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The functional role of all postsynaptic potentials examined from a first-person frame of reference

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Abstract: When assigning a central role to the neuronal firing, a large number of incoming postsynaptic potentials not utilized during both supra- and subthreshold neuronal activations are not given any functional significance. Local synaptic potentials at the apical dendrites get attenuated as they arrive at the soma to nearly a twentieth of what a synapse proximal to the soma produces. Conservation of these functions necessitates searching for their functional roles. Potentials induced at the postsynapses of neurons of all the neuronal orders activated by sensory inputs carry small bits of sensory information. The activation of these postsynapses by any means other than the activation from their corresponding presynaptic terminals, that also contribute to oscillating potentials, induce the semblance of the arrival of activity from their presynaptic terminals. This is a candidate mechanism for inducing the first-person internal sensory elements of various higher brain functions as a systems property. They also contribute to the firing of subthreshold-activated neurons, including motor neurons. Operational mechanism of inter-postsynaptic functional LINKs can provide necessary structural requirements for these functions. The functional independence of the distal dendritic compartment and recent evidence for *in vivo* dendritic spikes indicate their independent role in the formation of internal sensory elements. In these contexts, a neuronal soma is flanked by a large number of quasi-functional internal sensory processing units operated using very little energy, even when a neuron is not firing. A large number of possible combinations of internal sensory units explains the corresponding number of specific memory retrievals by the system in response to various cue stimuli.

Keywords: functional units; higher brain functions; internal sensations; inter-postsynaptic link; membrane hemifusion; semblance hypothesis.

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Introduction

The classical observation of the 'all or none' phenomenon of neuronal firing was made primarily by taking neuronal firing (somatic spike) as the central mechanism of the nervous system. The neuronal soma (cell body) and its processes have been receiving attention since the time neurons were separated from the reticula of cells and shown to be independent cellular units by the work of Ramón y Cajal (Shepherd, 1991). Neuronal firing is an essential step in the propagation of activity towards higher neuronal orders. Neurons can be grown individually in primary cell cultures, stimulated to fire and studied using electrophysiological recordings, and, more recently, observed using optogenetic tools. Conducting experiments and interpreting results by keeping neuronal firing at the center stage has been used in correlational studies with higher brain functions such as perception and memory (Zaidi et al., 2013; Sasaki et al., 2015). By taking neuronal firing as a unitary function, it was not necessary to examine supra- and subthreshold potentials or those potentials that degrade as they propagate towards the soma for any of their functional roles.

Computing neuronal firing patterns within a complex network of neurons interconnected through the synapses using artificial neural network studies by neuromorphic computing (Merolla et al., 2014) and deep learning (Hinton, 2014) have been facing challenges. Mapping the activity of sets of neurons in complex brain circuits, followed by computational analysis, modeling, and testing the models by manipulating the activity of specific sets of neurons, is viewed as a feasible method for understanding the nervous system (Kramer et al., 2009; Alivisatos et al., 2012). Decorrelated neuronal activity (Ecker et al., 2010) and the expectation of an improved interpretation of correlation in neuronal circuitry (Yatsenko et al., 2015) indicate the presence of an alternate mechanism occurring within the circuitry. When neuronal firing alone is examined, a very large number of postsynaptic potentials that are not contributing to neuronal firing are considered either redundant or insignificant. While searching for the mechanism of emergence of internal sensory elements contributing to various higher brain functions, it is necessary to re-examine the operation of the system using

alternate approaches. Since the internal sensations of higher brain functions are first-person properties to which only the owner of the nervous system has access, their formation is likely to have a still-unknown structure-function mechanism. The next feasible steps involve hypothesizing possible units of operation that can explain both first-person properties and third-person observations at various levels, followed by examining their probable computations along with actuating the mechanism in engineered systems.

Each postsynaptic potential at the postsynaptic terminal or dendritic spines (postsynapses) of neurons in all the neuronal orders connected from the sensory receptors has a bit of information about the sensory inputs from the environment. Since any condition that can induce postsynaptic potentials other than sensory inputs from the environment is able to provide similar bits of information to the system, conditions that lead to this can be examined as a mechanism for higher brain functions. Since such bits of information can undergo a natural computational process to provide internal sensory elements of higher brain functions, the mechanism cannot afford to ignore any one of the postsynaptic potentials. Surface or extracellular-recorded oscillating potentials have shown that recalled memories are associated with specific frequencies of oscillating potentials (Lisman and Buzsáki, 2008). Since memories are first-person internal sensations and recorded oscillating potentials have contributions from spikes originating from different locations of a neuron, the contributions of all the postsynaptic potentials need to be examined. Furthermore, recent findings regarding the presence of *in vivo* dendritic spikes (Palmer et al., 2012; Cichon and Gan, 2015; Sheffield and Dombeck, 2015) that involve 10 to 50 synapses (Antic et al., 2010) indicate their substantial contribution to the surface-recorded potentials. In these contexts, the potential mechanisms for the formation of internal sensory elements and their contribution to behavioral motor activity by all the postsynaptic potentials are examined.

Necessary solution for the nervous system functions

Different faculties of neuroscience have made a great many observations at multiple levels. This indicates the likelihood that the solution for the system is a unique one. This specific condition can be compared to a set of polynomials that intersect at one point in a graph providing a unique solution. Understanding the mechanism is similar to finding the solution using the Gauss-Jordan elimination method from a system of linear equations. In this process, when there is a leading variable in every column of a reduced row echelon matrix, a unique solution is expected. A similar approach can be taken to explain nervous system functions using the observations made from third-person examination conducted from various levels. It is necessary to first arrive at the lowest possible level of functional mechanisms for all the upper level brain functions and then examine the level at which these functions can be interconnected. For this, the process of reduction to the lowest levels must be carried out from the correct frame of reference. The common brain functions involve the formation of internal sensations of perception, memory, and consciousness. Their composition is expected to occur from first-person internal sensory elements induced at specific locations. In this context, the potential bits of specific sensory information of all the postsynaptic potentials are likely to have a contributory role. Examining third-person observed findings that can be interconnected with mechanisms for the induction of first-person internal sensations within the system is likely to provide the structure-function operational units.

The unique solution is expected to be used in mechanisms to explain the following: (1) Ability to explain the formation of the first-person internal sensation of retrieved memories. (2) The internal sensation of memory retrieval occurring at physiological time scales. (3) The operational mechanism for the formation of internal sensations expending less energy. (4) Provisions for reversing the changes occurring during associative learning over time to explain forgetting. (5) Memory retrieval occurring at physiological time scales capable of utilizing specific changes that took place at the time of associative learning. (6) Feasible structural changes occurring at the time of associative learning that are readily reversible explaining working memory, those that degrade slowly explaining short-term memory, and those that remain for a long period of time explaining long-term memory. (7) Ability to operate in an additive fashion such that changes occurring during different associative learning events can be combined with those that take place from new learning events through a biologically feasible computational process. (8) Ability to explain the consolidation of memories whereby (a) a mechanism for storage of memories is stabilized, (b) the units of internal sensations induced at different locations within the nervous system can be integrated, and (c) which can produce a third-person observation of an apparent transfer of locations of their formation over time. (9) Dependence of the formation of the inner sensation of memories on the frequency of oscillatory

patterns of surface or extracellular-recorded potentials at the cortex and hippocampus. (10) Correlation between the surrogate behavioral motor activities indicative of the formation of internal sensations of retrieved memories with the experimental finding of long-term potentiation (LTP). (11) Ability to explain the functional role of exocytosis of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors in recycling lipid membrane-bound vesicles contributing to LTP (Nicoll and Roche, 2013). (12) Ability to provide a framework for consciousness, which is related to memory in several aspects.

Postsynaptic potentials

The electrical potential triggered by neurotransmitter molecules at the postsynapses of the chemical synapses is called postsynaptic potential, which propagates through the dendritic tree towards the soma. Postsynaptic potential induced at an excitatory synapse is called excitatory postsynaptic potential (EPSP) and that induced at an inhibitory synapse is called inhibitory postsynaptic potential. The processes by which multiple postsynaptic potentials summate over space and time are called spatial and temporal summations, respectively. Generally, excitatory inputs arrive at the synapses on the dendrite terminal branches, whereas inhibitory GABAergic (gamma-aminobutyric acid) interneurons synapse on to the dendritic shafts especially at the apical dendritic trunk (Papp et al., 2001). The number of postsynaptic terminals and the nature of conduction of potentials vary among neurons depending on the latter's type and location. For example, neurons in the initial neuronal orders in the retina have only one to a few input connections and the depolarizing potentials are passively conducted to the next neuronal order synapses without spike production since the interneuronal distance is very short. The number of postsynaptic terminals (dendritic spines) that one cortical neuron receive ranges from approximately 5600 (monkey visual) to 60 000 (monkey motor) (Cragg, 1967), even though theoretical estimations range between 24 000 and 80 000 (Abeles, 1991). The number of dendritic spines in a human cortical pyramidal neuron ranges between 1.2 (basal) and 4.37 (apical) per micrometer (μm) length of the dendrite (Benavides-Piccione et al., 2013).

While propagating to the soma, EPSPs undergo a substantial degree of attenuation (Stuart et al., 1997). The spatial summation of nearly any 40–50 EPSPs (Palmer et al., 2014) or the temporal summation of less than this number of EPSPs can evoke an action potential, usually at its axon hillock. This occurs by an 'all or none' phenomenon. When the summed EPSPs exceed a certain voltage threshold, it elicits an action potential. In this regard, firing of a neuron is non-specific with regard to its inputs. When neuronal firing alone is examined, sensory bits of information within several specific postsynaptic potentials are ignored. Action potential propagates down the axonal branches to the presynaptic terminals (Figure 1A) where it triggers calcium influx, followed by

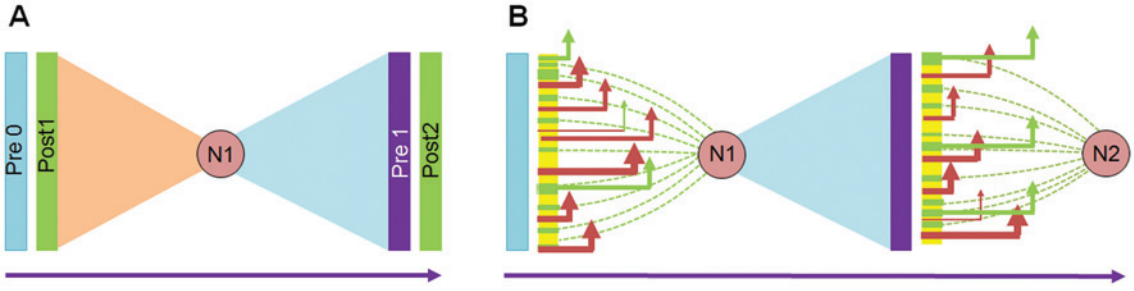

Figure 1: Schematic diagrams representing current assumptions and the reallocations of EPSPs that contributes to the neuronal firing. (A) Diagram showing the current view of neuronal firing after receiving inputs based on the 'all or none' phenomenon. EPSPs arriving at the neuron are not separated into those that contribute to neuronal firing and those that are redundant. N1, neuronal cell body. The postsynaptic terminals (Post1) that are activated resulting in the firing of neuron N1 are represented by the vertical green bar. The set of their corresponding presynapses (Pre0) is represented by the vertical blue bar. All the axonal terminals of the neuron N1, the presynaptic terminals (Pre1), are represented by the violet vertical bar. The set of their corresponding postsynapses (Post2) is represented by the green vertical bar. The long arrow below the diagram shows the direction of the flow of activity. (B) Diagram showing how only a fraction of the EPSPs (in green) arriving at neuron (N1) from the sensory inputs result in the neuronal firing. A large percentage of EPSPs (in yellow) both at the input and output levels of a neuronal firing are not accounted for firing of neuron N1 or N2. Only a fraction of EPSPs that are contributing to or resulting from neuronal firing are providing additional functions and are marked by green lines vertically pointing upwards. EPSPs that are not contributing to or resulting from neuronal firing can contribute to additional functions and are marked by orange lines vertically pointing upwards. The long arrow below the diagrams shows the direction of the flow of activity.

neurotransmitter release into the synaptic clefts (junctions between the pre- and postsynaptic terminals), which activates the postsynaptic terminals.

The pyramidal neurons of all the neuronal layers of the cerebral cortex usually have one large apical dendrite with a tuft of dendrites at its terminal, which anchors to layer 1 as the neuronal cell body migrates to the lower layers of the cortex during development. For example, in layer 5 of the primary visual cortex, the soma is 1500 μm away from the apical dendrites. Even though the amplitude of the local synaptic potential at the apical dendrites (~13 mV) is 40- to 60-fold higher than one synaptic potential proximal to the soma (0.2–0.3 mV), it attenuates by 900 times and provides somatic EPSP (~0.014 mV) nearly 20 times less than what one synapse proximal to the soma produces (0.2–0.3 mV) (Spruston, 2008). Therefore, the contribution from the synaptic activity occurring at the distal dendrites towards neuronal firing is much less. In addition, high levels of expression of regenerative voltage-dependent conductance and high-output impedance at the dendritic arbor contributes to the latter's electrical compartmentalization. These mechanisms provide a certain level of independence in the functions of the distal dendritic area and have the least influence on the output of a pyramidal neuron. Such a mechanism is thought to contribute to information storage (Wei et al., 2001; Polsky et al., 2004; Losonczy and Magee, 2006).

The conservation of the apical dendritic spine EPSPs indicates that these EPSPs serve a definite function that needs to be determined. It was also shown by computational studies that the properties of the dendritic plateau potentials have a less significant effect on the somatic plateau potentials (Gidon and Segev, 2012; Jadi et al., 2012). Depending on the resistive properties of the dendrites, length-dependent electrical filtering of the spike voltage induced at the dendritic spines and the morphology of the neuron, the voltage difference that reaches the soma varies. If the potentials at the dendrites contribute only minimally to the generation of action potential, then what are the functional attributes of those EPSPs generated at the apical dendritic spines? In other words, a question about the functional role for the conservation of occurrence of all the EPSPs emerges (Figure 1B). This becomes more important with the theoretical finding that action potentials sweeping backward from the soma towards the dendrites do not interfere with the maintenance of the independence of the dendritic spine's voltage-dependent computations (Behabadi and Mel, 2014). The EPSPs formed at the locations farther away from the soma or the apical dendritic spikes would not have been conserved if their minor contribution to the neuronal firing alone has been taken into account (Figure 2). These observations warrant searching for additional mechanisms for the contributions from all the postsynaptic potentials.

Physiological dendritic spikes

Long-lasting plateau potentials at the apical, basal, and tuft dendrites operate through voltage-gated calcium and sodium channels and *N*-methyl D-aspartate (NMDA) receptors (Magee et al., 1998; Larkum et al., 2007). Experiments using focal stimulation of dendrites have shown that such stimulation can induce dendritic spikes (Regehr et al., 1993; Polsky et al., 2009). More specifically, the synchronous activation of 10–50 neighboring glutamatergic synapses triggers a local regenerative potential called NMDA spike (Antic et al., 2010). Recent investigations have shown their occurrence at physiological conditions (Palmer et al., 2012; Cichon and Gan, 2015; Sheffield and Dombeck, 2015). Even though dendritic spikes are believed to be functionally associated with local inputs (Mel, 1994) and the isolated operations of a proportion of NMDA spikes are viewed to be significant in cortical information processing (Antic et al., 2010), their exact roles are not known. Isolated functions of distal dendritic area are also considered important in information processing (Wei et al., 2001; Polsky et al., 2004: Losonczy and Magee, 2006). The finding of large EPSPs of the dendritic spikes requiring spatial proximity of the associated synaptic inputs (Hardie and Spruston, 2009) indicates the presence of a mechanism that leads to the spread of potentials between the neighboring postsynapses. A recent work has shown that whisker stimulation-evoked LTP occurs independent of somatic spikes indicating that tactile perception associated with whisker stimulation can take place even without firing of the postsynaptic neuron under examination (Gambino et al., 2014). This indicates operation of an inter-neuronal inter-postsynaptic mechanism.

Neuronal firing (somatic spikes)

While searching for induction of internal sensory elements during higher brain functions, the correlational occurrence of neuronal firing may be examined. In this regard, an examination of the neuronal firing from both third- and first-person frames of reference can show some of the differences (Table 1). A neuron can fire under various circumstances. An examination of different conditions

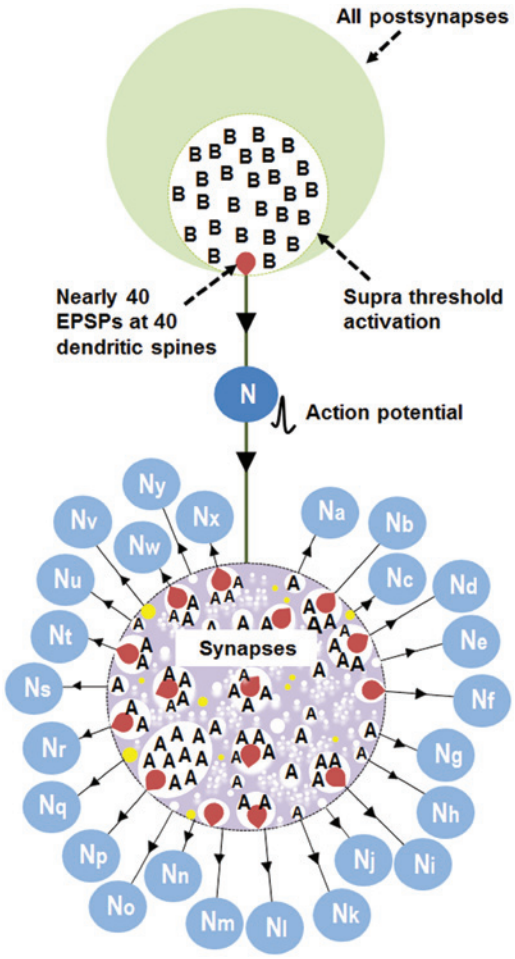

Figure 2: A representative diagram highlighting input EPSPs that are not utilized in the neuronal firing in two neuronal orders. At the postsynapses (inputs or dendritic spines) (Top circular area): The large light green circle represents all the synaptic inputs to a neuron. The white circle shows postsynapses marked in 'B' at which EPSPs arrive during supra-threshold activation. The small brick red circle represents 40 EPSPs that lead to firing of neuron N. Even though supra-threshold potentials are not contributing to the firing of neuron N, they have the capability to involve in operational mechanisms for inducing internal sensations. Arrows point in the direction of the spread of potentials. At the presynaptic terminals of neuron N, the arriving activity leads to different types of outcomes. The small circular areas in brick color are the ones where the action potential from neuron N contributes to the generation of action potentials in the neurons in the next neuronal order. The white areas surrounding the brick circular areas represent presynapses marked 'A' where the arriving activity does not lead to the generation of an action potential in the next neuronal order. However, activation of these presynapses leads to activation of their postsynapses and reactivation of inter-LINKed postsynapses to induce semblances. The areas marked in yellow represent those presynapses that do not contribute to the generation of action potentials or semblances. Similar to that explained at the postsynapses, the activation of presynapses that does not contribute to neuronal firing is expected to have some evolutionarily conserved, yet unknown mechanism. An energetically favorable, evolutionarily conserved mechanism is likely to explain a functional role for the EPSPs reaching all the postsynapses. By systematically utilizing these apparently surplus EPSPs, a potential mechanism can be operated. This review summarizes previous work to emphasize how a well-coordinated mechanism can operate in unison with the synaptically-mediated known neuronal circuitry.

associated with them can provide a detailed view of the limitations in examining neuronal firing in the search for discovering internal sensory elements that emerge from within the system. This examination is important in the context of the findings of various isolated functions of the distal dendritic area (Wei et al., 2001; Polsky et al., 2004; Losonczy and Magee, 2006; Antic et al., 2010).

1. When a neuron is not firing: a neuron can continue to receive postsynaptic potentials at its dendritic spines and not fire as long as the summated postsynaptic potentials remain below the threshold level. Many neurons at the higher neuronal orders will receive subthreshold activations secondary to the oscillating potentials recorded by surface or extracellular electrodes in the cortex and hippocampus (Vadakkan, 2013; Yaron-Jakoubovitch et al., 2013). The postsynaptic potentials induced at these sub-threshold activated neurons can be examined for potential functional roles. These subthreshold-activated neurons can undergo probabilistic firing, allowing weak inputs to increase spike probability.
2. Oscillating neuronal firing at rest: many neurons fire in groups at different locations within the nervous system, for example, in the cortex and hippocampus. These are observed along with oscillating surface or extracellular-recorded potentials. Since trigger points of autonomous activation are not present over the neuronal soma, the oscillatory pattern of neuronal firing occurs most likely secondary to the oscillating postsynaptic events. This indicates possibilities for interactions between the postsynapses. The present work examines these potential interactions.
3. Isolated firing of neurons at rest: spontaneous random activation of certain neurons that are not related to the oscillating potentials takes place without having any relationship to the observed behavioral motor changes.
4. Artificial stimulation of a neuron: artificial stimulation of different areas of the brain induces internal sensations along with motor effects (Selimbeyoglu and Parvizi, 2010). Stimulation at specific sensory cortices produces corresponding sensory hallucinations.

Table 1: Meaning of the firing of a neuron to a third-person observer and the owner of the nervous system.

	Third-person sensed neuronal changes	Third-person sensed motor changes	Changes sensed by the owner of the nervous system
During sleep	Oscillating pattern of neuronal firing	None	None. Maintain basic functions such as respiration
During awake rest state	Oscillating pattern of neuronal firing	None	Internal sensation of consciousness
Artificial stimulation	Neurons fire	Behavioral motor changes	Internal sensation of hallucination
Cue stimulus prior to associative learning	Some neurons fire	None or motor action secondary to memory retrieval	Sense the cue and retrieve memory of associatively learned item
Cue stimulus after associative learning	Firing of a new set of neurons that do not fire before learning	Spontaneous behavioral motor activity if animal cannot suppress them (lack of inhibitory controls)	Internal sensation of memory and accompanying behavioral motor activity
When a neuron is not firing	Subthreshold activation of neurons (either due to reduced inputs or due to inhibitory inputs)	None	Internal sensation of various higher brain functions

Recording the activity of a neuron can be studied by an observer for matching behavioral manifestations, while the owner of the nervous system can report the internal sensations to the observer. If EPSPs arriving at the dendritic spines do not add up to overcome the threshold for motor neuronal firing and produce muscle contractions, then it would not produce any behavioral motor activity and would not be sensed by a third person. Effects of the activation of a single neuron can be visualized by a third person with certainty if the neuron being activated is the (n)th neuron involved in a step that leads to motor activity. Mechanisms leading to the function of internal sensation are expected to result from operations that may or may not lead to or result from neuronal firing.

The higher the locations of stimulation from the sensory receptors, the more well formed are the hallucinations. Artificial stimulation of the motor cortical areas can lead to muscle contraction.

5. Firing of a new set of neurons in response to the cue stimulus after associative learning: it is known that the same (cue) stimulus causes a new set of neurons to fire after associative learning (Tye et al., 2008) (Table 2). Since the cue stimulus induces the internal sensation of memories of the item that was associatively learned with the cue stimulus, the mechanism that either leads to or results from the firing of a new set of neurons is associated with the formation of the internal sensation of memories. In this regard, the postsynaptic potentials specifically triggered by the cue stimulus that result in the firing of a new set of neurons are expected to propagate along a path where units of internal sensation are induced.

Table 2: A new set of neurons fire in the presence of a cue stimulus after associative learning.

	Set of neurons activated before learning	Set of neurons activated after learning
Stimulus A (before learning)	{x}	–
Stimulus B (before learning)	{y}	–
Stimulus A (after learning)	–	({x}+({y}-{z})+{w})

Prior to associative learning, stimulus A induces firing of a set of neurons {x}. This table examines all the additional sets of neurons that fire after learning. After learning, stimulus A will lead to firing of a set of neurons ({x}+{w}), where {w} is the new set of neurons that result from the learning-associated mechanism. In addition, it will also lead to firing of a set of neurons ({y}-{z}) that are activated by the item whose memory is retrieved. {z} is the set of neurons that fires with stimulus B, but will not fire with the stimulus A after associative learning.

Leading questions

The description of all the above findings prompts the following questions.

1. What is the likely mechanism operating at the dendritic locations that contribute to the formation of internal sensation of various higher brain functions?
2. What type of correlation can be expected between the underlying mechanism for the generation of internal sensations and third-person observed neuronal firing (somatic spike)?
3. What purpose does it serve by propagating activity, through neuronal firing, towards the higher neuronal orders?

The present work examines a testable mechanism involving all the postsynaptic potentials that can answer these questions.

Frame of reference to define the basic unit of internal sensations

In arriving at a solution to find the mechanism for internal sensations, the following approach can be used. Unlike other organs such as the heart and kidneys whose functions can be observed by third persons, higher brain functions such as perception, memory, consciousness, and thought process are internal sensations to which only the owner of the nervous system has access. Current investigations examine motor actions of speech and behavioral motor activity that inform a third-person observer about the first-person internal sensations (Figure 3). A third person can also observe changes occurring at systems, imaging, electrophysiological, cellular, and biochemical levels. Even though many studies have examined first-person reports of the subjects' internal sensations (Varela and Shear, 1999; Northoff and Heinzel, 2006; Overgaard et al., 2008; Baker, 2011; Howell, 2013), it is necessary to understand how internal sensations are formed. To deduce the location of induction and the properties of the units of its formation, it is necessary to view some parallel methods that were adapted in the past. For example, humans do not have a sensory system to sense electromagnetism. However, stimuli that arrive at the human sensory systems from different effects of electromagnetism, which are surrogate markers, have been used to understand the properties of electromagnetism. For example, when a conductor cuts a magnetic field perpendicularly, it induces a current in the conductor. Alternatively, when a current is made to flow through a stationary conductor located within a magnetic field, the conductor deflects. These third-person observations made at the lowest possible level of its induction enabled a thorough understanding of the properties of electromagnetism and lead to the development of a large number of engineered systems. Since internal sensations cannot be observed from a third-person view, a theoretical examination of the location and

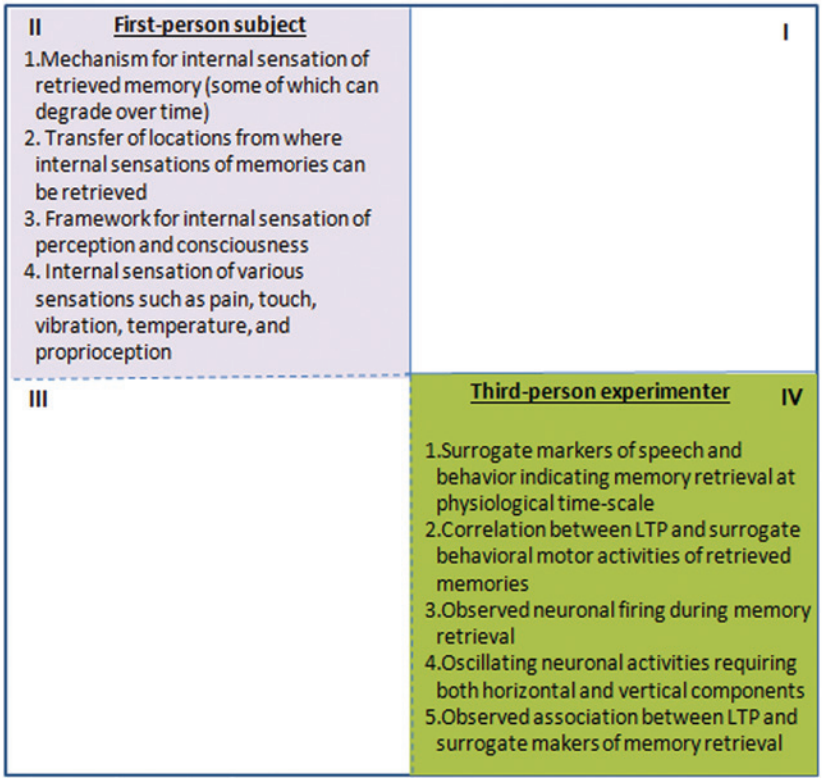

Figure 3: Schematic diagram showing frame differences in examining the first- and third-person sensible nervous system functions. Current experimental approaches that study possible correlations between sensory stimuli, behavioral motor activity and the neuronal firing are shown in the fourth quarter of the graph. The unique feature of the nervous system that differentiates it from other body systems is the formation of internal sensations of higher brain functions to which only the owner of the nervous system has access and is drawn in the second quarter of the graph. The solution can be found by examining the mechanism for the formation of internal sensations during higher brain functions such as perception and memory retrieval that are interconnected with the third-person observed behavioral motor activity and neuronal firing in response to sensory inputs. It is expected that a correlation between different features observed by a third person will become possible by understanding the mechanism that operates to produce first-person properties.

mechanism for induction from a first-person frame of reference, followed by replication in engineered systems is necessary for testing their occurrence.

First-person internal sensations of higher brain functions

Functional properties arising from specific operational mechanisms observed at various levels will become interconnected when reduced to an appropriate lower level (Machamer et al., 2000). At this level, it is expected that internal sensations get induced through an efficient operational mechanism, which can also directly provide sufficient potentials to drive specific behavioral motor actions. In this regard, hypothesizing operational units that can be used in large-scale computations to obtain expected results is a feasible approach. Since several nervous system functions are modular in nature and involve different types of internal sensations, theoretical derivation of the units followed by searching for the underlying computations will allow them to be understood. The mechanism is expected to operate in synchrony with the known synaptically connected neuronal circuits. Furthermore, the circuit changes should be flexible enough to accommodate changes induced by new associative learning. From the readily available third-person observed findings at various levels, feasible mechanisms for the formation of first-person internal sensations of various higher brain functions are examined (Table 1). Internal sensations of intentionality to carry out basic behaviors such as motor activity necessary for survival and reproduction are present even in lower forms of animals. This is expected to operate through a well-conserved mechanism across species.

How are the third-person observations from the system having the system properties of various internal sensations highly sensitive to the frequency of oscillating potentials? This becomes possible when the mechanism of formation of internal sensation is associated with postsynaptic potentials and also contributes to the oscillating potentials. By third-person observation of a single event of neuronal firing, only a subset of postsynaptic potentials out of the set of all postsynaptic potentials is taken into account, ignoring functional attributes of the remaining potentials, if any. A large number of sets of postsynaptic potentials can fire a neuron, making the observed neuronal firing not input specific. Can conserved occurrences of all the postsynaptic potentials be used to induce sensory equivalents towards the first-person internal sensation of higher brain functions such as perception, memory, and consciousness? How can their contribution to the internal sensation as a systems property be mechanistically explained?

One of the higher brain functions that can be used in experimentations for studying predictable changes is memory. Changes can be induced by associative learning and specific memories can be retrieved at a later period of time. By examining memory from the first-person frame of reference, it can be seen that internal sensations of working, short-, and long-term memories are temporarily induced processes based on how long the learning-induced changes can last. This leads to the question 'Is there a common mechanism for inducing the first-person internal sensation of working, short- and long-term memories at the time of memory retrieval resulting from changes that take place at the time of associative learning and degrade as a function of time?' How can such a mechanism be explained by utilizing all the postsynaptic potentials?

Formation of semblances as a systems property

The conditions, location, and mechanism that can explain both first- and third-person sensed functions of the nervous system through a specific operational mechanism was derived previously (Vadakkan 2007; 2013). Chemical neurotransmitter molecules are packed inside the synaptic vesicles in the presynaptic terminal. The infrequent arrival of activity at the presynaptic terminal will lead to a volley of neurotransmitter release that will activate the postsynaptic terminal to induce postsynaptic membrane potential. The activation of a postsynapse indicates that activity has arrived at its presynaptic terminal. In addition, continuous quantal release of neurotransmitter molecules occurring, even during rest and sleep, induces small potentials at the postsynaptic membrane. This imparts an intrinsic systems function (knowledge) that induction of any postsynaptic potential is secondary to the neurotransmitter release from the presynaptic terminal. In a default state of continuous induction of potentials at the postsynaptic terminal originating from quantal release, the activation of a postsynaptic terminal by any other means that can also contribute to the extracellularly-recorded oscillating potentials, is expected to induce cellular hallucination or semblance of the arrival of activity from its presynaptic terminal. Artificial stimulation of brain areas producing internal sensations of various sensory stimuli (Selimbeyoglu and Parvizi, 2010) strongly indicates the presence of

such an inducible systems operation. The fact that it has not been possible to completely block the quantal release in the laboratory indicates that it is a robust evolutionarily preserved mechanism for serving an important function.

Generating postsynaptic potentials in the absence of arrival of activity from the presynaptic terminal requires the activation of the postsynaptic terminal by alternate methods. Of the different higher brain functions, memory has a special advantage in that it can be tested at various structural and functional levels such as associative learning, storage, maintenance, and retrieval. Retrieved memory of an item can be taken as the net semblances of that item occurring at certain locations within the circuitry. This led to the hypothesis of formation of semblances from lateral entry of activity at a postsynaptic terminal in the absence of arrival of activity from its presynaptic terminal (Vadakkan, 2007; 2013). One of the possible mechanisms is generation of an inter-postsynaptic LINK (capitalized to emphasize its significance) during associative learning. Thereafter, activity arriving from the cue stimulus reactivates existing inter-postsynaptic functional LINKs and activates the second inter-LINKed postsynapse inducing semblance. The derivation of the sensory identities of semblances is summarized in Figure 4. The integral of the specific semblances induced by the cue stimulus matches the item whose memory is retrieved. As each new related learning event reinforces previous learning, there should be a mechanism for semblances from additional

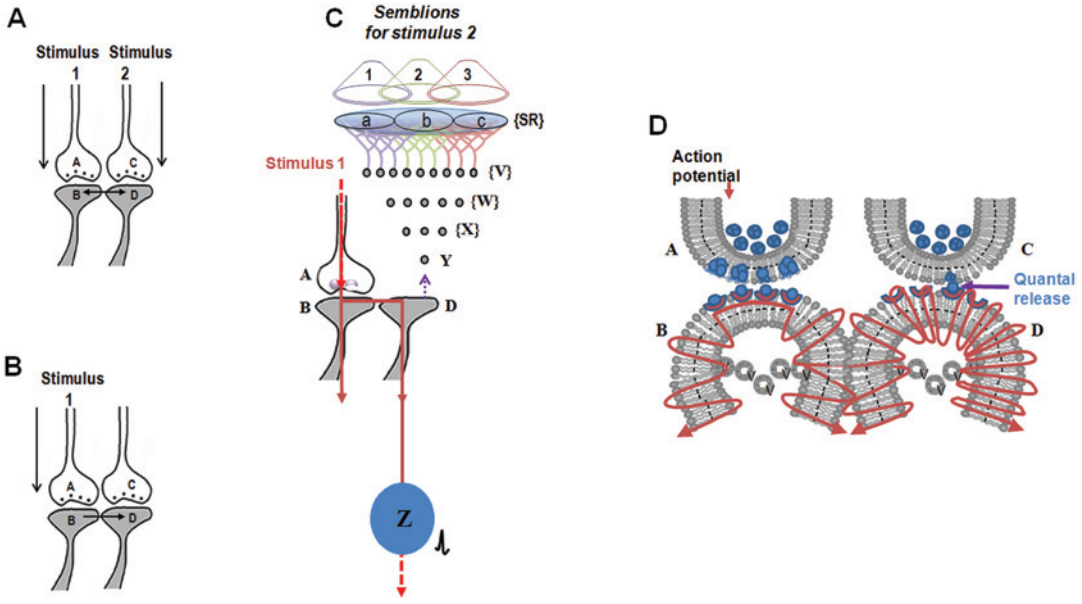

Figure 4: Inter-postsynaptic functional LINK, features of the plot, and formation of semblance.
(A) Simultaneous arrival of two stimuli that leads to the activation of two synapses A-B and C-D whose postsynapses B and D are abutted to each other results in the formation of a functional LINK B-D between them. (B) At a later time, when one stimulus arrives and activates synapse A-B, functional LINK B-D gets re-activated resulting in the activation of postsynaptic membrane D inducing semblance of activity arriving from presynapse C. (C) When postsynapse D is activated through inter-postsynaptic functional LINK B-D, in the absence of arrival of activity from its presynapse C (not shown), a semblance of arrival of activity from the presynapse occurs. The sensory content of the semblance (sensory hallucinations) can be extrapolated from examining the packets of minimum sensory stimuli capable of stimulating postsynapse D. The sensory identity of the semblance of activity occurring at postsynapse D consists of inputs from neuron Y. Neuron Y is normally activated by inputs from a set of lower order neurons {X}. Continuing this extrapolation towards the sensory receptor level identifies a set of sensory receptors {SR}. {a}, {b}, and {c} are subsets of {SR} that are capable of independently activating postsynapse D. Hypothetical packets of sensory stimuli activating sensory receptor sets {a}, {b}, and {c} are called semblions 1, 2, and 3, respectively. The activation of postsynapse D through inter-postsynaptic functional LINK B-D by the cue stimulus can lead to virtual internal sensation of semblions 1, 2, 3, or their integral. The cue stimulus-induced activation of postsynapse D reaches the soma of its neuron Z. If neuron Z already receives a baseline summated EPSP short of one EPSP to trigger an action potential, then the additional EPSP arriving from postsynapse D can add to the subthreshold EPSP, and fire neuron Z, resulting in latter's concurrent activation during memory retrieval; this neuron Z will not otherwise get activated without prior associative learning. (D) Diagram showing volley of neurotransmitter release at synapse A-B and the induced EPSP from postsynapse B reaches at postsynapse D through a partially hemifused inter-postsynaptic membrane segment (curved lines with arrows points in the direction of spread of EPSP). The unidirectional neurotransmission occurring at the synapses in response to the arrival of activity and the continuous unidirectional quantal release from single synaptic vesicles (in blue-filled circles) from presynaptic terminals set an ideal plot for the systems feature of semblance formation. (Modified from Vadakkan, 2013.)

functional units and their integration to the semblance for previously learned events. The concept of the inter-postsynaptic functional LINKs is in agreement with the expectations of K-lines proposed for explaining a broad framework for memory (Minsky, 1980).

Since the horizontal component of the high-frequency oscillating potentials in the hippocampus cannot be mediated through the chemical synaptic transmission alone, a mechanism for electrical coupling has been expected (Draguhn et al., 1998). The lateral entry of activity through the inter-postsynaptic functional LINKs is expected to provide an explanation for this coupling. Higher brain functions such as perception and memory are dependent on the conscious state of the system, which in turn depends on the frequency of oscillating surface or extracellular-recorded potentials. It was proposed that the computational product of all the background semblances induces C-semblance for consciousness (Vadakkan, 2010). The internal sensation of perception of color and contour is expected from the computational product of the semblances formed in a modular fashion at specific locations. The mechanism should also be able to explain findings of associated neuronal firing occurring during different sensory perceptions (Zaidi et al., 2013).

Specificity during dynamic computations of semblances

The arrival of sensory information from a specific cue stimulus provides inputs at a specific set of dendritic spines, reactivates a specific set of inter-postsynaptic functional LINKs and activates a specific set of inter-LINKed postsynapses. The internal sensation resulting from the natural computational product of the semblances during the arrival of a cue stimulus is expected to be unique for a given cue stimulus. The number of dendritic spines (postsynapses or postsynaptic terminals) is finite. Since physical properties of the items or events in the environment share many common features, several semblances will be used in a shared fashion. A new learning event can use either a new combination of inter-LINKed postsynapses to induce a new combinatorial semblance or induce a set of inter-postsynaptic functional LINKs for inducing specific memory at a later time. For adding new inter-postsynaptic functional LINKs during a new learning event, two mechanisms are possible. (1) If the neuron of the postsynaptic terminals is held at a subthreshold level by mechanisms that inhibit excitatory neurotransmission (described in a separate subtitle 'Maintaining subthreshold activation') or by inhibitory neurons, then the inhibitions can be reversed to disinhibit the neuron to fire. This can allow information to pass towards higher neuronal orders that will allow new associative learning events by inducing new inter-postsynaptic functional LINKs. (2) A second mechanism is by introducing new neurons along the pathway of two sensory stimuli that will induce the formation of new inter-postsynaptic functional LINKs at higher neuronal orders (Vadakkan, 2013).

Reversible inter-postsynaptic functional LINKs

It is necessary to examine the possible nature of inter-postsynaptic functional LINKs that can be reversed back at various time points and that can be stabilized for long periods of time. Knowledge about the nature of these LINKs is necessary to explain working, short-, and long-term memories. Different mechanisms of inter-postsynaptic functional LINKs with different half-lives that determine their functional existence are given below (Figure 5A–D).

1. Innately determined stabilized inter-postsynaptic membrane hemifusions are expected to be present at the time of birth. The semblances formed through these are necessary for carrying out basic survival instincts after birth such as breathing, sucking, and swallowing.
2. Acquired from associative learning events.
   (a) Electron microscopic pictures from the cortices show abutted postsynaptic membranes of different neuronal processes. These are normally separated by a hydrophilic region of the extracellular matrix space. The first change induced by any associative learning event is to bring the membranes in close contact with each other by the removal of the extracellular matrix aqueous environment associated with polar head groups of the membrane lipids as reported by experiments using artificial membranes (Burgess et al., 1992). This enables the transmission of potentials between the inter-LINKed postsynapses. This is expected to be one of the most energy-demanding processes (Cohen and Melikyan, 2004; Martens and McMahon, 2008). Therefore, this is a highly reversible mechanism suitable for functional LINK formation during those higher brain functions that are transient in nature. Ephaptic transmission can take place through this mechanism.
   (b) Conditions such as dendritic spine expansion can lead to partial hemifusion between two postsynaptic membranes and can occur in the presence

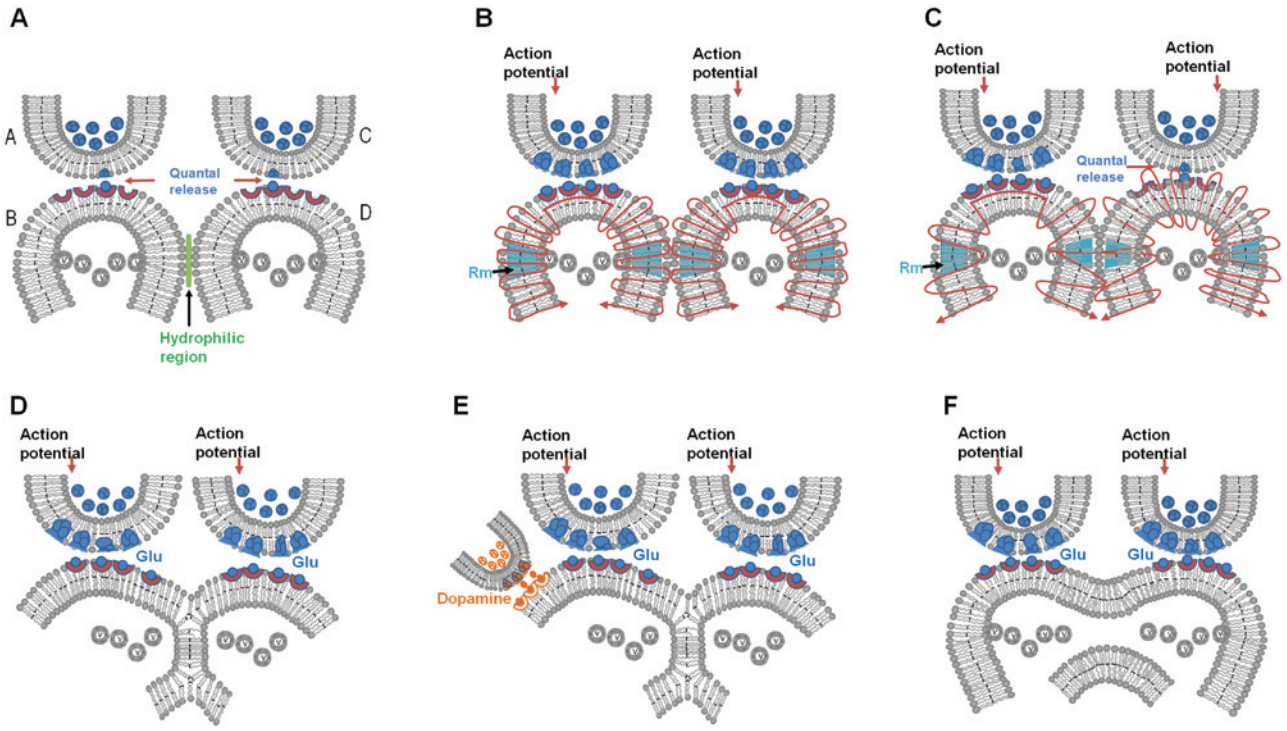

Figure 5: Formation of different types of inter-postsynaptic functional LINKs and their modifications.
(A) Presynaptic terminals A and C with synaptic vesicles inside (in blue color). One vesicle from each of these terminals is shown to release their contents to the synaptic clefts, the space between the presynaptic and postsynaptic terminals. This quantal release is a continuous process providing very small potentials to the postsynaptic membranes B and D. Postsynaptic terminals show the presence of membrane-bound vesicles inside them marked (V) containing GluR1 AMPA receptor subunits. Note the hydrophilic region between the postsynaptic membranes (in green). (B) Simultaneous activity arriving at the synapses leads to the enlargement of the postsynaptic membranes and the removal of the hydrophilic region between the postsynaptic membranes. The process of removal of water of hydration requires high-energy expenditure. Once water of hydration is removed, the postsynaptic membranes come in close contact with each other forming rapidly reversible inter-postsynaptic membrane functional LINK. (C) After the formation of inter-postsynaptic membrane functional LINK, EPSP arriving at postsynaptic membrane B crosses the functional LINK and reaches postsynapse D. Continuous unidirectional quantal release of single synaptic vesicles (in blue-filled circles) from presynapse C [responsible for miniature EPSP (mEPSP) recorded from the soma at rest] to postsynapse D sets the plot, where any sudden lateral activity arriving at postsynapse D (other than synaptic transmission from presynapse C) leads to the semblance of activity arriving from presynapse C. This is viewed as a systems property where the lateral movement of activity through the inter-postsynaptic functional LINK contributes to the horizontal vector contributing to the oscillating potentials at certain neuronal orders. Maintaining an optimal frequency of these oscillations is necessary for the formation of internal sensation of higher brain functions. This rapidly reversible mechanism likely occurs during working memory. (C) Schematic diagram showing how lipid membranes can lead to reversible partial hemifusion between the abutted postsynaptic membranes. The exocytosis of AMPA receptor vesicles (V) occurring from two abutted postsynaptic terminals (Makino and Malinow, 2009) makes the areas adjacent to the synapse more favorable for membrane reorganization that can favor membrane hemifusion. Note that only a partial hemifusion is shown in the diagram. It is readily reversible explaining the necessary reversible nature of the inter-postsynaptic functional LINK for working memory. Dopamine known to increase dendritic spine (postsynapse) enlargement (Wise, 2004; Yagishita et al., 2014) will readily induce complete hemifusion that can be retained for a long period of time. Rm: membrane segment marked in Turkish blue shows the area where membrane reorganization occurs due to membrane expansion and addition of vesicle membranes. (D) Reversible complete hemifusion between the postsynaptic membranes. If transmembrane proteins are inserted across the completely hemifused area during this period, they can stabilize the hemifused areas. This allows the cue stimulus arriving during the persistence of the hemifused state to induce semblances for memories. The persistence of memory depends on the half-life of the inserted transmembrane proteins and other changes taking place in the circuitry that determines the net semblance for memory. (E) Enlargement of postsynaptic terminals (dendritic spines) by dopaminergic input promotes reversible membrane hemifusion between them in normal conditions. A complete membrane hemifusion between the postsynaptic membranes is shown in the figure. (F) Inter-postsynaptic membrane fusion which can either reverse to independent membranes or become a non-reversible process. This is expected to occur during intense stimulations during LTP induction, promoted by viral fusion proteins, or occur during seizures. Alternations in membrane lipid composition, and the presence of fusogenic chemicals and proteins can also lead to fusion between the abutting membranes of the postsynapses. (Modified from Vadakkan, 2015.)

of their simultaneous activation. Reversible membrane hemifusion takes place very commonly in biological systems (Melikyan and Chernomordik, 1997; Kozlov et al., 2010) (Figure 5A and B). The membrane dynamics at the postsynaptic locations close to the synapses is favorable for controlled partial to complete hemifusion due to many factors and are discussed below.

(c) Further force induced by conditions that lead to increased enlargement of postsynaptic membranes by dopamine or intense stimulation can lead to reversible complete postsynaptic membrane hemifusion. One advantage is that the hemifused membrane segment can be stabilized by the insertion of transmembrane proteins for variable periods of time depending on the latter's half-lives. This mechanism enables prolonged maintenance of certain higher brain functions.

(d) Hemifused inter-postsynaptic membranes may undergo complete fusion. Reversal of the fused membrane segments back to hemifused state is expected to involve regulatory mechanisms through distinct stages (Mattila et al., 2015). Fusion between the postsynaptic membranes (dendritic spines) that belong to the same neuron will not result in any adverse consequences. Dendritic excrescences on the dendritic tree of the CA3 neurons are likely formed by this mechanism.

Comparison and contrast between learning and LTP

A strong correlation between experimentally induced LTP and surrogate behavioral motor activity indicative of expected retrieval of memory has been observed. LTP induction requires nearly one to a few minutes of time to show the induced changes, which do not match the physiological time-scale changes occurring during associative learning. Moreover, several reports of LTP temporal phases do not correspond with that of memory phases (Abbas et al., 2015). However, excluding the time-scale issues, LTP has shown strong correlation with the surrogate markers of retrieval of memory. Reversible inter-postsynaptic functional LINKs occurring *in vivo* can explain LTP (Vadakkan, 2013) and enables the following changes at different locations during learning. At locations of convergence of sensory stimuli, a new set of inter-postsynaptic functional LINKs can be formed during learning. At higher neuronal orders within the cortices, it can lead to the reversible formation of a very specific set of sparse inter-postsynaptic functional LINKs. The transient reactivation of previously formed specific functional LINKs induces semblances for the internal sensation of memories of previously learned items. This enables the system to continuously renew working memory as the animal moves through the environment.

High-frequency stimulation during experimental LTP induction can lead to dendritic spine swelling, which takes several seconds to fully manifest and leads to the formation of different types of inter-postsynaptic functional LINKs. We have previously demonstrated how these hemifusions can lead to the observed potentiated effects (Vadakkan, 2013). It is possible that instead of the rapidly reversible formation and transient reactivation of a new set of inter-postsynaptic functional LINKs that occur at physiological conditions, LTP induction leads to intense changes towards inter-postsynaptic membrane hemifusion promoted by dendritic spine swelling. It can even lead to membrane fusion. The potentiated effect due to inter-postsynaptic membrane hemifusion takes time to reverse. Since it is likely that some of the membrane fusion changes will not reverse, the potentiated changes will not return completely to the baseline as observed by some of the experimental results of LTP. The formation and reactivation of inter-postsynaptic functional LINKs occurring sparsely during physiological conditions make it difficult to accurately measure their effect *in vivo* using the currently available techniques. Even though reversibility of the changes under LTP stimulation protocols occurs at different time scales than physiological conditions, they can be used to examine similarities in the molecular changes. Even though strong stimulation protocols need to be used in LTP protocols, the finding of the correlation between the potentiated effect and memory has provided valuable information.

Lateral inter-postsynaptic events during LTP induction and associative learning

It is conceivable that the experimental conditions during LTP induction produce all the different forms of inter-postsynaptic functional LINKs depending on various factors. Findings associated with LTP at the postsynaptic side can be examined to understand the spectrum of reversible inter-postsynaptic functional LINK changes occurring *in vivo*. Examining the detailed cellular and molecular changes during LTP is likely to provide information about

the substrates and their contributions towards these mechanisms. Experiments showing that synaptic regions undergo LTP when EPSPs coincide with the peaks of the V(m) oscillations (Wespatat et al., 2004) support the view that lateral spread of activity through inter-postsynaptic functional LINKs contribute to the summation of EPSPs during LTP. It is observed that dendritic spines increase in volume initially, followed by the accumulation of AMPA receptors (AMPARs) on their surface (Kopec et al., 2006). This enlargement of dendritic spines is consistent with a probable mechanism for introducing close contact between the simultaneously activated abutted postsynaptic membranes by excluding the hydrophilic region between them (Burgess et al., 1992). This provides an initial step towards advanced stages of inter-postsynaptic functional LINKs. Experiment using blockers of soluble NSF (N-ethylmaleimide sensitive fusion protein) attachment protein receptor (SNARE) proteins introduced into the neuronal cytoplasm have demonstrated that some membrane fusion is taking place during LTP induction (Lledo et al., 1998). From this experimental result, a universal interpretation that can be reached is that the blockers of SNARE proteins introduced into the cytoplasm can access and block any membrane fusion mediated through SNARE protein. In this context, it can be interpreted that these blockers are likely blocking reversible inter-postsynaptic membrane hemifusion.

Postsynaptic membranes are anchored to the structural proteins of the extracellular matrix. For the stages of rapid membrane expansion, hemifusion and its reversal, it is expected to remove and add membrane segments at the regions of close contact between the postsynapses using a rapid mechanism. This requires molecular events for rapid reorganization of the postsynaptic membranes at the locations of their interaction. What mechanism can take place at physiological time scales to achieve this rapidly reversible process? Since rapid synaptic vesicle recycling occurs at the presynaptic terminal at physiological time scales and many molecular components utilized in this process are present at the postsynaptic terminal, a mechanism involving these components is likely to explain reversible partial and complete inter-postsynaptic membrane hemifusions taking place at physiological time scales. In contrast to the synaptic vesicle membrane fusion machinery at the presynaptic terminal, checkpoint mechanisms are expected to block the inter-postsynaptic hemifusion from undergoing fusion.

Mechanisms that can supply and uptake membrane segments to meet with the demands of the reversible inter-postsynaptic membrane hemifusion are expected to take place at physiological time scales. A large number of membrane vesicles containing AMPAR subunits are exocytosed during LTP induction. The glutamate receptor 1 (GluR1) AMPAR subunits redistribute into the dendritic spine head cytoplasmic volume after the induction of LTP (Shi et al., 1999). Further work has confirmed this (Passafaro et al., 2001) and showed increased spine volume with increasing functional AMPAR expression (Matsuzaki et al., 2001). The merging of Glu1AMPA receptor subunit-containing endosomes during LTP was also demonstrated (Park et al., 2004). Mice lacking the AMPAR subunit GluR1 showed reduced hippocampal CA3-CA1 LTP (Zamanillo et al., 1999) and impairment in specific spatial working memory (Reisel et al., 2002). During LTP, exocytosis of the AMPARs is associated with their lateral movement (Makino and Malinow, 2009) indicating that a lateral location close to the synapse is favorable for interacting with abutting postsynaptic membranes. In agreement with this, it was recently found that GluA1 subunits of AMPARs concentrate away from the center of the synapse towards the extrasynaptic locations, extending at least 25 nm beyond the synaptic specialization (Jacob and Weinberg, 2014). These findings indicate that in addition to the specific functional role of AMPARs, the lipid membrane recycling of the vesicles likely contributes to functional roles such as enlargement of dendritic spines and formation of different types of inter-postsynaptic functional LINKs (Figure 5).

Postsynaptic exocytosis of AMPARs during LTP requires a unique postsynaptic Q-SNARE protein for vesicle fusion (Jurado et al., 2013). Even though SNARE proteins can lead to membrane fusion through the intermediate stage of hemifusion, specific SNARE-operated molecular machinery is likely capable of arresting the mechanism at the stage of hemifusion (Giraudo et al., 2005; Liu et al., 2008). Another protein of importance is synaptotagmin 4, which is ubiquitously present at the postsynaptic compartment (Adolfsen et al., 2004) and has unique features to regulate Ca^{2+}-dependent exocytosis (Mori and Fukuda, 2011).

Leucine-rich repeat transmembrane proteins (LRRTM2) were shown to co-immunoprecipitate with the AMPAR subunits GluA1 and GluA2 in the *in vitro* overexpression system and regulate the surface expression of AMPA GluR1 subunits at the excitatory synapses (de Wit et al., 2009). In this study, knockdown of LRRTM2 in granule cells resulted in a small decrease in spontaneous AMPAR-mediated miniature excitatory postsynaptic current (mEPSC) amplitude compared to the control neurons. This indicates that knockdown of LRRTM2 results in reduction in the number or function of postsynaptic AMPARs. Knockdown of LRRTM2 also resulted in a 58% reduction in the strength of AMPAR-mediated EPSCs

compared to control cells even though mEPSP reduction was only small. What function imparted by LRRTM2 can achieve this? Experiments have not examined how many axonal tracts were stimulated by the stimulating electrode or how many dendritic spines of the single neuron from which the recording was carried out got activated by the stimulating electrode. Since mEPSP represents presynaptic release probability from all its functional synapses and since only a fraction of them is involved in the measured AMPA-EPSP, it is most likely that an extrasynaptic mechanism is involved. Current through the inter-postsynaptic functional LINKs between the dendritic spines of the recorded and other neurons that get stimulated by the stimulating electrode is a possible mechanism.

LRRTM2 was shown to be essential for maintaining LTP (Soler-Llavina et al., 2013). Since LTP can be explained in terms of lateral inter-postsynaptic functional LINK mechanism (Vadakkan, 2013), the role of LRRTM2 in facilitating AMPA GluR1 subunit exocytosis and related lipid membrane changes is a possible mechanism. The experimental finding that the extracellular domain of LRRTM2 is sufficient for its function in LTP (Soler-Llavina et al., 2013) strongly supports its possible role in reversible lateral inter-postsynaptic functional LINK formation at physiological time scales. Both SNARE and LRRTM proteins have very large extracellular domains (Laurén et al., 2003; Hofmann et al., 2006). This indicates the possibility that these proteins may have a significant role in interacting with the extracellular domains of the same molecules from the abutting membranes or that they may be interacting with structural proteins of the extracellular matrix. In these contexts, LRRTM2 and other factors that regulate surface diffusion of AMPARs (Henley et al., 2011; Opazo et al., 2012) are likely to influence inter-postsynaptic functional LINK formation.

Role of dopamine at the postsynaptic terminals

Dopamine is known to associate with motivation-induced learning (Koob, 1996; Wise, 2004). This can be explained by its action on the dendritic spines at a critical time window (Yagishita et al., 2014). This work has provided evidence showing that dopamine promotes dendritic spine enlargement (Figure 5E) during a narrow time window (0.3–2 s) after the glutamatergic inputs. The enlargement of dendritic spines can allow the abutting postsynaptic membranes to move close to each other, which can facilitate different types of inter-postsynaptic functional LINKs (Figure 5) during their coincident activation at locations of convergence of sensory inputs. This can explain the terminal effect of motivation-induced augmentation of learning. Retention of the hemifused state for a long period of time can lead to insertion of transmembrane proteins across the hemifused membrane segment and stabilize this area. This allows the cue stimulus to induce semblances for memories for long periods of time, which depends on the half-lives of the inserted transmembrane proteins and other changes taking place in the circuitry.

Islets of inter-LINKable and inter-LINKed postsynapses

It is known that the threshold for spike generation is higher at the dendrites than at the axonal hillock, primarily due to the reduced concentration of the sodium channels along the dendrites (Regehr et al., 1993) as evidenced by staining studies (Lorincz and Nusser, 2010). Local degenerative potentials (NMDA spikes) formed at the apical dendrites attenuate as they propagate towards the soma to induce action potential. The synchronous activation of 10–50 neighboring dendritic spines (glutamatergic synapses) necessary for evoking the NMDA spike is expected to have a physiological advantage. Since there is no evidence to suggest that simultaneous inputs from neurons at the lower neuronal order arrive at a cluster of dendritic spines at one of the next order neurons, alternate possibilities need to be derived. It was experimentally shown that the nearby neurons with similar orientation tuning have no correlated activity indicating that adjacent neurons share only a few percent of their inputs (Ecker et al., 2010). In this regard, a large potential can arrive at the recording neuron through one or a few of its dendritic spines, if they have established inter-postsynaptic functional LINKs with dendritic spines of different neurons in the same neuronal order (Figure 6).

Newly formed inter-postsynaptic functional LINKs from lateral synaptic changes can occur in a one-trial novel learning. As continuous learning progresses, it will lead to the addition of new inter-postsynaptic functional LINKs to the already LINKed islets of postsynapses. This is responsible for gradual cumulative learning and fast systems consolidation (Tse et al., 2007) and in turn induces specific semblances in response to a specific cue stimulus. The sigmoid nature of the summation of EPSPs within each dendritic compartment during focal extracellular synaptic stimulation experiments (Polsky et al., 2004) indicates that once one postsynaptic potential is evoked, it leads to

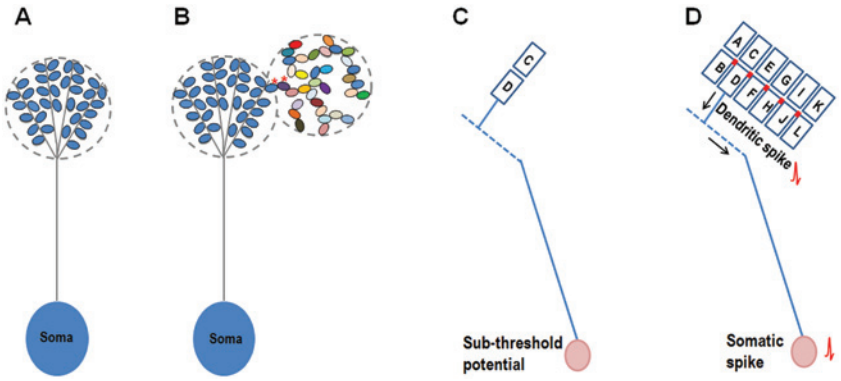

Figure 6: Schematic diagrams showing a possible mechanism for the generation of spikes at the dendritic locations.
(A) Dendritic tree with dendritic spines (blue) of an isolated neuron. (B) 10–50 neighboring spines (in different colors) that can be simultaneously activated during an NMDA spike and can be inter-LINKed (shown by red asterisks) to one of the dendritic spines of the neuron. (C) Schematic representation of a neuron that receives subthreshold potential short of a few potentials for triggering a somatic spike. On its dendritic tree is shown one dendritic spine D, which synapses with presynaptic terminal C. (D) Arrival of the additional potentials to dendritic spine D of the neuron through inter-postsynaptic functional LINK B-D and D-F during a dendritic spike that leads to triggering of a somatic spike (neuronal firing). Note that dendritic spines B, F, H, J, and L are likely to belong to different neurons.

a mechanism of cooperativity in recruiting postsynapses within the islets of inter-LINKable postsynapses. A cue stimulus contains a large number of subcue stimuli that were associatively learned in the past. Items or events in the environment have a large number of shared physical properties. Therefore, a cue stimulus alone can result in the activation of a large number of inter-postsynaptic functional LINKs which are mostly part of large islet of inter-postsynaptic functional LINKs, generating a large potential such as dendritic spike. In the context of the present work, the functional relevance of the third-person observed dendritic spike can be explained in terms of different first-person internal sensations – (a) non-specific semblances contributing to C-semblance for consciousness (Vadakkan, 2010), and (b) specific semblances for memory of previously associatively learned items or events.

Dependence on the frequency of oscillating potentials

Various higher brain functions are part of a spectrum of internal sensations, all of which take place in a background conscious state. Internal sensations are systems properties that are intimately linked to specific frequencies of oscillating surface or extracellular-recorded potentials. The oscillating potentials are expected to receive contributions from both horizontal and vertical component potentials. Changes in the frequency of oscillating potentials are likely secondary to changes in the horizontal component of the oscillating potentials. It was not possible to demonstrate the presence of gap junctions between the excitatory neurons to explain oscillatory potentials (Mercer, 2012). Since recurrent collaterals alone are not sufficient to explain the horizontal component of oscillating potentials, alternate mechanisms are expected to take place.

Based on the present work, physiologically occurring dendritic spikes that result in the synchronous activation of 10–50 neighboring glutamatergic synapses form a major contributor to the horizontal component (Figure 7). The relationship between the frequency of oscillating potentials and consciousness indicates that the contributions from the integral of non-specific semblances induced during dendritic spikes at the apical tuft region are likely a major contributor of C-semblance for consciousness (Vadakkan, 2010). The finding of changes in the frequency of oscillating potentials during and following the induction of sleep (Alkire et al., 2008) and anesthesia (Sanchez-Vives and McCormick, 2000) indicates that these induce changes in the conformation of C-semblance for the internal sensation of consciousness. Since a large number of continuously switching-specific internal sensations of higher brain functions are taking place in the background of a normal conscious state, all the postsynaptic potentials likely have a role in determining the specific qualities of internal sensations.

Maintaining subthreshold activations

Based on the present work, maintaining neurons at subthreshold states is functionally significant. Certain ion

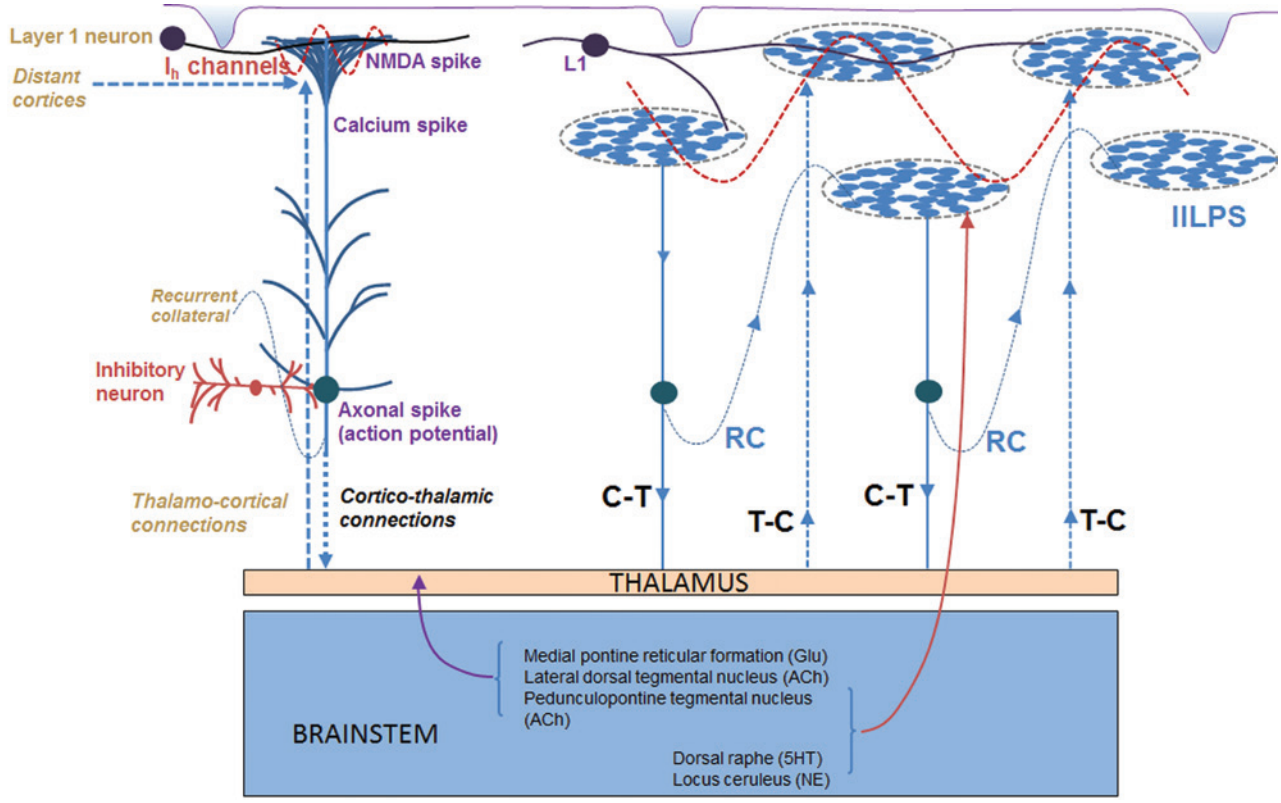

Figure 7: Diagram showing sources of potentials arising from different types of spikes and oscillations of surface-recorded potentials. Top left: a pyramidal neuron with different locations of spike generation. The source of surface-recorded EEG waveforms is likely to have more contributions from the NMDA spikes from the apical tufts since it is closer to the pial surface and the number of these spikes may outnumber the number action potentials that can have an effect at the level of the pial surface. Top right: five islets of inter-LINKed postsynaptic terminals are shown to represent the abundance of dendritic spines in this area allowing the formation of a large number of these islets. The islets are expected to be connected with each other through recurrent collaterals, layer 1 cortical neurons and cortico-thalamo-cortical pathways. This pattern of arrangement will provide a mechanism for long-range synchronization that is being recorded as EEG waveforms. Bottom: connections from the brainstem towards both the thalamus and cortex. These inputs have a major role in maintaining the oscillating potentials in the cortex. Note that cortico-thalamic and thalamo-cortical pathways form an integral part in maintaining oscillating potentials at the level of the islets of inter-LINKed postsynapses (IILPS). RC, Recurrent collateral; C-T, cortico-thalamic pathway; T-C, thalamo-cortical pathway; L1, layer 1 cortical neuron. (Modified from Vadakkan, 2015.)

channels support this function. I_h is a mixed sodium and potassium cation conductance activated by membrane hyperpolarization. I_h is mediated by the HCN family of ion channels that are highly expressed on the distal dendrites of cortical pyramidal and CA1 neurons (Magee, 1998; Williams and Stuart, 2000). Along with potassium channels, I_h controls the resting membrane potential of the dendrites of pyramidal neurons farther away from the soma. The action of I_h is considered similar to a bias current acting to regulate the voltage-dependent block of NMDA receptors by Mg^{2+} (Tang and Thompson, 2012). At the distal dendrites, I_h may serve as a shunt to maintain a steady subthreshold membrane potential. Subthreshold excitation of the terminal dendritic branch leads to binding of glutamate to the high-affinity NMDA receptors and blocks these receptors without conducting any current through them. On the arrival of a few additional EPSPs through the inter-postsynaptic functional LINK, blocked NMDA receptors can revert to a conducting state. The operation of such a mechanism can have functional significance in the operation of inter-postsynaptic functional LINKs and in maintaining neurons at subthreshold levels ready to spread to the next order of neurons. In the background state of oscillating potentials, any stimulus that reactivates inter-postsynaptic functional LINKs can provide potentials for triggering several subthreshold-activated neurons to fire in an AMPA GluR1-dependent and phase-locked manner (Kitanishi et al., 2015).

Functional units utilizing all the EPSPs

The present work has explained an all-postsynaptic potentials-inclusive functional operation of the system. Any postsynapse that can reactivate an inter-postsynaptic functional LINK is expected to induce units of internal sensations that get naturally computed, generating various internal sensations. Among all the EPSPs arriving at a neuron, one subset of EPSPs contributes to neuronal firing so that activity can be propagated towards higher neuronal orders to increase the probability of the formation of additional inter-postsynaptic functional LINKs. Other subsets reactivate inter-postsynaptic functional LINKs and induce semblances for internal sensations of various higher brain functions. They also add potentials to the neurons of the next neuronal orders. If the latter already receive subthreshold potentials, then they will fire action potentials. By taking into account those postsynapses where EPSPs that contribute to semblances for the formation of internal sensations of higher brain functions with or without contributing to the neuronal firing, a new unit for the nervous system can be defined (Figure 8). Since these units cannot function by themselves without being part of the system producing oscillating potentials, they can be called quasi-functional units.

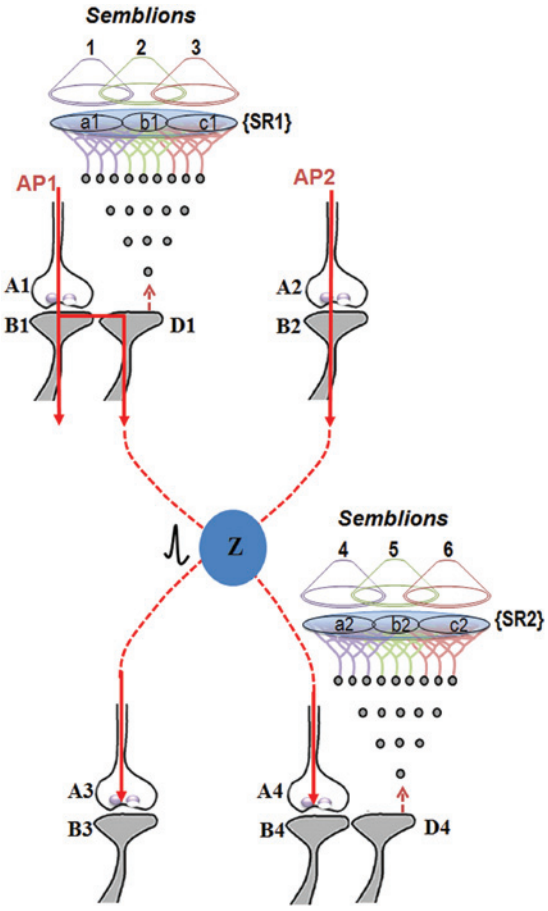

Figure 8: Schematic diagram showing an all-EPSP-inclusive quasi-functional unit of the nervous system.

Action potential marked AP1 activates synapse A1-B1, reactivates inter-postsynaptic functional LINK B1-D1, activates postsynapse D1 and induces semblance of activity arriving from latter's presynapse C1 (not shown). The nature of the semblance has been described previously (Vadakkan, 2013) and summarized in Figure 4C. Semblance consists of the hypothetical packets of sensory inputs (semblions) that are otherwise capable of inducing potentials at postsynapse D1 through its presynapse C1 (not shown). Action potentials arriving at nearly <40 synapses (represented by one synapse A2-B2) keep neuron Z at subthreshold potential ready to fire on arrival of the rest of the potentials to cross the threshold. In this context, the potential arriving through inter-postsynaptic functional LINK B1-D1 to postsynapse D1 can provide this potential and trigger neuron Z, which can explain how a new set of neurons is activated during memory retrieval (Tye et al., 2008). If neuron Z is a motor neuron, it can initiate motor activity as part of the behavioral motor activity. The net effect of the semblions from different neuronal orders results in the internal sensation of various higher brain functions. Semblances are also shown to form at the next neuronal order by the reactivation of inter-postsynaptic functional LINK B4-D4. Note that in contrast to a neuron and its processes, the proposed functional unit consists of a neuron, its processes, inter-postsynaptic functional LINKs, and the inter-LINKed postsynapses. Since the lateral spread of activity through inter-postsynaptic functional LINKs contributes to the horizontal component of the oscillating potentials, these units cannot function by themselves and are called quasi-functional units. AP, Action potential. (Modified from Vadakkan, 2013.)

Role of backpropagating somatic spike

Somatic action potentials propagate back towards the apical dendrites in a decremented manner, which is frequency dependent (Stuart et al., 1997). Their maximum rate of rise decreases with increasing distance from the soma. Even though backpropagation of somatic action potentials was found up to the level of the dendrite at which patch clamping was possible to carry out (Stuart et al., 1997), calcium imaging experiments showed that action potentials fail to propagate to the distal dendrites of the apical tuft (Schiller et al., 1995). This indicates that the formation of internal sensations at the postsynapses at which the dendritic spikes occur is likely free from interference by the backpropagating action potentials. It was theoretically found that the action potentials sweeping backward from the soma towards the dendrites do not interfere with the maintenance of the independence of the dendritic spine's voltage-dependent computations (Behabadi and Mel, 2014). It is also possible that

semblance would have already been induced at specific postsynapses by the time backpropagating potentials arrive at the postsynapses. This can allow the formation and reactivation of inter-postsynaptic functional LINKs at these dendritic spines that can contribute to specific internal sensations without any interference.

As an animal travels though the environment and continuously receives new sensory cue stimuli, its nervous system will be continuously retrieving different memories. This can be explained by the formation of new integral of semblances in response to a new cue stimulus. If and when the backpropagating somatic spike arrives at the postsynapses of a neuron, it is expected to induce non-specific semblances at a large number of postsynapses and can dilute the specific semblance formed, allowing forgetting. As the animal moves in the environment and continues to receive new sensory stimuli, these mechanisms enable the nervous system to evoke a series of new memories in response to a series of newly arriving stimuli.

Place cell firing in response to specific spatial sensory inputs

The firing of the CA1 neurons (place cells) (O'Keefe and Dostrovsky, 1971) is correlated with visual sensory inputs arriving from specific spatial location. Sensory inputs from different sensory organs arrive at the hippocampus after some orders of neurons. Spatial cues reactivate inter-postsynaptic functional LINKs inducing semblance of the associated items or events in that space. The potential arriving at the inter-LINKed post synapse reaches the latter's neuronal soma. If this happens to be a subthreshold-activated CA1 neuron just short of few millivolts for firing, it enables the neuron to fire (Figure 8) and will be counted as a place cell. This is in agreement with the experimental finding that a silent CA1 neuron becomes a specific place cell by the arrival of small potentials from spatial sensory inputs (Lee et al., 2012). Thus, potentials propagating through the inter-postsynaptic functional LINKs are sufficient for place cell activation along with inducing semblances of the associatively learned spatial features. Recent finding that calcium transients occurring at specific dendritic locations of a CA1 neuron predict spatial precision and place field properties (Sheffield and Dombeck, 2015) also matches with the present work. This is made possible by keeping CA1 neurons at subthreshold levels using spatially untuned somatic membrane potentials.

At locations of convergence of multiple sensory inputs such as the hippocampus, large islets of inter-postsynaptic functional LINKs are expected to be present. Since single action potentials may fail to reach the soma and complex spike bursts can often get transmitted more reliably (Lisman, 1997), the functional importance of the spike generation at the islets of inter-LINKed postsynapses may be examined. These are potential locations of convergence of sensory inputs where inter-postsynaptic functional LINKs are generated during associative learning and the arrival of sensory inputs evokes NMDA receptor-dependent multidendritic calcium spikes (Grienberger et al., 2014). The lateral spread of activity through the islets of inter-postsynaptic functional LINKs at the CA1 dendrites can provide the horizontal component for the oscillatory potentials along with inducing semblances for internal sensations of retrieved spatial memories. By increasing the horizontal component, the frequency of oscillating potentials reduces. This supports the predictive ability of the complex spike train dynamics for theta-related phase precision of the hippocampal pyramidal cells (Harris et al., 2002).

Internal sensations along with motor neuronal firing

When the normal EPSP of nearly 1 mV spreads through the inter-postsynaptic functional LINK to the inter-LINKed postsynapse (inducing semblance) reaches the latter's neuronal soma as the (n)th potential to achieve the firing threshold, the neuron fires. In this context, a single EPSP can lead to the firing of a subthreshold neuron that will be taken as encoding of new memories by an individual neuronal firing at the exact moment of learning, even after single presentations (Ison et al., 2015). Activating neurons at higher neuronal orders in the motor cortex can result in appropriate behavioral motor action unless these cortical neurons are under an inhibitory neuronal control (Figure 9). The nature of the motor neuron actions is intimately connected to the induced internal sensations that are in turn dependent on previous associative learning events. The motor activity that can also occur through pathways other than the motor cortex (Kawai et al., 2015) is likely taking place by the activation of subthreshold motor neurons. The muscle contraction by itself induces sensations such as proprioceptive stimuli from the joint capsules. These stimuli are used by the system to associate and optimize appropriate expected goals. A possible mechanism for this was explained previously (Sejnowski et al., 2014).

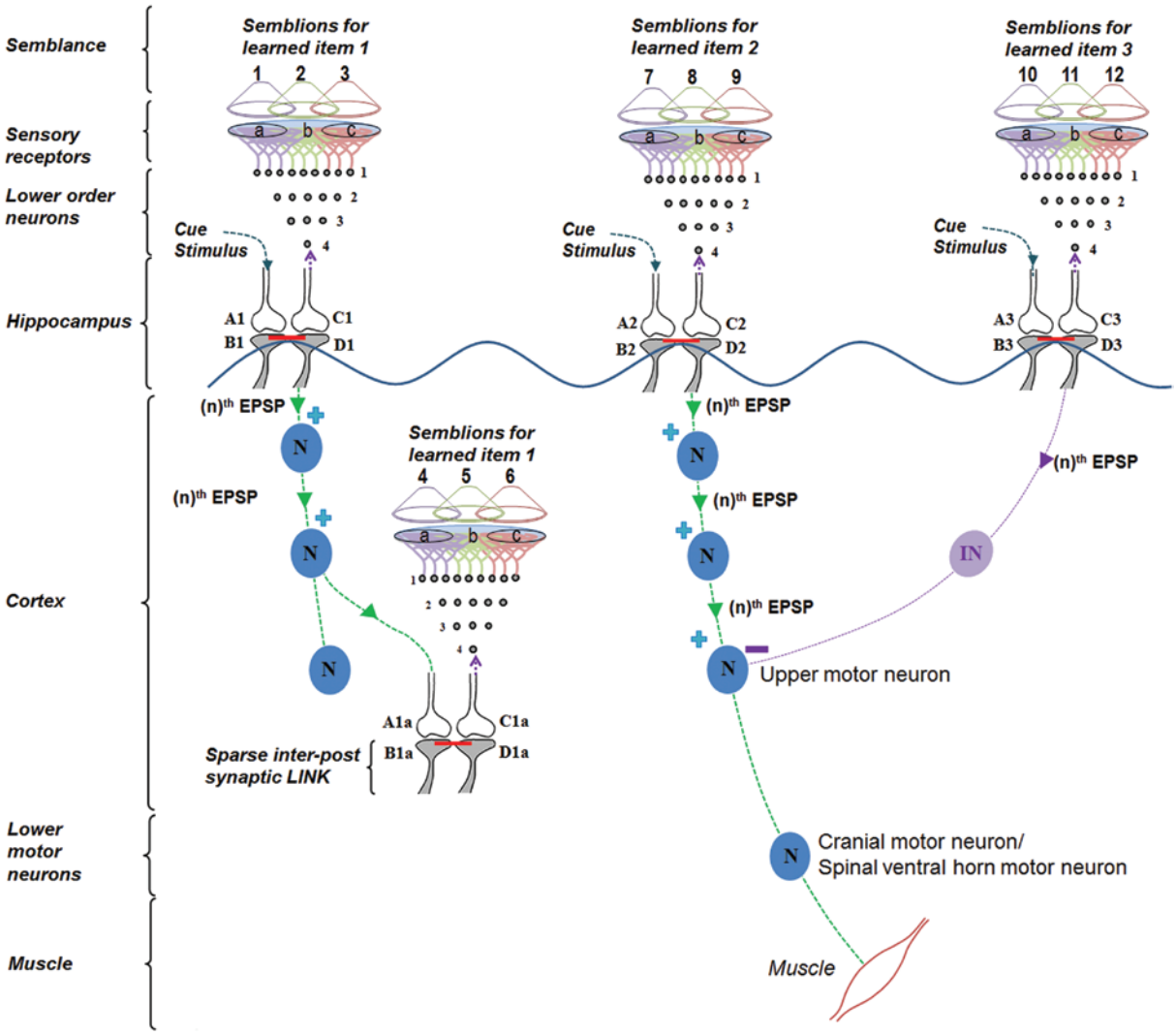

Figure 9: Diagram showing the formation of internal sensations and fine control of the motor activation by a cue stimulus. Oscillating neuronal activity results in the activation of many downstream neurons. They can be kept tonically inhibited under resting conditions (not shown) to subthreshold levels such that they can be disinhibited at the arrival of one or a few excitatory postsynaptic potentials (EPSPs). There were two associative learning events that occurred previously with the cue stimuli. The first one was with items 1 and 2. After this first step of associative learning, the cue stimulus was retrieving memories of items 1 and 2. Note the reactivation of a sparse inter-postsynaptic functional LINK in the cortex. Along with retrieving memory of the second item, cue stimulus also evokes a motor response using the motor neuron. At a later time, the same cue stimulus had undergone a second associative learning event with item 3. Following this second learning event, the cue stimulus evoked internal sensations (semblances) of learned items 1, 2 and 3. However, as the semblance for item 3 was evoked, it also resulted in an inhibition of the motor activity (note the output from postsynapse D3 providing inhibitory potentials to the upper motor neuron). This type of an event is an example of the behavioral inhibition occurring at the frontal cortices. Complexities of the internal sensations can be based on the nature of the cue stimulus, previous associative learning, and the type of the nervous system. Reward-induced associative learning may be facilitated by dopamine-induced enlargement of dendritic spines (Yagishita et al., 2014) that promotes possible inter-postsynaptic membrane hemifusion and its stabilization for a long period of time. Also note that the cue stimulus reactivates inter-postsynaptic functioanl LINKs at other cortical areas to evoke memories for learned item 1. Since the inter-postsynaptic functional LINKs are transient and need reinforcement for long-term persistence, the induction of a minimum number of inter-postsynaptic functional LINKs alone may not maintain the effect of learning for a long period of time. In the hippocampus, the reactivation of inter-postsynaptic functional LINKs in response to spatial stimuli is expected to induce semblances for memories associated with that space and the EPSPs arriving through the inter-postsynaptic LINK induce firing of subthreshold-activated CA1 neurons (place cells). This explains how spatial memories are associated with place cell firing. Formation of circuits in this manner can explain the induction of internal sensations along with simultaneous behavioral motor action. Three sensory cortices are marked to indicate that the sensory stimuli can be of different types. EPSP: excitatory postsynaptic potential. (*n*)th EPSP: the last EPSP necessary to achieve threshold EPSP to generate an action potential. Each motor action will evoke certain sensory stimulus in the form of proprioception that will act as a feedback stimulus to the system confirming that the motor action was executed. N: Excitatory neuron; IN: Inhibitory neuron. A and C: Presynaptic terminals; B and D: Postsynaptic terminals. Red line between B and D: Inter-postsynaptic LINK. (+) stimulation; (-) inhibition.

Role of inhibitory neurons

Various brain functions are under inhibitory control. The frontal cortex is known to mediate inhibition of certain types of behavioral motor activity during its development. An example is the involuntary inhibition of primitive motor activity. Certain behavioral motor activities can be inhibited voluntarily. The semblances can generate subjective conscious inner sensations that allow protracted unconscious generation of motor action resulting from the decision. It is necessary to examine the effect both at the levels of inhibitory outputs and the postsynaptic terminals (inputs) of the inhibitory neurons.

Inhibitory outputs

It is known that distinct groups of inhibitory interneurons differentially target dendritic tuft and perisomatic regions of pyramidal cells and control their rate, burst, and timing both in the neocortex (Ascoli et al., 2008) and hippocampus (Royer et al., 2012) and regulate the oscillatory nature of the surface or extracellular-recorded potentials. Inhibitory interneurons regulate the interaction between principal neurons within the hippocampus (Freund and Buzsáki, 1996). The presence of gap junctions between the inhibitory neurons can have a major role in maintaining oscillating potentials among them (Cobb et al., 1995; Benardo, 1997). Such a mechanism favors keeping several excitatory neurons tonically inhibited under resting conditions to subthreshold levels such that they can be disinhibited at the arrival of one or a few EPSPs either synaptically or via inter-postsynaptic functional LINKs. This can explain motor action in response to stimuli, with or without the induction of internal sensations.

Semblance can occur at the postsynapses (inputs) of the inhibitory neurons

Based on the present work, the mechanism of semblance should not depend on the cell type of the postsynaptic terminal at which it is induced. One possible role in inducing semblances can be explained with the example of nucleus accumbens (NAc). It is known that approximately 95% of the neurons in the NAc are GABAergic medium spiny (named because of high density of their dendritic spines) neurons (Robison and Nestler, 2011). They primarily express either D1 or D2 type of receptors. Dopaminergic inputs from the ventral tegmental area (VTA) arrive at the dendritic spines of the inhibitory neurons of the NAc. Through a different route, the effect of dopaminergic inputs to the prefrontal cortex (PFC) results in increased excitatory inputs to the NAc. These will lead to an increase in the size of dendritic spines of the inhibitory neurons of the NAc and in turn can lead to the formation of inter-postsynaptic functional LINKs between the spines. The net semblance at the level of these inter-LINKed postsynapses is likely contributing to pleasure. Based on the present work, the induction of inter-postsynaptic functional LINKs contributes to increased horizontal component and reduce the frequency of oscillations whenever a positive, pleasure or reward-inducing stimulus arrives. An example is the observation of reduction in the frequency of oscillating potentials during action selection (Stenner et al., 2015). Furthermore, it was found that local field potentials in the rat NAc and PFC are coupled at delta frequencies during instrumental behavior (Gruber et al., 2009).

Natural computation of units of internal sensations

The rules that govern the natural computation of semblances formed at the activated inter-LINKed postsynapses are likely to promote an energy-efficient formation of internal sensations of higher brain functions such as perception, memory, and consciousness. The integration of semblances for a specific internal sensation is likely taking place at one or few neuronal orders (Vadakkan, 2011). Oscillating potentials of a specific range of frequency inducing the internal sensation of consciousness can be considered a necessary systems property. The computational algorithms for the integration of all the semblances occurring during higher brain functions need to be identified. It could be using a simple overlap, and/or integration of all or selected semblions. The algorithm fitting also depends on the strength of the internal sensation induced. For verification of the mechanism, first-person internal sensations need to be replicated in engineered systems (McDonnell et al., 2014; Vadakkan, 2014) and will require concurrent computational work. The natural computation underlying higher functions is most likely modular in nature and it is dependent on maintaining a core conscious process which needs to be maintained as a functional keel of the system. The modular nature of different nervous system functions requires various independent computational processes taking place at the same time. The algorithm development for motor activities is comparatively easy as the motor actions are definite

end-points and can be incorporated within the circuitry that induces formation of internal sensations. In other words, the initial focus needs to be directed to reproduce the formation of internal sensations. The circuit formed out of this mechanism can self-organize through the addition of new inter-postsynaptic functional LINKs during new associative learning events, and the gradual reversal of existing inter-postsynaptic functional LINKs by the lack of their use that can lead to forgetting.

Dynamic reorganization of the circuitry

Gene expression and circuit changes

Since associative learning-induced transcriptional and translational changes take time to operate, their products are not expected to contribute to the immediate requirements of different higher brain functions at physiological time scales – for example, perception and working memory. Various mechanisms for inter-postsynaptic functional LINKs explained in the present work (Figure 5) can take place at physiological time scales in the presence of readily available pre-synthesized molecules. Regulation of gene expression profiles observed after associative learning (Alberini and Kandel, 2014) provides substrates for future associative learning events and is likely used for the stabilization of repeatedly induced inter-postsynaptic functional LINKs.

Cortical rewiring

The functional roles of observed cortical rewiring have been examined in terms of synaptically connected neurons (Chklovskii et al., 2004). Based on the present work, outgrowths from the neurons towards the presynaptic side and their formation of synapses during the interval of time after an associative learning event will inevitably lead to the induction of non-specific semblances, reducing specificity of a memory, unless repetition of learning occurs. This can be considered a homeostatic mechanism both to eliminate changes from less relevant and less frequent associative learning events and to increase the number of possible combinations of semblances to associatively learn more items or events from the environment. In this context, to add more specificity to the net semblances induced by related stimuli, there will be demands on the neuron to produce more outgrowths. In addition, continued learning induces a large number of inhibitory network circuitries as seen during the development of the frontal cortex for suppressing spontaneous behavioral motor activity.

Each new associative learning event will require induction of specific set of inter-postsynaptic functional LINKs. Since all the sensory inputs converge at the hippocampus, it is likely that the finite number of LINKable postsynapses will limit the number of associatively learnable items and events. However, for a given cue stimulus generation of thousands of new granule neurons on a daily basis will provide a large number of new postsynapses both at the level of the entorhinal cortex and at higher neuronal orders that lead to the formation of new inter-postsynaptic functional LINKs, if learning is repeated. During memory retrieval, a large number of new sets of semblances induced by the new combination of postsynapses for a given cue stimulus at the higher neuronal orders will improve memory. These features explain how the net semblances can be increased by repetition of associative learning at intervals of time. This can also explain how gradual forgetting occurs by reducing the net semblances, if no repetition of learning is done.

Since the types of sensory organs are limited and the objects in the environment share many physical properties, it is possible that every associative learning event shares many of the previously existing inter-postsynaptic functional LINKs from previous associative learning events. Since a large number of physical properties are shared, shared islets of inter-postsynaptic membrane hemifusions are expected to be maintained in spite of the formation of new neurons. The size of these islets is expected to be bigger at the neuronal orders closer to the granule neuron layer. Dendritic excrescences that are large clusters of postsynapses upon which a large number of presynaptic terminals from granule neurons synapse is expected to evoke semblances for shared physical properties.

Additional advantage with the inter-postsynaptic functional LINK

Inter-postsynaptic functional LINKs are expected to be present through different mechanisms with different half-lives as explained in Table 3. Beyond these advantages, a complete inter-postsynaptic membrane hemifusion (see Figure 5) can get converted to complete fusion under various conditions depending on protein-protein interactions (Hofmann et al., 2006), the presence of regulatory lipids (Fratti et al., 2004), and composition of lipid membranes (Karunakaran and Fratti, 2003). Inter-postsynaptic

Table 3: Different mechanisms of inter-postsynaptic functional LINKs operating at different locations of the nervous system.

Function	Necessary operation	Possible inter-postsynaptic functional LINK mechanism	Potential locations of formation
Perception	Very rapid formation and very rapid reversal	Pre-existing LINKs and newly formed LINKs by exclusion of water of hydration	Sensory cortices
Working memory	Rapid formation and reversal; provision for short-term retention of the mechanism	Close contact between the postsynapses by excluding the water of hydration and partial hemifusion	Cortex and hippocampus
Short-term memory	Mechanism lasting for a short period of time	Complete hemifusion	Hippocampus and cortex
Long-term memory	Mechanism to last for a long period of time	Complete hemifusion with trans-membrane protein insertion across the hemifused area	Hippocampus and cortex
Consciousness	Innate formation. Reversal of a proportion of operational units induces sleep	The majority with stabilized complete hemifusion and the rest with varying hemifusions formed during wake state	Dendritic tuft and other cortical areas

membrane fusion between the spines of a single neuron will not lead to any deleterious effects. Dendritic excrescences are likely formed by a large number of interconnected postsynapses found on the dendritic tree of the CA3 neurons. Inter-postsynaptic membrane fusion between the postsynapses of two different neurons can lead to cytoplasmic content mixing between different neurons (Figure 5E). Since it was found that gene expression profiles of two adjacent CA1 neurons differ in their expressed proteins (Cohen and Melikyan, 2004), mixing of the cytoplasmic contents of even two adjacently located similar type of neurons within a cortical layer can lead to cellular responses against unwanted cytoplasmic contents. This can lead to cytotoxic changes and trigger neurodegenerative changes.

Testable predictions

1. The presence of inter-postsynaptic functional LINK formed by excluding the hydrophilic region between the membranes that allow conduction of potentials across them can be tested. Since this is beyond the scope of direct imaging studies, development of novel techniques is necessary to demonstrate both structural and functional changes induced by this mechanism.
2. The presence of hemifused inter-postsynaptic membrane areas can be examined *in vivo*. Experiments using dye injection into the soma or expression of fluorescent protein within a neuron will only make the dendritic spines that belong to one neuron within an islet of inter-postsynaptic membrane hemifusion visible. In order to examine the inter-postsynaptic membrane hemifusion that physically separate the postsynaptic cells, microscopes of high resolution are necessary. Since the average surface area of a dendritic spine ranges from 0.61 to 3.14 μm^2 (Wilson et al., 1983) and the hemifused areas of few nanometers can serve the functions expected of the inter-postsynaptic functional LINK (Leikin et al., 1987), it is necessary to conduct dedicated high-resolution microscopic examination with three-dimensional reconstruction from areas of convergence such as the hippocampus, amygdala, and other regions within the cortex. By obtaining high-resolution electron microscopic images to visualize the lipid bilayers of the entire synapse (Kuwajima et al., 2013), the low-resolution images of the suspected areas of the inter-postsynaptic membrane hemifusions observed in some of the electron microscopic pictures (Burette et al., 2012) can be verified. Dedicated very high-resolution microscopic techniques that can resolve real-time changes at nanometer scales (Chen et al., 2014) are necessary to visualize membrane hemifusion changes occurring between the abutting postsynaptic membranes *in vivo*. Due to high-energy requirements, hemifusion is expected to involve a site-restricted process within a very small area of nearly 10 nm^2 (Leikin et al., 1987). In this context, concentration of GluA1 subunits of AMPARs at locations 25 nm away from synaptic specialization (Jacob and Weinberg, 2014) can be further examined. Even though membrane rotation and changes induced during tissue preparation may confound the results, low-resolution regions of potential inter-postsynaptic membrane hemifusion (Figure 2B and 4D in Burette et al., 2012) can be verified.
3. Injecting different neurons within the same neuronal order with different lipophilic fluorophores to stain their membranes followed by associative learning can

be used to study the hemifusion process using newly developed protocols (Floyd et al., 2008, 2009).

4. Advanced real-time microscopic examination may provide evidence for the reversible, yet stabilizable nature of the inter-postsynaptic membrane hemifusions both during LTP induction and associative learning. A reversal of this process can be tested during the reversal phase after LTP induction.
5. A robust checkpoint mechanism of specific SNARE proteins such as Q-SNARE possibly by interacting with complexin, syntaxin-3, or other postsynaptic proteins for arresting the membrane fusion process at the stage of membrane hemifusion can be searched.
6. Experiments can be carried out to test for the presence of innate mechanisms of inter-postsynaptic functional LINKs that are conserved within a species and are necessary to carry out survival behaviors such as breathing and feeding.
7. Dendritic excrescences can be examined for the presence of both inter-postsynaptic membrane hemifusion and fusion.
8. Since repeated associative learning can induce long-term changes by the introduction of transmembrane proteins across the hemifused membrane segments, studies can be undertaken to verify their presence.
9. By using the principle of operations explained here, the gold standard test of replicating the mechanism in engineered systems can be carried out.

Conclusion

Since the internal sensations of intentionality for basic survival and reproductive instincts have been evolutionarily preserved even in very low forms of animal species, the presence of a robust operational principle can be expected in every nervous system. The present work has explained the functional attributes for the conservation of all the postsynaptic potentials, including those that do not contribute to neuronal firing. All the potentials arriving at the postsynaptic terminals of a neuron have functional contributions, even when the neuron is not firing, when examined from a first-person frame of reference. The present work has also examined potential functional roles for compartmentalization of the distal dendritic segments and dendritic spikes *in vivo*. It has explained how the firing of a neuron is flanked by the formation and reactivation of internal sensory processing subunits. The reactivation of inter-postsynaptic functional LINKs is capable of providing the necessary potentials to subthreshold-activated neurons leading to third-person-observed firing of neurons at the next neuronal order, explaining a potential mechanism for motor activity. The integration of all the induced units of internal sensation that depends on previous associative learning events will lead to first-person properties of different higher brain functions along with behavioral motor activity in response to a stimulus. By examining the predicted anatomical changes, and undertaking large-scale computations of the units of internal sensations along with replicating the mechanism in engineered systems, the emergence of internal sensation explained by the present mechanism can be verified. The present work should be considered unproven unless verified by further experimental evidence.

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