Nonsensible (not directly with our senses) features of a system can be inferred from its sensible properties. Since we have a large number of constraints from findings in multiple levels of the nervous system, a derived solution that can explain all its features at those levels is likely correct even if we are unable to directly sense the formation of first-person inner sensation. Further, we can a) do retrodictive examinations, & b) make testable predictions for verification.			
	The findings.	***Constraints offered by the findings (on the left side) that direct the enquiry towards a correct solution.***	***Interconnected explanations by the semblance hypothesis (Please read this row after reading the hypothesis).***
1	Both associatively learned stimuli & prompt (cue) stimuli propagate through synaptically-connected neuronal circuit.	Mechanism should operate synchronous with the synaptically-connected circuitry.	Inter-neuronal inter-postsynaptic functional LINKs (IPLs) form and operate only when synaptic transmission takes place (Vadakkan, 2007; 2013).
2	Learning-induced changes occur in physiological timescales (in milliseconds)[Foot note1]	A learning-inducible change that occurs (& completed) in physiological timescales (to explain the ability to retrieve memory instantly following learning).	Propagation of potentials along the IPLs to the inter-LINKed spines takes place in physiological timescales of milliseconds (Vadakkan, 2007; 2013).
3	Memories that can be retrieved after long period after learning are also capable of getting retrieved immediately following learning (working memory).	Learning should generate retrieval-efficient changes within milliseconds. They can be used for memory retrieval immediately (working memory). These changes have a provision for remaining in a stable form for long period, responsible for long-term memory.	IPL formation takes place at the time of learning. When IPL reverses back, then its short duration can only generate working memory. Lifespan of IPL decides the duration of storage of memory. Long-term stabilization of IPLs lead to long-term memory (Vadakkan, 2010a; 2013).
4	When exposed to a cue stimulus, inner sensation of memory occurs in physiological timescales (in milliseconds).	A learning-induced change should be capable of inducing inner sensation of memory in physiological timescales (completed within this time).	Propagation of potentials along the IPL generates semblance over the inter-LINKed spine instantly as a system property (Vadakkan, 2013).
5	Memory is an internal sensation of an item/event having certain specific sensory features (qualia).	Mechanism is expected to have elements that can provide sensory features to the retrieved memory.	Integration of all the units of inner sensation generated on large number of inter-LINKed spines by a cue stimulus provide qualia (Vadakkan, 2010a).
6	Ability to store large set of learning-induced changes	Neurons and their processes are finite in	Inter-LINKed spines within the islets of inter-LINKed spines can be

	responsible for retrieving large number of memories.	number. Therefore, an efficient operation for storing large numbers of learning-induced changes becomes possible if common elements in each learning mechanism can be shared. Hence, each memory is expected to get induced from a combination of unitary mechanisms.	depolarized by any specific stimulus reaching it. Since items/events consist of combinations of sensory stimuli, different combinations of inter-LINKed spines can be used by different cue stimuli to generate corresponding memories (Vadakkan, 2010a).
7	Instant access to very large memory stores.	A specific cue stimulus should be able to induce a specific memory by combinatorial reactivation of a specific set of learning-induced unitary changes.	Inter-LINKed spines can be accessed by stimuli from any cue stimulus (Vadakkan, 2010a).
8	Absence of cellular changes during memory retrieval.	A passive reactivation of the changes that occur during learning should be getting used at the time of memory retrieval to induce units of internal sensations. This should take place at physiological timescales of milliseconds.	Since inter-LINKed spines persist from the time of learning, propagatoin of depolarization along the IPL does not require any new cellular changes (Vadakkan, 2010a).
9	During memory retrieval, firing of a subset of neurons that were not firing before learning in response to the same cue stimulus occurs.	Learning has opened certain new channels & cue stimulus leads to propagation of depolarization through these channels to provide additional potentials to a subset of neurons that are otherwise being held at subthreshold activation state (without firing). This will lead to firing of these set of neurons.	Formation of IPLs during learning will lead to propagation of depolarization across them to the inter-LINKed spines. This will provide additional potentials to the inter-LINKed spine's neurons and may fire those neurons (Vadakkan, 2013).
10	Brain operates in a narrow range of frequency of extracellularly recorded oscillating potentials.	Expected mechanism provides vector components of the oscillating potentials.	Synaptic transmission & near perpendicular propagation of depolarization across the IPL provides vector components.

			Reactivation of a set of IPLs at rest generates a background semblance, which is expected to generate inner sensation of a conscious state (Vadakkan, 2010b).
11	Motivation promotes learning. Motivation is associated with release of dopamine at different locations of the brain.	Motivation is associated with specific factors and their specific actions are expected to promote the learning-induced change and possibly to retain this change for longer period than that occur in its absence.	Dopamine is known to cause spine expansion (Yagishita et al., 2014). Expanding spines can augment IPL formation and retain the formed IPLs for long time that may trigger some stabilization steps.
12	Internal sensations of working, short, and long-term memories have similar qualia.	The same learning-induced change is retained for different durations. Long-term memory loses its clarity both due to loss of some unitary mechanisms & dilution of specificity by combining with newly formed units of inner sensations.	Memories of all durations take place by reactivation of inter-LINKed spines by depolarization propagating along the IPLs and generating units of inner sensations (Vadakkan, 2010a, 2013).
13	Working memory lasts only for a very short period of time.	Learning-induced change must have a quickly reversible mechanism.	IPL formation is a high energy requiring process as can be inferred from experiments using artificial membranes (Rand and Parsegian, 1984; Martens and McMahon, 2008; Harrison, 2015). Hence majority of IPLs are expected to reverse quickly.
14	Some of the same memories that are retrieved as working memories can be retrieved after a long period of time after the learning.	Learning-induced change must be able to undergo certain changes that will enable it to get maintained for a long period.	Stabilization of IPLs for long period can induce the same units of inner sensation. If the number of IPLs that can be reactivated by a cue stimulus after a long period decreases, then qualia of memory will reduce (Vadakkan, 2010a; 2013).
15	Simultaneous existence of previous two conditions (above two rows) within the system.	Learning-induced mechanism should have an initial quickly reversible change that under certain circumstances can progress towards a stage	When memory of a beneficial or deleterious item or event becomes advantageous for survival, then IPLs necessary for those memories are stabilized for long period (Vadakkan, 2010a; 2013).

		where it can get stabilized for long period of time.	
16	Internal sensation of memory in response to a cue stimulus varies with the nature of the cue stimulus.	Specific sensory features from the cue stimulus induce a specific combination of internal sensory units to generate specific features of memory being retrieved.	As the cue stimulus propagates through its path, depolarization propagates through a specific set of IPLs that induce a specific set of units of inner sensations for a specific memory (Vadakkan, 2010a, 2013).
17	After associative learning between two items, arrival of one of the items generates memory of the other item.	The learning mechanism should have features to explain how either one of the associatively learned items can act as a cue stimulus to generate memory of the other item. Hence, the mechanism should have the ability to show bidirectionality in it.	Semblance can be generated from either one of the inter-LINKed spines on the two sides of an IPL (Vadakkan, 2010a; 2013).
18	Even partial features of one of the associatively learned item is capable of retrieving memory of the second item.	The mechanism should have features to explain how stimuli from partial features of one stimulus can retrieve memory of the second item.	Partial stimuli propagate to generate inner sensation of a framework of an item or event. Due to the property of generalization (by virtue of spread of depolarization across the entire islet of inter-LINKed spines), it is expected to provide more features to the memory (Vadakkan, 2010a; 2013; 2019a).
19	Ability to store new memories without needing to overwrite the old ones	Sharing of unitary mechanism for common features, and provision for formation of new units with new associations are expected to be present in the system	Inter-LINKed spines within islets of inter-LINKed spines can be shared by any stimuli reaching them. Hence there is no need for overwriting old memories. Any few associations can get inter-LINKed to the existing islets of inter-LINKed spines (Vadakkan, 2010a; 2013).
20	Consolidation of memory (Transfer of storage locations of memory from the hippocampus to the cortex) over a span of 5 to 8 years.	Addition of specific learning-induced changes in the cortex over time using similar unitary sensory associations, and ability to generate memories by a global integrating mechanism.	Convergence of all sensory stimuli in the hippocampus leads to dense islets where inter-LINKed spines can be formed. Sparser IPLs are expected to be formed in the cortex. Neurogenesis and repetition of associative elements within each learning will lead to formation of

		Must go through a stage of surplus unitary mechanisms.	surplus IPLs in the cortex over time (Vadakkan, 2011a).
21	Mechanism uses pre-existing schemas (Tse et al., 2007). Schemas are expected to get used inter-changeably.	Changes induced by one learning are shared by another learning event. For this to occur, there must be shared unitary mechanisms in each learning event and presumably also in the memory retrieval mechanism.	Inter-LINKed spines can be used by any cue stimuli, allowing the unitary structural operations to get shared. It is also reasonable to assume that units of inner sensations induced from these inter-LINKed spines also get shared by similar elements in stimuli (Vadakkan, 2010a; 2013).
22	A constantly adapting dynamic circuit mechanism is expected.	Provisions should be present to accommodate large number of new learning events.	Since extracellular matrix space is minimal in the cortex, large number of spines from different neurons are expected to remain abutted to each other. They can be readily inter-LINKed depending on the nature of cue stimuli (Vadakkan, 2010a; 2013).
23	Framework of a mechanism that can generate hypothesis by the system.	When one of the elementary mechanisms of one associative learning event undergo association with a third elementary mechanism during a third associative learning, it will lead to an interconnected chain of associations (ICAs). When there are common elements in different ICAs, then the system will be able to generate a hypothesis of relationships between events/items.	When one spine each from two islets of inter-LINKed spines are inter-LINKed, any one spine from one islet establishes a relationship with any one spine in the second islet of inter-LINKed spines. When more than one islet of inter-LINKed spines is inter-LINKed in this manner, it leads to generation of hypothesis about something that will not occur ordinarily (Vadakkan, 2010a; 2013).
24	System needs a state of sleep for nearly one third of its operational time.	It is necessary to explain why the system won't be able to exist without sleep. i.e. Explain substantive nature of sleep in the operation of the system.	State of sleep is needed to keep postsynaptic depolarization by presynaptic terminal as a dominant state of the system. Only when this dominant state is maintained, then only a lateral activation of the postsynaptic terminal (spine) will induce units of inner sensation of a stimulus arriving from the environment through the

			presynaptic terminal (Vadakkan, 2016b). Since nothing comes from the environment, it is a hallucination (Minsky, 1980).
25	While living in space, requirement of sleep reduces by more than one hour.	Provide a mechanistic explanation why reduced sensory stimuli in space reduces the need for sleep.	Since sensory stimuli is less in space, number of reactivations of inter-LINKed spines is reduced. This reduces the time to set the system to its baseline dominant state of postsynaptic depolarization by its presynaptic terminal (Vadakkan, 2016b).
26	During memory retrieval, inner sensation of memory can occur with or without motor actions such as speech or behavioral motor actions.	The mechanism that generates inner sensation of memory should have a connection with the mechanism that generates motor action. There should be a provision for disabling this connection at will.	IPL mechanism can generate both units of first-person inner sensations and motor action reminiscent of arrival of the item whose memory is retrieved. The motor outputs can be inhibited while inner sensation is being generated (Vadakkan, 2010a; 2013).
27	It is difficult to inhibit a memory which is being retrieved.	A structural mechanistic explanation is needed.	IPL is an inter-membrane connection. Once IPL is present and functions, it is not possible to inhibit its function voluntarily. Additional inter-spine LINK with an inhibitory spine may become possible through future associative learning events (Vadakkan, 2007; 2010a).
28	Mean inter-spine distance on the dendrite of a pyramidal neuron is more than the mean spine diameter (Konur et al., 2003).	This opens the possibility for neuronal processes that belong to other neurons to occupy the inter-spine space. It is reasonable to expect some functional importance for such a scheme of inter-spine spacing. Since spines of different neurons occupy this space and ECM is often negligible (see Fig.13 in FAQ), some of the spines that belong to different neurons can	Abutted spines that belong to different neurons increase the probability for inter-neuronal inter-spine interactions. These interactions are the basis of IPL proposed by the semblance hypothesis (Vadakkan, 2010a; 2013).

		remain abutted to each other.	
29	Both learning and retrieval of memory are associated with firing of a set of neurons.	Both learning and memory retrieval allow potentials to propagate through certain gateways that allow certain neurons that are being held at sub-threshold activation states to fire action potentials. This gateway may be formed at the time of learning and are likely associated with generation of units of inner sensation of memory.	Both learning and memory retrieval allow propagation of potentials along the IPL. This leads to the arrival of more potentials to the axon hillock of the postsynaptic neuron. If arrival of these additional potentials can allow the subthreshold activation state of the neuron to cross the threshold for firing, it fires an action potential (Vadakkan, 2010a; 2013).
30	Place cells fire in response to specific spatial stimulus.	Mechanism that generates inner sensation of memory for a location is expected to have a mechanistic connection with firing of a set of CA1 neurons.	Place cells are CA1 pyramidal cells. When islets of inter-LINKed spines of overlapping dendrites of CA1 neurons receive spatial inputs, they provide potentials to their postsynaptic CA1 neurons. If these CA1 neurons are being held at subthreshold activation states, then they fire. This explains place cell firing (Vadakkan, 2013; 2016a).
31	Firing of an ensemble of neurons during a higher brain function.	Inner sensation generated during a higher brain function is related with firing of an ensemble of neurons.	Reactivation of IPLs during a higher brain function will add potentials from the inter-LINKed spines to their postsynaptic neurons. If these potentials add up to allow these neurons to cross the threshold, they will fire (Vadakkan, 2010a; 2016a).
32	Firing of separate sets of neurons during learning and memory retrieval.	Learning and generation of inner sensation of memory are associated with firing of separate sets of neurons.	When memory retrieval is immediately following learning, then lack of stimuli from the item whose memory is being retrieved is responsible for the difference. When memory is retrieved late, other associative learning events in between the learning and memory retrieval under examination will generate additional IPLs in the circuitry & will be responsible for the difference (Vadakkan, 2010a; 2016a).

33	Fast changes in both the magnitude and correlational structure of cortical network activity (Benisty et al., 2024).	Rapidly time-varying functional connectivity is responsible for such changes.	Changes in environmental stimuli, self-triggered thought processes, inner sensations of fear, anticipation, hunger, and comfort levels fluctuate moment to moment indicating reactivation of a new set of IPLs. This will change network activity (Vadakkan, 2019a).
34	Firing of a cortical neuron (axonal spike) is possible by summation of nearly 140 postsynaptic potentials (input signals) arriving from random locations. Each of these cortical neurons have tens of thousands of dendritic spines where postsynaptic potentials get generated.	These neurons must be maintained at a sub-threshold state in the background state and the mechanism of induction of internal sensation must be associated with providing additional postsynaptic potentials for crossing the threshold for firing of these neurons.	Recent modelling studies have shown that a pyramidal neuron that has tens of thousands of input connections can fire an action potential by spatial summation (summation at the same time) of nearly 140 EPSPs at the axonal hillock that arrives from randomly located dendritic spines (Palmer et al. 2014; Eyal et al., 2018). Based on calculations of energy per bit of information 2000 synaptic inputs are needed for neuronal firing (Levy and Calvert, 2021).
35	Any set of 140 input signals arriving from random locations on the dendritic tree can fire a neuron. Hence, there is extreme degeneracy of input signals in firing a neuron. A system operating by such a scheme was selected from large number of variations since this was offering functional advantage to the system.	Since such a scheme is expected to be used specifically, then a possible situation must be there. If a neuron is being held at subthreshold level by receiving nearly 130 inputs, then it needs 10 more input signals for its firing. If only a specific cue stimulus in a specific context can provide a specific set of input signals for 10 additional input signals, then this possibility can be tested.	Islet of inter-LINKed spines can provide an opportunity to pool all the potentials at one location from where it can be delivered in a summated manner. Dendritic spikes can be viewed resulting from it. These can reach the axonal hillock efficiently to cause neuronal firing for motor effect. Inter-LINKing with spines that receive different neurotransmitters at the islets can regulate these islets (Vadakkan, 2016a).
36	Many neurons are being held at sub-threshold activation state.	By holding a neuron at a certain potential below the threshold, it is possible to regulate the neuronal output conditional upon arrival of certain number of inputs. If these inputs can be made conditions for	Several neurons are being held at subthreshold activation states (Seong et al., 2014). At the islets of inter-LINKed spines summation of potentials from certain set of inputs can be guided to generate summated potentials and even

		an output, then it has operational significance	spikes that can decide motor outputs
37	Input signals (postsynaptic potentials) have maximum strength at the location of their origin, which is the spine head. As the potentials propagate, they get attenuated in the spine neck region. Further attenuation occurs as they propagate towards the neuronal cell body.	When signals from a stimulus attenuate, they may not contribute to an efficient learning mechanism. Furthermore, signals from different spines mix in the dendrite. Hence, most likely location for a learning mechanism that can maintain specificity until the time of its retrieval is expected to occur at the spine head region.	IPL occur between spine head regions between spines that belong to different neurons (Vadakkan, 2010a; 2016a).
38	Dendritic spikes occur by the summation of nearly 10 to 50 postsynaptic potentials (of the spines) at the dendritic region.	It is necessary to explain which spines contribute to the potentials and explain their significance.	Though not proved, semblance hypothesis proposed that most of the potentials that contribute to dendritic spikes originate from spines that belong to different neurons that for islets of inter-LINKed spines (Vadakkan, 2016a).
39	When current is injected into the dendrites of human layer 2/3 neurons they generated repetitive trains of fast dendritic calcium spikes, which can be independent of somatic action potentials (Gidon et al., 2020).	Explanation for spike is needed.	The islets of inter-LINKed spines can lead to generation of dendritic spikes. The net potential can drain through some of the spines depending on the several regulatory factors (Vadakkan, 2016a).
40	Inner sensation of certain higher brain functions occurs without any motor actions.	Either the motor action can be voluntarily suppressed or that there are no behavioral motor actions associated with it.	The apical dendrites in human layer 5 neurons are electrically isolated from that of the somatic compartment, possibly having independent operations of islets of inter-LINKed spines at those remote dendritic regions (Beaulieu-Laroche et al., 2018).
41	When two differential electrodes are placed at 2 extracellular locations, extracellular potentials can be recorded. They show oscillations. Brain operates only	While synaptic transmission provides one vector component, something else constitutes the other vector component/s that is/are	Propagation of depolarization along the IPL provides a vector component almost perpendicular to that of the synaptic transmission (Vadakkan, 2010a; 2013).

	when the frequency of these oscillations occurs within a narrow range.	expected to take place nearly perpendicular to the direction of synaptic transmission. Brain functions (both first-person & motor actions) are linked tightly to these vector components.	
42	Apical tuft regions of neurons of all the cortical neuronal orders are anchored to the inner pial surface resulting in overlapping of the dendritic arbors of neurons from different orders. This resulted from a sequence of movement of neuronal precursors during development.	Dendritic spines of neurons that belong to both the same (mainly) and different neuronal orders overlap with each other to serve certain functions.	Overlapping of dendrites that belong to different neurons facilitate formation of inter-neuronal inter-spine LINKs. Anchoring of apical tuft regions of all the cortical neuronal orders facilitates this (Vadakkan, 2016a, 2019a).
43	Following learning, initially there is conscious retrieval of memory and eventually this becomes sub-conscious after repeated retrievals.	The process by which repeated retrieval of a memory to a sub-conscious level must be able to explain a framework of a mechanism of consciousness.	Explained by the semblance hypothesis (Vadakkan, 2010b; 2019a). Once the retrieval of memories of a certain item becomes a routine, the inner sensations evoked by their IPL reactivations will be added on to the inner sensation of consciousness. Hence, such inner sensations will not be notice individually.
44	Experimental finding of long-term potentiation (LTP) has shown several correlations with behavioral motor actions that are surrogate markers of memory retrieval.	It must be possible to explain how cellular changes during LTP induction and learning are correlated & how this is related to the ability for memory retrieval.	Explaind by the semblance hypothesis (Vadakkan, 2019b) [Foot note2]
45	Learning takes place in milliseconds, whereas LTP induction takes at least 20 to 30 seconds and even more a minute.	Cellular changes during learning are expected to get scaled-up during LTP induction in a time-dependent manner. Need a cellular explanation for this.	Explaind by the semblance hypothesis (Vadakkan, 2019b).
46	Blockers of membrane fusion blocks LTP.	Need to explain the cellular location where they act and explain how it blocks LTP.	Explaind by the semblance hypothesis (Vadakkan, 2019b).

47	CA2 area of hippocampus is resistant to LTP induction. Induction of LTP here becomes possible by the removal of the peri-neural net proteins chemically.	Cellular mechanism responsible for LTP induction must be able to explain this. Perineural area is involved in the cellular mechanism of LTP induction.	Explaind by the semblance hypothesis (Vadakkan, 2019b).
48	Several seizures spread laterally to adjacent cortices.	Cellular mechanism responsible for seizures should be capable of spreading laterally.	Explaind by the semblance hypothesis (Vadakkan, 2016d).
49	Several seizures are associated with hallucinations.	Laterally spreading seizure mechanism should be able to explain how internal sensation of certain stimuli occur	Explaind by the semblance hypothesis (Vadakkan, 2016d).
50	Amyotrophic lateral sclerosis (ALS) pathology spreads laterally.	Some structural aspects of the normal operational mechanism aid in the lateral spread of neurodegenerative changes under pathological conditions.	Explaind by the semblance hypothesis (Vadakkan, 2016c).
51	Relationship between LTP, kindling, and seizures.	It is reasonable to infer that a structure-function-pathology relationship exists that can provide interconnecting explanations.	Explaind by the semblance hypothesis (Vadakkan, 2016d).
52	Transfer of injected dye from one CA1 neuron to the neighboring CA1 neurons is observed in animal models of seizures (Colling et al., Brain Res. 1996).	Need an explanation for a physical connection between two CA1 neurons through which dye can diffuse.	Explaind by the semblance hypothesis (Vadakkan, 2016d).
53	Loss of dendritic spines after kindling.	An interconnected explanation for kindling, seizures and LTP must also be able to be extended to explain loss of spines after kindling.	Explaind by the semblance hypothesis (Vadakkan, 2016d).
54	CA2 area of hippocampus is resistant to seizures.	In row 44, we saw that CA2 region is resistant to LTP induction. Hence, whatever causes resistance to LTP induction must also	Explaind by the semblance hypothesis (Vadakkan, 2016d).

		be causing resistance to seizure generation.	
55	Seizures and memory loss are caused by herpes simplex viral (HSV) encephalitis.	Mechanistic explanation for both these features is expected to provide some information about the relationship between these findings in HSV encephalitis.	Explaind by the semblance hypothesis (Vadakkan, 2016d).
56	Anesthetic agents alleviate seizures.	Mechanism of action of anesthetic agents should be able to explain how seizure generation and propagation are stopped by anesthetic agens.	Explaind by the semblance hypothesis (Vadakkan, 2016d).
57	Cognitive impairment in patients with seizure disorders.	Mechanism of learning, memory retrieval and behavioral motor actions are expected to be affected by the mechanism of seizures.	Explaind by the semblance hypothesis (Vadakkan, 2016d).
58	Intracellular electrophysiological correlate of epileptiform activity is paroxysmal depolarizing shift (PDS), which is a giant excitatory postsynaptic potential (EPSP).	A mechanistic explanation is needed for generation of a giant EPSP at the dendritic spine area during a seizure. It has a propensity to propagate laterally to other cortical regions. Need a mechanistic explanation.	Explaind by the semblance hypothesis (Vadakkan, 2016d).
59	Neurodegenerative disorders show loss of spines and neuronal death.	An explanation is needed for contiguous spread of pathology leading to spine loss and neuronal death. Causative factors should be acting at specific locations to explain all its features.	Explaind by the semblance hypothesis (Vadakkan, 2016c).
60	Dementia in neurodegenerative disorders.	Need an explanation for the role of spines in both generation of inner sensation of memory along with concurrent behavioral motor activity.	Explaind by the semblance hypothesis (Vadakkan, 2016c).
61	Perception as a first-person inner sensation.	A variant or a modification of the mechanism of	Explaind by the semblance hypothesis (Vadakkan, 2015b).

		induction of inner sensation for memory should be able to explain first-person inner sensation of perception.	
62	Apparent location of the percept different than its actual location.	Matching explanations using the mechanism of induction of units of inner sensation are needed.	Inner sensation of percept is generated by integral of all the perceptons. Hence, the actual location of an object need not necessarily match the percept. This becomes clear when there is a medium that shift the patch of light towards the eye (Vadakkan, 2015b).
63	Homogeneity in the percept for stimuli above the flicker fusion frequency.	A mechanism for fusion of inner sensation of continuous perception of a source of light that is affected by frequency of flickers is needed.	Since perceptons from IPLs located at different regions in response to one flicker has a temporal pattern of generation, overlapping formation of perceptons from consecutive flickers overlap and generate a continuous percept (Vadakkan, 2015b).
64	Perception of object borders.	A mechanistic explanation for the formation of first-person percept for object borders is needed.	Only stimuli from within the border region reaches the brain. When perceptons formed from these stimuli integrate, they generate inner sensation of percept to generate boarder. Similarly, stimuli from outside the borders also do the same to generate a contrasting border of the background (Vadakkan, 2015b).
65	First-person inner sensation of pressure phosphenes.	Mechanism of generation of first-person inner sensations is expected to provide an explanation for phosphenes triggered by pressure over the eyeball.	Stimulation of sensory paths anywhere along it before reaching the locations of their convergence can lead to reactivation of IPLs for generation of perceptons (Vadakkan, 2015b).
66	Orientation tuning of a population of neurons in V1 before and after training on a visuomotor task showed different sets of neurons responding (Failor et al., 2021).	Neurons that fire as a consequence of associative learning changes in the primary visual cortex varies with time.	Based on the semblance hypothesis, perception does not require a specific set of visual cortical neurons to fire. Instead, perceptons are generated at the inter-LINKed spines on either side of an IPL (Vadakkan, 2015b).

67	Flash-lag effect - When a flash is briefly presented in a specific location adjacent to the path of a uniformly moving object, the former is perceived to lag the latter.	Matching explanation using the mechanism of induction of units of inner sensation is needed. Needs to explain how perception is affected by relative time of arrival of a stimulus.	Explained based on the semblance hypothesis (Vadakkan, 2022). Visual pathway has synapses that cause synaptic delay. Overlapping reactivation of IPLs by continuous arrival of stimuli maintains perception; whereas a fresh stimulus undergo delay to initiate perception.
68	Inner sensation of consciousness.	Presence of a continuous operational mechanism for the generation of inner sensations that depends on/contributes to maintaining the frequency of oscillating extracellular potentials in a narrow range. The combined inner sensation is expected to generate inner sense of being conscious.	There is a baseline oscillating extracellular potentials as recorded by EEG. This shows testable propagation of potentials along many IPLs contributing to its horizontal component. Net inner sensation generated by reactivation of inter-LINKed spines during background state can contribute to inner sensation of consciousness (Vadakkan, 2010b).
69	Loss of consciousness by anesthetic agents.	Properties of anesthetic agents should be able to explain how the proposed mechanism of consciousness can be altered.	Explained by rapid chain formation of large number of non-specific IPLs (Vadakkan, 2015a).
70	Loss of consciousness during a generalized seizure and its reversal after seizure.	Mechanism of seizure generation should be able to explain how inner sensation of consciousness is lost.	Explained based on the semblance hypothesis (Vadakkan, 2016d). Rapid chain formation of large number of non-specific IPLs due to changes in ECM properties (e.g. Very low serum Na) or due to increased excitability of neurons.
71	Changes in consciousness with variations in the frequency of oscillating extracellular potentials beyond a narrow range.	Need an explanation how a narrow range of frequency of oscillating extracellular potentials is associated with normal state of normal state of consciousness.	Explained based on the semblance hypothesis (Vadakkan 2010b; 2015a). Unconscious states show large variations in the frequencies of extracellular potentials recordered from skull surface in EEG (Rusalova, 2006).
72	Effect of dopamine in augmenting anesthetic action.	Explain a mechanism how dopamine augments	Explained based on the semblance hypothesis (Vadakkan, 2015a).

		anesthetic action. This explanation must match with the explanation for the action of dopamine in augmenting learning (see row 11).	Since dopamine can cause spine expansion (Yagishita et al., 2014), it will augment non-specific IPL formation by anesthetic agents.
73	Phantom sensation or pain.	Explain a mechanism for the inner sensation of pain from a lost limb at the time of phantom sensation or phantom pain.	As long as the IPLs that have received inputs from a limb remains stable in the brain, any reactivation of this by stimuli arriving to this IPL through a different sensory input can evoke semblance of phantom limb or pain.
74	Referred pain.	Explain a mechanism for the inner sensation of pain from a location different from the location where the cause of pain is present.	Inputs two different locations converge into one IPL at a higher neuronal order region can lead to semblance of sensory input towards those regions (Vadakkan, 2010a, 2013).
75	Mechanism for innate behavior that enables survival.	A mechanism evolving from heritable changes to explain innate behavior in response to a stimulus.	Explained based on the semblance hypothesis (Vadakkan, 2020). Convergence of sensory stimuli having different velocities is programmed in the genetic code and executed during development that favor the formation of IPLs.
76	Presence of a comparable circuitry in a remote animal species explains universal nature of a biological mechanism.	Comparable features that show relationship of a mechanism that induces units of inner sensation using synaptically-connected neuronal circuitry among different species of animals.	Organization of neuronal connections suggesting the presence of a comparable IPL circuitry in Drosophila olfactory system is explained (Vadakkan, 2015b).
77	Neurodegeneration resulting from repeated general anesthesia (Baranov et al., 2009).	Need an explanation why the repeated induction of a mechanism of loss of consciousness by anesthetics can lead to loss of spines and eventual loss of neurons.	Explained based on the semblance hypothesis (Vadakkan, 2015a). Conversion of IPLs to inter-neuronal interspine fusion leading to degeneration is a testable mechanism.

78	More years of education (increased number of associative learning events) reduces dementia risk (Maccora et al., 2020).	Should be able to explain whether redundant learning-induced changes get induced by prolonged learning events.	Explained based on the semblance hypothesis (Vadakkan, 2013; 2019a). Redundant IPLs form during different learning events as new neurons get inserted into the circuit.
79	Specific brain regions appear to be associated with specific functions based on the lesions/ lesion studies.	These are most likely locations of converging fiber tracts or converging locations of specific input signals responsible for those functions.	It was possible to induce long-term potentiation (LTP) of different strengths from different locations of convergence inputs. Hippocampus having convergence of all the sensory inputs has shown maximum strength of LTP.
80	Astrocytic pedocytes cover less than 50% of peri-synaptic area in nearly 60% of the synapses in the CA1 region of hippocampus (Ventura and Harris, 1999).	Hippocampal mechanism of learning & memory must explain the suitability of distribution of astrocytic processes.	Explained based on the semblance hypothesis (Vadakkan, 2019a). Remaining free area of the spines favor inter-neuronal inter-spine interactions that form IPLs.
81	Present nervous systems have evolved over millions of years and are also the results of certain accidental coincidences.	It is expected to become possible to explain how the circuitry that provides all the features can be evolved through simple steps of variations and selection.	Explained based on the semblance hypothesis (Vadakkan, 2020). Sparking of the first-person inner sensations of all the features of an item in the environment on arrival of the fastest or first sensory stimulus from that item started providing survival advantage to animals in a predator-prey environment.
82	Dye diffuses from one neuronal cell to another as the cortical neurons move from periventricular region towards their destination indicating formation of an inter-cellular fusion pore (Bittman et al., 1997). This is followed by death of nearly 70% of these cells and survival of the remaining 30% cells.	It is expected to become possible to explain how an event of inter-cellular fusion leads to selection of variants that prevent further inter-cellular fusion. Since neurons cannot divide further, a transient stage of fusion is expected to trigger fusion prevention mechanism in the surviving neuronal cells. It is also necessary to explain whether this mechanism has any role in the unique functional	Explained based on the semblance hypothesis (Vadakkan, 2020). Dye diffusion indicates formation of fusion pores between neuronal cells. The first occurrence of inter-neuronal fusion is likely due to changes in membrane composition or lack of checkpoint mechanisms to arrest hemifusion from progressing to fusion.

		property of generation of first-person inner sensations in the nervous system.	
83	Following the above stage where dye diffusion is observed, significant neuronal death (70%) (Blaschke et al., 1996) and spine loss (13 to 20%) are observed.	There is a high probability that the surviving cells have acquires an adaptation.	Explained based on the semblance hypothesis (Vadakkan, 2020). Following death of 70% cells, an adaptation occurring in the surviving cells most likely prevents any future coupling between neurons that may result in inter-neuronal fusion. This adaptation is suitable for maintaining IPLs for generating useful functions.
84	Higher brain functions take place in a narrow range of frequency of oscillating extracellular potentials as evidenced by EEG (Rusalova, 2006).	a) Both the mechanism for learning and memory retrieval contributes vector components of the oscillating extracellular potentials. b) The specific mechanism for both learning and memory retrieval depends on the frequency of oscillating extracellular potentials.	Explained based on the semblance hypothesis (Vadakkan, 2010a; 2013).
85	Artificial triggering of spikes in one neuron in the cortex causes spikes in a group of neighboring neurons in the same neuronal order located at short distance (25–70µm) from the stimulated neuron (Chettih & Harvey, 2019).	It should be possible to explain a mechanism that can lead to lateral spread of firing between neurons of the same neuronal order within a short radius. Need an explanation for a mechanism through a path other than trans-synaptic route.	One explanation is propagation of depolarization across the IPLs between spines that belong to different neurons (Vadakkan, 2013). This also explains why only sparsely located neurons get fired, correlated in time.
86	The protein complexin blocks SNARE-mediated fusion by arresting the intermediate stage of hemifusion. Complexin is present in the spines. But docked vesicles are not found inside the spines (in contrast to what is observed in the presynaptic terminal). This leaves the question, "Which	It is necessary to explain an inter-membrane fusion process that can be mediated by SNARE proteins and blocked by complexin by arresting the process at or before the intermediate stage of hemifusion in the spines.	SNARE proteins provide energy for bringing together membranes against repulsive charges and overcoming energy barrier between abutted membranes (Oelkers et al., 2016). They also generate force to pull together abutted membranes as tightly as possible (Hernandez et al., 2012). By initiating the fusion process by supplying energy (Jahn

	inter-membrane fusion is getting arrested by complexin?"		and Scheller, 2006), SNARE proteins can lead to the formation of characteristic hemifusion intermediates (Lu et al., 2005; Giraudo et al., 2005; Liu et al., 2008). Protein complexin present within the postsynaptic terminals (Ahmad et al., 2012) is known to interact with the neuronal SNARE core complex to arrest fusion at the stage of hemifusion (Schaub et al., 2006).
87	Transcriptomic analyses show heterogeneity of even adjacent neurons of the same type in the cortex (Kamme et al., 2003).	This indicates that any mixing of the contents between these neurons is fatal to them. Hence, there will be a robust mechanism to prevent intercellular fusion.	Different mRNA profiles of adjacent neurons of even the same type indicate that any cytoplasmic content mixing will lead to homeostatic mechanisms such as spine or neuronal loss to prevent it (Vadakkan, 2016c). Ultimate purpose of it is to restrict structural aspect of IPLs to inter-membrane hemifusion.
88	Heterogeneity in clinical features and pathological changes in Alzheimer's disease (& other neurodegenerative disorders).	1. Many factors are likely involved in the operational mechanism. 2. There will be a universal mechanism that involves different neuronal types. Failure of any of these can explain heterogeneity.	A common mechanism is pathological conversion of normal maximum limit of hemifusion to pathological fusion. Clinical features depend on a) locations of IPL fusion that can damage spines & neurons, and b) formation of non-specific IPLs at different locations (Vadakkan, 2016c).
89	In excitatory neurons, spine depolarization can occur even without dendritic depolarization (Beaulieu-Laroche et al., 2018a; Beaulieu-Laroche et al., 2018b).	Why did such a mechanism get selected? What is the functional significance of depolarization of the spine head? Is there any link between depolarization of the spine heads, oscillating extracellular potentials & different brain functions?	IPL mechanism that generates units of inner sensation needs only depolarization of spines. Lack of firing of the postsynaptic neuron will lead to lack of motor output while units of inner sensation occur at an inter-LINKed spine (Vadakkan, 2013; 2019a).
90	Histological features of amyloid (senile) plaques and neurofibrillary tangles observed in normal aging (Anderton, 1997) are also the pathological	A mechanistic explanation for how & why intracellular neurofibrillary tangles & extracellular plaques that are key	The last stage of IPL formation is hemifusion, which is an intermediate stage of fusion. Various factors such as viral fusion proteins and membrane

	features in Alzheimer's disease & several other disorders in the spectrum of neurodegenerative disorders.	pathological features in neurodegenerative disorders are observed in normal aging (but without symptoms).	compositional changes can overcome the check point mechanisms converging IPLs to inter-neuronal inter-spine fusion. This will cause cytoplasmic content mixing. Since expression profiles of even adjacent neurons of same type are different, it leads to neuronal damage (Vadakkan 2016c).
91	Therapeutic agents developed for treating seemingly unrelated neurological diseases such as seizure disorders, Parkinson's disease, spasticity, and hallucinations can alleviate different headache pains.	Explanations for mechanisms of different disorders & the operational mechanism of the system should provide interconnected explanations for the effectiveness of therapeutic agents in different headaches.	By inhibiting voltage-gated sodium channels, it reduces neuronal excitability & prevent rapid IPL formation preventing seizures, prevents IPL formation between spines of spiny neurons of basal ganglia, reduce inputs via IPLs to upper motor neurons reducing spasticity, reverse/inhibit IPLs inhibiting/reducing inner sensation of headache pains.
92	Since learning is expected to generate certain new circuit connections, the circuit elements (like on a printed circuit board) must remain separate from each other.	Properties of both neuronal membranes and extracellular matrix should match with the new circuit connections, functional properties imparted by them and their reversal.	Even though extracellular matrix space seems negligible between the membranes, hydration layer between the lipid membranes shows high energy barrier in artificial systems (Rand and Parsegian, 1984; Martens and McMahon, 2008; Harrison, 2015).
93	"Representational drift" - meaning that when a brain function is repeated, set of neurons that fire changes with time (Schoonover et al., 2021; Marks& Goard, 2021; Deitch et al., 2021).	In the case of memory, it is necessary to show redundancy in its operational mechanism, presence of a common integration mechanism and shift in the locations from where function occurs.	Correlation between a brain function and neuronal firing will be true for those neurons that are being held at sub-threshold activation state and receive additional potentials through the same IPLs. Subthreshold activation state of a neuron can be affected by several factors. Additional learning events can lead to formation of new IPLs. These can change the set of neurons that fire (Vadakkan, 2019a).
94	The controversial views (pdf) expressed by Camillo Golgi against Ramón y Cajal's interpretations of results obtained from modified Golgi staining protocols.	The chemistry behind the modification of original Golgi staining protocol must be able to provide reasons for this controversy. Such an	Spines within the islets of inter-LINKed spines are connected via an oxidation state dependent manner (Vadakkan, 2022).

		explanation is expected to become possible when we understand the operational mechanism of the brain.	
95	Formation of new neurons in the hippocampus, especially in non-stationary environments.	The operational mechanism should be able to explain functional advantage provided by insertion of new neurons.	Both input and output connections of new neurons will continuously alter the existing circuitry. Repetition of same associative learning will make new IPLs at higher neuronal orders increasing number of sparse storage mechanisms (Vadakkan, 2011a).
96	Loss of spines and formation of new spines during learning (Frank et al., 2018).	There is a mechanism that leads to loss of spines during learning. Formation of new spines should accomplish something new that can facilitate further leanring.	The last stage of permitted intermembrane interaction leading to IPL formation is inter-membrane hemifusion, which is an intermediate stage of membrane fusion. Several factors can overcome the checkpoint needed to arrest the changes at the stage of hemifusion.
97	Generalization is seen in the Transformers of the large language models (LLMs) that use neural networks organized using a hidden layer.	A mechanistic explanation is needed to explain where and how the hidden layer operates. This must explain how the system generates an appropriate output in response to a new prompt that the system never got exposed in the past.	Basic concept of "islet of inter-LINKed spines" in the semblance hypothesis matches with that of the "attention heads" in the Transformers of LLMs (Vadakkan, 2024).
98	Gamma waveforms of oscillating extracellular potentials in the layers 2 & 3, & slower alpha and beta waves in deeper layers of the cortex (Mendoza-Halliday et al., 2024).	Reasons are necessary to provide explanation for high frequency of oscillations in layers 2 &3 & low frequency in deeper layers	Apical tuft region of neurons of all the cortical layers are attached to the marginal zone close to the pial layer (innermost covering layer of the cortex). Layer 1 cortical neurons that are mostly GABAergic send horizontal processes interconnecting several postsynaptic terminals of apical tufts. Hence, dendritic arbors of neurons of all the cortical layers overlap maximally in layer 2, followed by layers 3, 4, 5, and 6 in decreasing order. This increases the probability of formation of

			maximum number of synapses (vertical component) & inter-neuronal inter-spine interactions (horizontal component) in layer 2. This in turn explains high frequency of oscillations of potentials across neurons that are connected vertically (through synapses) & horizontally (through IPLs) in a decreasing order from layer 2 to 6 (Vadakkan, 2015).

IPL: Inter-postsynaptic functional LINK

Foot note1 If we provide a set of colors and picture against each color and ask people to learn the association in one second, most people will be able to learn two or more associations during this period. This means that associative learning can take place in milliseconds. What type of a change can occur in less than one second?

Foot note2 Around 30 specific experimental findings are related to the association between LTP, ability to learn, behavioral motor action at the of memory retrieval and biochemical changes following learning. Constraints arising from those findings were explained in an interconnected manner in this paper.