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Review

# Rapid chain generation of interpostsynaptic functional LINKs can trigger seizure generation: Evidence for potential interconnections from pathology to behavior

Kunjumon I. Vadakkan

*Neurosearch Center, 76 Henry Street, Toronto, ON M5T1X2, Canada*

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ABSTRACT

The experimental finding that a paroxysmal depolarizing shift (PDS), an electrophysiological correlate of seizure activity, is a giant excitatory postsynaptic potential (EPSP) necessitates a mechanism for spatially summating several EPSPs at the level of the postsynaptic terminals (dendritic spines). In this context, we will examine reversible interpostsynaptic functional LINKs (IPLs), a proposed mechanism for inducing first-person virtual internal sensations of higher brain functions concurrent with triggering behavioral motor activity for possible pathological changes that may contribute to seizures. Pathological conditions can trigger a rapid chain generation and propagation of different forms of IPLs leading to seizure generation. A large number of observations made at different levels during both ictal and interictal periods are explained by this mechanism, including the tonic and clonic motor activity, different types of hallucinations, loss of consciousness, gradual worsening of cognitive abilities, a relationship with kindling (which uses an augmented stimulation protocol than that used for inducing long-term potentiation (LTP), which is an electrophysiological correlate of behavioral makers of internal sensation of memory), effect of a ketogenic diet on seizure prevention, dendritic spine loss in seizure disorders, neurodegenerative changes, and associated behavioral changes. The interconnectable nature of these findings is explained as loss of function states of a proposed normal functioning of the nervous system.



## 1. Introduction

By developing a framework for an operation that can explain a large number of pathological findings at various levels, it may become possible to understand a disease process. This is particularly viewed as important in seizure disorders [1,2]. The existence of a wide variety of seizure types makes it seemingly hard to understand the common denominator that initiates seizures [3]. Identifying a cellular mechanism that allows the interconnection of different findings at the biochemical, cellular, electrophysiological, systems, imaging, and behavioral levels in seizure disorders remains a challenge and an opportunity to understand both the normal operation of the system and its potential pathologies. Even though many genetic aspects of the seizure disorders have been identified and abnormalities in the function of ion channels that lead to hyperexcitability of the neurons can explain motor aspects of the disease, several other features of seizure disorders remain elusive [4]. The primary reason for this is attributed to our lack of understanding of the normal operation of the nervous system itself [5]. Therefore, a reasonable expectation is that various findings in seizure disorders can serve as pieces of a large puzzle, which in turn, will allow us to understand the normal operational mechanism of the system.

The simultaneous loss of consciousness that blocks perception and memory along with the generation of a self-reinforcing cycle of motor activity synchronized over a large area of the motor cortex requires a mechanistic explanation. A unified model of the dysfunctions of the normal operations is also expected to explain the cognitive impairment and neurodegenerative changes associated with seizure disorders. The interconnectable aspect of the investigative approach is of paramount importance in identifying the exact nature of the basic pathology, which in turn, is required to develop therapeutic methods to prevent the disease progression. In these contexts, it is reasonable to expect that examination of any proposed mechanism that can explain both the generation of internal sensation of different higher brain functions

*Abbreviations:* AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; dendritic spine, spine or postsynaptic terminal or postsynapse; DHA, docosahexaenoic acid; ECM, extracellular matrix; EEG, electroencephalogram; EPSP, excitatory postsynaptic potential; GABA, gamma-aminobutyric acid; GluA1, AMPA receptor subunit A1; HCN, hyperpolarization-activated cyclic nucleotide-gated; IPL, interpostsynaptic functional LINK or LINK; islet, islet of inter-LINKed postsynaptic terminals; LC-PUFA, long chain polyunsaturated unsaturated fatty acid; LINK, interpostsynaptic functional link (IPL); LTP, long-term potentiation; MECP2, methyl CpG binding protein 2; meq/L, milliequivalents per liter; n-3 PUFA, omega-3 polyunsaturated fatty acid; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartate; PDS, paroxysmal depolarizing shift; Postsynapse, postsynapse terminal or dendritic spine or spine; SK channels, small conductance calcium-activated potassium channels; SNARE, SNAP (soluble NSF (n-ethylmaleimide-sensitive fusion attachment protein) receptor) proteins; VDCC, voltage-dependent calcium current.

*E-mail address:* kunjumon.vadakkan@utoronto.ca.

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and behavioral motor activity may provide valuable information about the pathogenesis of seizure disorders. In approaching this challenge, primarily, an examination of the diverse findings in seizure disorders from different levels is made with an aim to lay out what must be explained by the pathology of an ideal operational mechanism of the system. The following is a list of features that a unified model is expected to answer.

### 1.1. Clinical features

The aura of different hallucinations, focal and generalized tonic or clonic motor activity, and loss of consciousness observed in different seizure disorders require an interconnectable mechanistic explanation. Different studies indicate that repeated seizure activity produces altered functional reorganization of the motor cortex [6,7]. The expansion of seizure spread along the motor strip in one study [8] indicates that the cellular mechanism responsible for seizures is capable of spreading laterally. Even though motor activity during seizures can be observed by third persons, the first-person internal sensations of hallucinations during aura and loss of consciousness that cannot be accessed by the observers make it difficult to understand an interconnectable pathological mechanism from a third-person view.

### 1.2. Electroencephalogram (EEG) findings

The key intracellular electrophysiological correlate of epileptiform activity is paroxysmal depolarizing shift (PDS) [9], which is a discharge recorded in interictal EEG. Similar depolarization shifts were also observed as abnormal intrinsic dendritic events, when inhibitory postsynaptic potentials were suppressed [10]. The hypothesis that PDS is a giant excitatory postsynaptic potential (EPSP) [11] was confirmed by experimental verifications [12]. Scalp EEG recording of a focal interictal epileptiform spike or a sharp wave is thought to occur when PDSs are synchronized sufficient to spread over an area of 6 $cm^2$ of the cerebral cortex. The observed PDS raises several questions. What is the origin of the cellular mechanism that leads to the observed PDS? What possible mechanism can give rise to such a giant EPSP at the postsynaptic terminals (dendritic spines), has the propensity to propagate, and is also capable of reversing back after an interval of time? If they occur from dendritic events, then it is reasonable to expect an additional mechanism for the lateral spread of activity to the adjacent areas of the cortex.

### 1.3. Kindling and seizures

Hippocampal kindling is a commonly used model for human seizures in animals by inducing afterdischarges [13], which requires higher stimulation intensity than that is used for inducing LTP. In kindling models of epilepsy, kindling reduces the afterdischarge threshold for inducing a seizure [14]. In an experiment to study the difference in cellular changes between the repeated stimulations that induce LTP and afterdischarges, it was found that spatial memory errors were significantly higher in the ten afterdischarge-kindled group than in other groups after the first and fourth weeks [15]. This indicates that kindling results in cellular changes that are a direct accentuation of changes induced by LTP. This leads to the following questions. What type of a cellular change occurring during LTP can transition towards the kindling effects? Can such changes take place in an irreversible manner? Can such cellular changes explain the relationship between kindling and LTP?

### 1.4. Effect of repeated seizures

It was found that repeated stimulation lowers the threshold for more seizures to occur [16]. What cellular changes can occur in an additive fashion, most of which can be maintained stably, that lowers the seizure threshold for future stimulation events?

### 1.5. Cognitive impairment

Memory problems have been found even at the early stages of seizure disorders. Cognitive defects are reported in pediatric patients, even those with new-onset seizures [17]. Studies showing that cognitive–behavioral deficits can precede seizure onset [18] have raised the question of whether there is a bidirectional relationship between the cognitive deficits and seizures. In this context, questions were raised whether patients with cognitive impairment also have a higher risk of developing epilepsy [19]. How can cognitive impairment possibly relate to seizures? The question may be reframed as the following. What cellular changes induced by seizures can lead to an impaired internal sensation of retrieved memories?

### 1.6. Electrolyte changes

During seizure activity, it was found that the extracellular concentration of $Ca^{2+}$ decreases and $K^+$ increases [20–22]. A simultaneous reduction in $Ca^{2+}$ and an elevation in $K^+$ in the extracellular matrix (ECM) volume to the levels observed during seizure can prevent action potential propagation along the axons [23]. In spite of these ionic changes that are in favor of stopping the propagation of activity, seizure generation continues to takes place. Therefore, mechanisms other than synaptic transmission are expected for short-range synchronization [24]. What extrasynaptic mechanism can mediate seizure propagation?

### 1.7. Hyponatremia-induced complex seizures

When serum sodium drops below the concentration of 120 meq/L, the probability of triggering generalized seizures increases. What cellular mechanism can explain this? Since the generalized seizures occurring in this condition cannot be differentiated from primary generalized tonic–clonic seizures, examination of the role of hyponatremia may provide information regarding the cellular mechanisms leading to seizure generation.

### 1.8. Association with viral infections

Seizures are a common clinical feature of acute infections with herpes simplex virus and flaviviruses [25]. What cellular mechanism can be evoked by these viruses to induce seizures?

### 1.9. Ketogenic diet and seizure susceptibility

A ketogenic diet rich in lipids is used as a therapeutic method for treating seizures in pediatric patients [26,27]. Clinical, animal, and *in vitro* studies suggest that several long chain polyunsaturated fatty acids (LC-PUFAs) may be beneficial in reducing seizure susceptibility [28–33]. This indicates that lipid-driven molecular–cellular changes have a direct role in reversing the pathological changes that lead to seizures. How can a ketogenic diet contribute to a common mechanism that can also explain all the above findings?

### 1.10. Effect of anesthetic agents on seizure

In refractory and status epilepticus, anesthetic agents are used in controlling seizures. What possible cellular mechanism can lead to the stoppage of seizure when using anesthetic agents? Similarities in the loss of consciousness by complex seizures and anesthetic agents may provide a common mechanism from which the mechanism for seizure generation and propagation may be understood.

An examination of the events during seizure activity is carried out with the expectation that certain loss-of-function states of the normal operation will be able to explain all the diverse findings such as the initiation of seizure activity through PDS, a mechanism for the rapid lateral spread of activity that enables synchronized hyperexcitation across the

motor cortex for seizure generation, tonic–clonic motor activity, loss of consciousness, cognitive impairment, and neurodegenerative disorders. It is also expected to shed light onto a feasible relationship between LTP, kindling, and seizures and to demonstrate a possible role of enveloped viral infections in inducing seizures and the role of ketogenic diet in preventing seizures. Even though an imbalance between excitatory and inhibitory neuronal activity alone was found insufficient to explain a general mechanism for cortical seizures [34], the actual mechanism is expected to accommodate this observed imbalance in seizure disorders.

During the development, the nervous system undergoes a sequence of steps that lead to the structural organization of neuronal cells. This has an important role in the interaction between the neuronal processes that belong to different orders of neurons and are necessary to understand the structure–function mechanism derived by the present work.

## 2. Development of the cortical neuronal orders

The newborn neuronal cells from the periventricular zone move up along the vertically oriented processes of the radial glia towards the marginal zone at the pial surface [35]. The neurons that reach the subpial region anchor its processes to the marginal zone close to the pia and then descend back towards the direction of the ventricular zone area. As the new neurons arrive at their final destination, they continue to settle one above the other. Thus, the first set of neurons becomes the sixth neuronal layer of the cortex. This is followed by the fifth neuronal layer and so on. Because of the subpial anchoring of the apical dendritic tufts, the first neuronal cells that arrive from the periventricular zone which become neurons of cortical layers 4, 5, and 6 have proportionally increasing dendritic lengths. The terminal apical dendritic terminals of all the neurons in different neuronal layers remain at the marginal zone close to the pial surface. This allows an interaction between the dendritic spines of all the neuronal orders at this location. A similar trend of interactions can be observed at other neuronal layers as well. (Fig. 1).

Cortical layer 1 lacks pyramidal neurons and has two main types of GABAergic interneuron groups. They inhibit adjacent cortical neurons [36] and powerfully control the excitability of L2/3 pyramidal neurons [37]. They receive long-range axons from the thalamus and other cortical areas. All the layer 1 neurons receive monosynaptic excitatory input from L2/3 pyramidal neurons with the exception of neurogliaform cells [38].

## 3. Electrical compartmentalization of dendrites

Investigations during the last twenty years have shown that dendrites are highly excitable structures that generate spikes (action potentials or firing) [39–41] similar to the classically observed action potentials (axonal spikes) at the axonal hillock close to the soma. Synapses at the distal dendrites produce an EPSP of an amplitude more than 10 millivolts (mV), whereas those proximal to the soma produce an EPSP amplitude of 0.2–0.3 mV. As the EPSP arrives from distal dendrites to the soma, they attenuate from nearly 10 mV to nearly 0.014 mV (more than 900-fold attenuation) [39]. Therefore, postsynaptic potentials induced from synaptic activity at the distal dendrites contribute only minimally to the neuronal firing from spikes generated close to the axon hillock region. In addition, dendritic arbor has a high output impedance and a high level of expression of regenerative voltage-dependent conductance. This is viewed as providing a certain level of independence in the functions of the distal dendritic area and to contribute to the observed electrical compartmentalization within the dendritic arbor. The independent functional operation is thought to provide some mechanism for information storage [42–44]. However, details regarding how this is accomplished at the distal dendritic area are not yet known.

One of the dendritic compartments is the terminal dendritic branch that receives more than 80% of synaptic inputs to the neuron [45]. It has a uniform diameter of nearly less than 1 μm forming a highly resistant region with passive cable properties that allows the synaptic current from the connected dendritic spines to produce a significant depolarization of a large portion of its length. The baseline state of this region is attributed to the voltage-dependent blockade of N-methyl-D-aspartate (NMDA) receptors by $Mg^{2+}$. Synaptic activity-induced depolarization can trigger the activation of voltage-dependent sodium and calcium conductances, increase the voltage and unblock the $Mg^{2+}$-blocked NMDA receptors, and provide local spikes [42,46]. In the apical tuft dendrites, the synchronous activation of 10 to 50 neighboring glutamatergic synapses triggers a regenerative potential, namely an NMDA spike [40]. Following this experimental finding, NMDA spikes have been observed *in vivo* [47–49]. Studies indicate that dendritic spikes, especially NMDA spikes occurring at the dendritic tuft level, provide a major nonlinear depolarizing drive depending on the activity arriving from the connected network [50]. Different dendritic locations of origins of spikes and their representative traces are shown in Fig. 2.

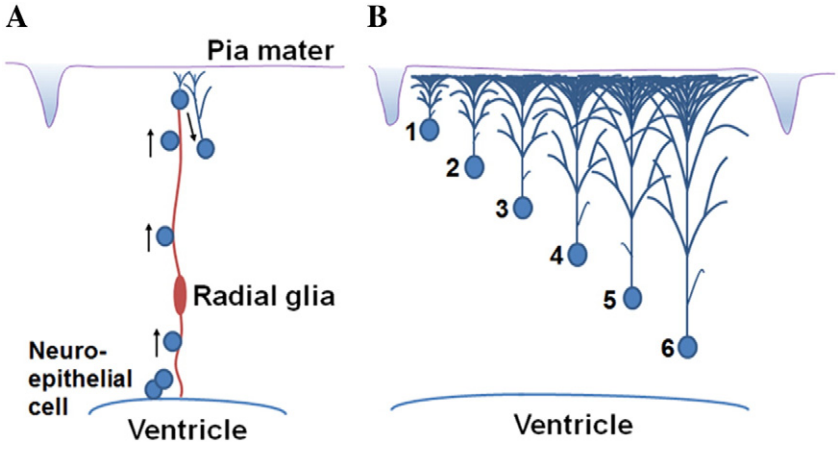


**Fig. 1.** Stages of neuronal migration and arrangement of neurons in different neocortical neuronal orders. Both figure panels are views of the vertical section through the cortex. A: Progenitor neuroepithelial cells in the fetal ventricular zone proliferate, and the newly formed daughter cells migrate along the processes of the radial glia towards the superficial layer of the cortical plate. The new cells develop processes, and the dendrites are anchored to the extracellular matrix structural proteins at this region. As new cells arrive at the superficial layer, the older ones get pushed towards the direction of the ventricular zone. However, their apical dendrites remain anchored to the superficial layer. Since the dendrites are already anchored to the superficial layer, the main dendritic stem elongates. This continuous process results in the displacement of the oldest cell layer, namely layer 6 located close to the ventricular zone and the last arrived cells to remain at the most superficial layer as neuronal order 1. B: Figure showing the dendritic trees of neurons that belong to different neuronal orders (numbered 1 to 6). Note that the dendrites of neurons of almost all the neuronal orders anchor at the subpial region, making this region rich in dendritic spines. As the dendritic spine density is very high at the cortical layers 1 and 2, the role of this arrangement contributing to the interspine interactions and oscillatory waveform of the cortical surface-recorded potentials are explained in the following sections.

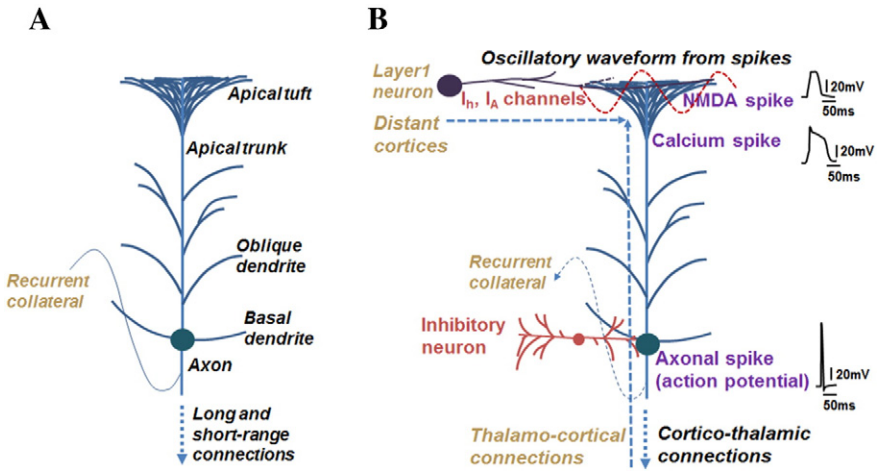


**Fig. 2.** Anatomy of pyramidal neurons and locations of spike generations. A: Diagram showing different locations of neuronal processes that are capable of producing regenerative potentials (spikes). These include apical tuft, apical trunk, oblique, basal, and axon. Synapses in distal dendrites produce EPSP of amplitude more than 10 mV; whereas those proximal to the soma produce EPSP amplitude of 0.2–0.3 mV. The EPSPs from distal dendrites attenuate from nearly 10 millivolts (mV) to nearly 0.014 mV (more than 900-fold attenuation) as they reach the soma [39]. B: Diagram showing the locations of spike generation and inhibitory mechanisms to regulate spike propagation. In the apical tuft, oblique, and basal dendrites, several dendritic conductances contributed by regenerative NMDA receptor current trigger dendritic plateau potentials with a rapid initial sodium spikelet followed by a plateau phase that collapses abruptly [46]. At the apical trunk, calcium spikes are generated. Axonal spikes (action potentials) are generated at the axon initial segment. The baseline activity of the $I_h$ channels at the apical tuft dendrites maintains the resting membrane potentials. The $I_A$ channels regulate potential changes at the apical trunk. Inhibitory inputs can regulate the net potentials reaching the soma. Both recurrent collateral and thalamo–cortical inputs control the generation and propagation of the spikes at different locations. Layer 1 cortical neurons that are mostly GABAergic send horizontal processes interconnecting several postsynaptic terminals of apical tufts. Representative traces of different spikes are shown (figure modified from [51]).

The second dendritic compartment is the distal apical trunk (near the base of the apical dendritic tuft) [52,53]. Unlike that of the terminal dendritic branch, the diameter of the distal apical trunk gradually increases towards the direction of the soma. Dual electrode recordings have shown that this electrical compartment can generate electrical properties independent of the soma [54]. Both calcium-dependent spiking and sodium-dependent spiking were identified and characterized in this dendritic region of pyramidal neurons [53,55–59].

## 4. Proposed cellular changes for inducing internal sensations and motor functions

A pair of surface electrodes over either the dura or the scalp can record the oscillating nature of the waveforms of the potentials between them. Even though the vertical component is provided by synaptic transmission between the neurons that are arranged in a vertical orientation, the lateral spread of activity through the recurrent collaterals alone is not sufficient to explain the horizontal component required for oscillating potentials. Therefore, an additional robust mechanism is expected to be present with a major contribution from the outer layers of the cortex. Since the dendrites that belong to the neurons of almost all the layers are anchored to the layer 1 area at the immediate subpial region (see development section above and Fig. 1B), a mechanism that arises from these dendrites providing a strong horizontal component of oscillating potentials is expected.

It was demonstrated that the average interspine (interdendritic spine) distance is greater than the average spine head circumference [60], increasing the probability for the dendritic spines of different neurons to abut each other. The observation that adjacent neurons share only a small percentage of their inputs [61] indicates that the dendritic spines located in the cortex receive their inputs from different origins. Furthermore, both the presence of synaptic contact (in a broad range between 0 and 85%) and the extent of synaptic coverage by the perisynaptic astrocytic processes vary extensively [62]. For example, in the stratum radiatum of the hippocampal area CA1, only 57 ± 11% of the synapses have astrocytic processes abutted to them, and of these, astrocytic processes surround only less than half of their synapses [63]. These findings increase the probability for specific dendritic spines that belong to different neurons to abut each other, which in turn, can lead to certain interactions when they are activated simultaneously.

The unique nature of the unidirectional continuous quantal release and the intermittent release of a volley of neurotransmitter molecules at the arrival of an action potential at the presynaptic terminal led to the proposal that an incidental activation of the postsynaptic terminal from a lateral direction (in the absence of arrival of activity from the presynaptic terminal) can induce units of internal sensations as a system property. This necessitates that abutted postsynaptic terminals form reversible interpostsynaptic functional LINKs (IPLs) that can serve as an ideal candidate mechanism [64,65]. The functional role of the IPL is summarized in Fig. 3. This has also allowed for the examination of the potential formation of virtual internal sensations of higher brain functions from a first-person frame of reference [66]. This mechanism can be examined for defects that can lead to hallucinations; changes in consciousness; tonic, clonic, and atonic seizure activities; and eventual cognitive impairment in seizure disorders.

### 4.1. Interpostsynaptic functional LINKs

Different mechanisms attribute to the formation of IPL and are shown in Fig. 4. Dendritic spines are anchored to the extracellular matrix (ECM) by structural proteins. Removal of the ECM aqueous environment associated with the polar head groups of the lipids of the outer membrane layer of the dendritic spines is a high energy-requiring process [67]. Mechanisms that lead to the enlargement of dendritic spines can result in interactions between the outer layers of their membranes and can lead to the induction of a state of close contact between them by excluding the hydrophilic region between them (Fig. 4B). Further interaction between these membranes can lead to reversible partial and complete hemifusions (Fig. 4C, D). Both innate and stabilizable-acquired mechanisms are expected to induce different types of IPLs between adjacent postsynaptic terminals for explaining the innate and long-lasting acquired response behaviors. The continued formation of IPLs between closely abutted postsynaptic terminals is expected to form an islet of inter-LINKed postsynaptic terminals [65]. The mechanism of IPL formation is expected to range between direct contact and partial to complete hemifusion between the membranes with a provision for stabilizing the latter for varying periods of time.

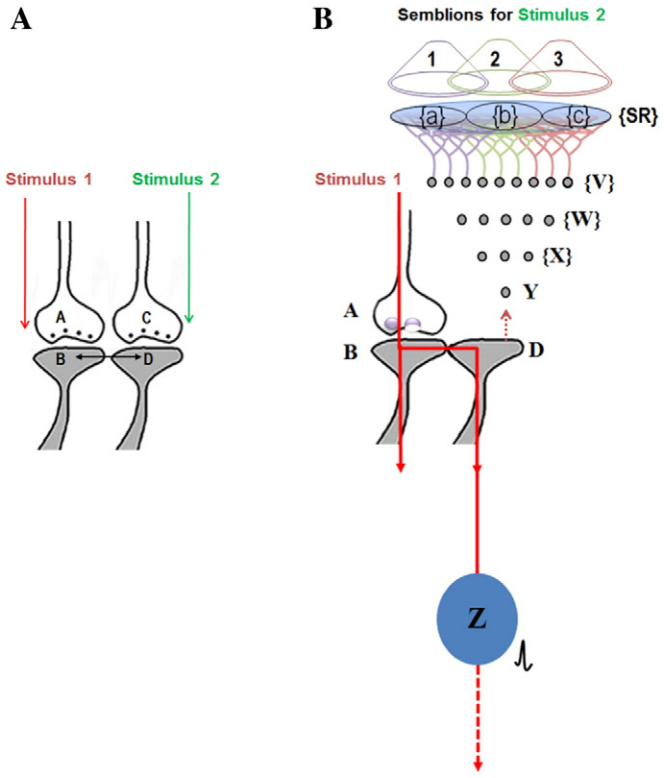


**Fig. 3.** Formation and reactivation of interpostsynaptic functional LINK (IPL) inducing internal sensations. A: During associative learning, sensory information arriving through different pathways is linked together at the locations of their convergence. In the figure, it is shown that, when associatively learned sensory stimuli 1 and 2 arrive at synapses A–B and C–D, an interpostsynaptic functional LINK (IPL) between postsynaptic terminals B and D is formed. B. After associative learning, when stimulus 1 arrives at the synapse A–B and activates postsynaptic terminal B, it reactivates the IPL and activates the LINKed second postsynaptic terminal D. When postsynaptic terminal D is activated in the absence of arrival of activity from its presynaptic terminal (not shown), a semblance (sensory hallucinations) of arrival of activity from the presynaptic terminal occurs. The sensory content of this can be estimated by examining the packets of minimum sensory stimuli capable of stimulating postsynaptic terminal D. This can be reached by extrapolating backwards from postsynaptic terminal D towards the sensory receptor level. It consists of inputs from neuron Y, which in turn, is 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} and are capable of independently activating postsynaptic terminal D. These hypothetical packets of sensory stimuli capable of activating sensory receptor subsets are called semblions. Activation of postsynaptic terminal D, through IPL B–D, by the cue stimulus can lead to the virtual internal sensation of semblions 1, 2, 3 or their integral or intersection. The lateral spread of activity through the IPL contributes towards the horizontal component for surface-recorded oscillating potentials. Stimulus-induced activation of postsynaptic terminal D may reach the soma of its neuron Z. If this can add to the subthreshold activation of neuron Z short of very minimal voltage, then it can cross the threshold to cause firing of neuron Z. This results in the concurrent activation of neuron Z along with the internal sensation of stimulus 2. If neuron Z is a motor neuron, it contributes towards behavioral motor activity that occurs concurrent with the formation of internal sensations of memory of the stimulus 2 (figure modified from [65]).

Membrane fusion through an intermediate hemifusion stage is highly prevalent in the biological systems [68,69]. In contrast to the continuous membrane fusion and fission steps of the synaptic vesicles at the presynaptic terminals, mechanisms are expected to be present at the postsynaptic terminals to prevent the conversion of interpostsynaptic membrane hemifusion to a fused state.

What alterations of the basic mechanism of the normal functioning of the nervous system can lead to seizure activity? In this context, the relationship between LTP, kindling, and seizures can be examined. It was possible to explain LTP in terms of interpostsynaptic membrane hemifusion [65]. A certain reorganization of the lipid membranes at the lateral aspect of the postsynaptic terminal close to the synapses is expected to take place from the exocytosis of vesicles containing GluA1 subunits of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. This makes this region of the postsynaptic membrane a suitable location for IPL formation [66]. Previous examinations have shown that synaptosomal-associated protein (SNAP) inhibitors block membrane fusion and attenuate LTP [70]. Even though the intracytoplasmic presence of SNAP inhibitors is used to block intracytoplasmic membrane fusion, in the context of the IPL mechanism that includes interpostsynaptic membrane hemifusion, additional mechanisms can be expected. Since LTP can be explained through the generation of IPL, including interpostsynaptic membrane hemifusion [65], and since SNAP inhibitors attenuate LTP, this additional mechanism can be verified. The observation of GluA1AMPA receptor subunits at the extrasynaptic locations 25 nm beyond the synaptic specialization [71] is in favor of the occurrence of different types of IPLs by utilizing the membrane reorganization taking place at the time of GluA1AMPA receptor subunit exocytosis. The suspected regions with only two layers between the postsynaptic membranes at locations adjacent to the synapses, instead of four layers of lipid membranes, [72] indicate the necessity for a thorough examination of the postsynaptic membranes for the presence of stabilized hemifused interpostsynaptic membrane areas.

The dendritic origin of the spikes that occur in the absence of depolarizing prepotentials in the hippocampal neurons was reported both during and after seizure [73]. Since dendritic spikes are comparable with the somatic spikes in several aspects and since the locations of the majority of the spiking neuronal soma are much deeper than the dendritic spine-rich subpial area where the apical dendrites of neurons from all the neuronal orders anchor, the surface-recorded oscillating potentials are likely receiving a major contribution from the dendritic spikes (Fig. 5). Postsynaptic terminals within an islet of inter-LINKed postsynaptic terminals can lead to the spread of potentials between them causing an additive effect that leads to the formation of large potentials at the locations of islets of inter-LINKed postsynaptic terminals. In order to prevent the formation of abnormally large potentials, it is necessary to maintain a certain level of intrinsic inhibition at the locations of islets during the resting state. This can be achieved through the $I_h$, $I_A$, and SK-type potassium channels, where they can serve as shunts to maintain a steady subthreshold membrane potential. Their function as bias currents to regulate the voltage-dependent blockage of NMDA receptors by $Mg^{2+}$ [41] is capable of explaining this. The arrival of activity from various environmental stimuli through the IPL during an awake state removes the inhibition and enables NMDA receptors to revert to the functional state.

## 5. Pathological states of interpostsynaptic functional LINKs

The lateral spread of potentials through the IPLs contributing to the horizontal component of oscillating potentials can be examined for their abnormalities that can lead to various findings in seizure disorders. With the example of hyponatremia, a condition that leads to global changes of cell swelling in the brain [74] and seizures, the probable changes to the normal operational mechanism can be explored. With the confined volume of the brain inside the skull, acute cell swelling can compress the abutted postsynaptic membranes together to exclude the water of hydration between them leading to the formation of reversible IPLs (Fig. 4A). Different factors such as dendritic spine enlargement and membrane compositional changes [75,76] can lead to the formation of these rapidly reversible IPLs (Fig. 4B, C, D). In this context, various observations in seizure disorders are examined for possible abnormalities of the formation of normal IPLs such as formation of nonspecific IPLs, stabilization of non-specific IPLs that prevent their reversibility, and conversion of IPL hemifusion to a fusion state.

### 5.1. Overexcitability of the dendritic segments

Overexcitability of the dendritic segments depends on the following factors: a) mechanisms for the arrival of additional potentials; b) level of

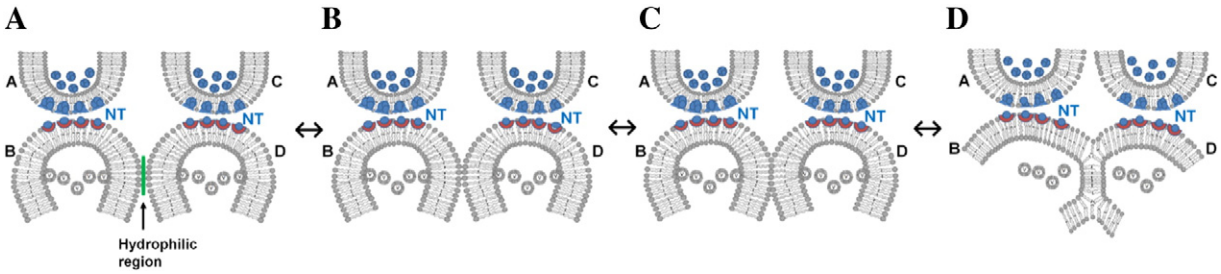


**Fig. 4.** Figure demonstrating different types of possible interpostsynaptic functional LINKs (IPLs). A: Two synapses A–B and C–D are shown. A and C are the presynaptic terminals. B and D are the postsynaptic terminals. Normally, the postsynaptic terminals are isolated from each other from depolarization coupling by the water of hydration between them. B: Formation of IPL by excluding the intermembrane hydrophilic region between them. C: Partially hemifused postsynaptic membranes B and D. Different factors that can overcome the energy barrier can lead to membrane hemifusion. D: Completely hemifused postsynaptic membranes B and D. Note that these different forms of IPLs can reverse back to their normal background state. Insertion of a transmembrane protein through the hemifused area in the figure D can prolong the life span of the hemifused membrane segment. Conversion of the hemifusion in figure D to a fusion state may remain nonreversible. Formation of nonspecific IPLs can occur in various pathological conditions that can lead to the induction of nonspecific semblances resulting in loss of consciousness, cognitive impairment, and uncontrolled firing of motor neurons resulting in seizures. NT: Neurotransmitter (figure modified from [51]).

intrinsic inhibitory voltage-dependent conductances such as $I_h$, $I_A$, and conductance through SK-type potassium channels; c) input impedance or leak conductance of the electrical compartment; d) steepness of the negative slope of the current–voltage (I–V) activation plot of the NMDA currents; e) voltage-dependent calcium currents (VDCC); and f) level of gamma-aminobutyric acid (GABA)ergic inhibition [41] through inhibitory neurons. The mechanical and exogenous factors that predispose organisms to seizures include mutated ion channels, severe electrolyte disturbances, acute inflammatory conditions, and increased temperature. The common converging mechanism in all the above conditions is change in the potentials at the postsynaptic terminal membranes. Overexcitation of postsynaptic terminals (dendritic spines) can lead to their enlargement. Pathologies such as inflammation can exert pressure on the abutted postsynaptic terminals compressing them towards each other and enabling them to overcome the energy barrier that prevents them from making close contact to each other [67]. This can lead to the formation of different types of IPLs (Fig. 4). Changes in the membrane composition that favor hemifusion [75,76] are a common factor. The extent of hemifusion can range from partial to complete. Any activity arriving at one of the hemifused postsynaptic terminals spreads towards the second postsynaptic terminal. When these changes occur between the postsynaptic terminals that belong to different islets of inter-LINKed postsynaptic terminals, then it can lead to a rapid chain generation-like spread of activity between these islets, which can lead to the rapid spread of seizure activity.

### 5.2. Paroxysmal depolarizing shift

The PDS has been viewed as a giant EPSP [9]. The cellular correlate of this interictal event consists of a sudden depolarizing voltage ranging from 20 to 50 mV that lasts for 50 to 100 ms. The following electrophysiological features of this giant EPSP were confirmed by experiments [12]: a) the synaptic currents underlying the PDS are large relative to the normally produced EPSPs, b) possibility to reverse the polarity by depolarizing the cell beyond the synaptic equilibrium potential indicating that the PDS is of synaptic origin, c) changes in membrane potential do not alter the frequency or probability of occurrence of PDSs, and d) amplitude is a monotonically decreasing function of the membrane potential in accordance with the decrease in synaptic driving force. These findings strongly indicate that a large EPSP is formed through a

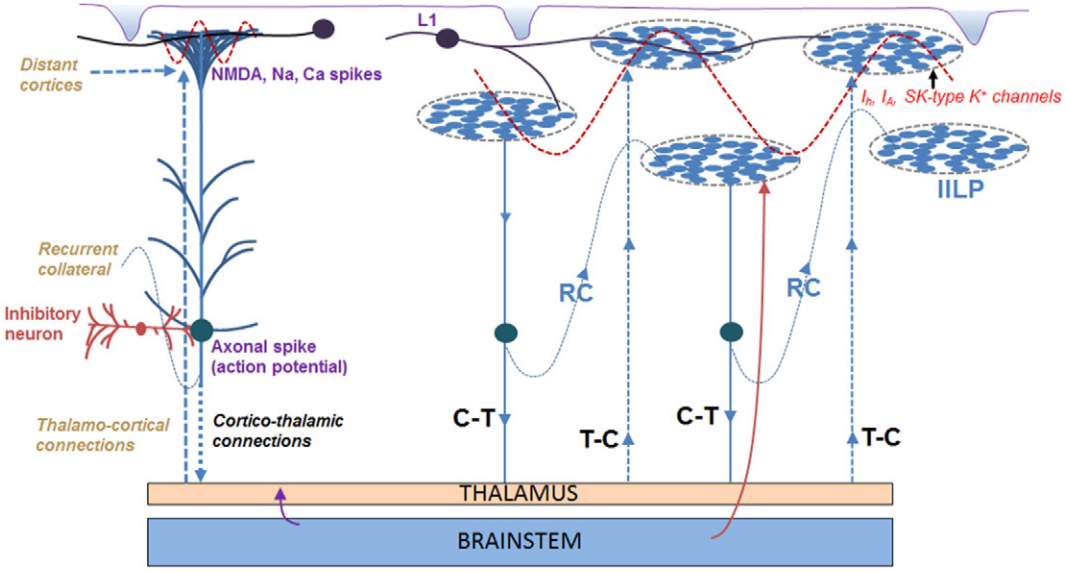


**Fig. 5.** Sources of potentials from different types of spikes contributing to the surface or extracellularly recorded potentials. Left: One pyramidal neuron showing locations where different spikes are generated. The NMDA spikes occurring close to the pial surface are likely to contribute significantly to the surface-recorded electroencephalogram (EEG) waveforms. Right: Five islets of inter-LINKed postsynaptic terminals (IILPs). Several postsynaptic terminals get inter-LINKed both by innate and acquired mechanisms to form islets of inter-LINKed postsynapses. These islets receive inputs from recurrent collaterals, cortico–thalamo–cortical pathways, and layer 1 cortical neurons. This pattern of interconnections can provide a mechanism for long-range synchronization. Cortico–thalamo–cortical pathway maintains a significant role in maintaining the oscillating nature of the potentials in the cortex. Cortex also receives inputs from the brain stem contributing to the frequency of oscillating potentials. RC: recurrent collateral; C–T: cortico–thalamic pathway; T–C: thalamo–cortical pathway. L1: layer 1 cortical neuron. IILP: islet of inter-LINKed postsynaptic terminals (figure modified from [51]).

postsynaptic mechanism. Since distal dendrites normally produce EPSP with an amplitude over 10 mV [39], the spatial summation of several of these EPSPs is a feasible mechanism to explain the PDS. Islets of inter-LINKed postsynaptic terminals that are expected to be under inhibitory control are normally not expected to create large EPSPs such as the PDS. However, pathological conditions that can lead to the formation of IPLs between the postsynaptic terminals that belong to different islets of inter-LINKed postsynaptic terminals. can provide summated EPSPs that can overcome the inhibitory mechanisms. Such a mechanism can also provide the propensity to spread across different islets of inter-LINKed postsynaptic terminals. This can explain a basic mechanism for PDS generation.

### 5.3. Abnormal background activity

Early experiments showed that the generation of spikes in penicillin-induced epileptogenesis occurs at the level of the dendrites [77]. Continued experiments confirmed the finding that PDS is an abnormal intrinsic dendritic event [10]. Based on the present work, the observed PDS can be explained in terms of spread of potentials through rapid chain generation of IPLs promoted by several factors. The formation of LINKs between the postsynaptic terminals belonging to different islets of inter-LINKed postsynaptic terminals results in long-range LINKs between the islets. Based on the IPL mechanism, dendritic spikes are formed from the simultaneous generation of potentials at the islets of inter-LINKed postsynaptic terminals. The depolarization spread between the islets of inter-LINKed postsynaptic terminals increases the horizontal component of the oscillating potentials and is possibly responsible for the slowing of the background activity (reduced frequency) in the EEG.

### 5.4. Interictal epileptiform spikes and sharp waves

The rapid chain generation of IPLs through several islets of inter-LINKed postsynaptic terminals can explain the formation of both the spike (nearly 70-millisecond duration) and sharp waves (less than 200-millisecond duration) recorded in the EEG. Spikes can be explained as generated by the lateral spread of activity through the pathologically formed IPLs that span areas comparatively smaller than those that lead to the generation of sharp waves. The summated dendritic spike potentials during the rapid chain generation of IPLs can explain their amplitudes. The generation of both spikes and sharp waves during the interictal period indicates that a large number of irreversible pathologically formed IPLs are present at those cortical areas. It also informs that strong inhibitory mechanisms are preventing their further lateral spread. If spikes and sharp waves persist for a long period of time, it can lead to the stabilization of the IPLs between different islets of inter-LINKed postsynaptic terminals, and this favors the continued occurrence of spikes and sharp waves.

### 5.5. Focal seizures

The spike or sharp-wave generating mechanisms can further spread to a much larger area of the cortex because of the following reasons: a) local conditions such as tumor or trauma or conditions that cause pressure effects leading to the removal of water of hydration between the outer layer of membranes of the dendritic spines, b) systemic effects such as gene mutations of certain channel proteins, c) electrolyte imbalance such as low serum levels of sodium, and d) changes in the lipid membrane composition [75,76]. The activity generated by spikes and sharp waves reaching the upper motor neurons in layer 5 of the motor cortex is prevented from spreading further because of the development of homeostatic inhibitory circuits. This inhibitory mechanism will be overcome by rapid chain generation of IPLs spreading across a large area. However, activation of the upper motor neurons of a limited area will result in focal seizures (Fig. 6). Focal seizures may spread further and remain restricted to certain cortices without leading to generalized seizures; for example, bilateral motor cortical seizure activity that leads to myoclonic jerks. Focal seizures can also originate at the deep structures. For example, medium spiny neurons in the striatum are expected to form different types of IPLs under the influence of dopamine-induced dendritic spine swelling. Therefore, any local pathological conditions can lead to the induction of focal seizures at the deep structures.

### 5.6. Seizure begets seizure

It is known that the aberrant excitability of terminal dendrites that causes burst generation at the apical trunk compartment of the dendritic arbor is associated with the activation of $I_A$, $I_h$, and conductance through SK-type potassium channels that normally prevent hyperexcitability [41]. It is not yet known whether these are primary events or secondary to changes in the dendritic input. Based on the present work, it could be induced secondary to abnormal IPLs that lead to a vicious cycle of events that result in seizures. The $I_A$ is a rapidly inactivating, voltage-gated $K^+$ conductance that is mediated by Kv4.2 potassium channels on apical trunk dendrites [78]. The $I_A$ channels get inactivated rapidly at voltages that are close to the resting potential. High frequency inputs inactivate $I_A$ channels and lower the threshold for regenerative spiking [79]. The attenuation of $I_A$ channels promotes seizures. This "seizure begets seizure" event is evident from the blockade of $I_A$ channels by 4-aminopyridine in an established *in vitro* model of seizures [80].

The $I_h$ is a mixed cation conductance mediated by the hyperpolarization-activated cyclic nucleotide-gated (HCN) family of ion channels that are highly expressed at the distal dendrites of the cortical and hippocampal CA1 pyramidal neurons [81,82]. An $I_h$-mediated decrease in input impedance was shown to attenuate the postsynaptic depolarization of the glutamatergic inputs and speed the decay of excitatory synaptic events, resulting in the reduced summation of EPSPs [3,83]. In agreement with these, different seizure models were made to operate by decreasing $I_h$ conductance [84,85]. In support of this, pilocarpine-induced status epilepticus induces progressive down regulation of HCN channel expression in a seizure-dependent manner [86].

Small conductance (SK-type) $Ca^{2+}$-activated $K^+$ channels are present at the terminal dendrites and dendritic spines. Long-lasting elevations of the intracellular $Ca^{2+}$ concentration at the active initiation site of the depolarization of plateau potential [42] activate SK-type channels, leading to the termination of this plateau potential [79]. Hyperexcitability in the denervated CA1 neurons is accompanied by a marked prolongation of plateau potentials possibly because of post-translational down regulation of the SK channels [87]. These features indicate that the pathological IPL-mediated PDS generation can lead to activity-dependent down regulation of $I_A$, $I_h$, and SK-type potassium channels, which in turn, will lead to a vicious cycle of continuous and prolonged spikes.

### 5.7. Generalized seizures

The interpostsynaptic islet-to-islet spread of activity leads to a wide-range lateral horizontal spread, which in turn, also increases the transsynaptic vertical spread of activity at higher neuronal orders. When the lateral spread of activity leads to the occurrence of the spikes over a wide area, it results in the activation of many subthreshold-activated motor neurons that result in a seizure. Homeostatic mechanisms to prevent rapid chain generation of interpostsynaptic functional LINKs such as $I_h$, $I_A$, and SK-type calcium channel activities and inhibitory neuronal activities normally get initiated. These mechanisms may fail globally in certain conditions. A typical example is change in the ECM composition occurring in severe hyponatremia. The rapid chain generation of interpostsynaptic functional LINKs initiated by close contact between the dendritic spines can overcome all the inhibitory mechanisms

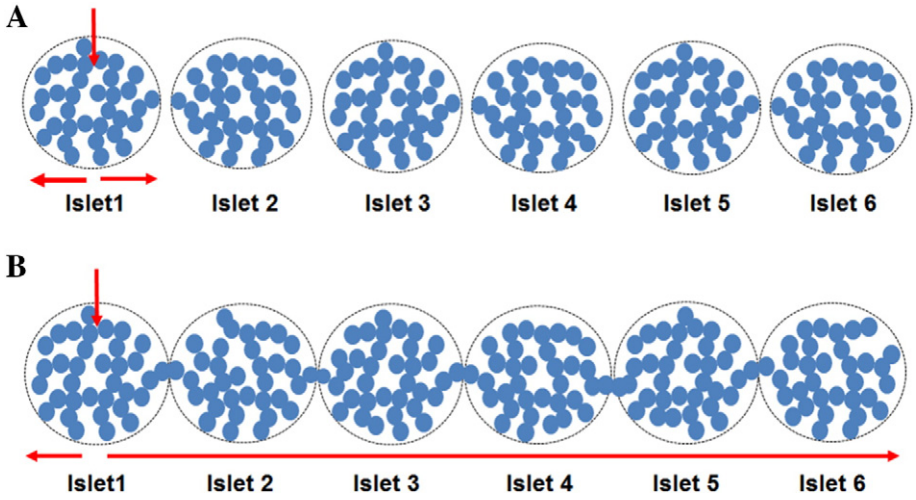


**Fig. 6.** Diagram showing islets of inter-LINKed spines and the inter-LINKs between different islets that result in lateral spread of seizure. A: Normal state of function of the dendritic spines. A set of six islets of inter-LINKed postsynaptic terminals (dendritic spines) are shown side by side. Each islet represents a cross-sectional view of the inter-LINKed dendritic spines assuming that they are in the same plane. For simplicity, the sizes of all the islets are drawn the same. In the first islet, a giant excitatory postsynaptic potential induced as an intrinsic dendritic event remains within this islet. B: Pathological state that leads to the generation and rapid spread of seizure activity. Large number of factors promote these. Factors that trigger paroxysmal depolarization shift (PDS) include the activation of mutated channel proteins and fusion proteins which inter-LINKs neighboring islets. Changes in lipid membrane composition and extracellular matrix electrolyte composition are factors that promote long-range interspine interaction. These lead to rapid chain-generation inter-LINKs between neighboring islets during a seizure. This is a transient change during the rapid seizure spread that reverses back. During this, some IPL hemifusions can undergo fusion that may remain irreversible for long periods of time, which can explain the pathology in status epilepticus.

and lead to the spread of seizure activity from one focus of origin throughout the entire cortex [88] (Fig. 7). In addition, there are several factors that can lead to abnormal nonspecific membrane hemifusion in large areas of the cortex. These include viruses [89,90], chemicals [91], and changes in the membrane composition [75,76]. A large number of factors can influence both hemifusion and fusion mediated by viral fusion proteins during acute viral infections as the mechanisms of viral fusion proteins for membrane fusion vary widely [92].

### 5.8. Hallucinations

The internal sensation of various sensory features of a compelling sense of reality occurs during an aura of seizure activity. Seizure activity occurring at or reaching different sensory cortices can lead to the reactivation of normally existing IPLs at these locations and resulting in the induction of hallucinations from respective sensory cortices as explained previously [93].

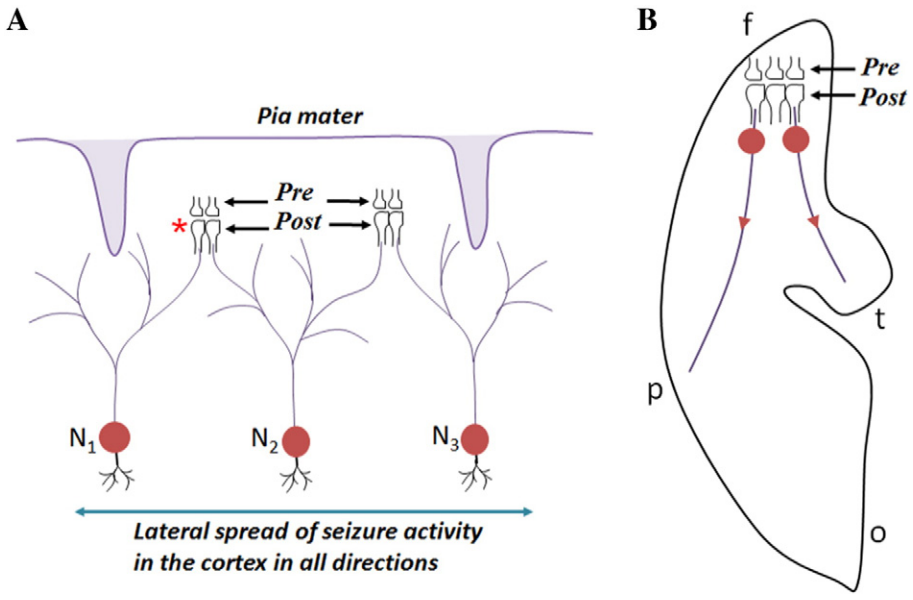


**Fig. 7.** Potential transcortical spread of seizure activity through interpostsynaptic functional LINK (IPL) mechanism. A: Intracortical lateral spread of epileptiform activity from one IPL (marked by red star) reaching the IPLs of neurons $N_1$ and $N_2$ and then to neuron $N_3$. This multilateral spread of activity primarily through the IPLs and interconnected through the neurons and recurrent collaterals, formation of large number of IPLs between the dendritic spines of the laterally arranged neurons in the cortical layers leads to lateral spread of activity to different cortical regions of the brain. B: Large number of IPLs between the dendritic spines of neurons at the frontal cortex (f). Two neurons that project to remote locations — parietal (p) and temporal (t) cortices are shown here. This leads to rapid spread of activity from a local epileptiform focus in the frontal cortex. Such spread of activity from a focal lesion from one cortex and spreading to multiple cortices is difficult to explain by transsynaptic route alone. Pre: presynaptic terminal. Post: postsynaptic terminal. o: occipital area.

### 5.9. Cognitive deficits

A large number of seizure-induced nonspecific IPLs that get reactivated in response to a cue stimulus can lead to a loss of specificity of the net semblances required for specificity of retrieved memory [64,65]. The hippocampus, one of the main locations in the brain where different sensory systems converge, is expected to have a large number of IPLs operating for associative learning. Seizure-induced formation of nonspecific IPLs in this region can have a major impact on the cognitive ability. Several of these nonspecific IPLs can get stabilized over time and can lead to long-lasting cognitive deficits. The preponderance for seizure pathology at locations where LTP can be induced (as evidenced by hippocampal pathology in several seizure disorders) provides support for the possible pathological conversion of IPL mechanisms generating seizures.

### 5.10. LTP to kindling change is explained by the conversion of hemifusion to fusion

Long-term potentiation is an experimental finding of long-lasting changes induced at the locations of groups of synapses between two consecutive orders of neurons, first demonstrated using hippocampal slices [94,95]. When a brief repetitive stimulation is applied at a group of axons synapsing to a second group of neurons, this induces sufficient changes at the locations of the synapses such that the application of a regular stimulus at the same location will become sufficient to induce a potentiated effect when recorded from the second group of neurons. The potentiated effect reverses back over time. The LTP has been found to be correlated with behavioral motor activity markers indicative of the formation of internal sensations of retrieved memories. This indicates that the cellular mechanisms associated with the internal sensation of retrieved memories share certain cellular mechanisms with LTP.

Previous sections have described the formation and the role of IPLs in inducing internal sensation during memory retrieval. In order to explain the formation of the long-lasting internal sensation of memory and also that of forgetting after associative learning, it is necessary to explain both stabilization and reversibility features of the IPLs. A strong interaction between the postsynaptic membranes which allows the spread of depolarization across them and mechanisms for stabilization of these interactions is required to accomplish this. One of the methods is the formation of interpostsynaptic membrane hemifusion that will allow mechanisms for both stabilization and reversibility [65]. The extrasynaptic postsynaptic membrane close to the synapse where GluR1AMPA receptor subunit exocytosis takes place undergoes membrane reorganization and was found to be a suitable location for interpostsynaptic membrane hemifusion. There are several intracellular proteins that mediate membrane fusion within the postsynaptic cytoplasm such as SNAP (soluble NSF (n-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE) proteins)). It is known that LTP induction triggers SNARE-dependent insertion of AMPA receptors on to the postsynaptic membranes [96]. The SNARE proteins are known to produce hemifusion intermediates [97]. Since LTP can be explained by the formation of IPLs, particularly hemifusion [65], and since unique postsynaptic SNARE fusion machinery is required for LTP [98], it is likely that these proteins may provide certain checkpoint mechanisms to prevent the transient stage of interpostsynaptic hemifusion from undergoing fusion.

We previously explained how a reversible IPL mechanism including interpostsynaptic membrane hemifusion can explain LTP [65]. Kindling is an experimental model for seizure, and it uses an augmented form of LTP. While the cellular mechanism inducing LTP is a reversible process, the augmented stimulation protocols used in kindling are expected to make these cellular mechanisms irreversible. In other words, the advanced mechanism that is responsible for kindling is expected to be a direct extension of the mechanism that induces LTP, which can become nonreversible. It is possible that the stimulating conditions applied for inducing LTP lead only to interpostsynaptic membrane hemifusion, which is reversible. In contrast, the high level of stimulation used in kindling induce afterdischarges that can lead to the conversion of interpostsynaptic membrane hemifusion to fusion between the abutted postsynaptic terminals (Fig. 8). Most of these membrane fusions fail to reverse back. Fused interpostsynaptic membranes that belong to different neurons can lead to the mixing of cytoplasmic contents. Since adjacent CA1 pyramidal neurons are heterogeneous in their expression profiles [99], continued cytoplasmic content mixing can trigger the removal of the fused spines as a homeostatic mechanism to prevent further neuronal injury. This mechanism can explain the observed loss of dendritic spines after kindling [100].

Repeated experimental seizure inductions in animal studies result in behavioral changes to progress from freezing during early stimulations to convulsions at later stages [101]. The duration and behavioral involvement increase when seizures are induced repeatedly [102]. The effect persists even when the animals are left unstimulated for even up to twelve weeks; the response to stimulation can be even higher than prior stimulations [103]. Repeated stimulation is found to lower the threshold for further seizures [104]. These findings indicate that repeated stimulation induces certain cellular changes in an additive fashion, most of which are maintained stably, that lowers the seizure threshold for the next stimulation. The formation and stabilization of interpostsynaptic membrane hemifusion and conversion of hemifusion to fusion can explain the above findings.

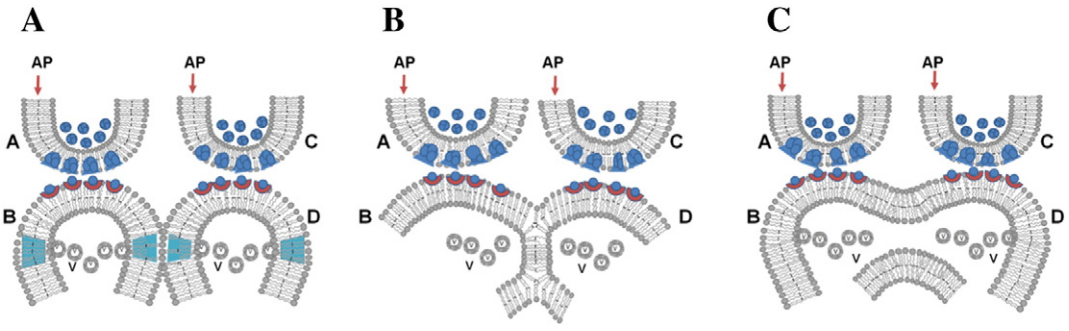


**Fig. 8.** Different stages of conversion of interpostsynaptic membrane interactions towards pathological membrane fusion. A: Diagram showing two pairs of synapses whose postsynaptic terminals have undergone partial hemifusion when action potentials arrive at these synapses simultaneously. B: Depending on various factors such as dendritic spine swelling and changes in membrane lipid composition, partial hemifusion can progress to form reversible complete interpostsynaptic hemifusion. C: Depending on the extent of the above factors, intensity of the seizure activity, and the presence of fusogenic chemicals and proteins, such as viral fusion proteins, seizure activity can lead to further progression of the hemifused stage of the postsynaptic membranes towards their fusion. Fusion may become reversible and is expected to be under the guidance of several mechanisms. Both intermittent fusion and permanent failure of the reversal of fusion can lead to neurodegenerative changes. Conversion of inter-postsynaptic membrane hemifusion to fusion is also expected to occur in experiments when stimulation intensity is raised from that is necessary to induce LTP to that is needed to induce kindling. A and C are presynaptic terminals. B and D are postsynaptic terminals. Glu: glutamate. AP: action potential. V: vesicles containing GluR1AMPA receptor subunits (figure modified from [51]).

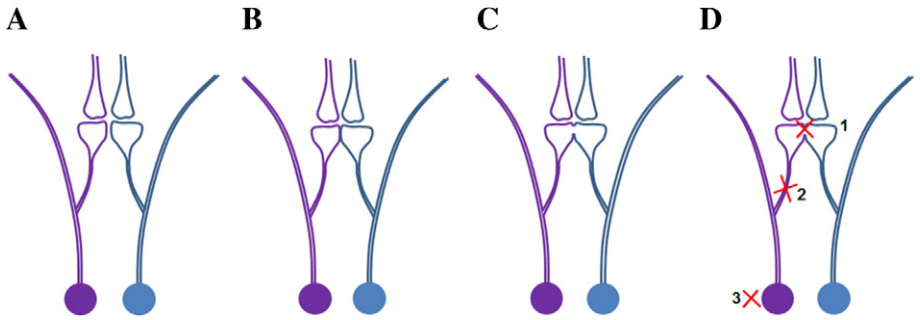


**Fig. 9.** Homeostatic cellular mechanisms protect the neurons involved in interpostsynaptic membrane fusion. A: Two neurons with one each of their dendritic spines abutted to each other. B: Associative learning events induce interpostsynaptic functional LINK (IPL) between the dendritic spines. Some of these LINKs form complete interpostsynaptic membrane hemifusions and get stabilized. C: Pathological changes such as changes in lipid membrane composition or control mechanisms that prevent conversion of hemifusion to fusion state can trigger interpostsynaptic membrane fusion. The cytoplasmic content mixing will lead to triggering of cytotoxic responses within the cytoplasm and nucleus. D: Different homeostatic cellular mechanisms secondary to IPL fusion. The first change is to initiate closure of the interspine fusion pore. It is possible that the aggregates of different proteins seen in different neurodegenerative disorders are part of the mechanism to seal off the fusion pore. If the fusion pore cannot be closed and if the cytoplasmic content mixing continues, this will trigger cellular mechanism for the removal of the dendritic spine at the narrowest region of the spine neck, explaining spine loss observed in several neurodegenerative disorders. If the above two mechanisms fail and if the cytoplasmic content mixing continues to take place, then a programmed cell death (apoptosis) initiated in one of the neurons can save the second neuron. The diagram shows three steps by which neuron on the left side starts cellular mechanisms to protect itself and the connected neuron. 1: Sealing of the fusion pore. 2: Removal of the dendritic spine. 3: Apoptosis of one of the neuron.

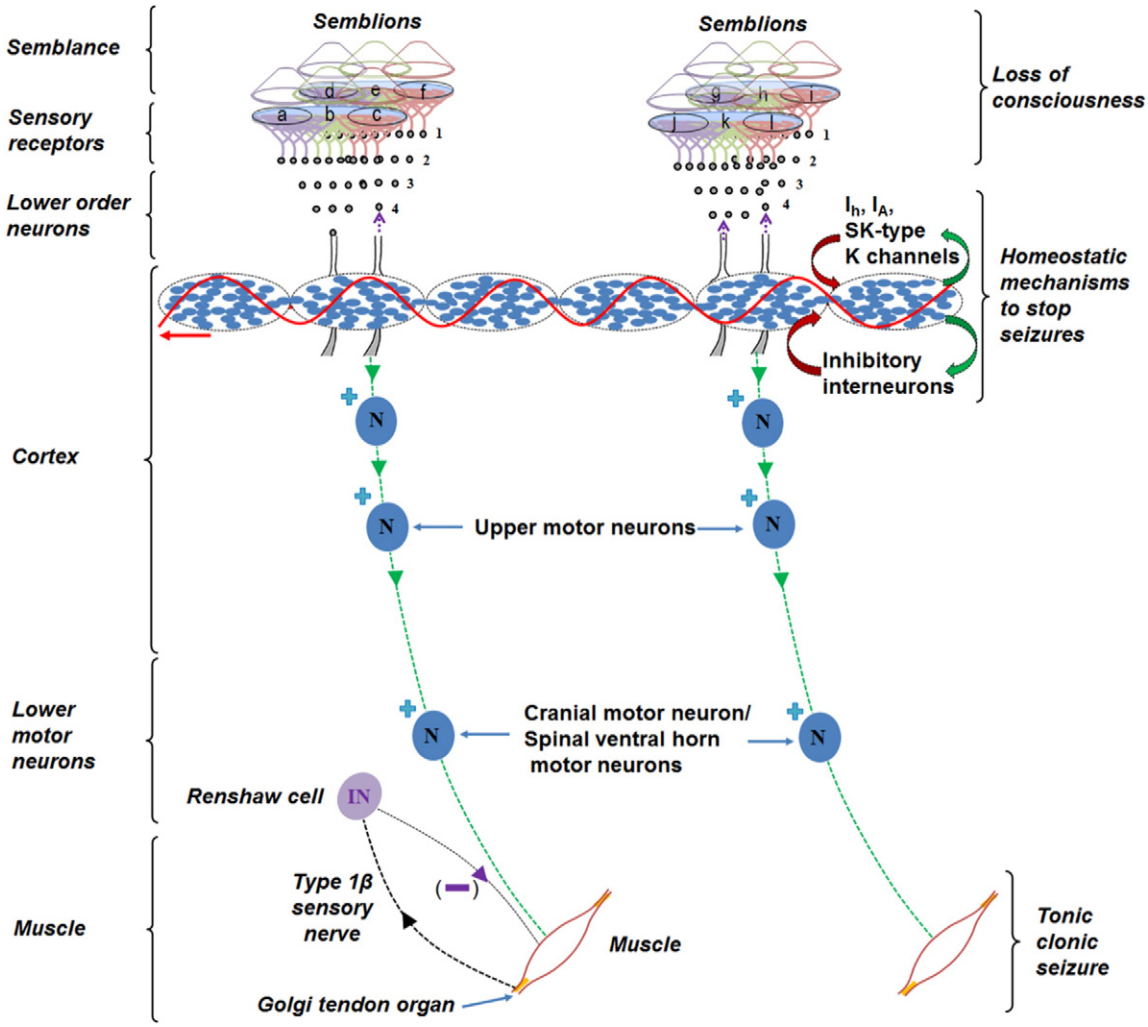


**Fig. 10.** Diagram showing seizure generation and homeostatic mechanisms reversing it. Rapid chain generation of a large number of IPLs (see Fig. 6) leads to induction of a large number of nonspecific semblances that lead to loss of C-semblance for consciousness. The transmission of potentials to higher neuronal orders in the cortex finally reaches layer 5 of motor cortical upper motor neurons that are at a subthreshold state making these neurons fire continuously. This will lead to tonic contraction of the muscles. The feedback control mechanisms activated from the Golgi tendon organs to the spinal cord Renshaw cells will lead to relaxation of the contracted muscle groups leading to the production of rhythmic tonic–clonic motor activity. At the motor cortical level, there is an activation of $I_h$, $I_A$, and SK-type potassium channels, where they act as bias current for voltage-dependent blockage of NMDA receptors by $Mg^{2+}$. In addition, activation of a large number of inhibitory interneurons in the cortex regulates firing of the excitatory upper motor neurons. These eventually lead to stoppage of the seizure activity within 1 to 2 min in normal conditions. N: neuron. IN: inhibitory action. (+): excitatory; (−): inhibitory.

### 5.11. Neurodegeneration associated with seizures

Neuronal death is frequently observed in seizure disorders, especially in status epilepticus. The etiology for these changes has been intensively investigated [105]. Based on the present work, the loss of function of certain aspects of the IPL mechanism can explain neurodegenerative changes. It is reasonable to expect that a well-controlled checkpoint mechanism that prevents conversion of interpostsynaptic membrane hemifusion to fusion exists. If this mechanism becomes defective and if the changes in the lipid membrane composition favor fusion [75,76], continuous seizure activity can predispose these abutted dendritic spines to undergo fusion (Fig. 8) similar to that expected in kindling experiments.

Interdendritic spine fusion leads to mixing of the cytoplasmic contents of two different neurons. Single-cell microarray studies have shown that the protein expression profiles of two adjacent CA1 neurons are different [99]. This indicates that any mixing of the cytoplasmic contents of two neighboring neurons can lead to toxic effects and induce the expression of several genes as a cellular response. Eventually, the initiation of cellular homeostatic mechanisms is expected to prevent such mixing and is summarized in Fig. 9. The first cellular response expected is to seal the fusion site to prevent the mixing of the cellular cytoplasmic contents. If it cannot be sealed, the next likely cellular mechanism will be aimed to remove the fused dendritic spine from the dendrite. This can explain the spine loss observed in different seizure conditions [106]. If this also fails, then sacrificing one neuron may save the other. In this context, a mechanism for programmed cell death of the neuron is likely to initiate. In contrast to intermittent seizures, status epilepticus can lead to a large number of acute hemifusions and fusions between inter-LINKed dendritic spines. This is expected to result in cellular responses that may trigger the immediate death of neurons. The acute changes observed by magnetic resonance imaging (MRI) studies following status epilepticus are likely to result from such acute cellular responses. Long-term changes can lead to gliosis and may explain the atrophy of the hippocampus observed in medial temporal sclerosis.

### 5.12. Loss of consciousness during complex seizure

An optimal conformation of C-semblance induced at the baseline level is expected to contribute to normal consciousness [107]. The formation of a very large number of nonspecific IPLs during seizure activity can result in increasing lateral spread of potentials and adds to the horizontal component of the oscillating potentials. This explains the reduced frequency of oscillations associated with the loss of consciousness during status epilepticus. Seizure activity localized to bilateral motor cortices alone (which can lead to myoclonic jerks) does not lead to loss of consciousness. This indicates that loss of consciousness from cortical causes requires spread of seizure activity to a much wider area of the cortices. High energy is required to maintain the newly induced nonspecific IPLs formed by close contact between the postsynaptic terminals by excluding the water of hydration between them [67]. Therefore, the majority of the seizure-induced IPLs are reversed over time. This explains how the slow waveforms return back to the near-normal frequency with the gradual return of consciousness back to the normal state following a seizure.

## 6. Related findings associated with generation of pathological IPLs

### 6.1. Seizure associated with viral infections

Seizure is a common clinical feature of viral encephalitis caused by herpes simplex and Japanese encephalitis viruses [25]. There is increasing evidence that these viruses release fusion proteins that promote membrane hemifusion and fusion [108–110]. This supports the role of viral fusion proteins in the formation of pathological IPLs in inducing seizures as described in the present work. It is likely that the extracellular (extradendritic spine) mechanism of the host cell for membrane hemifusion (IPL hemifusion) favors viruses to find neuronal cells for entry using their fusion proteins. This may become particularly important in acute HSV encephalitis where the infection affects the hippocampal region, an area of dense sensory input convergence where a high density of IPLs is expected to be present. An HHV-6 infection is reported to be associated with febrile seizures [111–114] and with meningoencephalitis [115]. It is known that specific HHV-6 proteins can lead to cell-to-cell fusion [116].

### 6.2. Effect of subpial resection as treatment

Even though the cortical neurons are synaptically connected in a vertical orientation, epileptiform activity propagates horizontally across the cortex in a nonuniform pattern [117,118]. Based on these findings, multiple vertical subpial resections have been done to alleviate seizures [119]. Here, the horizontal connections are severed to prevent the lateral spread of synchronous epileptogenic activity, while maintaining the vertical connections. One of the effects of this procedure in reducing seizure activity is likely by preventing the IPL-mediated rapid chain lateral propagation of seizure activity.

### 6.3. Anesthetic agents and burst suppression

Therapeutic seizure control is achieved clinically by burst suppression induced by anesthetic agents during which EEG recordings show a lack of electrical activity for several seconds in between periods of high-voltage bursts of activity [120]. It was previously shown how anesthetics can cause a loss of consciousness based on their action on lipid membranes that induces a large number of nonspecific IPLs [51]. Status epilepticus is expected to induce very large number of IPL fusions predisposing the system to a generally non-reversible state of "burst suppression." In surviving patients, it can lead to both dendritic spine and neuronal loss, resulting in permanent neurological injury. In the context

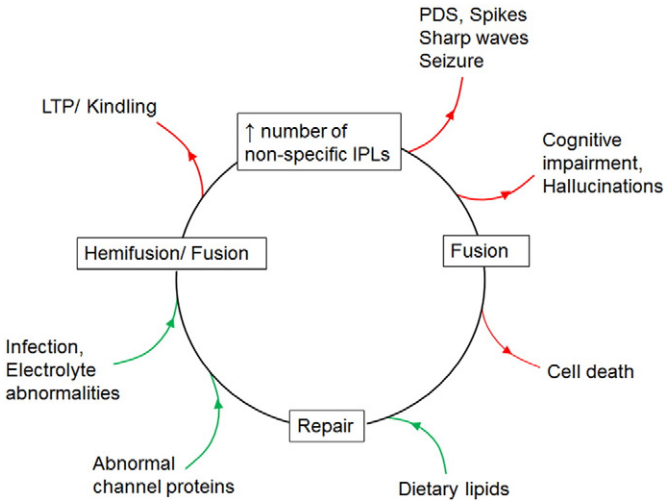


**Fig. 11.** Summary diagram showing how various features of seizure disorders are interconnected. Features observed at different levels can be explained in terms of pathological changes occurring at the level of interpostsynaptic (interdendritic spine) functional LINKs (IPLs). A large number of nonspecific hemifusions induced by various mechanisms such as changes in lipid membrane composition and viral fusion proteins can lead to the giant excitatory postsynaptic potential of PDS and seizure generation. Rapid chain generation of interpostsynaptic functional LINKs to adjacent regions can lead to the spread of seizure activity. Activation of nonspecific IPLs at the sensory cortices can explain hallucinations. Global activation of nonspecific IPLs leads to changes in the configuration of C-semblance resulting in loss of consciousness. Conversion of IPL hemifusion to fusion can explain experimental kindling, dendritic spine loss, and eventual cell death. Dietary lipids have a significant role in changing the composition of lipid membranes and in preventing pathological changes of normal IPLs.

of the present work, anesthetic agents in the treatment of status epilepticus are expected to induce rapid generation of large number of nonspecific IPLs except fusion and enable a reversible state of "burst suppression". It is known that anesthetic agents can induce neurodegeneration. A possible mechanism for this by IPL fusion was proposed previously [51]. In these contexts, it may require to select appropriate anesthetic agents based on the membrane lipid composition to achieve optimal therapeutic benefits in status epilepticus.

## 7. Diet and membrane composition

It is thought that a ketogenic diet may suppress seizures through reversing certain metabolic dysregulation [121]. It is known that a ketogenic diet works best in pediatric seizures [122], and they are thought to occur because of their easy access to the brain from the circulation [123]. The action of a ketogenic diet is correlated with the concentration of the total lipids and cholesterol in the plasma and is maximal after two to three weeks of initiation of the ketogenic diet [124]. It is observed that docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid (n-3 PUFA), raises the seizure threshold in the pentylenetetrazole (PTZ) model [125] and fish oil supplementation raises the amygdaloid afterdischarge seizure threshold [126]. Even though studies have shown that the ketogenic diet elevates serum long chain polyunsaturated fatty acids (LC-PUFA) [127,128], there are no mechanistic explanations for its role in preventing seizures.

Reversible membrane hemifusion and fusion are dependent on the lipid membrane composition [75,76]. The findings that the membrane lipid composition remained optimal when the dietary n-3 PUFA is more than 10% of total PUFA, but completely conformed to diet when the dietary n-3 PUFA is less than 10% of total PUFA [129] indicate the importance of maintaining adequate dietary n-3 PUFA. It is expected that, with optimal availability of dietary lipids, normal membrane lipid composition can be maintained if all the endogenous enzymes required for synthesis, elongation, desaturation, and assembly of the fatty acids are available in optimal amounts. Any deficiency in these factors can cause a predisposition to changes in the membrane composition that can lead to the formation of nonspecific IPLs leading to seizures. Based on the present work, the LC-PUFAs in the ketogenic diet or their modified forms get incorporated as the side chains of the lipid membrane triglyceride backbone, prevent nonspecific membrane hemifusion and fusion, and help prevent seizures. Moreover, unsaturated fatty acids confer negative spontaneous curvature to the membranes that promote hemifusion and disfavor formation of a fusion pore [130]. Future studies can be conducted to examine the role of key enzymes in the synthesis, elongation, and desaturation of lipids for optimizing membrane stability, which can prevent the membranes from undergoing fusion.

## 8. Relation between active seizures and behavioral motor changes

An expected normal circuit mechanism for the formation of internal sensation and concurrent behavioral motor activity was described previously [66]. When pathological conditions induce rapid chain generation of nonspecific IPLs, this can lead to loss of consciousness along with tonic and tonic–clonic seizures (Fig. 10). Generally, the generation of cortical inhibitory mechanisms will abort acute seizure activity within 1 to 2 min. Even though most of the nonspecific IPLs are reversed over time, recurrent seizure activity can make some of the nonspecific IPLs to get stabilized. This can lead to the formation of nonspecific semblances and activation of sets of nonspecific motor neurons in response to specific cue stimuli. This can explain changes in both cognitive abilities and behavioral motor activity.

## 9. Possible prevention of IPL-mediated seizure spread

If the presented mechanism is found to be true, then can we prevent the nonspecific rapid chain reaction that leads to the lateral spread of activity explained in the present work? Intermembrane interactions that lead to the formation of nonspecific IPLs are expected to have contributions from the following levels: a) membrane lipid bilayer compositional changes, b) ECM factors, c) intracytoplasmic factors, and d) external factors such as viral fusion proteins. Studying alterations in the neuronal lipid membrane composition and its parallel changes in the membranes of other cell types in the body, such as blood cells, in patients with seizures can be undertaken to compare with the healthy individuals to understand the details. It can lead to the identification of the role of genetics along the pathways of lipid synthesis, elongation, and desaturation steps that can find molecular biological therapeutic solutions. Since dietary lipids can influence the composition of the neuronal membranes, changes in diet with an aim to normalize an individual's lipid membrane composition can be implemented. Both the ECM proteins and ionic composition that maintain extracellular hydration and keep the membranes separated require further analysis. Discovering vaccines against enveloped viruses for inhibiting their ability to release fusion proteins is expected to prevent some of the IPL-mediated seizure disorders. In summary, the therapeutic effort to prevent the formation of nonspecific IPLs is expected to complement the current medications that suppress the function of abnormal ion channels in seizure disorders.

## 10. Conclusion

The present work has examined loss of function states of a proposed normal mechanism of the nervous system functions and has observed a feasible explanation for a large number of findings at various levels in seizure disorders. A summary of the vicious cycle of events of the neurobiological mechanisms, clinical features, laboratory findings, and homeostatic mechanisms is given in Fig. 11. Several seizure-generating etiologies can converge at different points of the path towards the derived common mechanism for seizure generation. Since both prolonged seizure activity and bust suppression-induced by anesthetics share the common feature of the formation of a large number of nonspecific IPLs, especially hemifusions, it has several implications. The insertion of transmembrane proteins across the hemifused segments of the nonspecific interpostsynaptic hemifusions can lead to cognitive impairments in both these conditions. Depending on several factors discussed in the present work, the hemifusion can advance to a fusion state that can lead to neurodegenerative changes in both these conditions.

The preventable aspects of the neurodegenerative changes resulting from interpostsynaptic membrane fusion discussed in the present work provide optimism in undertaking experiments to verify the proposed mechanism. Since it is possible to replace the membrane lipid composition using dietary lipid modification, further studies can be undertaken to verify the details of the mechanism. Large-scale reconstruction of high resolution electron microscopic (EM) images of the entire dendritic spine can provide information regarding different types of IPLs. These EM studies can further verify the formation of interpostsynaptic membrane hemifusion and fusion in LTP and kindling experiments, respectively. Based on the present work, advancing the research in lipidomics–genetics and proteomics of the enzymes involved in lipid synthesis, elongation, desaturation, and assembly can help in understanding the IPL-mediated seizure disorders. The testable mechanism presented here should be considered unproven unless verified by further experimental evidence.

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## Conflict of interest

U.S. patent application 14/068,835 pertains to an electronic circuit model of the interpostsynaptic functional LINK.

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