Internal sensation of pleasure can be explained as a specific conformation of semblance: Inference from electrophysiological findings

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Abstract

Semblance hypothesis was able to find a solution for the generation of first-person internal sensation of memory along with provisions for behavioral motor actions. The derived inter-postsynaptic functional LINK (IPL) mechanism was able to explain a large number of findings from different levels of the system ranging from perception to sleep. It was possible to explain long-term potentiation (LTP) as the effect of experimental scaling-up of the changes occurring during natural learning. By keeping the latter relationship as a baseline, it was possible to explain long-term depression (LTD) observed in the nucleus accumbens (NAc), a scaled-up change of a mechanism responsible for inducing internal sensation of pleasure. This mechanism provides inter-connectable explanations for the attenuation of postsynaptic potentials, reduced firing of medium spiny neurons and the finding that LTD induced by stimulation of one pathway to NAc occludes the LTD induction by another pathway.

1 INTRODUCTION

Current studies of different higher brain functions such as memory, perception, pleasure, anxiety, fear, hunger, thirst, aversion, reward, stress and pain are carried out by examining the surrogate behavioral markers exhibited by animals. Studies also correlate these functions to the sets of neurons at corresponding regions of the brain that fire and their firing rates. When these examinations are carried out, there is an implicit assumption that the animals are generating internal sensations associated with each of the above higher brain functions. For example, internal sensation of perception is generated only when a stimulus is present and that of the memory of an item is induced when a cue stimulus that was previously associated with the p learned item is presented. It is expected that once we understand the mechanism of induction of internal sensations, we should be able to understand the general operational framework for the generation of internal sensations of different brain functions.

The nervous system was examined to understand how changes generated during associative learning between two sensory stimuli are used to generate first-person internal sensation of memory of one item when the second item arrives as a cue stimulus (Vadakkan 2007, 2013, 2016). Changes

are expected to take place in the locations where the associatively learned stimuli converge. Due to the reasons that a) the neuronal processes at the location of convergence of two stimuli are the feasible locations where learning can make changes, b) integration of ionic changes occurring at the extracellular matrix (ECM) volume maintains a narrow range of frequency of oscillating extracellular potentials during system operations, and c) the presence of a huge redundancy of inputs arriving through the dendritic spines (spines or postsynaptic terminals) in firing a neuron (Vadakkan, 2018), necessitate interaction between the spines that receive converging inputs to generate specific learning mechanisms (Vadakkan, 2013, 2016). Since the gold standard proof for understanding the mechanism is replication in engineered systems, it is necessary to first undertake all the possible effort to verify the mechanism theoretically.

First, the derived mechanism was examined for its ability to operate in agreement with the constraints offered by a large number of findings from different levels of the system. These approaches led to the derivation of the formation of inter-postsynaptic functional LINKs (IPLs) between spines of different neurons where associatively learned stimuli converge. This mechanism was also found to have all the necessary background conditions for the generation of first-person internal sensations (Vadakkan, 2013, 2016) **(Fig.1)** that can be viewed as hallucinations (internal sensation of a stimulus in its absence) expected of a mechanism for memory in biological systems (Minsky, 1980). Since the internal sensation of memory has to conform to the sensory features of the item whose memory is getting retrieved, the mechanism is expected to have optimized during evolution. It was possible to explain how learning-induced changes can be artificially generated at specific locations where pathways that carry stimuli convergence to produce an electrophysiological finding called long-term potentiation (LTP) that has shown several correlations with learning (Vadakkan, 2019a). It is possible to view reversal of LTP (LTP decay) as the reversal of IPLs formed during learning, which can be responsible for physiological forgetting.

2 What information can electrophysiological findings provide?

LTP can be induced at the locations of converging excitatory inputs. The ability to induce LTP at a location indicates that there is a propensity for the abutted spines of different neurons to form IPLs, and that at physiological conditions this is likely an area where associative learning between two sensory inputs takes place (Vadakkan, 2019b). Since dopamine has a role in motivation-related associative learning (Wise, 2004), and since dopamine cause spine enlargement (Yagishita et al., 2014), a release of dopamine is expected to favor IPL formation and augment learning when associated with motivation. Even though most IPLs formed at physiological time-scales of milliseconds during learning reverse back quickly, some of them are made to progress to stages that can be stabilized for long-periods by membrane reorganization during exocytosis of vesicles containing AMPA receptor subunits (Vadakkan, 2018). For the duration of time that the IPL exists, arrival of one of the stimuli will induce units of first-person internal sensation of memory of the associatively learned item.

Based on the relationship between memory and LTP, specific electrophysiological findings at the locations responsible for different brain functions can be used to infer conformation of semblances generated at those locations. The present work has examined different circuit connections and electrophysiological findings at the locations of different higher brain functions to synthesize a common governing principle. By keeping the correlation between the internal sensation of memory and sensory features of the item whose memory is retrieved and that of LTP at a specific location

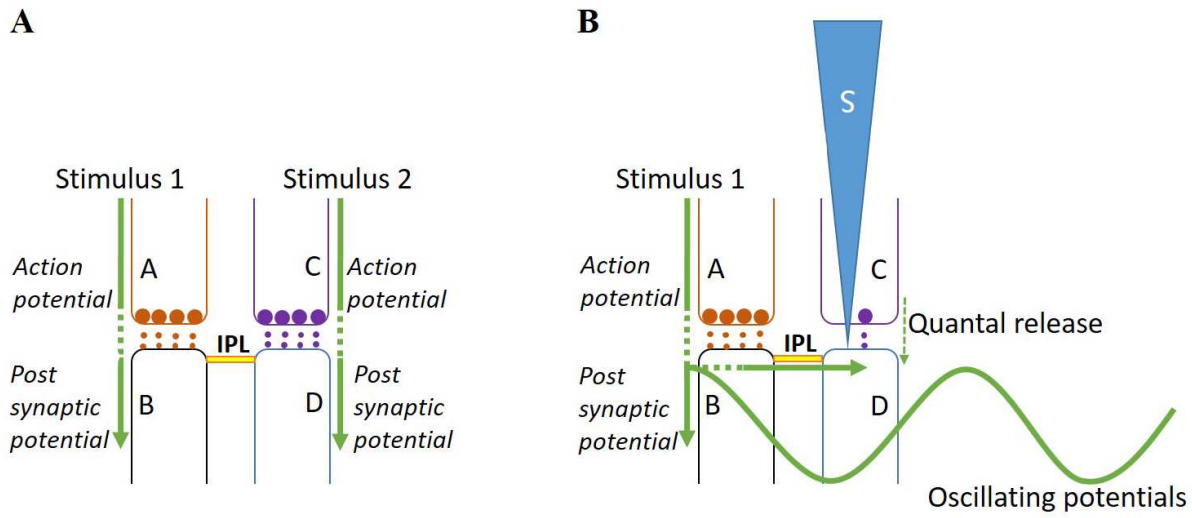

Figure 1: Changes that can induce units of internal sensations. **A**. During associative learning of stimulus 1 and 2, an IPL between postsynaptic terminals B and D of their synapses A-B and C-D is generated. IPL B-D is retained for different durations. Spines heads of B and D are continuously depolarized by quantally released neurotransmitter molecules from their presynaptic terminals A and C respectively and are depolarized intermittently by the arrival of action potentials at their presynaptic terminals. This background condition is a necessary condition for inducing units of internal sensations. **B**. During memory retrieval, arrival of stimulus 1 reactivates IPL B-D and depolarizes postsynaptic terminal D. In the above mentioned background state, any incidental lateral activation of postsynaptic terminal D sparks a cellular hallucination of a sensory stimulus arriving from the environment through its presynaptic terminal C. This matches the expectation of a mechanism for memory (Minsky, 1980). The transmission of potentials through synapse A-B and IPL B-D provides vector components of the oscillating extracellular potentials. Maintenance of a narrow range of its frequency is a necessary condition for inducing internal sensation of memory (Modified from Vadakkan, 2012, 2016).

as a reference, it is expected to understand the nature of conformations of internal sensations of a large number of higher brain functions. For this purpose, electrophysiological findings from studies of pleasure and reward are examined.

3 Nucleus accumbens connections

Medium spiny neurons (MSNs) constitute 95% of the cells in the NAc. Their spines receive excitatory inputs from medial prefrontal cortex (mPFC), hippocampus, amygdala, and thalamus, dopaminergic inputs from VTA and inputs from inhibitory interneurons **(Fig.2)**. Even though there were a large number of studies examining addiction and changes at single synapses on the spines of NAc (Nestler, 2005, Lüscher and Malenka, 2011, Pignatelli and Bonci, 2015), a cellular mechanism that can induce internal sensation of pleasure is lacking. Since first-person internal sensations of pleasure is an evolutionarily well-conserved operational mechanism, it is reasonable to expect the presence of robust structural features that has the ability to generate internal sensation of pleasure in this brain region.

Experiments have shown an intense relationship between glutamate and dopamine in the NAc

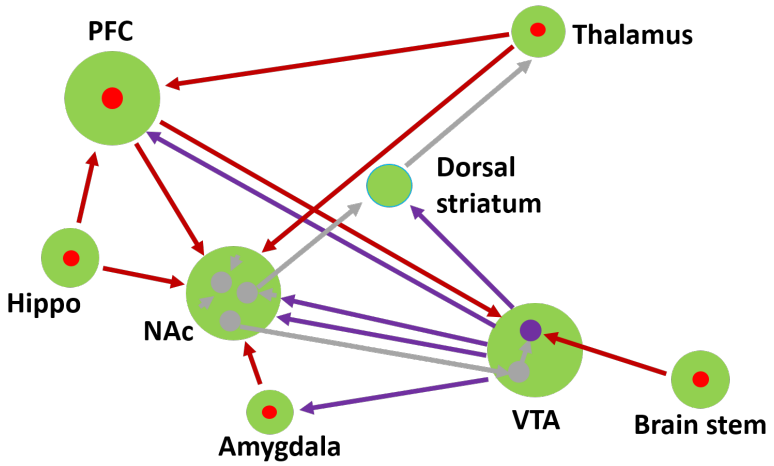

Figure 2: Input and output connections of NAc. Spines of MSNs in the NAc receive excitatory inputs (red arrows) from several regions. They receive dopaminergic inputs (violet arrow) from VTA. MSN spines also synapse with different types of inhibitory interneurons (small gray arrows). Large green circles: Different brain regions. Small circles: Predominant cell types (Red: excitatory; Gray: inhibitory; Violet: dopaminergic).

shell area (Stuber et al., 2010). Dopaminergic inputs from the ventral tegmental area (VTA) synapses with the necks or heads of spines that form synapses with excitatory inputs (Sesack et al., 2003). When rewards or conditioned stimuli that predict reward are presented, dopamine neurons in the VTA increase their firing (Schultz, 1998; Roitman et al., 2004) releasing dopamine in their synapses with the spines of NAc neurons. Drugs of abuse such as cocaine increase dopamine levels in the NAc (Luscher and Malenka, 2011).

4 Key findings in NAc that need an interconnected explanation

The major requirement for the operational principle of pleasure is to provide inter-connectable explanations for the findings at NAc. In this regard, the following findings at NAc provide an opportunity to verify the operational mechanism derived by semblance hypothesis.

1) A mechanism that generates the internal sensation of pleasure.

2) Exposure to cocaine leads to the attenuation of postsynaptic potentials. Furthermore, dopamine attenuates postsynaptic potentials elicited by stimulation of different excitatory inputs to the NAc shell region (Pennartz et al., 1992a), b). Dopaminergic input synapse with either the neck of the head region of the spines that synapse with excitatory inputs. Dopamine is known to cause spine enlargement (Yagishita et al., 2014). In this context, the question is, "How can dopamine attenuate the postsynaptic potentials?"

3) Electrophysiological recordings have shown that dopamine reduces the excitability in NAc neurons *in vitro* (O'Donnell and Grace, 1996). In response to natural rewards and cocaine exposure, a set of MSNs show depression of firing rate in a major set of NAc shell MSNs (Carelli, 2002; Ishikawa et al., 2009; Kourrich and Thomas, 2009; Mu et al., 2010). This finding has led to the proposal that reward is encoded by the reduced activity of MSNs in NAc (Carlezon and Wise, 1996; Roitman et al., 2005; Taha and Fields, 2006; Carlezon and Thomas, 2009). Where will this

finding fit in the mechanistic explanation of pleasure?

4) The electrophysiological finding of long-term depression (LTD) is the result of depression of the net excitatory postsynaptic potentials (EPSPs) arriving at the recording electrode to move below the baseline. It is an active process and is not a mere reversal of a mechanism responsible for LTP. LTD is observed at the spinous region of the MSNs of NAc (Brebner et al., 2005; Lüscher and Malenka, 2011).

5) Repetitive depolarization of VTA neurons induce LTD that occludes with the synaptically-evoked (from cortical afferents) LTD (Jones et al., 2000). This indicates that both these mechanisms share a common final path. Therefore, it is necessary to find a mechanism caused by the stimulation of either the cortical afferents or VTA afferents to the MSNs in the NAc that can induce NMDAR-dependent postsynaptic change that leads to LTD.

In this context, the question is "Can all the above findings be explained by a single mechanism in terms of the formation of IPLs?

5 Internal sensation of pleasure and its relationship with LTD in NAc

The ability to induce LTD at the synaptic region receiving inputs from both excitatory and dopaminergic inputs (to the spines on the excitatory synapses) along with inputs from inhibitory interneurons is expected to be related with the generation of pleasure. Since dopamine is known to cause enlargement of the spines of the excitatory synapses of the target region (Yagishita et al., 2014), it is necessary to find an explanation that satisfies all the above findings that also explain a mechanism for the generation of internal sensation of pleasure. By keeping the correlation between associative learning and LTP and the ability of the inter-LINKed spines to induce internal sensation of memory as a reference mechanism, an examination was carried out to arrive at a single mechanism that can explain all the above findings.

MSNs in the NAc receive inputs from excitatory, inhibitory and dopaminergic inputs. Since dopamine is released in the presence of substances of abuse, it is reasonable to expect enlargement of spines of MSNs that receive excitatory inputs. It is possible to deduce that internal sensation of pleasure is related to some form of semblance getting induced at this location where LTD can be demonstrated. At this point one can ask the question, "What type of an alteration in the semblances that can be anticipated from the unique configuration of inputs at the NAc and can give rise to the internal sensation of pleasure along with all the other findings?" Since LTD is an artificially-induced change, a similar change occurring at physiological time-scales is expected to occur in physiological conditions to induce the internal sensation of pleasure. The finding that LTD induced by low-frequency stimulation require activation of NMDARs (Dudek and Bear, 1992, Mulkey and Malenka, 1992) matches with the changes that can lead to IPL formation.

It is thought that inhibitory inputs have a role at the input level where information processing occur (Hangya et al., 2014). In this context, the following provide a feasible explanation. Dendritic tree arbors of different MSNs overlap. Dopamine causes expansion of spines at the excitatory MSN synapses, which will force the latter to form IPLs with the spines of neighboring inhibitory synapses that belong to different MSNs. The observations that some types of learning are associated with the ability to induce LTD suggest that LTD induction is associated with IPL formation and that LTD is not a mere reversal of LTP. IPL formation between excitatory and inhibitory spines will lead to the spread of hyperpolarization from the inhibitory spines to neutralize and even hyperpolarize the excitatory spines **(Fig.3)**. If excitatory postsynaptic spines are not depolarized when glutamate

is released from their presynaptic boutons, it will not relieve the Mg^{2+} block of NMDARs (N-methyl-D-aspartate receptors) (Lüscher and Malenka, 2012). The net effect will be depression of the sum of potentials arriving at the recording electrode, resulting in the observed LTD. It can explain attenuation of postsynaptic potentials when exposed to dopamine. This can also explain why both natural rewards and cocaine exposure lead to reduced firing of MSNs. Most importantly, generation of internal sensations at the inter-LINKed spines that receive excitatory and inhibitory inputs provides a unique solution. Only the configuration shown in Figure 3C can explain all the above features.

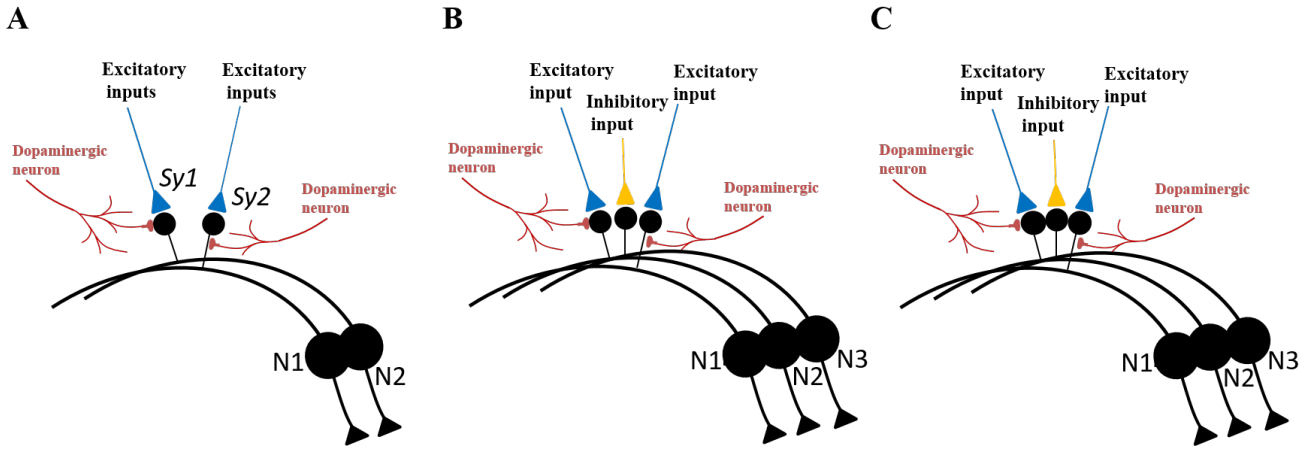

Figure 3: Interaction between the spines of MSNs of NAc that synapse with excitatory and inhibitory inputs. **A**. Excitatory inputs (in blue) synapse with (Sy1 and Sy2) spines (small black circles) of two different MSNs N1 and N2 (large black circles). Note that dopaminergic inputs reach either the spine head or spine neck of these spines. **B**. Inhibitory input (in yellow) to a spine of a third MSN N3, which is located between the spines that synapse with excitatory inputs shown in figure A. Note that all the spines are separated from each other by ECM preventing any spread of depolarization between them. **C**. Natural stimulants or cocaine abuse result in the release of dopamine that will enlarge the spines that synapse with the excitatory inputs, which lead to the formation of IPLs between the spines. Since the spine that synapse with the inhibitory input is spatially interposed between the expanding spines, inter-spine LINKs are formed between these spines. The spread of hyperpolarization to the inter-LINKed spines that receive excitatory inputs leads to the formation of a special semblance of pleasure. It can also explain attenuation of postsynaptic potentials and reduced firing of MSNs.

The occlusion of LTD induced by repetitive depolarization of VTA neurons with the synaptically-evoked (from cortical afferents) LTD (Jones et al., 2000) provides a unique opportunity to verify the structural features of the operating mechanism in the NAc. A minimum requirement for occlusion of LTD generated by stimulation through different routes is that these two pathways should converge to a single mechanism and that stimulation of either pathway can lead to the generation of same LTD. Repetitive depolarization of VTA stimulates dopamine release that will lead to the enlargement of the spines of MSNs to which excitatory inputs synapse. This can lead to IPL formation between enlarging spines of MSNs that receive excitatory inputs. Repetitive stimulation of cortical afferents also leads to expansion of spines to which they synapse, which will lead to the IPL formation between those spines. This explains the occlusion.

Since there are different types of inhibitory inputs that synapse with the spines of MSNs (Russo and Nestler, 2013), these spines located in between the expanding spines that synapse with ex-

citatory cortical afferents will lead to the IPL formation between them. Since the inputs to the MSNs are arriving from different locations, the configuration in **Figure 3C** provides the unique solution to explain all the findings. Depolarization of inter-LINKed spine inducing semblances is used as a reference mechanism. In this context, hyperpolarization at the inter-LINKed spines is expected to evoke a semblance with a conformation towards the opposite side, which can be called inverse semblance. Since the semblance for pleasure does not have any three-dimensional features similar to that of the internal sensation of memory, it can be speculated that they have one dimension less **(Fig.4)**. The current assumption is that inhibition of NAc MSNs is responsible for encoding reward (Carlezon and Wise, 1996; Roitman et al., 2005; Taha and Fields, 2006; Carlezon and Thomas, 2009). Formation of IPLs between the spines of MSNs that receive excitatory and inhibitory inputs and the induction of the internal sensation of pleasure provides suitable explanations that match with the above assumption.

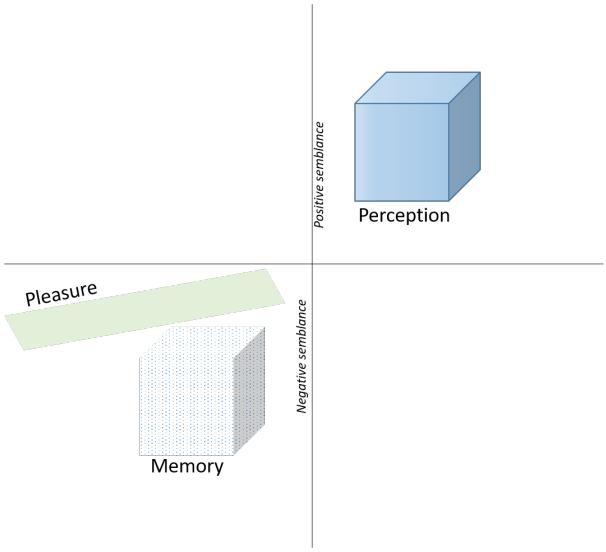

Figure 4: Graphical representation of semblances. Even though semblances themselves are virtual in nature, here internal sensation of perception is taken as a positive semblance for the purpose of comparison. In contrast, semblance of memory is plotted in the negative space. Cocaine cause dopamine release, enlargement of spins that synapse with excitatory inputs and form inter-LINKs between them. They also inter-LINK with spines that synapse with inhibitory inputs. Spread of hyperpolarization from the postsynaptic terminals of inhibitory synapses can neutralize and even hyperpolarize the membranes across all the spines within an islet of inter-LINKed spines from their baseline. When the spines of excitatory synapses get hyperpolarized, it can lead to the induction of inverse semblance responsible for the induction of pleasure. Since internal sensation of pleasure does not any three-dimensional features, its semblance is drawn in two dimensions. Future studies are expected to show a spectrum of conformations of semblances that form internal sensations associated with different brain functions.

6 Homeostatic changes during drug abuse and withdrawal

During a very lengthy drug-free period, a robust potentiation of AMPAR-mediated synaptic transmission was found at the synapses on the spines of NAc MSNs. A single exposure to cocaine at this time abruptly reverses the synaptic potentiation to depression (Kourrich et al., 2007). This can

be explained in terms of formation of IPLs between spines that receive excitatory and inhibitory inputs. After administering cocaine for 5 days and followed by 10–14 days of withdrawal, a single challenge dose of cocaine decreases AMPAR/NMDAR ratio at the same synapses (Thomas et al., 2001). Similarly, after weeks of cocaine withdrawal, a challenge dose that terminates withdrawal leads to endocytosis of AMPARs (Lüscher and Malenka, 2011).

Based on the IPL mechanism, exposure to cocaine leads to enlargement of spines, which predispose the spines to IPL fusion. In this context, endocytosis of vesicles containing AMPARs is a natural mechanism to prevent IPL fusion and it gets upregulated once animals are exposed to cocaine. During vesicle endocytosis, removal of membranes as vesicles from the lateral spine head region has the capability to reduce the size of spine head and prevents IPL formation. At locations where direct release of dopamine result in spine enlargement and generate internal sensations of pleasure, robust mechanisms are expected to have evolved to prevent any IPL fusion. Therefore, endocytosis of vesicles is an expected immediate consequence of dopamine release. Hence, endocytosis of vesicles containing AMPAR subunits observed during LTD induction (Brebner et al., 2005; Parkinson and Hanley, 2018; Diering and Huganir, 2018) can be viewed as a concurrently occurring homeostatic mechanism for preventing IPL fusion at locations of dopamine release.

How is it possible to explain the finding that expression of LTD does require endocytosis of postsynaptic AMPARs (Brebner et al., 2005)? It is necessary to note two things. First, LTD is an experimental finding that scales-up the natural changes occurring in the NAc. Secondly, following stimulation, it takes several minutes for LTD induction (see Brebner et al., 2005). From the previous paragraph, vesicle endocytosis is expected to take place immediately as the dopamine starts enlargement of the spines. When vesicle endocytosis is prevented during LTD stimulation, it can lead to expansion of the MSN spines that synapse with excitatory inputs **(Fig.3A)**. A fusion between two spine heads will lead to significant reduction in their total diameter (Note that when fusion between two perfect spheres of diameter 1 unit each into a single sphere occur, the diameter increases to only nearly 1.26 units instead of 2 units). This will significantly reduce the ability of these newly fused spines (that synapse with excitatory inputs) to form inter-LINKs with that of the spines that synapse with inhibitory inputs and will prevent LTD induction **(Fig.3C)**. Since normal LTD induction takes several minutes to manifest, all the above changes that will occur within this time-scale following endocytosis are blocked and prevent LTD induction.

The prolonged cocaine administration is expected to result in continuous endocytosis of vesicles to reduce the spine head size to prevent any inter-spine fusion. Due to this reason and based on the explanation provided by the present work that LTD induction requires formation of IPLs between the spines that receive inputs from both excitatory and inhibitory inputs, factors that prevent IPL formation are expected to prevent LTD induction. This can explain why prolonged cocaine self-administration result in the inability to elicit LTD at the input region of NAc MSNs (Martin et al., 2006). During the withdrawal period, there will be a gradual reversal of the above process causing a gradual increase in the AMPARs at the membrane surface (Boudreau and Wolf, 2005; Boudreau et al., 2007).

6.1 IPL fusion is a possible consequence of drug abuse

Even though robust homeostatic mechanisms are expected to occur, one can also expect certain changes that can break these regulatory mechanisms. In one study, "addicted" animals showed persistent impaired LTD and "non-addicted" animals regained the ability to generate LTD following two weeks after stopping cocaine self-administration (Kasanetz et al., 2010). Based on the present work, one probable reason for the impairment of LTD is that IPLs may have progressed

to one extreme end of the spectrum of IPL changes (Vadakkan, 2016) to cause IPL fusion that will result in the eventual loss of spines of MSNs during cocaine abuse as evidenced from previous reports (Spiga et al., 2014a, Spiga et al., 2014b).

6.2 Oscillations between VTA inhibitory neurons provide continuity of pleasure

Inhibitory neurons are known to have electrical gap junction between them that leads to the generation of oscillations between their firing in the VTA. These oscillations of potentials will be present at the outputs of these neurons at the synapses with the neurons of the next neuronal order. This can explain oscillations of potentials between the neurons in the NAc (O'Donnell and Grace, 1993). This can generate continuous electrical variations on the postsynaptic membranes of the inter-LINKed spines between the MSNs and result in continuous induction of internal sensation of pleasure when the substance of abuse is present within the system.

6.3 Lateral habenula and reward

Since the internal sensation of reward is closely related to that of pleasure, lateral habenula (LHb) is examined for the possible conformations of semblances for reward. Spines of LHb neurons synapse with inputs from excitatory, inhibitory and dopaminergic inputs (Meye et al., 2013). Studies of LHb have found that dopamine neurons are excited and inhibited by reward-predicting and non-reward-predicting targets, respectively; whereas many LHb neurons are excited by no-reward-predicting targets and inhibited by reward-predicting targets (Matsumoto and Hikosaka, 2007). In addition to rewarding, it was found that hyperactivity of the LHb neurons is associated with depression when GABA input is reduced (Shabel et al., 2014). In summary, the general circuit features and the electrophysiological findings in LHb are similar to that are seen in the NAc. This circuitry also suggests that spines that receive inhibitory input from inter-LINKs with spines that receive excitatory inputs within the islets of inter-LINKed spines and generate emotional aspect of reward.

7 Emerging principle

It was possible to view semblances at the inter-LINKed spines as internal sensations of memory (Vadakkan, 2013). It was also possible to view the simultaneous induction of semblances from both the inter-LINKed spines at the arrival of stimuli from an object as perception (Vadakkan, 2016). By plotting the semblances for memory as a reference mechanism, it is expected that any alteration from this general framework can allow different conformations for the internal sensations associated with different higher brain functions. Furthermore, the correlation between LTP and memory can also be used as a reference, electrophysiological findings at the synaptic regions responsible for different higher brain functions where different types of inputs converge can be used to understand the relative conformation of semblances for internal sensations associated with them. Summary of findings from NAc and LHb shows that inhibitory inputs into the excitatory input regions have led to the formation of IPLs between spines that receive different types of inputs generates pleasure and reward. It is also important to examine the role of cholinergic interneurons synapsing with the spines of MSNs in NAc for their participation in IPL formation.

Since pleasure is induced only for the duration of the presence of items or actions that induce pleasure, the formed IPLs tend to reverse back quickly once the pleasure-inducing stimulus stops. This is likely due to a homeostatic mechanism that prevents inter-spine fusion occurring due to spine expansion by dopamine. It is reasonable to expect the presence of multiple mechanisms to make sure the robustness of this action. In this context, membrane reorganization at the lateral aspect of the spines by endocytosis of AMPAR containing vesicles (Dong et al., 2015) that can reverse IPLs (Vadakkan, 2016) can act as a secondary mechanism. It is reasonable to expect that the latter is an evolved mechanism that gets triggered along with dopamine's action to prevent inter-spine fusion.

Even though, it was not yet possible to understand the sequence of appearance of neurotransmitters glutamate and GABA during evolution (Gou et al., 2012; Liebeskind et al., 2017), a feasible sequence may be as follows. As the excitatory neurons started receiving a large number of inputs, it was necessary to control the neuronal firing to regulate their output. This was achieved by the eventual selection of inhibitory neurons whose activity controlled the excitatory neuronal outputs. Glutamate is the major excitatory neurotransmitter. Glutamic acid decarboxylase (GAD) is an enzyme that catalyzes the decarboxylation of glutamate to form the inhibitory neurotransmitter GABA. It is known that the excitatory outputs are regulated using inhibitory neuronal activity at the input level (Palmer et al., 2012) and that GABAergic interneurons were present in the common ancestor of all amniotes (Tosches et al., 2018).

Cortex of the nervous system are under the effect of an inhibitory blanket (Karnani et al., 2014; Lovett-Barron et al., 2014). Detailed examinations have shown that in addition to inhibition at the output level (Karnani et al., 2014), inhibition also takes place at the dendritic (input) level (Lovett-Barron et al., 2014). Based on the IPL mechanism, continued associative learning led to the formation of islets of inter-LINKed spines between the spines of excitatory neurons. Moreover, enlargement of these spines by dopamine facilitated rapid IPL formation on occasions where such rapid changes are necessary. High density of spines of overlapping dendritic arbors, together with the thin ECM space between them has led to inter-LINKing of islets of inter-LINKed spines (that synapse with excitatory inputs) with that of the inhibitory inputs. With this, semblances started generating different modifications of internal sensations. Since the derived operational mechanism for pleasure is associated with LTD and since LTD occur secondary to IPL mechanism, it is possible that certain associations are pleasure-inducing and internal sensation of pleasure may have evolved as a survival strategy.

8 Discussion

Until now the explanations for the mechanism for generating pleasure was limited to its description as a brain function encoded by reduced activity of MSNs in NAc. It was not yet possible to explain how the observation of LTD at the synaptic regions associated with different emotions. Understanding its relationships with the generation of those emotions, the present work has provided a suitable explanation. The present work has provided a mechanistic explanation for the generation of internal sensation of pleasure that can interconnect with all the electrophysiological findings in the NAc. The findings made in the present work underscore the necessity to understand the location at which semblances responsible for a specific internal sensation is generated and how it is related to the firing of input and output neurons. Detailed diagrams of the distribution of IPL circuitry within the synaptically-connected nervous system is essential for understanding various related internal sensations and heterogeneous electrophysiological findings reported (Pennartz et

al., 1992,1993; Carelli, 2002) along with the above finding.

Based on the results of this work, LTD induction at a particular brain region will depend on the locations of stimulating and recording electrodes, stimulation parameters and the use of GABA inhibitors. It is necessary to highlight that such correlations require spatial co-ordinates of the tips of the stimulating and recording electrodes in relation to the afferent paths to accurately interpret the results. The electrophysiological properties at the regions of inter-LINKed spines provide some clues regarding the ratio of excitatory and inhibitory inputs to the spines of neurons at a particular region. An emerging general finding is that the nervous systems started developing emotions associated with different higher brain functions during its interactions with the environment and these internal sensations have shaped the evolution of the nervous system. For example, emotions have played a role in maintaining social life of humans.

The fact that LTP induction in most cortical regions often requires concomitant reduction of gamma-amino butyric acid (GABA) inhibition by low doses of the GABA-A antagonist bicuculline (Artola and Singer, 1987) or picrotoxin indicates that normally a small percentage of spines synapse with inhibitory inputs. It is necessary to verify whether the spines that synapse with these inhibitory inputs form IPLs within the large islets of inter-LINKed spines in physiological conditions. Since the conformation of semblances induced at the inter-LINKed spines determines the conformation of internal sensations induced at different locations, it is necessary to consider the effect of different types of inputs that synapse with the spines of neurons that can be part of the islets of inter-LINKed spines to make accurate conclusions. For example, the spines of the neurons in LHb receive input (serotonin is the neurotransmitter) from raphe nucleus, in addition to excitatory, inhibitory and dopaminergic inputs (Meye et al., 2013). It is necessary to understand what changes serotonin makes in the membrane potentials to estimate the nature of changes in semblances at that location.

The present work has examined a region of the nervous system where there are distinct pathways that can be stimulated and has specific findings in relation to a brain function. Pleasure is only a tip of the iceberg of internal sensations that are generated within the nervous system. Once we identify methods to graphically plot the conformation of semblances and understand the principle of their integration, it is expected that internal sensation of several brain functions will become clear. IPLs formed between the spines that receive excitatory and inhibitory inputs are expected to generate internal sensations that form the affective component associated with different higher brain functions. Variations in the number of spines that synapse with excitatory, GABAergic and several other types of inputs are expected modify depolarization of inter-LINKed spines in different ways and contribute to the generation of a spectrum of internal sensations associated with different brain functions.

LIST OF ABBREVIATIONS: AMPAR: Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor, EPSP: Excitatory postsynaptic potential, GABA: Gamma-amino butyric acid, IPL: Inter-postsynaptic (inter-spine) LINK, LHb: Lateral habenula, LINK: Inter-postsynaptic functional link, LTD: Long-term depression, LTP: Long-term potentiation, mPFC: Medial prefrontal cortex, MSN: Medium spiny neuron, NAc: Nucleus accumbens, NMDAR: N-methyl-d-aspartic acid receptor, Spine: Dendritic spine or postsynaptic terminal, VTA: Ventral tegmental area.

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

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