Disorder of a derived mechanism of nervous system functions, capable to have evolved, provides a testable explanation for age-related neurodegeneration

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Abstract

By viewing memories as first-person internal sensations, it was possible to derive a potential mechanism of nervous system functions. Accordingly, a spectrum inter-postsynaptic functional LINKs (IPLs) are the key structural changes responsible for encoding learning-changes in physiological time-scales of milliseconds that can be retained for variable lengths of time. The inter-spine interaction that lead to the formation of IPLs was examined for its feasibility to have evolved through the simple steps of variation and selection. A stage of significant spine and neuronal loss during the early stages of development indicates that a corresponding stage of IPL fusion that led to neuronal loss during evolution. In the surviving cells is expected that a mechanism for stabilizing IPLs for the rest of life was triggered. This sequence of events can be achieved if the initial stage of transient inter-neuronal inter-spine fusion can trigger the lifelong expression of specific proteins that can stabilize the intermediate stage of inter-spine hemifusion. This is supported by the presence of proteins within the spines that arrest fusion between the spines. Since IPL mechanisms are expected to be utilized during every event of learning, any defect in the continued expression of proteins that stabilizes IPLs at the stage of hemifusion can lead to age-related neurodegeneration.

1 INTRODUCTION

If we can understand the last stage of development (or evolution) of a system whose functional integrity defines our longevity, will it enable us to improve our longevity? The answer becomes "yes," if it involves a stage that we can artificially regulate. Defects in several organs can be managed by either replacing those organs or their functions. However, currently it is not possible to replace either the nervous system or its functions by artificial means, making brain death to be regarded as death. In this context, knowing the last stage of evolution of the nervous system (and development) may provide valuable information to undertake manipulations that can increase longevity. This motivates to examine any derived mechanism of nervous system functions for its suitability to have evolved.

There were also motivations for approaching the issue in a reverse direction. For example, it was asked, "Does understanding how or why a brain evolved helps to decipher how that same brain works?" [1]. These inquiries point to a difficult puzzle that does not provide any clue where to begin to solve them. This difficulty is due to the fact that we haven't yet understood how the brain generates first-person internal sensations within it with such details that are necessary to undertake the gold standard of its replication in an engineered system. In this context, to answer the above questions, it is necessary to build a hypothesis of brain functions and examine whether it is capable of evolving through the simple steps of variations and selection to reach its present state. Initially operated through reflexive motor actions, the system evolved to acquire robust motor capabilities as the prominent survival mechanism of animals in a predator-prey relationship. The system further evolved to acquire the capabilities to generate first-person internal sensations of memories of associations that were made in the past, which enabled it to control its motor actions for survival. Eventually, it led to the development of the faculty of thought process for decision making. This transition from reflexive motor action to the generation of internal sensation of memories, and to the hypothesis building is expected to evolve through certain key milestones, knowledge of which is essential to understand the brain development, function and its disorders such as age-related neurodegeneration.

Even though it is considered that selection acts upon neural output for behavior [2], it is equally important to consider the generation of suitable internal sensations that can provide informed decision making. Eventually, natural selection is expected to play a role in fine-tuning and maximizing the rewards by generating the best possible internal sensations for both memories and predictions. Over the course of evolution, generation of robust internal sensations has dominated over the ability to execute powerful motor actions towards achieving stable survival of the members of a species. Since the lower level elements are adapted to perform their higher level functions, it is viewed necessary to examine the evolutionary and developmental aspects of the system function [3]. It is expected that once we understand the mechanism of operation of the system, it can be examined for the potential stages of variations and adaptations that eventually started sparking internal sensations and were getting selected naturally.

Darwin's theory of natural selection [4] provides two main features that can be 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 features make some fitter variations in some members of the offspring that enable them to survive better than others. Eventually, the heritable traits of fitter variations will get spread in the population. In this process, the nerve cells are also expected to have undergone a large number of variations and eventual selection of fitter ones. Even though changes are observed at the synapses, dendrites and even neurons themselves [2], it has been difficult to understand the evolution of the nervous system using the interpretations of the structure and function [5]. Furthermore, it has been difficult to accept cortical structural patterns as the units of development and evolution [6]. Even though there are some evidence suggesting rapid evolution through minor changes in the existing neural circuitry [7], further progress has been difficult without knowing how the nervous system functions. In the above contexts, the major questions are, "Did natural evolution lead to the generation of any unitary structure-function mechanism?" "If so, what was the natural driving force behind it?" "How are these structure-function unitary mechanisms getting computed to generate meaningful internal sensations matching with the sensory features of an item that was associatively learned?" A reasonable expectation is that the hypothesis be explicit about the nature of networks and computations embodied in it [6].

Ontogeny is the development of a single individual, or a system within the individual, from

the fertilized egg to maturation and death [8]. The sequence of events during the ontogeny within a species was considered to represent the sequence of changes that its ancestors traversed during evolution by Ernst Haeckel with the exception of two types of deviations - change in position and change in order of succession of changes [9]. Therefore, it is reasonable to expect that a rough sketch of probable events during evolution can be made from ontogeny. It was found that in humans, compared to other primates, ontogeny of cognitive ability recapitulates cognitive phylogeny with two changes - changes in velocity and additional terminal changes [10]. Since evolution cannot make the nervous system to unwire to "start over," the solution that it has reached is constrained by its evolutionary history [5]. Therefore, once we understand the mechanism of nervous system functions, a forward moving sequence of events of evolution is expected to be revealed.

It was suggested that by focusing on the fundamental causes of neural system vulnerability, it might be possible to prevent or treat a wide range of late-life neural dysfunction [11]. Since aging is the most important risk factor for the development of neurodegenerative disorders such as Alzheimer's disease [12], it is natural that the last evolutionary stage of the nervous system may have to make compromises for the survival advantages that it has already obtained through evolution. Once we derive an operational mechanism, we can examine the presence of such a mechanism and whether it has features capable of evolving through the simple steps of variation and selection. Knowledge of the last stage of this process, which will be reflected on the last stage of ontogeny can be expected to provide a means to reverse, prevent or at least slow down the age-related neurodegeneration. In this approach, it is necessary to examine whether the circuit features that incorporate the operational mechanism have the feasibility to have evolved through the introduction of variations and selection of best fitting ones several times.

2 UNIQUE FEATURE OF FIRST-PERSON INTERNAL SENSATIONS

The circuitry that generates internal sensations is expected to have evolved from certain accidental coincidences that were evolutionarily well-optimised to get efficiently reproduced during different stages of development. Since ontogeny provides information regarding the events taken place when the nervous system was evolving, the true mechanism of operation of the system is expected to provide substantial evidence that matches with the stages of ontogeny. Present day nervous systems have been surviving in a predator-pray environment. These animals have multiple sensory systems and they use different sensory stimuli - 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 arrives the nervous system almost simultaneously and generate changes at locations wherever the sensory pathways converge. Later, when the item is away from the nervous system, the fastest or first arrived sensory stimulus induces internal sensations of late arriving or non-arriving sensory stimuli from that item. Thus, the key feature that differentiates the nervous system from other systems is its ability to generate first-person internal sensation of sensory features (memory) of an item, when one of the previously associated stimuli is presented. An operational mechanism for memory in 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 [13]. It is necessary to examine whether a derived mechanism that has features to generate hallucinations (internal sensations) can be evolved through the simple steps of variations and selection of the fittest ones. Initially derived by logical arguments, and later verified by using constraints available from a large number of findings from several levels, semblance

hypothesis has provided evidence for a probable mechanism of operation of the system [14-18]. A summary of the mechanism is given in **Fig.1**. Present work specifically aims to examine its evolutionary suitability. Formation of inter-postsynaptic functional LINKs (the word link is capitalized to inform its significance) (IPLs) during associative learning of two stimuli from the environment and re-activation of IPLs generating first-person internal sensation of memory of the second item upon the arrival of stimuli from the first item are the key features of its operational mechanism. Intentionality to feed, procreate and protect from harmful stimuli observed among lower forms of animals indicate that they arise from some form of internal sensations. It is possible that in the evolutionary process, several species of animals branched out after acquiring this property. Following this, the optimization of internal sensations took place differently in different species. Since there were only limited options for the neurons to self-organize during early stages of evolution, it is expected to involve simple steps.

2.1 Evolution of nervous systems on Earth

From the above section it is clear that for tricking the system to hallucinate it is necessary to maintain a dominant state of depolarization of the spine head by neurotransmitter molecules arriving from the presynaptic terminal. How can such a dominating state become possible? The following features have made this possible. a) At night, in the absence of light, number of cue stimuli arriving to reactivate the IPLs to induce internal sensations will be very minimal. b) This reduces the net background semblance and alters the conformation of C-semblance leading to sleep. This is also associated with reduced frequency of oscillating extracellular potentials. Since the continuous quantal release of neurotransmitter molecules occurs, even while sleeping that continuously depolarizes the spine heads (postsynaptic terminals), the dominant state of depolarization of postsynaptic terminal directed by presynaptic terminal is re-instated by sleep [17]. It is in this dominant state of the system that an incidental lateral activation of the inter-LINKed postsynaptic terminal induces hallucination (semblance). The day and night conditions on Earth gave rise to the evolution of the nervous systems that can operate only with sleep.

3 ROLE OF NON-ADAPTIVE DETERMINANTS FOR GUIDING EVOLUTION

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 [19]. At different stages of development, a significant number of neurons are found to die at different locations [20-23]. It was highly stressed that when there is cell death during development, it is necessary to attempt to uncover the benefits to be gained by such loss [24]. This argument was based on the view that neuronal death appears to have evolved to mediate a wide variety of adaptive functions during the development of the nervous system. It follows that neuronal death has paved the way for the eventual introduction of changes that are beneficial to the organism. In this context, the exact role of neuronal death in establishing neuronal connectivity for its functions is considered to have major importance [25]. Evolutionary conservation of the molecular mechanisms underlying apoptosis [26] is in agreement with the above views.

Dye injection experiments have shown neuronal coupling at early stages of the mitotic phase at the ventricular zone [27]. This is followed by a stoppage of neuronal coupling. Post-mitotic cells then migrate from proliferative ventricular zone to become layers in the cortical plate as a sheet

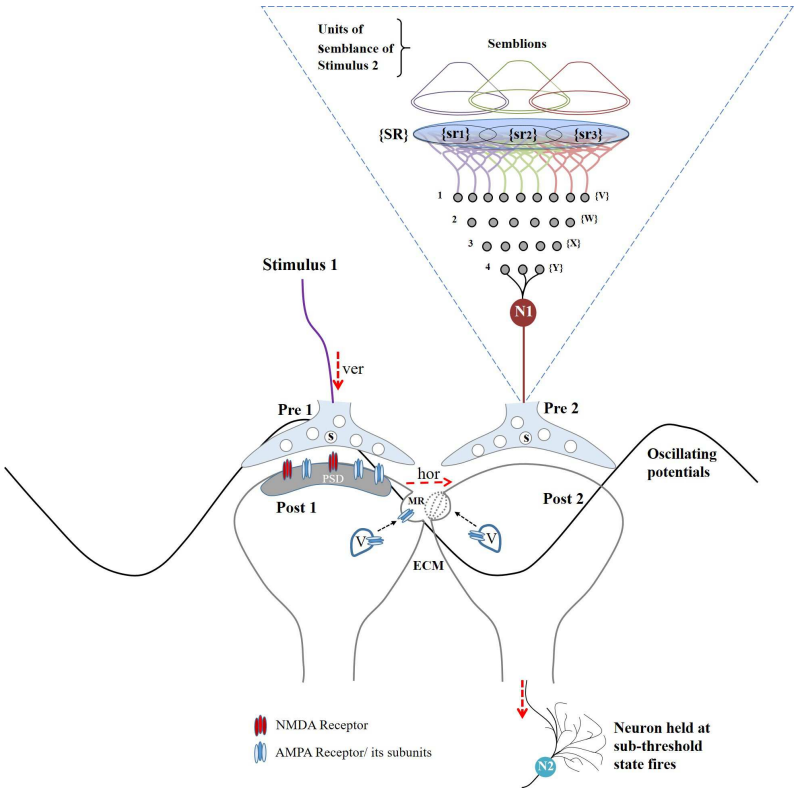

Figure 1: Learning induces inter-postsynaptic (inter-spine) interactive changes at physiological time-scales of milliseconds at the location convergence of sensory input pathways that can generate units of internal sensation during memory retrieval. When associatively learned stimuli 1 and 2 arrive through 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, inter-postsynaptic functional LINK (IPL) between Post1 and Post2 is generated. 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 within milliseconds during exocytosis of vesicles (V) containing AMPA receptor subunits at these locations. These are expected to occur in time-scales 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) needed to stimulate specific subsets sr1, sr2 etc. of sensory receptors SR whose activation is able to activate Post2. This requires 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 sense of the sensory properties of the associatively learned stimulus 2 and is shown inside a dotted triangle (Note that no synaptic transmission is needed in the circuitry within this triangle at the time of memory retrieval). Evolutionary changes are expected to optimize both the operational units and the circuit properties to obtain the best possible computational product of all the semblions induced at several inter-LINKed spines in the nervous system that can match with the sensory features of stimulus 2, which forms the memory of stimulus 2. This computation is a system property of systems where the perpendicular direction of synaptic transmission (ver: vertical) and propagation of the potentials along the IPL (hor: horizontal) contribute to a narrow range of frequency of oscillating extracellular potentials (shown as a waveform). ECM: Extracellular matrix; s: synaptic vesicle (Figure modified from [15].

[28]. Dye coupling between neuronal cells are also found during later stages of development [29-30]. These are followed by a stage where uncoupling between the neurons occur. The inter-neuronal coupling followed by uncoupling during different stages of ontogeny indicates that transient inter-neuronal fusion occurred during an early stage of evolution. The resulted mixing of the cytoplasmic contents between neuronal cells is a definite non-adaptive event since studies have shown that, at least in mature neurons, adjacent neurons of the same type within a neuronal order has different mRNA expression profiles [31-32]. What is the functional role of transient inter-cellular fusion? The balance of evidence in the presence of significant neuronal death and dye mixing between adjacent neurons during development indicates the following. a) Transient inter-cellular fusion, allowing mixing of the cytoplasmic contents between two neurons has become necessary to trigger certain cellular mechanisms, such as the expression of certain genes to prevent further inter-cellular fusion, and b) If inter-cellular membrane interaction provides any beneficial functions, then the a favorable adaptive function is stabilization of inter-cellular hemifusion stage that prevents it from progressing to fusion. It is reasonable to assume that evolution could not have found an alternate mechanism to stabilize the stage of inter-cellular hemifusion without first undergoing an inter-cellular fusion stage.

4 THEORY OF CONTINUITY OF MIND

Examination shows that cognitive domains of human and non-human primates are remarkably similar except that humans have the ability for abstract theoretical concepts. "What made humans, so unique?" According to Subiaul et al., [33] the best possible answer lies in the theory of continuity of mind by Charles Darwin [34] that has two components. 1) The mind is subjected to selection and change 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 question, "Can quantitative differences in the sensory systems result in qualitative differences?" [33]. 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 the segregation of new, functionally specific cortical areas [6]. The finding that the neocortex has undergone expansion primarily in surface area rather than the thickness since mammalian ancestor originated nearly 250 million years ago [36] supports Darwin's views. In agreement with this, cognitive skills resulting from general intelligence were shown to have strong empirical correlations with brain size and executive functions [36]. Can the computation of internal sensory units from a large cortical area provide improved cognitive abilities? The true operating mechanism is expected to provide the answers.

5 Major Stages of Development

For IPLs to form and function, the following are the most probable steps starting from the arrival of simple neuronal cells to the final circuitry. These stages are numbered arbitrarily. Following this, key ontological stages that match with some of the key milestones in the evolution are examined.

5.1 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. Eventually, neuronal cells with the unique property of excitability started emerging. Excitability is a feature whereby a stimulus can depolarize (change polarity of ionic distribution inside and outside the membranes) a location of the neuronal process, which can propagate to the remaining neuronal processes along the membranes. As the neurons moved away from each other, specialized neuronal processes were developed as input and output terminals. Expansion of cell membranes of these processes took place by the addition of new membrane segments through exocytosis of plasmalemmal precursor vesicles [37]. Both input and output terminals of neurons further branched out. Input terminals formed a treelike structure called a dendritic tree. Further specialization on the dendritic branches are the dendritic spines (also called postsynaptic terminals after they form synapses). The output processes at the end of axonal terminals are the presynaptic terminals.

5.2 Multi-cellular interactions

Excitable neuronal cells interacted with each other by transmission of depolarization as a means for inter-neuronal communication. 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 **(Fig.2)**. Among neurons that are close to each other, passive conduction of depolarization across the abutted cell membranes to transmit information from one cell to the next is found suitable [38]. As the neuronal cells moved away from each other, it was necessary to transmit information to long distances. Since elongation of the dendritic branches caused attenuation of postsynaptic potentials arriving from remote locations, it necessitated summation of these potentials close to the soma to form a large spike of depolarization called an action potential, which was able to propagate to long distances to reach all the output terminals of the neuron.

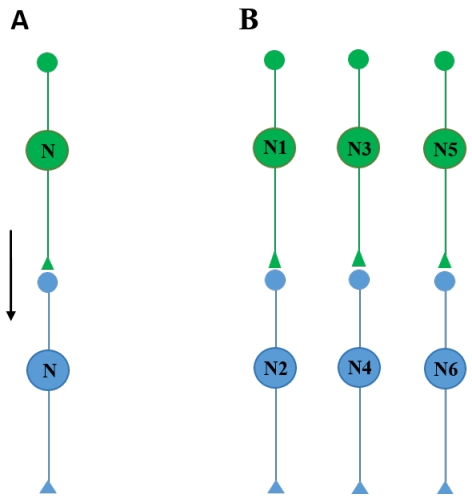

Figure 2: Neurons, their processes and synapses. A) Two neurons (marked N) that are connected through a synapse between the output region of one neuron and input region of another neuron. Direction of neurotransmission is shown by a black arrow. B) Six neurons (N1 to N6) formed from progenitor cells migrated to form two neuronal layers of three neurons each. The area in between the neuronal layers is dense in synapses. This is a common finding in the cortex. N: Neuronal cell body. Triangular shaped tip: presynaptic terminal: Rounded tip: postsynaptic terminal (dendritic spine).

5.3 Electrical isolation of spines of different neurons

When neurons that were formed from progenitor cells migrated after reaching the inner pial surface, they anchored their apical tuft region on the inner surface of the pia and moved towards the direction of the ventricle and settled in different neuronal layers. The regions between those neuronal layers were crowded with their synapses. The outer layers of the lipid membranes of different spines that belong to different neurons are electrically isolated due to the presence of electrostatic forces between them [39-41]. It is necessary to overcome these counteracting forces to enable interaction between the outer lipid membrane layers [42]. Since bringing lipid membranes close to each other is considered as one of the most energy-requiring processes [43-44], any changes that cause inter-spine interaction tends to reverse back to their initial position unless mechanisms for stabilizing those interactions take place.

5.4 Intra-neuronal inter-spine interaction

Neurons formed a large number of spines on their dendritic arbors **(Figs.3A,B)**. When two abutted spines of the same neuron receive associated sensory stimuli from the environment, an IPL was formed between them. Initial interaction was limited to removal of repulsive forces between the spines and was rapidly reversible. During the short period of its existence, when one of the associated stimuli arrived at one of the inter-LINKed spines, an incidental spread of depolarization across the IPL resulted in depolarization of the second inter-LINKed spine. Activation of an inter-LINKed spine from a lateral direction in the absence of its depolarization by its own presynaptic terminal sparked a hallucination (semblance) that it is receiving a sensory input through its presynaptic terminal (for details, see [15]. Semblance constitutes the basic element of internals sensation of memory [13]. This short-lasting hallucination that are formed at this stage is very primitive in nature **(Type I Semblance)**. Since the IPL is formed between the spines of one neuron, the motor output at the time of retrieval of primitive memory by either one of the associated sensory stimuli will be the same, which does not provide anticipated features of a conditioned learning paradigm. Type 1 semblance can be considered as the initial stage of the formation of semblances that further refined to form different internal sensations. Further refinement of the internal sensations is explained in subsections f) to k).

5.5 Stabilization of inter-cellular interactions

It is reasonable to expect that before the excitable neurons were formed, cells have already developed phagocytosis, which is a cell process to internalize and destroy other deleterious cells through the focal delivery of endomembranes at the locations of vesicle exocytosis [45-46]. 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 different types of AMPAR (alpha amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) subunits at the spine head region of postsynaptic terminals [47-49] **(Fig.4A)**. Since learning and LTP occlude each other in either direction [50-51], their cellular level mechanism is expected to have common shared features. The IPL mechanism provides matching explanations how learning changes occurring at physiological time-scales are scaled-up during LTP induction [18]. 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 on the lateral margins of the spine heads close to the synapse.

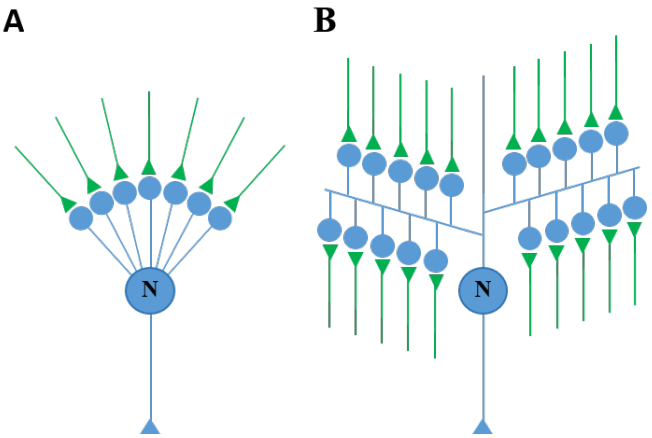

Figure 3: A) Presence of densely packed dendritic spines (inputs) on the dendritic branches of a neuron at the early stage of development. To prevent neuronal firing for every input arriving, selection of variations among neurons might have selected neurons having a threshold for firing. Neuronal firing was the major functional property within the system that allowed the propagation of activity to higher neuronal orders that provided basic motor functions. Note that many of the spines are abutted to each other that can lead to inter-spine fusion. B) A neuron shown with only two dendritic branches with several closely located spines on it. Note that these spines are almost abutted to each other.

Experimental findings support this [52]. This also matches with the finding that AMPA GluR1 subunits are concentrated on the postsynaptic membranes within 25nm from the outer synaptic margin [53].

When activity from two sensory inputs arrive at two abutted spine heads, it leads to exocytosis of AMPA subunit vesicles and add more membrane segments at the abutted locations that results in a membrane reorganization at the lateral spine head regions **(Fig.4B)**. Soluble NSF (N-ethylmaleimide sensitive fusion protein) attachment protein receptor (SNARE) proteins are known to mediate fusion of vesicles [54] containing AMPAR subunits with the spine membrane [55-56]. It is also known that SNARE protein pull membranes together very tightly [57]. These factors significantly overcome both the electrostatic forces and hydration that repels the membranes between the spines. The fraction of these changes that takes place at physiological time-scales of milliseconds are involved in the learning induced IPL formation. For the duration of persistence of the IPL that can maintain electrical continuity between the spines that will allow propagation of depolarization across them in either direction, it can induce units of internal sensation of memory.

5.6 Inter-neuronal inter-spine interaction and neuronal death

As the dendritic branches of neurons from different cortical layers overlap each other, and since the inter-spine distance is more than the spine diameter in the adult cortical pyramidal neurons [59], inter-spine interaction started occurring between spines of different neurons. Interaction between the spines that belong to different neurons is expected to provide an advanced stage of semblance **(Type II Semblance)**. This is because, spines of different neurons within a given layer of neurons in the cortex will start interacting laterally, which can start building a binding property within the system. Furthermore, since the outputs from the interacting spines belong to different neurons, it

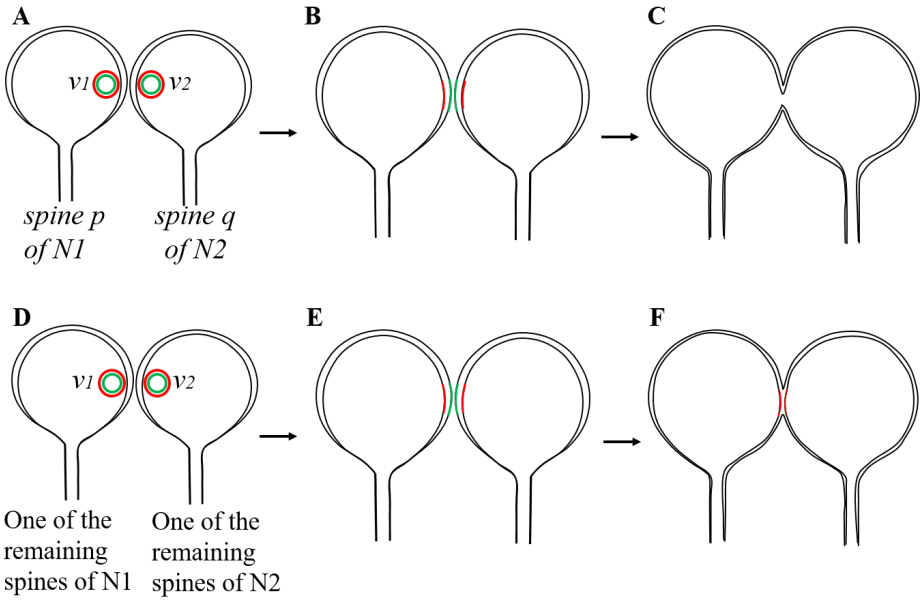

Figure 4: Events that lead inter-spine interaction to their fusion, which is followed by an adaptation that prevents fusion by the stabilization of the intermediate stage of hemifusion. Top row: Events at the spines of two neurons that lead to transient stage of inter-spine hemifusion. A) Cross-section 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 cytoplasmic contents between the cells can trigger loss of those spines from the dendrite as a measure to prevent cell death. If this cannot be achieved, continued mixing of cytoplasmic contents can lead to neuronal death. Bottom row: Events at the remaining spines of the same neurons that cannot 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 as in B. F) Transient fusion at one stage (shown in C) triggers mechanisms to restrict future fusion events between the remaining spines of different neurons by stabilizing the intermediate stage of hemifusion. The spine heads p and q undergo hemifusion at the location where intracellular vesicles are fused with the cell membranes (conceptualized from [58].

will provide the necessary features for the IPLs to operate as a conditioning paradigm. A general observation is that cells that have a tendency to undergo inter-cellular fusion has the property of exocytosis. For example, acrosome reaction in the sperm that occur prior to the intercellular event of sperm-egg fusion [58] is a common finding. It shows that when the locations of membrane reorganization at the sites of exocytosis in two cells get abutted to each other, it predisposes those cells to get fused to each other. In this context, even though the interaction between spines that belong to different neurons started generating Type II semblance, it also led to an adverse sequelae of inter-spine fusion. Regions of AMPA receptor subunit vesicle exocytosis at the spine

head regions are locations that are predisposed to fusion **(Fig.4C)**. Fusion between the spines that belong to different neurons will be deleterious to both the neuronal cells since mRNA profiles of even adjacent neurons of the same type within a neuronal order are different [31-32]. This can lead to the development of homeostatic mechanisms for survival, such as loss of spines [60-61] or death of one of the neurons that undergo fusion [20-23] by activating certain molecular cascades (for example, that of apoptosis). This stage of evolution is expected to reflect as one of the stages during ontogeny. A significant amount of neuronal death that occur at one stage of neuronal development (see section 3) supports this.

5.7 Adaptations that prevented inter-neuronal inter-spine fusion

Since inter-neuronal inter-spine interactions that form IPLs has a major beneficial feature of sparking internal sense of previously associated sensory stimulus, it started providing certain survival advantages. Maintaining this feature necessitated preventing inter-spine fusion. Note that hemifusion is a stable intermediate stage of fusion [62]. These suggest that inter-neuronal inter-spine fusion has permanently switched on certain molecular pathways either at the gene or protein level that prevented future inter-spine fusion of the remaining spines of those neurons by stabilizing the inter-spine hemifusion **(Step 1 fusion prevention)**. This adaptation to stabilize the intermediate stage of inter-spine hemifusion maintained the IPLs and continued to provide the benefits of semblance formation for the internal sensation of several higher brain functions throughout life **(Fig.4D)**. Moreover, since physical properties of a very large number of items in the environment are shared, the repeated arrival of these stimuli needed a robust inter-spine stabilizing mechanism to operate throughout life. Since bringing lipid membranes close to each other is a high most energy-requiring processes [43-44], the default state of the spines is to remain independent structures. Due to the same reason, it can be expected that IPL formation is restricted to the smallest possible area of the membrane. The latter enables to protect the spines from undergoing fusion while enabling the propagation of depolarization for inducing internal sensations. In addition, the smallest possible area of the IPL will be advantageous to concentrate the ionic channels for better propagation of depolarization across it. Furthermore, it can reverse back quickly once the mechanisms to stabilize the IPL stop when a specific set of stimuli from the environment are no longer associated. Molecules and mechanisms that cause AMPA receptor endocytosis present at the postsynaptic membranes [63-64] favors reversal of the IPL. These features of IPL can be viewed as part of a favorable adaptation that was selected. In this context, one may ask, “Are there any molecular evidence to suggest that fusion had occurred between the spines at one stage and it was restricted to hemifusion later?” Studies of the spine have shown the presence of molecules are involved in synaptic vesicle fusion at the presynaptic terminal; but with new functions. SNARE protein is an example. SNARE proteins are known to facilitate very fast synaptic vesicle fusion with the presynaptic terminal for releasing neurotransmitter molecules from those vesicles into the synaptic cleft. Specific SNARE-operated molecular machinery capable of arresting inter-spine fusion at the stage of hemifusion is present in the spine [65-66]. Formation of hemifusion intermediates is characteristic of SNARE proteins, including that of neuronal SNAREs [57, 67]. Another protein synaptotagmin takes part in synaptic vesicle fusion at the presynaptic terminal. One variant, synaptotagmin 4, which is ubiquitously present in the spines [68] has unique features to regulate Ca2+-dependent exocytosis [69]. Additional proteins are also involved in the exocytosis at the spines [70]. These specialized proteins provide checkpoint mechanisms to prevent any inter-spine fusion by restricting inter-spine interaction only to hemifusion **(Fig.4D)**.

5.8 Adaptations that refined internal sensations

In the process of refining semblances to match with the sensory features of the item whose memory is being retrieved, it is most likely that certain variations and selection of suitable ones took place. The present day nervous system has pyramidal neurons that have an average inter-spine distance more than the spine diameter [59] **(Fig.5)**. This is in support of the formation of IPLs between spines that belong to different neurons as a default mechanism. These IPLs have features expected of a conditioning paradigm where it generates a) both internal sensations of memory of the second associatively learned item at the arrival of the first one, and b) concurrent behavioral motor actions reminiscent of the arrival of the second stimulus when the associated first stimulus was presented. With the selection of these neurons, it was possible to generate IPLs wherever the neuronal pathways of associatively learned sensory stimuli converged. This increased the efficiency of the system by maximizing both internal sensations and matching behavioral motor actions.

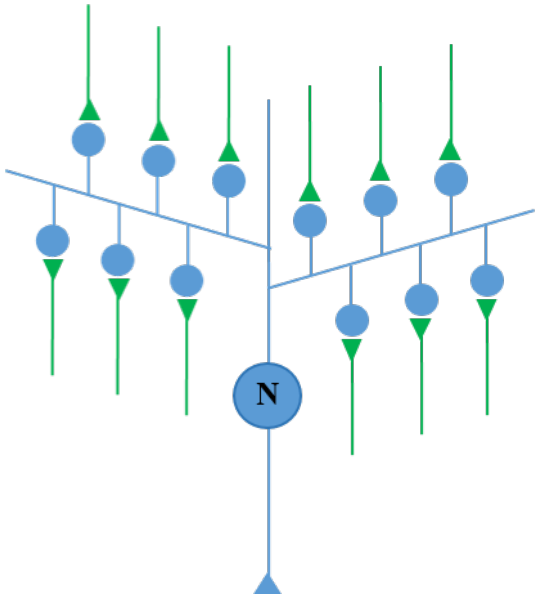

Figure 5: The selected new variant of neurons had mean inter-spine distance more than the spine diameter. Note the spacing between the dendritic spines (small blue round structures on the dendritic branches). This increased the probability of a spine belonging to one neuron to interact with a spine of another neuron. This provided generation of IPLs that were able to induce both units of internal sensations and motoric output expected of conditioned learning paradigms.

IPL mechanism started providing further advantages. Continued associative learning events allowed one spine to form IPLs with multiple spines and form large clusters of inter-LINKed spines. This favored the lateral spread of potential across the inter-LINKed spines. Since the direction of propagation of potentials through the IPLs is perpendicular to that of the synaptic transmission, it naturally led to oscillation of potentials involving large number of neurons of different neuronal layers of the cortex. This provided a binding property that provided natural computation of all the units of internal sensations. This refined the net semblance further **(Type III semblance) (Fig.6)**.

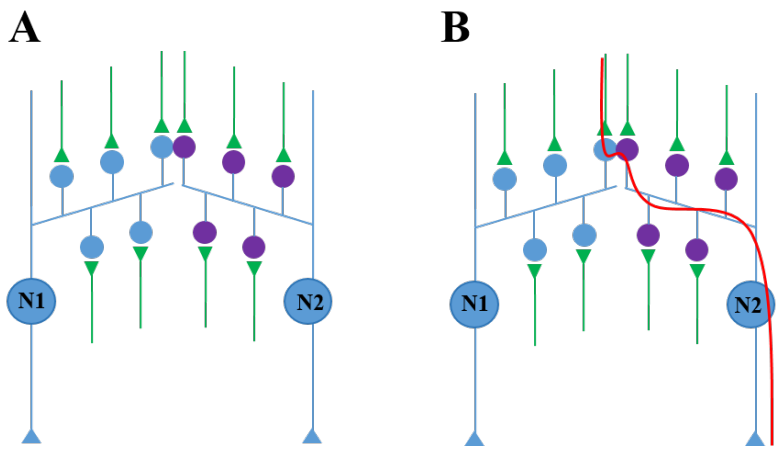

Figure 6: Inter-neuronal inter-spine interaction that leads to inter-postsynaptic functional LINK (IPL). A) Since the average inter-spine distance of new variants of neurons are more than their average spine diameter [59], it allowed spines from different neurons to become abutted to each other. In the figure, one spine each of neurons N1 and N2 (in blue and violet) are abutted to each other so that their simultaneous activation leads to the formation of an IPL between these spines. B) Formation of IPL enabled propagation of potentials in a lateral direction across them, which provides the vector component perpendicular to that of the synaptic transmission. Together they contribute to composite periodic signals across the neurons and their processes (shown by a waveform in red). The ionic changes generated by them in the ECM is responsible for the oscillating potentials recorded from the ECM.

5.9 Further refinement of internal sensations

Formation of different components of the extracellular matrix (ECM) separating the neuronal processes prevented inter-spine interaction by virtue of the by virtue of the presence of negatively charged side chains of proteoglycans that attract sodium ions, which in turn attract water molecules. This allowed the abutted spines to remain electrically separate by default **(Step 2 fusion prevention)**. In addition, different repulsive forces between the spines also prevent spread of depolarization in a non-specific manner within the system. Examination of electron microscopic pictures clearly shows that the ECM between the abutted spines of different neurons is very thin so that the insulating medium between those spines can be removed at the shortest possible distance to generate IPLs. Since high energy is required for excluding the insulating medium (hydration) [43-44], it is expected to be a highly reversible process and the initial formation of an IPL is highly reversible. Repeated formation of the same IPL can lead to its stabilization for varying period of time depending on several factors. As the number of IPLs within the system increased, it led to certain changes within their shared ECM space. The propagation of the potentials along the membranes has a proportional fluctuation of ionic changes in the ECM space. Fluctuations in ionic changes in the ECM space reflect on the recorded field excitatory postsynaptic potential (EPSP) changes [71]. Since the ECM space is being shared by all the neuronal processes, it allows integration of ionic changes generated in the ECM parallel to the intra-neuronal ionic changes **(Fig.7)**. Thus, the shared ECM space provides a unique opportunity to integrate the ionic changes occurring at different IPLs that are formed at the spine-rich area between the neuronal layers of the cortices (Note that since the dendritic arbor of neurons from different neuronal orders are anchored to the sub-pial region, their spines form IPLs in between different neuronal layers. This

can provide different extracellular waveforms depending on the location of extracellular recording electrodes). As the number of IPLs increased, it allowed binding of the units of internal sensations to form a more refined semblance **(Type IV Semblance)**. Ontogeny shows discontinuous oscillating extracellular potentials in EEG waveforms in prematurely born infants [72] (see subsection 6.3). Eventual filling of the discontinuities of oscillating extracellular potentials is expected to take place through the formation of additional IPLs.

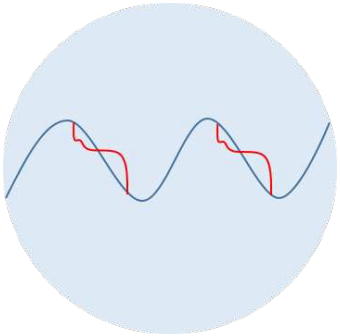

Figure 7: Oscillating extracellular potentials. Both learning and generation of internal sensations of higher brain functions occur only when a narrow range of oscillating extracellular potentials is maintained. These oscillations are the net effect of the large number of composite periodic signals (see **Fig.5B)** resulting from both synaptic transmission and propagation of potentials across the IPLs. Other factors such as recurrent collaterals and activity from feedback loops also contribute towards this.

5.10 Potential mechanism that further increases efficiency

There are a very large number of shared associations within the natural environment. At every moment, the system receives a very large number of (cue) stimuli from the environment that will force the system to induce internal sensations of their associated items. This will reduce the efficiency of the system significantly. This is expected to have generated several variations to avoid inducing separate internal sensations for them. The optimal variation is expected to suppress the semblances in response to all the common background stimuli and highlight only unique semblances induced by new features in the environment so that the animal can use the beneficial aspects of that environment and avoid sources of deleterious stimuli for its survival. What should be the features of the selected variation? The finding of continuous oscillating extracellular potentials at a narrow range of frequency suggests that the selected variation continuously reactivates all the inter-spine LINKs from common associations integrating all the induced semblances to form a net background semblance. This can be viewed as C-semblance, responsible for consciousness [73]. An optimal C-semblance provides a matrix upon which a more refined internal sensation of memory of the associatively learned items can be induced by the presence of a unique cue stimulus **(Type V Semblance)** (Table1). Even though the conformation of C-semblance will be largely influenced by the common associations of a given environment and species-specific features of neuronal assembly, it will also have contributions from all the previous associative learning events of an individual animal, which can explain the subjective aspect of consciousness.

Types of semblances	
I	Semblance at the inter-LINKed spines on the same neuron
II	Long-lasting semblance at the inter-LINKed spines on different neurons
III	Computation of large number of units of internal sensations in the background of oscillation of potentials between neuronal processes
IV	Semblance in the background of oscillating extracellular potentials due the presence of a continuous ECM space
V	Semblance induced in the background matrix of C-semblance

Figure 8: Table showing steps involved in different stage of evolution that eventually refined the net semblances to match with that of the item whose memory is being retrieved.

6 KEY MILESTONES OF ONTOGENY

6.1 Dendritic spine loss and neuronal death

The dendritic spine loss was studied in detail in mice. In young adolescent mice, 13% to 20% of the spines are eliminated in multiple cortical areas [60]. Focussed studies at L5 layer pyramidal neurons also showed a substantial loss of dendritic spines during the adolescent stage [60-61]. In comparison, apical dendrites of L2/3 pyramidal neurons show higher rates of formation and elimination of spines than L5 pyramidal neurons in both adolescent and adult mice [61]. Neuronal cell death is observed at various stages of neuronal development at different locations [20]. 70% of the cortical cells were found dying by embryonic day 14, which is reduced to 50% by embryonic day 18 [21]. Nearly 40% of the developing cortical interneurons are eliminated through Bax (Bcl-2-associated X)- dependent apoptosis during postnatal life [22]. Between 13 and 18 days of embryonic development, 67% of the motor neurons present in the motor column die [23]. Cell death also takes place in both subventricular and ventricular zones during embryonic development [74]. The above observations indicate that spine loss is a major stage during development. Since spine loss is not seen following this stage, it is reasonable to assume that it reflects an adaptive mechanism that triggered a cellular mechanism to prevent further loss of spines. The explanation that cells that were not able to generate successful adaptive mechanisms underwent apoptosis or cell death shows that there were additional factors regulating this process.

6.2 Anchoring of apical tuft regions of the dendritic tree to the inner pial surface

After reaching the inner pial surface area, neurons descent towards the direction of the ventricle. During this stage, their apical tufts remain anchored to the inner pial surface. This allows overlapping of the dendritic spines of the neurons that are finally settled in different cortical neuronal layers. This leads to the overcrowding of these spines that belong to different neuronal orders and makes it inevitable for the inter-neuronal inter-spine interactions to occur that lead to the

generation of IPLs.

6.3 Achieving continuity in oscillating extracellular potentials

Discontinuity of tracings in the electroencephalogram (EEG) among premature infants [72] suggests a discontinuity in the horizontal component of the oscillating extracellular potentials at the early stages of development. This is most likely due to insufficient number of IPLs. The eventual development of continuous EEG tracings matches with the formation of additional IPLs that leads to lateral spread of potentials across them. Continuity of oscillating extracellular potentials is expected to be a system property essential for integrating the semblances.

6.4 Regulation of IPL formation by dopamine

Dopamine is phylogenetically an old neurotransmitter molecule [75]. Following the initial presence, dopamine was absent for a long time during phylogeny. It is possible that dopamine was not efficient than other neurotransmitter molecules. Reintroduction of dopamine at a later stage in the evolution [75] matches with dopamine's spine enlargement action [76] that can promote IPL formation facilitating associative learning. The release of dopamine during motivation promoted learning [77] also have a similar mechanism. It was found that experiments that provided excess dopamine at locations where dopamine is known to have actions (such as the nucleus accumbens and striatal neurons) resulted in dye coupling between neurons [78-79] indicating that inter-spine fusion is at the extreme end of the normal IPL mechanism [16].

6.5 Regulation of excitation

Potentials arriving trough the IPLs formed by the spines of excitatory neurons might have led to excessive excitation of these neurons. Controlling this was possible only by selecting variants among cells that started expressing glutamate decarboxylase enzyme that catalyze the formation of gamma amino butyric acid (GABA) from glutamate. These inhibitory neurons started inhibiting the outputs of excitatory neurons, practically raising their threshold for action potential generation. It is possible to regulate the excitatory neurons at different levels [80-82].

6.6 Comparatively long duration for development in humans

Humans with advanced nervous system have a comparatively long duration for brain development after birth. This indicates that a) our nervous systems have undergone more stages during evolution than other animals, and b) exposure to the environmental stimuli has a role in optimizing the system along the lines of its evolutionary stages to generate IPLs for the generation of internal sensations that provide survival benefits.

6.7 Significant role of age in neurodegenerative disorders

The spectrum of IPL mechanisms has the vulnerability to progress towards IPL fusion. The known mechanisms to prevent fusion include a) mechanisms that are inherent to the lipid membranes due to repulsive forces between them [39-41], and b) action of modified proteins that prevent inter-spine fusion [65-66] (see subsection 5.7). These mechanisms can fail due to several age-related reasons. These include changes in expression of proteins necessary for a) synthesizing, elongating, and

modifying fatty acids, and b) maintaining checkpoint mechanisms that stabilize intermediate stage of hemifusion. Since maintaining an optimal IPL mechanism is necessary for cognitive abilities, any IPL fusion can lead to cytoplasmic content mixing, protein precipitation and triggering of spine loss and eventual neuronal death [83].

7 DISCUSSION

7.1 What does structure inform about function?

Following the last division, neurons migrate in a radial fashion, which is responsible for the columnar organization of neocortex in primates [84]. What determined the columnar nature of cortical neuronal assembly? Since net internal sensation is expected to be the result of a combined effect of all the units of internal sensations generated, the system might have optimized inter-spine interactions by a) maximizing an even distribution of inputs arriving the cortex, and b) organizing the neurons in layers that allow the dendritic arbor of all the neuronal layers mix with each other. In other words, the structure that we see is the result of evolution in an effort to naturally fine-tune internal sensations of various higher brain functions. Most importantly, it has facilitated the generation of memory of a previously associated item to match with that of the actual sensory stimuli that arrived from that item. The columnar organization has also facilitated to optimize the C-semblance (see subsection 5.10). The narrow range of frequency of oscillating extracellular potentials when recorded between specific locations in all the humans is the result of this optimization process. Humans and macaque monkeys diverged from a common ancestor nearly 23 million years ago [85]. The ratio between the surface area of neocortex of macaque monkeys and humans is approximately 1:10 without having significant differences in thickness [86] or cyto-architectural organization [87]. What changes might have contributed to the higher cognitive abilities of humans? According to Rakic and Kornack, the larger cortical surface area in humans compared to monkeys is likely due to two reasons. a) Formation of more founder cells at the periventricular region due to an increase in the number of initial mitotic symmetric cell divisions at the ventricular zone secondary to a delay in the initiation of the second phase of asymmetrical cell division, and b) Formation of 15-fold more post-mitotic cells in humans compared to macaque monkeys that are compacted within the cortex without affecting its thickness [35]. The dense arrangement of neurons increases the probability for spines that belong to different neurons to interact and generate comparatively more IPLs during a given associative learning event. This has also facilitated the formation of large islets of inter-LINKed spines that enables interconnecting several findings from the environment. This can facilitate induction of interconnected internal sensations that enables identification of relationships between disparate findings in the environment. This explains improved hypothesis building capabilities in humans.

7.2 Transient inter-cellular fusion is a necessary stage

Dye coupling occurs between the neuronal cells at different stages of ontogeny [27, 29-30]. How did this contribute to the evolutionary stages? Dye coupling can be explained in terms of IPL fusion. Dye coupling was followed by uncoupling as the cells migrated away from the ventricular zone towards the sub-pial zone. However, since the apical tuft region of all the neurons anchors to the sub-pial region before the cell bodies move towards the direction of the ventricle, it results in overcrowding of spines that belong to different neurons. This again leads to IPL fusion as evident

from a second stage of dye coupling [29-30]. This stage is also followed by uncoupling. Mixing of the cytoplasmic contents between neurons at these stages of evolution likely triggers the expression of proteins that prevent further inter-spine fusion by stabilizing the inter-spine interaction at the stage of hemifusion **(Fig.8)**. These events show that arresting the stage of IPL hemifusion is a probable adaptation that requires a transient inter-cellular fusion at one stage of evolution.

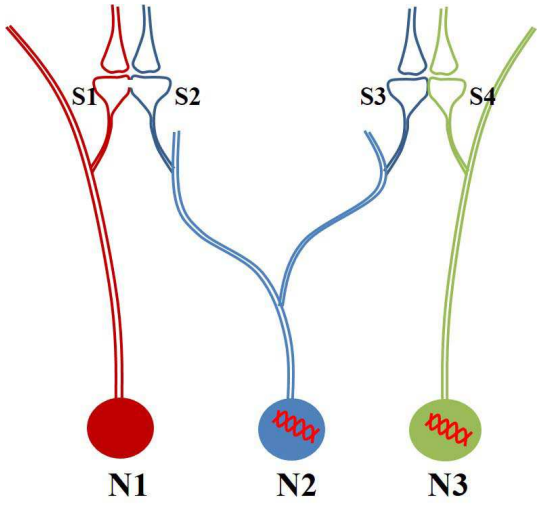

Figure 9: Inner-neuronal inter-spine fusion triggers long-lasting cellular mechanisms for stabilizing inter-spine hemifusion. Spines S1 and S2 of neurons N1 and N2 respectively undergo fusion at an early developmental stage. Since neuron N1 could not remove the spine S1, cytoplasmic contents from neuron N2 continued to mix with its cytoplasm and neuron N1 underwent apoptosis. However, entry of cytoplasmic content from neuron N1 to neuron N2 triggered 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 sensation.

The necessity for transient inter-cellular fusion at one stage of development can be viewed as an optimal event that prevents IPLs not to proceed beyond the stage of IPL hemifusion that maintains the basic mechanism necessary for the generation of internal sensations. In short, adult animals are dependent on developmentally-primed neurons for optimal IPL formation and maintenance. It is observed that a) 13% to 20% of the spines are eliminated in young adolescent mice in multiple cortical areas [60], and b) 70% of cortical cells are found to be dying by embryonic day 14 and get reduced to 50% by embryonic day 18 [21]. Since it may only be necessary for one or few spines out of large number of spines of a neuron to undergo fusion for triggering mechanisms to arrest any future fusion events by stabilizing the intermediate stage of hemifusion, it is reasonable to expect that all the surviving neurons have completed triggering this mechanism.

7.3 Vulnerable state of the spines continues

It was necessary to undergo inter-neuronal inter-spine fusion to permanently switch on a mechanism to sustain stable inter-spine interactions during the rest of the life of those neurons. At this juncture, it becomes very important to know "How long can a neuronal cell sustain such mechanisms?" Since aging is the most important risk factor for the development of neurodegenerative

disorders such as Alzheimer's disease [12], it is reasonable to view that aging leads to certain defects in this mechanism. The reports of spine loss at different time intervals following normal associative learning [88-89], show that IPL formation leaves the spines with some vulnerability to undergo IPL fusion. Furthermore, normal aging is associated with dendritic spine loss [90]. Losing spines reduce the computational elements available for generating various internal sensations. Continued loss of spines will eventually cause a functional decline in various cognitive domains, which is a hallmark of neurodegenerative disorders. Furthermore, introduction of excess dopamine at locations where dopamine is known to have actions (such as the nucleus accumbens and striatal neurons) results in dye coupling between neurons [78-79] indicates stabilizing mechanisms of inter-spine interactions are vulnerable to progress to IPL fusion.

7.4 Are the factors stabilizing IPL hemifusion used for controlled spine loss?

Since spine elimination is observed in several normal and pathological conditions [91], it may be operating by regulating the adaptive mechanism that was evolved to prevent the IPL fusion. Investigating this can provide further information.

7.5 Is it possible to artificially maintain the adaptive mechanisms?

Normal aging is associated with both dendritic spine loss and neuronal death [90]. Since IPL fusion is expected to lead to neurodegenerative disorders [83], it is probable that the neurons are able to maintain the mechanisms that stabilize IPL hemifusion. Can we identify those factors and find methods to prolong their supply? The finding that dopamine D4 receptor (DRD4) genotype can predict longevity in mouse and human [92] indicates that excess of dopamine in old age may promote IPL fusion and neurodegenerative changes. Maintaining optimal lipid membrane composition by preventing defects in lipid metabolic pathways of synthesis, elongation or saturation is another area that can be explored towards achieving this goal.

8 Conclusions

How did the human nervous system evolve to the present state? Theories of evolution beginning from Darwin have examined selection based on an increase in the brain size [93]. Compared to other primates, humans have higher order forebrain systems that have undergone major modifications [94]. However, a recent study has shown that the size of the human frontal lobes increased only proportional to the increase in size of other cortices [95]. Other work has shown that the prefrontal regions of both human and non-human primates holds about 8% of cortical neurons [96]. These findings necessitate a new explanation for the advanced cognitive abilities of humans. There are more synapses (both symmetrical and asymmetrical) per neuron in layer II and III in humans than in rat and mouse [97]. This may be contributing to the formation of more IPLs that can increase the internal sensations of the qualia of computed net semblances. Based on the semblance hypothesis, formation of large islets of inter-LINKed spines is necessary for hypothesis formation. Ability to stabilize the IPLs is necessary for long-term memory storage. To confirm that these are factors contributing to the higher cognitive abilities of humans, it is necessary to demonstrate the differences from that of the brains of chimpanzees [98]. Whether the increase in surface area of the cortex in humans has a) increased the number of IPLs and provided more functional units

for computation, or b) increased the size of islets of inter-LINKed spines, or c) increased their efficiency in building hypotheses is yet to be examined. It is also necessary to understand what kind of changes in the timing of the developmental stages (heterochrony) out of many kinds of possible events [99] might have led to the generation of different primates. The present work provides several heuristic avenues for further exploring this area of investigation.

The necessity of this work stemmed from the unknown nature of the mechanism of a) normal nervous system functions, and b) its disorders. When confronted with such a dilemma, we are left with one option to derive a theoretically suitable operational mechanism of the system using constraints from all the findings from different levels and examine whether it has features of a mechanism that was evolved through the simple steps of variations and selection. Based on the derived mechanism of IPLs, a unique cellular change that can store information for varying periods from which information can be retrieved in the form of first-person inner sensations concurrent with behavioral motor actions became possible. The IPL mechanism has the capability to inter-LINK additional spines during related learning, generating islets of inter-LINKed spines. This ability is expected to interconnect internal sensations of memory of large number of related items, triangulate sensory evidence and formulate hypotheses to make predictions about items and events in the environment. This matches with the expectations of a guiding principle for the improved cognitive capabilities as humans. Language enabled communication between members of the species and external storage of knowledge from other members who experienced the outcomes of learning different associations and the outcome of their behavioural actions. This enabled further fine-tuning of the inner sensations for directing actions to maximize the rewards for survival.

Even though studies have shown some increase in the cell survival when genetic manipulations against apoptosis were carried out, they did not gain any useful function [100-101]. In fact, such methods can stop the development of precise mechanisms that generate a spectrum of IPL formation necessary for learning and induction of various types of internal sensations. This is evidenced by the findings that normal brain development is severely affected when genes involved in apoptosis are genetically manipulated [102-103]. This indicates that manipulation of genetic make up of an evolved system in the middle of its development may in fact disturbs a heritable adaptation. Since evolution can only move forward in one direction [5], it can be inferred that the genes responsible for apoptosis were evolutionary selected to subserve a function and that a transient stage of inter-cellular fusion was a necessary stage in the evolution of the nervous system. It is viewed that once we understand the cause for neuronal cell loss during development, it may help to understand the pathophysiology of neurodegenerative disorders [25]. The unique observation of significant neuronal death at one stage of development provides crucial information about possible evolutionary stages of the nervous system **(Fig.9)**. The fact that the IPL mechanism derived by the semblance hypothesis has provided probable explanations for the different findings during ontogeny suggests its suitability to be an evolved mechanism. The inference made from these observations that transient inter-spine fusion is a necessary triggering event to permanently switch on certain mechanisms to prevent future inter-spine interactions to progress beyond inter-spine hemifusion needs experimental verification. Since this finding can allow us to prevent age-related neurodegenerative disorders to a certain extent, it provides optimism to verify the derived operational mechanism of nervous system functions.

LIST OF ABBREVIATIONS: AMPAR: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, Bax: Bcl-2-associated X, ECM: Extracellular matrix, EEG: Electroencephalogram EPSP: Excitatory postsynaptic potential, GABA: Gamma amino butyric acid, IPL: Inter-postsynaptic functional LINK, LTP: Long-term potentiation, NMDAR: N-methyl-d-aspartate receptor, Pre: Presynaptic terminal, Post: postsynaptic terminal, dendritic spine or spine, SNARE:

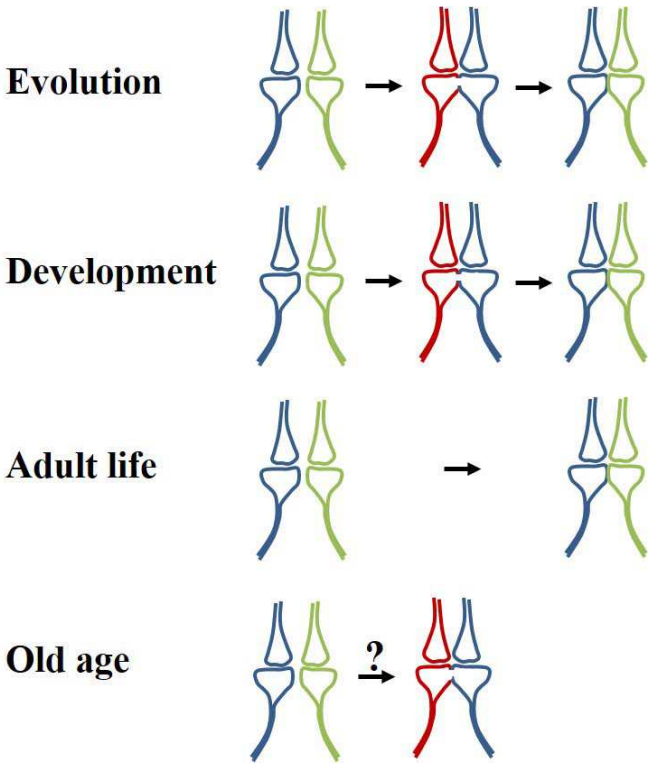

Figure 10: Potential evolutionary stages of the nervous system inform us regarding age-related neurodegeneration. A pair of synapses at the location of convergence of associatively learned sensory stimuli undergoes a transient stage of inter-postsynaptic fusion that triggers a mechanism to stabilize the IPLs at the stage of hemifusion. In other words, the event of fusion during development primes the neurons with the ability to restrict all the inter-spine interactions in adult life to the stage of hemifusion. Since the checkpoint mechanism most likely depends on gene expression to provide proteins that a) directly stabilize the hemifused area, and b) contribute their function as enzymes for generating stable lipid membrane composition, age-related changes can alter this mechanism. This opens the possibility to investigate the details of this checkpoint mechanism towards restoring it by artificial means.

soluble NSF (N-ethylmaleimide sensitive fusion protein) attachment protein receptor.

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

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