

Extreme degeneracy of inputs in firing a neuron leads to loss of information when neuronal firing is examined

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October 16, 2018

Abstract

Possible combinations of inputs in the order of 10^{100} can fire (axonal spike or action potential) a neuron that has nearly 10^4 inputs (dendritic spines). This extreme degeneracy of inputs that can fire a neuron is associated with significant loss of information when examination is limited to neuronal firing. Excitatory postsynaptic potentials (EPSPs) propagating from remote locations on the dendritic tree attenuate as they arrive at the axon hillock depending on the distance they propagate. Moreover, some EPSPs from remote locations will not even reach the axonal hillock. In this context, an operational mechanism at the location of origin of these EPSPs is necessary to preserve information for efficient storage. A similar mechanism is also expected at the location of origin of EPSPs generating dendritic spikes.

1 Introduction

Neurons were shown to have independent structural features by Santiago Ramn y Cajal using modification of staining methods developed by Camillo Golgi. This led to the neuron doctrine (Shepherd, 1991). Neurons can be grown individually and can make synapses between them in primary cell cultures, features that make them structural units of the nervous system. Effect of sensory stimuli on firing (axonal spike or action potential) of sensory neurons and the role of firing of motor neurons for the contraction of muscle fibers are well understood. Examination of neuronal activity has been facilitated by the development of tools to observe and control neuronal firing more efficiently (Kramer et al., 2009). Since firing of a neuron is the most distinct single identifiable event in the nervous system, a general view is that neuronal firing is a unitary function of the system. Neuronal firing has been studied in almost all the higher brain functions including perception of different sensations (Zaidi et al., 2013). During recent years, neurons have been named after different functions. It was suggested that by recording every action potential from every neuron and by manipulating the activities of specific sets of neurons within a circuit, algorithm that generate a higher brain function can be understood (Alivisatos et al., 2013). In these contexts, it is necessary to examine how neuronal firing imparts information to the system for the purpose of storing and retrieving that information.

Neurons in the cortical region on average has 2.4×10^4 to 8×10^4 input connections called postsynaptic terminals (dendritic spines or spines) (Abeles, 1991); these numbers can vary substantially

depending on the type of neuron and its location. While excitatory neuronal activities propagate towards the higher neuronal orders, the inhibitory neurons bring fine-control over such activity. In this context, excitatory neurotransmission is primarily examined. Even though it is theoretically possible to have nearly 40 to 50 EPSPs from synapses on the soma to fire a neuron, most of the time inputs arrive from randomly located synapses. There are two modelling studies that showed the number of inputs necessary to fire an action potential in a pyramidal neuron that receives tens of thousands of inputs. The first study showed that after providing sub-threshold synaptic inputs using 100 randomly distributed AMPA (alpha-amino-3-hydroxy-5-methyl-isoxazole propionic acid) and NMDA (N-methyl-D-aspartate) synapses over the entire dendritic tree, it was able to evoke somatic action potential with an additional 40 NMDA and AMPA synaptic inputs (Palmer et al., 2014). This shows that spatial summation of potentials from nearly 140 randomly distributed synaptic inputs on a pyramidal neuron as they arrive at the axon hillock can fire that neuron. Later, modeling study using L2/L3 pyramidal cells having nearly 20,000 to 30,000 dendritic spines show that nearly 135 synchronously activated excitatory axo-spinous synapses can generate an axonal spike (Eyal et al., 2018). It is to be noted that temporal (sequential arrival) summation of less number of EPSPs at the axonal hillock can also generate the same firing. For the purpose of this work, it is taken that nearly 140 randomly originating EPSPs fire the neuron.

In the above context, it is necessary to understand where information is stored and how neuronal firing is related to that information storage. Information arrives the nervous system from different sensory stimuli through sensory receptors. The stored information is retrieved as first-person inner sensations of memory. The following are some of the findings where internal sensations and neuronal firing are seen together. Artificial stimulation of different brain areas can produce internal sensations of various sensory stimuli along with firing of neurons (Selimbeyoglu and Parvizi, 2010). It is known that the same cue stimulus resulted in firing of an additional set of neurons while generating internal sensation of fear memory after associative learning (Tye et al., 2008). In order to explain the occurrence of internal sensations of higher brain functions concurrent with neuronal firing, it is necessary to provide a mechanistic explanation.

In the above contexts, the present work seeks to answer the questions, “Where is information stored in the nervous system?” “What is the substrate (engram) for storing information?” Search began with Hebb’s postulate (Hebb, 1949). One of its modifications namely synaptic plasticity and memory hypothesis (Martin et al., 2000) views engrams as spatially distributed synaptic weights within a network of neurons. In this view, an individual neuron takes part in different engrams due to their large number of synaptic connections. Since both storage of information during learning and retrieval of information during memory retrieval take place within milliseconds, it is necessary to search for a time-scale matched mechanism. However, until now it was not practically possible to undertake such studies. For example, one study that examined synaptic plasticity thesis (Hayashi-Takagi et al., 2015) used protein expression that does not match with the physiological time-scales at which learning takes place. Optogenetic techniques used to selectively mark individual neurons during memory encoding by concomitant activation of immediate early genes (Liu et al., 2012), whose expression times are far higher than milliseconds of time needed for associative learning also do not address the mechanism that takes place at physiological time-scales. Moreover, all the above studies used surrogate behavioral markers to assess the ability to retrieve stored information that in turn assessed the ability to learn. In these contexts, it is necessary to re-examine neuronal firing and tailor the focus to a specific mechanism of information storage occurring at physiological time-scales during learning that can be used for generating first-person internal sensation of memory at physiological time scales. Only by triangulating as many observations as possible that we will be able to understand the operational mechanism of the system (Munaf and Smith, 2018). To

understand the information storage mechanism, these should be time-scale matched observations.

2 Causes for apparent information loss when neuronal firing is examined

2.1 Attenuation of EPSPs arriving from remote dendritic locations

The number of input connections (dendritic spines) vary widely among the neurons. It ranges from one (passive conductance of potentials between the initial orders of neurons of the visual pathway without generating action potentials) to approximately 5,600 (in a monkey visual cortex) and 60,000 (in a monkey motor cortex) (Cragg 1967). EPSPs get degraded as they propagate towards the axonal hillock. As the distance of the dendritic spine from the axonal hillock increases, attenuation of EPSPs also increases (Stuart et al., 1997; Spruston, 2008; Major et al., 2013). Since spatial summation of nearly 140 EPSPs that are generated from randomly located synapses is required to elicit neuronal firing (axonal spike), further attenuation of EPSPs arriving from remote locations will require much more than 140 EPSPs to cause the same neuronal firing. This naturally leads to the question, “How can information be stored using attenuating EPSPs?” When threshold-operated neuronal firing is examined, an EPSP will find its most important function when it is providing the n^{th} EPSP required to trigger an action potential. But this is a rare event for any one EPSP arriving at the axon hillock. In this context, neuronal firing cannot be used to examine how information is processed in the system. Instead, it is reasonable to expect for the presence of a mechanism to preserve information at the origins of EPSPs.

2.2 Degeneracy of inputs in firing a neuron

To account for the attenuation of EPSPs, let us assume that on an average inputs from 140 spines are necessary to arrive at the axon hillock to get summated to generate one action potential at the axonal hillock of a neuron. Let us also assume that this neuron has 10,000 dendritic spines (inputs or postsynaptic terminals). If EPSPs arriving from exactly 140 of its dendritic spines can fire that neuron, then it shows that nearly $((1 \times 10^4!)/(140! \times (1 \times 10^4! - 140!))) = 2.79 \times 10^{318}$ sets of combinations of inputs are available from that neuron’s dendritic spines to fire that neuron (**Figure.1**). If we consider that a pyramidal neuron has only 3,000 dendritic spines, then the set of combinations will reduce to nearly 1.72×10^{244} . Note that these calculations were done only for fixed number of 140 inputs. For a neuron with 10,000 inputs, when possible number of combinations of inputs that can fire that neuron for inputs ranging from 141 to 10,000 is calculated, then the sum of these combinations reaches a very high value. This means that a gigantic number of combinations of inputs can cause the same neuronal firing. Therefore, when we see a neuron firing (axonal spike or action potential) (*in vivo*, at physiological conditions), it is not at all specific with respect to its inputs. This extreme redundancy of inputs in firing a neuron will cause an abandoning of information residing within each input when neuronal firing is used for interpretations. Extreme degeneracy of inputs in firing a neuron compels us to search for a mechanism for information storage and its retrieval occurring at the locations where inputs arrive, before they get attenuated.

2.3 Ignoring large number of EPSPs during supra- and sub-threshold activations

Since firing of a neuron takes place by an all or none process, EPSPs responsible for sub-threshold or supra-threshold activations of neurons are not taken into account when neuronal firing is examined (Figure 1). Let us examine one pyramidal neuron (excitatory neuron) with tens of thousands of inputs (dendritic spines). If 3000 inputs are activated simultaneously (supra-threshold activation) during the arrival of a sensory input, only one action potential will be elicited. Simultaneous arrival of 140 EPSPs from random locations at the axonal hillock is enough to induce that action potential. This means that when neuronal firing is examined, $(3000 - 140) = 2860$ EPSPs have to be viewed as wasted without having any functional use. In this context, it is necessary to examine means to preserve information that the system would have acquired while evolving. It is also necessary to preserve information when less than 140 EPSPs (sub-threshold activation) arrive at a neuron that do not result in eliciting an action potential. These situations strongly indicate the necessity to search for a possible mechanism operating at the individual locations where each input arrives.



Figure 1: Comparison between minimum number of inputs needed to fire a neuron (in red) and all the possible inputs (in red and blue) that can arrive at a pyramidal neuron having 10,000 inputs (dendritic spines). Lengths of the lines represent 10,000 inputs. A: Number of EPSPs (nearly 50) needed (in red, at the left end) to elicit neuronal firing by spatial summation, if EPSPs originate from synapses on the soma. Note that in this situation, there will be nearly 2.9×10^{135} combinatorial possibilities of sets of exactly 50 inputs that can fire that neuron. B: Number of EPSPs (nearly 140) needed (in red, at the left end) to elicit neuronal firing by spatial summation if EPSPs are originating from randomly located synapses. Note that in this situation, there will be nearly 2.79×10^{318} combinatorial possibilities of sets of 140 inputs that can fire that neuron. Empty area at the right end represents those EPSPs that arrive from remote locations and do not reach axonal hillock (these were not taken into account in the above calculations). Figure not to scale.

2.4 Some EPSPs are used to generate dendritic spikes

Similar to spikes at the axonal hillocks (neuronal firing), there are spikes occurring at the dendrites, which are called dendritic spikes. Depending on the channels involved, there are different types of dendritic spikes. Based on the strength of summated potentials, a rough estimate shows that they constitute synchronous activation of up to 50 neighboring glutamatergic synapses triggering a local regenerative potential (Antic et al., 2010). It is known that the surface positive potentials are generated mainly by synaptic inputs from other cortical and subcortical regions to the pyramidal neurons located between L2/3 to L4 regions (Douglas and Martin, 2004). These input locations can be information processing regions. Calcium dendritic spikes contribute to surface potentials that are recorded as electroencephalogram (EEG) (Suzuki et al., 2017). It is not yet known what contributes a vector component, for the oscillating surface potentials, in a perpendicular direction to the synaptic transmission occurring between orders of neurons arranged in one direction. Since dendritic spikes are related to both behavior and cognitive function (Xu et al., 2012; Smith et

al., 2013), it is reasonable to expect an operational mechanism that can explain both. Distal dendrites that generate spikes have a firing rate nearly five times greater than that occur at the cell body (Moore et al., 2017). Even though calcium spikes generally contributes to a burst of action potentials (Major et al., 2013) and NMDA spikes enhance action potential generation during sensory input (Palmer et al., 2014), when information arriving at the inputs generate these dendritic spikes first instead of axonal spikes (neuronal firing) examination of neuronal firing will lead to loss of information.

2.5 Dilution of information as it passes through few neuronal orders

There is already reduced specificity of information when sensory inputs reach neurons located after few neuronal orders. In order to compensate for this loss, memory retrieval process is expected to have a mechanism to bring specificity back. Even if we find such a recovery mechanism, examining neuronal firing will eliminate the friable pieces of information that reach after few neuronal orders. Since information is already getting diluted as they propagate through few neuronal orders, it is necessary to search for a mechanism that can preserve all the information that reaches at the input locations of these neurons.

3 Systems organized to preserve information have evolved

In sections 2.2 and 2.3, we have seen examples of conditions in which a neuron can get fired by either all or a minor fraction (even just 1 input if a neuron is at a baseline subthreshold state short of small amount of potentials to fire). How can an efficient information storage mechanism get evolved within such a system? Since specificity of information is expected to get preserved in systems that evolve to adapt to a predator-prey environment, it is reasonable to expect a mechanism where by all the EPSPs are utilized. Moreover, since very large number of EPSPs from apical dendrites do not reach the soma (Spruston, 2008) to induce a spike, the functional relevance of evolutionary conservation of EPSPs at the apical dendrites also needs re-examination. This leads to the question, “What mechanism of operation can retain information so that it can deliver this information in a specific manner in response to specific inputs by different cue stimuli?” For this to occur, it is reasonable to expect interactive changes taking place at the input level of the neurons. This is possible only when inputs at the location of convergence of sensory stimuli interact with each other to leave a signature at the time of learning.

4 A comparison with the degeneracy of codons

DNA contains stable information with the formation of embryo. External factors can regulate its transcription and usage. In contrast, nervous system is a storage device with very little information written in it at the time of birth that are responsible for innate behavior. The findings presented in this work argues for the presence of a writable storage device at the origins of inputs to a neuron. There should be mechanism to prevent overwriting of information. While most information gets lost following encryption, some information will get stored for long period of time. It should be possible to explain mechanisms for these. To understand how specificity of information is retained, it is necessary to understand the structural changes that occur at the region of inputs during learning and passive reactivation those learning-induced encryptions during memory retrieval. Provision for degeneracy at the level of the codons, especially at the third position, has

Codons	Number of bases in mRNA	Number of bases in a codon	Number of possible permutations of triplet codons	Number of amino acids	Nature of information
		4	3	4^3	20
<i>Example</i>	A, U, C, G		AGA, AGG, CGA CGU, CGC, CCG	Arginine	
Firing of a neuron (axonal spike)	Number of inputs to a neuron		Number of possible combinations of inputs that can fire a neuron with 10^4 input connections	Number of neuronal firing (outputs)	Nature of information
		30	not applicable	0	Few innately written information. Written during learning & retrieved during memory. Outputs are first-person inner sensations
<i>Examples</i>	140	$\sim 2.79 \times 10^{318}$	1		
	500	$\sim 2.53 \times 10^{860}$	1		

Figure 2: Comparison between degeneracy of codons and degeneracy of inputs in firing a neuron. DNA has stable information and is heritable. Since repetition of bases within a codon is allowed and since bases can be arranged in any order, permutations are calculated to find the number of possible codons. Degeneracy of the codons helps to maintain information stable with biological variations and mutations. In contrast, in the nervous system only very less information is encoded innately. Since during spatial summation, repetition is not possible and since it does not take into account order of inputs, combinations are calculated. Since there is only one output, extreme degeneracy of inputs will result in apparent loss of information when neuronal firing is examined. This directs us to examine the location of inputs for an information storage and retrieval mechanism. Note: Only spatial summation of EPSPs arriving at the axonal hillock without attenuation is used in the comparison table. In addition to combinations that are calculated (for spatial summation), permutations can be calculated since temporal summation of lesser number of inputs can fire a neuron. This increases the number of possible ways to cause neuronal firing.

the important advantage to accommodate mutational changes and biological variations. Extreme degeneracy of inputs in firing a neuron does not provide similar advantages when neuronal firing is examined (Figure 2). Instead, it directs us to examine the locations where inputs arrive for seeking an information storage and retrieval mechanism. Since outputs are equally important, one may ask “Why extreme degeneracy of inputs provides only one output (neuronal firing)?” This may be possibly due to limited number of muscles that can be put into action for behavioral activity.

5 Introduction of a new concept of a FIROME

Observation of extreme degeneracy of inputs in firing a neuron highlights the fact that there will be significant apparent loss of information when neuronal firing is examined (Figure 2). For avoiding the error of ignoring huge amount of specific information contained in the inputs to a neuron and

to understand the operation of the system, a new term FIROME is introduced. FIROME is a set of EPSPs that are summated to generate a spike at the location of spike generation. There are two types of FIROMEs. One for axonal spike, which is called FIROME-A and the second one that generates dendritic spike, which is called as FIROME-D. Since EPSPs attenuate as they propagate towards the location of spike generation, especially for axonal spike, examining them at the location of their origin is necessary to find the information storage mechanism. Therefore, FIROME-A at the locations of their origin is called as FIROME-Ao. Since EPSPs in FIROME-Ao undergo attenuation as they propagate towards the axonal hillock, sum of the values of EPSPs in FIROME-Ao will be much higher than in FIROME-A. Whereas, since FIROME-D is expected to occur at the origin of their EPSPs, it is expected to be nearly equal to that of FIROME-Do.

5.1 Operational mechanism at the origin of FIROME

It is necessary to store information at the location of arrival of inputs at physiological time-scales that can be utilized at a later time to retrieve this information in the form of first-person internal sensation as needed. In this regard, the following observations are guideposts that can permit discovering the mechanism. a) Since maximum information is contained at the origin of the inputs, a mechanism to retain this information is expected to take place at the level of the inputs (dendritic spines). b) If two sensory inputs are to be associated to store information, it should take place at the level of dendritic spines at the locations of their convergence. c) If this storage mechanism is maintained, it should generate internal sensation of one of the stimuli when the second stimulus arrives and vice versa. d) Narrow range of frequency of oscillating extracellular potentials at which all the higher brain functions are taking place indicate that oscillating potentials impart a binding property to the systems operations. Since oscillating extracellular potentials reflect ionic changes taking place at the neuronal membranes, the information storage and retrieval mechanism is bound to the oscillating extracellular potentials. e) Observing how one of the associatively learned stimulus use the stored information to generate units of internal sensation is expected to reveal the operation of the system.

5.2 Nature of information storage at the input level

It is necessary to deduce the operational mechanism of information storage at the input level using available observations. One is the observation of firing of additional neurons by the cue stimulus following learning (Schoenbaum et al., 1999; Tye et al., 2008). Secondly, at an excitatory synapse postsynaptic potentials on the spine undergo resistance at the spine neck as it propagates towards the dendritic branch (Koch and Poggio, 1983; Wilson, 1984) making spine head as the input region where information can be stored efficiently. This knowledge becomes essential in identifying an information storage mechanism. Using constraints offered by all the findings at different levels and by using the idea that if a mechanism X can explain all the findings, then that mechanism should be correct, it was possible to derive a mechanism (Figure 3). Since a biological mechanism for memory is expected to have a component for eliciting hallucination (an apparent perception of something not present) (Minsky, 1980), a suitable mechanism that allows the stored information to get retrieved as first-person internal sensation was searched. A suitable mechanism was found at the location of arrival of inputs and was described previously (Vadakkan, 2013).

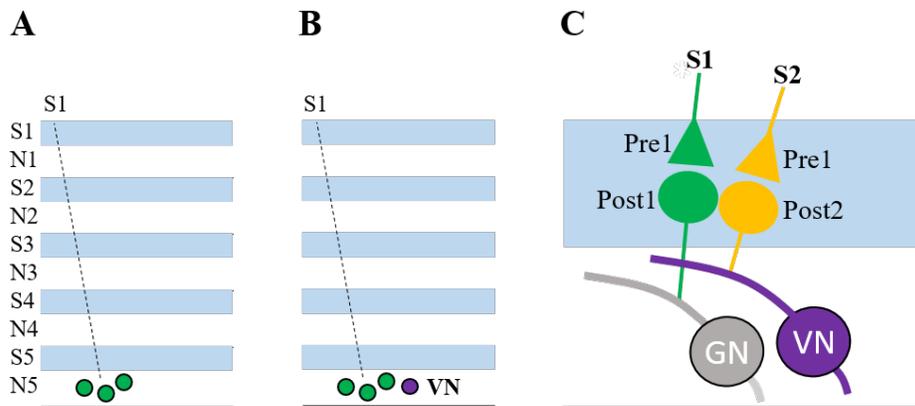


Figure 3. A testable mechanism for information storage at the input level capable of retrieval when one of the stimuli (cue stimulus) is presented. Diagram shows five neuronal orders starting from the sensory receptor level (S1: zone dense in sensory receptors; S2-S5: zone dense with synapses; N1-N5: zone with neuronal soma). Note that each neuron is expected to fire an action potential on receiving nearly 140 EPSPs from randomly located synapses on its dendritic tree. A) Before learning, arrival of sensory stimulus 1 leads to firing of a set of 3 neurons (in green). B) After associative learning, arrival of stimulus 1 (cue stimulus) alone causes firing of previously fired three neurons (in green) and an additional neuron (VN in violet). This indicates that learning has opened a new channel through which EPSPs from neuronal circuitry activated by stimulus 1 arrive at the additional neuron. Formation of a new channel should have occurred between the synapses of the two converging stimuli at physiological time-scales. Neuron VN most likely would have been remaining at sub-threshold activation state before learning. Change induced by associative learning provides a route for arrival of additional EPSPs to neuron VN resulting in its firing. A mechanism for learning should be able to provide an explanation for the arrival of additional potentials to VN. This is expected to take place most likely between the synapses at synaptic region S5 where stimulus 1 and 2 converge. C) Two neurons (GN and VN) each with only one dendritic spine, out of their total number of spines of the order of 10^4 , are shown. Stimulus S1 reaches at a synapse (pre1-post1) on the spine of neuron GN, which is not firing either before or after learning. Before learning, stimulus S2 reaches at a synapse (pre2-post2) on the spine of neuron VN and is providing the $(n-1)^{th}$ EPSP to it. Before learning, with stimulus S2 alone, VN is short of one EPSP to fire. After learning, VN fires with the arrival of stimulus S1 (cue stimulus) alone. This shows that neuron VN receives equivalent of two EPSPs by stimulus S1 after learning. Searching for the route through which this occurs indicates one possibility. When dendritic spines post1 and post2 at which stimuli S1 and S2 arrive respectively are abutted to each other (before learning), they undergo structural change during learning to generate an electrical connection between them. This is expected to take place at physiological time-scales. Information is stored in the form of this inter-spine connection. After learning, stimulus S1 can provide both $(n-1)^{th}$ (through the inter-spine connection) and n^{th} EPSPs to neuron VN and cause it to fire. As long as inter-spine electrical interaction persists after learning, arrival of stimulus S1 can fire neuron VN. In addition, arrival of stimulus S1 that depolarizes dendritic spine post2 from its lateral side is expected to spark a hallucination at spine post2 at physiological time-scales that it is receiving sensory stimulus from stimulus S2. Unique circumstances that lead to this was explained previously (Vadakkan, 2013). Size of the spines (post1 and post2) and neuronal somata (GN and VN) are not scaled and are not to be compared.

For retaining specificity associative learning should have unitary mechanism of operation at the input level. Since physical properties of large number of items in the environment are shared, sharing of the operational units by these items can provide an efficient operational mechanism. Furthermore, using combinations of unitary mechanisms provides opportunity to represent infinite number of items or events in the environment including those with complex features. Associatively learned sensory stimuli reach specific inputs of a neuron that form only a minute fraction of its total inputs. Yet, there is an operational mechanism that keeps the specificity while generating first-person internal sensation during memory retrieval. Based on the derived mechanism shown in Figure 3, it is conceivable that there should be a mechanism that allows integration of units of internal sensations through an inter-neuronal inter-spine mechanism, leaving neuronal firing as a path towards achieving behavioral motor actions. For efficient storage of information, the inter-spine mechanism should have the features described in Table 1.

1. Information storage and retrieval occur at physiological time-scales
2. One of the associatively learned stimuli can activate just one input and cause both firing of a neuron and at the same time store information with specificity
3. Retains specificity of stored information
4. Retrieves information as first-person inner sensations of sensory features
5. Retrieves information by integration of units of internal sensations
6. Storage and retrieval occur during both sub- and supra-threshold activations of a neuron
7. Information storage and retrieval mechanisms are interlinked with corresponding behavioral motor actions
8. Storage and retrieval occur at a short range of frequency of oscillating extracellular potentials

Table 1. Expected features of an information storage mechanism that provides constraints to arrive at a mechanism.

5.3 Firing of a group of neurons

Observation of firing of a set of neurons within a particular neuronal order in a specific brain region during a higher brain function implies that this set of neurons or their connections are associated with that function. More specifically, firing of a set of neurons is associated with generation of first-person internal sensation of a higher brain function with or without associated behavioral motor actions. Where do these functions come from? There are two major possibilities. The first possibility is: *One neuron receives inputs from two associatively learned stimuli through separate lower order neurons.* In agreement with this option, it was previously thought that dendritic branch receiving a cluster of inputs can have clustered plasticity (Govindarajan et al., 2006). There are three challenges. First, the time-scales needed for protein synthesis does not match with the mechanism of learning. Second, it does not explain a mechanism for the generation of internal sensation of memory of the second stimulus when first stimulus arrives after learning. Thirdly, there is only one output. In a conditioning paradigm, if the neuronal output is common to two associatively learned stimuli then one stimulus will not be able to provide motor output reminiscent of the second associatively learned stimulus. Single neuron receiving inputs from two associatively learned stimuli is likely to perform a common motor output. Since number of muscles in the body are limited, only combinatorial use of these muscles can provide movements in multiple directions.

In this regard, one muscle will have to contract in combination with different muscles to provide different behavioral outputs.

The second possibility is: *Two neurons each receive separate inputs from two associatively learned stimuli through separate lower order neurons*: Since each neuron receive separate inputs, it may appear that there is no possibility for any new function. Note that here each input has its own separate motor output. Now, as each input has separate motor outputs, we can ask the following question about a key incident when nervous systems evolved. Was it possible to have an accidental coincidence that allowed a key change during learning that provided the ability to induce internal sensation during memory retrieval? In other words, At one stage of evolution, as multiple sets of neurons connected through their synapses were lying in certain order, what would have happened? First, an accident had happened that allowed pathways to cross over so that paths of two sensory stimuli converged at some point. Secondly, an interaction should have occurred at the location of convergence that enabled one of the stimuli participated in learning to induce first-person internal sensation of memory and motor action reminiscent of the arrival of second stimulus. This should be an accidental occurrence and would have occurred by virtue of the unique features of the synaptically-connected neurons and features at the location where convergence occurred. Obviously, this interaction should have the capability to evade our attention for so long. This condition can be satisfied if the abutted spines that belong to different neurons at which associated stimuli arrive can interact with each other, as shown in Figure 3.

The inter-neuronal inter-spine interaction should also satisfy firing of additional neurons by the cue stimulus following learning (Schoenbaum et al., 1999; Tye et al., 2008). The firing of additional neurons were explained by increased synaptic strength as evidenced by increased AMPAR (AMPA receptor) trafficking towards the postsynaptic membrane (Tye et al., 2008). AMPAR vesicle exocytosis provides membrane segments for membrane reorganization at the lateral spine head region that favors inter-spine interaction that can explain both generation of internal sensations and firing of additional neurons (Vadakkan, 2013, 2016).

6 Conclusion

Any derived information storage mechanism at the location of inputs capable of explaining all the previous observations in an inter-connectable manner should prompt us to verify that mechanism in engineered systems. In this regard, derivation of a mechanism operated through the generation and reactivation of inter-neuronal inter-spine connections provides a candidate mechanism that can maintain specificity of information. Current methods are limited to examining dendritic spines on the dendritic branch of single neurons. By undertaking experiments to examine activation of abutted spines that belong to different neurons, the nature of inter-spine interaction will become clear. The usage of the word degeneracy perfectly fits with the condition explained in this work since the potentials are in fact degenerating (attenuating) as they propagate towards the soma. Extreme degeneracy of inputs in firing a neuron that ignores huge amount of specific information, apparent loss of information during supra-threshold activation of a neuron and the possibility for information storage, and retrieval even in the absence of neuronal firing during its sub-threshold activation indicate that neuronal firing does not contain specificity anticipated of a mechanism for information storage.

Acknowledgements: This work was supported by Neurosearch Center, Toronto.

Conflict of interest: U.S. patent 9477924 pertains to an electronic circuit model of the inter-postsynaptic functional LINK.

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