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Current Aging Science, 2020, *13*, 136-152

RESEARCH ARTICLE

A Derived Mechanism of Nervous System Functions Explains Aging-Related Neurodegeneration as a Gradual Loss of an Evolutionary Adaptation

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ARTICLE HISTORY

Received: July 04, 2019
Revised: November 30, 2019
Accepted: December 10, 2019

DOI:
10.2174/1874609813666191223092451

Abstract: ***Background*:** Solving the nervous system requires understanding how it generates inner sensations of "mind" within it. It was possible to derive a hypothesis of brain functions where the formation of a spectrum inter-postsynaptic (inter-spine) functional LINKs (IPLs) are the key structural changes responsible for encoding at the time of learning and are used for inducing the inner sensation of memory, both taking place at millisecond timescales. Since stages of ontogeny reflect possible stages of evolution, it is possible to examine whether IPLs have features of an evolved mechanism.

***Objective*:** To examine whether 1) IPLs have features of an evolved mechanism, 2) significant neuronal death during ontogeny leads to evolutionary adaptations for preventing cell death among the surviving neurons, and 3) loss of these adaptations lead to cellular changes that can cause aging-related neurodegeneration.

***Methods*:** Key milestone changes of the ontogeny of the nervous system were examined to test whether they match with a feasible sequence of steps that lead to the formation of IPLs.

***Results*:** Several developmental stages can explain a probable sequence of events that lead to IPL formation among synaptically-connected neurons. When internal sensations generated by the IPLs started providing survival advantage, evolution has started preserving the IPL circuitry. A stage of inter-spine fusion possibly leads to a) significant neuronal death during the early stages of development, and b) trigger an adaptation in the surviving cells to stabilize and prevent the IPLs from undergoing fusion. Since there are no irreversible steps for maintaining the stability of IPLs, aging-related factors may destroy the adaptation mechanism and destabilize the IPLs predisposing them to cause neurodegeneration.

***Conclusion*:** The derived testable IPL mechanism that can explain nervous system functions is capable to have evolved. An adaptation to prevent IPL hemifusion from progressing to fusion is likely the last stage of nervous system evolution. Since the IPL mechanism is utilized during every event of learning, any aging-related factors that can weaken this adaptation can cause IPL fusion and lead to neurodegeneration.

Keywords: Inter-cellular fusion, inter-cellular hemifusion, exocytosis, internal sensation, inter-spine fusion, spine loss, apoptosis.

1. INTRODUCTION

Defects of different organs are treated by either replacing them or their functions by artificial means. However, currently, it is not possible to replace the functions of the nervous system. This is primarily because we still do not understand its main function of the generation of inner sensations, such as those that occur during perception and memory that we refer to as occurring in our "mind". Conventional approaches first try to understand the mechanism of function of a system and then use that knowledge to examine its evolutionary stages. However, difficulty to understand how inner sensations are generated in the brain has prompted to take approaches in the opposite direction by asking, "Does understanding the cause and mechanism of evolution of this organ help to decipher how it works?" [1]. These opposite approaches that have not yet succeeded to solve the nervous system reveal the nature of difficulties. How is it possible to break this impasse?

Ontogeny is the development of a single individual, or a system within the individual, from the stage of the fertilized egg to maturation and death [2]. The sequence of events during the ontogeny of a species is considered to represent the sequence of changes that its ancestors traversed during evolution with the exception of two types of deviations - change in position and change in the order of succession of changes

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[3]. Hence, the key findings of ontogeny can help to verify whether any new circuit feature that explains the generation of internal sensations is an evolved mechanism or not. Since evolution cannot make the nervous system to unwire to "start over," the solution that it has reached is constrained by its evolutionary history [4]. This provides a unique opportunity to make an attempt to solve it. Furthermore, it is viewed that the existence of a specific mechanism of operation of the nervous system can be understood only by examining how non-adaptive determinants have guided its evolution [5]. Towards this goal, evolutionary preservation of death of even up to 70% of the cortical cells at one stage of development [6] can be examined to understand how it matches with the stages of evolution of the operational mechanism. Such an approach will also satisfy the views that when there is cell death during development, it is necessary to attempt to uncover the benefits to be gained by such loss [7] and that it is important to know the exact role of neuronal cell death in establishing neuronal connectivity for executing its functions [8]. It will also help to test the view that evolutionary conservation of the molecular mechanisms underlying apoptosis has a purpose [9].

How to move forward from this current state of difficulties to make progress? Since the main problem in examining evolution of the brain is the difficulty to study it directly [10], the only method to overcome this difficulty is to seek indirect approaches. One method is to first derive a theoretically feasible testable hypothesis of a mechanism, followed by examining how such a mechanism initiates and optimizes its functions as the nervous system undergoes a specific sequence of evolutionary stages. Even though it may look like a convoluted approach, such a method is necessary to solve the nervous system. If this becomes successful, then it provides an exceptional opportunity to examine the last stage of evolution of the system to understand how it influences the life-span of neurons. Building a testable hypothesis of brain functions will reach completion only by examining whether it has matching features of an evolved mechanism. This is the motivation behind this approach.

Initially operated through reflexive motor actions, the nervous system started acquiring robust motor capabilities as a prominent survival mechanism in a predator-prey relationship. Certain accidental coincidences within the system led to the generation of first-person internal sensations of memories of associations that were made in the past, along with the capability to execute appropriate motor actions for survival. Eventually, natural selection has fine-tuned and maximized the rewards by generating the best possible internal sensations of memories. Continued associative learning between a large number of items (directly) leads to a large chain of learning-induced signatures within the system. A large number of associations generate interconnections between their learning-induced changes either directly or indirectly. At this stage, arrival of one of the previously associated stimulus can generate internal sensations of not only the stimuli that were directly associated, but also of those that were not directly associated. This leads to generation of hypotheses between previously unknown associations between certain items. Verification of indirect associations improves the knowledge base of the species. Eventually, in the course of evolution, generation of robust internal sensations started dominating over the ability to execute powerful motor actions for survival. Any hypothesis of nervous system functions is expected to provide a mechanistic explanation for hypothesis building and should be compatible with evolutionary changes.

Even though changes are observed at the synapses, dendrites and even neurons themselves [11], it has been difficult to understand the evolution of the nervous system using interpretations of the available structure and function [4]. It has also been difficult to accept cortical structural patterns as the units of development and evolution [12]. Darwin's theory of natural selection [13] provides two main features that are useful while examining the evolution of the nervous system. 1) The offspring is produced with at least some heritable variations. 2) More offspring are produced than their environment can support. These criteria make some members of the offspring have fitter variations that enable them to survive better than others. Eventually, the heritable traits of fitter variations will spread in the population. Even though there is some evidence suggesting the occurrence of rapid evolution through minor changes in the existing neural circuitry [14], further progress has been difficult without understanding its most important function of the generation of internal sensations of various brain functions. This has forced us to examine a derived hypothesis of the nervous system functions for its suitability to evolve through simple steps of variations and selection to reach its present state. Examining its last evolutionary stage may provide knowledge about a wide range of late-life neural dysfunctions [15]. Since aging is the most important risk factor for neurodegenerative disorders such as Alzheimer's disease [16], the present approach is expected to provide some insights into the triggering factors for initiating their pathophysiology.

1.1. Unique Feature of First-Person Internal Sensations

Present-day nervous systems have been surviving in a predator-prey environment. Animals have different sensory systems that respond to corresponding sensory stimuli, such as light, sound, touch, taste, smell, vibration, etc. When an item or an animal (predator or prey) is close to the nervous system, different sensory stimuli from that item or animal arrive at the system almost simultaneously and generate changes at the locations where these sensory pathways converge. Later, when the item is away from the nervous system, the fastest or first arriving sensory stimulus induces internal sensations of the late-arriving or non-arriving sensory stimuli from that item. The same rule is expected while associating two stimuli from different items during learning. Thus, the key feature that differentiates the nervous system from other systems is its ability to generate first-person internal sensation of sensory features of an item (memory), when one of the previously associated stimuli is presented. First, it is necessary to find a theoretically feasible circuit mechanism that can generate internal sensations. If it becomes possible to derive a mechanism, stages of ontogeny can be examined to search for matching changes that enabled both initiation and fine-tuning of this mechanism.

An operational mechanism for memory in the biological systems is expected to generate hallucinations (inner sensation of a stimulus in the absence of that stimulus, at the time

of memory retrieval) as the basic property [17]. This directs us to examine the system for elements that can trick the system into hallucinating about the sensory features of the item whose memory is retrieved when exposed to a cue stimulus. It is necessary to examine whether such a mechanism can be evolved through simple steps of variations and selection of the fittest ones. Initially derived using logical arguments, and later verified by using constraints available from a large number of findings from several levels [18-22], the semblance hypothesis has provided evidence for a probable mechanism of operation of the system. A summary of the mechanism is given in Fig. (**1**). Key features of its operations include a) formation of inter-postsynaptic functional LINKs (capitalized to reflect its significance) (IPLs) during associative learning between two stimuli from the environment, and b) at a later time, upon the arrival of stimuli from the first item, re-activation of the IPLs generates first-person internal sensation of memory of the second item. Intentionality to feed, procreate and protect from harmful stimuli observed among lower forms of animals indicates that generation of different internal sensations is universal in nature and occurs by some modifications of the IPL mechanism.

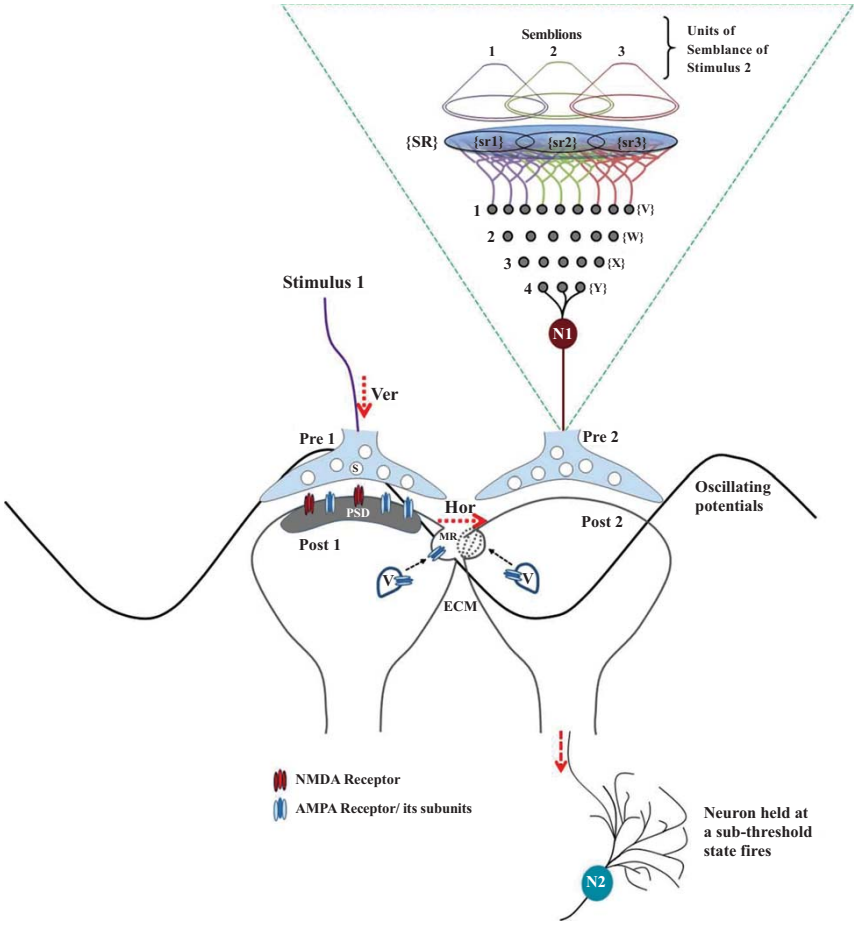

Fig. (1). Based on semblance hypothesis, learning induces inter-postsynaptic (inter-spine) interactive changes in physiological timescales of milliseconds at the location convergence of sensory input pathways. At a later time, these changes are used to generate units of internal sensations for memory. When associatively learned stimuli 1 and 2 arrive through presynaptic terminals 1 (Pre1) and 2 (Pre2) respectively at the location of their convergence where postsynaptic terminals (dendritic spines or spines) Post1 and Post2 are abutted, an IPL between Post1 and Post2 is formed. IPL changes range from removal of repulsive forces between the spine membranes to different stages of inter-spine membrane hemifusion (partial to complete) facilitated by membrane reorganization (MR) taking place at the lateral spine margins of the spine heads during exocytosis of vesicles (V) containing AMPA receptor subunits at these locations. These are expected to occur in timescales of milliseconds. At a later time, when stimulus 1 arrives at Post1, it reactivates the IPL and induces a hallucination (semblance) at Post2 that was previously activated by stimulus 2. Sensory qualia of units of internal sensations induced at inter-LINKed Post2 are determined by identifying a minimum set of stimuli (called semblion) that are otherwise needed to stimulate specific subsets {sr1}, {sr2} *etc*. of Sensory Receptors {SR} whose activation is able to depolarize Post2. This requires a natural retrograde extrapolation from inter-LINKed Post2 towards all the sensory receptors from which it used to receive inputs in the past. Semblance is a virtual first-person internal sensation of the sensory properties of the associatively learned stimulus 2 and is shown inside a dotted triangle (Note that no synaptic transmission, except postsynaptic potentials generated by quantal release of neurotransmitter molecules is needed in the circuitry within this triangle for inducing semblance at Post2). Evolutionary changes are expected to optimize circuit features to obtain the best possible computational product of all the semblions induced at several inter-LINKed spines in the system that can match with the sensory features of stimulus 2, which forms memory of stimulus 2. This computation is a system property of systems where the perpendicular directions of synaptic transmission (Ver: vertical) and propagation of potentials along the IPLs (Hor: horizontal) contribute vector components to a narrow range of frequency of oscillating extracellular potentials (shown as a waveform). ECM: Extracellular Matrix; s: synaptic vesicle (Figure modified from [19]). *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

1.2. Evolution of the Nervous Systems on Earth

For tricking the system to hallucinate (internal sensation of a stimulus in its absence) (Fig. **1**), there are some prerequisites. a) The cue stimulus is expected to trick the system by providing certain stimuli to generate a false sensation that a stimulus is coming from the item whose memory is being retrieved, b) The path travelled by the item whose memory is being retrieved should maintain a dominant state of a stream of activity along that path. Only in this context, an incidental insertion of a depolarization by the cue stimulus onto an intermediate input node or terminal (dendritic spine or postsynaptic potential), along the path through which the item whose memory is being induced has propagated in the past, will trick the system to hallucinate that it is receiving an input from the item whose memory is retrieved. Continuous depolarization of the spine head by the neurotransmitter molecules from the presynaptic terminal provides a suitable background state that can provide this expected default dominant state.

For bringing depolarization of the spine head by its presynaptic terminal to a dominant state, incidental lateral activations of the inter-LINKed spine heads by cue stimuli need to be stopped for a certain period of time. At night, visual stimuli for new associative learning events and visual cue stimuli that reactivate the IPLs for inducing internal sensations will be minimal. This makes nighttime suitable for the state of sleep. Since the quantal release of neurotransmitter molecules takes place continuously during sleep, it will continuously depolarize the spine heads. Hence, sleep can reset the state of depolarization of the postsynaptic terminal by its presynaptic terminal to a dominant state of the system [21]. In this dominant state, an incidental lateral activation of an inter-LINKed postsynaptic terminal induces hallucination (semblance) that the latter is receiving sensory inputs from the environment through its presynaptic terminal. In short, the day and night conditions on Earth have been forcing the development of an operational mechanism to evolve synchronously with them.

1.3. Theory of Continuity of Mind

Charles Darwin also proposed a theory regarding the mind [23, 24], which has two components. 1) The mind is subjected to selection and undergoes changes over time, and 2) Difference between human and non-human animal minds is quantitative and not qualitative. Latter is expected to explain why humans have the ability for abstract theoretical concepts, even though cognitive domains of human and non-human primates are very similar. It was found that neocortex has undergone expansion primarily in surface area than in thickness since the origin of mammalian ancestor 250 million years ago and cognitive skills have strong empirical correlations with brain size and executive functions [25]. Even though these findings are in agreement with Darwin's views, it raises the question, "How do quantitative differences in the system lead to qualitative differences?" [24]. Can the IPL mechanism provide an explanation? It was hypothesized that as brains get bigger, specific aspects of sensory stimuli may contribute correlational structure that leads to the formation of new functionally specific cortical areas [12]. At this point, it is necessary to find a mechanistic explanation of how an increase in the cortical surface area is related to increased cognitive abilities that are arising from different cortices.

2. MATERIALS AND METHODS

The present work examined various findings from both cell and neuronal development to assess whether the synaptically-connected circuitry that incorporates IPL mechanism can result from simple steps of variations and selection during evolution. Key ontological stages that can match with the corresponding milestones during evolution were studied. Examination was focused to understand whether there is feasibility for the occurrence of a sequence of events starting from single cells to the development and fine-tuning of the IPL mechanism to optimize internal sensations. Particular attention was given to the last stage of development (and evolution) and the nature of changes that can make the IPLs stable. It was also examined whether this stage involves a mechanism that can get degraded due to aging-related factors. Specifically, the occurrence of significant neuronal death during one stage of development was examined for mechanisms that can provide the surviving cells an ability to prevent their death during the stages that followed. Are such mechanisms vulnerable to get damaged by some aging-related factors? Only a mechanism with a perfect fit that can provide matching explanations while evolving through a sequence of variations and selection will be eligible to become the operational mechanism of the nervous system.

3. RESULTS

Most probable steps starting from the generation of simple excitable neuronal cells to the final circuitry that incorporates IPL mechanism were identified. Details of the probable preconditions and accidents that generated and fine-tuned the IPLs have become evident. It was found that the IPL mechanism has suitable features that can allow its formation among synaptically-connected neurons, through a probable sequence of evolutionary stages. These stages are explained below and are numbered arbitrarily.

3.1. Single Cell Structural Adaptations

Unicellular organisms developed robust mechanisms for membrane changes both during endocytosis to obtain nutrients from the surroundings and during exocytosis to remove waste products from inside the cell. Phagocytosis is a cell process for internalizing and destroying other deleterious cells through the focal delivery of endo-membranes at the locations of vesicle exocytosis [26, 27]. At one stage of development, cells with the unique property of membrane excitability started emerging. Excitability is a feature whereby a stimulus can depolarize (change polarity of ionic distribution inside and outside the membranes) a membrane segment of a neuron, which can propagate to the rest of the cell membranes. As the neuronal cells moved away from each other, specialized processes were developed as input and output terminals. Expansion of cell membranes of these processes takes place by the addition of new membrane segments through exocytosis of plasmalemmal precursor vesicles [28]. It is to be noted that membrane fusion is an important step for the expansion of plasmalemma at the growth cones of the

neuronal processes [29]. Both input and output terminals of the neurons further branched out. Input terminals are the dendritic spines (also called postsynaptic terminals, after they form synapses) that are formed on the branches of a tree-like structure called dendritic tree. The output processes at the ends of the axonal terminals are the presynaptic terminals.

3.2. Inter-Cellular Interactions

Excitable neuronal cells interacted with each other by transmission of depolarization between them. Among the neurons that are close to each other, passive conduction of depolarization across the abutted cell membranes from one cell to the next was suitable [30]. As the neurons started moving away from each other, inter-neuronal interaction further evolved to form chemical synapses with unidirectional neurotransmission as a method of communication between them (Figs. **2A** and **B**). As the neuronal cells moved farther away from each other, dendritic branches elongated and it resulted in the attenuation of the postsynaptic potentials as they propagate towards the cell body. It became necessary to summate the postsynaptic potentials near the soma to form a large spike of depolarization called "action potential" for its propagation to reach all the output terminals of the neuron. The outer layers of the lipid membranes of different spines that belong to different neurons are electrically isolated by the presence of electrostatic forces between them [31-33]. It is necessary to overcome these counteracting forces to generate any electrical interaction between the outer lipid membrane layers of different spines [34]. Since bringing lipid membranes to physically contact with each other is considered as one of the high energy-requiring processes [35, 36], inter-spine interactions tend to reverse back to their initial state if no mechanisms are initiated to stabilize the formed inter-spine interaction.

3.3. Exocytosis and Inter-Cellular Fusion

Locations of membrane reorganization at the sites of exocytosis predispose those locations to undergo fusion with other cells. For example, the acrosome reaction in the sperm that occurs prior to the intercellular event of sperm-egg fusion [37] is a common finding. Another example is the phagocytosis of a cell by another cell [26, 27]. The occurrence of exocytosis at the excitable membranes of neuronal cells can predispose those cells to undergo inter-neuronal fusion and can activate certain molecular cascades (for example, apoptosis) [6, 38-40] and cause death of several of those cells.

3.4. Dye Coupling Between the Neurons

Dye injection experiments have shown neuronal coupling at the early stages of the mitotic phase in the ventricular zone [41]. This indicates the formation of a fusion pore between these cells. This is followed by a stage of uncoupling between the neuronal cells that prevent any dye diffusion between them. Nearly 70% of the cortical cells are found dying by embryonic day 14, which is reduced to 50% by embryonic day 18 [6]. Post-mitotic cells then migrate from the proliferative ventricular zone to become layers in the cortical plate as a sheet [42]. Between 13 and 18 days of embryonic development, nearly 67% of the motor neurons present in the motor column die [39]. Dye coupling between the neuronal cells is also found for short periods during the later stages of development [43, 44]. The inter-neuronal coupling followed by uncoupling during different stages of ontogeny indicates

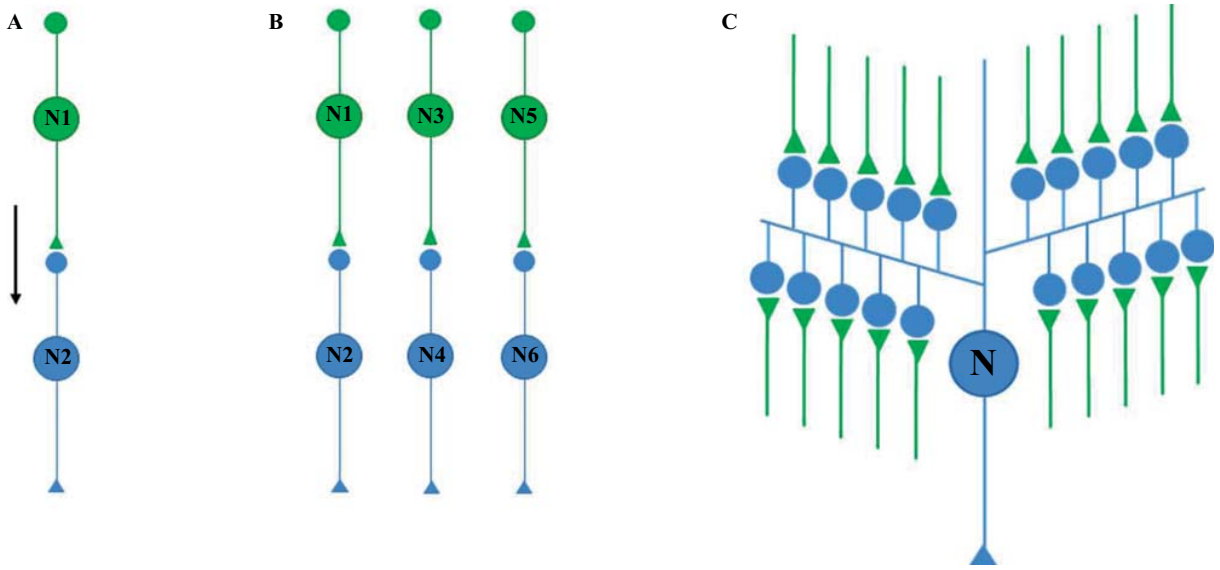

Fig. (2). Neuronal processes and synapses. **A**) Two neurons (marked N) that are connected by a synapse between one output region of a neuron (N1) and one input region of a second neuron (N2). Direction of neurotransmission is shown by a black arrow. **B**) Six neurons (N1 to N6) formed from progenitor cells migrated to form two neuronal layers of three neurons each. The area in between the neuronal layers is rich in synapses. Changes in the extracellular matrix potentials of this region reflect ionic changes across the membranes of neuronal processes. N: Neuronal cell body. Triangular shaped tip: presynaptic terminal: Rounded tip: postsynaptic terminal (dendritic spine). **C**) Densely packed dendritic spines (inputs) on two dendritic branches of a neuron at the early stages. To prevent neuronal firing for every arriving input, variations might have resulted in the selection of neurons having a threshold for firing. Neuronal firing allowed the propagation of action potential to all the output terminals of a neuron. Note that many of the spines are abutted to each other that can lead to inter-spine interaction. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

that a transient inter-neuronal fusion occurred during an early stage of evolution. Since studies have shown that within a neuronal order, mature adjacent neurons of the same type have different mRNA expression profiles [45, 46], it is expected that the cells will react in different ways when mixing their cytoplasmic contents occurs. When fusion occurs between two neurons, one type of response is blockage of the fusion pore and development of factors that resist further fusion events among the surviving cells. The second one is to induce the death of one of those neurons so that the other neuron can survive. This can explain beneficial functions provided by the transient inter-cellular fusion events to the surviving cells. Thus, the observation of neuronal death among a fraction of neurons suits the expectations of a non-adaptive determinant that is viewed as essential for guiding evolution [5].

Both dye diffusion between neuronal cells [43, 44] and death of a significant number of them that occur at one stage of the neuronal development [6] indicate that dye diffusion is likely associated with neuronal death. But, the pressing questions is, "Why would evolution maintain this?" Since apoptosis is prominent in the proliferating neuroepithelium of the developing cortex [47], one may ask "Is it possible that excess neuronal cells are produced first and surplus cells are removed by apoptosis?" These can be answered by the findings from the following studies. Genetic manipulations to prevent apoptosis did not show any "gain of function" states [48, 49]. Moreover, experiments that were undertaken to genetically block apoptosis resulted in severe defects in normal brain development [49, 50]. If changes that lead to apoptosis had no functional advantages, evolution would have de-selected the formation of excess number of cells in the first place. Since the death of the majority of neurons is evolutionarily conserved, it can be taken as an indirect indication for the possibility that the stage that leads to neuronal cell death provides an adaptive function to the surviving neuronal cells.

3.5. Intra-Neuronal Inter-Spine Interaction

If one assumes that neurons were having a large number of spines on their dendritic arbors at the initial stage of development (Fig. **2C**), then associated sensory stimuli reaching two abutted spines of the same neuron likely have formed an IPL between them. Initial interaction is limited to the removal of repulsive forces between the spines and is rapidly reversed. During the short period of its existence, a cue stimulus propagating through the IPL can provide an incidental lateral activation of an inter-LINKed spine and sparks a hallucination (semblance) that the latter is receiving a sensory input through its presynaptic terminal (for details, see Fig. (**1**) and [19]). This hallucination constitutes the basic element of the internal sensation of memory [17]. This short-lasting internal sensation generated at this stage is very primitive in nature (Type I Semblance) and only informs about some crude features of a previously associated stimulus. This property likely started providing some benefits for survival. Since the IPL is formed between the spines of a single neuron, the motor output at the time of retrieval of primitive memory by either one of the associated sensory stimuli would have been the same, and it did not provide anticipated features of a conditioning paradigm.

3.6. Exocytosis and IPL Formation

Significant membrane reorganization is expected to occur at the locations of exocytosis. Artificial stimulation of synapses during Long-Term Potentiation (LTP) stimulation initiates exocytosis of the vesicles containing AMPAR (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) subunits at the lateral spine head region [51-53] (Fig. **3**). Since learning and LTP induction occlude each other in either direction [54, 55], their cellular level mechanism is expected to have common shared features. The IPL mechanism provides matching explanations how learning-changes occurring at physiological timescales are scaled-up during the interval of at least 20 seconds between LTP stimulation and induction [22]. Since the contents of the vesicles are receptor subunits that need to be assembled and trafficked towards the postsynaptic membrane surface of the synaptic cleft, the most probable location of exocytosis of these vesicles is at the lateral margins of the spine heads close to the synapse. Experimental findings [56] support this (Fig. **3A**). This also matches with the finding that AMPA GluR1 subunits are concentrated on the postsynaptic membranes within 25nm from the outer synaptic margin [57]. When depolarisations from two sensory inputs arrive at two abutted spine heads, it leads to the exocytosis of AMPAR subunit vesicles (Fig. **3B-F**). Exocytosis of vesicles containing AMPAR subunits is a slow process and usually takes place in timescales of seconds. This process adds membrane segments at the abutted locations and results in membrane reorganization at the lateral spine head regions. Additional factors are expected to be involved in inter-spine interactions at millisecond timescales similar to that of the interaction between synaptic vesicles and presynaptic terminal membrane.

SNARE (soluble NSF (N-ethylmaleimide sensitive fusion protein) attachment protein receptor) proteins are known to mediate fusion of vesicles [58] containing AMPAR subunits with the spine membrane [59, 60]. This may facilitate membrane expansion at the lateral spine head margins where converging stimuli arrive during learning. These factors can significantly overcome both the electrostatic forces and hydration that repel the spine membranes. At least in a fraction of abutted spines where converging stimuli arrive during learning, these mechanisms are expected to cause learning-induced IPL formation in millisecond timescales. During the existence of an IPL, a cue stimulus that leads to the propagation of depolarization across the IPL will induce units of internal sensation of memory at the corresponding recipient inter-LINKed spine.

3.7. Inter-Neuronal Inter-Spine IPLs

From section 3.5, we have seen that the formation of intra-neuronal inter-spine IPLs was not able to provide a mechanism that can meet the expectations of a conditioning paradigm. When neuronal cells formed from progenitor cells at the ventricular margins migrated towards the pia, they anchor some of their processes on to the inner surface of the pia, then move towards the direction of the ventricle, and settle in different neuronal layers. The regions between those neuronal layers are crowded with spines of heterogeneous types of neurons. This naturally leads to the abutting of spines that belong to neurons of not only the same neuronal

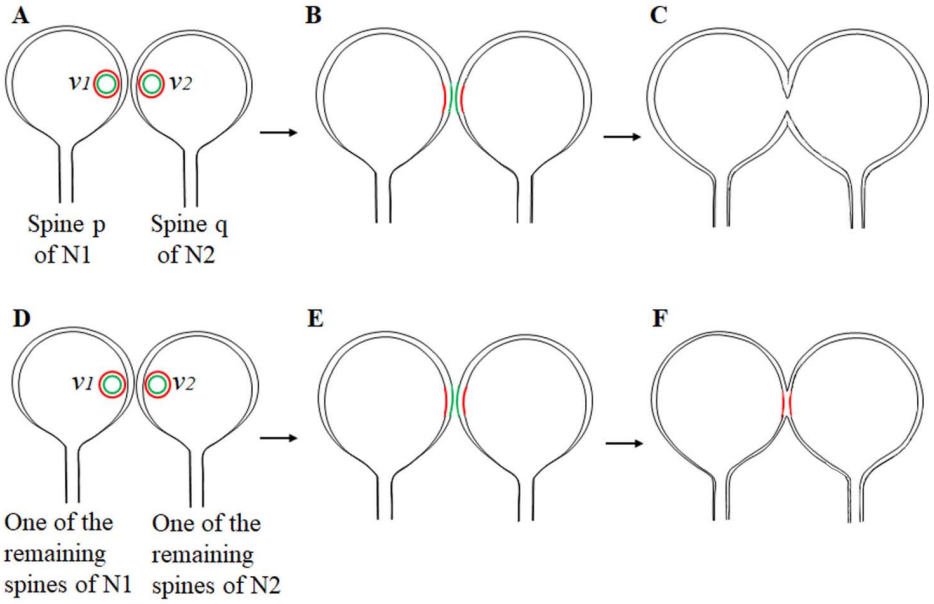

Fig. (3). Events that lead an inter-spine interaction towards their fusion, which is followed by an adaptation that prevents fusion by stabilizing the intermediate stage of hemifusion. Top row (A to C): Events at the spines of two neurons that lead to a transient stage of inter-spine hemifusion. **A**) Cross-section through two spine heads marked p and q each having one intracellular vesicle inside, located close to the regions where these cells are abutted to each other. **B**) Fusion of the vesicles with membranes of the lateral aspects of the spine heads shown in figure A leads to a slight increase in the total surface area of these spines. Spines surrounded by ECM will not be able to expand uniformly; instead, it often increases the curvature of the local membranes at the locations of exocytosis (not shown). **C**) Spine heads p and q undergo fusion. Dendritic spines of two different neurons act like two independent cells. If inter-neuronal inter-spine fusion persists, mixing of the cytoplasmic contents between the cells can trigger loss of those spines from the dendrite that will prevent cell death. If this cannot be achieved, continued mixing of cytoplasmic contents can lead to death of one or both cells. Bottom row (D to F): Events at the remaining spines of the neurons p and q do not progress beyond the stage of inter-spine fusion. **D**) Initial changes between the remaining spines of neurons N1 and N2 are similar to that shown in A). Vesicle exocytosis at the location of future inter-spine interaction (same as in B). **E**) Same changes as in figure B. **F**) The spine heads p and q are arrested at the stage of hemifusion at the location where intracellular vesicles are fused with the cell membranes (conceptualized from [37]. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

layer, but also of different layers. Eventually, accidents most likely initiated interaction between spines that belong to different neurons and led to the formation of IPLs between them (Figs. **4A-C**). Here, memory retrieval by each associated stimulus will lead to separate neuronal outputs. This provided the IPL mechanism necessary features to operate as a conditioning paradigm. The finding that cortical pyramidal neurons have mean inter-spine distance more than mean spine diameter [61] indicates that neurons with this feature were selected at one stage so that IPLs started forming between spines that belong to different neurons. Since motor outputs of conditioning learning provided survival advantage, factors that led to inter-neuronal inter-spine IPLs are expected to have selected. When the generation of corresponding motor outputs started providing appropriate sensory inputs, the system would have started functioning in a more meaningful way. The net semblance generated from these types of inter-neuronal inter-spine IPLs is expected to have provided an advanced form of semblance (Type II Semblance).

3.8. Adaptation that Prevents IPL Fusion

The lateral spine head regions, which are the locations of AMPAR subunit vesicle exocytosis, match with the expected locations for IPL formation that are predisposed to undergo fusion (Fig. **3C**). Since mRNA profiles of even adjacent neurons of the same type within a neuronal order are different [45, 46], any fusion between the spines that belong to different neurons will be deleterious to both the neuronal cells. However, since inter-neuronal inter-spine IPLs provide survival advantages for taking appropriate motor actions, evolutionary changes are expected to retain them without undergoing fusion. In other words, it was necessary to maintain the formation of inter-neuronal inter-spine IPLs and at the same time prevent them from undergoing inter-spine fusion that can cause spine loss and even neuronal death (Fig. **5**). In this context, the balance of evidence available from the observation of dye mixing between the adjacent neurons during one stage of development followed by stages that are devoid of such dye mixing [41] indicate the following. Transient inter-cellular fusion that results in the mixing of cytoplasmic contents between neurons became necessary to trigger certain cellular mechanisms, such as the expression of certain proteins that prevent further inter-cellular fusion (Step 1 fusion prevention). The most likely mechanism for this is stabilization of the inter-cellular hemifusion stage, which is a stable intermediate stage prior to the stage of fusion [62]. Hemifusion is also a suitable stage for long-term stabilization. This is expected to have evolved as an adaptation for maintaining the IPLs. As long as the factors that stabilize the IPLs can be maintained, they continue to provide the benefits of semblance formation (internal sensation). It is reasonable to as-

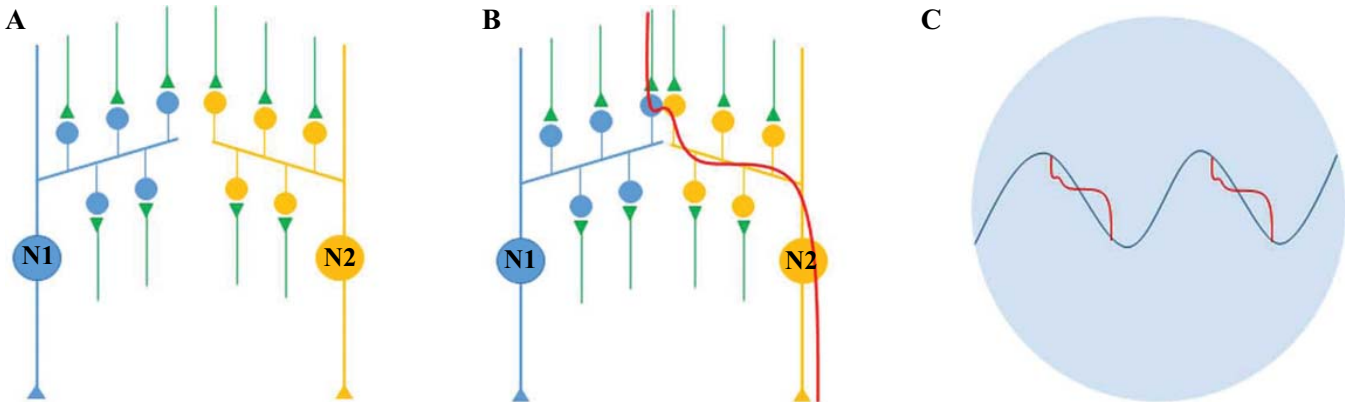

Fig. (4). Inter-neuronal inter-spine interaction that leads to inter-postsynaptic functional LINK (IPL) formation. **A**) The selected new variant of neurons with a mean inter-spine distance more than the spine diameter [61]. This increases the probability for the interaction between spines that belong to different neurons. Formation of IPL enables propagation of potentials in a lateral direction across them perpendicular to the direction of synaptic transmission. Formation of IPLs between the spines that belong to different neurons allows both induction of units of internal sensations and motoric output expected of a conditioning learning paradigm. **B**) The ionic changes generated both synaptic transmission and propagation of potentials along the IPLs contribute to the formation of composite periodic signals across the neurons and their processes (shown by a waveform in red). **C**) Net effect of a large number of composite periodic signals from both synaptic transmission and propagation of potentials across the IPLs form oscillating extracellular potentials. Propagation of depolarization through recurrent collaterals and feedback loops also contribute towards these oscillating potentials. Both learning and generation of internal sensations of higher brain functions occur only when the oscillating extracellular potentials are maintained in a narrow range of frequency. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

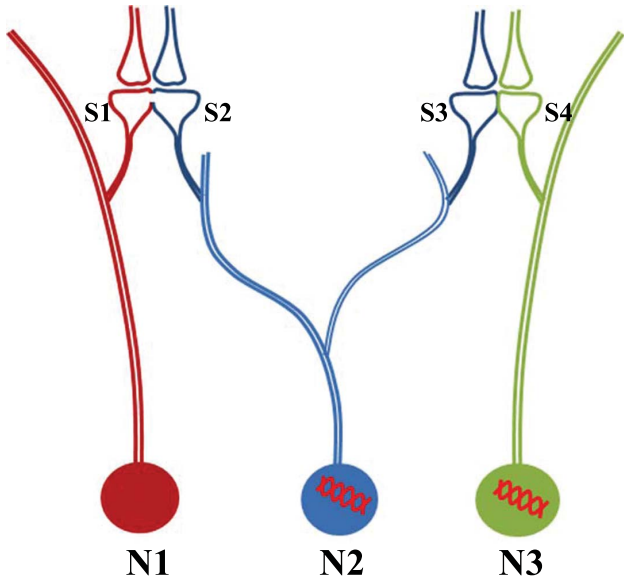

Fig. (5). Inter-neuronal inter-spine fusion triggers long-lasting cellular mechanisms for stabilizing inter-spine hemifusion. Spines S1 and S2 of neurons N1 and N2 respectively undergo fusion at an early developmental stage. Since neuron N1 cannot remove spine S1, cytoplasmic contents from neuron N2 continue to mix with its cytoplasm and neuron N1 undergoes apoptosis. However, entry of cytoplasmic content from neuron N1 to neuron N2 triggers molecular mechanisms in neuron N2 for arresting any future event of spine fusion at the stage of hemifusion. As a result, during learning, inter-spine interaction between spines S3 and S4 that belong neurons N2 and N3 respectively gets arrested at the stage of hemifusion generating a stable IPL that can continue to provide its function of inducing internal sensations. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

sume that evolution could not have found an alternative mechanism to stabilize the stage of inter-cellular hemifusion without first undergoing a stage of inter-cellular fusion.

Since bringing the lipid membranes close to each other is a high-energy requiring process [35, 36], it can be expected that IPL formation is restricted to occur at the smallest possible area between the interacting membranes. This provides a dual benefit of protecting the spines from undergoing fusion and at the same time, enables propagation of depolarization across the IPL for the induction of internal sensations. The smallest possible area of the IPL will be advantageous to concentrate the ion channels for better propagation of depolarization across it. Furthermore, the IPL can reverse back quickly to separate the spines once the mechanisms to stabilize a specific IPL cannot be maintained when specific stim-

uli from the environment stop arriving for a long period. Molecules and mechanisms that cause AMPAR endocytosis at the postsynaptic membranes reduce the spine surface area [63, 64] and favor reversal of IPLs. These features of the IPL can be viewed as part of the favorable adaptations that were selected.

3.9. Molecular Evidence for Arrest at the Stage of Hemifusion

Since the arrest of hemifusion is a favorable solution to stabilize the IPLs, one may ask, "Are there any molecular evidence that suggests the arrest of inter-spine fusion at the intermediate stage of hemifusion?". Molecules that are involved in synaptic vesicle fusion at the presynaptic terminal are present in modified forms within the postsynaptic terminal (dendritic spine). Till now, there were no circumstances that motivated us to investigate whether any of these molecules prevent inter-spine fusion. Indirect evidence suggests that regulatory mechanisms of some of these proteins are participating in preventing fusion. These likely factors can be deduced from the results of the experiments conducted for different purposes. The presence of unique SNARE proteins in the postsynaptic terminal [65] prompts us to examine their roles in fusion in more detail. It is known that SNARE proteins are involved in membrane fusion [66] and that they generate hemifusion intermediates [67]. Specifically, neuronal SNAREs can promote the arrest of fusion at the stage of hemifusion [68]. Since the structure of a complete hemifusion is a double membrane, it has suitable features to get stabilized that will enable long-term maintenance of IPLs.

Fusion driven by neuronal SNAREs is arrested at the stage of hemifusion by the regulatory protein complexin [69]. Experiments have shown the ability to permanently convert inter-membrane interaction to a stable hemifusion state in a fraction of cells, which has led to the conclusion that SNARE proteins can be regulated to generate a desired state of inter-cellular interaction with a minimum of regulatory influence [70]. This experimental result suggests that SNARE proteins have a role not only in intracellular fusion, but also in inter-cellular fusion events. Experiments have shown that certain specific conditions can lead to the preferential formation of hemifusion intermediates over fusion. For example, the low surface density of SNARE protein measured by SNARE protein/lipid ratio resulted in keeping the lipid membrane interaction limited predominantly to the hemifusion intermediate state [66-71]. Another example is the finding that increasing phosphatidylethanolamine in lipid bilayers increases the fraction of hemifusion events [68].

It was found that blockers of SNARE proteins that block membrane fusion events reduce LTP [72]. From the configuration of LTP induction protocol and the experimental introduction of the blockers of SNARE proteins into the spine, it is most likely that the location of action of these blockers is inside the spine. It also indicates that SNARE proteins are important at least to promote certain fusion events that are also necessary for LTP induction. Since a) learning and LTP induction can be explained in terms of IPL formation [22], b) a unique postsynaptic SNARE fusion complex is present within the spines that is necessary for LTP induction [65], and c) absence of reports of dye diffusion between the spines of different neurons following LTP, the unique postsynaptic SNARE protein machinery is most likely associated with the event of inter-spine hemifusion.

Complexin proteins are a universal feature of metazoans that predate their evolution [73] and are primarily restricted to the nervous system. They interact with the neuronal SNARE core complex [74] and arrest fusion at the stage of hemifusion [69]. Since complexin is present within the postsynaptic terminals [75], one can ask the following questions, "Why would a protein capable of arresting fusion at the intermediate stage of hemifusion be present normally within the spines?" "Since vesicles are not docked to the postsynaptic membranes [76], fusion between which membranes is arrested (at the stage of hemifusion) by complexin at the postsynaptic terminal?" Since learning mechanism takes place in milliseconds, any involved hemifusion is expected to take place within this timescale. Vesicle release by fusion involving variants of both proteins SNARE and complexin takes place at the presynaptic terminal in millisecond timescales. Since a) there are no docked vesicles at the postsynaptic membranes, b) learning in milliseconds and LTP induction that needs at least 20 seconds can be explained in terms of the IPL mechanism [22], of which inter-spine hemifusion is at one end of the expected spectrum of changes, c) complexin known to arrest fusion at the stage of hemifusion [69] is present within the spines [75], and d) blocking complexin blocks LTP [75], it is reasonable to view that protein complexin is involved in arresting inter-spine hemifusion at matching time-scales both during learning and following LTP stimulation.

It is known that even when different components necessary for SNARE mediated fusion arrive from different cells, it leads to fusion between the membranes of those independent cells [77]. This indicates that SNARE mediated fusion process is a general property that occurs between any two membrane bound structures. SNARE mediated fusion process can be carried out between artificial lipid vesicles in an artificial medium. One such experiment has shown that complexin molecules arrest SNARE mediated fusion at the intermediate stage of hemifusion [69].

It is known that a fraction of the synaptic vesicles gets docked at the presynaptic terminal membrane by temporarily getting arrested at the stage of hemifusion [78]. However, unlike the presynaptic terminal, there are no docked vesicles containing AMPARs at the postsynaptic membranes outside of the synaptic region [76]. Different studies have reported different time delays for exocytosis of AMPARs following synaptic activation and the shortest duration reported takes at least few seconds [79]. Hence, it is reasonable to expect that prior events that lead to AMPAR exocytosis can predispose those spines to further increase the surface area of their lateral spine head regions during subsequent activations. Associative learning events can promote those expanded spine regions to undergo IPL formation at physiological timescales of milliseconds, which is initiated by a SNARE-mediated fusion process and is arrested at the intermediate hemifusion stage by complexin. Thus, inter-spine interactions are facilitated by the dynamic nature of lateral spine membranes in contrast to the rigid membrane structure of the plasma membranes elsewhere on the neuron.

3.10. IPLs are Vulnerable to Undergo Fusion

In animal models of seizure generated by excessive excitation of the pyramidal neurons, dye injected into one CA1 pyramidal neuron transfers to several neighboring CA1 neurons [80]. Since the CA1 neurons are close to each other at the level of their dendritic spines (with less volume of Extracellular Matrix Space (ECM) between them), it is most likely that the dye diffusion occurred through a fused area between the dendritic spines that belong to different CA1 neurons. It indicates the possibility that conditions of excessive excitation predispose the IPLs to undergo IPL fusion. Introduction of excess dopamine at the locations where dopamine can cause enlargement of the spines (such as the nucleus accumbens and striatal neurons) leads to dye coupling between the neurons [81, 82], most probably by IPL fusion. These findings indicate that certain conditions can make inter-spine interactions vulnerable to undergo IPL fusion.

3.11. Further Refinement of Semblances

Different components of the ECM separating the neuronal processes prevent inter-spine interactions by virtue of the presence of negatively charged side chains of proteoglycans that attract sodium ions, which in turn attract water molecules. This insulating medium between the abutted spines keeps them electrically separate as a default state (Step 2 fusion prevention). Since high energy is necessary for excluding the insulating medium [35, 36], it is expected to be a highly reversible process. Repeated formation of the same IPL by repeated learning events can trigger homeostatic mechanisms, which will lead to the stabilization of the IPL that can persist for varying periods depending on several factors. Continued associative learning events lead to the formation of IPLs between different spines that belong to different neurons to form an islet of inter-LINKed spines (not shown in figures). This favors lateral spread of postsynaptic potentials across all the inter-LINKed spines that belong to different neurons and results in the induction of semblances of all the associatively learned items at that islet of inter-LINKed spines. This is likely to modify the net semblance further to match with the related features of the item whose memory is retrieved (Type III semblance).

3.12. Achieving Continuity of the Oscillating Extracellular Potentials

Propagation of depolarization along the membranes generates a corresponding fluctuation of ionic changes in the ECM space, which is reflected in the recorded field Excitatory Postsynaptic Potential (fEPSP) changes [83]. Since the direction of propagation of potentials through the IPLs and synapses is perpendicular to each other, they naturally provide vector components for the oscillating potentials when recorded between two locations of the ECM. This can be viewed as a binding system property for natural computation of all the units of internal sensations [19]. Since the neuronal processes share ECM space between them, it leads to the integration of ionic changes in the ECM space of the spine-rich area between the neuronal layers of the cortex (Fig. **4C**). This integration is expected to correlate with the binding of individual semblances induced at an islet of inter-LINKed spines. Based on the depth of recording electrode tips and distance between them, different amplitudes and periodicities of extracellular potential waveforms are observed.

In prematurely born infants, the oscillating extracellular potentials in the Electroencephalogram (EEG) show discontinuity in the waveforms [84]. This indicates an insufficiency in the horizontal component of the oscillating extracellular potentials and can be explained in terms of insufficient number of IPLs formed at the early stages of development. The eventual achievement of continuity of EEG tracings matches with the formation of additional IPLs that provides the lateral spread of potentials through them along the synapse-rich area between different neuronal layers of the cortex. Continuity of oscillating extracellular potentials and its maintenance at a specific range of frequency is expected to be a system property essential for integrating the semblances [19]. This is expected to occur along with the maintenance of electrical isolation between spines by the ECM. The sequence of events starting from the initial sparking of internal sensations to their optimization matches with the view that developmental aspects of the system function can provide information regarding the adaptation of lower-level elements to perform their higher-level functions [85].

3.13. A Potential Mechanism that Further Increases the Efficiency

Very large number of associated stimuli can arrive from items and events in a natural environment. At every moment, nervous system receives a large number of (cue) stimuli from the environment that will force the system to induce internal sensations of the associated stimuli that were arrived in the past. Retrieving internal sensations in response to a very large number of common non-beneficial and innocuous sensory stimuli will significantly reduce the efficiency of the system to survive. This is expected to have led to the generation of several variations to overcome the need for inducing separate internal sensations in response to a very large number of common environmental stimuli at a given time. This has most likely led to the generation of variants with different homeostatic mechanisms and has led to the selection of a variant with a unique mechanism.

What mechanism would have eliminated the need for inducing separate internal sensations in response to common stimuli from a given environment? By selecting the most probable mechanism that can match with the generation of oscillating extracellular potentials occurring at a narrow range of frequency, even at rest, the derived IPL mechanism of nervous system functions provides the following explanation. Generation of internal sensations in response to all the common sensory associations from the environment, even in the absence of arrival of any one of them, as a default mechanism eliminates the necessity to induce internal sensations in response to each individual sensory stimulus. Such a mechanism is expected to continuously generate an integral of semblances in response to all the common background stimuli at the background state, even when they do not arrive at the nervous system. This necessitates an autonomous reactivation of all the corresponding inter-LINKed spines. The induced net semblance may be viewed as C-semblance responsible for the background internal sensation that we call as "consciousness," which takes place only in a narrow range

of frequency of oscillating extracellular potentials [86]. Even though the conformation of C-semblance will largely be influenced by the common associations within a given environment and species-specific features of neuronal assembly, it will also have contributions from all the previous associative learning events made by an individual animal. This can provide a subjective component to the C-semblance. An optimal C-semblance provides a matrix upon which a cue stimulus will be able to induce more refined internal sensations of memories of the associatively learned items (Type IV Semblance) (Table **1**).

Table 1. Table showing steps involved in different stages of evolution that eventually refine the net semblances to match with the features of the item whose memory is being retrieved.

I	Semblance at the inter-LINKed spines on the same neuron
II	Long-lasting semblance at the inter-LINKed spines formed from different neurons
III	Semblances induced at the inter-LINKed spines within an islet of inter-LINKed spines
IV	Specific semblances induced in the background matrix of C-semblance

3.14. Augmentation of IPL Formation by Dopamine

Dopamine is phylogenetically an old neurotransmitter molecule [87]. Following its initial presence, dopamine was absent for a long period during phylogeny. Re-introduction of dopamine at a later stage during evolution [87] may have occurred by accident. Most probably, dopamine's ability to cause enlargement of the spines [88] was utilized to promote IPL formation and facilitate associative learning. The same action of dopamine on the spines can explain why it is released during motivation-promoted learning [89]. It was found that experiments that provide an excess of dopamine at the locations where dopamine is known to have actions (such as the nucleus accumbens and striatal neurons) result in dye coupling between the neurons [81, 82]. This indicates the possibility that excessive spine enlargement promotes inter-spine fusion. This can be viewed as an indirect evidence that dopamine in optimal concentration promotes IPL formation [19] and that in pathological conditions associated with excessive dopamine [90], the hemifusion end of the spectrum of IPLs gets converted to fusion.

3.15. Internal Sensation of Emotions

Different regions of the brain are associated with the generation of specific emotions. These regions have spines with receptors for different types of neurotransmitter molecules from different types of neurons. This indicates the possibility of IPL formation between spines (of synapses) that have receptors for different neurotransmitter molecules. Since these neurotransmitters generate a range of postsynaptic membrane potentials of different polarities ranging from depolarization to hyperpolarization and since islets of inter-LINKed spines are formed between spines that bind to different neurotransmitter molecules, semblances formed at these locations can have different conformations. Based on the composition of spines within the islets of inter-LINKed spines at different locations of the brain, the nature of net semblances can be responsible for internal sensations of different emotions. Systematic analysis of the organization of dendritic spines that receive different inputs and the conditions that generate IPLs between them are expected to provide information about the conformation of internal sensations generated at those locations.

3.16. Excessive Excitation and IPL Fusion

Depolarization arriving through the IPLs formed by the spines that receive excitatory inputs can sometimes lead to excessive excitation of the neurons of those spines and damage them. This would have led to the selection of variants among neuronal cells that are able to inhibit such excessive activations. One possible outcome of this is the appearance of neurons that express glutamate decarboxylase enzyme to catalyze the formation of Gamma Amino Butyric Acid (GABA) from glutamate. These inhibitory neurons started inhibiting the outputs of excitatory neurons by raising their threshold for action potential generation. They also started regulating the excitatory neurons at different levels [91-93]. In animal models of seizure that blocked the inhibitory neurons using tetanus toxin, it was observed that injection of dye into one CA1 pyramidal neuron results in the transfer of dye to several neighboring CA1 neurons [80]. This shows the possibility that any condition of excessive excitation leads to both the formation of new IPLs and the conversion of some of the new or existing IPLs to an IPL fusion state. Thus, the adaptations for stabilizing IPLs are fragile mechanisms that can lead to IPL fusion in different pathological conditions.

4. DISCUSSION

4.1. What Does Structure Inform About Function?

Following Darwin's proposal of the theory of continuity of mind [94], several studies have tried to examine the logic by which selection is carried out based on an increase in the brain size. Even though humans have a higher order forebrain system compared to other primates [95], one study has shown that size of the forebrain remains proportional to that of other cortices [96]. Another study has found that the prefrontal regions of both humans and non-human primates have almost equal percentage (8%) of cortical neurons [97]. Based on another study, larger cortical surface area in humans compared to monkeys is due to the formation of a) more founder cells at the periventricular region due to an increase in the number of initial mitotic cell divisions, and b) fifteen-fold increase in post-mitotic cells in humans (compacted in the cortex without affecting its thickness) compared to macaque monkeys [98]. Even though humans and macaque monkeys diverged from a common ancestor nearly 23 million years ago [99], the ratio between the surface area of neocortex of humans and macaque monkeys is approximately 10:1 without significant differences in thickness [100] or cellular organization [101]. How can the increase in surface area contribute to the increased cognitive ability?

Following the last division, neurons migrate in a radial fashion [102]. Attachment of the apical tuft regions of the dendritic tree of the neurons, from different cortical layers, to the inner pial surface increases inter-neuronal inter-spine interactions during a given associative learning event and also facilitates an increase in the size of the islets of inter-LINKed spines that associate several sensory stimuli from the environment. This allows a cue stimulus to induce interconnected internal sensations that identify relationships between disparate findings in the environment and can explain the hypothesis building capabilities of humans [103]. For a given associative learning, a cortex with a large surface area having proportionately large number of laterally located spines that belong to different neurons will be responsible for the following. a) Increase in the number of IPLs that provides more functional units for computation, b) increase in the size of islets of inter-LINKed spines, and c) increase the size and number of islets that increase the efficiency for generating hypotheses. Since humans have more synapses per neuron in cortical layers II and III than in rats and mice [104], it leads to the formation of more IPLs for given associative learning in humans. An increase in the number of IPLs proportionate to the increase in the cortical surface area provides an explanation expected for the improved cognitive abilities of humans compared to that of chimpanzees [105]. Additional factors are likely involved in many kinds of possible events [106] that have led to the generation of different primates.

4.2. A Comparatively Long Duration of Human Nervous System Development

Human brain development after birth that enables it to operate independently in the environment takes relatively more time than most other animal species. This indicates the possibility that exposure to environmental stimuli has a role in optimizing the operational mechanism of the nervous system. Based on the present work, it takes time to form a threshold number of IPLs using associative stimuli from the environment both to generate hypotheses that will maximize survival benefits and to retain high functional capabilities of the species. Based on the IPL mechanism, the long duration for achieving independent functioning indicates that the operating mechanism has a large number of unitary operations that can only be formed in a step-by-step manner to reach an optimal stage. Formation of islets of inter-LINKed spines and inter-LINKing of additional spines to them by new associative learning events match with these expectations.

4.3. Structural Adaptations

If few new neurons (granule cell layer) get inserted just before the region of convergence of different stimuli, it can lead to an increase in the number of IPLs when a particular associative learning or a related learning event is repeated after the insertion of new neurons. This increases the strength of a given association in the nervous system following repetitive learning events. But if a previous learning event or its components are neither repeated nor used in further learning, a) then the IPLs from its previous learning events are expected to reverse back, and b) the insertion of new neurons will result in the formation of new IPLs by unrelated associative learning events. The latter will dilute the net semblances induced by a cue stimulus involved in a previous learning event that occurred before the insertion of new neurons.

4.4. Spine Loss is Likely a Fail-Proof Mechanism

It was seen in section 3.8 that when IPL fusion takes place by at least one of the spines of a neuron during development, an adaptation can be triggered to stabilize all the future IPLs that its spines can make and prevent their conversion to IPL fusion that can damage that neuron. Once it is triggered, initial mechanisms for blocking the already formed IPL fusion is also expected to take place. This will allow the neuronal cell to continue to function normally by forming IPLs at its remaining spines during continuous associative learning events in life. If attempts to block inter-spine fusion fail, then losing the spine at the spine neck region may be triggered as a safety mechanism that can stop the effect of intercellular fusion. Such a mechanism can occur at different stages of spine maturation and stabilization [107, 108]. Spine loss observed at different time intervals following normal associative learning [109, 110] may be an indication that both the adaptation to prevent IPL fusion and mechanisms to block the formed IPL fusion may fail occasionally throughout life. Since spine elimination is observed in several normal and pathological conditions [111], possible mechanisms explained here can be verified.

4.5. Potential Effect of Aging in Neurodegenerative Disorders

IPL mechanisms can fail due to several aging-related causes. These include a) changes in expression of proteins necessary for synthesizing, elongating, and modifying fatty acids necessary to maintain membrane integrity, and b) failure to maintain checkpoint mechanisms that stabilize the intermediate stage of hemifusion. In addition, certain changes in the lipid membrane composition can change the action of SNARE proteins to promote hemifusion to fusion state [112]. Since age is the most important risk factor for the development of neurodegenerative disorders such as Alzheimer's disease [16], it is reasonable to expect that some aging-related factors lead to certain defects in maintaining the adaptation that stabilizes the IPL hemifusion stage. This can explain the aging-related loss of dendritic spines [113]. Since losing spines reduces the computational elements necessary for generating various internal sensations, continued loss of spines will eventually cause functional decline in various cognitive domains, which is a hallmark of neurodegenerative disorders [90].

4.6. Is it Possible to Artificially Maintain the Evolutionary Adaptation to Stabilize the IPLs?

Normal aging is associated with both dendritic spine loss and neuronal death [113]. This can be explained in terms of defects in the adaptive mechanisms for stabilizing IPL hemifusion that leads to IPL fusion. The finding that Dopamine D4 Receptor (DRD4) genotype can predict longevity in mice and humans [114] indicates that excess of dopamine in old age may promote IPL fusion and neurodegenerative changes. There can be several factors that determine these changes

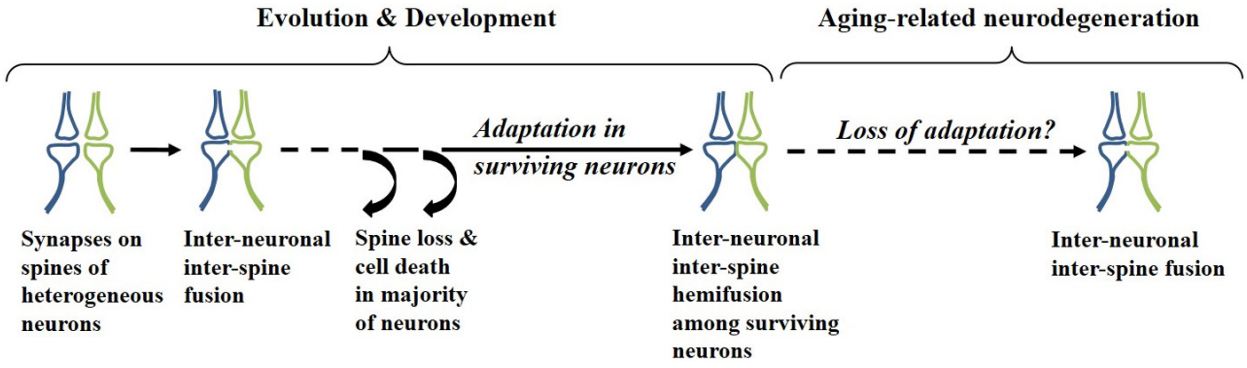

Fig. (6). Potential evolutionary stages of the nervous system may provide clues regarding aging-related neurodegeneration. At one stage of the development, majority of the neurons die. Following this, development of an adaptation allowed the remaining cells to survive without subjecting themselves to death by preventing any future inter-cellular fusion events. A transient inter-spine fusion with another neuron has likely primed the surviving neurons with the ability to arrest all the inter-spine interactions most likely at the stage of hemifusion. This matches with the properties expected of the derived IPL mechanism of the nervous system functions. Since arresting the inter-spine hemifusion most likely depends on gene expression to provide proteins that either a) contribute their functions as enzymes for generating stable membrane lipids or b) directly stabilize the hemifused area, it is reasonable to expect that aging-related changes can slow down this protective mechanism. This opens the opportunity to investigate the details of this probable checkpoint mechanism towards restoring it by artificial means. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

[90]. Maintaining optimal lipid membrane composition either by preventing defects in the lipid metabolic pathways of synthesis, elongation and saturation or by supplementing the appropriate lipids can be explored towards preventing neurodegeneration. Based on the inferences made from this work, one can ask, "Is it possible to identify the adaptations that prevent IPL fusion and artificially provide those factors with an aim to prolong the life span of neurons?".

CONCLUSION

Attempts to understand the operational mechanism of nervous system functions have been facing several challenges due to difficulties in understanding its most important function of generation of first-person properties. In this context, we are left with only one option of deriving a theoretically suitable operational mechanism using constraints from all the findings from multiple levels and verifying it using different methods. The derived IPL mechanism is able to explain a large number of third-person observed findings from multiple levels [103]. The derived solution can interconnect findings from multiple levels. This combined with the findings of the present work that IPL mechanism has features of an evolved mechanism matches the view that interactions between different levels of organization of the nervous system have occurred as it was evolving [115].

Since evolution can only move forward in one direction [4], the observations of both dye diffusion between neuronal cells and death of significant number of neurons for narrow windows of time during ontogeny lead to the inference that a) a transient stage of inter-cellular fusion that results in the death of significant number of neurons was necessary in the evolution of the nervous system, b) the above stage prevents cell death in the surviving neurons due to the initiation of an adaptive mechanism, and c) the interconnection between the above two can only become possible by the formation of a physical interaction between the cytoplasm of the dying and surviving cells as evidenced by the observation of dye diffusion between the cells. Furthermore, the evolution of IPL mechanism can provide a related explanation for the role of cell death in regulating the size and shape of mammalian forebrain [116].

IPL mechanism derived by the semblance hypothesis was able to provide probable explanations for different findings during ontogeny in an interconnected manner and suggests that the IPL mechanism has suitable features of an evolved mechanism. This provides further support for its suitability as the operational mechanism of the nervous system functions. It was viewed that once we understand the cause of neuronal cell loss during development, we may be able to understand the pathophysiology of neurodegenerative disorders [8]. Matching with this expectation, it was possible to obtain crucial information regarding the most probable last stage of the evolutionary sequence of events (Fig. **6**). Since this consists of a stage of adaptation that has features vulnerable to get lost during aging, it provides a testable mechanism for neurodegeneration. The optimism that it will become possible to find ways to develop therapeutic methods to replenish the damaged mechanism of adaptation that stabilizes the IPLs provides motivation to verify the findings made in this work.

LIST OF ABBREVIATIONS

AMPAR	=	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor
ECM	=	Extracellular Matrix
EEG	=	Electroencephalogram
EPSP	=	Excitatory Postsynaptic Potential
GABA	=	Gamma Amino Butyric Acid
IPL	=	Inter-Postsynaptic Functional LINK
LTP	=	Long-Term Potentiation
NMDA	=	N-methyl-d-Aspartate

Post = Postsynaptic Terminal, Dendritic Spine or Spine

SNARE = Soluble NSF (N-ethylmaleimide Sensitive Fusion Protein) Attachment Protein Receptor

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

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

Author is an editorial member of the journal Current Aging Science.

ACKNOWLEDGEMENTS

I thank two anonymous researchers for their insightful comments that helped to improve this manuscript. I thank Neurosearch Center, Toronto for providing support.

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