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Framework for internal sensation of pleasure using constraints from disparate findings in nucleus accumbens

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Abstract

It is necessary to find a mechanism that generates first-person inner sensation of pleasure to understand what causes addiction and associated behaviour by drugs of abuse. The actual mechanism is expected to explain several disparate findings in nucleus accumbens (NAc), a brain region associated with pleasure, in an interconnected manner. Previously, it was possible to derive a mechanism for natural learning and explain: (1) Generation of inner sensation of memory using changes generated by learning; and (2) Long-term potentiation as an experimental delayed scaled-up change by the same mechanism that occur during natural learning. By extending these findings and by using disparate third person observations in NAc from several studies, present work provides a framework of a mechanism that generates internal sensation of pleasure that can provide interconnected explanations for: (1) Ability to induce robust long-term depression (LTD) in NAc from naïve animals; (2) Impaired ability to induce LTD in "addicted" state; (3) Attenuation of postsynaptic potentials by cocaine; and (4) Reduced firing of medium spiny neurons in response to cocaine or dopamine. Findings made by this work are testable.

Key Words: Pleasure; Internal sensation; Mind; Memory; Long-term potentiation; Long-term depression; Nucleus accumbens; Drug addiction

Core Tip: Pleasure has been studied by examining animal behaviour and its correlations with molecular and electrophysiological changes. Drugs of abuse generate pleasure along with several seemingly unrelated changes in nucleus accumbens (NAc). When pleasure was examined as a first-person inner sensation, it was possible to arrive at a framework of a causal mechanism for its generation that can also provide inter-

connected mechanistic explanations for long-term depression (LTD) in NAc in naïve animals, impaired ability to induce LTD in addicted state, attenuation of postsynaptic potentials by both cocaine and dopamine, and reduced firing of medium spiny neurons in NAc by dopamine. Findings made by this work are testable.

INTRODUCTION

Around 269 million people used drugs of abuse in 2018 and nearly 35.6 million people suffer from drug use disorders globally[1]. Since drugs provide internal sensation of pleasure to which users can get addicted, it is necessary to understand the basic mechanism that generates pleasure and possible ways this leads to addiction. Current studies of brain functions such as perception, memory, fear, anxiety, pleasure, hunger, thirst, reward, aversion, and pain are carried out in animal models by examining behavioural motor actions indicative of those brain functions. During these examinations, there is an implicit assumption that nervous system generates internal sensations of each of those brain functions concurrently with behaviour. Studies have found correlations between behavioural motor actions and sets of neurons that fire and/or their firing rates in brain regions that have a predominant role in those brain functions. In addition, correlations are also found between behaviour and electrophysiological findings in those brain regions. To understand how the brain operates to generate inner sensations of each of the above brain functions, an interconnected framework of explanations is necessary. Even though it is not possible to directly test formation of first-person properties of inner sensations of a brain function, a first step will be to derive plausible mechanisms for their generation using constraints from several disparate findings associated with each brain function.

Learning is expected to generate testable changes that are used for generating first-person inner sensations of memory. By examining fine details of neuronal processes and their properties, it was possible to arrive at a learning mechanism from which inner sensations of memory can be retrieved[2,3]. A summary of the basis of derivation is as follows. Examination of a neuron having thousands of input terminals shows that subsets of nearly 140 input signals can fire that neuron[4,5]. Since input signals attenuate as they propagate towards neuronal soma, it is possible that even a small fraction of one input can fire a neuron, which is being held at a sub-threshold activation state short of that input fraction[6,7]. Associative learning between two stimuli (stimulus 1 and 2) is expected to take place at a location where signals from these stimuli converge. This led to searching for a specific location where learning can generate a specific physical change in millisecond timescales that can be retained for different durations and then enable a cue stimulus (either stimulus 1 or 2 or their components) to generate inner sensation of memory of the second stimulus to explain working, short-term and long-term memories[3].

Input terminals of a neuron are the dendritic spines (spines or postsynaptic terminals) that synapse with output terminals of many neurons in the previous neuronal order. Mean inter-spine distance between spines on the dendrite of a pyramidal neuron is more than the mean spine head diameter[8]. Hence, spines that are abutted to each other most likely belong to different dendrites. Electron microscopic views of cerebral cortex show abutted neuronal processes (including spines) with very minimal extracellular matrix (ECM) space between them. To satisfy requirements of classical conditioning paradigm, interactions between spines that belong to different neurons are necessary[3,9]. This led to the derivation of inter-postsynaptic (inter-spine) functional LINKs (IPLs) between spine heads that belong to different neurons as a general structural change taking place within milliseconds during learning. At a later time when one of the cue stimuli reactivates an IPL, it can depolarize the "inter-LINKed" second spine from a lateral direction. Head region of this inter-LINKed spine gets strongly depolarized during the intermittent arrival of action potentials at its presynaptic terminal when signals from a sensory stimulus

arriving from the environment reach that presynaptic terminal. Head regions of all the spines including the inter-LINKed spines are continuously getting depolarized by the quantal release of neurotransmitter molecules from their corresponding presynaptic terminals, even during sleep. These impart a dominant state that depolarization of a spine results from its presynaptic terminal. Such dominant states of spines of neurons from different neuronal orders can provide a dominant system state that activation of a spine occurs from a stimulus arriving from the environment and that activation of a specific set of spines occurs from arrival of a specific stimulus. In this context, a theoretical possibility is that any instantaneous depolarization of a spine from a lateral direction through an IPL can generate a hallucination (internal sensation of a stimulus in its absence) at the inter-LINKed spine about specific sensory features of the associatively learned second stimulus as a system property[3,9] (Figure 1). This is anticipated of a mechanism that generates memory in the nervous system[10]. This hypothesis called semblance hypothesis is found to agree with the constraints offered by a large number of findings from multiple levels of the system[9].

Ability to induce long-term potentiation (LTP) at a location can be regarded as resulting from the formation of IPLs between abutted spines of different neurons at that location that receive converging excitatory inputs[11]. Since (1) Membrane segments from intracytoplasmic vesicles that carry α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) subunits can re-organize the cell membrane of lateral spine head region; (2) GluR1 AMPAR subunits are located up to 25 nm beyond the synaptic margin[12], an ideal location for inter-spine interactions; and (3) Endocytosis of GluR1 AMPAR vesicles that uses fragments of membranes from lateral spine head regions is associated with a reversal of LTP (LTP decay)[13] that can be scaled-down to explain the reversal of formed IPLs as a mechanism for physiological forgetting, IPL formation can be viewed as a suitable change triggered by learning[9]. Since (1) Dopamine has a role in motivation-related associative learning [14]; (2) Dopamine lead to the persistence of one-trial hippocampus-dependent memory[15]; and (3) Dopamine cause spine enlargement[16], release of dopamine is expected to augment inter-spine interactions leading to IPL formation and facilitate learning in a motivated state[9].

Application of energy of a different configuration than that is necessary to induce LTP generates long-term depression (LTD) in specific brain regions. An example of such a location is nucleus accumbens (NAc), a brain region associated with generation of pleasure. Cellular changes following LTD stimulation lead to depression of net excitatory postsynaptic potentials recorded from the recording electrode. Since energy is required for stimulation, LTD is an active process and not mere reversal of a mechanism responsible for the decay of LTP[13]. Since experimental results show that it takes several minutes for LTD induction[17,18], it indicates that LTD induction involves time-dependent cellular changes similar to that of LTP induction[11]. Hence, it is necessary to explain time-dependent changes occurring at specific locations where LTD can be induced. Similar to LTP, LTD in the hippocampal synaptic areas is implicated in different types of learning[19-22]. Necessity for stimulation energy and significant delay for induction of LTD following stimulation indicate that several IPLs are formed during LTD induction, similar to that occur during LTP induction[11]. To understand the mechanism that generates internal sensation of pleasure, it is necessary to (1) Examine the neuronal connections to NAc; (2) Examine conditions that allow experimental induction of LTD at this brain region; and (3) Use constraints from all the findings at this region to derive a mechanism for internal sensation of pleasure that can be inter-connected with the remaining findings.

NAc CONNECTIONS

Studies have shown that NAc is primary site mediating reward behaviour and is associated with both reinforcing and addictive behaviours in response to drug use. 95% of cells in the NAc are medium spiny neurons (MSNs). MSNs are called "spiny" due to the abundance of spines on their dendrites. However, visual examination of patterns of distribution of spines on these MSNs[23,24] shows that mean inter-spine distance is comparable to that of the mean spine diameter, which almost matches with the finding in pyramidal neurons that mean inter-spine distance is more than the mean spine diameter[8]. Electron microscopic images of NAc show negligible ECM between cellular processes in many locations[25,26]. Hence, it is possible to infer that the nearest spine to one spine on the dendrite of an MSN is a spine on a different dendrite, which most likely belongs to a different neuron or occasionally to the same neuron.
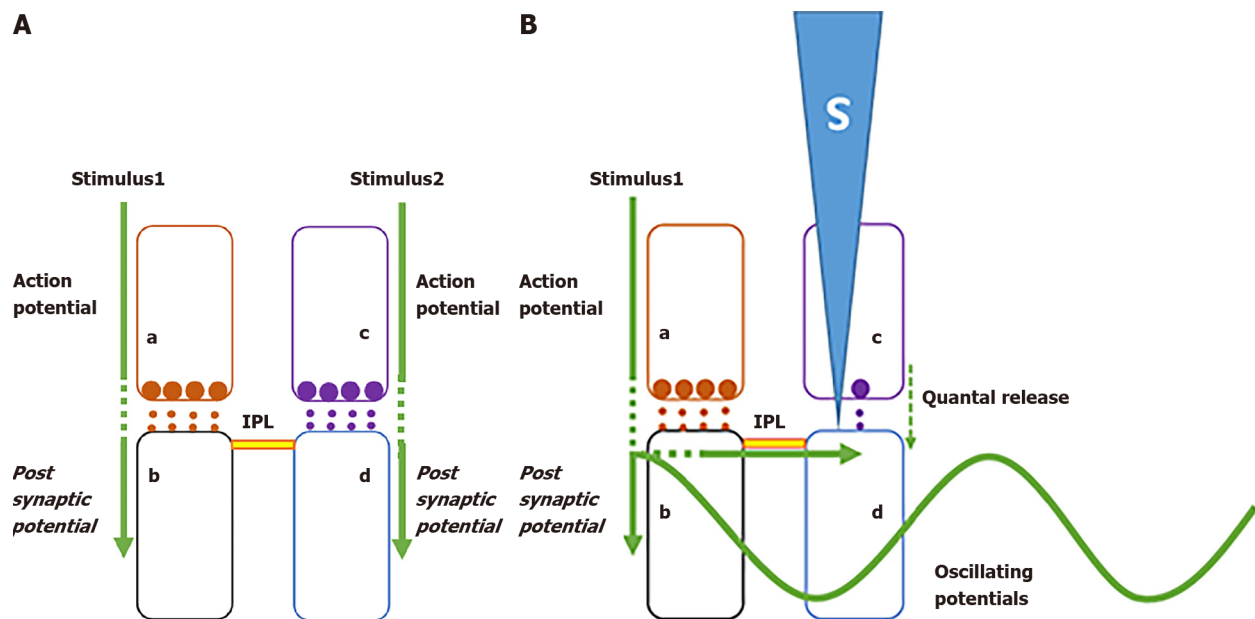
Figure 1 Generation of internal sensation of memory which is used as a reference mechanism to examine internal sensation of pleasure.
A: During associative learning between stimulus 1 and 2, signals from these stimuli propagate towards converging locations where inter-postsynaptic functional LINKs (IPLs) between postsynaptic terminals (spines) b and d occur. Spines b and d are depolarized intermittently when action potentials arrive at their presynaptic terminals a and c respectively, and the head regions of these spines are continuously being depolarized by quantally-released neurotransmitter molecules from their presynaptic terminals. These provide a dominant state that a spine is depolarized by its presynaptic terminal that in turn receive signals from stimuli from the environment and is a necessary background condition for generating internal sensation of memory; B: In the above mentioned background state, arrival of stimulus 1 reactivates IPL b-d to cause an incidental lateral activation of postsynaptic terminal d to spark a cellular hallucination (shown using a blue triangle marked S inside) of a sensory stimulus arriving from the environment through its presynaptic terminal c. Details of the method by which sensory qualia of semblions can be determined was described previously[3]. This matches with the expectation of a mechanism for memory[10]. Waveform: Synaptic transmission through synapse a and b and propagation of depolarization through IPL b-d contribute vector components of oscillating extracellular potentials whose frequency needs to be maintained in a narrow range for inducing internal sensation of memory. Specific electrophysiological findings in locations where sensory stimuli converge were found to correlate with behavioural motor actions indicative of specific brain functions. Long-term potentiation (LTP) that can be induced at locations where sensory stimuli converge is an example[87,88]. After application of a high-energy stimulus at a region rich in synapses and following a delay of at least 20 to 30 s[89,90], application of a regular stimulus at the same location generates a potentiated effect when recorded from the postsynaptic dendritic region or postsynaptic neuronal soma. Ability to induce LTP has shown several correlations with animals' ability to learn. It was possible to explain how learning-induced formation of IPLs is artificially produced in a delayed scaled-up manner during experimental LTP induction[11]. By keeping correlation between the ability to generate internal sensation of memory that matches with sensory features of the item whose memory is retrieved and the ability to induce LTP at specific locations[11], specific electrophysiological changes that can be induced at these locations can be examined to arrive at a mechanistic explanation for internal sensation of pleasure. Since there are specific electrophysiological changes that can be induced at locations responsible for different brain functions, a comparative examination can be carried out to understand how different internal sensations are generated (modified from[3]).

Several studies in addiction research have examined changes in synapses on the spines of MSNs in NAc[27-30]. Spines on the dendrites of MSNs receive excitatory inputs from hippocampus, amygdala, thalamus and medial prefrontal cortex. Separate set of spines of MSNs receives inhibitory inputs from ventral tegmental area (VTA) (Figure 2). Dopaminergic inputs from the VTA form additional synapses with the heads or necks of spines that synapse with excitatory inputs[31]. In striatum, certain dopamine functions necessitate spatiotemporal precision between dopamine release sites and receptor locations[32]. It is necessary to find how these connections are related to the generation of internal sensation of pleasure and the ability to generate experimental LTD in NAc.

KEY FINDINGS IN NAc THAT NEED INTERCONNECTED EXPLANATIONS

There are several disparate findings in NAc. Major requirement to understand the mechanism by which pleasure is generated is to reach a single mechanism that can provide inter-connected explanations for all those findings. Constraints offered by all the findings together provide an opportunity to derive a unique solution (Table 1).

Table 1 Key findings in nucleus accumbens and constraints provided by them

Finding	Constraint
LTD can be induced at the spinous region of MSNs of NAc[17,18,28]	Energy applied at the spinous region leads to depression of potentials at the recording electrode placed at the postsynaptic region or on MSN soma
LTD induction has a time delay following stimulation[17,18] comparable to that of LTP induction[13,14]	A time-dependent cellular change is taking place during the delay period following LTD stimulation
Similar to LTP, LTD is also NMDA receptor-dependent[82]	LTD induction takes place through activation of NMDA receptors of glutamatergic synapses
When rewards or conditioned stimuli that predict reward are presented, dopamine neurons in the VTA increase their firing[91,92] releasing dopamine in their terminals that synapse with spines of MSNs in NAc	Dopamine produces certain changes at the spines of MSNs that synapse with excitatory inputs
Drugs of abuse such as cocaine increase dopamine levels in the NAc[28]	Dopamine has certain actions on the spines of MSNs that synapse with excitatory inputs
Dopamine attenuates postsynaptic potentials elicited by stimulation of different excitatory inputs to NAc shell region[40]	Action of dopamine on spines of MSNs that synapse with excitatory inputs attenuates postsynaptic potentials when these excitatory inputs are stimulated through a mechanism
Dopamine reduces excitability of MSNs *in vitro*[93]	Action of dopamine on the spines of MSNs that synapse with excitatory inputs results in inhibition of MSNs through a mechanism
Exposure to cocaine leads to attenuation of postsynaptic potentials[42]	Action of cocaine leads to release of dopamine that acts on spines of MSNs that synapse with excitatory inputs and results in attenuation of postsynaptic potentials
In response to natural rewards and cocaine exposure, a major set of MSNs show depression of firing rate[43-46]	Rewards and drugs cause release of dopamine from VTA and dopamine's action on spines of MSNs that synapse with excitatory inputs result in reduced firing rate of MSNs through a mechanism
Synchronization of membrane potential states in a population of NAc neurons [53]	A mechanism through gap junctions between inhibitory neurons in VTA that provides inputs to NAc neurons and/or a mechanism at the level of spines of MSNs
Brain functions occur optimally in a narrow range of frequency of oscillating extracellular potentials especially that of background alpha rhythm as evident from electroencephalogram (EEG) findings[49]	Regional oscillations of extracellular potentials are expected to be related to oscillating extracellular potentials of the system
Summary of findings	**Inter-connected constraints**
Drugs cause release of dopamine from VTA, which in turn cause attenuation of postsynaptic potentials and depression of MSNs in NAc. Application of energy is able to induce delayed LTD through scaled up changes expected to occur normally at the synaptic region of NAc, which is likely responsible for generating internal sensation of pleasure	Dopamine does certain unique changes at the spines of MSNs of NAc that synapse with excitatory inputs to cause attenuation of postsynaptic potentials, depression of MSNs and promotes experimental induction of LTD. This inter-connected operation is expected to explain a mechanism that generates inner sensation of pleasure

Constraints provided by disparate findings can be used to find inter-connectable explanations for deriving a unique mechanism, which is expected to provide an explanation for the generation of internal sensation of pleasure. NAc: Nucleus accumbens; LTD: Long-term depression; MSNs: Medium spiny neurons; NMDA: N-methyl-D-aspartate; VTA: Ventral tegmental area.

MECHANISM OF PLEASURE AND INTERCONNECTED EXPLANATIONS FOR FINDINGS IN NAc

By keeping (1) the correlation between associative learning and LTP induction[11]; and (2) the ability of inter-LINKed spines of excitatory synapses to induce internal sensation of memory[3] as reference mechanisms, a reasonable expectation is that a mechanism for generating internal sensation of pleasure that satisfies constraints from different findings in NAc (Table 1) will become possible. Dendritic arbors of different MSNs overlap. Energy is applied to induce LTD at the synaptic locations of MSNs of NAc where spines present on different dendrites are abutted. One set of these spines receive inputs from excitatory neurons of different brain regions and another set of spines receive inputs from inhibitory neurons of VTA. In addition, the heads or necks of spines that synapse with excitatory inputs receive dopaminergic inputs[31] (Figure 3). Spines of excitatory synapses that also receive dopaminergic inputs enlarge by the action of dopamine[16]. Furthermore, a scaled-up electrophysiological change responsible for the generation of pleasure is expected to take place during experimental LTD induction at these synaptic locations.
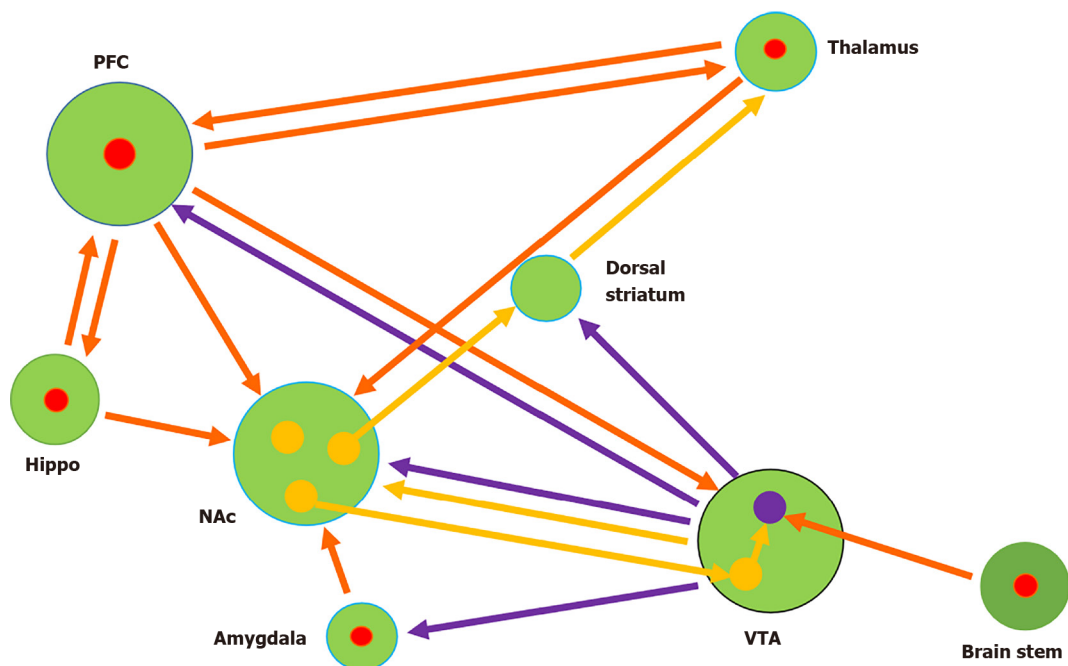
Figure 2 Input and output connections of nucleus accumbens. One set of spines of medium spiny neurons (MSNs) in the nucleus accumbens receive excitatory inputs (red arrows) from several regions. The same spines of MSNs that receive excitatory inputs receive dopaminergic inputs (violet arrows) from ventral tegmental area (VTA). Another set of MSN spines receive inputs from inhibitory interneurons (orange arrow) in the VTA. Large green circles: Different brain regions. Small circles: Predominant cell types within brain regions (Red: Excitatory; Orange: Inhibitory; Violet: Dopaminergic). PFC: Prefrontal cortex; NAc: Nucleus accumbens; VTA: Ventral tegmental area.
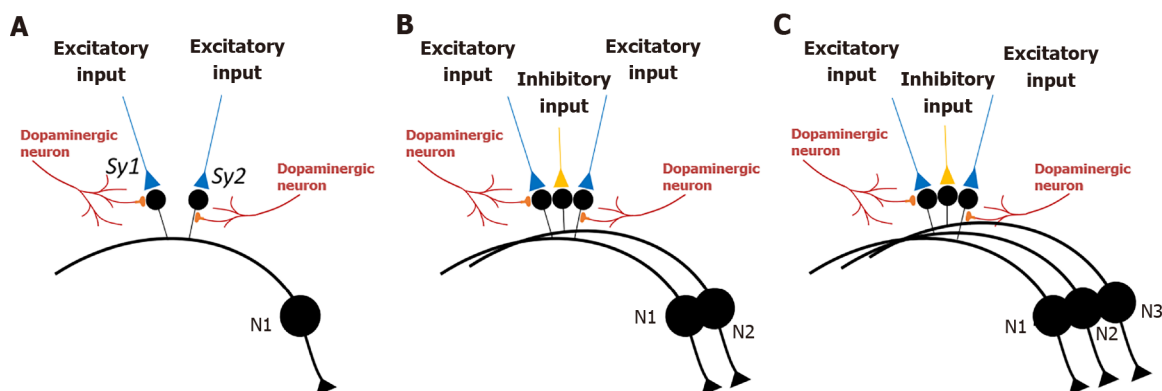
Figure 3 Interactions between spines of medium spiny neurons that synapse with excitatory inputs and spines of medium spiny neurons that synapse with inhibitory inputs. A: Adjacent spines (small black circles) on the dendrite of a medium spiny neuron (MSN) (N1) (cell body is drawn in a large black circle) that synapse with two excitatory inputs (in blue) to form synapses Sy1 and Sy2). Golgi staining shows that spines are physically well separated from each other on the dendrites of MSNs[23,24] such that the inter-spine space is occupied by spines of other dendrites or processes of other neurons or glial cells. This increases the probability that the nearest spine to a spine on the dendrite of a MSN is most likely a spine that belongs to another neuron, or in rare cases belongs to another branch of the same neuron. Note that dopaminergic inputs synapse either onto the head or neck region of spines that synapse with excitatory inputs; B: In between two adjacent spines of MSN N1 shown in figure A, there is a spine that belongs to a second MSN (N2). This spine synapses with an inhibitory input (in orange). All the spines are electrically insulated from each other by fluid extracellular matrix. Natural stimulants or cocaine abuse causes release of dopamine that will cause enlargement of spines that synapse with excitatory inputs. Since the spine that synapses with the inhibitory input is spatially interposed between the expanding spines, inter-postsynaptic functional LINKs are formed between those three spines; C: Same configuration of two spines of MSNs that synapse with excitatory inputs and one middle spine synapsing with inhibitory input. Here, these spines belong to three different MSNs.

There are two main methods by which LTD can be induced. (1) Low-frequency stimulation induces LTD that requires activation of N-methyl-D-aspartate receptors (NMDARs)[33,34]. Modest activation of NMDARs that can be used to induce LTD[28] may involve AMPAR endocytosis[35]; (2) By keeping postsynaptic depolarization below a threshold, a tetanic stimulation that normally induces LTP can induce LTD [36]. Removal of surface AMPARs occurs during induction of both NMDAR-dependent LTD[37,38], and metabotropic glutamate receptor-LTD[39,40]. Since endocytosis of vesicles containing AMPAR subunits during expression of LTD in NAc

[18] is associated with usage of membrane segments from lateral spine head regions that reduces spine size, it can lead to reversal of large number of existing IPLs. Even though reversal of existing IPLs can explain LTD similar to that of LTP decay[13], it is necessary to explain LTD as an active mechanism that requires energy for its experimental induction. Based on findings in NAc (Table 1), it is also necessary to explain (1) Attenuation of postsynaptic potentials by the effect of dopamine on MSN spines that synapses with excitatory inputs[41,42]; and (2) Reduced firing rate of MSNs[43-46], in addition to finding a matching explanation for the generation of internal sensation of pleasure. This has been remaining a challenge.

In the above contexts, main question is whether it is possible to explain internal sensation of pleasure and all the findings in Table 1 in terms of IPL mechanism. It is known that drugs of abuse such as cocaine lead to increased dopamine levels in the NAc[28]. Dopamine is known to cause spine enlargement[16]. Since dopaminergic inputs synapse with spines that receive excitatory glutamatergic inputs, this is expected to cause enlargement of those spines of MSNs. This forces these spines to form IPLs with all their abutted spines. Since some MSN spines synapse with excitatory inputs and others with inhibitory inputs, it is necessary to take into account the possibility for IPL formation between these spines (Figure 3B). In this context, IPL formation between MSN spines that synapse with inhibitory inputs and MSN spines that synapse with excitatory inputs can be examined in the light of the previous view that inhibitory inputs at the input level have a role in information processing[47]. It is necessary to combine all this information to obtain a solution for the challenge described in the previous paragraph.

Since LTP induction in the cortex usually requires low doses of gamma-amino butyric acid$_A$ (GABA$_A$) receptor antagonist bicuculline[48] for concomitant reduction of GABAergic inhibition, it shows the necessity to block activation of spines that synapse with inhibitory inputs. When spines that receive inhibitory inputs are in large numbers, such as in NAc, a mere reduction in GABAergic inhibition alone will not be able to induce LTP. This is because the numbers of spines that receive excitatory inputs are comparatively less to form IPLs between them alone to induce LTP. Now the question is, "What is the effect of application of energy on the MSN spines that receive excitatory inputs and MSN spines that receive inhibitory inputs that are distributed somewhat equally?" This increases the probability for the formation of IPLs between those spines. This can lead to propagation of hyperpolarization from the spines that synapse with inhibitory inputs to neutralize and even hyperpolarize the spines that synapse with excitatory inputs. In experimental LTD stimulation, this will result in depression of net potentials at the recording electrode responsible for LTD.

Now the question is, "Can formation of IPLs between MSN spines that synapse with excitatory inputs and MSN spines that synapse with inhibitory inputs explain the generation of internal sensation of pleasure?" At this juncture, a reasonable inference is that semblance generated at the location where LTD can be experimentally induced is associated with internal sensation of pleasure. Now, one can ask, "What type of a semblance can be anticipated based on the nature of inputs at the spines of MSNs and IPLs that are formed between them?" In physiological conditions, hyperpolarization of spines that receive inhibitory inputs is expected to propagate to spines that receive excitatory inputs through the IPLs formed between them. This is expected to generate a conformational change in the net local semblance induced from all the inter-LINKed spines of MSNs and contribute to internal sensation of pleasure (Figure 4). Brain functions such as pleasure take place only in a state of normal consciousness associated with a narrow range of oscillating extracellular potentials as evident from EEG findings[49]. Synaptic transmission at the synapses and propagation of potentials across the IPLs are expected to contribute vector components to both regional and system level oscillating extracellular potentials[3]. Narrow range of background oscillating extracellular potentials is expected to be generated from continuous reactivation of the large number of IPLs formed from common background stimuli to which nervous system is exposed[50,51]. The latter event continues to generate a background semblance in which internal sensation of pleasure is formed (Figure 4). Explanation for the functional significance of background semblance was explained previously[9].

Several inhibitory neurons in the VTA are expected to get activated through gap junctions between them similar to that contribute to cortical oscillations[52]. It can lead to synchronization of membrane potential states in a population of NAc neurons[53] and can explain how continuous reactivation of newly formed IPLs in NAc maintains pleasure. In physiological conditions, formation of IPLs between MSN spines that synapse with excitatory inputs and MSN spines that synapse with inhibitory inputs can explain how it leads to attenuation of postsynaptic potentials while getting
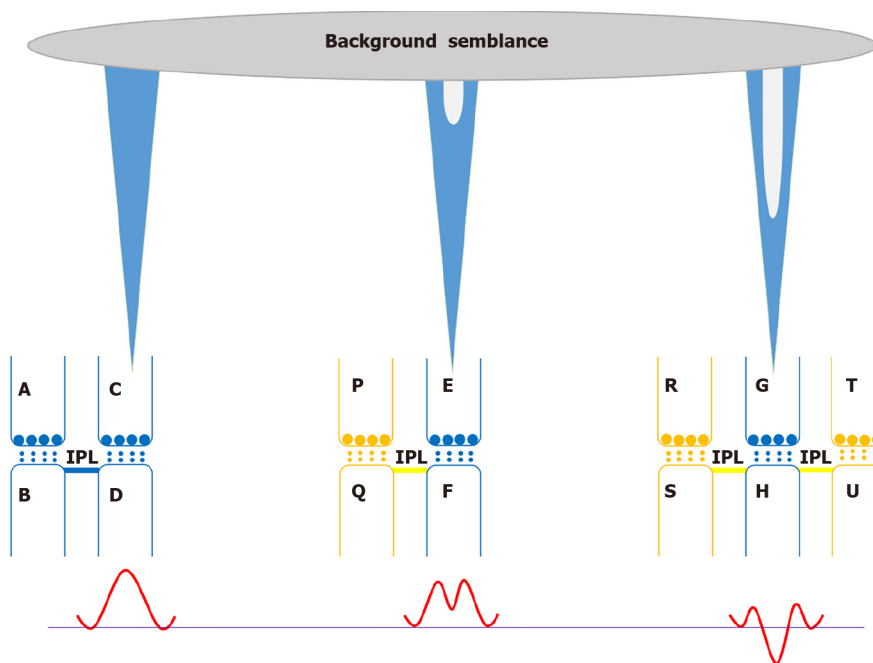
Figure 4 A schematic representation of units of internal sensations whose integral generates pleasure in a background net semblance of the system. Left: Normal semblance as shown in Figure 1. Inter-postsynaptic functional LINK (IPL) between spines B and D that receive excitatory inputs (in blue). An action potential arriving at presynaptic terminal A from a stimulus depolarizes its postsynaptic terminal B, which in turn propagates through the IPL B-D and depolarizes (shown as a positive waveform) inter-LINKed spine D. This generates units of internal sensations (shown as a blue triangle projected upwards from presynaptic terminal C that denotes semblance). Middle: Reactivation of an IPL between spine Q of a medium spiny neuron (MSN) that synapse with an inhibitory input (in orange) and another spine F of a MSN that synapse with an excitatory input (in blue) results in spread of hyperpolarization from spine Q to spine F. This leads to changes in both the waveform of spine depolarization (red waveform) and conformation of semblance (shown as a dip in the blue triangle). Right: Here, spine H that synapses with an excitatory input (in blue) forms IPLs with spines S and U that synapse with inhibitory inputs (orange). Net effect of hyperpolarization results in profound changes in both waveform of spine depolarization (red waveform) and conformation of semblance (shown as a deep dip in the blue triangle). Net effect of changes in semblances from all the inter-LINKed spines of MSNs in nucleus accumbens (NAc) is expected to generate a special semblance of pleasure.

exposed to dopamine[41]. In addition, it can also explain reduced firing of MSNs when animals are exposed to both natural rewards and cocaine[43-46]. The scaled-up change in experimental stimulation that generates LTD is a net effect of depression in the sum of potentials arriving at the recording electrode. A summary of these interconnected findings is shown in Figure 5.

HOMEOSTATIC CHANGES DURING DRUG ABUSE AND WITHDRAWAL

IPL formation involves interaction between outer membranes of spines by excluding the insulating fluid ECM[3]. Exocytosis of intra-cytoplasmic vesicles provides membrane segments that allow re-organization of the cell membrane at the lateral margins of spines that can promote IPL formation. Conversely, endocytosis of GluR1 AMPAR vesicles is associated with a reversal of LTP (LTP decay)[13]. Similar mechanisms can be expected to cause the formation and reversal of IPLs during LTD induction and decay respectively.

After 10 to 14 d of repeated *in vivo* cocaine exposure, both the ratio of AMPAR/NMDAR-mediated excitatory postsynaptic currents (EPSCs) and magnitude of LTD are reduced[17]. One of the reasons for a reduction in the AMPAR/NMDAR - mediated EPSC ratio is a decrease in the number of AMPARs. Based on the IPL mechanism, cocaine exposure results in the enlargement of spines that predisposes the IPLs formed between these spines to undergo fusion pore formation. In this context, endocytosis of vesicles containing GluR1AMPARs following cocaine administration can be viewed as a homeostatic mechanism for preventing IPL fusion. During vesicle endocytosis, usage of membrane segments from lateral spine head regions can reduce the size of spine heads and reverse extreme changes of IPLs such as IPL fusion. Endocytosis of these vesicles observed during experimental LTD induction[18,54,55] can be viewed as a scaled-up physiological response for preventing IPL fusion, especially in locations where dopamine is released. In this context, the finding that a challenge dose of cocaine after weeks of cocaine withdrawal terminates withdrawal
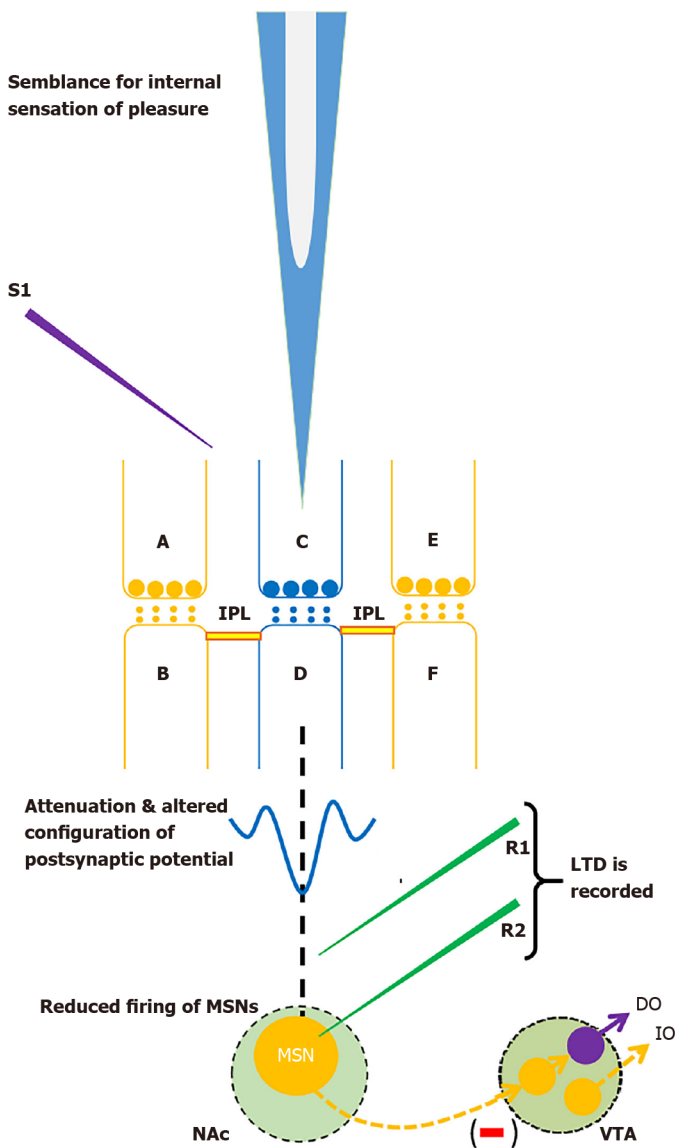
Figure 5 Nucleus accumbens circuitry that matches with constraints from several findings. Spines B and F belonging to different medium spiny neurons (MSNs) synapse with inhibitory inputs arriving through presynaptic terminals A and E respectively. Spine D on a third MSN synapses with excitatory input arriving through presynaptic terminal C. Two inter-postsynaptic functional LINKs (IPLs) are formed between spines B, D and F. These IPLs between spines that synapse with excitatory and inhibitory inputs lead to mixing of depolarization on the spines that synapse with excitatory input and hyperpolarization on the spines that synapse with inhibitory inputs. This leads to alternation of configuration of the net postsynaptic potentials as shown in a trace. Net semblance from a large number of inter-LINKed spines is expected to generate a special semblance for internal sensation of pleasure. Due to propagation of hyperpolarization, sum of potentials reaching many MSNs may not cross the threshold for firing, which leads to reduced firing of MSNs. A specific stimulation pattern applied at the presynaptic region using stimulating electrode S1 results in the formation of a large number of the above-mentioned types of IPLs in a time-dependent manner (inferred from delay between stimulation and long-term depression (LTD) induction[17,18]) resulting in LTD recorded from either recording electrode R1 (extracellular field recording) or R2 (whole-cell recording). Two inhibitory inputs to MSN and one inhibitory output from MSN are shown in orange. Excitatory synapse is shown in blue. Dopaminergic neuron of ventral tegmental area is shown in violet. DO: Dopaminergic output; IO: Inhibitory output; VTA: Ventral tegmental area.

along with endocytosis of AMPARs[28] can be considered as an augmented homeostatic mechanism.

During early withdrawal, administration of dopamine alone restores both spine structure and LTD[56] that can be explained in terms of IPL formation between MSN spines that synapse with excitatory inputs and MSN spines that synapse with inhibitory inputs indicating that the system is highly dynamic. During later periods of withdrawal, an increase in AMPARs at the membrane surface is observed[57,58]. During this time, a strong potentiation of AMPAR-mediated synaptic transmission is observed in the synapses on the spines of NAc MSNs. At this time, a single exposure to cocaine suddenly reverses the synaptic potentiation to depression[59]. This indicates that after a very lengthy drug-free period, the system reaches a near normal state and starts responding like a naïve system by forming IPLs between spines that synapse with excitatory inputs and spines that synapse with inhibitory inputs.

PATHOLOGICAL CHANGES FOLLOWING DRUG ABUSE

Inter-spine fusion is a possible consequence of drug abuse

Based on the IPL mechanism, conditions such as excessive drug use that cause excessive release of dopamine can lead to progression of IPLs to an extreme end of the spectrum of IPL changes, namely IPL fusion[6]. Defects in normal homeostatic mechanisms described in the above paragraph or changes in membrane composition can augment IPL fusion. Fusion between expanding spines matches with the previous observation of dye diffusion between neurons in NAc under the influence of dopamine[60]. Since transcriptomes of even neighboring neurons of similar type are different in the brain[61-63], IPL fusion that occurs between spines that belong to two neurons (Figure 3B and C) can lead to cytoplasmic content mixing and protein precipitation. An initial cellular response is expected to seal off the IPL fusion pore. When this fails, neurons are expected to protect themselves by removing fused spines from them[64], which can explain spine loss during cocaine abuse[65,66]. Loss of spines at the input regions of NAc MSNs in cocaine users will reduce the number of abutted spines and will reduce the probability of IPL formation. This will prevent experimental induction of LTD as evidenced from different studies[67,68].

Drug addiction

Major consequence of IPL fusion is the eventual loss of spines of MSNs[65,66] as a homeostatic mechanism to protect neuronal cells[64]. Since "non-addicted" animals regain the ability to generate LTD after two weeks of discontinuing self-administration of cocaine[68], it indicates that these animals may not have lost their spines. However during early stages of spine loss, the remaining spines can form IPLs to generate internal sensation of pleasure only if they can expand. This necessitates release of dopamine that in turn necessitates the availability of drugs. A natural consequence of this is initiation of drug seeking behavioural motor actions elicited through separate pathways. In later stages when more spines are lost, more amount of drug will become necessary even to maintain internal sensation of normal comfort. At this stage, reduced number of spines on MSNs will lead to persistent impaired LTD in "addicted" animals[68].

DISCUSSION

LTD can be experimentally induced in many brain regions and by different methods. Translating this to understand how it is related to conformational changes in semblance and the nature of internal sensations require examination of all the connections and findings at those regions. Excitatory neurons are controlled by inhibitory neurons both at the output level, for example, in the visual cortex[69] and at the input level[70,71]. The present work has explained a new testable function of inhibitory neurons at their output level. By explaining IPL formation between MSN spines that synapse with inhibitory inputs and MSN spines that synapse with excitatory inputs, it became possible to provide mechanistic explanations for previous assumptions that (1) Increased firing of VTA dopaminergic neurons encode an array of sensory, motor and cognitive variables[72]; and (2) Reduced activity of NAc MSNs encode reward[73-76]. The finding that coupling of potentials between MSNs were found to occur only in neurons that also showed dye coupling[60] matches with the IPL mechanism explained in the present work because IPLs with fusion pores can allow both dye diffusion through the fusion pore and propagation of potentials across the connecting membrane segments. The inference that input-specific filtering of excitatory inputs in the NAc is provided by dopamine[77] can be explained in terms of IPL formation between MSN spines that both synapse with excitatory inputs and enlarge under the influence of dopamine and MSN spines that receive inhibitory inputs.

Further examination is needed to understand the role of cholinergic inputs that synapse with the spines of MSNs in NAc[78]. It is also necessary to examine the difference in dopamine's actions on MSN spines in the shell and core regions of NAc [79,80] for their contributions on pleasure generation. Comparable findings in neurons of lateral hebenula, a brain region associated with reward, whose spines synapse with excitatory, inhibitory and dopaminergic inputs[81] can be examined to further understand this related brain function.

Fast kinetics of AMPA current in glutamatergic synapses allows initial depolarization of the spine head region. It is known that glutamate released from the presynaptic boutons is necessary to depolarize their spines, which will relieve blockage of NMDARs by Mg^{2+}[82]. Furthermore, postsynaptic depolarization below certain threshold induces LTD when tetanic stimulation that normally induces LTP is used[36]. Hyperpolarization from inter-LINKed spines that synapse with inhibitory inputs can provide suitable conditions for the above. It is also possible that timing of hyperpolarization propagating from an inter-LINKed spine that synapse with an inhibitory input also determines the conformation of semblance generated at the spines of excitatory synapses shown in Figures 4 and 5. Understanding details of the mechanism can provide information regarding selection of different types of glutamate receptors, their distribution and functional roles in different brain regions.

Based on the present work, sequence of appearance of neurotransmitters glutamate and GABA[83,84] is likely to provide information about the period when internal sensation of pleasure started appearing during evolution. The enzyme glutamic acid decarboxylase (GAD) catalyzes decarboxylation of glutamate to form GABA. Even though GABAergic interneurons were present in the common ancestor of all amniotes [85], it is difficult to trace the sequence of appearance of glutamatergic and GABAergic neurons. A possibility is that as neurons started receiving a large number of inputs, several combinations of IPLs started generating different internal sensations, which allowed natural selection of neurons that started expressing GAD. By selecting configurations of inputs that led to the formation of IPLs generating internal sensation of pleasure, animals were likely able to seek certain items and perform certain actions that were essential for survival, which those animals would not have performed otherwise.

CONCLUSION

By viewing pleasure as a first-person internal sensation, it was possible to extend IPL mechanism to formulate a framework of a specific mechanism taking place at the dendritic spine regions of MSNs in NAc responsible for pleasure. It matches with constraints provided by disparate findings such as the ability to induce robust LTD in NAc from naïve animals, impaired ability to induce LTD in addicted state, attenuation of postsynaptic potentials by cocaine, and reduced firing of MSNs in response to cocaine or dopamine. IPL mechanism that provided inter-connectable explanations for pleasure and disparate findings in NAc can be subjected to further verification. Since IPLs are expected to be of roughly $10nm^2$ in area as inferred from theoretical studies of membrane bilayers[86], advanced microscopic methods are necessary to detect their real-time formation, stabilization, and reversal in normal conditions and conversion to fusion states in addicted animals.

ACKNOWLEDGEMENTS

REFERENCES

1 **United Nations Office on Drugs and Crime**. World Drug Report 2020 (Set of 6 Booklets) United Nations; New York, NY, USA 2020. [cited 10 March 2021]. Available from: https://wdr.unodc.org/wdr2020/

2 **Vadakkan KI**. Semblance of activity at the shared post-synapses and extracellular matrices-A structure function hypothesis of memory. *iUniverse Publishers* 2007

3 **Vadakkan KI**. A supplementary circuit rule-set for the neuronal wiring. *Front Hum Neurosci* 2013; **7**: 170 [PMID: 23641209 DOI: 10.3389/fnhum.2013.00170]

4 **Palmer LM**, Shai AS, Reeve JE, Anderson HL, Paulsen O, Larkum ME. NMDA spikes enhance action potential generation during sensory input. *Nat Neurosci* 2014; **17**: 383-390 [PMID: 24487231 DOI: 10.1038/nn.3646]

5 **Eyal G**, Verhoog MB, Testa-Silva G, Deitcher Y, Benavides-Piccione R, DeFelipe J, de Kock CPJ, Mansvelder HD, Segev I. Human Cortical Pyramidal Neurons: From Spines to Spikes *via* Models. *Front Cell Neurosci* 2018; **12**: 181 [PMID: 30008663 DOI: 10.3389/fncel.2018.00181]

6 **Vadakkan KI**. The functional role of all postsynaptic potentials examined from a first-person frame of reference. *Rev Neurosci* 2016; **27**: 159-184 [PMID: 26540219 DOI: 10.1515/revneuro-2015-0036]

7   **Vadakkan KI**. The extreme degeneracy of inputs in firing a neuron leads to loss of information when neuronal firing is examined. *PeerJ Preprints* 2019; **7**: e27228v5 [DOI: 10.7287/peerj.preprints.27228v5]

8   **Konur S**, Rabinowitz D, Fenstermaker VL, Yuste R. Systematic regulation of spine sizes and densities in pyramidal neurons. *J Neurobiol* 2003; **56**: 95-112 [PMID: 12838576 DOI: 10.1002/neu.10229]

9   **Vadakkan KI**. From cells to sensations: A window to the physics of mind. *Phys Life Rev* 2019; **31**: 44-78 [PMID: 31759872 DOI: 10.1016/j.plrev.2019.10.002]

10   **Minsky M**. K-lines: a theory of memory. *Cog Sci* 1980; **4**: 117-133 [DOI: 10.1207/s15516709cog0402_1]

11   **Vadakkan KI**. A potential mechanism for first-person internal sensation of memory provides evidence for the relationship between learning and LTP induction. *Behav Brain Res* 2019; **360**: 16-35 [PMID: 30502355 DOI: 10.1016/j.bbr.2018.11.038]

12   **Jacob AL**, Weinberg RJ. The organization of AMPA receptor subunits at the postsynaptic membrane. *Hippocampus* 2015; **25**: 798-812 [PMID: 25524891 DOI: 10.1002/hipo.22404]

13   **Dong Z**, Han H, Li H, Bai Y, Wang W, Tu M, Peng Y, Zhou L, He W, Wu X, Tan T, Liu M, Zhou W, Jin W, Zhang S, Sacktor TC, Li T, Song W, Wang YT. Long-term potentiation decay and memory loss are mediated by AMPAR endocytosis. *J Clin Invest* 2015; **125**: 234-247 [PMID: 25437879 DOI: 10.1172/JCI77888]

14   **Wise RA**. Dopamine, learning and motivation. *Nat Rev Neurosci* 2004; **5**: 483-494 [PMID: 15152198 DOI: 10.1038/nrn1406]

15   **O'Carroll CM**, Martin SJ, Sandin J, Frenguelli B, Morris RG. Dopaminergic modulation of the persistence of one-trial hippocampus-dependent memory. *Learn Mem* 2006; **13**: 760-769 [PMID: 17142305 DOI: 10.1101/lm.321006]

16   **Yagishita S**, Hayashi-Takagi A, Ellis-Davies GC, Urakubo H, Ishii S, Kasai H. A critical time window for dopamine actions on the structural plasticity of dendritic spines. *Science* 2014; **345**: 1616-1620 [PMID: 25258080 DOI: 10.1126/science.1255514]

17   **Thomas MJ**, Beurrier C, Bonci A, Malenka RC. Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine. *Nat Neurosci* 2001; **4**: 1217-1223 [PMID: 11694884 DOI: 10.1038/nn757]

18   **Brebner K**, Wong TP, Liu L, Liu Y, Campsall P, Gray S, Phelps L, Phillips AG, Wang YT. Nucleus accumbens long-term depression and the expression of behavioral sensitization. *Science* 2005; **310**: 1340-1343 [PMID: 16311338 DOI: 10.1126/science.1116894]

19   **Kemp A**, Manahan-Vaughan D. Hippocampal long-term depression and long-term potentiation encode different aspects of novelty acquisition. *Proc Natl Acad Sci U S A* 2004; **101**: 8192-8197 [PMID: 15150407 DOI: 10.1073/pnas.0402650101]

20   **Dong Z**, Gong B, Li H, Bai Y, Wu X, Huang Y, He W, Li T, Wang YT. Mechanisms of hippocampal long-term depression are required for memory enhancement by novelty exploration. *J Neurosci* 2012; **32**: 11980-11990 [PMID: 22933783 DOI: 10.1523/JNEUROSCI.0984-12.2012]

21   **Dong Z**, Bai Y, Wu X, Li H, Gong B, Howland JG, Huang Y, He W, Li T, Wang YT. Hippocampal long-term depression mediates spatial reversal learning in the Morris water maze. *Neuropharmacology* 2013; **64**: 65-73 [PMID: 22732443 DOI: 10.1016/j.neuropharm.2012.06.027]

22   **Lemon N**, Manahan-Vaughan D. Dopamine D1/D5 receptors contribute to de novo hippocampal LTD mediated by novel spatial exploration or locus coeruleus activity. *Cereb Cortex* 2012; **22**: 2131-2138 [PMID: 22038910 DOI: 10.1093/cercor/bhr297]

23   **Robinson TE**, Kolb B. Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine. *Eur J Neurosci* 1999; **11**: 1598-1604 [PMID: 10215912 DOI: 10.1046/j.1460-9568.1999.00576.x]

24   **Robinson TE**, Gorny G, Mitton E, Kolb B. Cocaine self-administration alters the morphology of dendrites and dendritic spines in the nucleus accumbens and neocortex. *Synapse* 2001; **39**: 257-266 [PMID: 11169774 DOI: 10.1002/1098-2396(20010301)39:3<257::AID-SYN1007>3.0.CO;2-1]

25   **Hussain Z**, Johnson LR, Totterdell S. A light and electron microscopic study of NADPH-diaphorase-, calretinin- and parvalbumin-containing neurons in the rat nucleus accumbens. *J Chem Neuroanat* 1996; **10**: 19-39 [PMID: 8703362 DOI: 10.1016/0891-0618(95)00098-4]

26   **Carr DB**, O'Donnell P, Card JP, Sesack SR. Dopamine terminals in the rat prefrontal cortex synapse on pyramidal cells that project to the nucleus accumbens. *J Neurosci* 1999; **19**: 11049-11060 [PMID: 10594085]

27   **Nestler EJ**. Is there a common molecular pathway for addiction? *Nat Neurosci* 2005; **8**: 1445-1449 [PMID: 16251986 DOI: 10.1038/nn1578]

28   **Lüscher C**, Malenka RC. Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. *Neuron* 2011; **69**: 650-663 [PMID: 21338877 DOI: 10.1016/j.neuron.2011.01.017]

29   **Grueter BA**, Rothwell PE, Malenka RC. Integrating synaptic plasticity and striatal circuit function in addiction. *Curr Opin Neurobiol* 2012; **22**: 545-551 [PMID: 22000687 DOI: 10.1016/j.conb.2011.09.009]

30   **Pignatelli M**, Bonci A. Role of Dopamine Neurons in Reward and Aversion: A Synaptic Plasticity Perspective. *Neuron* 2015; **86**: 1145-1157 [PMID: 26050034 DOI: 10.1016/j.neuron.2015.04.015]

31   **Sesack SR**, Carr DB, Omelchenko N, Pinto A. Anatomical substrates for glutamate-dopamine interactions: evidence for specificity of connections and extrasynaptic actions. *Ann N Y Acad Sci*

2003; **1003**: 36-52 [PMID: 14684434 DOI: 10.1196/annals.1300.066]

32   **Liu C**, Goel P, Kaeser PS. Spatial and temporal scales of dopamine transmission. *Nat Rev Neurosci* 2021; **22**: 345-358 [PMID: 33837376 DOI: 10.1038/s41583-021-00455-7]

33   **Dudek SM**, Bear MF. Bidirectional long-term modification of synaptic effectiveness in the adult and immature hippocampus. *J Neurosci* 1993; **13**: 2910-2918 [PMID: 8331379]

34   **Mulkey RM**, Malenka RC. Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. *Neuron* 1992; **9**: 967-975 [PMID: 1419003 DOI: 10.1016/0896-6273(92)90248-c]

35   **Lüscher C**, Xia H, Beattie EC, Carroll RC, von Zastrow M, Malenka RC, Nicoll RA. Role of AMPA receptor cycling in synaptic transmission and plasticity. *Neuron* 1999; **24**: 649-658 [PMID: 10595516 DOI: 10.1016/s0896-6273(00)81119-8]

36   **Artola A**, Bröcher S, Singer W. Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex. *Nature* 1990; **347**: 69-72 [PMID: 1975639 DOI: 10.1038/347069a0]

37   **Beattie EC**, Carroll RC, Yu X, Morishita W, Yasuda H, von Zastrow M, Malenka RC. Regulation of AMPA receptor endocytosis by a signaling mechanism shared with LTD. *Nat Neurosci* 2000; **3**: 1291-1300 [PMID: 11100150 DOI: 10.1038/81823]

38   **Carroll RC**, Beattie EC, von Zastrow M, Malenka RC. Role of AMPA receptor endocytosis in synaptic plasticity. *Nat Rev Neurosci* 2001; **2**: 315-324 [PMID: 11331915 DOI: 10.1038/35072500]

39   **Waung MW**, Pfeiffer BE, Nosyreva ED, Ronesi JA, Huber KM. Rapid translation of Arc/Arg3.1 selectively mediates mGluR-dependent LTD through persistent increases in AMPAR endocytosis rate. *Neuron* 2008; **59**: 84-97 [PMID: 18614031 DOI: 10.1016/j.neuron.2008.05.014]

40   **Park S**, Park JM, Kim S, Kim JA, Shepherd JD, Smith-Hicks CL, Chowdhury S, Kaufmann W, Kuhl D, Ryazanov AG, Huganir RL, Linden DJ, Worley PF. Elongation factor 2 and fragile X mental retardation protein control the dynamic translation of Arc/Arg3.1 essential for mGluR-LTD. *Neuron* 2008; **59**: 70-83 [PMID: 18614030 DOI: 10.1016/j.neuron.2008.05.023]

41   **Pennartz CM**, Dolleman-Van der Weel MJ, Kitai ST, Lopes da Silva FH. Presynaptic dopamine D1 receptors attenuate excitatory and inhibitory limbic inputs to the shell region of the rat nucleus accumbens studied in vitro. *J Neurophysiol* 1992; **67**: 1325-1334 [PMID: 1534574 DOI: 10.1152/jn.1992.67.5.1325]

42   **Beurrier C**, Malenka RC. Enhanced inhibition of synaptic transmission by dopamine in the nucleus accumbens during behavioral sensitization to cocaine. *J Neurosci* 2002; **22**: 5817-5822 [PMID: 12122043 DOI: 10.1523/JNEUROSCI.22-14-05817.2002]

43   **Carelli RM**. Nucleus accumbens cell firing during goal-directed behaviors for cocaine vs. 'natural' reinforcement. *Physiol Behav* 2002; **76**: 379-387 [PMID: 12117574 DOI: 10.1016/s0031-9384(02)00760-6]

44   **Ishikawa M**, Mu P, Moyer JT, Wolf JA, Quock RM, Davies NM, Hu XT, Schlüter OM, Dong Y. Homeostatic synapse-driven membrane plasticity in nucleus accumbens neurons. *J Neurosci* 2009; **29**: 5820-5831 [PMID: 19420249 DOI: 10.1523/JNEUROSCI.5703-08.2009]

45   **Kourrich S**, Thomas MJ. Similar neurons, opposite adaptations: psychostimulant experience differentially alters firing properties in accumbens core vs shell. *J Neurosci* 2009; **29**: 12275-12283 [PMID: 19793986 DOI: 10.1523/JNEUROSCI.3028-09.2009]

46   **Mu P**, Moyer JT, Ishikawa M, Zhang Y, Panksepp J, Sorg BA, Schlüter OM, Dong Y. Exposure to cocaine dynamically regulates the intrinsic membrane excitability of nucleus accumbens neurons. *J Neurosci* 2010; **30**: 3689-3699 [PMID: 20220002 DOI: 10.1523/JNEUROSCI.4063-09.2010]

47   **Hangya B**, Pi HJ, Kvitsiani D, Ranade SP, Kepecs A. From circuit motifs to computations: mapping the behavioral repertoire of cortical interneurons. *Curr Opin Neurobiol* 2014; **26**: 117-124 [PMID: 24508565 DOI: 10.1016/j.conb.2014.01.007]

48   **Artola A**, Singer W. Long-term potentiation and NMDA receptors in rat visual cortex. *Nature* 1987; **330**: 649-652 [PMID: 2446147 DOI: 10.1038/330649a0]

49   **Palva S**, Palva JM. New vistas for alpha-frequency band oscillations. *Trends Neurosci* 2007; **30**: 150-158 [PMID: 17307258 DOI: 10.1016/j.tins.2007.02.001]

50   **Vadakkan KI**. Framework of Consciousness from Semblance of Activity at Functionally LINKed Postsynaptic Membranes. *Front Psychol* 2010; **1**: 168 [PMID: 21833231 DOI: 10.3389/fpsyg.2010.00168]

51   **Vadakkan KI**. A pressure-reversible cellular mechanism of general anesthetics capable of altering a possible mechanism for consciousness. *Springerplus* 2015; **4**: 485 [PMID: 26380161 DOI: 10.1186/s40064-015-1283-1]

52   **Whittington MA**, Cunningham MO, LeBeau FE, Racca C, Traub RD. Multiple origins of the cortical γ rhythm. *Dev Neurobiol* 2011; **71**: 92-106 [PMID: 21154913 DOI: 10.1002/dneu.20814]

53   **Goto Y**, O'Donnell P. Network synchrony in the nucleus accumbens in vivo. *J Neurosci* 2001; **21**: 4498-4504 [PMID: 11404437]

54   **Parkinson GT**, Hanley JG. Mechanisms of AMPA Receptor Endosomal Sorting. *Front Mol Neurosci* 2018; **11**: 440 [PMID: 30568574 DOI: 10.3389/fnmol.2018.00440]

55   **Diering GH**, Huganir RL. The AMPA Receptor Code of Synaptic Plasticity. *Neuron* 2018; **100**: 314-329 [PMID: 30359599 DOI: 10.1016/j.neuron.2018.10.018]

56   **Cannizzaro C**, Talani G, Brancato A, Mulas G, Spiga S, De Luca MA, Sanna A, Marino RAM, Biggio G, Sanna E, Diana M. Dopamine Restores Limbic Memory Loss, Dendritic Spine Structure, and NMDAR-Dependent LTD in the Nucleus Accumbens of Alcohol-Withdrawn Rats. *J Neurosci*

2019; **39**: 929-943 [PMID: 30446531 DOI: 10.1523/JNEUROSCI.1377-18.2018]

57   **Boudreau AC**, Wolf ME. Behavioral sensitization to cocaine is associated with increased AMPA receptor surface expression in the nucleus accumbens. *J Neurosci* 2005; **25**: 9144-9151 [PMID: 16207873 DOI: 10.1523/JNEUROSCI.2252-05.2005]

58   **Boudreau AC**, Reimers JM, Milovanovic M, Wolf ME. Cell surface AMPA receptors in the rat nucleus accumbens increase during cocaine withdrawal but internalize after cocaine challenge in association with altered activation of mitogen-activated protein kinases. *J Neurosci* 2007; **27**: 10621-10635 [PMID: 17898233 DOI: 10.1523/JNEUROSCI.2163-07.2007]

59   **Kourrich S**, Rothwell PE, Klug JR, Thomas MJ. Cocaine experience controls bidirectional synaptic plasticity in the nucleus accumbens. *J Neurosci* 2007; **27**: 7921-7928 [PMID: 17652583 DOI: 10.1523/JNEUROSCI.1859-07.2007]

60   **O'Donnell P**, Grace AA. Dopaminergic modulation of dye coupling between neurons in the core and shell regions of the nucleus accumbens. *J Neurosci* 1993; **13**: 3456-3471 [PMID: 8340817]

61   **Cembrowski MS**, Bachman JL, Wang L, Sugino K, Shields BC, Spruston N. Spatial Gene-Expression Gradients Underlie Prominent Heterogeneity of CA1 Pyramidal Neurons. *Neuron* 2016; **89**: 351-368 [PMID: 26777276 DOI: 10.1016/j.neuron.2015.12.013]

62   **Tasic B**, Menon V, Nguyen TN, Kim TK, Jarsky T, Yao Z, Levi B, Gray LT, Sorensen SA, Dolbeare T, Bertagnolli D, Goldy J, Shapovalova N, Parry S, Lee C, Smith K, Bernard A, Madisen L, Sunkin SM, Hawrylycz M, Koch C, Zeng H. Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. *Nat Neurosci* 2016; **19**: 335-346 [PMID: 26727548 DOI: 10.1038/nn.4216]

63   **Tasic B**, Yao Z, Graybuck LT, Smith KA, Nguyen TN, Bertagnolli D, Goldy J, Garren E, Economo MN, Viswanathan S, Penn O, Bakken T, Menon V, Miller J, Fong O, Hirokawa KE, Lathia K, Rimorin C, Tieu M, Larsen R, Casper T, Barkan E, Kroll M, Parry S, Shapovalova NV, Hirschstein D, Pendergraft J, Sullivan HA, Kim TK, Szafer A, Dee N, Groblewski P, Wickersham I, Cetin A, Harris JA, Levi BP, Sunkin SM, Madisen L, Daigle TL, Looger L, Bernard A, Phillips J, Lein E, Hawrylycz M, Svoboda K, Jones AR, Koch C, Zeng H. Shared and distinct transcriptomic cell types across neocortical areas. *Nature* 2018; **563**: 72-78 [PMID: 30382198 DOI: 10.1038/s41586-018-0654-5]

64   **Vadakkan KI**. Neurodegenerative disorders share common features of "loss of function" states of a proposed mechanism of nervous system functions. *Biomed Pharmacother* 2016; **83**: 412-430 [PMID: 27424323 DOI: 10.1016/j.biopha.2016.06.042]

65   **Spiga S**, Talani G, Mulas G, Licheri V, Fois GR, Muggironi G, Masala N, Cannizzaro C, Biggio G, Sanna E, Diana M. Hampered long-term depression and thin spine loss in the nucleus accumbens of ethanol-dependent rats. *Proc Natl Acad Sci U S A* 2014; **111**: E3745-E3754 [PMID: 25122682 DOI: 10.1073/pnas.1406768111]

66   **Spiga S**, Mulas G, Piras F, Diana M. The "addicted" spine. *Front Neuroanat* 2014; **8**: 110 [PMID: 25324733 DOI: 10.3389/fnana.2014.00110]

67   **Martin M**, Chen BT, Hopf FW, Bowers MS, Bonci A. Cocaine self-administration selectively abolishes LTD in the core of the nucleus accumbens. *Nat Neurosci* 2006; **9**: 868-869 [PMID: 16732275 DOI: 10.1038/nn1713]

68   **Kasanetz F**, Deroche-Gamonet V, Berson N, Balado E, Lafourcade M, Manzoni O, Piazza PV. Transition to addiction is associated with a persistent impairment in synaptic plasticity. *Science* 2010; **328**: 1709-1712 [PMID: 20576893 DOI: 10.1126/science.1187801]

69   **D'Souza RD**, Bista P, Meier AM, Ji W, Burkhalter A. Spatial Clustering of Inhibition in Mouse Primary Visual Cortex. *Neuron* 2019; **104**: 588-600.e5 [PMID: 31623918 DOI: 10.1016/j.neuron.2019.09.020]

70   **Palmer L**, Murayama M, Larkum M. Inhibitory Regulation of Dendritic Activity in vivo. *Front Neural Circuits* 2012; **6**: 26 [PMID: 22654734 DOI: 10.3389/fncir.2012.00026]

71   **Lovett-Barron M**, Kaifosh P, Kheirbek MA, Danielson N, Zaremba JD, Reardon TR, Turi GF, Hen R, Zemelman BV, Losonczy A. Dendritic inhibition in the hippocampus supports fear learning. *Science* 2014; **343**: 857-863 [PMID: 24558155 DOI: 10.1126/science.1247485]

72   **Engelhard B**, Finkelstein J, Cox J, Fleming W, Jang HJ, Ornelas S, Koay SA, Thiberge SY, Daw ND, Tank DW, Witten IB. Specialized coding of sensory, motor and cognitive variables in VTA dopamine neurons. *Nature* 2019; **570**: 509-513 [PMID: 31142844 DOI: 10.1038/s41586-019-1261-9]

73   **Carlezon WA Jr**, Wise RA. Microinjections of phencyclidine (PCP) and related drugs into nucleus accumbens shell potentiate medial forebrain bundle brain stimulation reward. *Psychopharmacology (Berl)* 1996; **128**: 413-420 [PMID: 8986012 DOI: 10.1007/s002130050151]

74   **Roitman MF**, Wheeler RA, Carelli RM. Nucleus accumbens neurons are innately tuned for rewarding and aversive taste stimuli, encode their predictors, and are linked to motor output. *Neuron* 2005; **45**: 587-597 [PMID: 15721244 DOI: 10.1016/j.neuron.2004.12.055]

75   **Taha SA**, Fields HL. Inhibitions of nucleus accumbens neurons encode a gating signal for reward-directed behavior. *J Neurosci* 2006; **26**: 217-222 [PMID: 16399690 DOI: 10.1523/JNEUROSCI.3227-05.2006]

76   **Carlezon WA Jr**, Thomas MJ. Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis. *Neuropharmacology* 2009; **56** Suppl 1: 122-132 [PMID: 18675281 DOI: 10.1016/j.neuropharm.2008.06.075]

77   **Christoffel DJ**, Walsh JJ, Hoerbelt P, Heifets BD, Llorach P, Lopez RC, Ramakrishnan C, Deisseroth K, Malenka RC. Selective filtering of excitatory inputs to nucleus accumbens by dopamine and serotonin. *Proc Natl Acad Sci U S A* 2021; **118** [PMID: 34103400 DOI: 10.1073/pnas.2106648118]

78   **Tepper JM**, Bolam JP. Functional diversity and specificity of neostriatal interneurons. *Curr Opin Neurobiol* 2004; **14**: 685-692 [PMID: 15582369 DOI: 10.1016/j.conb.2004.10.003]

79   **Pennartz CM**, Dolleman-Van der Weel MJ, Lopes da Silva FH. Differential membrane properties and dopamine effects in the shell and core of the rat nucleus accumbens studied in vitro. *Neurosci Lett* 1992; **136**: 109-112 [PMID: 1635660 DOI: 10.1016/0304-3940(92)90660-y]

80   **Pennartz CM**, Ameerun RF, Groenewegen HJ, Lopes da Silva FH. Synaptic plasticity in an in vitro slice preparation of the rat nucleus accumbens. *Eur J Neurosci* 1993; **5**: 107-117 [PMID: 7903183 DOI: 10.1111/j.1460-9568.1993.tb00475.x]

81   **Meye FJ**, Lecca S, Valentinova K, Mameli M. Synaptic and cellular profile of neurons in the lateral habenula. *Front Hum Neurosci* 2013; **7**: 860 [PMID: 24379770 DOI: 10.3389/fnhum.2013.00860]

82   **Lüscher C**, Malenka RC. NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harb Perspect Biol* 2012; **4** [PMID: 22510460 DOI: 10.1101/cshperspect.a005710]

83   **Gou ZH**, Wang X, Wang W. Evolution of neurotransmitter gamma-aminobutyric acid, glutamate and their receptors. *Dongwuxue Yanjiu* 2012; **33**: E75-E81 [PMID: 23266985 DOI: 10.3724/SP.J.1141.2012.E05-06E75]

84   **Liebeskind BJ**, Hofmann, HA, Hillis DM, Zakon HH. Evolution of animal neural systems. *Annu Rev Ecol Evol Syst* 2017; **48**: 377-398 [DOI: 10.1146/annurev-ecolsys-110316-023048]

85   **Tosches MA**, Yamawaki TM, Naumann RK, Jacobi AA, Tushev G, Laurent G. Evolution of pallium, hippocampus, and cortical cell types revealed by single-cell transcriptomics in reptiles. *Science* 2018; **360**: 881-888 [PMID: 29724907 DOI: 10.1126/science.aar4237]

86   **Leikin SL**, Kozlov MM, Chernomordik LV, Markin VS, Chizmadzhev YA. Membrane fusion: overcoming of the hydration barrier and local restructuring. *J Theor Biol* 1987; **129**: 411-425 [PMID: 3455469 DOI: 10.1016/s0022-5193(87)80021-8]

87   **Bliss TV**, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* 1973; **232**: 331-356 [PMID: 4727084 DOI: 10.1113/jphysiol.1973.sp010273]

88   **Nicoll RA**. A Brief History of Long-Term Potentiation. *Neuron* 2017; **93**: 281-290 [PMID: 28103477 DOI: 10.1016/j.neuron.2016.12.015]

89   **Gustafsson B**, Wigström H. Long-term potentiation in the hippocampal CA1 region: its induction and early temporal development. *Prog Brain Res* 1990; **83**: 223-232 [PMID: 2203099 DOI: 10.1016/s0079-6123(08)61252-2]

90   **Escobar ML**, Derrick B.   Long-term potentiation and depression as putative mechanisms for memory formation. In Bermudez-Rattoni F. Neural plasticity and memory, from genes to brain imaging. Chapter 2. Boca Raton: CRC Press, 2007

91   **Schultz W**. Predictive reward signal of dopamine neurons. *J Neurophysiol* 1998; **80**: 1-27 [PMID: 9658025 DOI: 10.1152/jn.1998.80.1.1]

92   **Roitman MF**, Stuber GD, Phillips PE, Wightman RM, Carelli RM. Dopamine operates as a subsecond modulator of food seeking. *J Neurosci* 2004; **24**: 1265-1271 [PMID: 14960596 DOI: 10.1523/JNEUROSCI.3823-03.2004]

93   **O'Donnell P**, Grace AA. Dopaminergic reduction of excitability in nucleus accumbens neurons recorded in vitro. *Neuropsychopharmacology* 1996; **15**: 87-97 [PMID: 8797195 DOI: 10.1016/0893-133X(95)00177-F]