A mechanism of nervous system functions capable to have evolved: by generating an inducible variant of inter-cellular fusion

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Abstract

A realistic hope has been that it may become possible to understand the steps of evolutionary changes from ontogeny, which may assist in understanding the mechanism of nervous system functions. However, explaining how first-person internal sensations are formed in the nervous system makes this approach very difficult. In this context, if it becomes possible to derive an operational principle by using constraints from observations at different levels, then it will enable examining whether it is possible to arrive at its specific circuit features from single neuronal cells using simple steps of introducing variations and selection. In this context, semblance hypothesis is examined. Inter-neuronal inter-spine interaction leading to the formation of inter-postsynaptic functional LINK (IPL) is necessary for generating units of internal sensations and their computation. The results show its suitability as an evolved mechanism. Significant neuronal and spine loss during ontogeny indicate that following these events, IPLs resulted from the selection of a suitable variation. This can only be achieved through transient inter-neuronal inter-spine fusion, which leads to inducible molecular changes for keeping the spines separate by arresting fusion at the stage of hemifusion. The importance of sustaining this one-time induced IPL mechanism for retaining cognitive functions throughout life is discussed.

1 Introduction

"Does understanding how or why a brain evolved helps to decipher how that same brain works?" (Striedter 2007). This is a thought-provoking question and is associated with a difficult puzzle that does not provide any clue where to begin to solve it. This difficulty is due to the fact that we haven't understood how the brain generates first-person internal sensations within it with details that will enable us to undertake the gold standard of replication in an engineered system. In this context, to answer the above question it is necessary to build a hypothesis of brain functions and examine whether it is capable of evolving to reach its present stage. At one stage of evolution, motor capabilities were the prominent survival mechanism of animals in a predator-prey relationships. Initially, operated through reflexive motor actions, the system further evolved to acquire the feature of first-person internal sensations of memories of past events and associations. Eventually, it led

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to the generation of thought process for informed decision making. This transition from reflexive motor action to the internal sensation of memories, and to hypothesis building is expected to have evolved through certain key milestones, knowledge of which is essential to understand the brain development, function and its disorders.

Since generation of first-person inner sensations is the key function of this system that enables the animal to take decisions based on previous experiences, the changes in the system is expected to fine-tune and maximize the rewards by generating the best possible internal sensations of both memories and predictions. In this regard, while considering the fact that selection acts upon neural output for behavior (Arbas et al. 1991), it is equally important to consider the generation of suitable internal sensations that can provide informed decision making. In fact, internal sensations have dominated over the ability for motor action for survival. In the above contexts, it is expected that once we understand the mechanism of operation of the system, it will reveal the stages of evolution of neuronal processes that gradually started generating internal sensations within the system.

Darwin's theory of natural selection (Darwin 1859) has two main features. 1) Offspring are 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. The heritable traits of fitter variations will eventually get spread in the population. In this process, the nerve cells are also expected to undergo a large number of variations. Some examples of changes that are observed at the synapses, dendrites and even neurons themselves were reviewed (Arbas et al. 1991). The difficulties in understanding the evolution of the nervous system, using the interpretations of structure and function were discussed previously (Niven and Chittka 2016). In the context of the difficulty in accepting cortical structural patterns, both as the units of development and evolution (Finlay and Brodsky 2007), the major question is "Did natural evolution led to the generation of any type of unitary structure-function mechanism?" "If so, what was the natural driving force behind it?" "How are these unitary mechanisms associated with selecting variations to optimize the computations that generate internal sensations?"

Even though there are some evidence suggesting rapid evolution through minor changes in existing neural circuitry (Chittka et al. 2012), further progress is difficult without knowing how the nervous system functions. Ontogeny is the development of a single individual, or a system within the individual, from the fertilized egg to maturation and death (Smith 1960). Even though 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 (Russell 1916), Haeckel himself identified two types of deviations from this - change in position (heterotopy) and change in order of succession of changes (heterochrony). However, it is reasonable to expect that using ontogeny a rough sketch of probable events during evolution can be made. 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 (Parker and McKinney 1999). Since evolution cannot make the nervous system to unwire to "start over," the solution that it has reached are constrained by its evolutionary history (Niven and Chittka 2016). Therefore, once we understand the mechanism of nervous system functions, a forward moving sequence of events are expected to be reached.

A reasonable expectation is that hypothesis development for understanding brain evolution will require that the hypothesis be explicit about the nature of networks and the nature of the computations embodied in it (Finlay and Brodsky 2007). It is viewed that evolution can cause phase transitions to bring new phases with new properties with their own internal grammars that

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describe their computational complexity (Solé 2016). Our task is to examine how the nervous system generated its cognitive abilities that provides an exemplary advantage for survival as an autonomous system. The difficulty is that inner sensations of higher brain functions are first-person properties to which only the owner of the nervous system has access. One of the methods to solve the system is to derive a basic operational principle explaining how first-person internal sensations are generated by using constraints from all the third-person observations from different levels. The strength of the solution depends on whether it can triangulate findings from different levels of both normal and "loss of function" states of the system. It is also viewed necessary to examine top-down effects such as the evolutionary and developmental aspects of the system function, since the lower level elements are adapted to perform their higher level functions (Ellis 2018). One method of verification is to examine whether the circuit features that incorporate the operational mechanism have the feasibility for getting evolved through the introduction of variations and selection of best fitting ones several times, to arrive at the present day nervous systems.

1.1 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-established to get efficiently reproduced during different stages of development. Since ontogeny provides information regarding the events taken place as the nervous systems were evolving, the true mechanism of operation of the system is expected to provide substantial evidence to match 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 they converge to associate them. 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) from an item, when one of the associated stimuli from that item 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 (Minsky 1980). 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 (Vadakkan 2007, 2013, 2016a, 2019). A summary of the mechanism is given in **(Figure 1**. Present work specifically aims to examine its evolutionary suitability. Formation of inter-postsynaptic functional LINKs (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 self-feed, procreate and protect from harmful stimuli among lower forms of animals indicate that they generate some form of internal sensations. It is possible that several species of animals branched out after acquiring this property. Since there were only limited options for neurons to self-organize, it is expected that the event of evolution involves simple steps.

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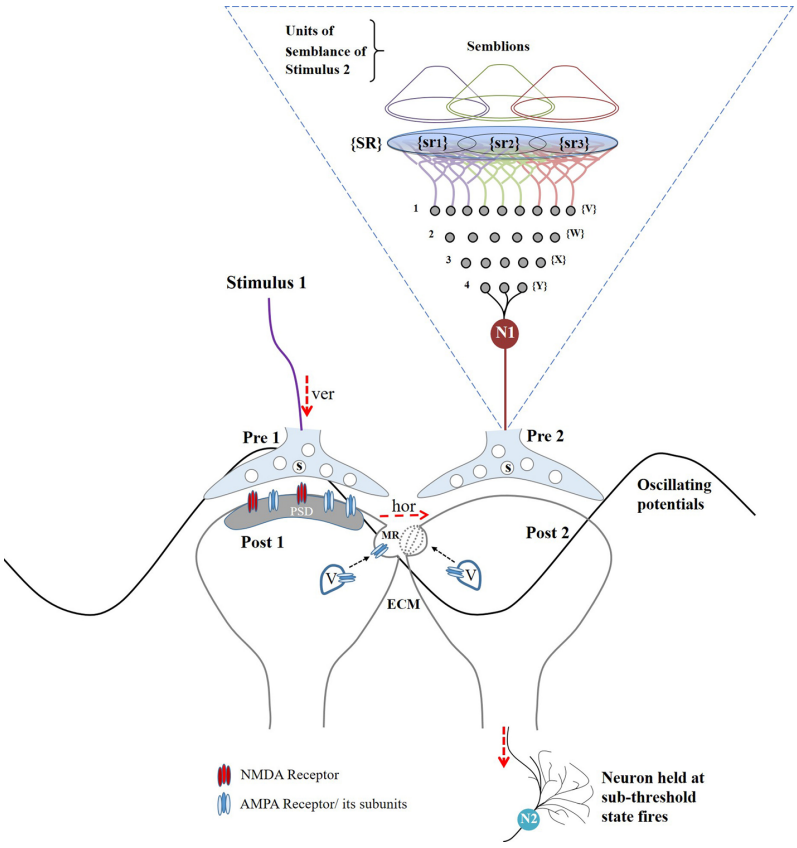

Figure 1: Learning induced change that can generate units of internal sensation during memory retrieval. When associatively learned stimuli 1 and 2 arrive through presynaptic terminals 1 (Pre 1) and 2 (Pre 2) respectively where postsynaptic terminals Post 1 and Post 2 are abutted, inter-postsynaptic functional LINK (IPL) is generated. This is facilitated by membrane reorganization (MR) taking place at the lateral spine margins of the spine heads in milliseconds by exocytosis of vesicles (V) containing AMPA receptor subunits at these locations. For memory retrieval, when stimulus 1 arrives at postsynaptic terminal 1 (Post 1), it reactivates the IPL and induces semblance (hallucination) at the postsynaptic terminal 2 (Post 2) that was previously activated by stimulus 2. The sensory qualia of units of internal sensations induced at the inter-LINKed postsynaptic terminal Post 2 are determined by identifying a minimum set of stimuli (called semblion) needed to stimulate specific subsets sr1, sr2 etc. of sensory receptor set SR whose activation is able to activate Post 2. In order to identify the sensory qualia of semblions, a retrograde extrapolation from the inter-LINKed Post 2 towards all the sensory receptors from which it used to receive inputs in the past is carried out. The semblance is a virtual first-person internal sensation of the sensory properties of the associatively learned stimulus 2 and is shown in an inverted dotted triangle (Note that no neurotransmission is taking place in the circuitry within this triangle at the time of memory retrieval). When the best possible computational product of all the semblions induced at several inter-LINKed spines in the nervous system that match with the sensory features of stimulus 2 is generated, it forms memory of stimulus 2. This computation is a system property of systems where the perpendicular direction of synaptic transmission (ver: vertical) and propagation of potentials along the IPL (hor: horizontal) contribute to a specific range of frequency of oscillating extracellular potentials (shown as a wave form). ECM: Extracellular matrix; s: synaptic vesicle (Figure modified from Vadakkan 2013).

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1.2 Role of non-adaptive determinants in 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 (Dumont and Robertson 1986). Significant number of neurons were found to die at different locations at different stages of development (Glucksmann 1951; Blaschke et al. 1996; Southwell et al. 2012; Lance-Jones 1982). The molecular mechanisms underlying apoptosis were shown to be evolutionarily conserved (Metzstein et al. 1998). 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 (Oppenheim 1991). 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. This shows 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 as one of major importance (Dekkers et al. 2013).

Dye injection experiments have shown neuronal coupling at early stages of the mitotic phase at the ventricular zone (Bittman et al. 1997). This was followed by its reversal. Post-mitotic cells then migrate from proliferative ventricular zone to become layers in the cortical plate as a sheet (Rakic 1995). Dye coupling between neuronal cells were also found during later stages of development (Gutnick and Price 1981; Yuste et al. 1995). These were followed by uncoupling between neurons. These inter-cellular coupling followed by uncoupling during different stages of ontogeny indicate that transient forms of inter-neuronal fusion had occurred during different stages of evolution. The resulting mixing of the cytoplasmic contents between 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 are different as evidenced by their different mRNA expression profiles (Kamme et al. 2003; Cembrowski et al. 2016). 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 favours the following. a) Transient inter-cellular fusion that triggers mechanisms to prevent such fusion events is a probable variation that was selected during evolution. b) Transient inter-cellular fusion, allowing cytoplasmic content mixing is necessary to trigger certain cellular mechanisms to prevent inter-cellular fusion, and c) the selected variation that cause transient inter-cellular fusion leads to expression of genes to prevent IPL mechanisms to undergo IPL fusion.

1.3 Theory of continuity of mind

The importance of understanding the circuit mechanism that generates cognitive abilities is regarded as important in understanding hereditary variations in cognition (Chittka et al. 2012). 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. (Subiaul et al. 2007) the best possible answer lies in the theory of continuity of mind by Charles Darwin (Darwin 1871), which 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?" (Subiaul et al. 2007). How does an increase in brain size subserve additional functions? One hypothesis is that as brains get bigger, more specific aspects of

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sensory stimuli may provide the correlational structure necessary to allow the segregation of new, functionally specific cortical areas (Finlay and Brodsky 2007). It is estimated that the mammalian ancestor originated nearly 250 million years ago and since then the neocortex has undergone expansion primarily in surface area rather than the thickness (Rakic and Kornack 2007). In agreement with this, cognitive skills resulting from general intelligence were shown to have strong empirical correlations with brain size and executive functions (Burkart et al. 2017). Can computation of internal sensory units from a large cortical area improve the cognitive abilities? It is reasonable to expect that the true operational mechanism can provide answers.

2 Major Stages of Development

Following are the most probable steps starting from the arrival of simple neuronal cells to the final circuitry that can provide the expected operational mechanism. These stages are numbered arbitrarily. Following this, key ontological stages that match with some of the key milestones in the evolution are examined.

2.1 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. 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 other 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 the neuronal processes takes place by the addition of new membrane segments through exocytosis of plasmalemmal precursor vesicles (Pfenninger 2009). Both input and output terminals of neurons further branches out. Input terminals formed a tree-like structure called dendritic tree. Further specialization of the dendritic branch tips is called dendritic spines (also called postsynaptic terminals after they form synapses). The output processes at the end of axonal terminals are presynaptic terminals.

2.2 Multi-cellular interactions

When excitable neuronal cells started interacting with each other, their inter-cellular communication was to generate a provision for transmitting depolarization to the neighbouring neurons. 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.2A)**. In neurons that are close to each other, passive conduction of depolarization along the cell membranes to transmit information from one end of the cell to the next cell is found suitable (Dowling 2009). As the neuronal cells moved away from each other, it was necessary to transmit information to long distances. It was necessary to summate the depolarisations arriving at the axon hillock region of a neuron to form a large spike of depolarization called an action potential, which was able to propagate to long distances. An alternate explanation is also possible. Since branching of input connections generated arrival of a large number of inputs at

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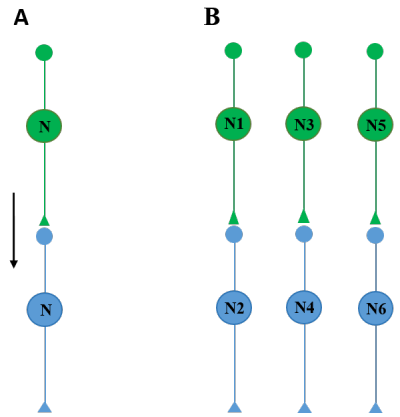

Figure 2: Neuronal cells and their processes. A) Two neurons (marked N) that are connected through a synapse between the output region of a neuron and input region of another neuron. Direction of neurotransmission is shown by a black arrow. B) Six neurons formed from progenitor cells migrated to form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

the same time, instead of responding to every input, neurons might have developed a threshold for firing an action potential that can be propagated to all its output terminals.

2.3 Electrically isolating the spines from each other

The first order of neurons in a chain of synaptically-connected neurons acquired sensory receptors that depolarize the membrane when they receive sensory inputs from the environment. When neurons that were formed from progenitor cells migrated, they formed several neuronal orders **(Fig.2B)**. This also allowed the regions in between those neuronal orders to get crowded with synapses. How was the synaptically-connected neurons separated from each other? The outer layers of lipid membranes of the spines of a neuron are electrically separated due to the presence of electrostatic forces between them (Disalvo et al. 2008; Song et al. 2014; Dreier et al. 2018). It is necessary to overcome the counteracting electrostatic forces for enabling interaction between the outer lipid membrane layers (Jahn et al. 2003). This is **Step 1 fusion prevention**. Bringing lipid membranes together is considered as one of the most energy-demanding processes (Cohen and Melikyan 2004; Martens and McMahon 2008).

2.4 Intra-neuronal inter-spine interaction

Neurons formed densely located spines on their dendritic arbors **(Figs.3A, B)**. When two abutted spines of the same neuron received associated sensory stimuli from the environment, an IPL was formed between them. This interaction was limited to removal of repulsive forces between the spines. This IPL was a rapidly reversible one. 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 that it is receiving sensory input through its presynaptic terminal (for details, see Vadakkan 2013). Semblance is an element of hallucination

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expected to form within biological systems for generating internals sensation of memory (Minsky 1980). This short-lasting hallucination is responsible for the qualia of the internal sensation and it is very primitive. Note that this hallucination is occurring from a first-person perspective and only the system senses it as an internal sensation. This crude form of hallucination that lasted only for a very short time is **Type I Semblance**.

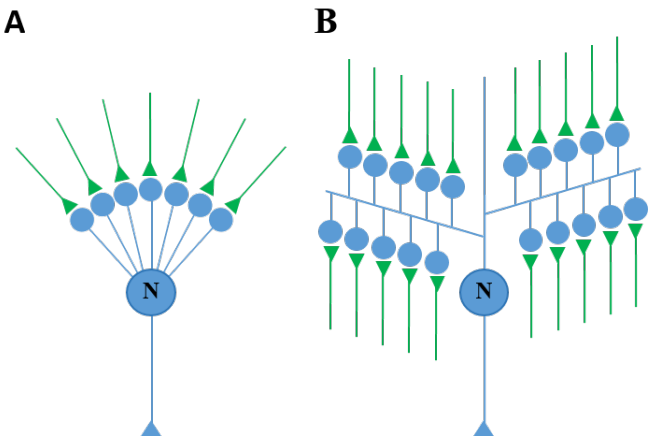

Figure 3: A) Highly dense dendritic spines (inputs) on a neuron at the early stages of development of single neurons. As the number of inputs increased, to prevent neuronal firing for every input arriving, selection of variations among neurons brought neurons with threshold for firing. Neuronal firing was the major functional property within the system that allowed propagation of activity to higher neuronal orders that allowed basic motor functions. Note that many of the spines are abutted to each other that can allows 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.

Type 1 semblance can be considered as the initial stage that further developed to form various internal sensations. Semblance (hallucination) is generated due to unique circumstances that are prevailing at the location of inter-spine interaction. Its occurrence necessitates one essential feature – *to trick system to momentarily hallucinate, something else should be dominating all the time*. What is dominating is the continuous activation of the spine head by the quantal release of neurotransmitter molecules from the presynaptic terminal and intermittent depolarization of the postsynaptic terminal when a volley of neurotransmitter release occurs when action potentials arrive at its presynaptic terminal. Transient IPLs between the spines of the same neuron provide only transient generation of internal sensations and outputs. Further refinement of the internal sensations generated in the system is explained from sections 2.9 to 2.12.

2.5 Suitability of Earth for the evolution of the nervous systems

From the above section, it is clear that for tricking the system to hallucinate, the depolarization of the spine head by neurotransmitter molecules arriving from presynaptic terminal should dominate. How can the system make sure the existence of such a dominating state? For this, it should also be possible to achieve one or more of the following. a) Minimize all the lateral activations through the IPLs. At night, in the absence of light, number of cue stimuli arriving to induce internal sensations will be very minimal. In this context, night time without light provided a suitable period that prevented lateral activation by light stimuli. In effect, this is equivalent to

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shutting down the system. b) For minimizing lateral activation, it is necessary to minimize all the incoming sensory stimuli by shutting down the system. c) Block the integration of units of internal sensations, if such a mechanism exists. These factors allowed depolarization of spine heads by neurotransmitter molecules from the presynaptic terminals to dominate. In other words, sleep became a substantive part of the system operation that periodically re-instates the dominant state of postsynaptic terminal depolarization resulting from the arrival of neurotransmitter molecules from its presynaptic terminal (Vadakkan 2016b). It is in this dominant state of the system that an incidental lateral activation induces hallucination (semblance). In other words, the system gained the property to induce units of internal sensations of the associated second stimulus at the arrival of the first or fastest arrived stimulus (cue stimulus). Transient IPLs between the spines of the same neuron provide only transient generation of internal sensations and outputs.

2.6 Stabilization of inter-cellular interactions

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 (Lee et al. 2007; Vashi et al. 2017). 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 vesicles containing different types of AMPAR (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) subunits at the spine head region of postsynaptic terminals (Shi et al. 1999; Passafaro et al. 2001; Park et al. 2006) **(Fig.4A)**. Since learning and LTP occlude with each other in either direction (Moser et al.1998; Whitlock et al. 2006), their cellular level mechanism is expected to have common shared feature. The IPL mechanism provides matching explanations how learning changes occurring at physiological timescales are scaled-up during LTP induction (Vadakkan 2019). 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 expected to occur on the lateral margins of the spine heads close to the synapse. Experimental findings also support this (Makino and Malinow 2009). This also matches with the finding that AMPAR GluR1 subunits are concentrated on the postsynaptic membranes within 25nm from the outer synaptic margin (Jacob and Weinberg 2015).

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 membrane reorganization at the lateral spine head regions **(Fig.4B)**. SNARE proteins are known to mediate fusion of vesicles containing AMPAR subunits with the spine membrane (Lu et al. 2001; Kennedy et al. 2010). It is also known that SNARE protein pull membranes together very tightly (Hernandez et al. 2012). These factors significantly overcome both the electrostatic forces that repel the membranes and hydration exclusion between the spines. This leads to the formation of electrical continuity between the spines that will allow propagation of depolarization across them in either direction.

2.7 Inter-neuronal inter-spine interaction

IPLs between the spines of the same neuron are transient in their interaction. Moreover, these IPLs will reduce the surface area of inputs, which will defeat the very purpose of their structural feature. Stabilizing such IPLs will not provide much functional advantage since the type I semblance is very primitive in nature. Furthermore, since inter-LINKed spines belong to the same neuron, it

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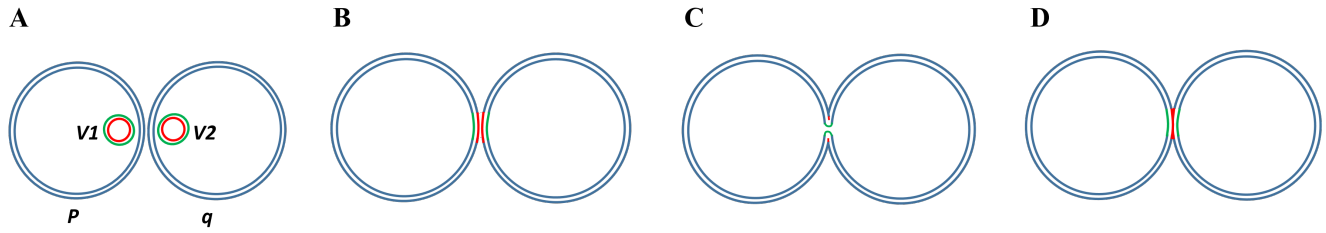

Figure 4: Inter-spine interaction that led to their fusion, which was followed by generation of variation that prevents fusion by forming hemifusion. A) Cross-section through two spine heads marked p and q each having one intracellular vesicle inside them close to the locations where these cells are abutted to each other. B) The fusion of the vesicles with membranes of the lateral aspects of the spine heads shown in Figure A) leads to mild enlargement of the total surface area of these spines. Spines surrounded by ECM will not be able to able to expand uniformly; instead, it often increases the curvature of the local membranes at the locations of exocytosis (not shown). C) The spine heads p and q undergoes fusion. Dendritic spines of two different neurons act like two independent cells. When inter-neuronal inter-spine fusion remains, mixing of cytoplasmic contents will cause spine loss and eventual neuronal death. From ontogeny, it is deduced that transient fusion at one stage is necessary to trigger mechanisms to restrict future fusion events of their spines with spines of other neurons only up to the stage of hemifusion. D) The spine heads p and q undergo inter-spine hemifusion at the location where intracellular vesicles are fused with the cell membranes (conceptualized from (Wassarman and Litscher, 2008).

will provide only a single output. In contrast, interaction between spines that belong to different neurons, is expected to provide an advanced **Type II Semblance**. This is because, large number of neurons within a given order of neurons 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 will provide the benefits of operating as a conditioning paradigm. Since the inter-spine interaction is between two different neurons, the nature of such interactions will be determined by the differences in the composition of lipid membranes of these different neurons.

2.8 Inter-neuronal inter-spine fusion and neuronal death

Cells that are undergoing exocytosis have the tendency to undergo inter-cellular fusion. For example, acrosome reaction in the sperm that occur prior to the intercellular event of sperm-egg fusion (Wassarman and Litscher 2008) 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 fuse to each other. In this context, even though the interaction between spines that belong to different neurons generated improved semblance, it also led to an adverse sequelae to advance to inter-spine fusion. In the case of synaptically-connected neurons, regions of AMPA receptor subunit vesicle exocytosis at the spine head regions are locations that are predisposed to fusion **(Fig.4C)**. A fusion between 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 (Kamme et al. 2003; Cembrowski et al. 2016). This can lead to the development of homeostatic mechanisms for survival, such as loss of spines (Zuo et al. 2005; Tjia et al. 2017) or cell death (Glucksmann 1951; Blaschke et al.1996; Southwell et

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al. 2012; Lance-Jones 1982) by activating certain molecular cascades (apoptosis) of one of the cells that undergoes fusion. This major event during evolution is expected to reflect as a stage of ontogeny. A significant amount of neuronal death that occur at different stages of neuronal development (section 1.2) supports this.

2.9 Variations that prevented inter-neuronal inter-spine fusion

Loss of spines and eventual damage to the neurons led to selection of variations that acquired features to prevent inter-spine fusion. This is **Step 2 fusion prevention**. However, inter-spine interaction has a major beneficial feature that sparks an internal sense of previously associated sensory stimulus. In order to utilize the beneficial aspect of semblance formation, it is advantageous to a variation that gave the benefits of IPL formation, but at the same time prevents inter-spine fusion. This led to select a variant with a robust mechanism to arrest progression of IPL formation before the stage of fusion. Since hemifusion is a stable intermediate stage of fusion (Wong et al. 2007), it is an optimal stage at which variations in molecules can be brought in place to arrest fusion **(Fig.4D)**. However, mechanisms to stabilize the IPLs somewhere between hydration exclusion and the stage of complete hemifusion are possible. All these stages are totally reversible. If the system continuously receives same associative inputs, then homeostatic mechanisms are able to stabilize the IPLs. Since the physical properties of a very large number of items in the environment have shared properties, repetition of activation of a large number of pairs of sensory stimuli was inevitable. This led to stabilization of several IPLs for a long period of time.

Since the default state is to prevent any type of inter-spine interaction (by steps I and II of fusion prevention), it is reasonable that resistance has developed against any type of inter-spine interactions. It is possible to find mechanisms towards achieving this goal. First, IPLs are restricted to smallest possible area of the membrane, which protects the spines from undergoing fusion; but at the same time enabled propagation of depolarization to induce internal sensations. The smallest area of IPL will also be advantageous to concentrate the ionic channels for better propagation of depolarization across it. Moreover, it can reverse back quickly once mechanisms to stabilize the IPLs stop (i.e. when the arrival of associative stimuli from environment stops). Secondly, molecules and mechanisms that can cause AMPA receptor endocytosis are expected to have selected at the postsynaptic membranes (Beattie et al. 2000; Awasthi et al. 2018). These features of IPL can be viewed as part of a favorable variation that was selected.

In this context, one may ask, "Are there any molecular evidence to suggest that fusion would have occurred between the spines at one stage and it was restricted to hemifusion later on?" Examination of postsynaptic terminal shows the presence of molecules with variations of function that are involved in synaptic vesicle fusion at the presynaptic terminal. SNARE protein is an example. SNARE proteins are known to facilitate very fast synaptic vesicle fusion with the presynaptic terminal for releasing neurotransmitter molecules within them to the synaptic cleft. Specific SNARE-operated molecular machinery capable of arresting the mechanism at the stage of hemifusion is present in the postsynaptic terminal (Giraudo et al. 2005; Liu et al. 2008). Hemifusion intermediates are characteristic of SNARE proteins, including that of neuronal SNAREs (Hernandez et al. 2012; Lu et al. 2005). Another protein synaptotagmin takes part in synaptic vesicle fusion at the presynaptic terminal. One variant, synaptotagmin 4, which is ubiquitously present at the postsynaptic compartment (Adolfsen et al. 2004) has unique features to regulate Ca^{2+}(calcium)-dependent exocytosis (Mori and Fukuda 2011). Additional proteins are also involved in the exocytosis at the spines (Kennedy and Ehlers 2011). These specialized proteins provide checkpoint mechanisms to prevent any inter-spine fusion by limiting inter-spine interaction

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to hemifusion **(Fig.4D)**.

2.10 Variations that refined internal sensations

Initially, semblance was in a crude form of internal sensation of the previously associated items. A major variation whereby new types of neurons that had average inter-spine distance more than the spine diameter as observed in pyramidal neurons (Konur et al. 2003) started appearing **(Fig.5)**. This led to the formation of IPLs between spines that belong to different neurons. This led to two distinct features for the operation of the system. They are 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 appearance of these neurons, the number of IPLs formed during an associative learning event increased. The number of units of internal sensations induced in response to a cue stimulus also increased proportionately. This increased the efficiency of the system by maximizing the number of internal sensory units for memory.

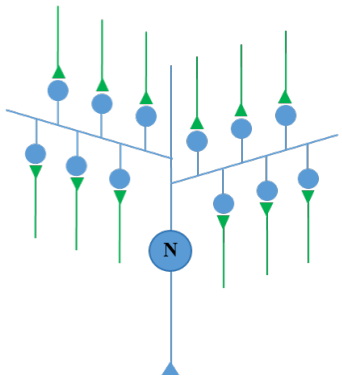

Figure 5: The selected new variant of neuron had mean inter-spine distance more than the spine diameter. Note the spacing between the dendritic spines (small blue round structures on the dendritic branches). This increased the probability of a spine belonging to one neuron to interact with a spine of another neuron. This in turn increased the number of inter-neuronal inter-spine IPLs.

The above feature led to the refinement of internal sensations so that the sensory qualia of memories are close to that of the item whose memory is being retrieved. With the beginning of the formation of inter-neuronal inter-spine IPLs, continued learning events allowed several IPLs to get inter-LINKed to form large clusters of inter-LINKed spines. This favored the horizontal spread of potential along the inter-LINKed spines. Since the direction of propagation of potentials through the IPLs is perpendicular to that through synapses involved, this led to oscillation of potentials involving large number of neurons of different neuronal orders of the cortex. This provided certain binding property for computing the units of internal sensations. This refined the net semblance and is the **Type III semblance (Fig.6)**.

2.11 Further refinements of internal sensations

Formation of ECM separating the neuronal processes prevented inter-spine interaction by virtue of the presence of hydrophilic properties that allowed the abutted spines to remain separate by

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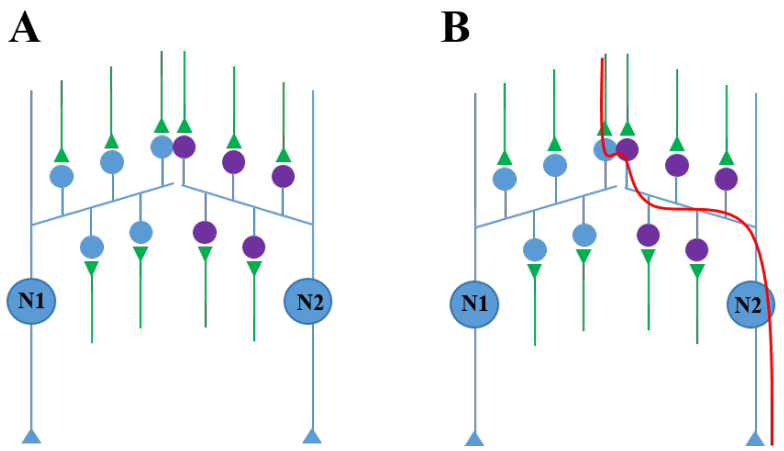

Figure 6: Inter-neuronal inter-spine interaction that leads to inter-postsynaptic functional LINK (IPL). A) Since the average inter-spine distance of new variants of neurons are more than their average spine diameter, it allowed spines from different neurons to become abutted to each other. In this figure one spine each of neurons N1 and N2 (in blue and violet) are abutted to each other so that their simultaneous activation can lead to the formation of an IPL between those spines. B) Formation of IPL enabled propagation of potentials in a lateral direction along them, which provides one vector component. This along with the vector component formed by the synaptic transmission at right angles to it contribute to composite periodic signals across the neurons and their processes (shown by a waveform in red). The ionic changes caused by them across the membranes within the extracellular matrix contribute to oscillating potentials recorded from the extracellular matrix (not shown).

default. This is **Step 3 fusion prevention**. In addition, different repulsive forces also prevent spread of depolarization in a non-specific manner within the system. In short, ECM provided an insulating medium that prevented the spread of depolarization between non-LINKed spines.

There were two important developments that led to further refinement of semblances. First is the continuity of ECM between the spines and secondly increasing number of IPLs formed within the system. The propagation of the potentials along the membranes has proportional fluctuation in ionic changes in the extracellular matrix space. The variations in ionic changes in the ECM space are reflected on the recorded field EPSP changes (Buzsáki et al. 2012). 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 between different neuronal types that belong to different neuronal orders. In other words, as the number of IPLs increased this allowed binding of the units of internal sensations that generated a more refined semblance, which is **Type IV Semblance**. The ontogeny shows discontinuous oscillating extracellular potentials in EEG waveforms in prematurely born infants (Selton et al. 2000) (section 3.4). Eventual filling of discontinuities of oscillating extracellular potentials is expected to take place through the formation of additional IPLs.

2.12 Process that led to self-awareness of internal sensations

There are a very large number of common shared associations that are part of the natural environment. At every moment, the system receives a very large number of (cue) stimuli from the

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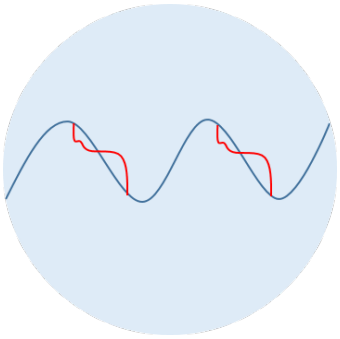

Figure 7: Oscillating extracellular potentials. Both learning and generation of internal sensations of higher brain functions occur only at a narrow range of oscillating extracellular potentials. These oscillations are the net effect of large number of composite periodic signals (see Fig.5B) resulting from both synaptic transmission, propagation of potentials across the IPLs, neuronal firing, recurrent collaterals and activity from feedback loops.

environment that will force the system to induce internal sensations of their associated items. This will reduce the efficiency of the system significantly. This resulted in several variations to generate an optimal condition. The selected variation continuously activates all the inter-spine LINKs for common associations and integrates all the induced semblances to form a net semblance called C-semblance responsible for consciousness (Vadakkan 2010). This occurs in a narrow range of frequency of oscillating extracellular potentials. Conformation of C-semblance will be influenced by all the previous associative learning events, which can explain subjective changes in consciousness. The background matrix of C-semblance provided both awareness of the self and that of the environment. An optimal C-semblance provides a matrix upon which a more refined internal sensation of memory of the associatively learned second item is formed in the presence of the first item. This is **Type V Semblance**.

Since the new variation resists formation of all types of IPLs, the system that maintains robust mechanisms to form a large number of IPLs also have the capability to reverse majority of these IPLs back quickly, which allowed them to have working memory. IPLs that can last for more time can explain short-term and long-term memories. Motivation induced dopamine release that cause spine enlargement enables stabilization of IPLs and their long-term maintenance.

2.13 Nature of internal sensations in different species of animals

The nervous systems of lower species in the animal kingdom are likely generating semblances of different types described above (shown in Table 1) or their subtypes. It is possible to undertake a comparative study of the structural details of the possible inter-neuronal interactions to understand the nature of internal sensations that they can use for survival. In lower species, IPLs may be formed by direct interaction between neuronal cells or their few neuronal processes. IPLs can be formed even if the spines are not formed. The same effect induction of semblances can occur when depolarization propagates from one postsynaptic zone on a neuronal process to the neighbouring postsynaptic zones. The generated internal sensations are likely become optimized for their survival needs. Due to the limitations of IPLs that can be formed in lower forms of animals, they have limited scope for associative learning. The qualia of internal sensations depends on the complexity of the neuronal circuitry, the nature of interactions between the postsynaptic zones over the neuronal processes, development of extracellular matrix space, and the ability to generate

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oscillating potentials to refine the internal sensations.

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 enlisting different types of semblances generated during neuronal development.

3 Key Milestones of Ontogeny

3.1 Dendritic spine loss during development

In young adolescent mice 13% to 20% of the spines were eliminated in multiple cortical areas (Zuo et al. 2005). There is substantial loss of dendritic spines in L5 layer pyramidal neurons during adolescent stage (Zuo et al. 2005; Tjia et al. 2017). Apical dendrites of L2/3 pyramidal neurons show the higher formation and elimination rates than L5 pyramidal neurons in both adolescent and adult mice (Tjia et al. 2017). These observations indicate that spine loss was a major stage of ontogeny. This eventually resulted in variations that limited IPL fusion to progress only to the stage of hemifusion.

3.2 Neuronal death during development

Neuronal cell death has been observed at various stages of neuronal development and different locations within the nervous system (Glucksmann 1951). 70% of cortical cells were found to be dying by embryonic day 14 and it reduced to 50% by embryonic day 18 (Blaschke et al. 1996). Nearly 40% of developing cortical interneurons are eliminated through Bax (Bcl-2-associated X)-dependent apoptosis during postnatal life (Southwell et al. 2012). Between 13 and 18 days of embryonic development, 67% of the motor neurons initially present in the motor column die (Lance-Jones 1982). Cells in the ventricular zone undergo sporadic cell death by apoptosis. Based on the present work, apoptosis is triggered by inter-cellular fusion and that such a stage during evolution has led to variations whereby an initial transient cytoplasmic content mixing acted as a stimulus to trigger molecular mechanisms for preventing any further inter-cellular fusion (section 2.8), while still generating mechanisms for the formation of different IPLs. Even though artificially preventing apoptosis at one stage of development can increase the number of cells, it will prevent the development of precise mechanisms for restricting the formed IPLs from undergoing fusion. This is evidenced by the findings that normal brain development was severely affected when genes

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involved in apoptosis were genetically manipulated (Kuida et al. 1996; Haydar et al. 1999). Since evolution can only move forward in one direction (Niven and Chittka 2016), 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.

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

After reaching the inner pial surface area, when neurons descent towards the direction of the ventricle their apical tufts were anchored to the inner pial surface. This allowed overlapping of dendritic spines of neurons that are located in different cortical neuronal layers. This led to overcrowding of the spines that belong to different neuronal orders and made it inevitable for the occurrence of inter-spine interactions that lead to the generation of IPLs.

3.4 Achieving continuity in oscillating extracellular potentials

Discontinuity of tracings in the electroencephalogram (EEG) among premature infants (Selton et al. 2000) suggests the discontinuous formation of IPLs at the early stages of development. The eventual development of continuous EEG tracings matches with the formation of additional IPLs in the lateral direction that led to lateral spreading of potentials through them. This is essential for integrating all the background semblances for the generation of C-semblance at a narrow range of oscillating extracellular potentials.

3.5 Regulation of IPL formation by dopamine

Dopamine is phylogenetically an old neurotransmitter molecule (Yamamoto and Vernier 2011). From the effect of dopamine on spine expansion, it can be seen that dopamine may cause IPL fusion for a brief period of time that may allow cytoplasmic content mixing between the spines that belong to different neurons. This is evident from findings such as dye coupling between neurons of the nucleus accumbens (O'Donnell and Grace 1993). The spine enlarging action of this neurotransmitter would have led to the avoidance of dopamine immediately following this evolutionary stage. Due to the development of a robust mechanism to prevent any inter-spine interactions (section 2.8), the system had to find ways to circumvent this resistance to form IPLs during certain special circumstances by introducing new variations. Reintroduction of dopamine at a later stage in evolution (Yamamoto and Vernier 2011) matches with dopamine's spine enlargement action (Yagishita et al. 2014) that promotes associative learning. The release of dopamine during motivation promoted learning (Bromberg-Martin et al. 2010) also have a similar mechanism. At locations of release of dopamine, it is reasonable to expect the selection of mechanisms for reversing any IPL formation for protecting those spines.

3.6 Regulation of excitation

Potentials arriving trough IPLs formed by the spines of excitatory neurons led to excessive excitation of these neurons. It necessitated controlling this excessive excitatory activity. This led to selection of variants that produced glutamate decaboxylase enzyme that catalyze the formation of GABA (gamma amino butyric acid) from glutamate. Neurons expressing this enzymatic activity were selected and started inhibiting the outputs of excitatory neurons, practically raising their

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threshold for action potential generation. It was possible to regulate the excitatory neurons at different levels (Palmer et al. 2012; Lovett-Barron et al. 2014; Karnani et al. 2014). Since inhibitory interneurons are known to have electrical synapses between them, oscillations of extracellular potentials likely present at some brain regions such as the ventral tegmental area may also lead to oscillations of potentials between neurons at their output locations such as the nucleus accumbens.

At this stage, some of the spines of that synapse with inhibitory inputs inter-LINKed with spines that received excitatory inputs. In this situation, lateral activation of inter-LINKed spines led to hyperpolarization of the spines of excitatory synapses that generated semblance of different conformations. These are expected to induce internal sensations different feelings and emotions.

3.7 Comparatively long durations for development in humans

Humans with advanced nervous system have a comparatively long duration for brain development after birth. This indicates a possible role of environmental stimuli in optimizing the system that had to undergo a long route to incorporate all the beneficial variations during evolution for the generation of internal sensations.

3.8 Age is the most important contributing factor for neurodegenerative disorders

Prevention of inter-spine interaction that can lead to different types of IPLs is the default mechanism. This was evolved due to the occurrence of IPL fusion at one stage of development and it necessitated the selection of variants that prevent formation of IPL fusion. The mechanisms to prevent fusion include a) mechanisms that are inherent to lipid membranes due to repulsive forces between them (Disalvo et al. 2008; Song et al. 2014; Dreier et al. 2018), and b) modified proteins that prevent IPL fusion (Giraudo et al. 2005; Liu et al. 2008) (section 2.8). When these mechanisms fail due to aging, it will predispose to spine fusion. This will lead to cytoplasmic content mixing, protein precipitation and triggering of spine loss and eventual neuronal death (Vadakkan 2016c).

4 Discussion

4.1 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 (Rackic 1988). 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 such combinations by maximizing the even distribution of inputs arriving the cortex. This increases the number of possible combinations of interactions between spines that are possible when associative inputs arrive from the environment. This may have evolved in an effort to naturally fine-tune the internal sensation of memory of an item with that of the actual sensory stimuli from the item. The columnar organization may also be facilitating to maximize C-semblance (section 2.11). Hypothesis building capabilities in humans are expected to result from the formation of large islets of inter-LINKed spines. Efficient long-term memory in humans, in contrast to other primates indicates development of mechanisms to stabilize IPLs for long period.

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The ratio of surface area of the neocortex between macaque monkey and humans is approximately 1:10 without having significant difference in thickness (Blinkov and Glezer 1968) or in a cyto-architectural organization (Shkol'nik-Yarros 1971). Humans and macaque monkeys diverged from a common ancestor nearly 23 million years ago (Fleagle 1988). 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 (Rakic and Kornack 2007). These changes are likely contributed to the comparatively large number of inter-LINKable abutted spines that can increase the number of IPLs formed for a given associative learning and enabled optimization of internal sensations of memory of an item. The details of this is likely to obtain when we fully understand the computational algorithm of the units of internal sensations within the cortex.

4.2 Transient inter-cellular fusion is a necessary stage

Dye coupling was followed by uncoupling as the cells migrated away from the ventricular zone towards the sub-pial zone. However, the apical tuft region of all the neurons anchored to the sub-pial region before the cell bodies moved back towards the direction of the ventricle. This led to overcrowding of spines that belong to different neurons. This has again led to IPL fusion as evident from a second stage of dye coupling (Gutnick and Price 1981; Yuste et al. 1995). This stage was also followed by uncoupling. The cytoplasmic content mixing at this stage of evolution likely triggered the expression of proteins that prevented fusion by halting the process at the stage of hemifusion **(Fig.9)**. This event provides evidence that IPL hemifusion is a cell fate that required a transient inter-cellular fusion at one stage of evolution.

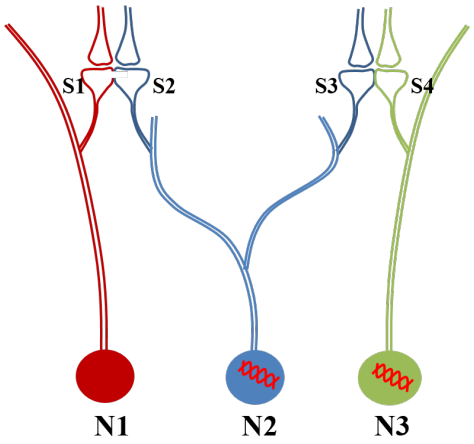

Figure 9: Inner-neuronal inter-spine fusion triggers long-lasting cellular mechanisms for hemifusion. Fusion between spines S1 and S2 of neurons N1 and N2 respectively undergo fusion at an early developmental stage. As a result neuron N1 dies. Entry of cytoplasmic content from neuron N1 to neuron N2 triggered long-lasting molecular mechanisms in neuron N2 for arresting future events by its spines at the stage of hemifusion. As a result, during learning IPL formation between spines S3 and S4 that belong neurons N2 and N3 respectively is getting arrested at the stage of hemifusion.

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The necessity for a transient inter-cellular fusion at one stage of development indicates the possibility that certain gene expression and molecular events are triggered by such an event. Once the mechanisms for inducing inter-spine hemifusion start functioning fully, it will maintain the formation and stabilization of IPLs for generation of internal sensations. In short, adult animals are dependent on developmentally-primed neurons for optimal IPL formation and maintenance. Since a) 70% of cortical cells were found to be dying by embryonic day 14 and it reduced to 50% by embryonic day 18 (Blaschke et al. 1996), b) 13% to 20% of the spines were eliminated in young adolescent mice in multiple cortical areas (Zuo et al. 2005), and c) it is only necessary for one spine out of large number of spines of a neuron to undergo fusion for triggering mechanisms to arrest any future fusion events at the stage of hemifusion, it is reasonable to expect that all the remaining neurons have completed triggering this mechanism by the time they reach adult stage.

4.3 Vulnerable state of spines continues

Inter-cell fusion is one of the early inter-cellular change necessary for killing harmful cells. It is a basic cellular mechanism needed for fusion between sperm and egg for zygote formation. In the case of inter-neuronal inter-spine interaction, it was not possible to avoid fusion altogether. What evolution has adapted is the strategy to undergo a transient fusion that will trigger intracellular mechanisms in both the cells to stop any future inter-cell fusion events. In this regard, the cells can prevent inter-cellular fusion only as long as such mechanisms can persist. At this juncture it becomes very important to know "How long can a neuronal cell sustain such mechanisms?" One possible mechanism to limit the harm caused by inter-cellular fusion in neurons can be achieved by virtue of the structure of the spines. In the event of an inter-neuronal inter-spine fusion occurs, neurons can trigger spine loss to save the cell from causing further damage. However, losing spines reduces the computational elements available in the nervous system. Continued loss of spines will eventually cause a functional decline, which is a hallmark of neurodegenerative disorders. In summary, even though, the inter-spine interaction provided the benefit of inducing units of internal sensations, this evolutionary stage has left the neurons in a vulnerable state. In the above context, preventing the spine from undergoing fusion is a constant challenge for the neurons. This can be observed from reports of spine loss at different time intervals following normal associative learning (Lai et al., 2012; Sanders et al., 2012) and indicate the vulnerable state of the spines.

4.4 Is it possible to optimize the terminal stages of ontogeny?

The derived operational mechanism has shown its suitability as an evolved mechanism, which has selected a robust step to prevent IPL fusion. The elements of this mechanism that prevent IPL fusion is very crucial to prevent inter-spine fusion that can lead to spine loss and eventual neuronal death. Normal aging is associated with both dendritic spine loss and neuronal death (Dickstein et al. 2013). Aging is the commonest cause of neurodegenerative disorders such as Alzheimer's disease. Since IPL fusion is expected to lead to neurodegenerative disorders (Vadakkan 2016c), factors that can prevent IPL fusion may prolong the life of the nervous system. Can we identify those factors and use them for our benefits? In the interim, the finding that DRD4 genotype can predict longevity in mouse and human (Grady et al. 2013) indicates that excess of dopamine in old age may promote 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.

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5 Conclusions

The necessity of this work stemmed from the unknown nature of both the mechanism of the nervous system functions and that of its evolutionary stages. 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 variations and selection. As the nervous system evolved, it was able to accommodate information about associations between large numbers of properties of items and events from the environment. This necessitated storing information and then retrieving information as first-person internal sensations. Variations and selection of the fittest ones were continued towards generating a computational product of internal sensations for memory, matching with that of the sensory features of the item that was associatively learned. Nervous systems that can form large islets of inter-LINKed spines are expected to allow combinations of internal sensations provided a survival advantage since they use the internal sensation of memories and utilize the ability to build hypotheses to make predictions about items and events in the environment. This is expected to be the guiding principle that improved cognitive capabilities as humans evolved. Language enabled communication and storing 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.

By using simple variations, how did the neuronal cells gain the capability to develop into a system that can generate first-person internal sensations within them? If it is formed by simple steps, why did it remain difficult to understand the operational mechanism? There were several accidental coincidences that led to the development and optimization of this system. First, the continuous depolarization of the spine head by quantal release of neurotransmitter molecules provided a dominant state for the system. Intermittent unidirectional activation of the spines by different stimuli arriving from the environment also facilitated to maintain this dominance. Secondly, lack of light stimulus during night on Earth augmented this dominant state for the development of more efficient systems. This dominant state of unidirectional activation of a synapse enabled an incidental lateral activation of the recipient side (inter-LINKed postsynaptic terminal) to momentarily hallucinate that it is receiving sensory stimulus from the environment through its donor side (presynaptic side). The oscillating extracellular potentials provided the system property of semblance (internal sensations) only when the frequency of these oscillations occurs in a narrow range. The difficulty in understanding the system prevailed due to the first-person nature of the internal sensations and difficulties in making a theoretical approach towards the solution. Since the present work has found that the derived mechanism has suitable features for a system to have evolved, it supports undertaking further verification.

How did the human nervous system evolve to the present state? Theories of evolution starting from Darwin have examined selection based on increase in brain size (Cartmill 1982). Compared to other primates, humans have higher order forebrain systems that have undergone major modifications (Preuss 2006). 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 (Barton, and Venditti 2013) indicting that the mechanism of natural selection can be best understood by examining how they participate in distributed networks. Another work has shown that prefrontal regions of both human and non-human primates holds about 8% of cortical neurons (Gabi et al. 2016). This findings necessitates 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 human than in rat

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and mouse (DeFelipe et al. 2002). This may be contributing to the formation of more IPLs that increase the qualia of computed net semblances. Based on the present work, formation of large islets of inter-LINKed spines is necessary for hypothesis formation and ability to stabilize IPLs is necessary for long-term memory that are special features of humans. 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 (Preuss 2004). Whether the increase in surface area of cortex in humans has increased the number of IPLs and size of islets of inter-LINKed spines or their efficiency in functioning or providing more functional units for computation is yet to be examined. It is also necessary to understand what kind of changes in the timing of developmental stages (heterochrony), out of many kinds of possible events (Smith 2003), might have caused the branching between different primates. The present work provides several heuristic avenues for further exploring this area of investigation.

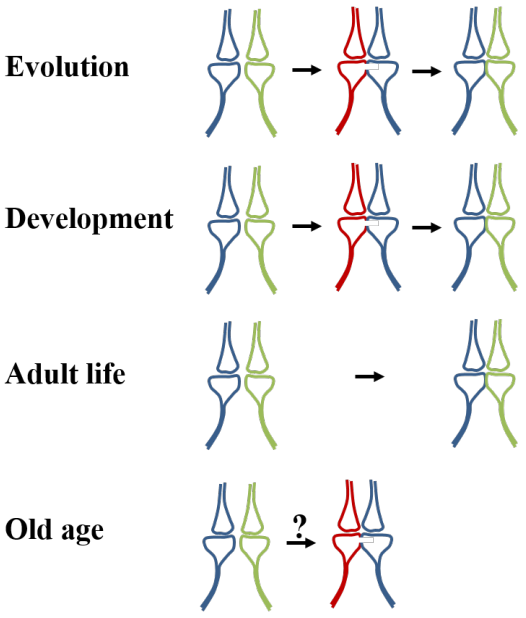

Figure 10: What is evolution and development informing us? Figures on left column: A pair of normal synapses. Middle column: Fusion between spines that belong to different neurons. Right column: Hemifusion between spines that belong to different neurons. The event of fusion during evolution let the system of neurons to progress through hemifusion state to form IPLs for generation of internal sensation. The event of fusion during development primed the neurons with the ability to restrict all the future fusion events (IPL formation) in adult life to the stage of hemifusion. Is this function compromised in old age? It is necessary to investigate how long the neurons can sustain the acquired function and whether we can artificially assist this process.

A general view is that once we understand the cause for neuronal cell loss during development, it may help to understand the pathophysiology of neurodegenerative disorders (Dekkers, Nikoletopoulou, & Barde, 2013). The unique observation of significant neuronal death at one stage of development provides crucial information about the evolutionary stages of the nervous system (Fig.9). This indicates a plausible mechanism by which evolution has preserved and optimized the function of generation of internal sensations by maintaining IPLs through inter-spine hemifusion. The inference made from these observations that transient fusion is a necessary triggering event for expression of genes to arrest inter-spine fusion at the stage of hemifusion and prevent further inter-spine fusion needs experimental verification. Does this information allow us to develop prevent

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disorders arising from fault of such a mechanism? Even though studies have shown some increase in cell survival when genetic manipulations against apoptosis were carried out, they did not gain any useful function (Hoeppner, Hengartner, & Schnabel, 2001; Reddien, Cameron, & Horvitz, 2001). This indicates that manipulation of genetic make up of an evolutionarily developed system in the middle of its development may in fact disturb a selected variation obtained through non-genetic methods. A mechanism triggered by transient inter-spine fusion during development is expected to be sustained throughout the lifespan. A realistic hope is that since the IPL formation is the final stage of ontogeny, it may become possible to discover methods to prevent malfunctioning of this mechanism.

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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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