimuli. From the inter-LINKed spine's perspective, its strong depolarization means that an action potential has reached its presynaptic terminal by a stimulus from the environment stimulating a minimum set of sensory receptors. Since the default state of an inter-LINKed spine is that it receives input from its presynaptic terminal all the time, any incidental lateral activation of the inter-LINKed spine is expected to induce a hallucination that it is receiving input from the environment through its presynaptic terminal. In other words, cue stimulus tricks the inter-LINKed spine to hallucinate momentarily. For such a hallucination to occur, the default number of depolarizations of the postsynaptic terminal by its presynaptic terminal should be maintained above a certain threshold limit. At this point, one will expect a universally present suitable mechanism in all the animals on Earth (for the mechanism, see subsection 4.5). In this state, any lateral activation of an inter-LINKed spine is expected to induce hallucinations (first-person internal sensations) in physiological timescales of milliseconds. This induction of units of internal sensations meets the expectations of a mechanism for memory [16]. It can be viewed as a first principle of the system.

It is expected that internal sensations induced at the inter-LINKed spines are integrated to generate memory that matches with the sensory features of the item whose memory is being retrieved. In this context, the constraint that internal sensations are induced only when oscillating extracellular potentials are maintained in a narrow range of frequency needs a matching explanation. To satisfy this, induction of internal sensations is expected to be a system property where both synaptic transmission and propagation of potentials through IPLs at near perpendicular directions contribute some of the vector components of oscillating extracellular potentials. Depolarization propagating through an IPL to the inter-LINKed spine can fire a motor neuron at the same or higher neuronal order, if that neuron is being held at sub-threshold state short of a few or even a fraction of one postsynaptic potential (Fig. 5C). This can explain how motor activity reminiscent of associatively learned item can be generated.

2.3. Inducing sensory qualia involves a step of natural retrograde extrapolation

The next stage of the derivation is to characterize the sensory qualia of a unit of internal sensation induced at the inter-LINKed spine. It is to be emphasized that the sensory qualia are a first-person property. Devising a method to identify its virtual sensory features is a novel step that provides entry to the virtual space of mind. Even though sensory qualia of internal sensation are not third-person accessible, we can theoretically construct it as follows (Fig. 8). Cellular hallucination induced by the cue stimulus at the laterally activated inter-LINKed spine is about a sensory stimulus arriving from the environment through its presynaptic terminal. This leads to the question, "Activation of which sensory receptors can ordinarily arrive at the inter-LINKed spine's presynaptic terminal?" In order to obtain the answer, it is necessary to make retrograde extrapolation from the inter-LINKed spine towards those sensory receptors from which activity normally reaches at that inter-LINKed spine. From a set of all the sensory receptors {SR} reached, it is necessary to identify a subset of minimum sensory receptors whose activation is sufficient to cause an action potential to arrive at the presynaptic terminal of the inter-LINKed spine that is being tricked to hallucinate. Minimum sensory stimuli that can activate this subset of sensory receptors is viewed as a unit of internal sensation called semblion [13]. The very step of extrapolating from the inter-LINKed spine towards the sensory receptors for identifying semblions

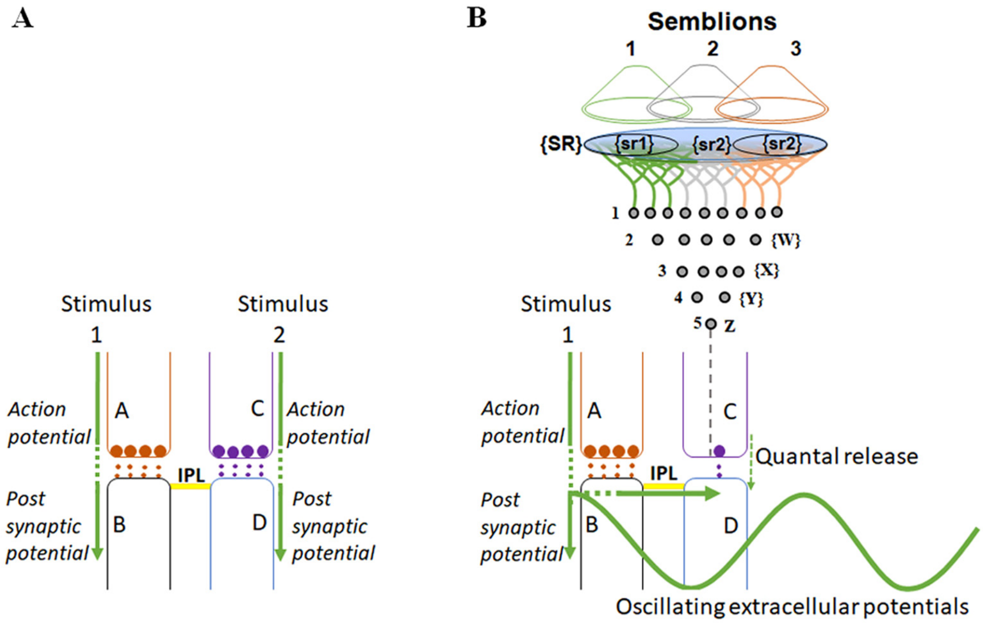

Fig. 8. Reactivation of an IPL results in lateral activation of an inter-LINKed spine to induce units of internal sensation. **(A)** When stimulus 1 and 2 are associatively learned, it generates an IPL between postsynaptic terminals B and D. At a later time, IPL B-D is reactivatible by the arrival of either one of the stimuli. An IPL is stabilizable for different durations and is reversible once the stabilizing factors are removed. **(B)** During memory retrieval, arrival of stimulus 1 reactivates IPL B-D and depolarizes postsynaptic terminal D. Postsynaptic terminal D is normally continuously depolarized by quantal release of neurotransmitter molecules from its presynaptic terminal C and is heavily depolarized intermittently by the arrival of action potentials at its presynaptic terminal C. For postsynaptic terminal D, it always receives sensory inputs from the environment via presynaptic terminal C. In this background state, any incidental lateral activation of postsynaptic terminal D can spark hallucination of arrival of a sensory stimulus from the environment through its presynaptic terminal C. Lateral activation of inter-LINKed spine inducing hallucinations is the intersection between real and virtual spaces described in Fig. 1. The content of the hallucination that forms internal sensation is estimated by a retrograde extrapolation from postsynaptic terminal D towards the sensory receptors to find the identities of minimum sensory stimuli that can stimulate it as follows. A set of neurons {Y} can activate presynaptic neuron Z. A set of neurons {X} can activate {Y}. Depolarization can also arrive through existing IPLs at these levels. Continuation of the extrapolation reaches a set of sensory receptors {SR}. Activation of subsets of minimum number of sensory receptors {sr1}, {sr2}, and {sr3} from set {SR} is enough to activate postsynaptic terminal D. A hypothetical minimum sensory stimulus capable of activating one of the above subsets of sensory receptors that can activate postsynaptic terminal D is called a semblion and is the unit of internal sensation of memory. Induction of internal sensation of memory is determined by the frequency of oscillating extracellular potentials. Some of its vector components are contributed by propagation of depolarization through synapse A-B and IPL B-D (Figure modified from [13,25]).

(units of internal sensations) involves a shift from third person to first-person frame of reference. Since very large number of subsets of sensory receptors are present within the set {SR} whose activation can cause an action potential to arrive at the inter-LINKed spine's presynaptic terminal, many sets of semblions are expected to get induced at a given inter-LINKed spine. This is also determined partly by previous associative learning events that have created IPLs in the dendritic arbor regions of the lower order neurons.

2.4. Natural computation of units of internal sensations

Integration of different semblions induced at each of the laterally activated inter-LINKed spines in a combinatorial manner to generate a net semblance at physiological time-scales results in memory. What is the mechanism of this integration? Since both synaptic transmission and the lateral spread of potentials through IPLs are expected to contribute some of the vector components to keep the frequency of oscillating extracellular potentials within certain specific range (Fig. 9) at which the system operates, it is reasonable to view its suitability for integrating all the semblions. Even though an induced semblion does not have any orientation, it is expected to get oriented with respect to the remaining semblions like pixels in a digital image so that the computational product of units of internal sensations will have 3-D features. Next step is to find out which semblions are used and by what algorithm that an internal sensa-

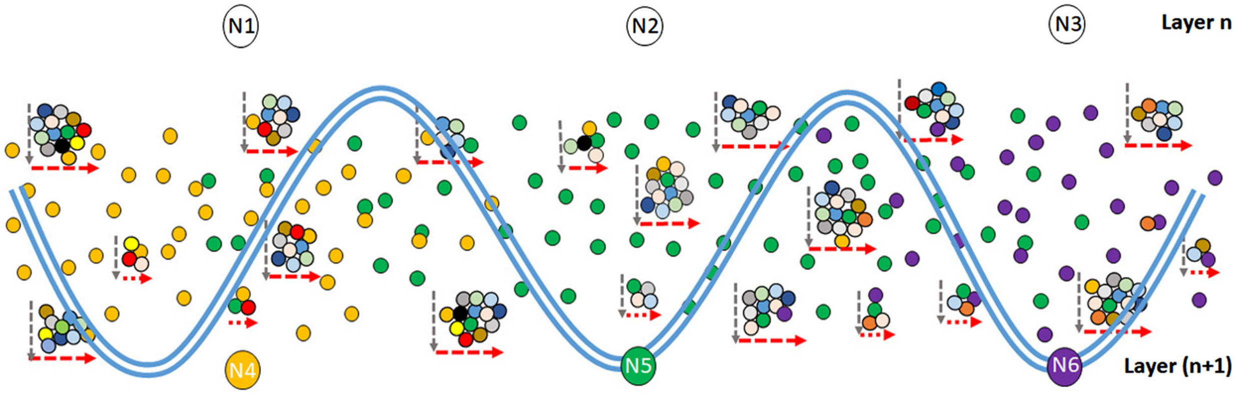

Fig. 9. Oscillating extracellular potentials and some of its vector components. The operational mechanism of the nervous system is expected to match with the findings that a) a narrow range of frequency of oscillating extracellular potentials is essential for the induction of internal sensations of different higher brain functions, and b) internal sensations alter with the alteration of this frequency. Synaptic transmission and spread of potentials through the IPLs (spines are shown in small circles of different colors) can provide vector components that act in near perpendicular directions (shown by broken arrows of different colors) to contribute to the descending slope of the oscillation of extracellular potentials (shown as the large waveform). Vector components for the ascending slope can be provided by thalamo-cortical projections and recurrent collaterals to the cortical neurons, depending on the cortical locations. The spread of potentials through the islet of IPLs (shown in clustered circles of different colors) can provide large fractions of the horizontal component of these oscillating potentials. In the resting state, lateral activation of a large non-specific set of inter-LINKed spines can contribute to a matrix of net C-semblance most probably responsible for internal sensation of consciousness. In this background state, a cue stimulus is expected to induce the internal sensation of a specific memory. This general scheme is suitable to explain the binding property of oscillating potentials. Both IPL formation and its reactivation are expected to take place even in the absence of firing of neurons of the participating spines, in special conditions [22]. N1 to N3 and N4 to N6 are neurons that belong to two adjacent cortical neuronal layers.

tion of memory matching with the features of the item whose memory is being retrieved is generated. Is it overlapping of selected semblions that decide qualia of internal sensation? Do semblions induced at the inter-LINKed spines at the lowest neuronal order have more weight in determining qualia? Do semblions induced at the inter-LINKed spines at the level of the highest neuronal order determine specificity of qualia? These are questions that will need to be addressed. This approach towards seeking qualia of internal sensations matches with the expectation that connectivity between neuronal processes will provide highly informative constraints on the computational process [12].

It is reasonable to view that specificity of a cue stimulus determines the net semblance generated by integration of different semblions induced by that cue stimulus. As specificity of a cue stimulus for retrieving a specific memory reduces, it is expected to induce more than one net semblance, generating more than one memory. An animal can then use additional cue stimuli to reach the correct memory. Another factor that can fine-tune the system is movements of animals back and forth from an item. This provides a spectrum of time-intervals between the fastest arriving stimuli from an item in relation to the late-arriving or non-arriving stimuli from that item and gives several fine-tuning opportunities for the circuitry to match the internal sensation of memory with that of the sensory features of an item.

3. Operation of mind

There are three elements that are necessary for the operations of the mind. First, the system is expected to have an internal recognition system, independent of any external stimuli, that forms a background state of the mind. Secondly, the system should be able to generate internal sensations of different brain functions. Thirdly, it should be possible to explain how internal sensations of emotions and feelings are generated in the mind using specific findings from locations responsible for them.

3.1. Mind at its background state

It is expected that the mechanism of generation of internal sensations as hallucinations is related to a conscious state during which functions such as perception, learning, and memory retrieval take place. Consciousness has both species-specific and subjective features. It is tightly associated with a specific range of frequency of background oscillating extracellular potentials (Fig. 9). In examining the physics of mind, it is necessary to ask the question, "How does the internal sensation of consciousness form and what is its functional significance?" Consciousness is viewed as a property associated with binding of different sensations in the nervous system [63,64]. The repeated arrival of the stimuli originating from the body and the environment will repeatedly trigger internal sensations of associatively learned features. When something occurs repeatedly within a biological system, the system will trigger homeostatic mechanisms to reduce energy expenditure. This is expected to have generated mechanisms to avoid the necessity to induce separate internal sensations for each one of the common associations arriving from the body or the environment.

One method to achieve this is by the continuous lateral activation of all the inter-LINKed spines for the common associations as a default mechanism (that will otherwise be laterally activated one by one by different common stimuli) to generate a net background semblance. By closely examining the system, it is reasonable to expect that during continuous oscillations of extracellular potentials in the awake resting state, reactivation of several IPLs takes place to laterally activate their inter-LINKed spines that otherwise can get laterally activated by common stimuli. Net semblance induced by this will eliminate the necessity to induce separate internal sensations in response to common sensory stimuli that continue to arrive from one's own body and the environment. In fact, the net background semblance removes the necessity to form separate internal sensations generated by commonly associated stimuli. This net semblance can be viewed as C-semblance of consciousness [29,30].

A suitable framework emerging is that by maintaining background state of C-semblance during awake state, animals can associatively learn new associations. When C-semblance is maintained, it will allow induction of specific internal sensations of memory in response to specific cue stimuli from a previous learning event (Fig. 10). This provides information about beneficial or deleterious nature of an item, which is essential for survival. If new associative learning events get repeated continuously beyond certain threshold times, then semblances at their inter-LINKed spines get integrated with the C-semblance. Thus, repeated exposure to newly associated stimuli will continuously update the conformation of C-semblance and provide a subjective component of consciousness. One drawback is that once a stimulus becomes familiar, then the nervous system may not be conscious of its presence. This may bring some survival challenges. For example, the system may not pay attention to commonly available food items. This may have led to the introduction of separate internal sensations of appetite and pleasure. Internal sensation of awareness of operations in a conscious mind can be viewed as a sub-domain within the larger domain of C-semblance. Only very few operations can be carried out in a conscious mind at one time. The arrival of any additional sensory stimuli during these operations may generate appropriate motor actions without conscious awareness of such actions.

Synchronous activation of nearly 10 to 50 neighboring glutamatergic synapses triggering a local regenerative potential at the dendritic regions is a dendritic spike [23,65]. It is suitable to be explained as lateral activations of spines within an islet of inter-LINKed spines and is likely contributing to C-semblance. Observation of a waveform of dendritic calcium spikes near the cortical surface [66] matches with anticipated oscillating extracellular potentials by the IPLs contributing to C-semblance. In the background state of mind formed by C-semblance, internal sensations of perception and memory take place. Explanation for several features of visual perception and presence of comparable circuitries in remote species were described previously [28].

3.2. Phantom limb and referred pain explain retrograde extrapolation for qualia

Phantom sensation from a lost limb can be explained as follows. Sensory inputs from different locations that belong to the same dermatome (area of skin from where sensory inputs propagate to the sensory neurons of one spinal segment) reach the neurons of the same spinal segment. Examination of dermatomes of the leg shows that all the sensory roots also innervate either lower abdominal or gluteal regions. Stimuli arriving from these regions can reactivate IPLs in the cortical regions and semblance of both their locations and sensory qualia are generated by natural retrograde extrapolation from the laterally activated inter-LINKed spines (see Fig. 8). The sensory content of the semblance involves regions where extrapolations reach. This is expected to generate virtual sensory features of the limb from where sensations were arriving in the past and explains how phantom limb is sensed.

Referred pain is pain felt in a remote area different than an injured area. It may or may not be innervated by the same spinal roots that innervate the injured area. A typical example is referred pain felt in areas other than left side of the chest during myocardial infarction (heart attack). In addition to the excitation of spinothalamic tract cells in the cervical (except C7 and C8) and upper thoracic segments, afferent information is also carried through the vagal nerve to C1-C2 region [67]. Afferent routes through which stimuli propagate from a site of injury (that includes vagal

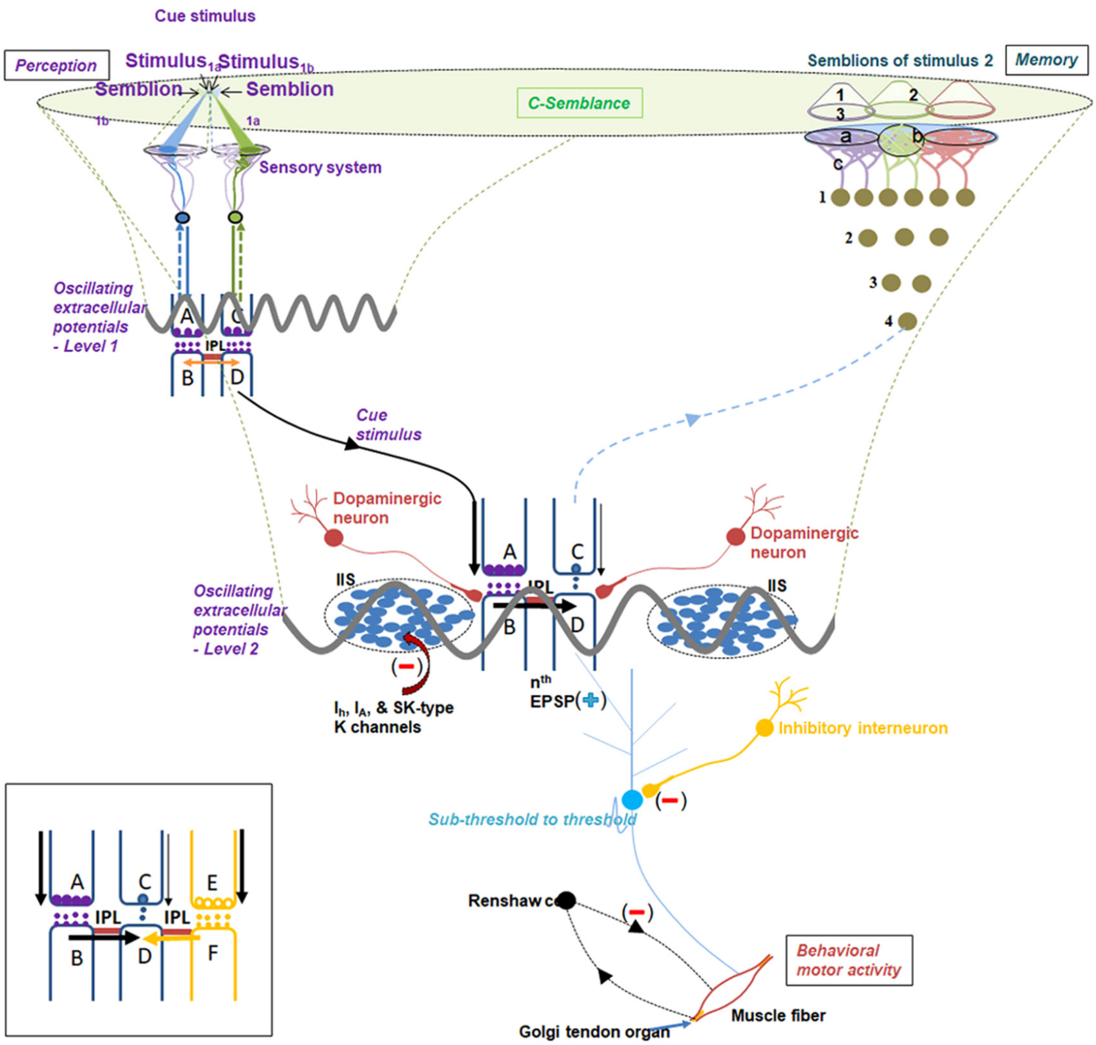

Fig. 10. A framework for the functional organization of the nervous system by the IPLs and their modifications. On the left upper corner, cue stimulus generates internal sensation of perception at the corresponding cortex. Further propagation of activity to the location of its previous convergence with a second associatively learned item leads to the activation of synapse A-B (middle area of the diagram) and cause incidental reactivation of previous associative learning-induced IPL B-D between spines B and D of two excitatory synapses. This elicits an internal sensation (semblance) at inter-LINKed spine D of memory of second associatively learned stimulus, which is shown at the right upper corner. The sensory identity of the semblance for memory is estimated by identifying the minimum sensory stimuli that can activate presynaptic terminal C as shown in Fig. 8. Propagation of depolarization during IPL reactivation and synaptic transmission in perpendicular directions contribute to the vector components of the descending slope of oscillating extracellular potentials. Any abnormal excitability of terminal dendrites is prevented by the activation of I_A, I_h, and conductance through SK-type potassium channels. Potentials arriving at inter-LINKed spine D propagate to the soma of neuron (N) of postsynaptic terminal D. If neuron N or one of its higher order neurons is a motor neuron, then it leads to a matching behavioral motor action. Oscillating extracellular potentials activate several upstream neurons. Among these, motor neurons are expected to be kept at subthreshold states by inhibitory interneurons. When the arrival of a cue stimulus provides additional potentials to activate a neuron held at sub-threshold state, it can lead to an associated behavioral motor action. These motor neurons are further fine-regulated at their output levels by inhibitory interneurons. Motor response is perceived by the system in the form of proprioception or perception of speech that provides feedback about the motor actions taken in response to perceived cue stimulus. Continuous lateral activation of inter-LINKed spines for common shared associative stimuli from the body and environment provides background state of C-semblance that provides a framework for consciousness. Circles: in army green - excitatory neurons; in brick red - dopaminergic neurons; in yellow - inhibitory neurons. IIS: Islet of inter-LINKed spines. Neuronal orders are marked from 1 to 4. **Inset**: If postsynaptic terminal F of an inhibitory synapse E-F is abutted to inter-LINKed spines B and D of two excitatory synapses, they can form inter-LINKs with each other upon simultaneous activation. When the inhibitory synapse is activated, arrival of a stimulus at presynaptic terminal A will lead to mixing of depolarization and hyperpolarization at inter-LINKed spine D. These are inferred from matching electrophysiological finding of LTD in nucleus accumbens and lateral habenula. This will result in alteration of semblance occurring at inter-LINKed excitatory spine D and is expected to generate internal sensations of pleasure and reward respectively at the corresponding brain regions.

nerve) determine the locations where retrograde extrapolation from the laterally activated inter-LINKed spines will reach (see Fig. 8). This can explain referred pain of myocardial infarction, for example, in the upper left abdomen.

3.3. Generation of different types of internal sensations in the mind

It was previously viewed that the dimensionality of mind can be understood scientifically [68,69]. Very large number of internal sensations such as hunger, thirst, pain, pleasure, anxiety, stress, fear, intentionality, and other conditions such as motivation, aversion, and feelings of reward are generated within the mind. It is reasonable to expect that they can be explained in terms of special semblances that are induced at specific locations in the nervous system due to special circuit features, the type of neurotransmitter released at the arrival of certain environmental stimuli, and also by the pathological conditions of the system. One method that can be used to understand the nature of semblances in these brain functions is to relate them with the semblance for memory. Also, by relating associated electrophysiological changes at those locations with that occurring at locations responsible for memory, it will become possible to understand the nature of different internal sensations.

Long-term potentiation (LTP) is an electrophysiological finding at locations where sensory stimuli converge after they propagate through several orders of neurons and it has shown several correlations with learning and memory [31]. By comparing the modifications in circuit features and the corresponding changes from LTP, it is expected to understand the conformation of semblances induced at those locations and their differences from that of memory. With this aim, two brain regions having specific circuit features and electrophysiological properties - nucleus accumbens (NAc) and lateral habenula (LHb) were examined [27].

A peculiar feature of NAc is that alongside the synapses from excitatory inputs, inhibitory inputs also synapse with different dendritic spines of medium spiny neurons. Inhibitory neurons have been examined for their role at the neuronal output level [70,71], dis-inhibitory control [72], and inhibition of circuitries at the input (dendritic spine) level [73,74]. In the latter case, it can lead to a new feature different from its inhibitory functions. Since spines of medium spiny neurons of NAc receive either excitatory or inhibitory inputs, IPL formation between these spines that belong to different neurons is expected to occur. Hyperpolarization of spines at the inhibitory synapses can lead to lowering of the baseline potentials of inter-LINKed excitatory spines resulting in the electrophysiological finding of long-term depression (LTD). It is also expected to alter the conformation of net semblances to generate the internal sensation of pleasure. LHb associated with reward also show similar features [27] (Fig. 10 inset).

4. A single solution can explain findings from different levels

Operational mechanism of IPL provided explanations for very large number of third person observed findings from multiple levels matching with the constraints provided by them (Table 1). It was also possible to explain and interconnect several normal and "gain or loss of function" states of the system (Fig. 11). Furthermore, inter-connectable nature of these explanations allowed triangulations of observations made by different sub-fields of brain sciences (Fig. 12), which is considered as a necessary step to bring scientific certainty [7]. Following are some examples. IPL mechanism was able to provide time-scale matched explanations for the triad of learning, LTP induction and behavior associated with memory retrieval [31]. Similarly, it was possible to triangulate contrasting features arising from different "loss or gain of function" states. A typical example is the triad of loss of memory, hallucinations with some similarities to that in schizophrenia [40], and seizures [35] observed in neurodegenerative disorders [41]. Features of the mechanism that need mention are listed in the following subsections.

4.1. Inter-neuronal inter-spine plasticity

The IPL mechanism that progresses from the first stage to the last stage that allows its reversal after time-intervals ranging from a few seconds to years following learning (Fig. 6) can be viewed as a broad spectrum of inter-spine plasticity changes. Inter-spine membrane interaction is governed by many factors. It was reported that plasma membranes tend to get reorganized at the locations of exocytosis of intracytoplasmic vesicles [75,76]. Since membrane segments of these vesicles get integrated into the plasma membrane [77], it can increase the surface area of the cell membrane. Curvature changes at the vesicle exocytotic regions [78] can contribute to different stages of membrane fusion

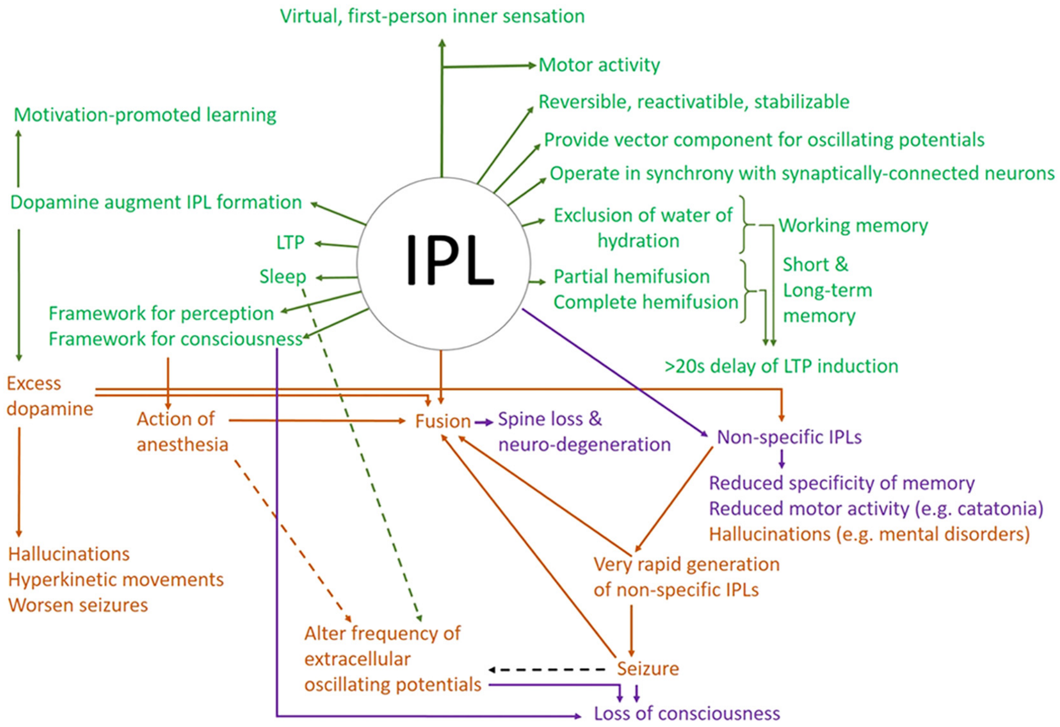

Fig. 11. Inter-postsynaptic functional LINK is at the core of the interconnected circuitry that provides different functions. Upper half shows normal functions and features of the system (in green). Gain or loss of function states (in copper and violet colors respectively) can be explained in terms of altered properties of IPLs. This allows triangulations between several findings from both normal and loss or gain of function states of the system. In addition, the ability to provide explanations for LTP and sleep further strengthens the evidence. These multiple inter-connectable features provide supporting evidence for the suitability of IPLs as the structure-function mechanism of the system. IPL: Inter-postsynaptic functional LINK.

[79] at the lateral spine head regions. Since glutamate receptor1 (GluR1) subunits of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are located at the spine head locations 25 nm from the synaptic margin [80], these are likely locations where vesicles containing these subunits get externalized, and it matches with the location of expected IPL formation. IPL mechanism can explain LTP induction [31]. Since recent findings suggest that there is no absolute requirement for a specific AMPAR subunit to support LTP [81], any vesicle exocytosis that increases the surface area of membranes at the lateral spine head region provides an explanation for their role in the IPL formation in millisecond time-scales. Motivation is associated with the release of dopamine in the dopaminergic synapses onto the spines of excitatory synapses [18], which is known to cause enlargement of those spines [82] facilitating the IPL formation. Various factors that can affect ECM properties are also expected to regulate the IPL formation and its reversal.

4.2. The mind operates only in a narrow range of frequency of oscillating extracellular potentials

Excitatory postsynaptic potentials (EPSPs) recorded from an ECM field are field EPSPs, which reflect variations in ionic changes caused by neuronal membrane potential changes [83]. The difference in the potentials recorded by two laterally separated electrodes at the same depth in the ECM shows oscillations. Continuity in the electric fields recorded from common ECM space necessitates exploring how changes in the membrane potentials are coupled between neurons [84]. Since the internal sensation of memory of an associatively learned item occurs only in a narrow range of frequency of oscillating extracellular potentials, sources of potentials that contribute some of the vector components to these oscillating extracellular potentials are expected to be associated with the mechanism of operation of the nervous system.

Experimental data from mouse barrel cortex have shown that while action potential activity was incoherent in two nearby neurons in layer 2/3, oscillations of their intracellular membrane potential (V_m) remain coherent [85]. What

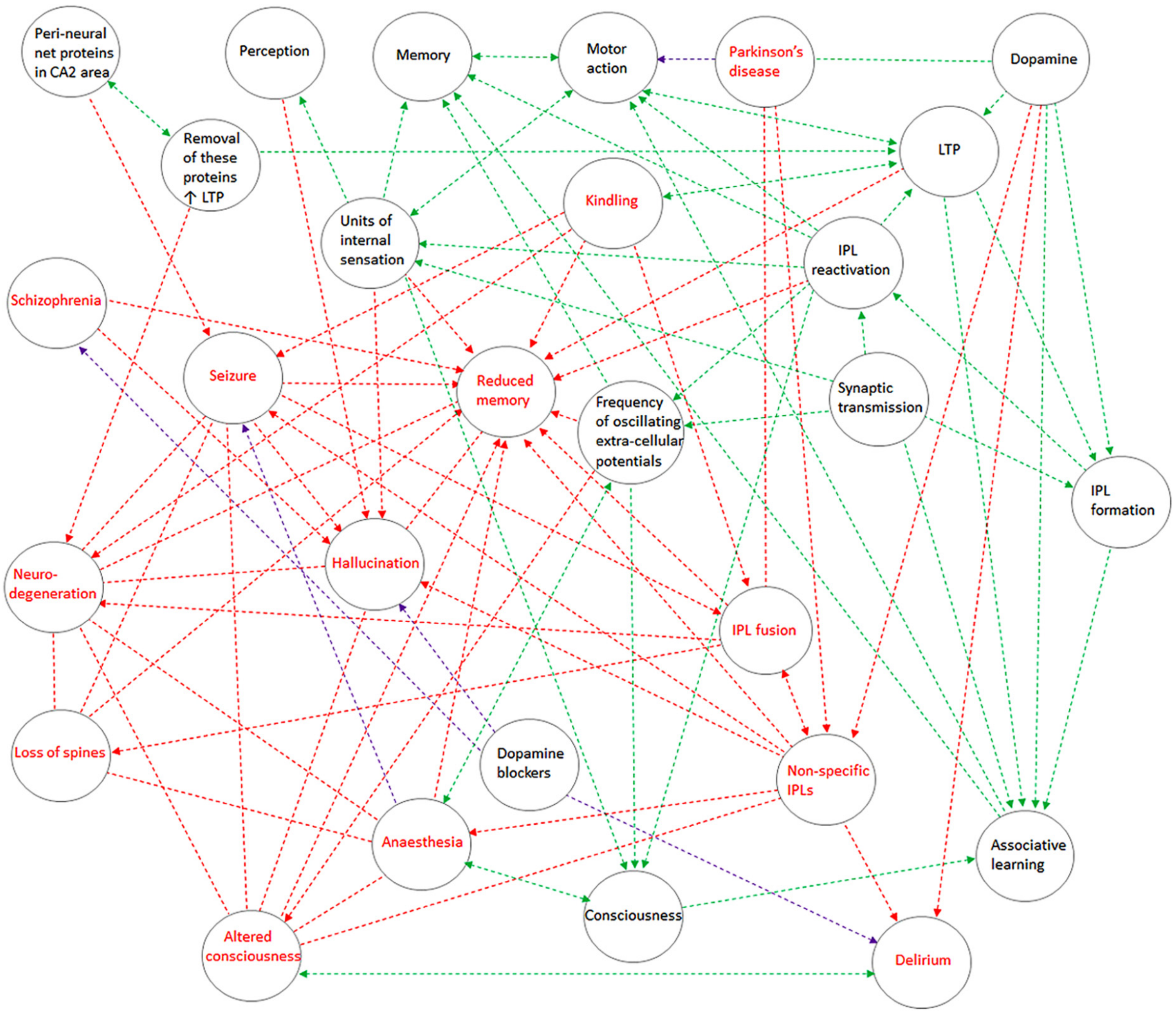

Fig. 12. IPL mechanism enables many triangulations between normal findings, loss/gain of function states and effect of pharmacological agents. Ability to inter-connect findings from multiple levels supports the existence of IPL mechanism that can be further verified. Green lines: normal functions, Red lines: pathological conditions, Violet lines: action that reduces the effect, Single arrows: unidirectional effect, Double-headed arrows: bidirectional effect.

factor might be synchronizing the membrane potentials? Previous studies have suggested that the contribution of an action potential to the extracellular potential is small (up to 1 mV) and remains in the perisomatic region [86,87] for only a short period (0.5 ms). From these observations, it is reasonable to infer that a mechanism is operating remotely from the soma to contribute to the oscillating extracellular potentials. Since potentials generated by synaptic transmission and propagation of postsynaptic potentials through IPLs occur at near perpendicular directions, their corresponding extracellular ionic effects are suitable sources that can contribute vector components to either descending or ascending slopes (depending on the location) of oscillating extracellular potentials. Other vector components are contributed by either thalamo-cortical projections or recurrent collaterals or both to the cortical neurons. This can explain why both learning and memory retrieval take place only in a narrow range of frequency of oscillating extracellular potentials, which has a major role in providing a binding (synchronizing/integrating) function (Figs. 8–10).

4.3. Role of extracellular matrix

Initial stage of IPL formation depends on the exclusion of water molecules from the inter-neuronal inter-spine space. The rapid formation and reversal of this type of IPL requires dynamic ECM features. Hence, properties of

ECM can influence how efficiently learning-induced changes take place. In this context, properties of ECM that contains mostly anchored proteins [88] is a determining factor in the formation and reversal of IPLs especially for working and short-term memories. Studies of the properties of ECM [89], particularly that of molecules such as glycosaminoglycans [90] that are highly negatively charged for holding ions and water between abutted spines are expected to provide information about the formation, reversal, and maintenance of IPLs. Increased glymphatic flow through ECM volume during sleep [91] matches with the expectation that in the absence of learning, spines remain at their lowest size possible during sleep. An increase in ECM volume due to oedema can reduce the ability to form and maintain IPLs for generating a background C-semblance, which can lead to alterations in consciousness. Changes in the ECM properties and accumulation of abnormal proteins or deposits in the ECM in neurodegenerative disorders can alter the normal generation and function of IPLs.

4.4. Circuitry that generates mind is the primary circuitry

Since the generation of internal sensation of different higher brain functions within the mind is the major function of the nervous system that has been undergoing fine-tuning throughout evolution, IPL circuitry that provides this function can be regarded as the primary circuitry. The extreme degeneracy of inputs in firing a neuron [22] shows that a readily observed firing by synaptically-connected neurons can occur by combination of inputs in the order much higher than 10^{100}. Furthermore, the system is expected to hold several neurons at sub-threshold levels so that few or even a fraction of one postsynaptic potential arriving through IPLs are expected to fire those neurons. Due to these reasons, it is not possible to generalize that neuronal ensembles encode internal sensations of any higher brain function. Instead, this can only be viewed as a correlated finding. Actual mechanism that generates mind should be able to explain how this correlational finding is manifested.

4.5. Substantive nature of sleep for maintaining normal mental functions

A memory is a hallucination of a sensory stimulus [16] that can be induced in response to a cue stimulus. Necessity for maintaining a dominant state of depolarization of the inter-LINKed spines by their presynaptic terminals to induce hallucination is explained in subsection 2.2. A naturally evolved system is expected to have mechanisms that maintain and optimize this dominant state. Continuous quantal release of neurotransmitter molecules at every synapse, at all times including sleep, can re-establish this dominant state so that the inter-LINKed spines can be tricked during the daytime to hallucinate to generate memory [25]. There is beauty in the evolution of physics of mind that occurred in perfect harmony with the day and night conditions on Earth. Dreams occur during rapid eye movement (REM) stage of the sleep cycle, which is maximal at the end of sleep. It is possible that reactivation of very large number of IPLs to laterally activate their inter-LINKed spines during this stage generates a net semblance that provides a special internal sense of consciousness. During this stage, lateral activation of inter-LINKed spines is likely responsible for inducing different internal sensations of dreams.

4.6. Language is an operation in the mind and speech is motor output

The first step in language processing involves perception of sounds along with a) their associative learning with other sounds or other types of stimuli and/or, b) generation of internal sensation of retrieved memories of previous associations. This is also expected to contribute potentials for generating motor movements of tongue muscles to produce sound to communicate the internal sensations to other people (semantics of language are delivered as syntax of speech), which is often regulated by information from other learning events. From subsection 1.2 we have seen that there should be provisions for specific coding for each association and formation of clusters of coded associations within the system. Learning of a language starting from its alphabets onwards leads to the formation of IPLs, which will eventually generate very large number of islets of inter-LINKed spines. Clusters of inter-LINKed spines can form mega-clusters and can operate in a large combinatorial manner to form libraries of information storage. Since a very large number of combinations of internal sensations are possible through the IPL mechanism, it can provide an explanation how an unbounded number of meaning-bearing elements can be associated with objects in the environment [92,93]. At this point one may ask, “Why only humans have developed an advanced type of language?” A feasible explanation is given in section 5.

4.7. What do BOLD signals of fMRI inform about the mind?

Many higher brain functions are being studied using fMRI. How do operations of mind relate to the blood oxygenation level dependent (BOLD) signals of fMRI? Both associative learning and memory retrieval can take place in milliseconds. But positive BOLD signal change takes nearly few seconds following cognitive performance [94]. Hence, it is necessary to understand the temporal relationship between normal operations of mind and the delayed occurrence of oxygenation in these locations. The emerging questions are, “What is the functional role of oxygen in these locations?” “Can IPL mechanism provide a testable explanation for oxygen release that occur after a significant delay compared to milliseconds needed for both learning and memory retrieval?” This becomes highly important since most memories are working memories that last only for a few seconds, necessitating fast reversal of most of the newly formed IPLs. It can also be observed that working memory lasts for durations that roughly match with the duration of the presence of BOLD signals following learning (more than thirty seconds to stop following cognitive performance and nearly ten seconds to stop following neuronal activity at the same location [94,95]). In this context, it is necessary to examine whether delayed oxygenation has any role in reversing IPLs. Since hydration exclusion is a high energy requiring process [96], the initial stage of fast reversal occurs by rapid reinstatement of hydration between the spine membranes. Even though oxygen is used for oxidative phosphorylation in mitochondria for generating ATP, it is necessary to examine whether oxygen leads to an oxidation-state dependent reversal of IPLs. At a deep level, one can even ask whether in mammals lack of enzyme to synthesize vitamin C [97], which is a reducing agent is associated with these changes.

4.8. Neurodegenerative changes alter the mind

It is expected that one end of the spectrum of IPL mechanisms is IPL hemifusion, which is an intermediate stage of fusion. It is expected that this IPL mechanism has robust checkpoints to prevent its conversion to a fusion state. Any defect in this regulatory mechanism or alteration in membrane lipid composition can lead to the conversion of IPL hemifusion to fusion. Since gene expression profiles of adjacent neurons are different [98], any mixing of cytoplasmic contents between two adjacent neurons is expected to overload the ubiquitination process that removes abnormal proteins and leads to protein precipitation. Even though this IPL fusion is expected to reverse back, like what is observed during fusion pore closure during exocytosis [99], persistence of fused areas can trigger different neurodegenerative changes [41]. Since IPL fusion can lead to loss of spines and eventual loss of neurons, it can lead to alterations in the net semblance. This is expected to change both the background states of mind and the ability to induce internal sensations in response to different cue stimuli.

4.9. Mental disorders are disorders of the mind

Formation of non-specific IPLs can lead to non-specific semblances resulting in memory problems. An ordered lateral activation of non-specific sets of inter-LINKed spines can lead to pathological hallucinations [40]. An observation of mention is the effectiveness of electroconvulsive treatment (ECT) that alleviates symptoms of endogenous depression. Based on the present work, high energy used during ECT can generate very large number of non-specific IPLs like that were explained to occur both during LTP induction [31] and seizures [35]. This can lead to many non-specific semblances, which will alter conformation of net semblance of internal sensations responsible for depression and will reduce depression. The same process also can explain previous reports of cognitive impairments following ECT [100,101]. Change in the method of delivery of current in modern ECT procedures [101] may explain why cognitive side effects have reduced [102].

4.10. IPL mechanism shows features of an evolved mechanism

Key milestones during ontogeny of the nervous system can be used to verify whether the IPL mechanism has features of an evolved mechanism. Diffusion of dye between the neuronal cells at two instances in a specific stage of ontogeny [48,103] indicates that transient inter-cellular fusion occurs at this stage. Why would evolution retain this event? What advantage does it provide? Secondly, 70% of cortical cells were found dying by embryonic day 14 in mice [49]. Evolutionary conservation of this finding also indicates that the surviving neuronal cells have developed certain adaptive mechanisms. Even though the studies were not undertaken to examine whether the above two findings occur at the same time, it is reasonable to view that transient inter-cellular fusion is likely triggering some adaptive mechanism to prevent future inter-neuronal fusion and cell death. This is supported by the following. Presence of protein complexin known to stabilize hemifusion stage of the fusion process [50] within the spines [51] can prevent potential inter-spine fusion. Since both learning and experimental findings of LTP can be explained in terms of IPL mechanism [31], and since one end of the spectrum of IPL change (inter-spine hemifusion) can get converted to a pathological state of IPL fusion, findings from ontogeny support the evolution of IPL changes (Fig. 6) [47]. Further support for its evolutionary basis comes from its ability to explain the functional significance of large surface area of the human cortex (see section 5).

5. Theory of continuity of mind and the ability to generate hypotheses

Even though humans and non-human primates have similar cognitive domains, humans can generate abstract theoretical concepts. “What made humans, so unique?” According to Subiaul et al. [104], the best possible answer lies in the theory of continuity of mind by Charles Darwin [105] that has two components. 1) The mind is subjected to selection and changes over time, and 2) having directly descended from other living organisms, human and non-human animal minds have only quantitative but not qualitative differences. This has led to the questions, “Can quantitative differences in the sensory systems produce qualitative differences?” [104]. “How does an increase in brain size provide additional functions?” One hypothesis is that as brains get bigger, more specific aspects of sensory stimuli may provide the correlational structure necessary to allow segregation of new, functionally specific cortical areas [106]. The finding that neocortex has undergone expansion primarily in the surface area rather than thickness since mammalian ancestor originated nearly 250 million years ago [107] needs an explanation how the increase in surface area, which increases the number of laterally located neurons provides advanced cognitive abilities. Then only Darwin’s views will be supported. This study also found that cognitive skills resulting from general intelligence have strong empirical correlations with brain size and executive functions.

Beginning with the theory of evolution by Darwin, several works examined selection based on an increase in the brain size [108]. Humans and macaque monkeys diverged from a common ancestor nearly 23 million years ago [109]. The ratio between the surface area of neocortex of humans and macaque monkeys is approximately 10:1, without having significant differences in thickness [110] or cyto-architectural organization [111]. How did this finding contribute to higher cognitive abilities of humans? Compared to other primates, humans have higher order forebrain systems that have undergone major modifications [112]. However, prefrontal regions of both humans and non-human primates hold about 8% of cortical neurons [113]. Furthermore, one study has shown that the size of human frontal lobes has increased only proportional to the increase in size of other cortices [114].

Can a tenfold increase in the cortical surface area explain the increased cognitive abilities of humans compared to macaque monkeys? Since surface area is large, human nervous system can form very large number of IPLs and islets of inter-LINKed spines that allow it to make very large number of associations. This leads to the formation of relatively more and larger islets of inter-LINKed spines in the brains of humans compared to that of macaque monkeys. Novel associative learning events can lead to the inter-LINKing of spines with the already inter-LINKed spines within the islets of inter-LINKed spines. When a specific cue stimulus arrives at one of the inter-LINKed spines, it induces interconnected semblances at all the inter-LINKed spines including those spines located farther away within an islet. Even though inter-LINKs between two spatially distant spines within a large islet of inter-LINKed spines was not the result of a direct associative learning, the relationship between their internal sensations through other inter-LINKed spines within a large islet allows the system to interconnect between two previously unrelated items. It is to be noted that similar connections through inter-LINKed spines of different islets should be present in enough locations to generate net integral of internal sensations of the relationship of sufficient strength that generates a hypothesis (Fig. 13). In other words, ability to make a hypothesis depends on the number of associative learning events carried out in the past, especially those of unrelated subject areas. This ability can be increased by continued associative learning from unrelated knowledge areas. Hypothesis building ability will be limited by the maximum number of inter-LINKed spines within the islets that can be formed in a nervous system and the need for separating unrelated islets of inter-LINKed spines.

At every layer of the cortex, there are more neurons arranged laterally than vertically. Similarly, compared to the thickness of the synaptic region between cortical layers, the span of their lateral extensions throughout the cortex is

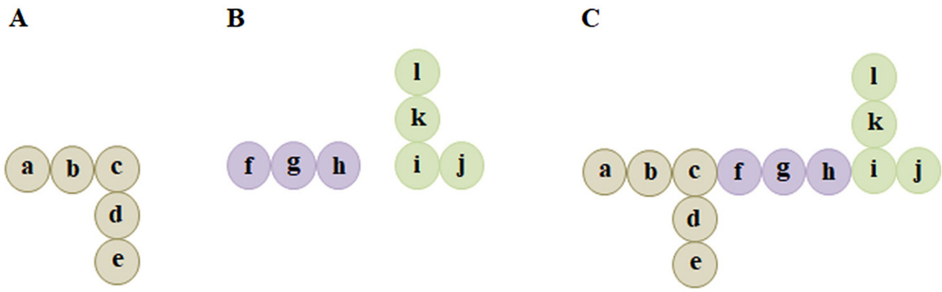

Fig. 13. Hypothesis generation depends on the clustering of different islets of inter-LINKed spines and this ability is proportional to the cortical surface area. **(A)** Generation of one islet of inter-LINKed spines (see Fig. 7B) formed by different associative learning events in one knowledge area. When a stimulus arrives at postsynaptic terminal c, it causes lateral activation of other inter-LINKed postsynaptic terminals a, b, d and e within that islet and generates semblances of associatively learned items from them. **(B)** A hypothetical condition where the nervous system can be exposed to two different areas of knowledge. This is expected to generate two separate islets of inter-LINKed spines, some of which can take place in the neighboring locations. **(C)** Condition when a single nervous system is exposed to all the above three sets of knowledge areas. In addition, associative learning events that involve abutted spines that belong to different islets can also occur. These result in the formation of inter-LINKs between c and f, and h and i. This has now created a large islet of inter-LINKed spines. When a stimulus arrives at postsynaptic terminal c, it can reactivate all the IPLs and laterally activate all the inter-LINKed postsynaptic terminals a to l of this large islet. This allows the system to relate between the internal sensations induced at all the postsynaptic terminals from a to l and allows to generate hypotheses (Note that a threshold number of units of internal sensations from different locations will be needed to generate an internal sensation). Since the stimulus that activated postsynaptic terminal c cause lateral activation of l only through a single inter-LINKed postsynaptic terminal g, then the system can make the prediction that c is related to l only through g (and therefore through the sensory stimuli that activate them). Note that new knowledge areas can emerge in the future and it may become possible to establish interconnections between c and l through a different route. A system can undertake continued associative learning of multiple unrelated knowledge areas only if non-LINKed spines are present in the immediate neighborhood of islets of inter-LINKed spines to which new sensory inputs can arrive during learning. Since the expansion of an islet by inter-LINKing more spines can occur in a lateral direction, learning abilities are proportional to the cortical surface area. For different animals having the same number of neuronal layers, cognitive abilities will be proportional to their cortical surface areas. This explanation matches with the Darwin's theory of mind.

very large. Hence, both the number and size of the islets of inter-LINKed spines will increase proportional to the cortical surface area. Based on the inter-LINKs that can be formed between spines that are already part of different islets of inter-LINKed spines, each hypothesis is expected to find previously unknown relationships and make testable predictions (Fig. 13). Since hypothesis generation depends on simultaneous generation of internal sensations during the arrival of a stimulus, a cortex with large surface area that has undergone very large number of associative learning events is superior to those with small surface area. Based on this explanation, Darwin's theory of mind [105], and Finlay and Brodsky's interpretations [106] are correct. Furthermore, the above property enables systems with large surface areas to perform a very large number of combinatorial outputs for the function of language. Another evidence is the finding of more synapses per neuron in layers II and III in humans than in rats and mice [115]. Increased number of synapses indicates the presence of increased number of spines, which will lead to a proportional increase in the number of IPLs formed. Such differences may contribute to higher cognitive abilities of humans compared to that of chimpanzees [116].

6. Testable predictions

Predictions are expected from any causal mechanism for a phenomenon [8]. The IPL mechanism provides the following testable predictions that can be verified.

- On the dendritic spines that have surface areas ranging from 0.61 to 3.14 μm^2 [117]. IPLs are expected to have areas of only few squire nanometers. Hydration exclusion, which is the initial stage of IPL reverses back quickly. This can be verified by developing dedicated techniques.
- IPLs formed by partial and complete hemifusion can be verified using high-resolution microscopes. (Note that any method to expand ECM will break apart different types of IPLs.)
- Stabilization of hemifusion stage of IPLs by different mechanisms will be present [14]. Presence of stabilized IPLs formed by complete hemifusion can be verified by electron microscopy.

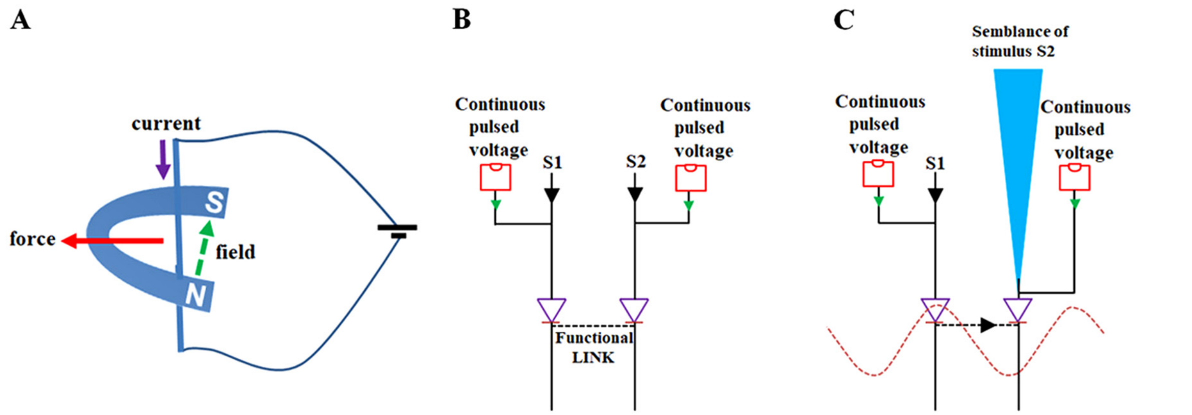

Fig. 14. Comparison between first principles of electromagnetism and semblance induced at the inter-LINKed spine. **(A)** When a conductor carrying current cuts the magnetic field in a perpendicular direction, the conductor deflects in a perpendicular direction with a force (rotational force in motors). Similarly, when a conductor (not carrying current), is made to cut the magnetic field (using windmills, waterfalls), current flows through the cable (not shown here). **(B)** When anodes of two diodes continuously provide pulsed current to their cathodes and when sensory stimuli S1 and S2 arrive at those anodes, it will result in the flow of current to the cathodes and a functional LINK is formed between cathodes of two abutted (not shown) diodes (designing a circuit and suitable components are necessary). **(C)** Later, when one stimulus S1 reactivates the LINK, it will laterally activate the inter-LINKed second cathode and induce semblance of second stimulus S2 as a system property of systems where current flow from anode to cathode and through the functional LINK provide vector components for descending slope of oscillating extracellular potentials (ascending slope is provided by recurrent collaterals and input cables traversing through the region of diodes (not shown)) that binds the operations of the system together (see subsection 4.2).

- Artificially changing the frequency of oscillating extracellular potentials in the olfactory glomerulus in the fly *Drosophila* will alter smell perception [28].
- Injecting different neurons, whose spines can undergo IPLs, with different lipophilic fluorophores to stain their membranes [118] followed by repetition of an associative learning event is expected to demonstrate partial and complete hemifusion stages of IPL formation [13].
- A robust mechanism by specific SNARE proteins (such as Q-SNAREs) will arrest membrane hemifusion (possibly by interactions with postsynaptic proteins such as complexin and syntaxin-3) [14].
- Different types of IPLs will occur following LTP stimulation. A reversal of this process will occur during the reversal phase following LTP induction [31].
- For a given distance between the stimulating and recording electrodes, strength of LTP induced at different locations will depend on the number of inter-spine LINKs formed during the delay time after stimulation [31].
- Kindling will generate inter-spine fusion in the synapse-rich area between the electrodes [35].

7. Physics of mind

Like the effect of electromagnetism that generates either current or mechanical force, basic operation of the IPL that induces units of internal sensations along with provision to initiate motor action can be viewed as the first principle of the nervous system functions. A comparison between electromagnetism and induction of internal sensation is given in Fig. 14. Electrically separated interface between the membranes of abutted spines with very thin ECM forms a "writable" medium where associations between stimuli from the environment can make their mark. This is the basis of the formation of IPLs. For the duration IPLs are maintained stable, the written code will remain stable, and it will be possible to access stored information as first-person internal sensation of memory. In agreement with the view of the psychological space as a coordinate space having some dimensions [119], starting a science of mind [68] using the IPL mechanism is possible.

7.1. Replication in engineered systems

The gold standard test of replication of the mechanism in engineered systems will have a dual benefit of verifying the IPL mechanism and transferring the knowledge to artificial systems that can assist life on Earth. Since there are

1.12 million cataloged and 9.92 ± 1.1 million predicted animal species on Earth [120], it increases the probability that trial and error methods to assemble electronic circuit units will lead to the generation of a system that mimic one of their nervous systems. New methods will be necessary to verify their ability to generate internal sensations [121]. Main expectation from undertaking these studies is to understand the principle of computation of semblions for a given system having specific patterns of synaptic connections and IPLs between neuronal processes. When we reach this stage of progress, the physics of mind will become clear. When replication in the engineered systems move towards higher levels of organization, discovery of the principles of physics of self-organizing mind [122] can be used to examine the system operations.

7.2. The physics of mind can influence physics

Physicists have been debating whether an objective understanding of the external world requires making corrections for the subjective experiences of perception [123,124]. The measurement problem in quantum mechanics refers to the difficulty in understanding the probabilities of location of a photon or a sudden transition of an electron to a definite location when a measurement is carried out. Some physicists argue that if probabilities are subjective judgments, then quantum states are subjective judgments within the mind [125]. Since there are also concerns about the influence of perception on measurements [126], it leads to the question, “Does the mechanism of visual perception have any role in the collapse of wave function that has been investigated by quantum mechanics?” A realistic hope is that both theoretical examination of this work and experiments to verify the mechanism of generation of first-person internal sensations of perception [28] will provide more insight.

8. Conclusion

It was necessary to work in the absence of direct empirical evidence to derive a solution for the operational mechanism of first-person internal sensations. To find the solution for a system that needs explanations for all the findings from multiple levels, it is necessary to use constraints from all those findings to arrive at the solution. This is an inevitable fact and is the most important feature of the approach used in this work. At the center of this investigation was the search for a solution-point that can spark hallucinations responsible for memory [16]. From Fig. 2, the solution is likely to be an unexpected one in comparison to most of the findings observed by different sub-fields of investigations. The solution also needs a multi-connector property (see Fig. 11). To view how the solution must be providing a unifying role at the center, it is necessary to examine its relations with observations from different fields of brain science simultaneously. It is expected to provide a picture similar to Fig. 2D. Ability to interconnect depolarization evoked by a cue stimulus with the reactivation of learning-induced mechanism, induction of units of internal sensations and provision of potentials to generate motor actions in millisecond time-scales provide the anticipated multi-connector property to the derived IPL mechanism. IPL mechanism also matches with the anticipation that a new domain item may become necessary instead of reduction of findings from one field alone during inter-field integration to bridge different fields of science [127]. As expected, the derived solution of IPL mechanism is a new domain item, which was found only subsequent to the identification of unitary structural locations that were then examined for properties that can induce a unitary mechanism.

Tracing this mechanism back to the early stages of its evolution with the help of findings from ontogeny informs that an accident that started tricking the system to hallucinate about previously associated items in a cue-specific manner provided survival advantage. It was the beginning of an operation that eventually generated the mind. Through many evolutionary steps, circuit organization was fine-tuned to match the internal sensation of memory of items with the actual sensory features of those items. Animals that were able to refine IPL circuit mechanisms to generate hypotheses and take appropriate motor actions had a survival advantage. Due to this reason IPL circuitry that generates the most important and unique function of the nervous system - generation of internal sensations, can be viewed as its primary circuitry. Circuit features that generate behavior as an optional output, determined by internal sensations, is its secondary circuitry. Even though this is a significant deviation from previous approaches, it provides a much-needed explanation why we were having difficulties in understanding this system.

It has been a long journey starting from the circumstances and accidents that initiated sparking of internal sensations within an assembly of cells and its refinement over millions of years that has brought us to this point where it is possible to read this print to make internal sensations of the mechanism that it describes. Non-sensible nature of first-person internal sensations by third-person observers challenged us to seek a new method to discover its solution. Since there can be only one unique solution, the natural expectation is that this solution must be able to explain disparate findings from multiple levels in an interconnected manner. Fulfilling these expectations provides proof for the claims that the present work has submitted. Verification of testable predictions and undertaking of the gold standard test of its replication in engineered systems are the next necessary steps. Since this work holds a high level of optimism to unify findings from different sub-fields of brain science, both the new method used here and the solution that was obtained must be subjected to thorough scrutiny with an aim to falsify its claims.

Declaration of competing interest

Author holds a U.S patent (number 9477924) that pertains to an electronic circuit model of the inter-postsynaptic functional LINK described in the work.

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